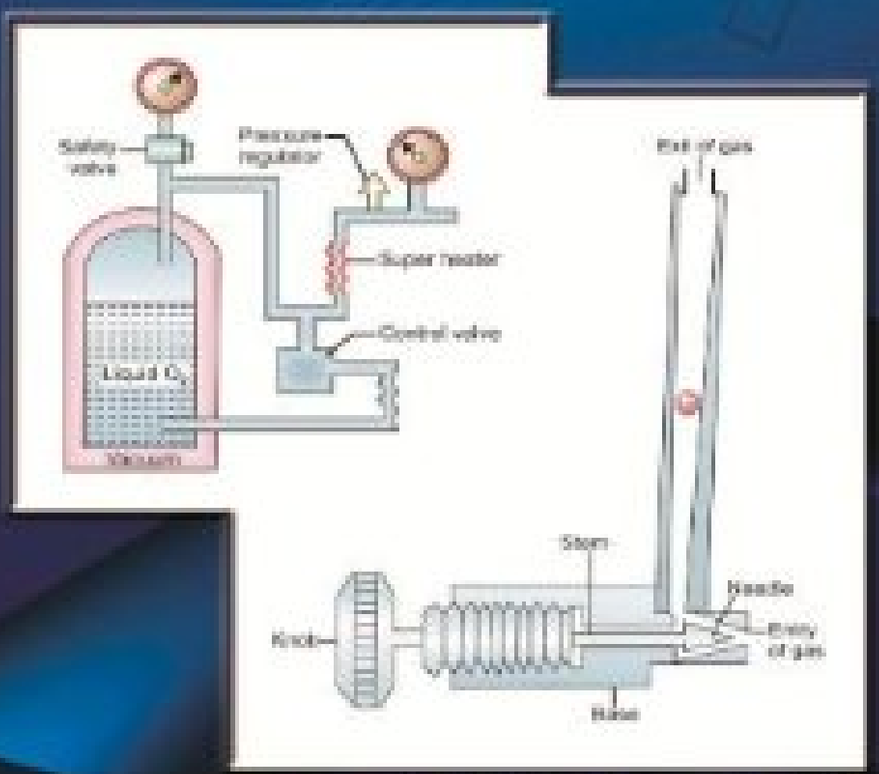
Textbook of Anesthesia for Postgraduates



TK Agasti

JAYPEE

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Anaesthesia
for Postgraduates

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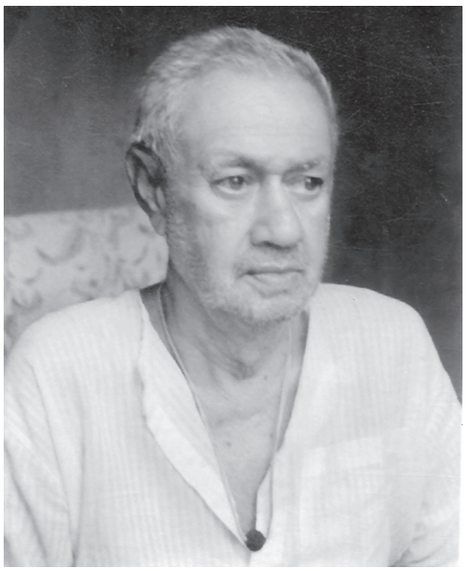
To
My loving father

Late Shri Anil Kumar Agasti



You are not more in front of my eyes
As you have taken your seat within it
So, today you are everywhere
In the blueness of sky
In the greeness of earth

—Rabindra Nath Tagore

Foreword

Textbook of Anaesthesia for Postgraduates is a very comprehensive textbook for all postgraduate students, as well as for fresh anaesthesiologists who have just stepped into the vast world of clinical practice of anaesthesia. This book includes many basic facts of the subject which are often omitted or considered unimportant in other books. In every chapter the reference to the historical aspect makes this book even more interesting. The language of this book is very subtle, smooth and easy for all readers. The author, a young and eminent anaesthetist with tremendous clinical experience has tried his best to explain the subject by putting himself in the shoes of the fellow students. He has also tried to conglomerate the aspect of anatomy, physiology, pathology, pharmacology, medicine and surgery related to the text in each chapter to make this book a thorough and complete one and I am sure it will help all the concerned greatly.

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Foreword

This book is written by a young anaesthetist who works hard in different super specialist hospital in Kolkata and in 200 beds Disha Eye Hospitals which is a super specialist ophthalmic institution, serving the whole Eastern Zone of India. I have gone through all the pages of this book and think it will be a very helpful to all the postgraduate students and even the budding anaesthesiologist who have just completed the postgraduate course. This is because it contents many necessary chapters which are written very elaborately and in much lucid language. Each chapter of this book covers the preclinical and clinical aspect of it. So, it will cause the students to avoid the reading of many preclinical and clinical books to pass the examination and to face the viva. It will help the students to participate in quiz competition also.

Still I think there are many lacks in this book which will be removed in subsequent edition by adding more chapters.

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Foreword

When Dr Agasti asked me to write the foreword for his book on *Textbook of Anaesthesia for Postgraduates*, I was definitely taken aback. I did see him obsessively writing notes between intervals in the hospital and even at home. But that it would cumulate into a book of anaesthesiology is something, I could not conceive. I am an Ophthalmic Surgeon for the last 25 years who enjoys ophthalmology without knowing a word of ophthalmic anaesthesia and that is courtesy Dr TK Agasti. He is our anaesthetist from my very initial days of practice. I tried to understand why he picked a novice like me to write the foreword for his book but when I went through the book, I assimilated the fundamentals and also the core of the subject, anaesthesia. As colleagues, we always shared that anaesthesia was not to eliminate pain for the patient during a surgery. It was about taking their fear away and reassuring them of the procedure they were undergoing.

In ophthalmic surgery you can loose or fight to save an eye but you cannot loose a patient. Dr TK Agasti has been doing this for us over years. His meticulous pre-operative assessment and his wonderful inclination towards safety during and after surgery has made us so relaxed as surgeons. I understand it has aptly reflected in his writing. He would work with a patient pre-operatively then struggle during anaesthesia.

He hails from a small town in East Midnapore where he has been groomed by his affluent family to serve patients rather than to take medicine as a career. The book reflects this. It is not aimed to dish out student popular stuff and get a good sale but brings out the flavour of anaesthesia which is safety and relaxation of the patient and their family to the procedure through meticulous service towards them.

I wish him and his book the very best.

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Preface

The anaesthesiology is a subject which is mainly studied at the postgraduate level, after passing MBBS, without giving much emphasis during the undergraduate course. But, this interesting branch of medical science involves the knowledge of all preclinical and clinical subjects just like the branch of medicine of medical science. When this knowledge is incorporated with some special knowledge of patient's condition during trauma, pain, severe medical illness, surgery and anaesthesia, then a new subject called anaesthesiology is evolved.

Just like specialising on the subject of medicine, the specialisation in this subject of anaesthesiology also does not involve a single organ such as skin, eye, heart, etc. or a single system such as gastrointestinal system, nervous system, etc. Moreover, this subject of anaesthesiology links many disease processes with surgery and handles many cardiotoxic drugs which are not used by the specialists of other disciplines of medical science. It also involves multiple sophisticated and complicated machines and equipments for the delivery of anaesthesia, monitoring of patients during surgery and also during recovery of already very sick patients which cannot be imagined in other subject of medicines.

Moreover, this subject of anaesthesiology is very vast. It is linked with all the disciplines of medical science and also infiltrates the other specialities like critical care, trauma, pain management, intensive care, etc. This branch of medical science has also changed drastically during the last few years in terms of technology, for maximum safety of patients. All these lead to extreme work load, necessity of advanced knowledge and intense responsibilities of anaesthesiologist.

There are many books which helps the students during the study of postgraduate course in anaesthesiology. But still the students are required to take the help of many preclinical and clinical books of anatomy, physiology, pharmacology, medicine, etc. for meticulous understanding. So referring to too many books confuses the students causing irritation and even helplessness. Hence, in this book an earnest attempt has been made to fill all the gaps so that students do not have to go through other preclinical and clinical books.

There is no end to knowledge. So as the provider of knowledge, no book can be complete. If an author shift towards the more completeness of a book, then its volume increase tremendously which may also be irritating and troublesome to many students. So, there should be a compromise between the information provided and the volume of book. Every new book gives some new information and I have tried my level best to collect all these information in my book which helps the students without going through many books, I think.

Many chapters are also lacking in this edition of my book which I commit to provide in the subsequent editions. So, I am regretful to my readers. I think there are many mistakes in this first edition of my book which is very obvious. For this I also apologise to my readers. I make an earnest appeal to all my readers to communicate with me regarding any mistake in my book and/or suggestions, if they have any.

At the end there is nothing more to write. So, thanking all, I start my first voyage towards the deep and vast ocean of knowledge of all readers of my book.

TK Agasti

Acknowledgements

I am extremely grateful to all my colleagues who consistently inspired me to write a book which will cover the anatomy, physiology, pharmacology, medicine and historical aspects of all the chapters which are lacking in most of the commonly read books. I am greatly indebted to by wife Dr B Agasti who consistently inspired me to write a book which is get rid of complex scientific experiments and their inferences that make the students very tired and confused. I am paying my sincere and boundless thank to Dr Debasish Bhattacharya, Director of Disha Eye Hospitals at Barrackpore, Kolkata, West Bengal, India for being my friend, philosopher and guide. I will also take the opportunity to thank to Dr S Basak a world famous ophthalmologist for being my inspiration.

Dr SM Basu and Dr Anupam Goswami has taken the pains of thoroughly reading this book and have given the foreword. So, I extend my sincere gratitude to them. Finally, I am grateful to all my patients who had submitted themselves for anaesthesia and permitted me to learn the subject of anaesthesiology. At last, I am also very grateful to M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi for publishing this book in a very presentable manner in a very short time.

Contents

1 Anaesthetic Machine

INTRODUCTION

The Boyle's anaesthetic machine is a continuous flow type of equipment which is used for administration of inhalational anaesthesia and artificial ventilation. It receives gas supply from gas supply unit consisting of cylinders or pipelines, controls this flow of gas to the flow metre, reduces their pressure to the desired safe level, vapourises the volatile anaesthetic agents and finally delivers the gas mixture to a breathing circuit.It was introduced first by HEG Boyle in 1917. After that it was modified at different times which is discussed in 'Inhalational anaesthesia' chapter. Now, it has become more modernised and sophisticated by attaching ventilators, O_2 failure alarm, hypoxic guard, gas analysing component, different monitors measuring vital parameters of body, electronic sophisticated vapouriser, etc. Now the Boyel's anaesthetic machine have become made extremely sophisticated by incorporating many built in safety features and devices and one or more microprocessors that can integrate, enhance and monitor all the components of the machine. These microprocessors now also provide option for sophisticated ventilator modes, automated record keeping and net working with local or remote computer monitors and as well as with hospital information system. So, it is now called as the anaesthetic work station. Due to this extreme sophistication lots of adverse outcome are now coming infront related to the malfunction of machine. This mainly because of the nonfamiliarity of an anaesthetic machine or work station with the anaesthetist. So this preventable adverse outcome resulting many mishaps can easily be avoided by increasing the familiarity of machine with the anaesthetist through proper education and proper checking the function of machine previously (Fact file-I).

A modern anaestheic machine consists of the following basic components. There are: (i) gas supplying unit such as pipeline or cylinders, (ii) pressure gauges, (iii) reducing valves or pressure regulators, (iv) flow meters, (v) vapouriser, (vi) ventilators, (vii) circle breathing system, (viii) common gas outlet, (ix) monitors, and (x) miscellaneous such as emergency O_2 flush, nonreturn pressure relief valve, O_2 supply failure alarm, hypoxic guard, suction apparatus, etc. (Fact file-II).

GAS SUPPLY UNIT

Pipeline

Now, in a big hospital or nursing home the supply of gases such as O_2, N_2O, compressed air, etc, through pipelines to the anaesthetic machine situated at different OT, or ventilators in ICU, ward, etc, from a central source is a common feautre. The advantages of sypplying gases through these pipelines from a central source are that it is easy, convenience, economic

FACT FILE- I

Safety features of modern anaesthetic machine

The safety features of modern anaesthetic machine are:

1. Noninterchangeable screw thread (NIST) system for connection of colour coded hose to machine from pipeline for central gas supply system and pin index system for cylinders.
2. Colour coded pressure gauge.
3. When O_2 pressure will be low, the supply of N_2O to patient will be cut off.
4. O_2 and N_2O ratio monitor and controller, called hypoxic guard.
5. Colour coded flow meters.
6. O_2 will be the last gas to be added to the mixture, i.e the flow metre for O_2 should be at the right most position.
7. Inspired O_2 concentration (FiO_2) monitor or analyser.
8. Oxygen supply failure alarm.
9. Alarm during disconnection of ventilator.
10. The anaesthetic machine using central gas pipeline should have atleast one O_2 cylinder in reserve.

FACT FILE - II

The components of an anaesthetic work station are:

1. Provision of secondary source for supply of gases in the event of failure of primary source.
2. Provosion of safe delivery of anaesthetic gases and vapours.
3. Provision for inbuilt breathing system with circle circuit.
4. Provision for any respiratory support of patient by sophisticated automatic ventilators with full range of patient's need.
5. Provision for monitoring the full range of patient's physiological parameters with display.
6. Provision for monitoring the full range of function and settings of all the components of machine with audio and visual alarm.
7. Provision for automatic record keeping.
8. Provision for online access to information for expert decision.
9. Provision for appropriate connection to an anaesthetic gas scavenging system.
10. Provision for suction vacum system with regulator.
11. Provision for auxilliary O_2 flow metre with suplemental O_2 supply.
12. Storage facility for items of everyday use.

and avoid frequent changing of cylinders. There is also less chance of explosion and increased patient's safety. But the high initial cost is the only disadvantages of it. The pipeline system for delivery of gases consist of (i) a central supplying unit using tank, or concentrator or cylinders for O_2, only cylinders for N_2O and cylinders or compressor for compressed air, and (ii) distributing pipelines with their outlet located at the point of use. The supplying pipeline is made up of high quality copper alloy which prevents the decomposition of gases and has bacteriostatic property. The usual pressure of gases kept in pipeline is about 400KPa. The size of the pipeline differs according to the demand. The pipes of 42 mm of diameter are usually used for leaving the central supply unit and the smaller diameter tubes of 15 mm are used after repeated branching. They also have specific colour code according to the gas they carry (Fig. 1.1).

The network of central pipelines ultimately terminate in the OT, ICV and/or ward at their outlet which is mounted on the wall or suspended from the ceiling. These outlets of pipeline at the point of use is easily identified by their specific colour code, shape and the name of gas stamped on them. They accept the matched and quick connect / disconnect 'Schrader' probe of a flexible colour coded hoses which ultimately connect the outlet of central pipeline to the anaesthetic machine. The anaesthetic machine end of these hoses may be connected with the machine permanently by screw and thread system where the thread is gas specific and not interchangeable, known as non-interchangeable screw threat (NIST) system, or through the ususal yoke assembly with pin index system located on the metal yoke bar of anaesthetic machine where the cylinders are usually attached. The previously described non interchangeable screw and thread system of connection which attaches the hosepipe with the pipeline outlet and the anaesthetic machine is also known as the diameter index safety system (DISS) where a hose of a particular diameter can only be connected to the machine. But the disadvantage in this system is that there is delay in connection with this system. So, the quick connect / disconnect 'Schrader' couplers are preferred. Where its other end is connected to the machine through pin index system (Fig. 1.2).

At the central gas suppling room from where the pipelines are distributed there should have a low pressure alarm which will detect the failure of supply of gas through pipeline. A reserve bank of cylinders should be available if primary supply through pipeline fails. An anaesthetist is only responsible for the supply of gas from the terminal outlet of pipeline to the anaesthetic machine, while only engineering department will be responsible for gas pipelines behind the wall. There is also risk of rupture or fire in pipeline carrying O_2 gas under high pressure from central source to machine due to worm out or damage of it. So for maintenance and to avoid any mishap the pipelines should be tested from time to time according to the guidelines laid by the international or national committee such as tug test to detect wrong connection, single hose test to detect cross connection, etc. (Fig. 1.3).

The central sources of gases which are distributed by the pipeline may be a storaged tank or cylinder manifold or O_2 concentrator for O_2, only cylinder manifold for N_2O and cylinder manifold or compressor machine for compressed air. In the oxygen storage tank the O_2 is stored as liquid between –160° and –170°C temperature at pressure of 5 to 10 atmosphere. Actually, the O_2 storage tank acts as huge thermo flask which is made up of double layer steel with vacuum between them. The innersides of these two steel layers is lined by a chemical, named perlite. The vacuum between these two steel layers acts as an insulator and maintain the temperature of inside of the tank. During the use of tank the evaporation of liquid O_2 requires heat which is known as the latent heat of evaporation and it is taken from the remaining liquid O_2. Thus it helps to maintain such low temperature of the remaining liquid portion of O_2 inside the tank. By a coiled copper tubing the cold O_2 gas which comes out from tank is warmed for use.

Fig. 1.1: Wall mounted outlet of the central oxygen pipeline

Fig. 1.2: Flexible colour coded Schrader probe

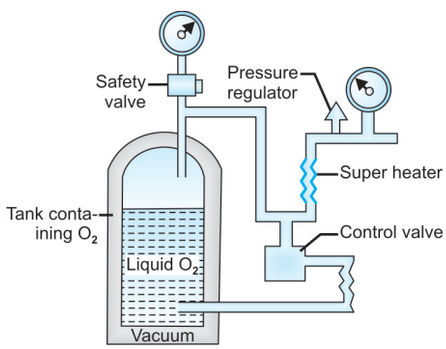


Fig. 1.3: The schematic diagram of O_2 tank

Then a pressure regulator allows the gas to enter the pipelines with pressure at 400 KPa. There is a safety valve on the tank which allows the gas to escape in emergency when excessive pressure builds up inside the tank during no use or under demand use of O_2. During excessive use of O_2 the control valve which is usually kept closed is opened and it allows the liquid O_2 to pass through an uninsulated coils of copper tube. During passage of liquid O_2 through this uninsulated copper tube, it evaporates within the tube and can supply more gas. The storaged O_2 tank usually rests on a weighing balance. It measures the mass of liquid O_2 in tank and thus gives an idea of the total contents of it. A differential pressure gauge is also used which measures the difference of pressure between the liquid O_2 at the bottom and the gaseous O_2 at the top of the tank and gives an idea of the total contents of a tank. This is because as the liquid O_2 evaporates, its mass and pressure at bottom decreases, so by measuring this difference in pressure between the bottom and the top the actual contents of the tank is calculated. At one atmospheric pressure and 15°C temperature 1 litre liquid O_2 gives 842 litres of gaseous O_2. When the supplying tanks of hospital become empty then liquid O_2 is pumped in the tank from an outside O_2 tanker by a cryogenic hose assembly. During this process of filling the spillage of cryogenic liquid O_2 on the handling person can cause frost bite, cold burns, and hypothermia. Reserve bank of cylinders should always be kept ready when O_2 is used from a storage tank particularly in case of sudden accidental failure. The O_2 tank should always be housed away from the main hospital building due to fire hazard (Fig. 1.4).

Other than storaged tank, manifold system is also used in a small hospital or nursing home as a central source of supply of O_2, N_2O, and compressed air. In this system large bulk cylinders (Type E) are used and divided into two groups which

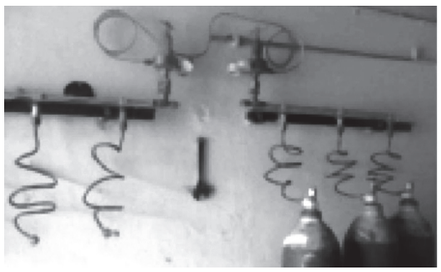


Fig. 1.4: Cylinder manifold

alternately supply gases in the pipe line. The number and size of cylinders in each group depends on the expected demand of gas used by the hospital. All the cylinders of each group are connected to a common pipe line through a nonreturn valve and a pressure gauge. This common pipeline from each group then in turn is connected with the distributing pipeline system through a check valve and a pressure regulator. In each group all the cylinders are opend at the same time and allows them to empty simultaneously. When all the cylinders of one group become empty, then the manifold system allows the supply to change over automatically to another group of cylinders. This change over is achieved through a pressure sensitive automatic device that also activates an electric audio signal to alert staff. At the same time the exhausted group of cylinders are turned off automatically. All the exhausted cylinders of previous group are then replaced by fresh full cylinders immediately. The manifold system for the supply of N_2O gas may cool to very low temperature due to the latent heat of vapourisation. So, the water vapour of atmosphere may condense or even freeze on the outer surface of the pipeline. This can block also the pipeline and the flow of N_2O if it contains some water vapour which is freezed inside the pipe line at this very low temperature. So, a thermostatically controlled heater may be needed at the outlet of N_2O manifold system to warm the gas at 47°C which prevents the condensation of water vapour within the gas of pipeline and allow uninterrupted flow of it. Like the O_2 tank this manifold system for central supply of O_2, N_2O and compressed air should also be housed in a well spaced and ventilated room which is constructed by fire proof tiles. This room should be located away from the main hospital building and on the ground floor for the easy access of transport trucks. This room which is used to store tank or manifold system of cylinders should not be used as the general store room for the other empty and full cylinders which are not in use. So, all the empty cylinders should be removed immediately after exhausted. The motor driven compressor for the central supply of air and the O_2 concentrator for the central supply of O_2 and the central vacuum plant should also be located there. The central vacuum pipeline should be provided with colour code, separate pressure gauge and high and low pressure signal device.

The compressed, oil free medical air which is cleaned by filters is also supplied in hospital through pipelines to run many power driven tools in ICU and OT and for other clinical use at pressure of 400 KPa. They may be supplied from manifold system consisting of large cylinders containing compressed air or more economically by a motor dirven compressor. The anaesthetic machines and the blender of most intensive care ventilators accept the connection from the 400 KPa outlet of compressed air pipeline.

The O_2 concentrator is a device which extract O_2 from air by differential absorption method and supply it. They become a small one which is designed to supply O_2 only for a single anaesthetic machine or a single ventilator. Otherwise it can be large enough to supply adequate O_2 through pipeline system. The small O_2 concentrators are of light weight, portable and can be used at remote location or for domestic purpose. In this O_2 concentrator machine there is a compressor which first filter air from atmosphere and then compressed it. After that this compressed air is exposed to multiple columns of zeolite (hydrated

aluminium silicate of alkaline earth metal) molecular sieve at a certain pressure which retain N_2 and other unwanted components of air except the O_2 and argon. Hence the argon cannot be separated from the concentrated O_2 produced by this type of machine. Thus maximum concentration of O_2 by 95% in volume is achieved. The columns of zeolite molecular sieve in O_2 concentrator which absorb N_2 and other gases releases them again in atmosphere when it is heated and vacuum is applied. This O_2 concentrator can be used in vast majority of cases, but not in circle system. This is because in this system its use leads to gradual accumulation of argon. However this can be avoided only by high gas flow. The main disadvantage of O_2 concentrator is its high initial cost which can be recovered easily later by free O_2 supply. The other disadvantages of it are risk of fire, contamination of zeolite sieve and sometimes malfunction.

Cylinder

Boyle's anaesthetic machine is equipped with O_2 and N_2O gas cylinder which are used when there is no provision for pipeline supply of gases or during emergency when the pipeline supply of gases have failed. These gas cylinders are made up of light weight seamless molybdenum steel designed to withstand intense internal pressure when gases are stored in gaseous (O_2) or liquid form (N_2O) under high pressure. The cylinders which are used in MRI suit are made up of aluminium, However the very large bulk cylinders are made of manganese steel. Very light weight cylinders of O_2 also can be made from aluminium alloy with fibre glass covering by epoxy resin matrix. These are used for domestic or transport purposes in ambulance or mountaineering purposes (Fig. 1.5).

The cylinders supplying gases are identified by their specific colour code, labelling stamped on their shoulder and plastic or paper collar. In the past different countries use different colour for their cylinders

Fig. 1.5: Shoulder of cylinder with engraved marking

containing different gases and there was no pin index system. So, with time when this colour is lost and the level is indistinguishable, then any interchange of N_2O and O_2 cylinder during attachment to the anaesthetic machine can lead to mortality. So an international standard which is given in table was laid out regarding the colour code and pin index (discussed later) by which the cylinders can easily be identified and cannot be interchanged when they are attached to the anaesthetic machine (i.e. it is practically impossible to attach any cylinder to wrong yokes). There are two international standard of colour code according to the school of UK and USA. However, in India UK standard is followed (Table 1.1).

The cylinders are also manufactured in different sizes which are usually named by alphabet from A to L. Among these the size A is the smallest and size L is the largest. The smallest sized A cylinder can hold 1.2 L of water and the largest sized L cylinder can hold 50L of water. Among these the A and H size cylinders are not used for medical purposes. The cylinders which are attached with the anaesthetic machine are usually of D and E size and the cylinders of size J are commonly used for cylinder manifold system for central supply. The O_2 and N_2O cylinder of size D contains 400 L of O_2 and 940 L of N_2O respectively. Whereas the O_2 and N_2O cylinder of size E contain 680 L and 1800 L of O_2 and N_2O respectively. A full O_2 cylinder of any size at atmospheric pressure can deliver O_2 which is 130 times of its original capacity.

The O_2 is stored in a cylinder as a gas at a pressure of 1900 psi and N_2O is stored in a cylinder as a liquid at a pressure of 750 psi. So, the cylinder which contain a gas in the form of liquid such as in N_2O and CO_2 is partially filled. Hence, this amount of partial filling of cylinder is described as the filling ratio and is defined as the weight of fluid in a cylinder divided by the weight of water required to fill the cylinder. The cylinders containing gases in liquid form are not filled up fully. This is because the partial filling of cylinders with liquid such as in the case of N_2O and CO_2 reduces the risk of explosion due to the sudden dangerous increase in pressure within the cylinder sudden increase in evaporation of liquid gas during sudden increase in temperature of atmosphere. So, in cold country such as in UK the filling ratio in N_2O and CO_2 cylinder is kept at 0.75, whereas in hot countries the filling ratio of these two types of cylinders is kept at 0.67.

Only a gas containing cylinder during its emptying at constant temperature shows a linear and proportional decrease in cylinder pressure. But this does not happen in case of cylinder which are filled with gas as liquid such as N_2O and CO_2. Here, initially the pressure in side the cylinder remains constant, because more gas is produced by

Table 1.1: Colour coding of medical gas cylinders

Name of gas	*Colour of body*	*Colour of shoulder*	*Physical state in cylinder*
N_2O	Blue	Blue	Liquid / gas
O_2	Black (UK) Green (USA)	White (UK) Green (USA)	Gas
CO_2	Gray	Gray	Liquid / gas
Air	Gray (UK), Yellow (USA)	White (UK) Black quarter (UK) Yellow (USA)	Gas

evaporation from liquid to replace the gas that is used. After that once when all the liquid has been evaporated to gaseous state, then the pressure in the cylinder starts to decrease with the process of emptying. So, the O_2 pressure gauge shows continuously the contents of a cylinder which is proportional to the gauge pressure and the N_2O pressure gauge does not show the actual content of the cylinder. The N_2O pressure gauge shows a constant pressure of N_2O gas which is present above the liquid and till the later is completely depleted. Then the pressure in the gauge starts to drop. So, the N_2O pressure gauge does not show the actual contents of its cylinder till the whole liquid is completely evaporated to gas. During the emptying of such cylinder containing gas as liquid, the temperature of it also decreases. This is because of the withdrawn of latent heat for vapourisation of liquid within the cylinder from the outside atmosphere, leading to the formation of ice on the outside of the cylinder. As the pressure gauge of N_2O cylinder can not tell the total content of it, so a full N_2O cylinder can only be identified by comparing the weight of it with that of an empty one, or in other way a full cylinder will give a ringing sound when tap by a metal while a empty will give a dull thud sound.

The cylinders are tested following manufacture at regular intervals, usually 5 years, by:

i. visual inspection from outside or inside (endoscopic),
ii. tensile test where strips of a cylinder are cut longitudinally and stretched till they elongate with yield point not being less than 15 tons/sq inch,
iii. flattening test where one cylinder is kept in between two compression blocks and pressure is applied to flatten it till the distance of these two blocks becomes 6 times of the thickness of the cylinder wall without crack,
iv. bend test where a strip of 25 mm width is cut from the cylinder wall and equally divided into 4 strips which are then bend inwards till the inner edge is apart proving cylinder wall will not develop any crack,
v. impact test where three longitudinal and three transverse strips are cut from a cylinder wall and struck by mechanical hammer with mean energy needed to produce a crack it should not be less than 5 ft lb for transverse strip and 10 ft lb for longitudinal strip,
vi. pressure or hydraulic or water jacket test where the cylinder is subjected to high pressure which is more than 50% of their normal working pressure without damage. All these test are usually done for at least one out of every 100 cylinders. The gases and vapours should be free of water vapour when stored in cylinders. Becasue water vapour may freeze and block the exit port of cylinder when the temperature of cylinder valve decreases tremendously on opening. All the cylinder after filled with gas should be stored in a dry, well ventilated, fire proof room and not subjected to extremes of heat. They should not be stored near flammable materials like grease or oil, etc., or near any source of direct heat or fire (Fig. 1.6).

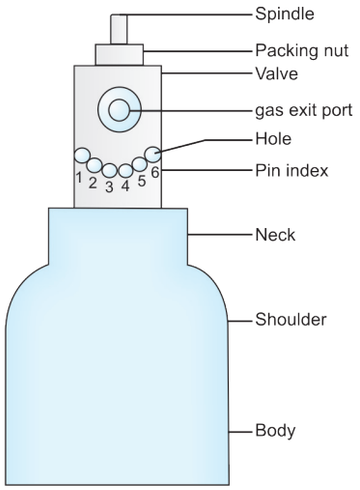


Fig. 1.6: The different parts of a cylinder and different combination of pin index.Gas exit port accommodates the yoke nipple and the hole accommodate the pine of pin index system

A cylinder has four parts such as body, shoulder, neck and valve. The size of the body of a cylinder varies according to the designations which are named as A to L and is painted according to the colour code. The upper part of the cylinder which is called as the shoulder suddenly becomes narrow. This is called as the neck. The shoulder and the neck of a cylinder is also painted according to the colour code which may be the same with the body or not. The neck ends in a tapered screw thread into which the valve of a cylinder is fitted. This thread between the neck and the valve of a cylinder is sealed by a special material which melts if the cylinder is exposed to excessive heat suddenly, and allows the contents of a cylinder to escape avoiding the risk of explosion. There is a plastic disc around the neck whose colour and shape indicates the year when the cylinder was last examined. The marks engraved on the shoulder of a cylinder are: date of last test performed, test pressure, chemical formula of the contents of this cylinder and tare weight (weight of empty cylinder). Every cylinder should also have a paper lebel which is sticked on the body or will hang from the neck. This will show: cylinder size code, specification of contents (which include name, chemical symbol, pharmaceutical form, proportion of gases in a gas mixture), batch number, maximum cylinder pressure in bars, nominal cylinder contents in litre, filling and expiry date, direction of use, hazard and safety instruction, storage and handling precaution, etc. (Fig. 1.7).

At the top every cylinder is fitted with a valve which is known as the cylinder valve. Several types of cylinder valves like flush type, bull nosed, straight type, angle type, etc., are available. But the noninterchangeable flush type of valve with pin index system which is commonly used to attach a cylinder at the yoke bar of anaesthetic machine will be discussed here. It is screwed into the neck of a cylinder via a threaded connection which is sealed by a special material with

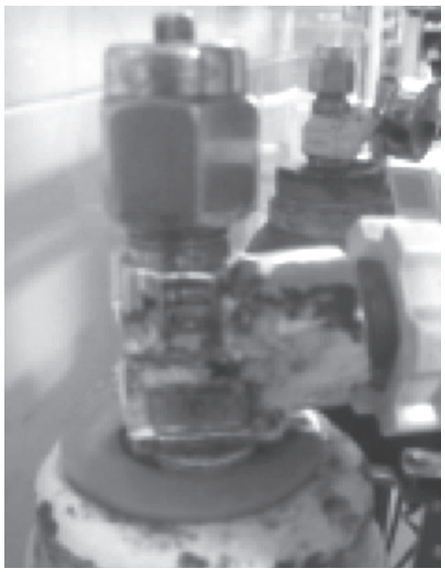


Fig. 1.7: Bull nose type of cylinder valve.

low melting point. This cylinder valve is made of brass and plated with chromium or nickel which allow the rapid dissipation of heat, if generated due to compression during filling (Fig. 1.8A).

The chemical formula of gas by which the cylinder is filled up is engraved on its valve. The valve seals the contents of a cylinder and is used to start, regulate and stop the flow of gas from the cylinder by a spindle which is described below. On the top of the cylinder valve there is an on/off stem or spindle with packing nut. When this stem is turned with a spanner, then it allows the gas to flow through its outlet situated on the valve. In modern modification the top of the valve is so designed that the on and off of the cylinder can be done by manual turning of the stem or spindle with the packing nut without the need of a spanner. There is an outlet hole and another two holes below the previous one at one side of the cylinder valve which fits with the yoke assembly of Boyle's machine through a specific noninterchangeable pin index system consisting of a nipple and two pins. A compressible yoke sealing washer named Bodok seal should be placed between the anaesthetic machine and the cylinder valve to make a gas tight joint when the cylinder is connected to the machine at the yoke assembly. Corresponding to the two pins of the pin index system, there is also two holes on the same side of cylinder value below the outlet port. If the yoke nipple is damaged or the pins of yoke assembly and the holes of cylinder valve are not aligned properly (i.e. pin index of a particular cylinder valve does not match with the yoke assembly), then the gas exit port of the cylinder valve will not seal tightly against the Bodok washer and the gas will leak. The Bodok washer is made of carbon impregnated rubber with a metal ring around it. It is 2.4 mm thick and only one seal is allowed inbetween the cylinder valve and the yoke assembly to fit the cylinder without leak. The excessive tightening of the screw of yoke assembly to press the cylinder valve against this seal may also damage it (Fig. 1.8B).

Fig. 1.8A: CO_2 cylinder with flush type cylinder valve

The cylinder valves are usually wrapped by a plastic covering after filling to protect it from anything which can enter the exit port and block it. The valve should be slightly opened and then closed before connecting the cylinder with the anaesthetic machine. This procedure usually cleans dust, oil, and grease from the exit port which would otherwise enter the anaesthetic machine and may damage it.

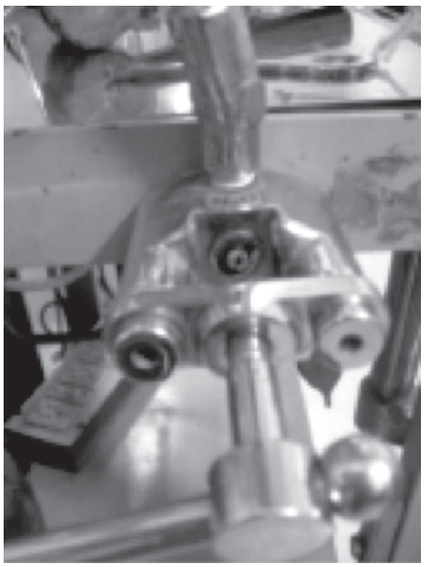


Fig. 1.8B: Pin index system (Yoke assemble)

The cylinder valve should be turned on slowly during use when attached to the anaesthetic machine. Because it prevents the sudden rise in pressure and temperature of gas while flowing through in the machine's pipe line. During closure of cylinder, overtightening of valve should also be avoided. Because it may damage the seal between the valve and the neck of a cylinder (Fact file- III).

Bourdon Pressure Gauge (Fig. 1.9)

It is attached with the anaesthetic machine to measure the pressure of gas with in the cylinder such as O_2, N_2O, and compressed air, or pipe lines after connecting with the anaesthetic machine. However, one which is designed to measure the pressure of cylinder should not be used for pipeline and vice versa. Because it may lead to inaccurate result and can cause damage to the pressure gauge. Inside this type of pressure gauge there is a robust, but flexible coiled tube made of copper alloy. It is closed at its inner end and is connected through a lever to a needle pointer which moves over a dial indicating pressure. The other end of this coiled tube is opened to a gas supply line coming from cylinder or pipeline (Fig. 1.10A).

Fig. 1.9: Bourdon pressure gauge

Fig. 1.10A: Bourden pressure gauge

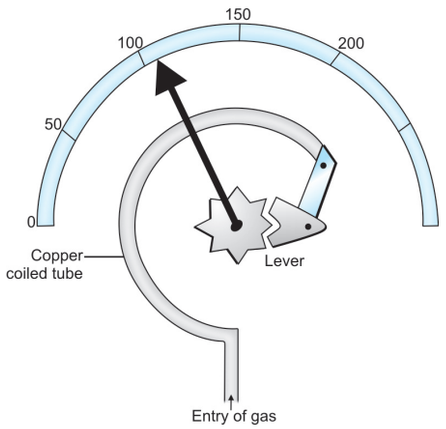


Fig. 1.10B: The mechanism of action of Bourdon pressure gauge

FACT FILE- III

Machine inlets

Most anaesthetic machines have three separate inlets each for O_2, N_2O and air. Some machines also have a 4th inlet for CO_2, helium or Heliox. However, the compact models of machine lack the air inlet. These inlets of machine which are connected with the pipelines are separated from the inlet of machine which are connected with the cylinder. So the machines have separate pressure gauges at pipelines inlet and cylinder inlet to measure their respective pressure. However, there are many machines which (we commonly use in our country) have no separate inlets for the pipeline and cylinder and the pipeline supply is attached at the inlet of machine where the cylinders are attached. In the machines where there is separate inlet for pipeline (and cylinder), a colour coded hose pipe is used to connect the outlet of pipeline to the anaesthetic machine through a noninterchangeable DISS that prevents incorrect hose attachment. At this connection a filter is attached which helps to filter the gas and a one way check valve is attached which prevents the retrograde flow of gas in the pipeline. At the cylinder inlet of machine the cylindrs are attached to the machine through a yoke assembly that utilises PISS (pin index safety system)to prevent wrong connection of cylinders. The yoke assembly includes PISS, a washer, a gas filter and a check valve that prevents retrograde gas flow. In some machines there have an extra O_2 or air inlet which is used to drive the ventilator.

After turning on the valve and opening the cylinder the gas under high pressure first starts to flow into this colied copper tube of pressure gauge and causes it to uncoil or straight out. Then this movement of the tube during uncoiling causes the needle pointer to move on dial and indicates pressure of gas inside the cylinder or pipeline. Each pressure gauge is calibrated for a particular gas, colour coded and bears the name and symbol of gas for which types of gas cylinder or pipeline it is used. At the front, every pressure gauge is protected by a cover of heavy fibre glass. So, in case of any breakage of coiled copper tube, the gas escape from behind, rather than the front. The measured pressure in the pressure gauge is depicted in unit such as KPa or lbs/sq.inch or Kg/sq.cm. When the central pipeline for O_2 supply is connected to the anaesthetic machine, then the pressure gauge at the connection shows 4 bars or 60 psi pressure (Fig. 1.10B).

Reducing Valve or Pressure Regulator

The gases are usually presented to anaesthetic machine under different high pressure from different types of cylinders or pipelines. So, they are passed through a single or multiple reducing valves which are placed between the cylinder or pipelines and the rest of the components of anaesthetic machine to decrease their high variable pressure to a safe constant operating pressure before reaching the gas to flow metre. Otherwise in the absence of these valves when the pressure of a cylinder decreases with use, then in order to maintain the supply of gas to patient at a constant flow and pressure, continuous adjustment of flow metre is required. These reducing valves also allow a delicate control of gas flow through flowmetre and protect the different sophisticated component of anaesthetic machine against the sudden surges of high pressure of gases (Fig. 1.11).

In this type of pressure regulator or reducing valve there are two chambers such as a high pressure chamber and a low pressure chamber, connected through a gap which is guarded by a valve. The high pressure chamber gets its gas flow through its inlet directly from cylinder. The small valve intervening between the high and low pressure chamber is attached to a diaphragm

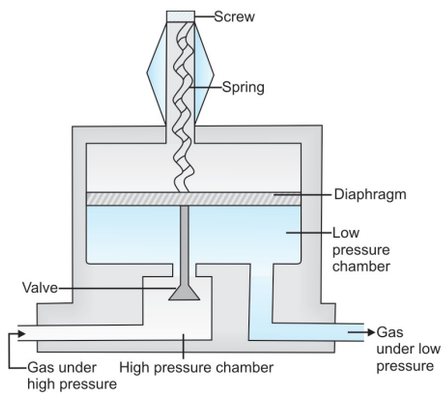


Fig. 1.11: The mechanism of action of reducing valve

which is again attached to a spring through which the pressure regulator can be adjusted to get the supply of gas flow at a constant low pressure. After entering the gas into the high pressure chamber directly from cylinder the force exerted by the gas under high pressure tries to close the gap by the small valve and decrease the gas flow to low pressure chamber from high pressure chamber. On the other hand, the opposite opening force exerted by the spring and diaphragm tries to open the valve. Then a balance is reached between these to forces leading to a constant fixed opening or gap which leads to a constant flow of gas under fixed desired pressure to low pressure chamber from high pressure chamber and ultimately passes out (Fig. 1.12).

If the gas in cylinder contains water vapour, then when the gas with water vapour enter the low pressure chamber from high pressure chamber, then due to loss of heat due to expansion of gas in low pressure chamber, there is chance of ice formation inside the regulator causing malfunctioning of it. There is also the chance of rupture of diaphragm leading to mulfunctioning of it. So, these regulators should be serviced at regular intervals and the rubber diaphragm is checked and renewed. The control of high pressure in pipeline is also achieved by a flow restrictor (a separate type of device which control the flow of gas) and a second stage pressure regulator. If there is only flow restrictor and no pressure regulator for pipeline, then when there is some change in pipeline pressure, the flow metre should be adjusted accordingly. A one way valve is also placed within the cylinder supply line within the anaesthetic machine next to the inlet of yoke. Their function is to prevent the back flow and loss or leakage of gas through an empty yoke (if a cylinder is not connected there) from working cylinder. They also prevent the transfilling of gas when one cylinder is full and working and the other cylinder is empty. Recently this one way valve is incorporated with in the design of a pressure regulating or reducing valve.

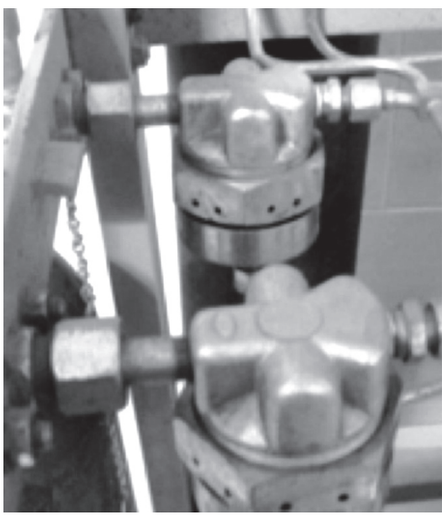


Fig. 1.12: Reducing valve

This type of reducing valve is also called the preset pressure regulator, because by adjusting the screw before hand during manufacturing we can adjust the diaphragm and subsequently the valve which is situated between the high and low pressure chamber. Thus we will be able to keep a fixed low pressure in low pressure chamber from which the gas will be delivered continuously at low pressure to the flow meter. In India BOC uses the preset regulator or reducing valve which are set to deliver gases at constant low pressure of 60 lbs/sq.inch by adjusting the screw and thus subsequently adjusting the inside diaphragm and valve of regulator. There is another type of preset pressure regulator which is called the Adam's valve. These are used in many anaesthetic machines (Fact file - IV).

Pressure regulators are so adjusted that the anaesthetic machine uses both the gas from pipelines when the pipeline pressure is 50 psi or greater and cylinder valve is also simultaneously open. So, when the gases from pipeline are being used, the cylinder valve should be closed. This is because the machine will always use gas from the source that has higher pressure. But, sometimes if the pipeline pressure drops below that supplied by cylinder and its valve is open, then some gas will be withdrawn from the cylinder. Thus gradually the cylinder will be exhausted without the knowledge of anaesthetist and then it will not help during emergency.

FACT FILE- IV

After passing through the Bourdon pressure gauge and check valve the gases from pipeline and cylinder passes through a common pathway to the flowmetre. The pressure regulator situated on the cylinder supply line are so adjusted that in this common pathway the gas pressure coming from the cylinder is always lower than the gas pressure coming from the pipeline. So, it allows the machine to use preferentially the gas from pipeline, still if the cylinder is left open (unless the pipeline pressure drops below the gas line pressure coming from cylinder attached with machine). A high pressure relief valve is also sometimes provided in some machines distal to pressure regulator. It sets open when the supply pressure from cylinder or pipeline exceeds the machine's maximum safety limit in case of failure of pressure regulator. Some machines also use a second pressure regulator instead of this relief to drop both the pipeline and cylinder pressure in case of the failure of first one. This is known as two stage pressure regulation. This two stage pressure regulation is also needed for an auxiliary O_2 flowmetre, to drive gas to power the pneumatic ventilators, or for the O_2 flush mechanism. The pressure in the supply of O_2 is reduced more than that of N_2O. This differential reduction of pressure between these two gases is important for the proper functioning of N_2O/O_2 flow linkage safety device, i.e. in the failure of the supply of O_2, the N_2O will not also flow. This safety device sense the pressure of O_2 through a small piloting pressure line that is derived directly from gas inlet or second regulator. If the pressure in this pilot line falls below a threshold level, it shuts off the valve preventing the flow of N_2O. Modern machines also uses some proportioning safety devices (discusses in text) with the pressure of this threshold shutt off valve which proportionately reduces the flow of N_2O gas when the flow of O_2 reduces below 25% in total gas mixture. All machines also have an O_2 supply low pressure sensor that activates an electric alarm or a gas whistle when the inlet gas pressure of O_2 goes below the threshold value. The gas lines proximal to the controlling knob of flow valve of rotameter is considered as the high pressure circuit and the gas lines distal to it upto the common gas outlet is considered as the low pressure circuit of machine.

Flow Metre (Fig. 1.13)

It is incorporated into the Boyle's anaesthetic apparatus to measure the flow rate

Fig. 1.13: Flow metre (Rotameter)

of gases such as O_2, N_2O and air passing through them. The flow metre used in anaesthetic machine is also known as the rotameter. The other type of flow metre used in industry are: Waterside, Heidbrink, Connell, Foreggar, etc. The flowmetre consists of a series of specially designed glass tube (Thrope tube) with rotating bobbin inside it to measure the flow of individual gases in the flow metre. The tubes are placed within a chromium plated metal casing and in front there is a transparent plastic window which helps in clear reading and protection of flow metre tube from damage and dust. A detachable radiolucent plate is also provided at the back of the metal casing of flowmeter to facilitate the observation of a working and rotating bobbin within the tube during use in a darkened operation theatre. A flow metre basically has two components such as flow control valve and flow metre tubes with rotating bobbin inside it (Fig. 1.14).

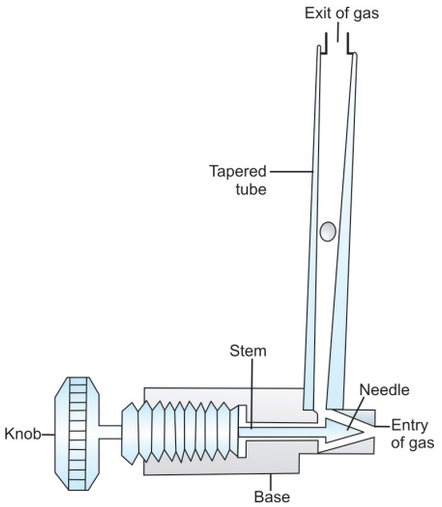


Fig. 1.14: The flow control valve and the tubes of flow metre

The flow control valves control the flow of gas through the tubes of flow metre by manual adjustment of its knobs. It is situated at the base of the flow metre and its body is made of brass. The stem of the adjusting knob screws into the body of flow control valves and ends as a needle which is placed at the site of inflow of gas to the tube of flow metre. The flow control knobs which are attached to the stems of flow control valve are labelled and colour coded for their respective gases. In some design the O_2 control knob is larger and has a longer stem than the other stems and knobs used for other gases. So, this makes it easily recognisable and acts as a safety measure. In some designs a flow control knob guard is attached to protect against the accidental adjustment of flow metres (Fig. 1.15).

The tubes of flow metre are especially made of tapered glass tube with a rotating bobbin inside it. They are set strictly in vertical position on the body of flow control valve. Because inclined position of tube gives incorrect reading by causing friction of bobbin on the wall of the tube and thus producing resistance during the flow of gas. Each tube is individually calibrated at room temperature and one atmospheric pressure for that gas which

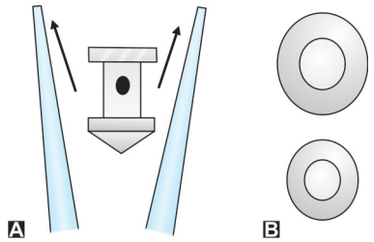


Fig. 1.15A: The route of flow of gases through the tubes of flow metre. **B** shows that the gap between the bobbin and tube wall increases as bobbin goes up

flows through it giving accuracy of about ±2% in measuring the rate of flow of gases. For flows below 2 L/min the measuring units are 100 ml/min and for flows above it the measuring units are L/min. The rotating bobbin or ball in the flow metre tubes which shows us the rate of gas flow through it are made of light aluminium. They are held floating within the tube by the gas flowing around it through the gap between the tube's wall and bobbin. During floating the effect of gravity on the bobbin is counteracted by the flow of gas. When the bobbin is lifted by the flow of gas, then the upward pressure caused by the gas and the weight of the bobbin is in equilibrium at that height of bobbin showing the rate of flow of gas. The flow metre tubes are tapered in such a fashion that the clearance or gap between the bobbin and the tube wall gradually widens from the bottom to the top. So, at low flow rate the clearance between the bobbin and the wall of the tube is longer and narrower acting as a tube and at these circumstances the flow is laminar, governed by the viscosity of gas. On the other hand, at high flow rate the clearance between the bobbin and the wall of the tube is wider and shorter acting as a orifice. Thus, under these circumstances the flow is turbulent and governed by the density of gas. So, each flow metre is calibrated for its specific gas, according to its density and viscosity (Fig. 1.16).

The flow metre can give inaccurate result if the bobbin sticks to the wall of the

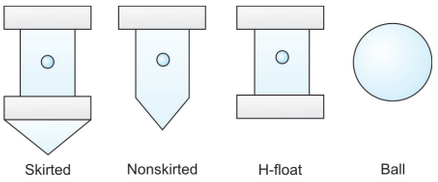


Fig. 1.16: Different types of bobbin used in rotameter

tube due to dirt from contaminated gas supply and / or due to static electricity caused by the continuous friction arising from rotating bobbin during floating. The problem of dirt can be eliminated by using filter at the gas inlet site of anaesthetic machine and the problem of static electricity can be solved by making the bobbin of antistatic material or applying some antistatic spray over it or coating the tube's interior with a conductive substance which grounds the system and reduces the effect of static electricity. At the upper margin of the bobbin there are many cuts or slits (flutes) at the sides. So, when the gas flows by the side of it, the flutes cause the bobbin to rotate. There is radiolucent dot on the bobbin and it indicates that the bobbin is rotating and is not stuck to the wall of the tube. There are two bobbin stops which are made of spring and is situated at the extreme either end (top and bottom) of the tube. It always ensures the visibility of bobbin during operation at the extremes of flow. According to the shape and size different types of bobbins are also used in the flow metre such as ball, nonrotating H float, skirted and nonskirted. But usually the ball and the skirted varities are commonly used in anaesthetic machine. The reading of the flow metre is taken from the top of the bobbin. But when a ball is used then the reading is generally taken from the midpoint of the ball. When very low flow is required such as in circle breathing system, then an arrangement of two flow metre tube for each gas which are attached in series in rotameter are used for the fine adjustment of flow. But these two tubes are controlled by single flow control valve and knob (Fig. 1.17).

The O_2 tube of a flow metre is kept at extreme right of all the gas tubes. Because when it is placed at extreme left of all the tubes, then if any crack develops in a flow metre distal to it, O_2 may leak through this distal crack and may deliver hypoxic mixture to the patient. So, to avoid this problem O_2 is the last to be added to the gas mixture and is finally delivered to the back bar of anaesthetic machine. During mechanical ventilation pressure rises at the common gas outlet when the bag is compressed by ventilator or manually. This is transmitted back to the gas in the tube of flow metre above the bobbin which results in the drop of it during inspiration and inaccurate reading. This can be prevented by attaching a flow restrictor at the down stream of flow metre (Fact file - V).

Antihypoxic Devices

There are many devices which are incorporated in the modern anaesthetic machine to stop the flow of N_2O in the absence of flow of O_2 or there should be a minimum 25% concentration of O_2 in the gas mixture or the machine will give audible alarm when O_2 pressure drops in the pipeline of machine. These antihypoxic devices are consists of hypoxic guard and O_2 failure alarm. This hypoxic guard device maintain minimum 25% flow of O_2 in the gas mixture or when O_2 flow is reduced below 25% of total flow then the N_2O flow will be automatically reduced. It works by mechanical, pneumatic or electronic principle. In mechanical method the N_2O and O_2 flow control valves are linked together by a chain. This chain relays the movement of O_2 knob to the N_2O knob. So, when the O_2 flow control knob is turned to reduce the flow of this gas, then the chain link will also move and reduce the flow of N_2O as if always a minimum 25% of O_2 mixture can reach to the patients or without the flow of O_2, the N_2O will not flow alone. The O_2 flow control knob can be independently opened further. But it cannot be closed below a setting that will produce less than 25% O_2 in the gas mixture if N_2O is used. In pneumatic method there is special type of valve known as the ratio mixer valve where O_2 is exerting pressure on one side of the diaphragm and

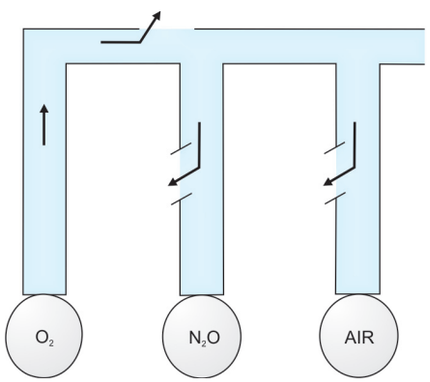


Fig. 1.17: How the O_2 will leak from cracks at different sites if its tube is placed at extreme left

FACT FILE - V

The flow metres of anaesthetic machines are classified either as a constant pressure variable orifice flow metre which are commonly used (and is already described in text) or a electronic flow metre. In electronic flow metre the amount of pressure drop caused by a flow restrictor is the principle for the measurement of gas flow and the amount of flow is displayed digitally and/or graphically. In such circumstances a backup conventional auxiliary O_2 flow metre is also provided for emergency. In anaesthetic machine where electronic flow metre is used, there separate flow metre each for O_2, N_2O and air is used in the flow control section before the gases are mixed together.

In the constant pressure variable orifice flow metre when the gas starts to flow, it gives pressure at the under surface of the bobbin and raise it in the tube. As the bobbin raises the gas flows around it and the bobbin will stop at that position when its weight is equivalent to the difference in pressure above and below it. This pressure difference is constant whatever may be the rate of flow and the position of bobbin in tube. However, it depends on the cross sectional area of tube and the weight of bobbin. At the bottom of the tube where the diameter is small, a low flow of gas will create higher pressure at the under surface of the bobbin and raises it more than the top of the tube where the tube widens and high flow of gas will create less pressure under the bobbin and raises it less, though the pressure difference between below and above of the bobbin is constant.

N_2O on the other side. Thus when there is increased flow of N_2O, then it will also cause increased flow of O_2 maintaining a minimum 25% concentration of it. But when O_2 flow is only increased, the flow of N_2O will not increase. In electronic device a paramagnetic O_2 analyser is used to analyze the mixture of gases which are sampled continuously. Then if due to any reason the O_2 concentration falls below 25% in the inspired gas mixture, then the flow of N_2O will also be stopped and give an alarm (Fig. 1.18).

In O_2 supply failure alarm when the pressure in the pipeline of machine carring only O_2 drops below a certain fixed lavel then the O_2 is directed through a whistle to produce a sound causing alarm. This alarm is activated only when the pressure of O_2 in the machine gas pipeline falls below 200 KPa. This alarm cannot be switched off unless the O_2 supply is restored.

Vapourisers

A vapourisers is a device by which a controlled amount of volatile anaesthetic agent is added to the fresh gas flow mixture after vapourising it from liquid. Initially all the types of vapourisers are divided under two broad headings: variable bypass vapourisers and measured flow vapourisers (Fig. 1.19).

In variable bypass vapourisers the fresh gas flow is first splitted into two so that only a small portion of it passes through the vapourisers and when it passes over the liquid volatile anaesthetic agent in the vapourising chamber it becomes saturated with the vapour of this anaesthetic agent. Then, it leaves the vapouriser to mix with the remaining fresh gas flow that has gone through the bypass. The final desired concentration is achieved by varying the splitting ratio between the bypass gas and the gas that enters the vapourising chamber of a vapouriser using an adjustable valve (regulating dial). On the otherhand, vapouriser can be designed so that it heats the anaesthetic liquid to a temperature above its boiling point and make it a gaseous state which is then allowed to leave the vapouriser in calculated amount (measured) controlled by regulating dial to mix with the fresh gas flow in achieving desired concentration of it. These are known as the measured flow vapourisers. The example of this measured flow vapouriser are TEC-6, TEC-6 plus, D-TEC, where desflurane is only used.

The variable bypass vapourisers are again divided into two types such as draw over vapourisers and plenum vapourisers. In draw over vapourisers a portion of fresh gas flow regulated by controlled knob is allowed to simply flow over the liquid volatile anaesthetic agent and to pick up the vapour of this agent. They are of low resistance and the anaesthetic vapour leaving the vapouriser is not saturated with the vapour of liquid anaesthetic agent. The splitting valve which divides the gas flow to the vapourisers and to the by pass channel is of wide bore and works over a wide range of flow rates. This type of vapouriser is also known as the 'inside the circuit' vapouriser, because being of low resistance and having no unidirectional valve, it acts as a continuous component of the circuit of the anaesthetic machine. On the otherhand, in plenum (which means high resistance, and unidirectional) vapouriser the carrier gas which enters the vapourising chamber of vapouriser is made to be saturated by the vapour of volatile anaesthetic agent present in the vapouriser and pressurised (cause is described later) so that it is rather forced to mix with the bypass fresh gas flow than it simply blows over the surface of the volatile liquid anaesthetic agent in vapourising chamber taking the unsaturated vapour of it like draw over vapouriser. The vapourising chambers of plenum vapourisers act as pressurised chamber containing saturated vapour of volatile anaesthetic agent at all times from where continuous flow of gas saturated with anaesthetic agent comes out. This is made possible by increasing the capacity of vapourisation of liquid volatile anaesthetic agensts to very high level by adding wicks and baffles inside the vapourising chamber, and restricting the exit of gas from the chamber by control valve than the vapourising capacity.

These plenum vapourisers are also called the 'outside the circuit' vapourisers, because they do not acts as the part of anaesthetic circuit due to high resistance and spilitting valve is of narrow bore. They do not act over the wide range of flow rate like draw over vapourisers and so it allow the vapouriser to calibrated very accurately. The examples of the draw over vapourisers are: Boyel's ether bottle vapouriser, Goldman vapouriser, Oxford miniature vapouriser (OMV), EMO vapouriser and TEC-3 vapouriser. The TEC-3 vapouriser is a draw over vapouriser but temperature compensated.

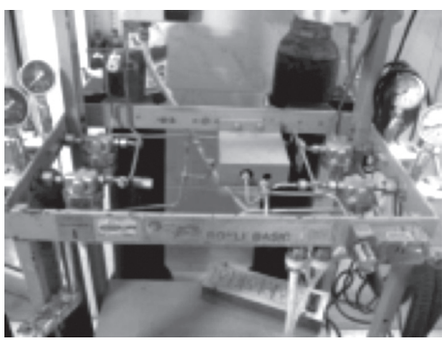


Fig. 1.18: Oxygen failure alarm

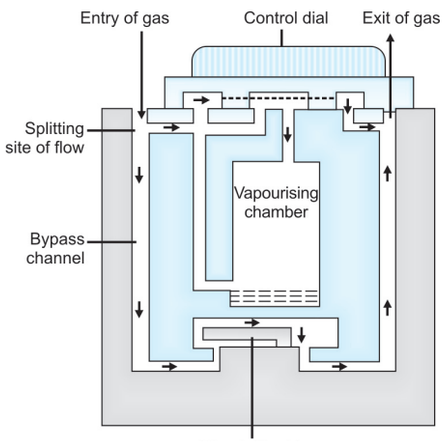


Fig. 1.19: This is a schematic diagram of TEC-5 plenum vapouriser

The examples of plenum vapourisers are: all the temperature compensated (TEC) vapourisers of Datex ohmeda series such as TEC-4, TEC-5, TEC-7 and Drager vapouriser 19 and 2000 series. These different models or types of plenum vapourisers differ among them only in their interior design regarding the arrangement of baffles and wicks to increase the capacity of vaporization made by different companies to remove some technical disadvantages of previous one, but their basic mechanism of action is same. The old model plenum TEC-3 vapouriser is out of market now. At present the commonly used model of plenum vapourisers are TEC-5 and TEC-7 of Datex ohmeda series and Drager vapouriser of 19 and 2000 series. The Aladdin vapouriser which is discussed in more details in chapter is another example of plenum vapouriser with electronic control for vapourisation. The TEC-6 vapouriser which is developed to use only desflurane is the example of measured flow vapouriser (Fig. 1.20).

All the plenum vapourisers are temperature compensated. It means with cooling of volatile anaesthetic agent during vapourisation, the delivered vapour concentration of it after vaporization of anaesthetic agent does not reduce. This is achieved by controlling the splitting ratio of fresh gas flow which enter the vapouriser by a temperature sensitive bimetallic strip which is made of two strips of metal with different coefficients of thermal expansion bonded together. It allows more flow into the vapourising chamber by bending as the temperature decreases and vice versa. This bimetallic strip or temperature sensitive valve is located in the vapourisation chamber in TEC-2 model. Whereas in the TEC-3, 4 and 5 model it is situated outside the vapourisation chamber (Fact file -VI).

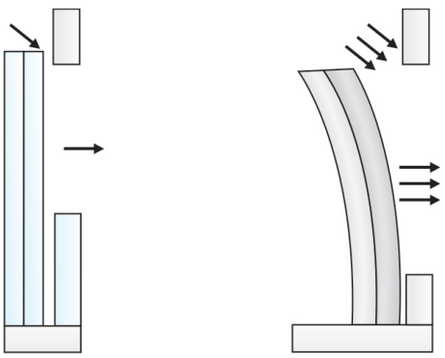


Fig. 1.20: The mechanism of action of bimetallic strip causing thermocompensation of vapouriser

All the variable bypass plenum vapourisers are flow compensated and its explanation is described below. On entering the vapouriser the fresh gas flow is splitted into two streams. The main larger stream of gas flows through the bypass channel and the smaller narrow stream of gas flows through the vapourising chamber of vapouriser. After vapourisation these two gas streams again reunite when they leave the vapouriser together. This is controlled by a regulating dial which dictate how much gas will enter the vapourising chamber, then after being completely saturated with anaesthetic agent, will be reunited with the fresh gas flow coming through bypass channel. The vapourising chamber of a plenum vapouriser is such designed that the gas leaving it is always fully saturated with vapour of volatile liquid anaesthetic agent before it joins with the gas of bypass stream whatever may be the amount of fresh gas flow into the vaporising chamber. This is achieved by increasing the surface area of contact between the gas entering the vapourising chamber and the volatile liquid anaesthetic agent by adding wicks soaked by the agent and a series of baffles. Thus whatever may be the rate of fresh gas flow through vaporising chamber the delivered concentration of anaesthetic agent can be controlled by both controlling the flow of gas entering the vapourising chamber and thus controlling the rejoining of gas saturated with anaesthetic agent with the main gas flow by controlling the dial. Thus it will not be influenced by the rate of fresh gas flow through vaporizer like the draw over vapriser such as goldman, ether vaporiser, etc. In modern designs the anaesthetic concentration of volatile anaesthetic agent supplied by vapouriser is independent

FACT FILE -VI

Electronic vapourisers

The vapourisers where the volatile anaesthetic agents are vaporized by heating it electrically such as TEC-6 desflurane vapourisers or where there is a elctronically regulated flow control valve located at the outlet of vapourising chamber but vapourisation is done by conventional blowing the gas over the volatile liquid anaesthetic agent like other variable bypass vapourisers such as Aladin Cassette vapourisers are called the electronic vapourisers.

The boiling point of desflurane is 22°C. Thus it boils almost at room temperature. So, its vapopur pressure is very high which is near about 681 mm of Hg at 20°C (Halothane = 243°C, Isoflurane = 240°C, Sevoflurane = 160°C). Again the potency of it is near about 1/5th than that of other volatile anaesthetic agent. Hence all these characteristic of desflurane presents a unique delivery problem of it and is solved by the development of TEC-6 vapouriser where only desflurane is used. In this vapouriser there is a reservoir containing desflurane which is heated electrically to 39°C to vaporize it. So, this reservoir always contains the dense vapour of desflurane at the pressure of 2 atmosphere. On the other hand, no fresh gas from flow metre is allowed to flow over the desflurane for vapourisation of it through by pass channel like other variable by pass vapourisers. Rather the measured amount of pure vapour of desflurane is allowed to flow from the reservoir which is regulated by a control dial and to mix with the fresh gas flow coming from flow metre to make the desired delivered concentration of it. Thus, it maintains a desired constant concentration of desflurane over a wide range of fresh gas flow rates.

In Aladin Cassette vapouriser the volatile liquid anaesthetic agent is not vaporized by heating electically like TEC-6 vapouriser. Here like other conventional plenum vapouriser the fresh gas flow from flow metre is divided regulated by control dial and a portion is allowed to flow through vapourising chamber to vaporize the anaesthetic liquid. However, this vapourisation is conducted into a agent specific colour coded cassette (Aladin cassette). The anaesthetic machine accept one casette at a time and recognise this cassette through magnetic lebelling. Unlike the traditional vapourisers, here the liquid anaesthetic agents can not escape from it during handling and so it can be carried in any position.

of gas flow through vaporising chamber between 0.5 to 15 L/min. Hence, they are flow compensated. But the changing of composition of gas from 70% N_2O to 100% O_2 may increase the concentration of anaesthetic agent due to the greater solubility of N_2O in volatile liquid anaesthetic agents. In comparison to the flow compensated vaporisers the draw over vapourisers are not flow compensated, because under certain dial setting the portion of gas entering the vapourising chamber varies with the rate of fresh gas flow, and the gas coming out from the vapourising chamber is not fully saturated. Thus the rejoining of gas mixed with variable concentration of anaesthetic agent to the main gas flow is not controlled. During vapourisation due to the loss of latent heat of vapourisation the cooling of anaesthetic agent occurs and makes it less volatile, reducing vapourisation. So, in order to compensate this heat loss two measures are taken. One, the vapouriser is made up of such material which has high density, high specific heat and high thermal conductivity such as copper. So it acts as heat reservoir and readily gives heat to the cooled anaesthetic agent, maintaining its temperature and vapourisation nearly constant. Two, a temperature sensitive valve made of bimetallic strip allows more flow into the vapourising chamber by bending as the temperature decreases and vice versa.

All the modern vapourisers are agent specific. So, filling of them with wrong agents should be avoided. For example filling of an halothane specific vapouriser by sevoflurane would lead to anaesthetic concentration in under doses and vice versa. This is because the vapour pressure of halothane at one atmospheric pressure and 20°C is 243 mm of Hg, whereas the same of sevoflurane is 160 mm of Hg. So, if sevoflurane is used in halothane TEC-7 or TEC-5 vapouriser, it will cause near about 40% lesser amount of anaesthetic concentration to be released and vice versa. So, the modern TEC-5 and TEC-7 vapourisers (TEC-4 is also obsolete now) are equipped with agent specific filling ports and colour coded agent specific filling devices to prevent the use of wrong agent in wrong vapourizer. In older vapourisers during IPPV there may be transient reversal of flow of fresh gas and pressure into the vapouriser through the by pass channel and it will lead to the delivery of unpredictable concentration of anaesthetic agent. This is known as the pumping effect which is more pronounced with low gas flow. Hence in modern vapourisers some change in design and placement of a one way check valve limit the occurance of this problem. During transport or due to any reason if vapourisers are tilted excessively then the anaesthetic agent may spill over and flood the by pass channel of vapouriser which may lead to sudden delivery of dangerously high concentration of anaesthetic agent when first used. So, during handling of it when not attached to machine, excessive tilting of vapouriser should be avoided.

Ventilator

All the modern anaesthetic machines are equipped with ventilator for IPPV during anaesthesia which are of bag in bottle type in most of the cases. They have mainly the CMV mode for ventilation, but some have the facilities to provide other few more mode for ventilation modes such as SIMV, CPAP and PEEP. These bag in bottle type of anaesthetic ventilators have mainly two basic components: a driving unit and a control unit. The driving unit consists of a chamber with tidal volume ranging from 0 to 1500 ml and an ascending or descending type of bellow receiving fresh gas flow within it. In paediatric version the tidal volume in chamber ranges from 0 to 400 ml, whereas in adult version the tidal volume in chamber ranges from 100 to 1500 ml. The controll unit of the ventilator contains variety of controlling knobs, display system and alarms. The controlling knobs include the respiratory rate, tidal volume, airway pressure, I/E ratio, power supply, etc., to regulate the IPPV of patient during anaesthesia (Fig.. 1.21).

In these types of bag in bottle ventilator compressed air or O_2 is used as the driving pressure. On entering the driving chamber of ventilator this driving gas forces the bellows down in case of ascending type of bag in bottle ventilator and delivers the fresh anaesthetic gas mixture to the patient which was accommodated in side the bellow during the previous expiratory phase of respiratory cycle. The volume of driving gas entering the chamber is always equal to the tidal volume and remains completely separated from the fresh gas flow which remarks in side the bellow. Then during expiration the bellow again ascends due to the flow of fresh gas mixed with expired gas within it and the driving gas comes out (Fig. 1.22).

There are another type of bellow known as the descending bellow. Here, during expiration the gas sucked from patient into the bellow by a weight placed at the base of it. So, the probable advantage of this type of descending bellow is the absence of expiratory resistance. This advantage is not available in ascending bellow as it is claimed that the pressure required to fill the bellow both by fresh gas from machine and expired gas from patient adds some expiratory resistance to patient and may

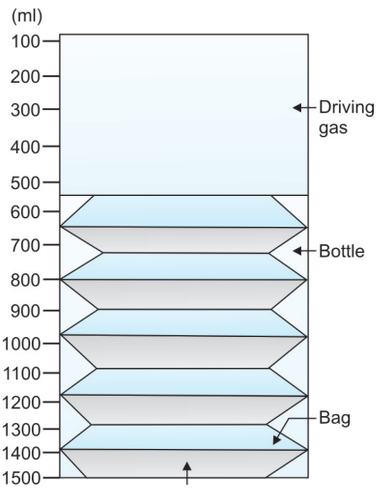


Fig. 1.21: The mechanism of action of a bag in bottle type of ventilator

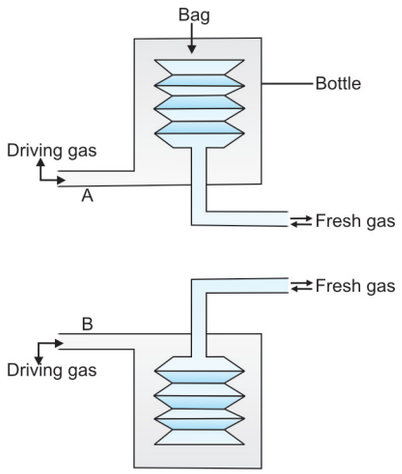


Fig. 1.22: Ascending (A) and descending (B) type of bag in bottle ventilator

prevent complete exhalation. Therefore, it is claimed that ascending bellow provides a degree of PEEP (2 to 4 cm of H_2O) which may otherwise be beneficial.

The another advantage of ascending bellow is that it collapses to an empty position and remains stationary at that empty position if there is any leak in bag or disconnection of circuit. Whereas in descending design of bellow it automatically hangs down to fully expanded position, even if there is any leak or disconnection of circuit and may continue to move almost normally. In such condition the driving gas would also be able to enter the bellow through the leak and dilute the anaesthetic gas mixture within it which is not possible in ascending variety.

The arrangement in descending bellow also allows the driving control unit to be placed above the bellow in the free standing version. So the bellow of it could be placed on the lower shelf of an anaesthetic machine with the controls panel easily at hand. However the descending bellow is now no longer popular (Fact file- VII to IX).

Miscellaneous

Non return pressure relief valve

It is situated on the back bar of anaesthestic machine after the vapouriser or at the common gas outlet. Here it acts as nonreturn valve and helps to prevent the effect of back pressure on the vapourisers or flow metre during positive pressure ventilation by ventilator or manual. It also opens when the back bar pressure exceeds 30 KPa and acts as pressure relief safety valve.

Emergency O_2 flush

It is presented in the machine as nonlocking button and when is activated by manual

FACT FILE - VII

Other than the bellows in bottle which is squeezed pneumatically it may be inflated or deflated without bottle by a piston that is powered by gas and is attached to the bellow by a lever. The advantage of this principle is that it removes the potential danger of mixing between the driving gas which is situated outside the bellow and the patient's gas which is situated inside the bellow. The another advantage of this principle is that the piston may be driven by a smaller quantity of gas from cylinder. So, it is very valuable where there is scarcity of gas. The Manley Servovent and Oxford Mark 2 ventilators work on this principle. The bellows may also be moved mechanically by motor and suitable levers and gears. The speed of motor can be changed to produce the varieties of flows both during inspiration and expiration. This principle is used in the Drager E series of ventilatos. In some ventilators, the bellows are not used, instead a long wide bore hose pipe is substituted. In this method the driving gas is directly pushed into the breathing system with the fresh gas by ventilator, but it does not mixed with the fresh gas due to long length of hose pipe. The example of ventilator working on this principle is Penlon Nuffied 200 series.

FACT FILE - VIII

There are now many major advances in the working principles of ventilator which are used in intensive care unit and also anaesthetic ventilator. Among these the two most important parts are electronic flow valve and microprocessor. In an electronic flow valve first current is allowed to pass through an wire coil (solenoid) to produce a magnetic field which moves the ferromagnetic piston and closes and open the valve with the help of a spring. The movement of the valve depends on the flow of current and thus control the movement of driving gas by corresponding amount of closing and opening of it. As this valve is used in high pressure gas pathways, so the little movement of valve is enough to control the flow of driving gas very quickly varying between 1 to 120 litre/min. The response time of this type of solenoid valve is only 5 milliseconds and is very compact to be fitted easily in a small equipment.

The microprocessor part of a ventilator controls the electrical signal to the electronic flow valve of it. They are usually programmed to provide a wide variety of ventilatory modes and response. Most of the ventilators now work on this principle but they only differ according the user display, variable programming and the quality of components.

FACT FILE - IX

Description of function of a commonly used bag in bottle type of anaesthetic ventilator attached with anaesthetic machine.

This represents a model of a pneumatically driven bag in bottle type of ventilator with an arrangement of ascending bellows. There the driving gas is controlled by electronic flow valve which is again under the control of microprocessor to provide a wide range of ventilatory function.

Inspiratory

In this phase, the pressurised driving gas is first passed through a filter and a regulator to enter the electronic flow valve which is held shut when not in use. Then the gas passes to the bottle that contains an arrangement of ascending bellow and compresses the bellow forcing the fresh gas to flow through a wide bore hose into a breathing system for inspiration of patient. This driving gas also supplies a small pneumatic valve which closes the expiratory port and prevents the fresh gas destined for inspiration from escaping.

The passing of driving gas through electronic flow valve is controlled by a microprocessor which receives information from the ventilator setting of front panel by anaesthetist, fresh gas flow through the anaesthetic machine and inspiratory flow to the patient. Thus the changes in these flows will also change the flow of driving gas through the electronic flow valve and consecutively control the tidal volume which depends on the force on the bag caused by driving gas.

Expiratory valve

At the end of the time cycled inspiratory phase the microprocessor instructs the electronic flow valve to close and a second valve to open. Thus, the driving gas passes away to the atmosphere from bottle through second valve and causes its pressure to fall to zero. This allows the exhaled gas from patient mainly from dead space and fresh gas to enter the bellow. If Bain circuit is used then this exhaled gas comes from the patient through the wider external tube which is attached to the input of ventilator. When the bellow becomes full and its pressure is raised above the atmosphere then the expiratory port opens and expired gas from alvesli containing CO_2 escapes to the atmosphere through output channel. At the same time the driving gas leaving the bellow also passes out through the output channel.

pressure then pure O_2 at the flow rate of 30 to 70 L/min is supplied to the patient from the common outlet of anaesthetic machine bypassing the flow metre and vapourisers. It also is used to flush the breathing circuit or to rapidly refill the breathing bag. It should not be activated when the minute volume divider ventilator is in use. Injudicious use of this emergency O_2 flush may dilute the anesthetic gases and will cause the inadequate depth of anaesthesia and awareness. It may cause barotrauma also when the patient is connected to a completely closed breathing circuit.

Common gas outlet and O_2 analyzer

All the anaesthetic machine has only one common outlet supplying fresh anaesthetic gases mixed with O_2 to breathing circuit in contrast to multiple inlets which supply different gases to the machine. Modern machines are equipped with devices which measure the flow of gases through this common outlet and gives signal during detachment of this outlet from the breathing circuit.

It is fundamental to monitor the inspired O_2 concentration (FiO_2) or partial pressure of it in the gas mixture delivered to the patient. Without an O_2 analyser which measures the inspired O_2 concentration an anaesthetic machine is always incomplete and general anaesthesia should never be administered. It is placed in the inspiratory or expiratory limb if close circuit is used. Otherwise, if the circuit has one limb, then it should be placed at the patient's end of it. But it should not be placed at the fresh gas line. Due to O_2 consumption by patient the partial pressure of O_2 in expiratory limb is slightly lower than that of the inspiratory limb. An audible alarm can be set for high and low concentration of O_2 such as 40% and 28% respectively.

Three types of O_2 analyzers which measures FiO_2 are used in modern anaesthetic machine. These are: paramagnetic, fuel cell (or galvanic), or Clark electrode (polarographic). The paramagnetic sensor works on the principle that only O_2 is attracted by the magnetic field whereas the other gases are repelled. This attraction and repulsion of individual gas depends on their concentration and partial pressure in the sample gas. It is costly than the others and has no consumable parts without requiring frequent replacement. Its response time is very fast than the galvanic and Clark electrode O_2 analyzers and can differentiate the partial pressure of O_2 between the inspired and expired air as it measures the inspired and expired O_2 concentration simultaneously on breath by breath basis. However, this analyzer is affected by water vapour in sample gas. Therefore a water tap is incorporated in the design. The another advantage of this paramagnetic sensor is, it is self calibrating. The galvanic and polarographic sensor is also called the electrochemical sensor, because both of them contain the anode and cathode electrodes embedded in an electrolyte gel which is separated from the gas sample by an O_2 permeable membrane. After diffusing through the membrane, O_2 reacts with the electrode in the gel and produces a current which is proportional to the concentration and partial pressure of it in the sample gas. Thus they measure the partial pressure of O_2 as a percentage. These galvanic and polarographic O_2 analyzer have slow response time (20 to 30 seconds), because they are dependent on membrane diffusion of O_2. These sensors have limited life span to about 1 year, because of the exhaustion of material of it due to continuous exposure to O_2. It needs regular service and calibration is achieved by using 100% O_2 and room air (21% O_2). It reads only inspiratory or expiratory O_2 concentration and water vapour does not affect its performance.

N_2O and other inhalation anaesthetic agent concentration analyzer

The measurement of inspired and end tidal concentration of N_2O and other inhalational anaesthetic agents are very important, mainly when the circle system is used. This is because the expired inhalational anaesthetic agents are recirculated and are added to the fresh gas flows which is also carrying the volatile anaesthetic agents. So, the ultimate inspired concentration of inhalational anaesthetic agents is different from the setting of vapouriser, especially during low flow. Hence, the modern analyzers can assure the inspired concentration of all the inhalational anaesthetic agents such as N_2O, halothane, isoflurane, sevoflurane, desflurane, etc. The principles by which the concentration of inhalational anaesthetic agents are measured are: infrared technique, ultraviolet ray absorption technique, mass spectrometry, Raman spectroscopy, Piezoelectric quartz crystal oscillation technique, etc.

In infrared technique a light of wavelength of 4.6 nm is used for N_2O. On the otherhand an infrared light of wavelength of 8 to 9 nm is used for other volatile anaesthetic agents. This is to avoid interference from the methane and alcohol that happens at the lower 3.5 nm wavelength. Some infrared analyzers are not agent specific. These must be programmed by the user for specific agent being administered. Incorrect programming result in incorrect result. In Piezoelectric oscillation technique a lipophilic coated Piezoelectric quartz crystal is used which undergoes continuous changes in its frequency of oscillation when lipid soluble inhalational anaesthetic agent is exposed to it. This changes in oscillation is directly proportional to the concentration of agent. Mass spectrometer is used to analyze the inhalational anaesthetic agents on breath to breath basis. In this technique the principle of action is to change the particles of sample gas by bombardment of them with electron beam and then to separate the components arising from this bombardment by a magnet into different spectrum according to their specific mass: charge ratio. The relative concentration of ion in a spectrum of a specific mass: charge ratio is

Table 1.2: Various methods used to analyse gases

Methods	*O_2*	*CO_2*	*N_2O*	*Volatile agents*
Infrared	-	+	+	+
Galvanic	+	-	-	-
Polarography	+	-	-	-
Paramagnetic	+	-	-	-
Raman spectroscopy	+	+	+	+
Mass spectrometry	+	+	+	+
Piezoelectric oscillation	-	-	-	+

determined by the concentration of a particular agent in gas mixture (Table 1.2).

Measurement of tidal and minute volume

During GA the measurement of tidal volume and from it the measurement of minute volume is very critical which the anaesthetic machine performs by Wright spirometer (respirometer), hot-wire anemometer, ultrasonic flow sensor and pneumotochograph etc. These are used in all the modern sophisticated anaesthetic machine to measure the exhaled tidal volume by attaching them in breathing circuit near the exhalation valve. Some machines measure the inspiratory tidal volume by attaching these just distal to the inspiratory valve. However, in the latest model of Datex-Ohmeda machine these are attached near the Y-connection of patient to measure the actual delivered and exhaled tidal volume.

In Wright respirometer there is a rotating vane which is surrounded by multiple slits and this vane is attached to a pointer on a dial. When the gas passes through it then the slits which surround the vane create a circular flow and rotate the vane with pointer on front dial. The vane does 150 revolutions for each litre of gas passing through it. In clinical use the respirometer reads accurately the tidal volume within the range of 4 to 24 L/min. A minimum flow of 2 L/min is required for the respirometer to function accurately. A paediatric version of spirometer is also now available which can measure the tidal volume in the range of 15 to 200 ml per breath. A sophisticated version of this Wright spirometer uses the reflection of light technique to measure the tidal volume more accurately. Other modification of this Wright spirometer is the use of semiconductive device where the tidal volume is measured from the changes in magnetic field and converting it electronically.

The hot-wire anemometer is used in Drager-Fabius anaesthetic machine to measure the tidal volume. Here, electrically heated fine platinum wires are used. The cooling effect of these wires by increasing gas flow through it causes a change in electrical resistance which is proportion to the gas flow and is determined by the current needed to maintain a constant wire temperature. In ultrasonic flow sensors an upstream and downstream ultrasonic beams are passed at an angle from where the shift of doppler frequency is measure which is proportional to the flow of gas or tidal volume. In pneumotachograph the parallel bundles of tubes of small diameter in a chamber or a mesh screen is used which provide resistance to air flow and drop of pressure. This drop of pressure across the resistance is sensed by a differential pressure transducer and is proportional to the flow rate. Thus calculation of flow rate over time measures the tidal volume. Moreover analysis of this volume, pressure and time relationship will give us the potential valuable information about lungs and airway mechanics.

2 Anatomy and Physiology of Respiratory System

INTRODUCTION

An anaesthesiologist must acquires an extensive knowledge, regarding the anatomy and physiology of respiratory system before taking any care of his patients in the operating room, ITU and the intensive care unit. This is because mastery on the anatomy and physiology of respiratory system is the principal prerequisite to understand the mechanism of gas exchange that occurs during anaesthesia, surgery and in different disease processes of patients in OT and in intensive care unit.

From anaesthetic point of view the anatomy of respiratory system is divided into two main heading such as (i) the conducting part including trachea, bronchus and its multiple divisions up to alveolus, and (ii) the actual lung parenchyma.

TRACHEA

The trachea or wind pipe is a membrano-cartilaginous structure. It extends downwards as a continuation of larynx from the lower margin of cricoid cartilage.

Course and Measurement

The trachea as a continuation of larynx begins at the level which lies opposite to the C_6 vertebra or at the lower border of cricoid cartilage. It then passes downwards to end opposite to the sternal angle by dividing into the right and left bronchus (plural-bronchi). This bifurcation of the trachea or begining of the bronchus corresponds with the lower border of T_4 vertebra in supine position or T_6 vertebra in standing position. But, in the newborn the trachea bifurcates at the higher level, opposite to the T3 vertebra.

The length of an adult trachea is about 10 to 11 cm. The external diameter of trachea is about 2 cm in adult male and 1.5 cm in adult female. The internal diameter of trachea is approximately 12 mm in adult. In new born, the internal diameter of trachea is only 3 mm, which persists upto 3rd year of life. Thereafter, the lumen increases by about 1 mm for each year upto the 12th year, after which it remains fairly constant. So, this knowledge is fairly important for an anaesthetist in selecting the size of an ET-tube during the intubation in children. In children, the trachea is deeply placed and more movable, whereas in adult it is superficial and more fixed. Moreover, in children the left brachio-cephalic vein and the summit of the arch of aorta crosses the trachea at higher level than adult near supra-sternal notch. So, low tracheostomy is risky in children than adult.

The trachea moves with flexion and extension of head and with respiration. With deep inspiration, the trachea moves 2.5 cm downward and during expiration this same length is moved upwards. The extension of head and neck which is an ideal position to maintain an unobstructed airway in an anaesthetized patient usually increase the length of trachea by about 20 to 30%. In some clinical situation, where a patient is intubated with head in a flexed position and the ET-Tube just passes beyond the vocal cords, then the subsequent extension or hyperextension of head and neck may withdraw the tube above the cords.

Structure

The trachea consists of a number of incomplete C-shaped cartilagenous rings. On the posterior surface, the two free ends of these incomplete cartilagenous ring are connected by strong fibroelastic membrane and involuntary trachialis muscles.

The C-shaped cartilagenous rings are made up of hyaline cartilage. The total number of cartilagenous rings varies between 16 to 20 in an adult male. Among all the rings the first is broadest and the last is triangular in shape which is called carnia. It hooks upwards from the lower margin of trachea and then surrounds the commencement of two bronchi. The carnia represents a ridge in the interior of tracheal bifurcation and acts as a guide for the surgeon during bronchoscopic or other endoscopic examination of trachea or bronchi.

The mucous membrane of upper respiratory tract at the level of carnia is most sensitive area and is associated with the cough reflex. So, the carnia is often considered to act as the last line of defense, causing expulsion of the aspirated foregin body by violent cough. As the cartilagenous ring of trachea is absent posteriorly, so it allows the expansion of oesophagus during the deglutition of food. The air pressure in the trachea is negative in relation to the atmosphere during inspiration.

Therefore, the positive pressure from outside might collapse the trachea. In order to avoid this, the tracheal wall is composed of elastic and rigid cartilagenous rings to maintain the potency of lumen. For this purpose the cartilage cells are nature's best choice than bone cells. Because the cartilage requires no separate blood supply and they get nutrition only by diffusion from the nearest capillary plexus.

The interior of the trachea is lined by pseudo-stratified ciliated columnar epithelium, resting on a basement membrane with numerous serous and mucous glands. The epithelial cells are single layered with different heights and different nuclear positions. Hence, this layer shows apparent stratification under light microscope and is called pseudo-stratified. The taller cells in this pseudo-stratified epithelium present cilia and each cell supports about 270 cilia. The electron microscope shows that each cilia contains 11 microtubules. Among these, 2 microtubles are in the centre and other 9 are at the periphery. The mucous secreted by the goblet cells of mucous glands entrap dust, other foreign particles and bacteria. Then these entrapped particles are swayed by the ciliary beats towards the upper part of the trachea and the larynx. Then, they are expelled by the cough reflexes. Thus, the mucuous membrane helps in the defensive mechanism of respiratory passage by acting as a muco-ciliary barrier. The cilia in the epithelium is present as far as up to the terminal bronchiole where they give way to the squamous cells without cilia (Figs 2.1A and B).

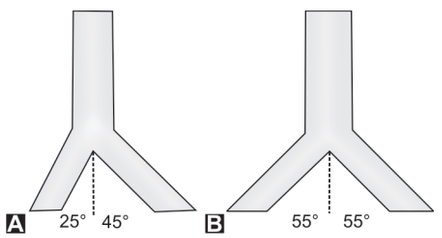
The glands and cartilages are present up to the begining of the preterminal or terminal bronchioles. The bronchioles less than 1 mm in diameter do not have cartilage in their walls. As the bronchiole is traced distally, it is found that the cartilaginous rings recede gradually and is replaced by irregular plates which occur sporadically until the diameter of the bronchhiole comes down to 0.6 mm and then they disapear completely. If it is progressed more downwards continuously along the bronchial tree then it is also found that the tubular outline of bronchial wall start to change. Gradually small projections appear from all the directions in increasing numbers. This area is now termed as the respiratory bronchiole and the small projections are known as the alveolar ducts, leading to the air sacs. The walls of the bronchioles contain more smooth muscle. Of which the largest amount of muscle relative to the thickness of the wall is present in the terminal bronchioles. Smooth muscles are found in the walls of all the airways down up to the level of alveolar duct and most abundant in the terminal bronchiole. On the contrary, the trachea and bronchi have cartilages in their walls, but relatively little smooth muscle.

Bronchus

The trachea bifurcates into two main bronchous — right and left. Then, each main bronchus enters the corresponding lung through their hilum. After that each bronchus divides and subdivides into successive smaller bronchi and finally produce terminal respiratory bronchioles which merge with the alveolar sacs and ultimately terminate into the alveoli which constitute the lung parenchyma.

Right Bronchus

The right bronchus passes downwards and to the right from the bifurcation of trachea and makes an angle of 25° with the midline. It enters the hilum of right lung at the level of 5th thoracic vertebra.



Figs 2.1A and B: Angle of the main bronchi, A. in the adult, B. in the children

In children under the age of 3 years, the angulation of two main bronchi at the carina is equal on both sides. The right bronchus is wider, shorter and more vertical than the left bronchus. The length of the extra-pulmonary part of the right bronchous is about 2.5 cm. It is more wider becasue it supplies the more voluminous right lung. It is more vertical because the trachea at its bifurcation deviates more towards the right side. So, a foreign body in the trachea is usually aspirated into the right lung. However, the short length of right bronchus makes the approach to the lumen of it difficult when it is required during thoracic anaesthesia (Fig. 2.2).

Within the lung, first the right principal or primary bronchus divides into three secondary or lobar bronchus to supply the each lobe of right lung (right lung has three

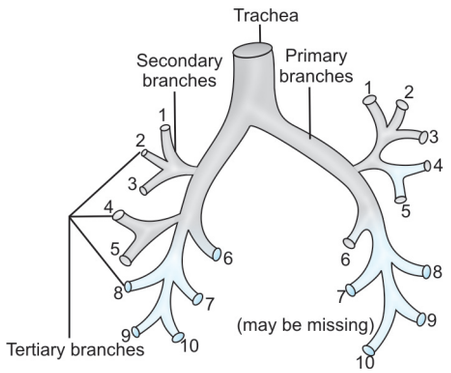


Fig. 2.2: Distribution of tertiary bronchi in right and left lungs

Upper lobe
1. Apical bronchus
2. Posterior bronchus
3. Anterior bronchus

Right middle lobe	Left middle lobe
4. Lateral bronchus	4. Superior lingular bronchus
5. Medial bronchus	5. Inferior lingular bronchus

Lower lobe

6. Apical bronchus	6. Apical bronchus
7. Medial basal (cardiac)	7. Medial basal (sometimes missed)
8. Anterior basal bronchus	8. Anterior basal bronchus
9. Lateral basal bronchus	9. Lateral basal bronchus
10. Posterior basal bronchus	10. Postrior basal bronchus

lobes). Then each secondary or lobar bronchus subdivides into segmental or tertiary bronchus. Thus, there are ten segmental or tertiary bronchus in right lung. The area of the lung supplied by tertiary or segmental bronchus is known as the broncho-pulmonary segment which acts as an independent respiratory district or unit. So, there are ten broncho pulmonary segments in right lung.

This ten broncho-pulmonary segments supplied by ten tertiary or segmental bronchus in right lung are:

a. *Upper lobe:* apical, anterior, posterior
b. *Middle lobe:* medial, lateral
c. *Lower lobe:* apical, anterior basal, posterior basal, medial basal, lateral basal.

Each broncho-pulmonary segment is wedge in shape with there base directed towards the surface of the lung. These segments are separated from one another by intersegment areolar septa which prevent the spread of infection from one segment to another. The branches of the pulmonary artery follow the segmental or tertiary bronchi and are segmental in distribution. Whereas, the tributaries of pulmonary vein run through the intersegmental septa and are intersegmental in drainage. Thus, the area of the lung drained by an intersegmental tributary of pulmonary vein is known as the broncho-vascular unit which includes a number of broncho pulmonary segments. Hence, the surgical resection of a broncho-pulmonary segment produces obvious haemorrhage (Fig. 2.3).

Now, the tertiary or segmental bronchus divides and subdivides and then finally end into smaller branches which enter the lung lobules through their apices. These smaller divisions of bronchus which enter the lung lobules are called the preterminal bronchioles. Thus, a preterminal bronchiole is the part of a conducting system which supply a lung lobule. A preterminal bronchiole is intralobular and is devoid of cartilages and glands. The lung lobules are self-contained and bounded by connective tissue septa which has no anastomotic connections with other adjacent lobules. In every lung lobules each preterminal bronchioles then divides into 3 to 7 terminal bronchioles. After that each terminal bronchiole again subdivides dichotomously by 3 successive orders into respiratory and then into terminal respiratory bronchioles. Each terminal respiratory bronchioles then terminate by branching into 2 to 11 alveolar ducts. The alveolar ducts are cone shaped and thin walled tubes with squamous epithelial lining. The number of alveolar ducts in each lung is about 2 million. Each alveolar duct then further divides or end by branching into 2 to 4 atria. Numerous air saccule open off from the atria. The total number of air saccule in each lung is about 4 million. Ultimately each air saccule gives rise to 30 alveoli (Fig. 2.4).

About 16 orders of division of respiratory passage takes place from the principal bronchus to the terminal bronchioles.

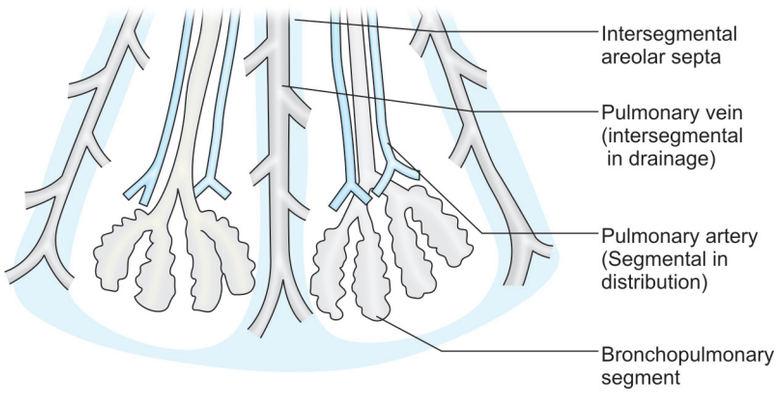


Fig. 2.3: Bronchopulmonary segments and their relations with pulmonary blood flow

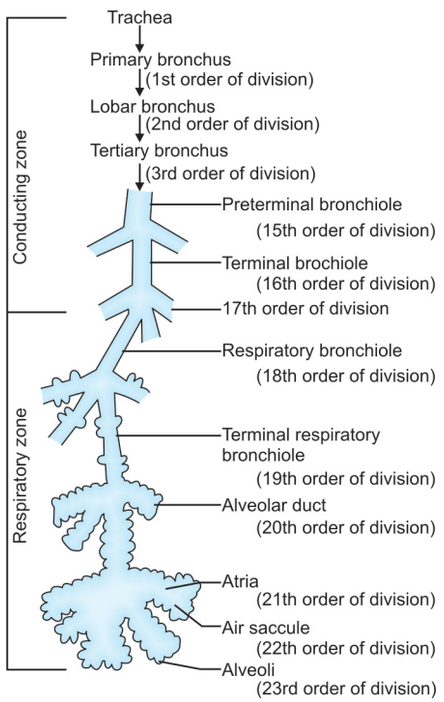


Fig. 2.4: Acinus (or primary lobule) is a subunit of pulmonary tissue consisting of respiratory bronchiole, alveolar ducts, atria and alveoli. Intercommunications exist between acini. Thus disease can spread from acinus to acinus. But functional deficiency in any part of one acinus can be compensated by by-pass mechanisms via these anastomotic channels. Secondary or lung lobule is the unit of pulmonary tissue served by a preterminal bronchiole. They are self-contained and bounded by connective tissue septa. It has no anastomotic connections with other lobules

The next 7 orders of division occur from the terminal bronchiole to the alveoli. The total number of terminal bronchioles in each human lung is about 33,000. Each terminal bronchiole subdivide into respiratory bronchiole. Respiratory bronchiole exibit alveolar outpockets from the side walls. Respiratory bronchiole divides into terminal respiratory bronchiole. The total number of terminal respiratory bronchioles in each human lung is about 2,60,000.

Therefore, 23 orders of division are encountered from the principal bronchus to the alveoli. The total number of alveoli in each lung is estimated to be about 150 million. Hence, the total number of alveoli

in both the lungs of an adult is about 300 million. All these alveoli of both the lungs together represent the total surface area of about 70 to 100 sq metres. The total number of alveoli in both the lungs of a new born is about 20 million and by about 8 years after birth the adult number is reached (Fig. 2.5).

The area of lung supplied by one terminal respiratory bronchiole is known to take part in gaseous exchange. So, from the functional point of view the area supplied by one terminal respiratory bronchiole is known as the functional pulmonary unit or lung unit. Thus, one lung unit consists of one terminal respiratory bronchiole, 3 successive orders of dichotomous subdivision of terminal respiratory bronchioles into alveolar duct and from alveolar duct to atria, air saccules and alveoli. Each lung unit or pulmonary unit is also called acinus. Intercommunication exist between two acinus or lung unit and also between acinus and respiratory bronchioles. Thus, the disease can spread from one acinus to another acinus and functional deficiency in any part of an acinus can be compensated by by-pass mechanism via these anastomotic channels to another acinus. The total number of alveoli in each lung is about 150 million (including those alveoli connected to the respiratory bronchioles).

Respiratory bronchioles and air passages distal to it are lined by simple squamous epithelium resting on a basement membrane and surrounded externally by intense pulmonary capillary plexus. But, lyumphatic plexus is absent from the terminal respiratory bronchioles and distal to it. The part of the bronchial tree extending from trachea up to the terminal bronchiole i.e. the first 16 generations of air passages is called the conducting zone and does not take part in gas exchange. This is lined by ciliated columnar epithelium. The Part of the respiratory passage extending from respiratory bronchioles to the alveoli, i.e. the distal 7 generations of air passage is called the respiratory zone and take part in gas exchange, because it is lined by squamous epithelium. Glands and cartilages are present up to the beginning of the preterminal bronchioles. These multiple divisions of respiratory passages greatly increase the total cross sectional area of the airways from 2.5 cm^2 in the trachea to 11,800 cm^2 in the alveoli. So the velocity of air flow in the small airways declines from very rapidly to a small value (Fig. 2.6).

Thus, the divisions and subdivisions of respiratory passage from trachea to alveoli may be summarised as follows:

- Principal bronchus (1st order)
- Secondary or lobar bronchi (2nd order)
- Tertiary or segmental bronchi (3rd order)
- Preterminal bronchioles (15th order)
- Terminal bronchioles (up to that 16 order of division)
- Respiratory bronchioles (18th order)
- Terminal respiratory bronchioles (19th order)
- Alveolar duct (20th order)
- Atria (21st order)
- Air saccules (22nd order)
- Alveoli (total 23 order of division)

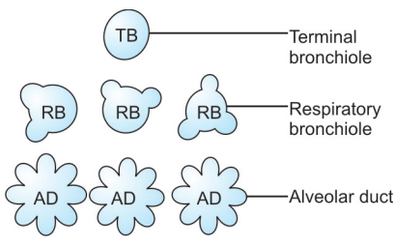


Fig. 2.5: A definitive flow of air is maintained up to the terminal bronchiole. Beyond this point the actual flow of air stops and air movement is effected by diffusion. One terminal bronchiole (TB) gives rise to 3-5 respiratory bronchiole (RB), and diameter of each RB = diameter of TB. Each RB gives rise to several alveolar duct (AD) of similar diameter to RB

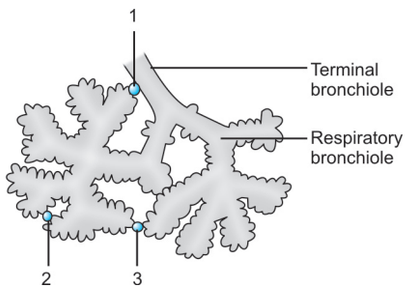


Fig. 2.6: Anatomical intercomunicating channels in acinus. These exist at three levels. 1. between one or more atria and the related terminal bronchiole. 2. between the alveoli of atria of same respiratory bronchiole. 3. between the alveoli of adjacent respiratory bronchioles. These alveolar connections are known as the pores of Kohn

Left Bronchus

The left principal or primary bronchus is longer, narrower and more oblique than the right one. The length of the extra pulmonary part of it is about 5 cm. It makes an angle of 45° with the trachea at the midline and passes downwards and to the left below the arch of the aorta. It then enters the left lung through its hilum at the level of the 6th thoracic vertebra.

Then, the left principal or primary bronchus divides only into upper and lower secondary or lobar bronchus to supply the respective lobe of the left lung, because the left lung is divided only into two lobes (whereas the right principal on primary bronchus divides into three secondary or lobar bronchus). After that the left upper secondary lobar bronchus again divides into 5 tertiary or segmental bronchi: apical, anterior, posterior, upper lingular, and lower lingular. The lower secondary lobar bronchus divide into 4 or 5 tertiary or segmental bronchi: apical, medial basal (may be missing), lateral basal, anterior basal and posterior basal (Fig. 2.7).

So, the nine or ten broncho-pulmonary segments of the left lung, supplied by the tertiary or segmental bronchi are:

- Upper lobe: apical, anterior, posterior, upper lingular, lower lingular.
- Lower lobe: apical, medial basal (may be missing), lateral basal, anterior basal and posterior basal.

Structure of Bronchus

As discussed before, within the lung a principal bronchus divides successively

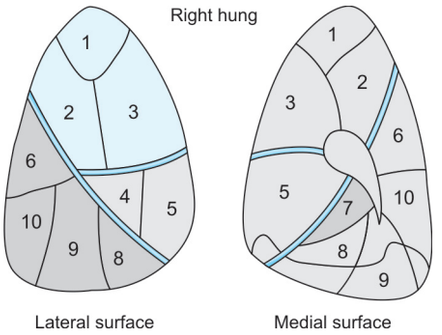


Fig. 2.7: Bronchopulmonary segments of right lung:
1. Apical segment of upper lobe, 2. Posterior segment of upper lobe, 3. Anterior segment of upper lobe, 4. Lateral segment of middle lobe, 5. Medial segment of middle lobe, 6. Apical segment of lower lobe, 7. Medial basal segment of lower lobe, 8. Anterior basal segment of lower lobe, 9. Lateral basal segment of lower lobe,10 .Posterior basal segment of lower lobe

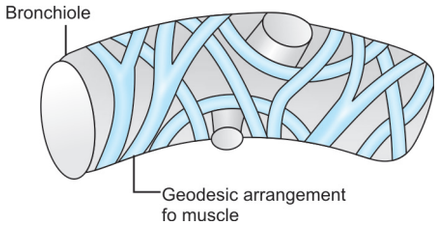


Fig. 2.8: The arrangement of muscle fibres on a bronchiole. The principal aim of this arrangement of muscles fibres in bronchiole is to permit the alterations of the length and width of the airway tube, during various phases of respiration. So, this type of arrangement of muscle fibres on airway is of great importance. This arrangement of muscle fibre on airway is known as the 'geodesic network' . A geodesic line in defined as the shortest distance between two points on a curved surface. Therefore, a geodesic pattern is the ideal method of withstanding or producing maximum pressures in a tubular structure without any tendency of being slipped of fibres along the surface of the tube

into secondary (lobar), tertiary (segmental) and numerous subtertiary branches up to alveoli. All these branches of bronchi run in the interlobular septa accompanied by the corresponding branches of the pulmonary arteries, pulmonary veins and bronchial vessels, till the preterminal bronchioles is reached when it leaves the interlobular septa and enter into the pulmonary or lung lobule at its apex. Actually the smaller branches of bronchi which leave the interlobular septa and enter the lung lobule are generally known as the bronchioles. A bronchiole is intralobular (not interlobular) and is devoid of cartilages and glands (Fig. 2.8).

Structurally, a bronchus is consist of from outside inwards are:

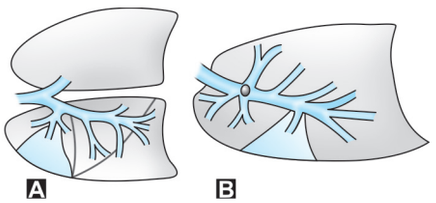
i. Fibro-elastic coat,
ii. Irregular plates of hyaline cartilages,
iii. Involuntary bronchial muscles which are helical in arrangements, and run in opposite directions, winding like a shoe - lace pattern,
iv. Mucous membrane which is ciliated columnar in nature and provided with goblet cells, mucous glands and numerous serous glands. Ultrastructurally, ten types of epithelial cells are present in the epithelial layer of tracheo bronchial air passage. Among them, the important cells are: ciliated, serous, goblet, brush, intermediate, clara and argentaffin cells.

In the bronchial mucous membrane the ciliated columnar cells are abundant in number and the ciliae are wrapped by low viscous or more serous fluid with their tip projected into it. This serous fluid is secreted by the serous cells and the mucous is secreted by the goblet cells. The brush cells are absorptive in functions. The intermediate cells are somewhat undifferentiated and probably help in regeneration of ciliated or secretory cells. The clara cells are nonciliated and are concerned with the secretion of some amount of surfactant. The argentaffin cells belong to the diffuse endocrine system of APUD cells series and secrete serotonin or histamine in response to the chemical or nervous stimuli.

Applied Anatomy

i. The breath sound over the right lung is more and distinctly audible than the left, because the trachea comes in more close contact with the right lung than the left one.
ii. Since the right principal bronchus is shorter, wider and more vertical than the left bronchus, so a foreign body is more likely to be aspirated in the right lung.
iii. The apical tertiary segment of the lower lobe (in supine position) and posterior tertiary segment of the upper lobe (lying on side) are the more common sites for lung abscess, becasue these segments are the most dependent part of lung in recumbent position. In such condition, the patient is advised to lie in the prone position which allows the infected material from these segments to accumulate in the principal bronchi and in the carina and subsequently the purulent material is expectorated out by stimulating the cough reflex (Fig. 2.9A and B).

Such natural drainage by adopting different postures may have some drawbacks. For example, pus from the apical segment of lower lobe may trickle in prone position through the opening of the middle lobe bronchus, because the mouths of the two bronchi are facing each other. In order to avoid such incidence, segmental resection of the apical segment of the lower lobe should be done. The apical segment of the lower lobe is most frequently involved in aspiration pneumonia (Memdelson's syndrome).



Figs 2.9A and B: Materials relationship between the posture and the common site of lung abscess. A. When a patient lies on his side, the common site of lung abscess is the posterior segment of the right upper lobe. Because inhaled mateirals easily collect in this broncho pulmonary segment. B. When a patient lies on his back, the common site of lung abscess is the apical segment of the right lower lobe

iv. The posterior segment of the right upper lobe is the most frequent site of tuberculosis.
v. The patency of middle lobe bronchus of both the lungs are particularly vulnerable to glandular swelling. Because they are closely related to the tracheobronchial group of glands (Fig. 2. 10).

LUNG

Actually the lungs are more a space than an organ. It is composed of serous coat, subserous coat and pulmonary substance or parechyma itself (from outside inwards). The serous coat invests the entire lung except the hilum and is derived from the pulmonary pleura. The subserous coat consists of thin elastic fibro-aleolar tissue and invests the whole lung under the serous coat. It again projects into the interior of the lung through the hilum as numerous fibro elastic septa and divide and subdivide the lungs. The smallest spaces between these septa are called the lung lobules. Each lung lobule is provided with one preterminal bronchiole and about 20,000 lobules are present in each lung.

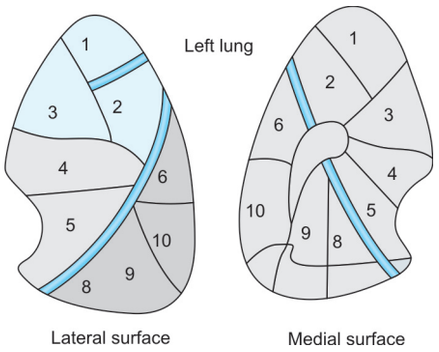


Fig. 2.10: Bronchopulmonary segments of left lung:

1. Apical segment of upper lobe, 2. Posterior segment of upper lobe, 3. Anterior segment of upper lobe, 4. Superior lingular segment, 5. Inferior lingular segment, 6. Apical segment of lower lobe, 7. Medial basal segment of lower lobe (may be missing), 8. Anterior - basal segment of lower lobe, 9. Lateral - basal segment of lower lobe, 10. Posterior - basal segment of lower lobe

Though the lung lobule is the anatomical pulmonary unit, but the alveoli is the functional or physiological unit of lungs. However, on the otherhand gas exchange occurs not only at the alveolar level but also in the respiratory bronchioles, alveolar ducts, atria and air saccules level. So, the area of lung supplied by the terminal respiratory bronchiole is actually the functional pulmonary unit. Hence, from the functional aspects the exact anatomical differences between these structures such as alveoli, air saccules, atria, alveolar ducts, etc. are not of great importance. The pulmonary alveoli are polygonal or polyhedral in shapes and are packed very tightly within the lung lobule. On an average, each alveolus is about 200 to 300 µm in diameter at functional residual capacity level and is sorrounded– by about 1800 capillary segment. The total length of the pulmonary capillary bed of both the lungs measures about 1500 miles and contains about 150 ml of blood. Each alveolus is lined by thin squamous epithelial cells with an insoluble thin film of lipoprotein, called surfactant spreading over it. The average thickness of this thin film of surfactant is 50Å in human being (Fig. 2. 11).

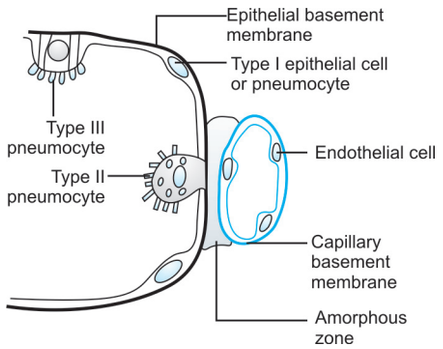


Fig. 2.11: Histology of the alveolus. In type I pneumocyte, the nucleus is situated at the angle of alveolus and its thin cytoplasmic extensions line most of the alveolar surface. Type II granular pneumocyte projects into the alveoli and are covered by microvilli. They produce surfactant and are essentially reserved cells which undergo hyperplasia when the type I pneumocytes are injured. Type III pneumocytes are pyramidal in shape with thick microvilli and contain filaments extending through the cell body. It resembles the chemoreceptor cells and have phagocytic property

Many structures interven between the air in the alveoli and the blood in the pulmonary capillaries and constitutes the pulmonary air-blood barrier through which gaseous exchange takes place. These structures are:

a. The flattened epithelial cells of alveoli which is about 0.05 µm thick,
b. The basement membrane upon which the alveolar epithelial cells rest,
c. The basement membrane of capillary endothelium on which the capillary endothelial cells rest. At some places these two basement membranes are fused, while in other places these are separated by an interval which is occupied by some undifferentiated mesenchyme or leucocytes,
d. the flattened endothelial cells of the capillaries. The total thickness of this air-blood barrier is about 0.2 to 0.5 µm.

The air surface of the alveoli is corrugated. This is due to the presence of capillaries and various subcellular structures. The alveoli share walls with the neighbouring alveoli and constitute a interalveolar septum between the two. Sometimes, there are some gaps in this septum which are called the alveolar pores. Thus, there is direct connection between the two alveoli through these pores.

There are three types of cells that line the alveoli and form the alveolar wall. These are: type I alveolar cells or membranous pneumocyte, type II alveolar cells or granular pneumocyte and type III alveolar cells or alveolar phagocytes. The type I alveolar cells are simple squamous epithelial cells and are connected with each other by tight junctions. They make up to 97% of the alveolar surface area and take part in gaseous exchange. The nucleus of these cells are situated at any one angle of it and a thin cytoplasmic extension lines most of the alveolar surface. The type II alveolar cells project into the alveoli and are covered by microvilli. They secret surfactant which by reducing the surface tension of alveolar living fluid helps to prevent the

collapse of alveoli during expiration. The surfactant fluid is rich in phospholipids, the principle constituent of which is dipalmitoyl phosphatidyl choline. The type II alveolar cells posses proliferative power and may replace the type I cells when they are injured. Alveolar phagocyte or type III alveolar cells are derived from the monocytes of blood. They appear within the alveoli by active migration through the air blood barrier. These cells phagocyte the bacteria, dust particles and other debris materials which enter the alveoli. Then, they move towards the bronchioles where the phagocytosed materials are eliminated by coughing. In congestive heart failure, alveolar phagocytes engulf the extravasated red blood cells and produce brick red or pinky sputum. So, these cells are sometimes also called the heart failure cells.

Pulmonary Vessels

Pulmonary Arteries

Each lung is provided with one pulmonary artery which is derived from the pulmonary trunk arising from right ventricle and conveys deoxygenated blood to the lung. Within each lung the branches of the pulmonary artery follow the division and subdivision of the bronchial tree and supply the corresponding bronchopulmonary segments by forming capillary plexus around the alveoli. So the pulmonary arteries are segmental in distribution. Usually, they supplies the deoxygenated blood to the alveolar capillary plexus and nutrition to the respiratory part (not conducting part) of the lung. The branches of the pulmonary and bronchial arteries anastomose with each other around the intrapulmonary part of bronchi and bronchioles, but they have different vascular pressure. In stenosis or embolism of pulmonary artery the bronchial artery supply the nutrition to the respiratory part of the lungs.

Pulmonary Veins

Each lung presents two pulmonary veins–upper and lower and so there are total four pulmonary veins. Upper pulmonary vein of right lung drains the blood from the upper and the middle lobes. While the upper pulmonary vein of the left lung drains the blood only from the upper lobe. Lower pulmonary vein drains the blood from the lower lobe of the respective lung. The pulmonary vein begins from the capillary plexus around the alveoli and terminates directly into the left atrium. In the peripheral part of the lung the pulmonary veins are intersegmental in position (whereas pulmonary arteries are segmental in distribution) and receive the blood from a number of broncho-pulmonary segments. Pulmonary vein does not convey 100% oxygenated blood from the alveoli to the left atrium. Because it receives some deoxygenated blood from the deep bronchial veins.

Bronchial Arteries

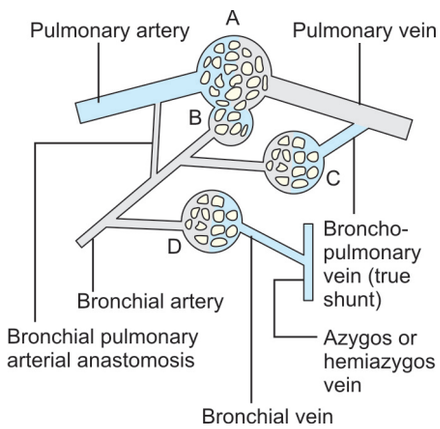
Usually they are three in number — two on the left side and one on the right side. The two left bronchial arteries, supplying the left lung arise from the thoracic aorta, and the single right bronchial artery, supplying the right lung arises either from an intercostal artery or from the upper left bronchial artery. In addition to these three main bronchial arteries, there are other many smaller bronchial arteries.

On entering the lung through hilum, the bronchial arteries make themselves embeded in the connective tissue layer around the bronchus and then run along the divisions and subdivisions of the bronchial tree, until the distal end of the terminal bronchiole is reached. Up to this level the bronchial arteries supply the O_2 and nutrition to the conducting part of the airways and then ultimately drain through bronchial vein into the azygos, hemiazygos, or intercostal vein.

After reaching the terminal bronchiole, the bronchial arteries start to break into multiple branches and produce a distinct set of capillary plexus. Gradually this capillary plexus fuses with the plexuses that is formed around the alveoli by the branches of pulmonary artery and ultimately drain through the pulmonary veins. Some branches of bronchial artery form plexuses around the airways below the level of terminal bronchiole and ultimately drain directly into the plumonary vein through broncho-pulmonary vein. They constitute the true shunt (Figs 2.12A to D).

Bronchial Veins

These veins consist of two systems—superficial and deep. The superficial bronchial veins drain blood from the pleura and the conducting part of bronchi. From the right lung the superficial veins drain into the azygos vein, whereas from the left lung it drains into the hemiazygos and left superior intercostal vein. The deep bronchial vein receive blood from the respiratory part of bronchi and terminate into one



Figs 2.12A to D: Relationship between the bronchial and pulmonary circulation.

A. Represents the pulmonary capillary network around the alveoli, atrium, alveolar duct and respiratory bronchiole (gas exchanging part). It is supplied by the pulmonary artery and drained by the pulmonary vein.

B. Represents the bronchial capillary network which joins with pulmonary capillary network (A) and drains through the pulmonary vein.

C. Represents the capillary network around the bronchi which does not communicate with pulmonary capillary. These vessels form the bronchopulmonary veins and empty into the pulmonary veins (true shunt).

D. Represents the bronchial capillary network around the lobar and segmental bronchi (conducting airway). These networks form true bronchial veins which drain into the azygos, hemiazygos or intercostal veins.

of the pulmonary veins. Thus, the superficial bronchial veins drain into the right heart and the deep bronchial veins drain into the left heart (true shunt).

Therefore, the lungs get its nutrition from two sources: (i) the conducting part of the respiratory passage upto the beginning of respiratory bronchiole or the distal end of terminal bronchiole is supplied by the bronchial arteries, and (ii) the respiratory part is supplied by pulmonary arteries via the pulmonary capillary plexus.

Innervation of Lungs

The lungs are innervated by both the sympathetic and parasympathetic nerves. The post-ganglionic sympathetic fibres are derived from the 1st to 4th thoracic ganglia, inferior cervical ganglion and sometimes from the middle cervical ganglion of sympathetic chain. The parasympathetic supply to the lungs is derived from the vagus and joins with the sympathetic fibres to from the posterior pulmonary plexus behind the roots of the lungs. The fibres from these posterior plexus also pass in front of the root of the lungs and again form the anterior pulmonary plexus.

The pulmonary plexuses (posterior and anterior) divides into two—periarterial and peribronchial plexus. The peribronchial plexus again divides into two—extra chondrial and intra-chondrial plexus, in relation to the cartilagenous ring. On reaching the non-cartilagenous part of the bronchial tree these two plexuses again reunite and continue distally as one. For parasympatheitc system, the peripheral ganglia are found at the level of the bronchial tree. The short postganglionic fibres arise from this peripheral parasympathetic ganglia and reach the bronchial smooth muscle, gland, and other structures.

In all the probability, the glands of bronchial tree are innervated by only vagus. Regarding the vessels, vagus carries the cholinergic vasodilator fibres and sympatheitc carries the adrenergic vasoconstrictor fibres.

MECHANISM OF RESPIRATION

Introduction

The respiration is divided into two processes: Inspiration and expiration. Among these, the inspiration is defined as active and the expiration is defined as passive process. In quiet resting state of breathing, the inspiration persists for about 1 second and the expiration persists for about 2 to 3 seconds. So, in adult the normal respiratory rate varies between 16 to 20 per minute. In infant, this respiratory rate ranges between 30 to 40 and in children it ranges between 25 to 30 per minute. The inspiration involves the expansion of chest cavity by (i) the downward movement of diaphragm, so as to increase longitudinal length and (ii) the elevation of the ribs by contraction of the intercostal muscle so as to cause the increase in antero-posterior and transverse diameter of chest. As expiration is passive process, so it involves all the reverse movement which occurs in inspiration. Thus, respiration is accompanied by respiratory muscles which again is controlled by the respiratory centre.

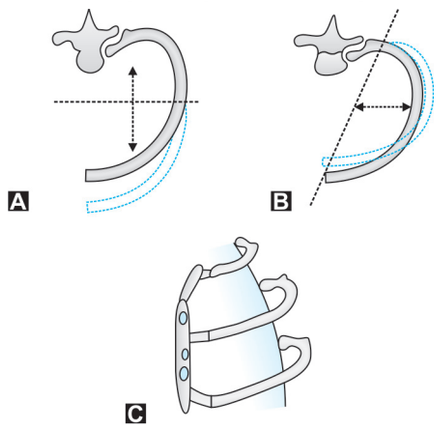
Respiratory Muscles

The respiratory muscles have got no inherent rhythmicity for constraction. But, they contract at a certain intervals by the motor impulses, originating from respiratory centre situated at the cortex (voluntary), midbrain, medulla and pons in brain. Diaphragm is a large, dome shaped sheet of muscle and separates the thoracic cavity from the abdominal cavity. It is the only principal muscle of inspiration that take part in quiet breathing. But, it is not absolutely essential for breathing. Because in absence of it other muscles also can take the responsibility of it. Contraction of diaphragm increases all the three diameters (vertical, anteroposterior, transverse) of thorax and helps in inspiration (Figs 2.13A to C).

On the otherhand, it (diaphragm) is the only inspiratory muscle in neonates and infants. Because all the ribs at this age are horizontal and movements of the ribs by contraction of the intercostal muscles can not increase the diameters of the thorax. The oblique direction of the ribs appears after the age of second year. Hence, the respiration below the second year is predominantly abdominal in type, depending only on diaphragm. Again the diaphragm becomes essential for maintenance of respiration during anaesthesia, because the intercostal muscles become early paralysed and become inactive during anaesthesia than the diaphragm. Besides these, in condition of paralysis of the intercostal muscle due to disease or spinal and epidural anaesthesia, only the diaphragm can maintain the basic respiration. This diaphragmatic respiration is known as the abdominal type of respiration.

The diaphragm is supplied by the phrenic nerve which takes origin from the spinal cord by the anterior roots of 3rd, 4th and 5th cervical spinal nerve. So, during high central neuroaxial block such as thoracic epidural where the level of anaesthesia extends below the level of the cervical segments, the respiration also can be maintained only by the diaphragm. This is because maximum intercostal muscles become paralysed in such condition.

The intercostal muscles move the ribs and thus help in inspiration and expiration



Figs 2.13A to C: A. Pump - handle type of movement, B. Bucket–handle type of movement, C. Ribs and their movements at manubrio - sternal joint

with the diaphragm. Among them the external intercostal muscles elevate the ribs and cause active inspiration. While the internal intercostal muscles depress the ribs and cause active expiration. But, we will have to keep in mind that the internal intercostal muscle does not take part in normal passive expiration. External intercostal muscles run obliquely downward and forward from the upper ribs to the lower ribs. So, when they contract they elevate the lower ribs. This pushes the sternum outward and increases the antero-posterior diameter of the chest. In this movement the transverse diameter of thoracic cavity also increases along with the AP diameter, but to a lesser extent. On the other hand, the internal intercostal muscles run obliquely downward and posteriorly from upper ribs to lower ribs. Therefore, contraction of these muscles cause downward pull on the rib cage which is opposite to the movement of inspiration and thus produce expiration. The movements of the upper six ribs increase mostly the antero-posterior diameter of the thorax. Whereas the movements of the lower ribs widen mainly the transverse diameter of the thorax. The electromyographic studies suggest that the lower intercostal muscles are active in quiet breathing and upper intercostal muscles are only involved progressively during deep respiration. Increase in 1 cm of circumference of thorax during inspiration allows about 200 ml of flow of air into the lungs.

The scalene group of muscles and the sternomastoid muscles are active only during deep and active inspiration. The scalene group of muscles elevate the first and second ribs, while the sternomastoid muscle elevates the clavicle. In quiet respiration the first and second ribs and the clavicle remain fixed and does not take part in respiration. The pectoral group of muscles and serratus also help in only forced inspiration. It works only when the bones of upper limbs are fixed. The erector spinal muscles make the thoracic part of the vertebral column straight and helps it to act as a pivot against which other muscles can act and bones can move. Thus, it also facilitates the spreading of the lower ribs with widening of the infra-sternal angle and so help in deep inspiration. The quadratus lumborum muscle fixes the last rib and helps in the action of diaphragm during deep inspiration. The other accessory muscles that take part in decreasing the resistance of air flow and help in respiration are the mylohyoid, digastric, alae nasai, platysma, cheeck muscles, lavator palati, laryngeal muscles, tongue muscles, the posterior neck muscles, etc. During muscular exercise when the ventilation increases manifold, then all the accessory muscles of respiraton including the trapezius and back muscles also take part in the action.

As previously said that the expiration is a passive process and it is due to the elastic recoil property of lungs and thoracic cage, so during inspiration the potential energy is gained due to the contraction of the inspiratory muscle and during expiration this stored energy is released by the elastic recoil property. But, only the few muscles come into action during forced expiration. These are the flat muscles of anterior abdominal wall (external and internal oblique, transversus abdominis, rectus abdominis), lattissimus dorsi and internal intercostal muscles. The contraction of the muscles of the anterior abdominal wall aid in expiration by pulling the rib cage downward. Muscles of the anterior abdominal wall also compress the abdomen and increases the intra-abdominal pressure. Thus, it displaces the diaphragm upwards and the volume of thoracic cavity is diminished, causing expiration. In normal breathing they are practically inactive, but during coughing, sneezing, etc, they become highly active. Latissimus dorsi also reduces the thoracic volume by compressing the thorax from behind.

The anteor-posterior diameter of thorax is increased by the elevation of the ribs, mainly from 2nd to 6th. An oblique axis passes through the costovertebral and costotransverse joints of the neck of the ribs of one side and the costochondral junction of the opposite site. When the ribs move around this axis, then the antero-posterior diameter of thorax is increased. This is caused by the contraction of external intercostal muscles of one side and the internal intercostal muscles of the opposite side due to their same fibre direction. This movement of ribs is called the pump-handle type of movement. In this type of movement, the body of sternum moves forward during elevation of the ribs (at the sterno-manubrial joint) during inspiration and swings backward during expiration. The first rib and the manubrium sterni form a rigid unit and do not move in quiet breathing, except during forced inspiration. The 2nd to 6th ribs sloped downwards and forwards with their cartilages. So, their elevation cause forward and upward movement of the body of the sternum and increases the antero-posterior diameter.

The 7th to 10th ribs is sloped downward and forward, but their cartilages are directed upwards and medially to join the body of the sternum. So, the movement of these ribs around this oblique axis causes backward movement of the sternal body at the sterno-manubrial joint and diminishes the antero-posterior diameter. Therefore, two opposite forces work together at the sterno-manubrial joint. Movement of upper ribs produces forward movement and movement of lower ribs produces backward movement. Thus, this explain the formation of sternal angle at the junction between the manubrium and the body of the sternum.

The transverse diameter of thoracic cavity is increased by two methods—active and passive. Active process is observed between 7th to 10th ribs. Here, the movement takes places around an axis which passes through the costovertebral and the costosternal joint of the same side. Movement of these ribs around this axis

causes elevation of the middle portion of the ribs, resembling bucket handle type of movement and increase the transverse diameter of thorax. Movement of 2nd to 6th ribs around the oblique axis which increases the antero-posterior diameter also increases the transeverse diameter of thorax passively. This passive increase of transverse diameter is facilitated by the curved nature of the articular surfaces of the costotransverse joint.

The vertical diameter of thorax increases due to up and down piston like movement of diaphragm. It also helps to increase the transverse diameter. Initially during inspiration when the diaphragm contracts, the lower ribs become fixed and the central tendon or vault of the diaphragm descents. This central descent of diaphragm causes downward displacement of the upper abdominal viscera and bulging forward of the anterior abdominal wall. When a limit of the forward bulging of the anterior abdominal wall is reached then the descent of diaphragm ceases and the central tendon becomes fixed. After that, during further contraction of diaphragm, i.e. when the central tendon is fixed, the lower ribs are elevated by the bucket handle type of movement and the volume of thorax is further increased by widening of the transverse diameter. In quiet breathing the range of this piston like diaphragmatic movements is about 1.5 cm which can be increased between 6 to 10 cm in forced respiration. In normal respiration, when the diaphragm descends about 1.5 cm, the thoracic volume is increased by about 400 cc. Normally out of 500 cc of tidal air, 400 cc is due to this 1.5 cm movement of diaphragm.

SUMMARY

The lungs can be inflated or deflated by two ways:

i. By downward and upward movement of the diaphragm which increases or decreases the volume of chest cavity and subsequently the volume of lungs.
ii. By elevation and depression of the ribs which increases and decreases the antero posterior and transverse diameter of the chest cavity and subsequently the volume of lungs.

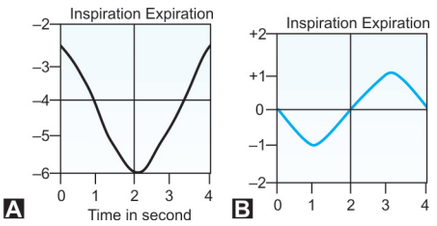
The normal quiet breathing is almost entirely accomplished by the movement of diaphragm. During inspiration diaphragm contracts and increases the volume of lungs, the mechanism of which is described before and air is rushed in. During expiration the diaphragm simply relaxes. Thus due to the elastic recoil property of the lungs, chest wall and abdominal structures all compress the lungs and air is rushed out.

But, during heavy or active breathing the second method of expansion of lungs by the rib cage comes into play. In natural resting position, the ribs are slanted downwards. But, when the rib cage is elevated by the muscular contraction, then the ribs project forward and upward directly. Thus, the sternum also moves upward and forward away from the spine, increasing the antero-posterior diameter of thoracic cavity. With the forward elevation of the ribs, there is also buckle handle type of movement of ribs which increase the transverse diameter of the rib cage. Therefore, the muscles that elevate the chest cage are called the muscles of inspiration and the muscles that depress the chest cage are called the muscles of expiration. So, the muscles of inspiration are: the external intercostal (main inspiratory muscles), the sternocleidomastoid (by lifting the sternum upward), anterior serratus (by lifting many of the ribs where it is attached), scaleni (by lifting the first two ribs). The last three muscles are called the helping inspiratory muscles. The muscles of expiration are : abdominal recti (by pulling downward the lower ribs and at the same time with other abdominal muscles by compressing the abdominal contents upward against the diaphragm) and internal intercostal (by pulling the ribs downward due to the downward and backward direction of their attachment).

Intrathoracic and Intrapulmonary Pressure

Under normal resting condition when there is no inspiration or expiration, then the intra-thoracic pressure, more precisely called the intrapleural pressure is sub atmospheric and measures about –2 mm of Hg. In similar condition the intra-alveolar or intra-pulmonary pressure is zero i.e equal to the atmospheric pressure.

The chest wall and the lung is covered by a thin layer of membrane which is known as the parietal and visceral pleura, respectively. This two layers of pleura are separated by a thin layer of fluid, called the pleural fluid which lubricates the movement of lungs within the chest cavity. The pressure within the space, between these two pleura, is called the intrapleural pressure. Theoretically, this intra pleural pressure is -8 to -10 mm of Hg. This negative intra pleural pressure is caused by the more rapid absorption of pleural fluid by the lymphatics and by the capillaries of the visceral pleura, since such lymphatics and capillaries are belonged to the low pressure pulmonary circulatory system. On the other hand, the value of pressure on the pleural surface due to the contact between the visceral and parietal pleura is about + 6 mm of Hg. So, the resultant practical intra pleural pressure which we measure is the theoretical intra pleural pressure due to absorption of fluid plus the intra pleural contact pressure i.e –8 + 6 or –2 mm of Hg. But, this value is an average one. Actually, the intrapleural pressure at the base of the lungs which is normally about –2 mm of Hg at the start of the inspiration, decreases to about –6 mm of Hg at the end of inspiration in quite breathing. Strong inspiratory efforts increase this negative intrapleural pressure to values as low as –30 mm of Hg or more, producing corresponding greater degrees of lung inflation (Figs 2.14A and B).



Figs 2.14A and B: A. It is the graphical representation of changes in intrathoracic or intrapleural pressure during respiration. B. is the graphical representation of changes in intra-pulmonary or intraalveolar pressure during respiration

Such negative intrapleural pressure which helps the lungs to inflate allows the visceral and parietal pleura to come in close contact with each other as if they are glued together. But, the presence of thin intraplural fluid allow the free movement of these two pluras when the chest contracts and expands. The lungs tissues possess an inherent elastic property to recoil from the chest wall, but this negative intrapleural pressure prevents this. Thus, the intrapleural pressure being subatmospheric keeps the lungs in apposition with the chest wall and make it partially inflated. But, if the chest wall is opend to atmosphere, the lungs will collapse due to its inward recoling elastic property and due to the absence of subatmospheric intraplural pressure. On the otherhand, if the lungs lose their recoil property or elasticity, it remains in inflated or expanded condition and becomes barrel shaped. It is estimated that one-third of the inward recoiling elastic force of the lungs is derived from the stretched elastic fibres within it such as elastin, collagen, etc. and two thirds from the surface tension of the fluid, lining the alveoli.

At rest, when there is no inspiration or expiration the intrapulmonary or intra-alveolar pressure is maintained at 0 mm of Hg (i.e. same as the atmospheric pressure or 760 mm of Hg). So, at this condition no air enters in or comes out of the lungs. During inspiration, as lungs expand due to more and more subatmospheric intrapleural pressure which is again due to expansion of chest wall, then the intra-alveolar or intra pulmonary pressure gradually falls and air rushes into the lungs. Thus, during inspiration the intra-alveolar pressure gradually falls from 0 mm of Hg to about –2 or –6 mm of Hg (at that time intrapleural pressure also falls from –2 mm of Hg to –6 or –10 mm of Hg or more). During deep inspiration this intrapleural pressure becomes more sub-atmospheric and this is due to the active contraction of respiratory muscles. That active contraction of respiratory muscles try to create more negative intrapleural pressure and subsequently more negative intra-alveolar pressure to overcome the different resistances such as elastic recoil of lung, frictional resistance due to deformation of tissues of the lungs and thorax, and frictional airway resistance which prevents the expansion of thorax and lungs from the entry of air into it. At the end of the inspiration maximum sub atmospheric intra pleural pressure is maintained. During forced inspiration, intra-alveolar and intra-pleural pressure may be as low as -40 mm of Hg and -50 mm of Hg respectively. At the end of inspiration, intra-alveolar pressure gradually comes back from sub atmospheric to 0 or atmospheric level, like at the begining of inspiration, due to filling of lungs by air and thus air flow ceases (Fig. 2.15).

During normal expiration, the volume of thoracic cage and the volume of lung decreases passively due to the inward elastic recoiling property of lung parenchyma and chestwall tissues. Thus, the intra-alveolar or intrapulmonary pressure rises above the atmospheric level. It generally goes up to + 3 or + 4 mm of Hg and permits exit of air from the lungs. At that time the intrapleural pressure also comes back from -6 mm of Hg to –2 mm of Hg, but always remains –ve. When forced expiratory efforts are made with closed glottis, such as during muscular exercise, defaecation or micturition. etc, then the intrapulmoanry pressure may go up from +10 mm of Hg to +40 mm of Hg. In coughing and

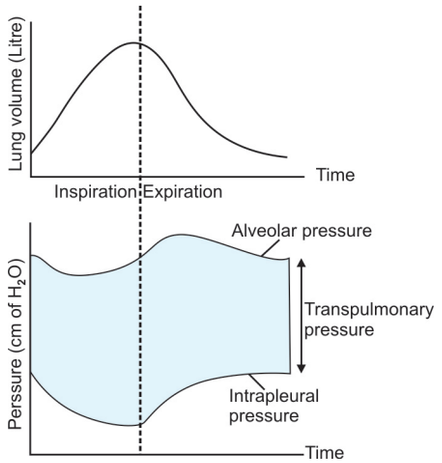


Fig. 2.15: Changes in alveolar pressure, intrapleural pressure, transpulmonary pressure and lung volumes during normal inspiration and expiration

sneezing, the intrapulmonary pressure may also go far above the normal level and may be +100 mm of Hg with glottis closed. At the end of the expiration, when air stops to exit then the intra-alveolar pressure again gradually comes down to atmospheric or zero level.

Thus, it is to be noted that during normal inspiration and expiration the changes of pressure within the lungs (or the intra-alveolar pressure) go both above and below the '0' line or the atmospheric pressure. But, pressure changes in the pleura (i.e intra-pleural pressure) always remain below the '0' line or sub atmospheric level (i.e negative) and pressure level in the abdomen always remain above the '0' line (i.e positive). The difference between the intra-alveolar pressure and the intra-pleural pressure is called the transpulmonary pressure. Actually it is the pressure difference between the inside and outside of the lungs and is equivalent to the elastic forces of the lungs that tends to collapse it at the each moment of respiration.

The physical principles that determine the respiration are the production of pressure gradient between the interior of the lungs and the atmosphere. According to the physical laws, the air will flow from the higher pressure head to the lower one.

During inspiration, the intra-alveolar pressure falls below the atmospheric one and so air rushes in. But during expiration, the intra-alveolar pressure goes above the atmospheric pressure level and air goes out. Thus, the normal breathing is called the negative pressure breathing. But, if the atmospheric pressure is raised above the intra-alveolar pressure to push the air into the lungs during inspiration, then this type of respiration is called the positive pressure beathing which is used in general anaesthesia with complete muscle paralysis.

Compliance of the Lungs

The compliance is a stretching force which is opposite to the elastic force that tries to collapse the lungs. It is measured as the change of volume of lungs during expansion of it for each unit increase of transpulmonary pressure. The average total compliance of both the lungs together in an adult human being is 200 ml per cm of H_2O (or 0.2 L/cm of H_2O) transpulmonary pressure. It means that for increase in every cm of H_2O of transpulmonary pressure, the total volume of both the lungs will expand to 200 ml. Therefore, the compliance of single lung is 100 ml per cm of H_2O (or 0.1 L/cm of H_2O).

Usually, the compliance of lungs is represented diagrammatically by two curves. Among these, one is called as the inspiratory complaince curve and the other is called as the expiratory compliance curve. While the entire diagram represents the total compliance of the lungs.

It is previously told that compliance which is defined as the stretching force is opposite to the elastic forces (or elasticity). So, compliance of lungs is best understood and calculated from it (elasticity). On the other hand, elasticity has two components: (i) elasticity caused by the lung tissue or parenchyma itself, and (ii) elasticity, caused by the surface tensin of fluid lining the inside of alveoli. The elastic forces (elasticity) of the lung parenchyma is caused by the interwoven elastin and collagen fibres, situated in the parenchyma of lungs. In completely collapsed lungs these fibres are in completely contracted state. Thus, when the lungs expand these fibres become stretched and thereby exerts an elastic forces which prevents the expansion and reduce the compliance (Fig. 2.16).

The elasticity caused by the surface tension of alveoli is more interesting. On the inner side of the alveolar wall there is always some thin layer of fluid. So, when the lungs are filled with air, there is always an interface between the fluid and the air in the alveoli. This fluid and air interface in the alveoli is responsible for the surface tension which try to collapse the alveoli and subsequently the lungs. This is because, when a fluid have a surface with air, then the fluid molecules on the interface with air have a force of strong attraction for one another. This is called the surface tension. As a result, the fluid surface towards the air always tries to contract and takes the smallest spherical shape. Thus, the alveoli with their fluid surface try to collapse, forcing the air out of the lungs. This elastic force caused by the fluid-air surface tension in the alveoli is two-third of the total lung elasticity. On the other hand, the tissue elasticity due to stretching of elastin and collagen fibres represents only about one third of the total lung elasticity.

The surfactant is a chemical surface active agent which greatly reduces the surface tension of liquid. This chemical agent or surfactant is present in the fluid lining the alveoli and subsequently reduce the contractile elastic force of the lungs due to surface tension (not due to elastin and collagen fibres of lung parenchyma). In the absence of this surfactant, the surface tension in the alveoli and subsequently the contractile elastic forces due to this surface tension will increase tremendously and then, it is not possible to inflate the lungs. This chemical agent or surfactant is the complex mixture of many phospholipid, proteins and ions. Among these components the most important components are: Dipalmitoyl phosphatidylcholine (DPPC), apoproteins and calcium ions. They act by not completely dissolving in the fluid, lining the alveoli, but remain spread over the surface of the fluid that lines the inner side of the alveoli.

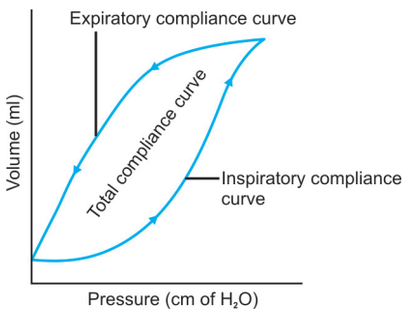


Fig. 2.16: Two compliance curves of lung

Due to surface tension alveoli tends to collapse. Thus a increased pressure is generated within the alveoli. This pressure or contractile force can be calculated from the following formula of Laplace law :

$$\text{Pressure (P)} = \frac{\text{2 wall tension (T)}}{\text{Radius of alveolus (r)}}$$

From the above formula, it is noted that the pressure which is generated in the alveoli from its contraction due to surface tension is inversely proportional to the radius of that alveolus. It means that the smaller the radius of the alveolus will be, the greater will be the alveolar pressure generated by the increased collapsing force due to increased surface tension. Therefore, when the alveoli decrease in size during expiration, then the pressure tending to collapse or collapsing force will increase and thus a vicious cycle will be established. But, in practical this does not occur, because as the alveoli are coated with surfactant which reduces the surface tension and as the alveoli decrease in size during expiration, so the amount of surfactant per unit area of alveolar surface will also increase and reduces the surface tension more than the expected. Thus, the action of surfactant will be more efficient when the alveoli will decrease in size. Therefore, contrary

to Laplace's law, the smaller alveoli can be inflated more easily than a larger one in the presence of surfactant. If there was no surfactant, the larger alveoli would tend to inflate further at the expense of smaller ones which would collapse.

The radius of a normal adult alveoli is 100 micrometers. The normal value of surface tension in such alveoli created by the lining fluid with normal amount of surfactant varies between 5 to 30 dynes/cm. Then, the intra-alveolar pressure is calculated to 4 cm of H_2O. In newborn the radius of the alveoli is 50 micrometers which is half than that of the adult. In such situation pressure generated by collapsing alveoli due to the surface tension will be doubled, with normal amount of surfactant. This is more significant in premature newborn where the radius of alveoli is more or less one quarter than that of an adult person. Here, pressure inside the alveoli due to collapse increases to four fold. Further, many premature newborn has little or no surfactant in their alveoli. So, their lungs have extreme tendency to collapse which is sometimes as great as eight times than that of a normal adult person. This explains why such patients need high positive pressure ventilation.

RESPIRATORY CENTRE AND ITS REGULATION

The normal rate of respiration in an adult healthy individual is about 14 to 18 per minute, with a tidal volume of about 500 ml. But the rate and depth of respiration i.e. the total pulmonary ventilation per minute varies according to the requirements of the body.

The important functions of respiration are:

i. To supply the adequate amount of O_2 and to eliminate CO_2,
ii. To regulate H^+ ion concentration of blood,
iii. To maintain the temperature balance of the body
iv. To excrete volatile substances like ammonia, ketone bodies, alcohol, water vapour, etc.
v. To help in circulation. During inspiration the intrathoracic pressure falls and intra-abdominal pressure rises. This is one of the most important factors that help in the return of venous blood to heart and lymph in the circulation.

Whenever these requirements increase, then the respiration is stimulated. For example, when the metabolic rate increases due to any cause, then the necessity for supplying more oxygen and the necessity for eliminating more CO_2 will also rise. In this condition, blood will tend to become more acid and heat production will be more. So, to maintain these factors at the normal level, respiration will also have to be stimulated. This is also found in muscular exercise, when the pulmonary ventilation rises enormously. On the other hand, during sleep the metabolic requirements are low, hence the respiration is also depressed. As a whole, it can be stated that the total pulmonary ventilation is directly proportional to the metabolic need of the body. Since, as the rate and depth of respiration can be accurately adjusted according to the body needs, so it is necessary that there must be an efficient mechanism for its regulation.

The spontaneous respiration is produced by the rhythmic discharge of impulses from some motor neurons of higher respiratory centre which are situated in the brain and that innervate the respiratory muscles through the cervical and thoracic segment of spinal cord. This rhythmic discharges of impulses from the respiratory centre that produce spontaneous repiration are regulated by the alternations of the arterial PO_2, PCO_2 and H^+ concentration (chemical regulation). Again this chemical control of breathing is supplemented by a number of other nonchemical stimuli (nervous regulations) that also have influences on it (Fig. 2. 17).

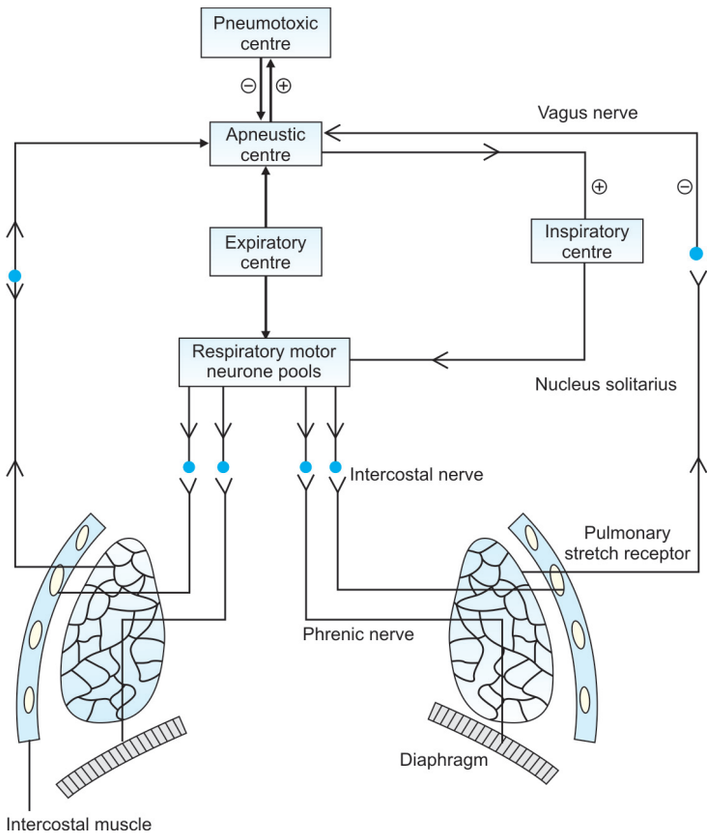


Fig. 2.17: Diagrammatic representation of central respiratory mechanism

Usually, two separate neural mechanisms regulate the respiration. Among these one is responsible for the voluntary control and the other is responsible for the automatic rhythmical control. The centre for voluntary control of respiration is located in the cerebral cortex and sends impulses directly to the respiratory motor neurons (not the respiratory centre) supplying the diaphragm and the intercostal muscles, situated in the spinal cord (cervical and thoracic segment) via the corticospinal tracts. On the otherhand, the automatic rhythmical control of respiration is driven by a group pacemaker cells situated in the brainstem, medulla and pons which are called together the respiratory centre (RC). Impulses from these cells activate rhythmicaly the motor neurons in the cervical and thoracic segment of the spinal cord that innervate the inspiratory muscles. Those in the cervical segment of spinal cord activate the diaphragm via the phrenic nerves and those in the thoracic segment of spinal cord activate the external and internal intercostal muscles.

The motor neurons to the expiratory muscles are inhibited when those supplying the inspiratory muscles are activated and vice versa. This is called the reciprocal innervation of RC. Thus, the mechanism of regulating the respiration has been arbitarily divided into three parts: Respiratory centre, nervous regulation and chemical regulation.

Respiratory Centre

It has been suggested that there are certain collection of nerve cells in the brainstem, medulla and pons (although they does not form a descrete structure) that control the respiratoy movements of chest wall and diaphragm. These collection of nerve cells together is called the respiratory centre which under normal circumstances generate the rhythm of breathing and organize respiration. However, this organisation of the respiratory centre is very complex and include several subcentres. These subcentres on each side consists of inspiratory centre, pneumotoxic center, apneustic centre and expiratory centre which are located at various level of the brainstem, medulla and pons.

These respiratory subcentres are bilateral with the same and contralateral sided control. They also freely communicate with each other. Connections exist within the similary acting centres of the opposite sides and within the oppositely acting centres of the same side. For example an impulse that stimulates one centre, will inhibit the other and vice versa. But the center of one side controls the respiratory muscles of the same side. Thus, the respiratory centre of right side is connected to the spinal motor neurons of the phrenic and intercostal nerves, supplying the muscles of respiration of the right side.

Though, there is much uncertainty regarding the actual site of the origin of respiratory rhythmicity, but still it is generally thought that there is an inherent rhythmicity in the certain groups of respiratory neurons in the brainstem which is modified by other affarent inputs. At present the established theory is that the first primary inspiratory drive comes from the apneustic centre to the inspiratory centre. Then, the inspiration starts with the increasing activity of the inspiratory centre. During inspiration, the tonic impulses from the apneustic centre also excite the pneumotoxic centre to sent in turn the inhibitory impulses from pneumotoxic centre to the apneustic centre. At the height of inspiration, the inhibitory impulses from the pneumotoxic centre, as well as inhibitory impulses from the pulmonary stretch receptors through vagus depress the apneustic centre. Thus, inspiration is ceased and the expiration starts passively. Expiration is normally a passive process during quiet breathing. But, it becomes active during exercise. During expiration the same inhibitory effects on the apneustic centre are no longer present and so inspiration starts again. Thus, this process is repeated again and again. It is probable that the medullary inspiratory centre is not under direct control of pneumotoxic centre, but under the direct control of pontine apneustic centre. With the inhibition of the inspiratory centre, the expiratory centre starts functioning, keeping in mind that in quiet breathing expiration is passive. The expiratory centre functions actively only during active expiration, but not during quite breathing.

SUMMARY

i. The activity of two feedback mechanism such as the inhibitory vagal affarent impulses from pulmonary stretch receptors and the negative impulses from pneumotoxic centres have got probably no direct inhibitory control upon the inspiratory centre or direct stimulating effect upon the expiratory centre.
ii. The apneustic centre probably sends tonic discharges simultaneously to the inspiratory centre and to the pneumotoxic centre.
iii. The inspiratory centre discharges impulses to the spinal motor neurons supplying the respiratory muscles for normal inspiratory efforts.
iv. The pneumotoxic centre in its turn discharges inhibitory impulses to apneustic centre.
v. The apneustic centre being inhibited by the inhibitory impulses from the vagi and also from the pneumotoxic centre ceases to stimulate the inspiratory centre.
vi. The inspiratory centre ceases its activity and expiration follows passively.

Nervous Regulation

In nervous regulation of respiration, the respiratory centres are regulated by few reflexes conducted through different nerves and centres. These are as follows:

Vagus Nerve

The rhythm and the depth of respiration are controlled by reflexes from the lungs itself which pass through the vagus. This

reflex is called the Hering-Breuer reflex. This is an inflation reflex and the pulmonary stretch receptors are responsible for this. These receptors are unencapsulated and are found in the smooth muscle of the airway without an end organ. They are generally believed to be responsible for signalling the changes of mechanical state of the lungs to the brain. During inspiration the stretching of pulmonary tissue send inhibitory impulses to the apneustic centre which subsequently for this inhibitory effect fails to send stimulatory impulses to inspiratory centre. When inspiration is going on, then due to the gradual increase of the volume of lungs more and more inhibitory impulses pass to the apneustic centre and at the maximum inhibition of apneustic centre inspiration stops. Then, passive expiration starts and the inhibitory impulses to the inspiratory centre gradually wane. When this inhibitory impulses over the inspiratory centre completely wane or totally withdrawn during expiration, then inspiration again starts.

The afferent nerve endings responding to both the mechanical and chemical factors regulating the respiration also have been described. They are situated in the epithelium of the airways and extend from the trachea to the respiratory bronchioles. They are concentrated mainly at the carina and at the points of branching of the bronchial tree. There affarent pathway is the vagus. They are activated by some chemical irritants such as ether, smoke, dust, etc., and mechanical stimuli such as foreign body, secretion, etc. Stimulation of these receptors results in hyperpnoea and laryngeal or bronchial spasm. All these are also vagal reflexes.

J-receptors (juxta-pulmonary capillary receptors) are situated on the walls of the alveoli and also possibly on the smaller airways. Like the other lung receptors, their afferent pathway is also vagas. They can respond to numerous different stimuli, but they are chiefly stimulated by the increase in insterstitial fluid between the capillary endothelium and alveolar epithelium which may be caused by pulmonary oedema, microembolism, pneumonia or irritant gases. There is evidence to suggest that stimulation of these J-receptors cause tachypnoea, bronchoconstriction and contraction of the adductor muscles of the larynx. But since the causes of their stimulation often have other effects, so it is difficult to think that these effects are due to the J-receptor stimulation alone.

Sinus and Aortic Nerve

This sino-aortic nerve consists of sinus and aortic nerve. The sinus nerve (affarent) arises from the carotid sinus (baroreceptor) and carotid body (chemoreceptor) and passes along the glossopharyngeal nerve to end in the medulla in close relation with the respiratory, cardiac and vasomotor centre. On the otherhand, the aortic nerve (afferent) arises from aortic arch (baroreceptor) and aortic body (chemoreceptor) and passes along the vagus nerve to end in the medulla in close relation with the respiratory, cardiac and vasomotor centre. So, they regulate the respiration during the changes of blood pressure, arterial CO_2 and O_2 tension, and H^+ concentration.

CO_2 excess will stimulate the respiration by reflexly acting through the carotid and aortic bodies. Alteration of H^+ concentration due to any other causes such as in metabolic acidosis or alkalosis other than changes in CO_2 concentration will also act in the same way as CO_2. Oxygen lack will also stimulate the respiration by reflexly acting through the carotid and aortic bodies. But its direct action on the respiratory centre is depression of respiration. Rise of blood pressure will also depress the respiration, but fall of blood pressure will stimulate the respiration. They act through the baroreceptors such as the carotid sinus and the aortic arch.

Impulses from Higher Centres

Certain and several parts of the cerebral cortex, hypothalamus, limbic systems, vasomotor centre and other parts of the brain also reflexly alter and regulate the respiration through respiratory centre.

Other Factors

There are certain other factors which also affect the respiratory centres reflexly. These are: cough, yawning, hiccough, sneezing and other reflexes arising from the body surface and viscera (such as thermoreceptor, pain receptor, touch receptors etc. also affect respiration). Reflexes arising from the muscles and joints increases pulmonary ventilation during exercise and is partly due to the impulses originating from the active muscles and joints.

Chemical Regulation

The respiratory centres are highly sensitive to the alterations of chemical composition of the blood. Changes in the CO_2 tension, O_2 tension and H^+ ion concentration of blood alter the pulmonary ventilation profoundly. In any case, the main purpose is to adjust the respiration in such way that it may be able to meet the demands of the body adequately during emergency. The effects of these changes are briefly summarised below.

The chemical regulatory mechanism adjust ventilation in such a way that the alveolar PCO_2 is normally held constant, the excess H^+ in the blood are combated, and arterial PO_2 is raised, when it falls to a potentially dangerous level. The respiratory minute volume is proportionate to the metaboic rate, but the link between the metabolism and the ventilation is CO_2, but not O_2. The link between metabolism and ventilation is established by the receptors in the carotid and aortic bodies which are stimulated by the rise in arterial PCO_2 or H^+ concentration or decline in PO_2.

Effects of Alteration in CO_2 Tension

The arterial PCO_2 is normally maintained at 40 mm of Hg (between 35 to 45 mm of Hg) because the respiratory centre is extremely sensitive to the slight alteration

in arterial CO_2 tension. A slight rise of CO_2 concentration in the inspired air increases respiration enormously. Respiration increases at first in depth and then in rate and last by both. Thus, the total pulmonary ventilation is raised. The degree of stimulation of respiration shows a quantitative relationship with the increase of CO_2 tension. The total pulmonary ventilation is so nicely adjusted that the alveolar CO_2 tension which is proportional to the arterial CO_2 tension (if there is no abnormality in diffusion at alveoli) remains more or less constant. This reflex works maximally up to the inspired CO_2 concentration of 5%. But, if the percentage of CO_2 concentration in the inspired air goes above 5%, then this adjustment fails and consequently the alveolar CO_2 content rises. So, breathing of air containg up to 5% CO_2 will not do any harm, although respiration will be stimulated. But, if the inspired CO_2 content is raised further, the alveolar CO_2 tension will rises in spite of hyperventilation. This will lead to the accumulation of CO_2 in the blood and thereby cause the toxic effects of CO_2 narcosis (headache, confusion and coma).

CO_2 acts on the respiratory centre both by directly (centrogenic) acting on it and by reflexly acting through the carotid and aortic bodies (reflexogenic). During anaesthesia the threshold level of arterial CO_2 tension which stimulate the respiratory centre increases. Thus, in anaesthetized condition respiratory centre becomes insensitive to CO_2 or threshold level for stimulation becomes high.

Effect of Changes in H^+ Concentration

The changes of H^+ ion concentration in blood also alter the pulmonary ventilation. Duing metabolic acidosis respiration rises and during metabollic alkalosis it falls. The purpose of it is briefly stated as follows:

During acidosis due to only metabolic causes, respiration increases and more CO_2 is eliminated from the alveoli. This lowers the alveolar CO_2 tension below the normal. Consequently more and more CO_2 comes out of the blood stream into the alveoli which is formed by the reaction between H^+ and HCO_3^-. Thus, the H^+ ion concentration of blood is lowered and metabolic acidosis is compensated. On the other hand, during metabolic alkalosis respiration is depressed $\rightarrow$ less and less CO_2 is washed out $\rightarrow$ alveolar CO_2 tension increases $\rightarrow$ less CO_2 diffuses out of the blood $\rightarrow$ more CO_2 accumulates in the blood stream $\rightarrow$ increase in H^+ ion concentration of blood $\rightarrow$ combat alkalosis. Thus, blood reaction is maintained by adjustment of the pulmonary ventilation during metabolic acidosis and alkalosis. But, this is applicable to metabolic causes only. In respiratory acidosis and alkalosis this is not applicable, because here lungs or respiratory system does not act as compensatory organ. Because they them selves are the cause of respiratory acidosis and alkalosis.

The mode of action of H^+ ion in regulating respiration is same as CO_2. So, as the action of CO_2 and H^+ ion is same, it is thought that the action of CO_2 is not due to its own effect, but due to the associated change in H^+ ion concentration. There is controversy that whether it is the intracellular H^+ or CO_2 which regulates the activity of the respiratory centre. CO_2 is more easily diffusible through the cell membrane than H+ ion. So, it is probable that CO_2 diffuses inside the respiratory neurons which is carried here by blood from the different body tissues and inside the cell with the help of carbonic anhydrase this CO_2 is changed to H_2CO_3.

Then, intracellular H_2CO_3 is ionized and H^+ ions are liberated. Now the intracellular H^+ ions are supposed to be the sole factor, regulating the rhythmical activity of the respiratory centre.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \ D \ H^+ + HCO_3^-$$

Effect of Changes of Oxygen Tension

The effect of changes of O_2 tension on respiratory centre can be described under two headings: the effects of oxygen lack and the effect of oxygen excess.

Oxygen lack act on the respiratory centre reflexly through the carotid and aortic chemoreceptors and it is stimulating in effect. But, the direct effect of O_2 lack on the respiratory centre is depression. The effects of oxygen lack on the respiratory centre will vary according to the severity and the rapidity with which the lack is produced. If severe oxygen lack is produced very rapidly, then the results will be disastrous. Here, we will discuss only the effects of the gradual reduction of oxygen concentration or tension (perssure). It is seen that O_2 tension in the inspired air can be reduced to13% without any appreciable change of respiration and any discomfort on the part of the subject. But, with the further reduction (more than 13%) of O_2 concentration, respiration starts rising with a feeling of uneasiness. This shows that the respiratory apparatus is much less sensitive to oxygen lack (hypoxia) than to CO_2 excess (hypercapnoea). On the other hand, we can say that the CO_2 tension is the strongest stimulus in adjusting respiration. Oxygen lack or hypoxia will be stimulus, only when it is sufficiently reduced. In many circumstances, hypoxia and hypercapnoea exist together and they act synergistically. When they act separately in different circumstances, then the effect, including the blood pH, is also different. If the O_2 lack is gradual as in high altitude, it stimulates the breathing. Thus the alveolar and the arterial CO_2 tension fall and alkalosis is produced which got depressing effect on the respiration. But, the excess of alkalis are excreted by the kidney and alkalosis is combated.

It is previously stated that the reflex effect of hypoxia, acting through the carotid and aortic chemoreceptors, is to stimulate the respiratory centre. But the direct effect of it on respiratory centre is depression. However, as the reflex effect is dominant, so respiration is found to increase. 60% oxygen mixture can be

breathed continuously for any length of time without any distress. 75% O_2 mixture can be tolerated for several days, after which ill effects appear. Pure oxygen (100%) at 1 atmospheric pressure can be breathed for few hours without any ill effects. But when the oxygen pressure is raised to several atmospheres, the patient develops convulsions and die rapidly. Human beings develop bad effects in less than one hour (fainting, fall of BP etc), if they are exposed to oxygen at 4 atmospheric pressure.

Breath Holding

Respiration can be voluntarily inhibited for some time but eventually this voluntary control is overridden. The point at which the breathing can no longer be voluntarily inhibited is called the 'breaking point'. Breaking is due to the rise in arterial PCO_2 and the fall in PO_2. Individuals can hold their breath longer after removal of the carotid bodies. Breathing 100% O_2 before breath holding raises arterial PO_2 initially, so that the breaking point is delayed. The same is true for hyperventilation with room air, because CO_2 is blown off and arterial PCO_2 is lower at the start. Reflex and mechanical factors also appear to influence the breaking point. Psychological factors also play an important role and subjects can hold their breath longer when they are told that their performance is very good than when they are not.

METABOLIC FUNCTIONS OF LUNG

Except the gas exchange and chemical control of blood, the lungs have also many metabolic functions. For example, lung is the major site of inactivation of 5 HT, bradykinis and noradrenaline. Near about 30% of these compounds are metabolised during their single passage through the lungs. But, this is not applicable for adrenaline. This metabolic function of lungs is very selective. This is because, more than 90% of PGE1, PGE2, PGF2 are metabolised during single passage of these compounds through lungs. Whereas PGA1, PGA2 and prostacyclin are not metabolised by lungs.

There are different converting enzymes in the endothelial cells of the pulmonary capillary wall. They catalyses the angiotensin I (A-1) to angiotensin II (A-II) which is a very potent vasoconstrictor. Lungs also secrete certain substances like SRS-A (slow reacting substance of anaphylaxis) and histamine during anaphylaxis. Prostacyclin, a potent vasodilator and inhibitor of platelet aggregation are also secreted by lungs. Its generation at the lungs is sitmulated by A-II, hyperventilation and their peptides. Hyperventilation acts by streteching of the lung tissues.

3 Pulmonary Physiology Related to Anaesthesia

PULMONARY CIRCULATION

Physiological Anatomy

Lungs gets its blood supply from two sources: pulmonary arteries, arising from the pulmonary trunk and bronchial arteries, arising from the aorta. The pulmonary trunk arises from the right ventricle and is only 5 cm in length. It divides into right and left main branches (right and left pulmonary artery) that supply the right and left lungs, respectively. The wall of the pulmonary artery is thin, elastic and distensible. But, the cross section of it is like that of the aorta. Through the pulmonary trunk the total output of right ventricle which is same as that of the left ventricle passes to both the lungs. The right and left main branches of pulmonary trunk i.e. right and left pulmonary arteries then breaks up into multiple branches such as the smaller pulmonary arteries, arterioles and capillaries which form a very rich network around the alveoli.

The branches of pulmonary arteries are short and all the branches of it even the arterioles and capillaries have larger diameters than their systemic counterpart. Thus, the three properties of it such as wide diameter, thin wall and distensibility give the pulmonary arterial system a large compliance which is near about 7 ml/mm of Hg. This total compliance of the whole pulmonary arterial system is similar to that of the entire systemic arterial system, though the former is of much lower volume than the later. Thus, it allows the pulmonary arterial system to accommodate the total output of right ventricle which is similar to that of left ventricle or systemic circulation, though of low volume. Like the pulmonary arteries, pulmonary veins are also short and the main pulmonary veins are four in number. They drain into the left atrium.

Pulmonary arteries carry the nutrition and deoxygenated blood to the alveoli. Alternatively, bronchial arteries carry the oxygenated blood and nutrition to the bronchial tree and the supporting tissues of the lungs (parenchyma). Bronchial arteries arise from the aorta. Then, it breaks up into capillaries around the alveoli and the bronchial trees. These capillaries which formed from the bronchial artery around the alveoli ultimately join with the capillaries a round the alveoli which is formed from the pulmonary artery and subsequently drain into the pulmonary vein. On the otherhand, the capillaries formed around the bronchial tree from bronchial arteries drain into the systemic venous system through the azygous vein. Bronchial artery carries about 1 to 2% of cardiac output. So, the deoxygenated blood of the bronchial veins which drain in the oxygenated blood of pulmonary vein also carry 1 to 2% of CO. Thus, the left ventricular output is 1 to 2% greater than the right ventricle and contains 1 to 2% deoxygenated blood. This is called the intrapulmonary true shunt. Thus, the nutrition and O_2 supply to the pulmonary tissues comes from the deoxygenated blood through pulmonary artery and as well as from the oxygenated blood through the bronchial artery.

Total Blood Volume in Pulmonary Circulation

At any moment, both the lungs together contain approximately 450 to 500 ml of blood. It is about 9% of the total blood volume of the body. Of this total pulmonary blood volume, only about 70 ml of blood remains in the pulmonary capillary of each lung at any moment. The remainder is divided equally to fill the pulmonary arteries and veins. On the otherhand, the total blood flow in a minute through both the lungs together is about 4 to 5 litres. This is sum of the right ventricular output plus the blood flow through the bronchial arteries.

The total amount of blood volume, flowing through the pulmonary circulation varies under different physiological and pathological conditions. This variation of quantity of pulmonary blood flow may change from as little as half of the normal value to twice of it. During inspiration, the intrapleural and the intra alveolar pressure falls. Therefore, more blood flows into the lungs. This is also facilitated by the elongation of capillaries due to stretching and their dilatation due to negative pressure. Thus, during inspiration lungs hold 10% more of the total pulmonary blood volume. During expiration the reverse occurs. If high pressure builts up in the lungs during expiration, such as in coughing, playing trumpet, applying IPPV with high pressure, etc, then as much as 250 ml of blood can be expelled out from the pulmonary circulation to the systemic circulation. On the otherhand, during haemorrhage the loss of blood from the systemic circulation

can be compensated by the shift of blood from the lungs to the previous system.

If there is any pathology on the left side of the heart causing obstruction to the blood flow, then it also causes to dam up the huge amount of blood in the pulmonary circulation. Sometimes, it may increases up to 100%, causing large increase in pulmonary vascular pressure. But, as the volume of systemic circulatory bed is 9 times greater than that of the pulmonary circulation, so a small amount of shift of blood from the systemic circulation to pulmonary circulation has greater effect on it, with mild or no effect on previous one.

Pressure in the Pulmonary Circulatory System

The right side of the heart and the pulmonary circulatory system is a low pressure system than the left side of the heart and the systemic circulatory system. In human being, the systolic pressure of right ventricle averages to about 25 mm of Hg. So, subsequently the systolic pressure in the pulmonary artery is also about 25 mm of Hg. But, the diastolic pressure in the right ventricle suddenly comes down to 0 or 1 mm of Hg, whereas the diastolic pressure in pulmonary artery does not fall precipitously to this value. The diastolic pressure in PA falls slowly to around 8 mm of Hg as blood flows away from the pulmonary artery to the capillaries of the lungs. Thus, the mean pulmonary arterial pressure results in 15 mm of Hg, whereas the mean pressure in RV remains at 25 mm of Hg (Fig. 3.1).

The mean hydrostatic pressure in the pulmonary capillary is about 8 mm of Hg. Whereas, the mean hydrostatic pressure in the major pulmonary veins and the left atrium varies between as low as 1 mm of Hg to as high as 5 mm of Hg, according to the position of the body. So, the average pressure in pulmonary veins and LA is 2 mm of Hg in the recumbence position.

Clinically, it is not feasible to measure the pulmonary venous and LA pressure directly in the human being. This is because it is not possible to pass a catheter directly through the right side of the heart into the pulmonary veins and LA (i.e. left side of the heart) through pulmonary capillary. So, we try to measure the pressure of the left side of the heart indirectly with moderate accuracy by wedging a balloon situated at the tip of a catheter which is introduced into the pulmonary capillary (but actually this is not the pulmonary capillary, it is the smallest branch of the pulmonary artery) by passing it through the large systemic veins, RA, RV and PA. After wedging of balloon in the smallest branch of the pulmonary artery, the blood flow is stopped in this vessel and then the tip of the catheter directly communicates with the venous side of the pulmonary circulatory system and LA beyond the balloon. Thus, the tip of the catheter senses the pressure in this smallest branch of PA which is proportional to the pulmonary venous system and LA. This is called the pulmonary capillary wedge pressure (PCWP), which is clinically taken as the pulmonary venous and LA pressure and is about 5 mm of Hg. This PCWP is usually 2 to 3 mm of Hg greater than the actual LA pressure.

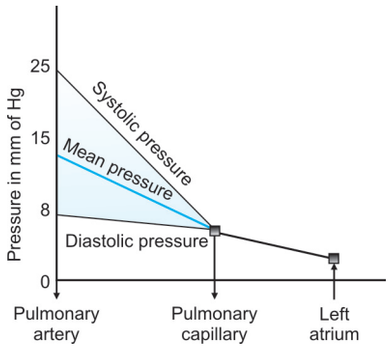


Fig. 3.1: The pressure of pulmonary artery, pulmonary capillary and left atrium

Distribution of Pulmonary Blood Flow

The distribution of pulmonary blood flow in the lungs is not uniform. It is different at different areas. This is because lung tries to accomplish adequate oxygenation of blood which is the most important function of it. So, to achieve this blood has to be more distributed to those areas of lungs where the alveoli are better ventilated. Thus, the distribution of pulmonary circulation is governed by the following mechanisms or principles. These principles are :

(i) Effect of alveolar O_2 tension on local pulmonary blood flow

This is a very unique feature of lungs. When the O_2 concentration in the alveoli decreases below 70% (or alveolar O_2 tension is < 70 mm of Hg), then the local blood vessels in the pulmonary tissue constrict and PVR increases locally. This causes shifting of blood to the other parts of lungs where it is well ventilated and try to compensate the hypoxia. This increase in PVR may be 6 fold in extreme hypoxia. This is opposite to the effect, found in the systemic circulation where hypoxia causes vasodilatation and increases circulation. But, the mechanism of pulmonary vasoconstriction in response to hypoxia is not clearly known. The probable theory is that the local pulmonary vasoconstriction is accomplished by some chemical substances secreted by the hypoxic epithelial cells.

(ii) Effect of hydrostatic pressure gradient on pulmonary blood flow

Another important factor which causes different amount of blood flow through the different areas of lungs is the hydrostatic pressure gradient. The hydrostatic pressure is nothing but the weight of blood column in a blood vessel. The difference between the highest (top) and the lowest point (bottom) of the lung is 30 cm in upright position. This height of lung causes difference in the hydrostatic pressure in pulmonary artery of the apex and the base of the lungs and is about 23 mm of Hg, however taking into account that pressure in pulmonary artery at the level of the heart is zero. This can be explained in

another way that in a standing person the pulmonary arterial pressure at the top of the lung is 15 mm of Hg less (–15 mm of Hg) than the pulmonary arterial pressure at the level of the heart and the pulmonary arterial pressure at the base of the lung is 8 mm of Hg higher (+8 mm of Hg) than that at the level of the heart. Thus, the difference of hydrostatic pressure in pulmonary artery at the apex and the base of lung is 8 – (–15) or 23 mm of Hg. This also can be calculated in another way that the pulmonary arterial pressure increases or decreases by about 1 cm of H_2O per centimeter of change of vertical distance of the lung. This change of hydrostatic pressure in pulmonary artery is due to the influence of gravity on the distribution of pulmonary circulation and is important because this is of a low pressure system.

(iii) Effect of cardiac output (CO) and exercise on pulmonary blood flow

Actually, the CO and exercise effect the total amount of pulmonary blood flow, but not the local distribution of it in lungs. Heavy exercise and increased CO increase the pulmonary blood flow near about five to seven times, but with very little increase in pulmonary arterial hydrostatic pressure. This increased blood flow in the lungs is accomplished by: increasing the number of opened capillaries and distending it. These two changes in pulmonary vasculature decrease the PVR. So, there is little increase in pulmonary arterial pressure (Fig. 3.2).

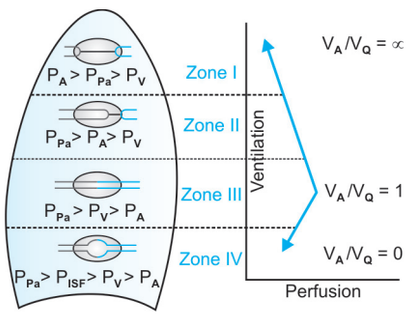


Fig. 3.2: The difference of distribution between ventilation and perfusion and VA / VQ ratio at different parts of the lung

(iv) Effect of alveolar pressure and pulmonary venous pressure on pulmonary blood flow

The Increased alveolar pressure and pulmonary venous pressure decreases the pulmonary blood flow. On the other hand, the distribution of pulmonary blood flow in the lungs not only depends on the pulmonary alveolar pressure and pulmonary venous pressure, but also on the interaction between the pulmonary arterial pressure (P_{Pa}), alveolar pressure (P_A) and pulmonary venous pressure (P_{Pv}). Thus, lungs can be divided into three zones:

Zone I

In this region $P_A > P_{Pa} > P_{Pv}$ and this region is situated at the apex of the lungs. Thus, at this area as the alveolar pressure outside the vessels is greater than the capillary pressure, so no blood flow will occur through the wall of these alveoli and no gaseous exchange will take place. Hence, this region (zone 1) acts as alveolar dead space. Normally, no or little area of zone 1 exists. But, it greatly exists or increases in oligemic shock (where P_{Pa} is further reduced) or IPPV (where PA is further increased).

Zone II

It exists below the zone 1 and here $P_{Pa} > P_A > P_{Pv}$. So, in this region blood starts to flow through pulmonary capillary. Since P_{Pa} gradually increases downwards along this region of the lung, and P_A remains constant, so the mean driving pressure (P_{Pa} - P_A) for blood flow increases linearly downward in this area, causing more and more blood to flow from upper to lower limit of this zone. On the otherhand, as P_A, P_{Pa}, P_{Pv} changes continuously with respiration and cardiac cycles, so at a given time a particular point in zone 2 may shift to either zone 1 or zone 3 making it (zone 2) a dynamic area.

Zone III

It lies in lower portion of the lung below the zone 2, where $P_{Pa} > P_{Pv} > P_A$. So, here the blood flow depends on the pulmonary arteriovenous pressure difference (P_{Pa} - P_{Pv}), but not on the P_{Pa} - P_A difference. As in this region the pulmonary vascular pressure (P_{Pa} - P_{Pv}) always exceeds the alveolar pressure (P_A), so the vessels remain permanently open and blood flows continuously. If we go downwards along the zone 3 then we will see that gravity will cause the increase in both the P_{Pa} and P_{Pv} but at the same rate, so that the driving pressure (P_{Pa} - P_{Pv}) remains unchanged. On the otherhand, the pressure outside the vessels i.e. pleural pressure (P_{Pl}) increases from above downwards, but at a rate lesser than that of P_{Pa} and P_{Pv}. So, the transpulmonary distending pressure (i.e P_{Pa} - P_{Pl} and P_{Pv} - P_{Pl}) increases gradually downwards along the zone 3. Hence, the radii of vessels increase, vascular resistance decreases and blood flow further increases from upper to lower limit of this zone.

Zone IV

Normally, a small amount of fluid flows into the pulmonary interstitial space from pulmonary intravascular space and is cleared immediately and adequately by the lymphatics. But when the pulmonary vascular pressure is very high such as in volume overload, pulmonary hypertension, pulmonary embolism, mitral stenosis etc, then the excessive amount of fluid transduates in the interstitial compartment which cannot be cleared by lymphatics. Thus, the expansion of the pulmonary interstitial space by fluid causes increased pulmonary interstitial pressure (P_{ISF}) and exceeds P_{Pv}. Thus, at the base of the lung a zone is created where $P_{Pa} > P_{ISF} > P_{Pv} > P_A$. This is called zone 4. In this zone the flow of blood through pulmonary capillaries is governed by the $P_{Pa} - P_{ISF}$ value, which is less than the $P_{Pa} - P_{Pv}$ value. Therefore, in zone 4 blood flow is less than zone 3. Again as P_{ISF} increase in zone 4, it causes vascular compression and increased vascular resistance which further decreases the blood flow in this region.

Throughout the whole lung when P_{Pa} and P_{Pv} increases gradually, then three things happen:

i. If both increases from low to moderate range, then recruitment of more alveoli is the principle. So zone 1 will become zone 2, zone 2 will become zone 3 and so on.
ii. If P_{Pa} and P_{Pv} increases from moderate to high range, then distension of the vessels is the principle. So, vessels of zone 3 dilates and blood flow increases. Thus the area of zone 3 increases.
iii. If P_{Pa} and P_{Pv} increases from high to very high ranges, then the zone 3 vessels will become so dilated that they leak fluid and transudation occurs. Thus, zone 3 vessels converted to zone 4 vessels.

Dynamics of Pulmonary Capillary Circulation

After entering into the lung parenchyma pulmonary arteries are ultimately divided and subdivided into pulmonary capillaries which lined the alveolar walls. So, finally the alveolar walls are covered by so many capillaries that they lie side by side touching with one another, as if the alveolar wall is bathed by a sheet of blood flow. Therefore, the alveolar gas is separated from the capillary blood by a number of anatomical layers. From capillary side these layers are: capillary endothelium, basement membrane of this endothelium, interstitial space (IS), epithelial basement membrane and alveolar epithelium (type I pneumocyte). The interstitial space (IS) lying between the basement membrane of endothelial (capillary) and epithelial (alveolus) cell layers contains some connective tissues which make the lung parenchyma. These connective tissues are made of elastic fibres, tissue fibrils, fibroblasts and macrophages, and is continuous with the connective tissues around the airways and blood vessels of the lungs. Thus, the perialveolar or perivascular space is continuous with the interstitial tissues space which surrounds the terminal bronchioles, other airways and its associated vessels, because both the spaces contain the same connective tissues of the lungs. Lymphatics start in the interstitial space at the level of terminal bronchiole and flow upwards towards the bronchi and trachea. But it is absent beyond it towards the alveoli (Fig. 3.3).

The endothelial and the epithelial cells are not tightly attached with one another. There are multiple holes at their (cells) junctions which provide potential path for the fluid to move from capillaries to IS and finally from IS to alveoli and vice versa. The holes between the endothelial cells of pulmonary capillary are relatively larger than that of the epithelial cells of alveoli and is therefore termed as loose. On the otherhand, the holes between the epithelial cells are smaller and therefore is termed as tight. The pulmonary capillary permeability (K) is thus the expression of the sizes of these holes and its subsequent function.

During the development of lungs, the bronchi and the arteries as a tissue of bud invaginate into the pleural cavity at the level of hilum with the connective tissues sheath (lung parenchyma) around them which ends at the level of the terminal bronchiole and become continuous with the connective tissues of the IS between the alveolar epithelium and capillary endothelium. Thus, the potential space around the bronchi and arteries containing the connective tissues is continuous with the IS between the alveolar epithelium and capillary endothelium, containing the same connective tissues. The pressure in this interstitial space is negative and progressively increases from distal to proximal i.e from alveoli to bronchi. This negative interstitial pressure in the connective tissues surrounding the vessels, bronchi and bronchioles exerts a radial outward force of traction which tends to hold them open and increases their diameter.

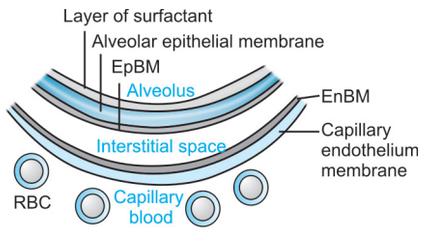


Fig. 3.3: This is a schematic diagram of structures intervening between the alveolar air and capillary blood.
EpBM = Epithelial basement membrane,
EnBM = Endothelial basement membrane.

When the CO is normal, the time taken by the blood to pass through pulmonary capillaries is 0·8 sec. But when the heart rate and CO increases, then this capillary circulation time is shortened to 0.3 sec. But this shortening of time has no pronounced effect on the gaseous exchange. This is because more and more capillaries are opened up with increased CO and within only a fraction of a second blood can take up O_2 and excretes its CO_2.

The dynamics of pulmonary capillary circulation and the exchange of gas and fluid between the pulmonary capillaries and alveoli are qualitatively same as that of the systemic capillary circulaion. But, they differ only quantitatively.

The difference between the dynamics of pulmonary and systemic capillary circulation are:

i. The mean pulmonary capillary hydrostatic pressure is 7 mm of Hg (the mean left atrial pressure is 2 mm of Hg and the mean pulmonary arterial pressure is 15 mm of Hg), whereas the mean systemic capillary hydrostatic pressure is 17 mm of Hg.
ii. The interstitial fluid pressure (or hydrostatic pressure in IS) in the lungs is negative and is about −8 mm of Hg. Whereas the interstitial fluid pressure in the peripheral tissues is not so negative, rather positive.
iii. The colloidal oncotic pressure of pulmonary capillary due to the presence of plasma protein is about 28 mm of Hg and this is equal to that of systemic capillary. The pulmonary capillaries are loose. So, protein molecules

continuously come out in the IS from capillary. Therefore, a colloidal oncotic pressure is formed in this space which is about 14 mm of Hg. This is approximately ½ of the colloidal oncotic pressure of interstital space of peripheral tissues.

Thus, the net forces governing the transcapillary fluid movement in the interstitial space of lung tissue can be calculated as follows. This net force (F) is equal to the difference between the pulmonary capillary hydrostatic pressure (P_{in}) and the hydrostatic pressure in the IS (P_{out}) and between the capillary colloidal oncotic pressure (O_{in}) and the interstitial colloidal oncotic pressure (O_{out}). P_{in} pushed the fluid out of the capillary in the IS, but P_{out} opposes this force. On the otherhand, O_{out} draws the fluid in the capillary from IS, but O_{out} opposes this force.

So, $F = K \{(P_{in} - P_{out}) - \sigma(O_{in} - O_{out})\}$; K is the filtration coefficient and is related to the total capillary surface area per mass of tissues, and σ is the permeability coefficient of capillary endothelium to albumin. when the value of σ is one, it indicates endothelium is completely impermeable to albumin and zero value of σ indicates free passage of albumin and other particles. The pulmonary endothelium is partially permeable to albumin. So the interstitial albumin concentration is one half of that of plasma. Therefore, the O_{out} must be about 14 mm of Hg (one half of that of plasma).

Therefore, $F = \{7 - (-8)\} - (28-14) = 15 - 14 = +1$

This net forces (F) which governed the movement of fluid from pulmonary capillary to IS and subsequently in the alveoli can also be calculated from another angle.

i. The forces which tries to move or push the fluid from pulmonary capillary into IS are :
   Capillary hydrostatic pressure = 7 mm of Hg
   IS oncotic pressure = 14 mm of Hg
   Negative IS hydrostatic pressure = 8 mm of Hg
   So, the total outward force which pushes the fluid from capillary to IS = 7 + 14 + 8 = 29 mm of Hg
ii. The forces which try to draw the fluid from IS to capillary [i.e the opposite force of (i)] are :
   Plasma colloidal oncotic pressure = 28 mm of Hg
   Thus, the total outward filtration pressure from capillary to IS is :

Total outward driving force (29 mm of Hg) − Total inward driving force (28 mm of Hg) = 1 mm of Hg.

Therefore, the net outward driving force (F) = + 1 mm of Hg

So, this slight positive outward filtration pressure continuously causes the movement of small amount of fluid from the pulmonary capillaries into the IS and subsequently from IS to alveoli. Then, part of this fluid evaporate through the alveoli and the remaining part is pumped back into the circulation through the pulmonary lymphatic system. This also explains why the alveolar surface remains always dry and there is constant lymphatic flow which is about approximately 500 ml/day (10 to 20 ml/hour). Again, when the extra fluid appears in the alveoli from exogenous source then it will simply be sucked into the IS of lung, mechanically through the openings between the alveolar epithelial cells. This excess fluid is then further carried out through the pulmonary lymphatics into the circulation. Thus, under normal situations, the alveoli are kept constantly dry except that a small amount of fluid which sips from the epithelial cells on their alveolar surface to keep them moist.

Pulmonary Oedema

The pulmonary oedema may be regarded as an exaggeration of this pulmonary capillary dynamics. It occurs when the transudation of fluid is more than its reabsorption capacity through the lymph and gradually accumulates in the IS i.e when the safety and the reserve factors which are described later fail. The alveolar epithelial membrane is usually impermeable to albumin, but permeable to water and gases. Thus, when the fluid accumulates in IS, then it also moves from IS to the inside of the alveoli and produces the full picture of pulmonary oedema. So, the mechanism of formation of pulmonary oedema is same as that of the formation of systemic oedema, elsewhere in the body. The most commonly factors which play the important roles in the formation of pulmonary oedema are:

(i) Increased pulmonary capillary hydrostatic pressure

It may be due to any cause such as pulmonary hypertension, LVF, fluid overload, disease of mitral valve, etc. All these factors will cause the rapid increase in pulmonary venous pressure and subsequently the pulmonary capillary hydrostatic pressure, producing blood of IS and alveoli with fluid.

When the pulmonary artery pressure rises above 30 mm of Hg, then it is called the pulmonary hypertension. It again can be due to four mechanisms.

(a) Increase in pulmonary blood flow

It occurs when the left (L) to right (R) shunt is present e.g VSD, ASD etc, In these conditions blood flow through the lungs increases 3 times more than that of the left ventricular output. If these states persist for few years, then pulmonary vascular resistance begins to rise due to some structural changes in pulmonary vessels. Thus, the pulmonary artery pressure rises further. Eventually, if the pressure on the right side of the heart exceed than that on the left side, then the left to right shunt is reversed and subsequently the right to left shunt with central cyanosis appears.

(b) Increase in left atrial pressure

It is due to the aortic or mitral valve disease or left ventricular failure which increases the left atrial pressure with dilatation and/or hypertrophy. Thus, subsequently the

back pressure from left atrium causes the pulmonary arterial hypertension.

(c) Rise in pulmonary vascular resistance

It occurs in massive pulmonary embolism and in some lung diseases (such as chronic bronchitis, COPD, emphysema, etc). In chronic lung diseases pulmonary hypertension is due to the combination of chronic hypoxia and obliteration of pulmonary vascular bed by disease process itself.

(d) Over transfusion

Excessive IV transfusion of any fluid may lead to increased pulmonary capillary hydrostatic pressure and pulmonary oedema.

(ii) Increased pulmonary capillary permeability

It is due to some chemical injury of the pulmonary capillary membrane, caused by bacterial endotoxin (septicaemia), breathing toxic gases, ARDS, ALI etc. In each of these cases, there is rapid leakage of both the plasma protein and fluid out of the capillaries into both the IS and alveoli. This further increases O_{out} and subsequently the effective or net filtration pressure (F). Thus, a vicious cycle sets up to produce pulmonary oedema.

(iii) Dimished pulmonary capillary colloidal osmotic pressure

It is very unlikely that it can be the cause of pulmonary oedema in clinical situations, but can intensify the process, initiated by other causes.

(iv) Pulmonary lymphatic obstruction

It is unlikely to be the primary cause of pulmonary oedema, but might be an important secondary factor.

(v) Extremely negative pleural pressure

Normally, the negative intrapleural pressure is subsequently transmitted to the peribronchial, perivascular and IS space. So, this negative (or subatmospheric) IS hydrostatic pressure (P_{out}) promotes the slow loss of fluid into this space across the capillary endothelial holes by suction. But if due to any cause, sudden extremely negative intrapleural and subsequently sudden excessive negative IS hydrostatic pressure is developed, then there is excessive accumulation fluid in IS across the endothelium (exceeding absorption by lymph) and will cause pulmonary oedema. Causes of excessive negative intrapleural pressure are: vigorous spontaneous respiration against an obstructed airway. This may be due to upper airway mass, severe laryngospasm, severe inflammation and oedema of the upper airway, vocal cord paralysis, strangulation, vigorous pleural suctioning (e.g thoracocentesis), etc.

(vi) Neurogenic pulmonary oedema

It occurs in patients with head injury or other intracranial pathology. It is thought to be due to intense centrally mediated pulmonary vasoconstriction by sympathetic stimulation due to CNS injury. Hypoxia has no role as an aetiological factor in this type of pulmonary oedema and administration of O_2 does not help to restore the permeability of this type of injured and leaky capillary membrane.

Thus, the causes of pulmonary oedema are divided under two broad headings: (i) haemodynamic or cardiogenic pulmonary oedema and (ii) noncardiogenic pulmonary oedema. In the former, there is increase in the pulmonary capillary hydrostatic pressure due to cardiac problems causing increase in net filtration pressure across the capillary membrane. But, in the later there is increase in permeability of the capillary membrane without any increase in pulmonary hydrostatic pressure due to cardiogenic causes. The difference between these two etiologies can often be diagnosed by measuring the pulmonary artery occlusion pressure (PAOP) and the protein content of oedema fluid. If the PAOP is >18 mm of Hg, then it indicates that increased hydrostatic pressure is the cause of pulmonary oedema and vice versa. And if the protein content in the fluid of pulmonary oedema is high, then increased permeability without any increase in the hydrostatic pressrue of pulmonary capillary is the cause of pulmonary oedema.

The normal value of left atrial pressure is 1 to 5 mm of Hg. In healthy individual, it never rises above +6 mm of Hg, even during heavy exercise. This small change in left atrial pressure, even during strenous exercise has virtually no effect on pulmonary circulation. This is because, it merely expands the existing capillaries and opens up more and more capillaries, so that the blood flows easily and causes better oxygenation without increasing the hydrostatic pressure. But, when the left heart fails, then blood begins to accumulate in the left atrium. As a result, the left atrial pressure may rise from its normal value to 30 to 40 mm of Hg. The initial rise of pressure up to 7 mm of Hg in left atrium has very little effect on pulmonary circulation. But, when this pressure rises above 7 or 8 mm of Hg, then there is equal and parallel increase in the pulmonary arterial pressure. When the left atrial pressure rises above 30 mm of Hg, then pulmonary oedema is likely to develop.

Pulmonary Reserve and Safety Factors

There are some pulmonary reserve and safety factors which prevents the formation of pulmonary oedema, when there is moderate, but not severe change in pulmonary capillary hydrostatic pressure (PCHP) occurs. It is found experimentally that PCHP must rise to a value which is at least equal to the colloidal oncotic pressure of plasma, before significant pulmonary oedema occurs. In human being the normal plasma colloid oncotic pressure is 28 mm of Hg. Therefore, one can expect that PCHP must increases from the normal level of 7 mm of Hg to more than 28 mm

of Hg to cause pulmonary oedema. This is called the reserve factor for the development of pulmonary oedema. Thus, the reserve factor against the development of pulmonary oedema is 28 − 7 = 21 mm of Hg increase of PCHP.

On the other hand, if the PCHP gradually elevated over prolonged period, at least > 2 weeks, then the lungs become more resistant to pulmonary oedema due to starting of compensatory mechanism. This is because the lymph vessels increase their capability of carrying more fluid away from the IS as much as 10 fold. Therefore, in chronic MS, PCHP is frequently measured to 40 to 50 mm of Hg without any development of pulmonary oedema. This is the maximum safety factor of pulmonary oedema.

If the PCHP rises rapidly slightly above the safety factors level, then the pulmonary oedema ensures within an hour. The rapidity of development of pulmonary oedema depends on the speed of increase of PCHP above the safety level (Table 3.1).

Stages of pulmonary oedema

Pulmonary oedema is regarded as an exaggeration of the pulmonary capillary dynamics of fluid exchange which continuously operates under the normal physiological condition within reserve. So, pulmonary oedema develops in stages when the reserve is gradually burnt out. These stages are:

Table 3.1: Mechanism of hypoxia

A.	Increased alveolar-arterial PO_2 difference
	a. Right to left shunt
	b. Increased areas of low V_a / V_a ratio
	c. Low mixed venous PO_2 ↓CO ↑O_2 consumption iHb concentration
B.	Low alveolar PO_2
	a. Low inspired O_2 tension FiO_2
	b. High altitude
	c. Alveolar hypoventilation
	d. Increased O_2 consumption
	e. Third gas effect (diffusion hypoxia)

Stage I

In this first phase, excessive accumulation of fluid in the IS is not totally countered or compensated by increased lymph flow which may go up to 10 times. Thus, fluid gradually accumulate in IS and lungs become stiff. So, at this initial phase, patient only becomes tachypnoeic due to gradual decrease of the pulmonary compliance. Thus, this phase is only called as the interstitial pulmonary oedema and is only diagnosed by chest X-ray which shows the increased interstitial markings and peribronchial cuffing.

Stage II

In this phase, the fluid begins to reach and fill the alveoli in addition to IS, but being only confined to the angles between the adjacent septa.

Stage III

In this phase, the flooding of alveoli with the capillary fluid occurs and many alveoli are compeletly filled with fluid containing no air. Initially, this is most prominent in the dependent portion of the lungs and later spreads through out the whole lungs. So, this phase is called the alveolar flooding phase. Blood flows through this wall of fluid filled alveoli without any gas exchange and causes large increase in the intrapulmonary shunt (these are not true shunt). So, hypocapnia (due to hyperventlation of the non affected part of the lung) and hypoxia (due to shunting of blood) is the characteristic of this stage.

Stage IV

Finally the flooding of alveoli with oedema fluid is of sufficient magnitude, spreading all over the lungs and spills over into the airway as froth. This is frequently pink in colour, because of the rupture of many capillaries and increased diapedesis of erythrocytes. In this stage gas exchange is severely compromised. So, progressive hypercapnia and severe hypoxaemia will follow due to the both airway obstruction and massive intrapulmonary shunting.

ALVEOLAR VENTILATION (V_A)

Alveolar ventilation is the pulmonary factor which control the oxygenation of blood and excretion of CO_2 through lungs. It is a part of minute volume and is so calculated as L/min. We know that the minute volume is the total inspired volume of gas in one minute. So,

Minute volume = Tidal volume (V_T) × Respiratory rate (f) (Table 3.2).

All the inspired gases do not reach the alveoli and does not take part in the process of gaseous echange. Some remain in the airway and later exhaled with the alveolar gas. So, that part of the ventilation which remains in the airway without taking part in gaseous exchange is known as the dead space (V_D) ventilation. Therefore, the alveolar ventilation is defined as the volume of inspired gases in one minute which only take part in gaseous exchange. Thus,

Alveolar ventilation (V_A) = {Tidal volume (V_T) − Dead space (V_D)} × Respiratory rate (f)

or $V_A = (V_T - V_D) \times f$

The normal value of alveolar ventilation is 3·5 to 4·5 L/minute or 2 to 2·4 L/minute/metre^2 of body surface area in adult. From the above equation we can easily say that alveolar ventilation depends on three factors such as tidal volume, dead space and respiratory rate. When the tidal volume decreases or dead space increases or

Table 3.2: Effect of variations of respiratory rate and depth (tidal volume) on alveolar ventilation

	A	*B*
Tidal volume (ml)	400	200
Dead space (ml)	150	150
Respiratory rate (per min)	20	40
Minute volume (in litre)	8	8
Alveolar ventilation (in litre)	(400-150) × 20 = 5	(200-150) × 40 = 2

respiratory rate decreases, then the alveolar ventilation dramatically falls. But fortunately in healthy adult, the dead space decreases with decrease of tidal volume, so that the effect on the alveolar ventilation is lessened. Hyperventilation is not a very effective way of increasing the alveolar PO_2 (or preventing hypoxia) as washing out the CO_2 (or preventing hypercarbia). But, hypoventilation is potentially a disastrous cause of hypoxia than hypercarbia. On the otherhand a rise of small alveolar CO_2 concentration due to hypo ventilation will further produce a fall in alveolar O_2 tension, unless extra O_2 is added to the inspired air. So, in a patient under anaesthesia with spontaneous respiration, any reduction of V_A due to any changes in respiratory rate, tidal volume, and dead space, or any anaesthesia induced changes such as V_D/V_T ratio, compliance, FRC/CC relationship, work of breathing, etc, cause arterial hypoxaemia. Thus, it is always advisable to administer (Fig. 3.4) a minimum 33% of O_2, with all the anaesthetic gas mixtures to prevent hypoxia during anaesthesia. We know that V_A is not distributed evenly through out the whole lungs. The right lung

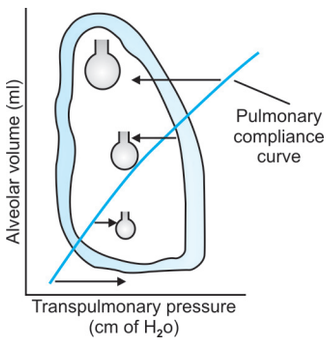


Fig. 3.4: As the intrapleural pressure relatively increases from top to the bottom of lung, so the alveolar volume decreases from apex to base of the lung. The calibre of air passages also decreases from apex to the base of the lung. The red line represents the transpulmonary pressure and alveolar volume curve. The less compliant, large alveoli in apex of the lung is situated at the flat upper portion of the curve. Whereas the more compliant, small alveoli in the base of the lung is situated at the steep lower portion of the curve and receive the largest share of tidal volume

is better ventilated than the left and the lower dependent area gets more ventilation than the upper apical area. This is due to the gravity induced gradient of transpulmonary distending pressure which decreases from above downwards allowing the more potentiality of distension of alveoli if necessary which are now less distended and smaller in lower dependent area of lung.

Truly, the lung is a viscoelastic structure. Within the visceral plural sac it is just like a plastic bag, containing gel. When it is not within the chest wall, gravity cause the bag to bulge outward at the bottom and inward at the top. But within the chest wall the present shape of the lung is maintained by relatively more negative intrapleural pressure at the top than the bottom of the pleural cavity. So, the intra pleural pressure (P_{Pl}) at the bottom is relatively more positive (i.e. less negative) than the top. The intrapleural pressure increases from top to bottom at the rate of 0·25 cm of H_2O / cm. The height of an upright lung is 30 cm. Thus the pleural pressure (P_{Pl}) increases by 30 cm × 0·25 cm of H_2O / cm = 7·5 cm of H_2O from top to the bottom of the lung. But intraalveolar pressure (P_A) is same throughout the whole lung. Thus the transpulmonary distending pressure ($P_A - P_{Pl}$) is greater at the top than the bottom.

This difference in transpulmonary pressure which helps to distend the alveoli have placed the different sized alveoli of different areas of lungs at different points on the pulmonary compliance curve. So, alveoli in the upper part of the lung remain maximally inflated and this is due to the higher trans pulmonary distending pressure at the top. Thus, they are relatively less compliant and undergo little further expansion during inspiration. On the otherhand, the alveoli at the base of the lung remain little inflated due to the lower transpulmonary distending pressure. So, they are more compliant and later may undergo more expansion during inspiration. The alveolar ventilation is also affected by the airway resistance and inspiratory time. A short inspiratory time and increased resistance will prevent the alveoli from reaching the expected change in volume during inspiration. This is described further below.

Time Constant and Alveolar Ventilation

The inflation of alveoli or alveolar ventilation depends on the time constant (T). It is defined as the time which the alveoli would, take to reach its final volume, if adequate gas flow rate is maintained throughout the inflation. The time constant again depends on the resistance and the compliance of the lung. This is calculated as:

Time constant = Resistance × Compliance

In normal lung, the compliance is 0.1 L/cm of H_2O and resistance is 2 cm H_2O/L/S. So, the time constant is 0.2 second. Increase in resistance and decrease in compliance give rise to longer time constant. It means alveoli will take a long time for a given volume of inflation. In such condition short inspiratory time during tachypnoea will result in poor ventilation of those zones of lung which have long time constant due to the increase in resistance and decrease in compliance. As a result there will be increase in V_A/Q mismatch.

Normally, the resistance and compliance is not uniform through out the whole lung. The compliance of normal functioning individual alveoli differs from top of the lung to its bottom. Again, normally the resistance of individual airway differs widely depending on their length and its caliber. Therefore, a variety of time constant for inflation of alveoli will exist throughout the whole lung. Thus, regional variations in resistance and compliance not only impair the alveolar filling, but also asynchrony. So, during inspiration as some alveoli may continue to fill, while others are empty.

VENTILATION (V_A) / PERFUSION (Q) RATIO OR V_A/Q RATIO

V_A/Q ratio express the amount of ventilation against the amount of perfusion at any

given regions of lungs at any certain time. Therefore, the lungs are usually divided into 4 zones in reference to V_A/Q ratio, as the ventilation and perfusion is not the same at different areas of the lungs. We know from the previous discussions regarding the distribution of perfusion and ventilation that both of them increase linearly from above downwards in normal upright position of lung, but not in same proportion. Perfusion increases more rapidly than ventilation while the distance is going down from top to the bottom of lungs. Thus, the V_A/Q ratio also decreases gradually from top to the bottom of the lungs. Normally the alveolar ventilation is approximately 4 L/min and pulmonary perfusion is about 5 L/min. So, the overall on average V_A/Q ratio of lung is about 0.8. But, it can range from zero (no ventilation, only perfusion at the bottom) to infinity (only ventilation, no perfusion at the top where ventilation is going wasted). Thus, the zero V_A/Q ratio refers to the true pulmonary shunt and infinity V_A/Q ratio refers to the alveolar dead space. Usually, in a normal healthy lung V_A/Q ratio ranges between 3·3 and 0·63 with major area remaining close to the value of 1. Apex of the lung is less perfused in relation to their ventilation ($V_A/Q > 1$ and near about 3·3), whereas the base of the lung is somewhat over perfused in relation to their ventilation ($V_A/Q < 1$ and near about 0·63). Thus, the bottom of the lungs is relatively hypoxic and hypercarbic compared with the top of the lung, where ventilation is going wasted. (Fig. 3.5).

The importance of V_A/Q ratio is that it tells us the efficiency with which the lung unit works, i.e. absorb O_2 and eliminate CO_2. Low V_A/Q ratio of one part of lung is compensated by the high V_A/Q ratio of another part of lung. But practically this does not happen, because less oxygenation of one part of a lung is not compensated by better oxygenation of other part of lung like excretion of CO_2. This is explained in further details below. Thus an inequal V_A/Q ratio have different effect on the arterial

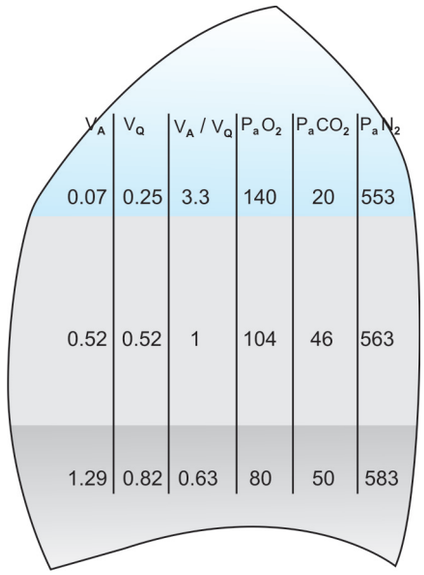


Fig. 3.5: The regional difference of alveolar ventilation (V_A), perfusion (V_Q) and V_A/V_Q ratio. This figure also compares the top with the bottom of the lungs which has low ventilation (iV_a), high perfusion (^hVq) and low V_a/V_q ratio. This bottom area is relatively more hypxoic and more hypercarbic

O_2 and CO_2 tension (P_aO_2 and P_aCO_2). The blood passing through the underventilated alveoli tends to retain CO_2 and can not take up adequate O_2. So, blood passing through this area is hypoxic and hypercarbic. On the otherhand, the blood passing through the over ventilated alveoli, at the top of the lung gives up excess CO_2 as a compensatory of under ventilated alveoli, but cannot take up increased amount of O_2 as a compensatory for under ventilated alveoli. This is due to flatness of the upper part of O_2 dissociation curve and less solubility of O_2 than CO_2 in blood (CO_2 is 20 times more soluble than O_2). Thus, due to uneven V_A/Q ratio the gradient between P_ACO_2 and P_aCO_2 remains small (so, the P_ACO_2 or $ETCO_2$ can be considered as equivalent to P_aCO_2), but the gradient between P_AO_2 and P_aO_2 remains high.

The concept of alveoli of zero and infinity V_A/Q ratio with the concept of physiological shunt and physiological dead space.

The alveoli of zero V_A/Q ratio means, there is no ventilation, but presence of adequate perfusion. So, the air which is already present within this type of alveoli will come in equilibrium with the PO_2 and PCO_2 of venous blood without getting further O_2 from air and excreting CO_2. Normally the PO_2 and PCO_2 of venous blood is 40 and 46 mm of Hg respectively. Therefore, the PO_2 and PCO_2 of air of these type of alveoli with zero V_A/Q ratio will be 40 and 46 mm of Hg, respectively.

The alveoli of infinity V_A/Q ratio means, there is only presence of ventilation but no perfusion. Therefore, the PO_2 and PCO_2 of these alveolar air becomes equal to the humidified inspired air, because inspired air loses no O_2 and gains no CO_2. Normally, the PO_2 and PCO_2 of humidified inspired air is 149 and 0 mm of Hg, respectively. So, the PO_2 and PCO_2 of these type of alveolar air will be 149 and 0 mm of Hg, respectively.

Now, when there is optimal alveolar ventilation and perfusion, then there is optimal exchange of O_2 and CO_2 through the alveolar membrane. Therefore, the alveolar air PO_2 remains at 104 mm of Hg which lies between that of the inspired air (149 mm of Hg) and that of the venous blood (40 mm of Hg). Similarly, the alveolar air PCO_2 remains at 40 mm of Hg which lies between 46 mm of Hg in venous blood and 0 mm of Hg in inspired air (Fig. 3.6).

So, under normal healthy condition the average alveolar air PO_2 and PCO_2 is 104 and 40 mm of Hg, respectively.

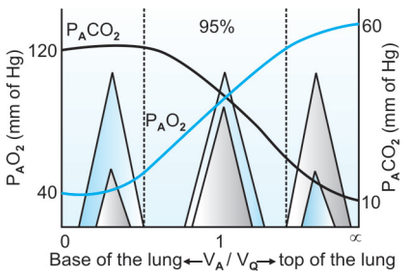


Fig. 3.6: Distribution of V_A/V_a ratio at different parts of lungs. Blue triangle is the perfusion and red triangle is the ventilation. 95% of the lung volume has matched ventilation and perfusion ratio

When the V_A/Q ratio is below normal, then the blood flowing through these alveolar capillaries is not properly oxygenated. Therefore, a portion of venous blood that does not undergo any gasseous exchange through the alveolar capillaries due to less ventilation returns back to systemic circulation. This is called the shunted blood and the total quantity of shunted blood per minute in normal conditions is called the physiological shunt. The greater the physiological shunt, the greater the amount of blood fails to be oxygenated, while passing through the lungs. This physiological shunt is measured by analyzing the concentration of O_2 in both the mixed venous blood and arterial blood and calculating the cardiac output. From these values, the physiological shunt is obtained by the formula below:

$$\frac{\text{Physiological shunt}}{\text{Cardiac output}} = \frac{(\text{Normal concentration of } O_2 \text{ in arterial blood}) - (\text{Measured concentration } O_2 \text{ in arterial blood})}{(\text{Normal concentration of } O_2 \text{ in arterial blood}) - (\text{Measured concentration } O_2 \text{ in mixed venous blood})}$$

This physiological shunt is also called the venous admixture. The venous admixture in normal individuals is typically less than 5%. This physiological shunt or venous admixture is usually expressed as a fraction of total cardiac output and is calculated clinically by obtaining a sample of mixed venous blood from pulmonary artery catheter and by arterial blood gas measurement (Fig. 3.7).

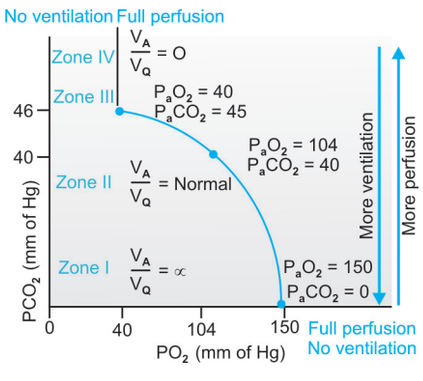


Fig. 3.7: V_a/V_q curve

When the V_A/Q ratio is above normal, then there is far more available O_2 in alveoli than can be transported away by the flowing blood. Thus some of the alveolar ventilation is wasted. When this wasted alveolar ventilation is summed up with the wasted ventilation of the anatomical dead space, then we will get the physiological dead space. This physiological dead space can be measured by analyzing the tidal volume and PO_2 and PCO_2 in the arterial blood and expired air, respectively. From these values, physiological dead space is obtained by the formula below:

$$\frac{\text{Physiological dead space (VD)}}{\text{Tidal volume (VT)}} = \frac{(\text{Arterial } CO_2 \text{ tension } (P_aCO_2)) - (CO_2 \text{ tension in expired air } (P_ECO_2))}{(\text{Arterial } CO_2 \text{ tension } (PaCO_2))}$$

This above equation is also called the Bohr equation. In this equation we can place P_ACO_2 instead of P_aCO_2 because in normal healthy adult P_ACO_2 is usually equivalent to P_aCO_2. In chronic obstructive lung disease, there is both the features of obstruction of small air ways and emphysema. The alveoli beyond the obstruction are not ventilated with uncompromised perfusion. So, the V_A/Q ratio approaches to zero. On the other hand, in emphysematous part of the lung, most of the ventilation is wasted because of inadequate blood flow. So, the V_A/Q ratio approaches to infinity. Thus in COPD, some area of lungs show excessive physiologic shunt and some areas show excessive physiologic dead space. So, both of these conditions produce severe V_A/Q mismatch and seriously impair the effectiveness of lung's function.

ALVEOLAR OXYGEN TENSION, PULMONARY END CAPILLARY OXYGEN TENSION, ARTERIAL OXYGEN TENSION, MIXED VENOUS OXYGEN TENSION

Alveolar oxygen tension (P_AO_2) (Table 3.3)

When a gas is kept in a container, it gives pressure on the surface of its walls. Thus, the pressure or tension of a gas in the container is due to the multiple impacts or bombardment of its moving molecules against the surface of the container. In case of a mixture of gases, the total pressure exerted by this gas mixture on container's wall is the summed up forces of impact of all the molecules of different gases against the container's surface at any given moment. This means the pressure exerted by a single gas component of a mixture is directly proportional to the concentration of this gas in the total mixture. This is called the partial pressure of that gas in mixture. In the atmospheric air there are mainly two gases N_2 and O_2 and their respective proportion or concentration is 79% and 21% respectively. (The actual composition of air is 78.62% N_2, 20.84% O_2, 0.04% CO_2 and 0.5% H_2O). The total pressure of atmospheric air at sea level is about 760 mm of Hg. Thus, it is clear from the previous discussion on the molecular basis that pressure (which for the individual gase of a mixture is called the partial pressure) contributing by each gas in a mixture is directly proportional to their concentration in it. So, 79% pressure of 760 mm of Hg i.e 600 mm of Hg is exerted by N_2 and 21% pressure of 760 mm of Hg i.e. 160 mm of Hg is contributed by O_2. Thus, the partial pressure of N_2 in the air is 600 mm of Hg, the partial pressure O_2 in the air is 160 mm of Hg and the total pressure of air at sea level is 760 mm of Hg (as other gases which are present in the air are in vary minimal concentration, so here they are deliberately omitted from this calculation). The partial pressure of

Table 3.3: Diffusion coefficient of different gases

Gases	*Diffusion coefficient*
O_2	1
N_2	0.53
CO_2	20.3
He	0.95
CO	0.81

individual gases in a gas mixture is designated as PO_2, PN_2, PH_2O, etc.

When air, containing little or no water vapour is breathed in, it is immediately humidified in the respiratory passage by water vapour, evaporating from the surfaces of the airway. Then, the partial pressure exerted by these water molecules in the inspired air is called the partial pressure of water vapour (PH_2O). The quantity of evaporation of water from the surfaces of respiratory passages and its concentration in the inspired air depends on the temperature. At normal body temperature of 37°C, the concentration of water vapour in the inhaled air is 6.2%. Therefore, the water vapour pressure at 37°C in inspired air is 6.2% of 760 mm of Hg or 47 mm of Hg. The greater will be the temperature, the greater will be the water vapour concentration and its pressure in the inspired air. Alternativley, the lower will be the temperature, the lesser will be the water vapour concentration and its pressure in the inspired air. Thus, water vapour pressure at 0°C is 5 mm of Hg and at 100°C is 760 mm of Hg. So, the partial pressure of N_2 and O_2 in the inspired air after full humidification at 37°C will come down to 564 and 149 mm of Hg respectively (564 mm of Hg N_2 + 149 mm of Hg O_2 + 47 mm of Hg H_2O = 760 mm of Hg humidified inspired air).

O_2 is continuously absorbed from alveoli into the blood and then new O_2 is continuously breathed in into the alveoli from atmosphere. When more and more O_2 is absorbed into the blood from alveoli (e.g. exercise) or less new O_2 enters in the alveoli (e.g. respiratory depression, high altitude etc) then the lower will be the concentration and partial pressure of O_2 in the alveoli (P_AO_2). Alternatively, when less O_2 is absorbed into the blood from alveoli (e.g. rest) or higher its concentration is in inspired air (e.g. O_2 therapy), then the higher will be its concentration and partial pressure in the alveoli (P_AO_2). Therefore, the concentration and subsequent partial pressure of O_2 in the alveoli is controlled by: (i) the rate of absorption of O_2 in the blood, (ii) the rate of entry of new O_2 in the alveoli, and (iii) the presence of CO_2 or other gases in the alveoli. Therefore, the alveolar O_2 tension (P_AO_2) can be calculated by the following formula:

$$P_AO_2 = P_IO_2 - P_aCO_2 / RQ$$

RQ = respiratory quotient, P_IO_2 = inspired O_2 tension and P_aCO_2 = arterial CO_2 tension which is equivalent to the alveolar CO_2 tension (P_ACO_2).

When the air enters the body from atmosphere, it rapidly becomes saturated at 37°C (i.e body temperature) with water vapour and reaches the alveoli where it mixed with CO_2. The partial pressure of water vapour and CO_2 in alveoli at 37°C are 47 mm of Hg and 40 mm of Hg, respectively. So, the next 673 mm of Hg (760 − 47 − 40 = 673 mm of Hg) accounts for the combined partial pressure of N_2 and O_2. The partial pressure of N_2 in air or alveoli is 569 mm of Hg.

Therefore, P_AO_2 = 673 − 569 = 104 mm of Hg.

Thus, the P_AO_2 is 104 mm of Hg when a normal healthy adult person breaths atmospheric air at sea level. But if the patient breaths only 100% O_2, then the alveolar gas contains only O_2, CO_2 and water vapour, and no N_2.

In such situations,

$$P_AO_2 = P_IO_2 - P_aCO_2 - PH_{2O}$$
$$= 760 - 40 - 47$$
$$= 673 \text{ mm of Hg}$$

(RQ is usually not measured).

Another simple method of estimating P_AO_2 (in mm of Hg) is to multiply the percentage of inspired O_2 concentration by 6·7. Thus at 40% of F_IO_2, the P_AO_2 is 6·7 × 40 = 268 mm of Hg and at 100% F_IO_2, the P_AO_2 is 6·7 × 100 = 670 mm of Hg at normal atmospheric pressure.

Pulmonary End Capillary O_2 Tension

Oxygen passes from alveoli to pulmonary capillaries by passive diffusion and thus oxygenates the blood. At the end of diffusion, the pulmonary end capillary O_2 tension (P_CO_2) is more or less equal to the P_AO_2. Therefore, P_AO_2 - P_CO_2 gradient is normally insignificant. But, if there is any impairment of diffusion of O_2 across the alveolar capillary membrane, then the P_AO_2 - P_CO_2 gradient will increase. The diffusion of O_2 from alveoli through the pulmonary capillary depends in many factors. These factors are:

A. The rate of diffusion of O_2 across the alveolar capillary membrane.
B. The pulmonary capillary blood volume or flow.
C. The transit time.
D. The capacity of binding of O_2 with Hb.

A. The rate of diffusion of O_2 across the alveolar capillary membrane

This again depends on the following factors:

i. the thickness of the respiratory membrane
ii. the surface area of the respiratory membrane
iii. the diffusion coefficient of gases (here O_2)
iv. the difference of partial pressure of the gases (here O_2) between alveoli and capillary.

(i) Thickness of respiratory membrane

The O_2 diffuses from alveoli into the RBC through different layers or membrane which constitute the respiratory or alveolar capillary membrane. These layers are: layer of fluid lining the alveolus containing surfactant, alveolar epithelium composed of thin epithelial cells, an epithelial basement membrane, a thin interstitial space between alveolar epithelial basement membrane and capillary endothelial basement membrane, capillary endothelial basement membrane and capillary endothelial membrane. The average thickness of this respiratory membrane is 0.4 to 0.6 µm. Sometimes, it is as thin as 0.2 µm. This extreme thinness of respiratory

membrane facilitates the diffusion of O_2 from alveoli to blood, because the rate of diffusion of gases through the membrane is inversely proportional to the thickness of it. Any factor that increases the thickness of respiratory membrane, such as oedema, fibrosis, deposition of substances, etc, significantly interfere the diffusion of gases (O_2) across the respiratory membrane.

(ii) Total surface area of respiratory membrane

The large capillary surface area of alveoli also greatly facilitate the diffusion of O_2. The total surface area of respiratory membrane is about 70 square meter in a normal healthy adult male. The total quantity of blood present in the alveolar capillaries at a given moment is 60 to 140 ml and this small amount of blood is spread over such a big surface area. So, it is easily understood how O_2 is easily diffused from the alveolar air to the pulmonary capillary blood through this such huge surface area. When the surface area for diffusion is reduced such as in emphysema, then the diffusion is significantly impaired. In emphysema, the alveoli are coalesced due to the rupture of their wall and new alveoli are formed. This new alveoli are larger than the original one, but the total surface area of respiratory membrane is greatly reduced.

(iii) Diffusion coefficient of gases (Table 3.4).

The diffusion capacity of gases through respiratory membrane is expressed as the diffusion coefficient, because diffusion of gases from alveoli to capillary blood is dictated by the diffusion coefficient of that gases. It depends directly on the solubility of the gases in water and inversely on the square root of their molecular weight (mW). Thus, diffusion of gases from alveoli to pulmonary capillary blood through the respiratory membrane first depends on their solubility characteristic in water. Further, the solubility of individual gas in water depends on their partial pressure in their gaseous phase at the one side of the membrane and their concentration (expressed in volume of gas dissolved in each volume of water) on the other side of the membrane. This relation is expressed as the solubility coefficient in water at body temperature for individual gases. On the other hand, the solubility determines the partial pressure of gas in its liquid phase which again dictates the net diffusion of it between its gaseous and liquid phase. Thus the solubility coefficient can be calculated from the Henry's law, which is expressed as:

Solubility coefficient = Concentration of dissolved gas ÷ partial pressure.

From the solubility coefficient table, it is found that CO_2 is 20 times more soluble in water than O_2 and O_2 is 2 times more soluble in water than N_2. So, for a given partial pressure CO_2 diffuses 20 times more rapidly from capillary blood to alveoli than O_2 from alveoli to capillary blood and O_2 diffuses 2 times more rapidly than N_2.

(iv) The difference of partial pressure of the gases between the alveoli and capillary (Table 3.5)

There are some types of molecules which are physically or chemically attracted to the water molecules, while others are repelled. This is called the solubility. The more solubility means the more gas molecules are attracted to water molecules and dissolved within it without building up excess pressure within the solution which is expressed by the free gas molecules in water but not dissolved within it. Alternatively, in the case of those that are not readily attached to water molecules, are repelled and make an impact or force on the surface or the membrane. Thus, they develop a pressure on the surface with fewer dissolved molecules. So, the solubility of a gas is inversely proportional with the development of partial pressure which means increased solubility decreases the partial pressure, exerted by the gas.

Now, it is clear from the previous discussion that after dissolving in water or body tissues every gas exerts a pressure on the surface or the membrane according to their solubility (in the same way as a gas in liquid phase or a gas in gaseous phase). This is because every dissolved gas molecule moves randomly and have kinetic energy. When a mixture of gases exerts a pressure then the individual pressure exerted by individual gases are called the partial pressure. Again this partial pressure of a gas in a liquid phase depends on their concentration in the liquid and the solubility coefficient of that gas (Henry's law) in this liquid.

The pressure difference across the alveolar membrane represents the difference between the partial pressure of gas in alveoli and the partial pressure of gas in the capillary blood. The partial pressure

Table 3.4: Solubility coefficient of different gases

Gases	*Solubility coefficient*
O_2	0.024
N_2	0.012
CO_2	0.57
He	0.008
CO	0.018

Table 3.5: Partial pressure of gases (mm of Hg) in the different inspired and expired air

Gases	*Atmospheric air*	*Humidified air*	*Alveolar air*	*Expired air*
N_2	597 (80%)	563	563	566
O_2	159 (20%)	150	150	120
H_2O	4	47	40	27
CO_2	-	-	47	47
Total pressure (mm of Hg)	760	760	760	760

means the total number of molecule of a particular gas striking on a unit area of surface in a unit time either as gas in gaseous phase (in alveoli) or as gas in liquid phase (in capillary blood). Therefore, the partial pressure difference represents the net tendency for the gas molecules to move through the membrane to any of their phase. So, when the partial pressure of any gas (as for example O_2) in the alveoli is greater than the partial pressure of gas in the blood, then the net diffusion from the alveoli into the blood occurs. Similarly, when the partial pressure of any gas (as for example CO_2) in the blood is greater than the partial pressure of it in the alveoli, then net diffusion from the blood into the alveoli occurs (Fig. 3.8).

B. Pulmonary capillary blood volume or flow

The pulmonary capillary blood volume, especially the volume of red cells which are able to take up the O_2 is also a very important factor for diffusion of O_2 and CO_2 between the alveoli and capillary. Thus, anaemic patients tend to have low diffusion factor and a polycythemic patients have a higher one.

C. The transit time

The capillary transit time which also have an impact on the diffusion of O_2 from the alveoli to capillary can be estimated by dividing the pulmonary capillary blood volume by cardiac output. Thus the normal capillary transit time is 70 ml ÷ 5000 ml/min = 0.8 sec. But the majority of diffusion of O_2 occurs within the first third (0.3 sec) of this transit time. Thus, virtually a complete equilibrium of O_2 tension between the alveolus and the blood has been established at the venous end of capillary within this small time, providing a large safety of margin. So, during exercise almost complete equilibrium of O_2 still occurs, though the transit time may be reduced to 2/3 of the normal, i.e. 0.1 sec.

D. Capacity of binding of O_2 with Hb

The rate of binding of O_2 with Hb also appears to be the rate limiting factor for diffusion of O_2 from alveolus to the capillary. This is further discussed else where.

Arterial O_2 Tension (PaO_2)

When breathing air, the tension of O_2 (PO_2) in the air of the alveoli averages to about 104 mm of Hg. Whereas, the PO_2 in the venous blood entering the pulmonary capillary at its arterial end averages only about 40 mm of Hg. Therefore, the initial pressure difference which cause the O_2 to diffuse into the pulmonary capillary from alveoli is 104 − 40 = 64 mm of Hg (Fig. 3.9).

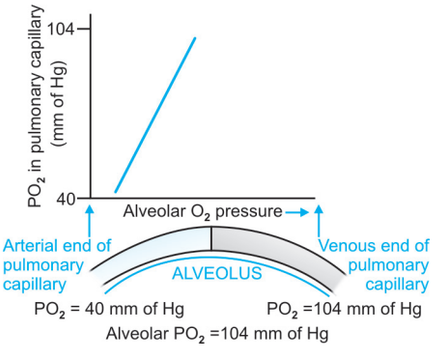


Fig. 3.9: Diffusion of O_2 from alveolar air into the pulmonary capillary blood

After diffusion from alveoli in the capillary blood, the O_2 build up a tension in it and reaches an equilibrium. Thus, the PO_2 of blood that enter the left atrium is also like that of alveolar PO_2 and averages about 104 mm of Hg. But, the blood coming from lungs to the heart with PO_2 of 104 mm of Hg constitute 98% of the cardiac output. (Fig. 3.10).

Another 2% of the cardiac output comes from the bronchial veins which is

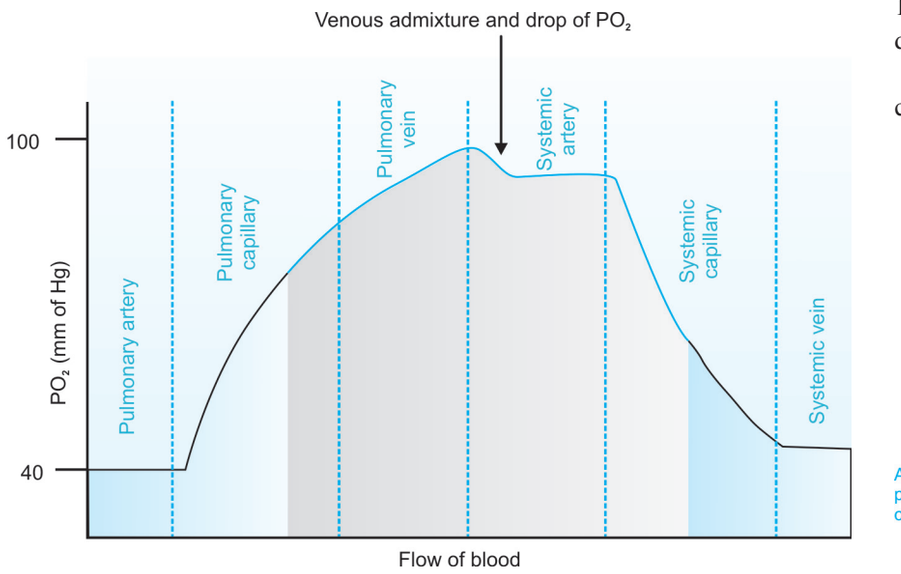


Fig. 3.8: The changes in PO_2 while blood is flowing through systemic vein, to right ventricle, to pulmonary artery, to pulmonary capillary, to left ventricle, to systemic artery, to systemic capillary, and again to systemic vein

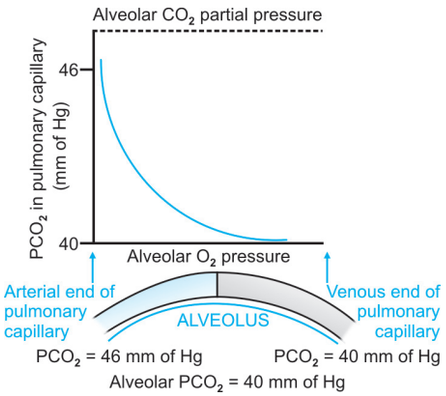


Fig. 3.10: Diffusion of CO_2 from pulmonary capillary blood into the alveolar air

not oxygenated. Normally 2% of the cardiac output passes from aorta through the bronchial circulation and supplies mainly the deep tissues of the lungs. This blood is not exposed to lung air for ventilation and comes back to left atrium with PO_2 about 40 mm of Hg which is similar to that of systemic venous system. This blood flow is called the shunt (true) flow. When this deoxygenated shunted blood (PO_2 = 40 mm of Hg) combines with the oxygenated blood of pulmonary vein (PO_2 = 104 mm of Hg) then this is called venous admixture of blood and PO_2 in left ventricular blood comes down to 97 mm of Hg from 104 mm of Hg. Then, this venous admixtured blood enters the heart and pumped into the aorta with PO_2 of it about 97 mm of Hg. This is the actual systemic arterial O_2 tension (P_aO_2). When this oxygenated arterial blood passes through different tissues, the PO_2 comes down in stages at different site which is shown in figure of O_2 cascade in the chapter of 'O_2 and CO_2'.

Alveolar and arterial O_2 tension difference ($P_AO_2 - P_AO_2$)

When a patient is breathing air at sea level in 37°C temperature, then normal P_AO_2 is 104 mm of Hg and P_aO_2 is 97 mm of Hg. So, the normal alveolar to arterial O_2 tension difference (P_AO_2-P_aO_2 or A–a gradient) is 104 − 97 = 7 mm of Hg, and normally it lies below 15 mm of Hg. But it may vary between 5 and 25 mm of Hg, and gradient increases progressively with increase of age up to 20 to 30 mm of Hg. This is due to the progressive increase in closing capacity (cc) in relation to FRC with increased age. From age, the P_aO_2 can be calculated by the following formula:

$$P_aO_2 = 102 - Age/3$$

The $P_AO_2 - P_aO_2$ is the most common mechanism of hypoxaemia. The A − a gradient for O_2 depends on V_A/Q ratio, shunt and mixed venous O_2 tension. It is directly proportional to V_A/Q mismatch and shunt and inversely proportional to the mixed venous O_2 tension. Thus, $P_AO_2 - P_aO_2$ difference is influenced by the following factors.

(i) V/Q ratio

From the aspect of ideal V_A/Q ratio, no alveoli are ideal. Some are overventilated or some are overperfused. So, the blood from different parts of the lungs after passing through the alveolar capillaries and after taking part in gaseous exchange with different PO_2 mixes at the venous end of pulmonary capillary and flows through the pulmonary vein to the left atrium. There final PO_2 i.e P_aO_2 is definitely lower than P_AO_2. Therefore, more V_A/Q mismatch results in more $P_AO_2 - P_aO_2$ difference.

(ii) Shunt (Fig. 3.11)

The blood which passes without any gaseous exchange is called shunted blood. As more and more blood passes through the shunt and mixes with the oxygenated blood, coming from different alveoli with different V_A/Q ratio at the left side of the heart, then $P_AO_2 - P_aO_2$ difference will increase. Shunt can be classified into two: true and false. True shunts are those that do not pass through the alveolar capillary or not through the lungs at all. They are also called the anatomical shunt. The examples of anatomical or true shunts are bronchial circulatory system, reverse ASD, reverse VSD, reverse PDA, etc. False shunts are those that pass through the alveolar capillary, but due to different pathological condition they can not take part in gaseous exchange. They are also called the physiological shunt and indicate mainly the zero V_A/Q zones of the lung.

The venous admixture or shunt causes reduction in arterial O_2 content and increase in arterial CO_2 content. Further due to the shape of the O_2 and CO_2 dissociation curve, this small reduction of O_2 content is reflected as a large reduction in arterial PO_2 (about 7 mm of Hg), whereas this small increase in CO_2 content is reflected by only a small increase in arterial PCO_2 (less than 1 mm of Hg). The arterial PO_2 is, therefore, the best indication of the amount of venous admixture or shunt than the arterial PCO_2. So, the high $P_AO_2 - P_aO_2$ difference is due to V_A/Q mismatch or true shunt and can be detected only by giving the subject 100% O_2 to breath. If there is small increase in arterial PO_2, then the $P_AO_2 - P_aO_2$ difference or hypoxemia is due to true shunt. Up to the presence of 50% shunt, changes is FiO_2 have virtually no effect on P_aO_2 (Table 3.6).

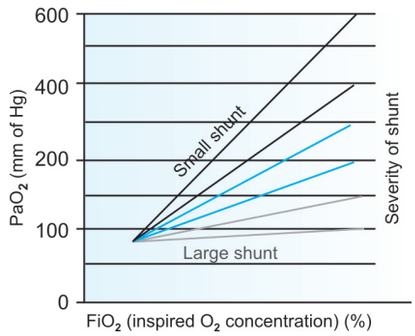


Fig. 3.11: The effect of various concentration of inspired O_2 concentration on arterial O_2 tension (PaO_2) with various amount of shunt. In case of very large shunt there is very little benefit with increasing inspired O_2 concentration

(iii) Venous admixture and O_2 tension in mixed venous blood (Fig. 3.12).

When the blood passes through different organs or tissues of body then the

Table 3.6: Classification of 'true shunts'

Site	*Physiological*	*Pathological*
Intrapulmonary	Bronchial vein	Blood coming from alveoli with V_A/V_a = 0 (zero), such as atelectasis, neoplasm, collapse etc.
Extrapulmonary	i. Thebesian veins	Right to left shunt through ASD, VSD, PDA and other congenital abnormality of heart.
	ii. Arteriosin usoidal vessels	
	iii. Arterioluminal vessels	

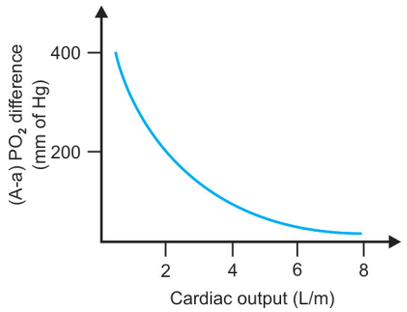


Fig. 3.12: The relationship between cardiac output and (A-a) PO_2 difference due to venous admixture. As cardiac output increases (A-a) PO_2 decreases and (A-a) PO_2 rises steeply at low cardiac output

Table 3.7: Causes of changes in mixed venous O_2 tension (PVO_2)

A.	**Increased**
1.	Left to right shunt
2.	Cyanide poisoning (reduced tissue uptake of O_2)
3.	Hypothermia (reduced tissue uptake of O_2 due to decreased consumption)
	Sampling error
4.	↑Cardiac output
5	↑FiO_2
B.	**Decreased**
1.	Decreased O_2 delivery to the tissues such as hypoxia, ↓ cardiac output, anaemia, abnormal haemoglobin.
2.	Increased O_2 consumption by the tissues such as exercise, shivering, fever, thyrotoxicosis, malignant, hyper-thermia etc.

Table 3.8: Causes altering dead space

1.	Age	Increase
2.	Posture	
	Standing	Increase
	Lying	Decrease
3.	Neck	
	Extension	Increase
	Flexion	Decrease
4.	Artificial airway	Decrease
5.	IPPV	Increase
6.	Hypertension	Increase
7.	Emphysema	Increase
8.	Tracheostomy	Decrease
9.	Anaesthetic circuit	Increase
10.	Face mask	Increase
11.	Hypotension	Increase
12.	Pulmonary emboli	Increase

extraction of O_2 from blood by these different organs or tissues depends on the rate of metabolism of that tissues and the fraction of cardiac output supplied to these tissues. So, the partial pressure of O_2 in venous blood coming from different tissues are different. When these venous blood coming from different organs or tissues with different PO_2 reach at the right side of the heart, they mix and produce the venous admixture with given O_2 tension in mixed venous blood. The causes which reduce the mixed venous blood O_2 tension (PVO_2) such as increased metabolism and low cardiac output increases the $P_AO_2 - P_aO_2$ difference. Low cardiac output tends to increase the effect of V_A/Q mismatch and subsequently its effect on shunt and ultimately their effects on PO_2 and PVO_2. On the otherhand, low cardiac output reduces the venous admixture secondary to the increased pulmonary vasoconstriction due to lower mixed venous O_2 tension (compensatory phenomenon) (Table 3.7).

Concentration of Hb also has an effect on O_2 tension of mixed venous blood and subsequently on A-a oxygen gradient. Low Hb concentration can depress mixed venous PO_2 and increase the A-a oxygen gradient.

Mixed Venous O_2 Tension (PVO_2)

Mixed venous O_2 tension represents the overall balance between the delivery and the consumption of O_2. The normal value of it in a healthy adult is 40 mm of Hg. A true mixed venous blood sample for measurement of O_2 tension should must be obtained from SVC, IVC and right heart. So, it should be obtained by pulmonary artery catheter. Other details regarding PVO_2 is described in previous paragraph.

DEAD SPACE

When a person breaths, then all the air taking during inspiration does not take part in the gaseous exchange. Some of the air reach the alveoli and take part in gaseous exchange, but some simply fill the respiratory passages such as nose, nasopharynx, trachea, etc, where gas exchange does not occur. Thus, the part of the inspired air which does not take part in gaseous exchange is called the dead space air. During expiration the dead space air is expired first, followed by the exit of air from alveoli that takes part in gaseous exchange. Therefore, the dead space is very disadvantageous for gaseous exchange i.e oxygenation of blood and elimination of CO_2 and for removing the expiratory gases from lungs. Normally 2/3 of each breath takes part in gaseous exchange and this portion or volume of breath is called the alveolar ventilation. Whereas, the remaining 1/3 of each breath does not take part in gaseous exchange and this portion or volume of breath is called the dead space or dead space ventilation (Table 3.8).

The dead space is actually composed of two components: anatomical dead space and alveolar dead space. The sum of the two is referred to as the total or physiological dead space. Normally, in healthy adult the anatomical and physiological dead space is nearly equal and is about 150 ml each. This is because in a given healthy subject the anatomical dead space remains fixed and all the alveoli are functional, with no alveolar dead space. But, in some persons this physiological dead space may be as high as 10 times of the anatomical dead space and it is due to the presence of some partial functioning or completely nonfunctioning alveoli in some parts of the lungs which increases alveolar dead space.

Anatomical Dead Space

It is that portion of the total or physiological dead space which occupy only the conducting path of the respiratory passage. It varies with the age, sex and size of the lung. Normally, in a healthy adult the approximate value of it is 2 ml/Kg or 150 ml. But in young women, it is as

low as 100 ml and in old man it can rise as much as up to 200 ml. The anatomical dead space is reduced when the neck is flexed and tongue falls back (30 ml reduction). It also can be reduced by pneumonectomy, tracheostomy, etc. On the otherhand, antomical dead space is increaed by protrusion of jaw and extension of neck (40 ml increase). In supine position, the antomical dead space is equal to the total or physiological dead space as alveolar dead space becomes zero or negligible due to the obliteration of zone 1. But in erect posture the alveolar dead space increases from zero to 60 or 80 ml due to the creation of Zone 1. So, physiological dead space also increases.

Alveolar Dead Space

It is that portion of the total or physiological dead space that occupy or ventilate the nonperfused alveoli. So, in that portion of the lung, ventilation goes wasted. It increases when the zone 1 area increases such as in upright position, hypotension, low cardiac output state, etc.

Total or Physiological Dead Space

As the total or physiological dead space is the sum of the anatomical and alveolar dead space, so when any of the above two dead space increases, then the physiological or total dead space also increases. The examples are: old age, upright position, high respiratory rate (inspiratory time < 0.5 sec), administration of atropine, COPD, asthma, pulmonary embolism, hemorrhage, hypotension, etc.

Apparatus Dead Space

It is the volume of gas that is present in any anaesthetic apparatus between the patient and the point in the system where rebreathing of exhaled gases ceases to occur, for example the expiratory valve in Magill system, the side arm in Ayre's T-piece, etc. The volume of apparatus dead space in Magill system is 125 ml. So it is very important for an anaesthetised small children.

Dead space and alveolar ventilation

Alveolar ventilation (V_A) is the major determining factor of the alveolar O_2 and CO_2 tension which later subsequently determine the O_2 and CO_2 tension of blood. On the otherhand, dead space is the major determining factor of alveolar ventilation. So, it is easily understood how the dead space (V_D) controls the alveolar and arterial O_2 and CO_2 tension through alveolar ventilation from the formula below:

$$V_A = (V_T - V_D) \times F$$

V_A = Alveolar ventilation, V_T = Tidal volume, V_D = Dead space, F = Respiratory rate.

For a healthy adult person, if V_T = 450 ml (6 ml/Kg), V_D = 150 ml and F = 12/min,

then, $V_A = (450-150) \times 12 = 3600$ ml/min.

The dead space (total or physiological) to tidal volume ratio (V_D/V_T) also provides a useful expression of the efficiency of ventilation. Normal V_D/V_T ratio is 0·25 to 0.4. It averages to 0.3 which means dead space is 30% and ventilation is 70% of tidal volume. In patient with obstructive airway disease V_D/V_T ratio may increase to 0.6 or 0.7 (60 or 70%). It means dead space is increased to 60 to 70% and ventilation is reduced to 40 to 30% of total tidal volume, or ventilation which is grossly inefficient. V_D/V_T ratio also increases with age which can be roughly estimated from formula:

$$V_D/V_T = 33 + \text{Age}/3 \text{ percent.}$$

This is due to the more vascular obliteration with age. The V_D/V_T ratio also can be derived by the Bohr equation :

$$\frac{V_D}{V_T} = \frac{P_ACO_2 - P_ECO_2}{P_ACO_2}$$

P_ACO_2 = alveolar CO_2 tension, P_ECO_2 = expired CO_2 tension. In normal healthy adult P_ACO_2 is equivalent to P_aCO_2 and P_ECO_2 is the average measured over several minutes. So, this equation is useful clinically, because we can measure the V_D from this equation.

For example, P_ACO_2 = 40 mm of Hg, P_ECO_2 = 28 mm of Hg and V_T = 500 ml.

So, $V_D/V_T = (40-28)/40 = 12/40$

or $V_D = 12/40 \times 500 = 150$ ml.

Table 3.9: Components and its percentage that constitute the resistance of breathing Elastic resistance 65%

Nonelastic resistance
Airway resistance 28%
Viscous nonelastic resistance such as bones, muscles, etc, 7%

RESISTANCE (TABLE 3.9)

During respiration i.e. inspiration and expiration, the chestwall and lungs move out and in and the air flows in and out through the airways and lungs. But, the movement of chestwall with lungs and the flow of air through it is always associated with some impedence. This impedence is called the resistance. This is due to the friction during movement between the tissues of chestwall and lungs, and during the flow of air between the air and its passage. Generally, this resistance is overcomed by creating a pressure gradient between the atmosphere and alveoli which is accomplished by work of breathing. Thus, the resistance is defined as the unit change of pressure gradient causing unit volume of air to flow.

The resistance is divided under two broad headings: elastic resistance and nonelastic resistance. The elastic resistance is imparted by the elastic recoil property of the lungs and chestwall, and also by the surface tension acting at the air fluid interface in the alveoli. Elastic resistance is measured in terms of compliance as the later is opposite to the elastic recoil property of the lungs and chestwall which contributes to the elastic resistance. On the otherhand, the nonelastic resistance is imparted by the friction of air in the air passage during its flow through it and by the friction among the tissues during movement of the non elastic part of the lungs and chestwall, such as bones, muscles, etc.

The work of breathing necessary to develop the pressure gradient to overcome the elastic resistance is stored as potential energy which is subsequently used during

passive expirations. Whereas, the work of breathing necessary to overcome the non-elastic resistance is expressed as heat.

Elastic Resistance

From the previous discussion, it is now clear that the elastic resistance is due to the elastic recoiling property of the lung tissues, the soft chestwall tissues and the surface tension in the alveoli. Again the elastic recoiling property of the lungs and the chestwall is due to their high content of elastin and collagen fibres. Clinically, the resistance offered by these elastin and collagen fibres cannot be measured directly and isolatedly. Similarly, the only measurement of elastic resistance offered by the surface tension is not so helpful clinically. Therefore, the whole elastic resistance is measured indirectly by the compliance (Fig. 3.13).

Elastic Resistance Due to the Elastic Recoiling Property of Lungs and Chestwall

The elastic recoiling property of the lungs and chestwall greatly determine the elastic resistance and is calculated indirectly by the compliance. Because compliance is opposite to resistance i.e compliance = 1/resistance (or vice versa) and it is also reproduced like resistance by the pressure volume curve. If the lungs are affected by fibrosis (e.g interstitial pulmonary fibrosis) where the elastin and collagen fibres are replaced by the fibrous tissue, then the elastic resistance will increase and the compliance will decrease. Thus, the lungs become stiff and the pressure - volume curve will shift downwards and to the right. On the otherhand, in emphysema the total mass of elastin and collagen fibres are reduced and the recoiling property of the lungs are lost. Thus, it becomes voluminus and the elastic resistance will decrease with increase of compliance. So, the pressure - volume curve is shift upwards and to the left (Table 3.10).

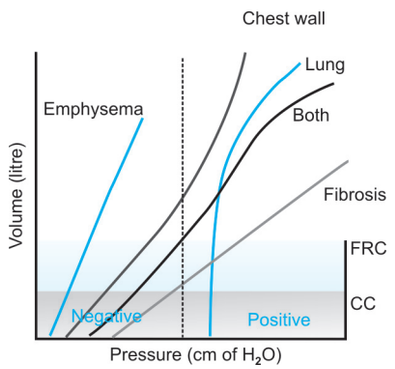


Fig. 3.13: The compliance or pressure volume relationship of lung (red line), chestwall (green line) and both together (blue line)

Table 3.10: Composition of surfactant (approximate)

DPPC (Dipalmitoylphosphatidylcholine)	65%
Neutral lipids	12%
Other phospholipids	8%
Proteins	8%
Phosphotidyl glycerol	5%
Carbohydrate	2%

Elastic resistance due to surface tension

Another important factor affecting the elastic resistance of lung is the surface tension which is due to the gas-fluid interface, present in the alveoli. This surface tension or force tries to reduce the gas-fluid interfacing area and favours the alveolar collapse. Thus, it increases the pressure gradient required for per unit of air to flow to increase the volume of lungs or to prevent the collapse of alveoli. This is known as the elastic resistance due to surface tension. If the lung is filled with saline, then surface tension will become zero due to the absence of air-fluid interface. In such condition, the elastic resistance will measure only the tissue elastic resistance. Whereas, the resistance obtained from the alveoli filled with air measures both the tissue elastic resistance and elastic resistance due to surface tension.(Fig. 3.14).

Normally, the elastic resistance due to surface tension is reduced by the presence of surfactant. In the absence of surfactant, the alveoli will collapse due to increased surface tension or the inward retraction force, especially during expiration when the alveoli gradually become smaller. This is because when the alveoli gradually become more and more smaller, then the surface tension gradually increases following the Laplace law. This is because as the fluid molecules come more and more closer, then the attraction force between these molecules increase. This has theoretically two disadvantages:

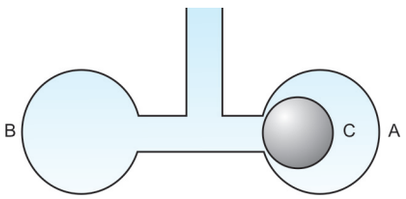


Fig. 3.14: According to Laplace law P = 2T/R

Story 1: The two alveoli A and B are of same size, but alveoli A has no surfactant. The radius of alveoli A is 0.5 cm and surface tension is 10 dynes/cm, whereas the radius of alveoli B is 0.5 cm and surface tension is 5 dynes/cm, due to the presence of surfactant. Then, the intraalveolar pressure of alveoli A will be P = 2 ´10/0.5 = 40 dynes/sq cm. The intra-alveolar pressure of alveoli B with surfactant of same radius will be P = 2 ´ 5/0.5 = 20 dynes/sq cm. So, due to high pressure in alveoli A, the air will flow from it to alveoli B and gradually the alveoli A will reduce in size. On the otherhand, alveoli B will increase in size. Hence, in this story alveoli A needs surfactant to reduce the intraalveolar pressure.

Story 2: The two alveoli C and B of different radius, but of same surface tension. The radius of alveoli C is 0.2 cm and surface tension is 5 dynes/cm, whereas the radius of alveoli B is 0.5 cm and surface tension is 5 dynes/cm. Then the pressure within alveoli C will be P = 2 × 5/0.2 = 50 dynes/sq cm. While the pressure within the alveoli B will be P = 2 × 5/0.5 = 20 dynes/sq cm. So the smaller alveoli C will drain in alveoli B and will reduce in size. Hence, in this story alveoli C needs more surfactant than B, though surface tension is same, because its radius is small.

Story 3: In the presence of surfactant the smaller alveoli will have less surface tension due to crowding of the surfactant molecule in a small space. For example, there are two alveoli C and B. The radius of alveoli C is 0.2 cm and surface tension is 1 dynes/cm. Whereas the radius of alveoli B is 0.5 cm and surface tension is 5 dynes/cm. Then, the pressure within alveoli C will be P = 2 × 1/0.2 = 10 dynes/sq cm. Whereas the pressure within the alveoli B is 20 dynes/sq cm. Thus, the gas will flow from alveoli B to alveoli C, untill the two alveoli reach to equal size and volume become stable

i. Smaller alveoli have greater surface tension and have more tendency to collapse than a larger alveoli. So, each small alveolus will progressively discharge into a large one and ultimately a gigantic alveolus would be left.
ii. Retractive forces of the lung due to increased surface tension should increase as the lung volume decreases. So, the lung volume will decrease in vicious manner and ultimately it will completely collapse.

This above phenomenon can be explained by the Laplace law. According to the Laplace law: P = 2 T/r. Here, P is the pressure at inside of the alveolus which increases or decreases according to the size of the alveolus and again depends on the surface tension. T is the surface tension and r is the radius of the alveoli. From the Laplace law, it is easily understood that smaller alveoli with smaller radius (r) have increased intraalveolar pressure which indicates its collapsing nature due to increased inward retraction force or increased surface tension. On the other-hand, we can say that the collapse of alveoli is more likely when the surface tension increases or alveolar size decreases. Thus, the alveolar collapse is directly proportional to surface tension and inversely proportional to the radius of the alveolus.

Moreover, within the alveolus the ability of surfactant to reduce the surface tension is directly proportional to its concentration. So, when the alveoli become smaller during expiration or due to any cause, the concentration of surfactant on the lining fluid of alveoli will be increased and the surface tension will be more effectively reduced, offsetting the increased surface tension due to the reduction of the size of alveoli. Alternatively, when the alveoli are over distended, the concentration of the surfactant on the lining fluid is reduced and the surface tension is less effectively reduced. Thus, a balance is reached when larger alveoli are prevented from over distension and smaller alveoli are prevented from collapse.

Compliance

Compliance is also termed as stretchability. In character it is opposite to the elasticity which is described before. Elasticity tries to squeeze the lungs and chestwall, and offers resistance for air to flow in the lungs. Whereas, it is countered by the stretchability of both the lungs and chestwall which is called the compliance. Thus, the elasticity or the resistance which prevents the air to flow in the lungs is measured indirectly in the form of stretchability or compliance which facilitates the air to flow in the lungs (Fig 3.15).

For air to flow in the lungs, a pressure gradient must have to be developed which will help to overcome the elastic and the nonelastic resistance of the lungs and chestwall. So, the compliance (C) is defined as the unit change in volume of lung for unit change in developed pressure and is calculated by dividing the total change in volume (ΔV) of lung by the total distending pressure (ΔP) which causes this change. Whereas, the resistance is defined as changes in distending pressure divided by changes in volume.

Thus, C (L/cm of H_2O) = ΔV (in L) / ΔP (cm of H_2O)

Compliance may be calculated isolatedly taking only the chestwall (Cw) or the lung (CL) component or both together (CT). So, the equation of compliance of individual component can be represented as:

i. C_L litre/cm of H_2O = ΔV litre/transpulmonary pressure gradient or ($P_A - P_{Pl}$) cm of H_2O
ii. C_W litre/cm of H_2O = ΔV litre/transmural pressure gradient or ($P_{Pl} - P_{atmos}$) cm of H_2O. (Fig. 3.16).

Thus C_T litre/cm of H_2O = ΔV litre/transthoracic pressure gradient or ($P_A - P_{atmos}$) cm of H_2O. [C_T is the total compliance]

The normal C_L value is 200 ml/cm of H_2O or 0.2 L/cm of H_2O. Any pathological condition of lungs such as pulmonary oedema, atelectasis, emphysema, etc, can affect the C_L. The normal C_W value is also 200 ml/cm of H_2O or 0.2 L/cm of H_2O. Any pathological condition of chestwall such as pain, injury, trauma, paralysis, osteoarthritis, etc., can also affect the C_W. Thus, the normal total compliance (lung and

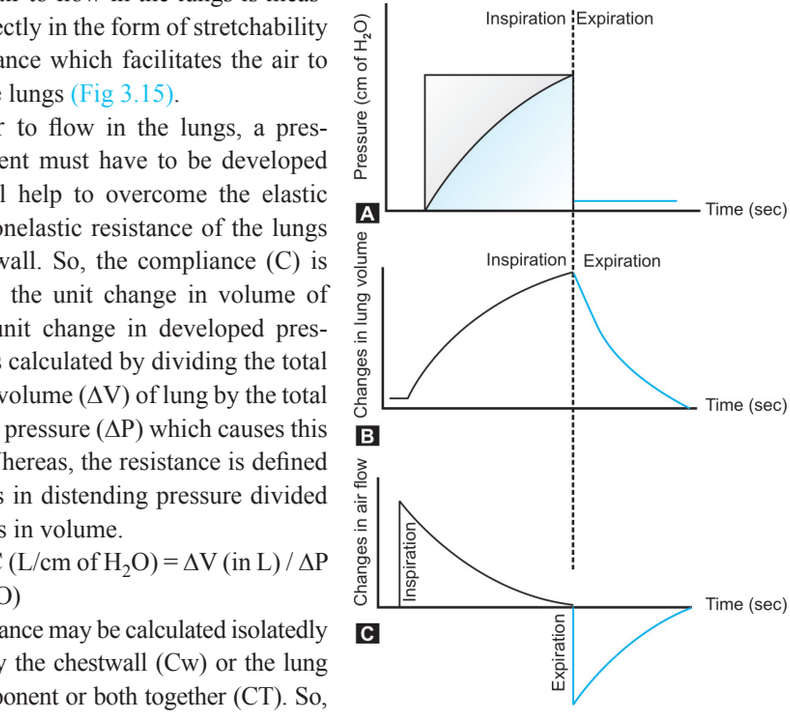


Fig. 3.15: Compliance

Figs 3.16A to C: Picture A represents the graphic changes in intrapulmonary pressure during IPPV when a constant pressure is applied (square wave). Line x represents the sudden rise of intrapulmonary pressure produced by a pressure gradient to overcome the both elastic and nonelastic airway resistance. Among these the red area represents the nonelastic airway resistance and the blue area represents the elastic resistance. The pressure gradient to overcome the nonelastic resistance is maximum initially and then decreases exponentially. Whereas, the pressure gradient require to overcome the elastic resistance is minimum initially and then increases exponentially. Alveolar filling ceases when the pressure from elastic forces balance the applied pressure. Expiration is passive and intrapulmonary pressure suddenly comes down to zero level with the ending of inspiration and initiation of expiration. Fig. B and C show the changes in lung volume and air flow respectively which correspond to the Fig. A

chestwall together) is 100 ml/cm of H_2O or 0.1 L/cm of H_2O. This is expressed by the following equation:

$1/C_T = 1/C_L + 1/C_W$

The transthoracic pressure gradient which helps to flow air inside the lungs first increases to peak value to overcome the nonelastic airway resistance and to inflate the stiff alveoli. Then, it decreases to somewhat lower plateau value to inflate the more compliant alveoli. Alternatively the pressure gradient required to overcome the elastic resistance is minimum initially, but then increases exponentially. If patient is on PEEP, this must be substracted from this peak or plateau value of transthoracic pressure before calculating the compliance.

Nonelastic Resistance

This is due to the friction created between the air and the wall of its passage, during the flow of it through the trachea and the bronchial tree (in case of anaesthetized person the anatomical dead space portion in the breathing system should also be included) and due to the friction among the tissues (such as bones muscles, etc.) during the movement of lungs and chestwall. The nonelastic resistance due to the movement of tissues are not considered clinically, as it is very minimal. So, we will take into account here only the frictional resistance due to the flow of air through the trachea- bronctrial tree. Usually, there are three patterns of airflow: laminar flow, turbulent flow and orifice flow.

The laminar flow occurs in tubes where its sides are parallel and when the velocity of flow is below the critical level. In the centre of the laminar flow the velocity is highest and it decreases gradually towards the periphery.

For an air to flow, a pressure gradient has to be developed. So, the relationship between the developed pressure gradient (P) and the rate of flow of air or the change in volume of lung is known as the airway resistance (Raw). Thus the equation of airway resistance is:

$$\text{Raw (cm of } H_2O\text{/L/S)} = \frac{\text{P (cm of } H_2O)V}{(L/S)}$$

According to Poiseuille's law:
Pressure gradient (P) = Flow (v) × 8 length of tube (L) × viscosity (μ) / π radius4 (r). Therefore,

$$R_{aw} = \frac{8L \times \mu \times V}{\pi r^4 \times V} = \frac{8L \times \mu}{\pi r^4}$$

The value or normal airway resistance is 0.5 to 2 cm of H_2O/L/S.

When the flow of air exceeds the critical velocity, then the laminar flow becomes turbulent. The important feature of this turbulent flow is that the drop of pressure during flow of air along the airway is not directly proportional to the flow rate, but is proportional to the square of it. Therefore, the pressure increases much more than the increase in flow. So, the resistance in turbulent flow will also increase much more than the laminar flow and is proportional to the gas flow which is opposite to the laminar flow. Therefore, in the turbulent flow the equation is:

$$\text{Pressure gradient} = \frac{V^2 \times \text{Gas density}}{r^5}$$

Therefore, during turbulent flow the resistance (R_w) = P/V

$$\text{or, } R_{aw} = \frac{V^2 \times \text{Gas density}}{r^5 \times V}$$

$$\frac{V \times \text{Gas density}}{r^5}$$

So, the nonelastic airway resistance in turbulent flow is directly proportional to the amount of flow (V) and the density of gas and is inversely proportional to the fifth power of the radius (r^5). Therefore, the turbulent flow is extremely sensitive to the airway caliber (Table 3.11).

Hence, the turbulence generally occurs during the high gas flow, at sharp angles and during certain change of airway diameter. Whether the flow will be turbulent or laminar usually depends on the Reynolds number. The equation of Reynolds number is:

$$\text{Reynolds number} = \frac{\text{Linear velocity} \times \text{Diameter} \times \text{Gas density}}{\text{Gas viscosity}}$$

If the Reynold number is below 1000, then the flow of gas will be laminar. Whereas Reynold number above 1500 produces turbulent flow. The gases with low density/viscosity ratio have less Reynold number and produces the laminar flow. Thus, they reduces the airway resistance. For example, helium (He) and O_2 mixture has least density/viscosity ratio and less likely to cause turbulent flow with reducing the airway resistance. So, it is useful clinically during severe turbulent flow caused by the upper airway obstruction.

The orifice flow occurs when it meets a severe constriction. The equation for orifice flow is equal to the turbulent flow. So, here the drop of pressure or the gradient is proportional to the square of flow rate and gas density replaces its viscosity. As density is used as a numerator in the equation of resistance of gas flow, so it is easily understood why the low density gas such as helium dimishes the resistance to flow. It diminishes the flow of resistance three fold as compared to air in severe obstruction.

The orifice flow occurs in larynx. Whereas the turbulent flow is mainly confined to trachea and main bronchi during most of the respiratory cycle. On the otherhand, laminar flow is found in the airway below the main bronchi. This is because though the division and subdivision of airway below the main bronchi reduce the individual diameter, but the total cross sectional area of airway increases due to this branching. Thus, the resistance in large bronchi is low because of their large diameter and also the resistance in small bronchi is low because of their large total cross sectional area. So, the velocity of air flow also decreases causing laminar flow. But during bronchoconstriction the diameters

Table 3.11: Density/viscosity ratio of O_2, N_2O and He

Gases	*Density*	*Viscosity*	*Den/Vis*
O_2	1.11	1.11	1
N_2O and O_2 (60:40)	1.41	0.89	1.49
He and O_2 (80:20)	0.33	1.08	0.31

of smaller bronchi and bronchioles reach such a critical level that the laminar flow is converted to the turbulent flow with increase of resistance.

WORK OF BREATHING

Ventilation is the main function of lungs. So, for ventilation air has to enter into it. But three resistance factors has to be overcomed for entry of air into the lungs. These are: (i) elastic recoiling resistance of the chest wall and lungs (elastic resistance), (ii) frictional resistance due to the flow of air in the airways (nonelastic resistance) and (iii) the tissue frictional resistance (nonelastic resistance). So, work has to be performed by the respiratory muscles to overcome all these three resistance by stretching the elastic tissues of the lungs and chestwall (elastic work) and by moving the nonelastic tissues (viscous resistance work) and thus by creating a pressure gradient which helps to move the air through the airways (airway resistance work). Thus, the total work of breathing done against all these resistance during inspiration is stored as potential energy in the inspiratory muscles. Later, it is used passively during expiration to expel the gases. So, the overcoming of expiratory resistance in normal individual is nonactive (used from stored energy) as the entire expiratory cycle is passive. But this not applicable in obstructive airway diseases, where expiration is also active.

The increased inspiratory resistance is overcomed by the increased effort of inspiratory muscles. But when the expiratory resistance increases then the lung volume also increases as a compensatory phenomenon such that tidal volume (V_T) reaches to FRC level. Thus, the greater energy stored at a higher lung volume tries to overcome the added expiratory resistance. Except that excess expiratory resistance also stimulate the expiratory muscles to work more (Fig. 3.17).

We know :

Work = Force × Distance

But, Force = Pressure × Area

and, Distance = Volume /Area

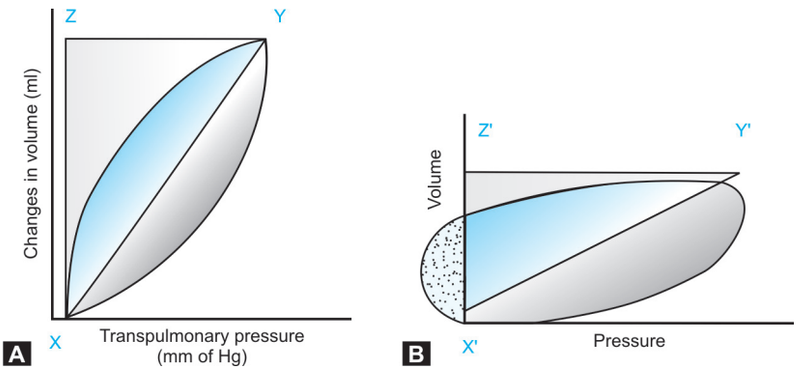
Thus, Work = Pressure × Volume

So, the respiratory work (gm × cm) can be expressed as the product of pressure (gm / cm^2) and volume (cm^3).

During optimum conditions, in a normal healthy adult the respiratory muscles work only with 10% efficiency and 90% energy is dissipated as heat due to the elastic and airway resistance. For that, only 2 to 3% of total O_2 consumption of body is used. But it can raise up to 50%, if the patient suffers from pulmonary diseases. The estimated total work for quite breathing in a healthy adult ranges from 0.3 to 0.8 Kg-meter/minute.

When the work of breathing is increased by increasing the depth of respiration but not in rate, then the work done only against the nonelastic airway resistance will increase. On the otherhand, when the work of breathing is increased by increasing the respiratory rate, then only the work done against the airway resistance will increase.

Thus, when these two phenomenons are summed up, then there is optimal increase in the depth and frequency of respiration where the total increase in work of breathing is minimal. This phenomenon can be explained by another way. The increased work required to overcome the increased elastic resistance is accomplished by not increasing the tidal volume (V_T) or the depth of respiration, but by increasing the rate of respiration. Whereas the increased work required to overcome the increased airway resistance is accomplished by not increasing the respiratory rate, but by increasing the depth of respiration. So, patients suffering from pulmonary oedema, interstitial fibrosis, etc, where elastic resistance increases favour rapid shallow breathing. Whereas patients suffering from asthma, COPD, etc, where the only airway resistance increases favour deep and slow breathing. Again, when there is both the increase in elastic and airway resistance, then the patient tries to minimize the work of breathing by altering the tidal volume and respiratory rate in optimal.



Figs 3.17A and B: Pressure and volume curve or the compliance of lung. Fig. A is for the normal patient and Fig. B is for the anaesthetised patient. In Fig. A, the XY line indicates compliance which is about 100 ml/cm of H_2O. In Fig. B the X 'Y' line indicates compliance which is about 50 ml/cm of H_2O. Fig. A is the picture of highly compliant, small, dependent alveoli situated at the base of the lung. Whereas Fig. B is the picture of less compliant, medium sized alveoli situated normally in the middle of the lung. The dimensions of pressure multiplied by volume is the work of breathing. In the picture, the total area shown by red, blue and grey colour represent the total work of breathing. The red area represents the inspiratory work necessary to overcome the airflow resistance during inspiration. The triangle XYZ represents the fraction of total inspiratory work which is necessary to overcome the elastic resistance. The blue area represents the passive expiratory work. In Fig. B, the dotted area represents the active expiratory work necessary to overcome the airflow resistance during forced expiration

Lung Volumes and Capacities

For clinical anaesthesia practice the different lung volumes and lung capacities are very important parameters to an anaesthetist. The difference between the lung volumes and lung capacities are that when the two or more lung volumes are combined together then we get the lung capacities. There are four basic lung volumes which are usually measured. Then, from these lung volumes the different lung capacities are computed. As for examples, the sum of the 4 basic lung volumes which are described below is equal to the maximum capacity of lung i.e. the total lung capacity (TLC) to which the lung can be maximally inflated. A simple method of studying the different lung volumes is called the spirometry and the instrument is called the spirometer (Fig. 3.18).

Lung Volumes

(i) Tidal volume (V_T)

It is the volume of air which is inspired or expired during each normal breath. The normal value of V_T in an adult male is 500 ml.

(ii) Inspiratory reserve volume (IRV)

It is the maximum extra volume of air that can be inspired with full force after the normal inspired tidal volume. The normal value of IRV in an adult male is about 3000 ml.

(iii) Expiratory reserve volume (ERV)

Similar to IRV, it is the extra volume of air that can be expired maximally with full force after the normal expired tidal volume. The normal value of ERV in an adult male is about 1000 ml.

(iv) Residual volume (RV)

It is the volume of air that still remains in the lung after the most forceful expiration (i.e after the expiration of normal tidal volume and ERV). The normal value of residual volume in an adult male is about 1200 ml (Fig. 3.19).

Lung Capacities

(i) Inspiratory capacity (IC)

It is the inspiratory tidal volume plus the inspiratory reserve volume (i.e. IC = V_T + IRV) after a normal expiration. So, it is the amount of air that a person can maximally breath in after a normal expiration. The normal value of IC in an adult male is about 3500 ml.

(ii) Functional residual capacity (FRC)

It is the volume of air which is equal to the ERV plus RV (i.e FRC = ERV + RV). So, FRC is the amount of air that remains in the lungs after a normal tidal expiration. The normal value of FRC in an adult male is about 2300 ml. It is a very important parameter for lung function test in the clinical anaesthesia practice, because its value markedly changes in different types of pulmonary diseases. So, it is often desirable to measure this parameter. FRC can not be measured directly from spirometer, because RV can never be expired on the spirometer for its measurement, but this volume constitutes near about half of the FRC. So, to measure the FRC spirometer is used indirectly by applying the N_2 washout method or helium wash out (or dilution) method or body plethysmograph. The beauty of FRC parameter is that it indicates a volume of lung where the inward elastic recoil property of lung becomes equivalent to or is balanced by the outward stretching force on lung which is called compliance. The FRC also defines a volume of lung from where the normal breathing of tidal volume takes place. There are multiple factors which affect the FRC. These are:

i. Sex and age: Female has 10% less FRC value than male. The relation between

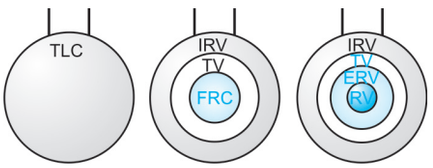


Fig. 3.18: Different lung volumes
TLC = Total lung capacity,
TV = Tidal volume
IRV = Inspiratory reserve volume,
RV = Residual volume,
ERV = Expiratory reserve volume.

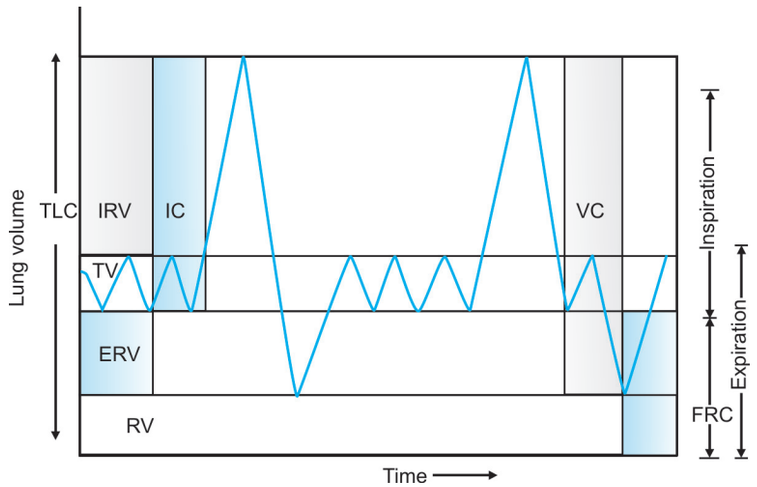


Fig. 3.19: The graphical representation of different lung volumes
TV = Tidal volume, IR V = Inspiratory reserve volume,
RV = Residual Volume,ERV = Expiratory reserve volume,
IC = Inspiratory capacity, TLC = Total lung capacity,
FRC = Functional residual capacity, VC = Vital capacity.

age and FRC is discussed later under the heading of closing capacity (cc).

ii. Posture: FRC is reduced in supine or prone from upright position. This is due to the reduction of chest compliance in lying down condition, as diaphragm is pushed upward by the abdominal viscera. Up to the 30 degree change in inclination, there is no change in FRC. But, it occurs maximally between 60° and 90° inclination from upright position.

iii. Obesity: Obesity is inversely proportional to FRC. This is because it directly reduces the lung compliance. Height is also an important determining factor of FRC and is also directly proportional.

iv. Lung diseases: Any pulmonary disease which affect the compliance of lung or chestwall or both (characteristic of restrictive pulmonary disorder) are associated with low FRC.

v. Anaesthesia: Induction of anaesthesia also reduces the FRC. It is due to both the decrease in compliance and increase in elastic recoil property of lung in anaesthesia during both spontaneous respiration and IPPV.

vi. Post operative period: FRC is also reduced in the postoperative period due to the abdominal distension, pneumoperitoneum, spasm of abdominal and thoracic muscles due to pain etc.

vii. PEEP: Positive end expiratory pressure (PEEP) always increases FRC and is an important mode of management in different lung diseases where FRC < CC.

During expiration the lung is reduced in volume and there comes a point at which some small airways begin to close. This volume of lung when the small airways begin to close during expiration is called the closing capacity (CC). On the other-hand, the closing volume (CV) is the volume of lung which represents from the starting to the end of closing of all the small airways during expiration. Then, the remaining volume of the lung is the residual volume (RV). So CC = CV + RV (Fig. 3. 20).

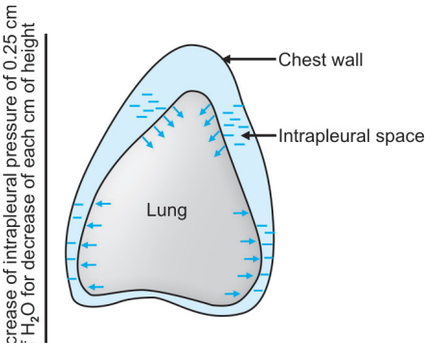


Fig. 3.20: Lung is a viscoelastic structure. So, it tends to collapse from the chest wall and tries to take a globular shape. The top of the lung collapses inward and the base of the lung tries to spread outward.Thus, a relatively more negative pressure is created at the top of the intrapleural space and a relatively less negative pressure is created at the base of the intrapleural space. So the intrapleural pressure increases from top to bottom of the lung by 0.25 cm of H2O per cm of decrease of height

(iii) Vital capacity (VC)

VC is a frequently measured clinical index of pulmonary function test. It is the largest amount of air that can be expired after a maximal inspiratory effort. It equals to the IRV plus V_T plus ERV. The normal value of VC in an adult male is about 4500 ml/ or 60 to 70 ml/Kg. The fraction of VC which is expired in the first one second during forced expiration is also an important parameter for lung function test and gives additional information. This is designated as FEV_I and is called as the timed vital capacity. For example, in some disease where airway resistance is increased such as in asthma, COPD etc, VC may be normal, but the FEV_I is reduced. It gives a useful information about the strength of respiratory muscles. In addition to the body height, weight, posture, etc., VC is also dependent on the chest and the lung compliance.

(iv) Total lung capacity (TLC)

It is defined as the maximum volume of lungs which can be inflated with the greatest possible effort. It equals to the VC + RV. The normal value of TLC in an adult male is about 6000 ml. (Fig. 3.21).

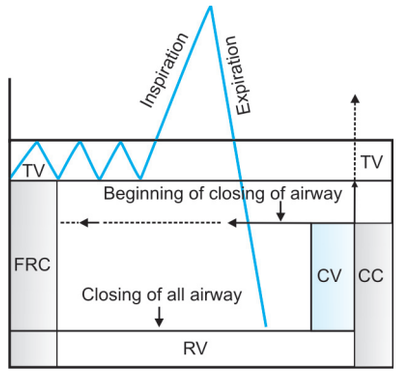


Fig. 3.21: The relationship between the functional residual capacity (FRC), closing capacity (CC) and closing volume (CV)

(v) Airway closure and closing capacity (CC)

During expiration when the lung volume is gradually reduced, then at certain volume of lung the small airways begin to close and therefore prevent any further expulsion of gas from the related alveoli. This causes the trapping of air in the concerned alveoli beyond the closed airways. The lung volumes at which this phenomenon begins to occur is called the closing capacity. This phenomenon of closing of airways first occure at the small airways in the dependent parts of the lungs. Then, with more and more forceful expiration larger airways are also gradually involved in closing. The mechanism of this airway closure is discussed in more details below.

The lung is made of a viscoelastic tissue. So, it tries to take the globular shape within the chest wall. Thus, the top of the lung collapses inward and the bottom of the lung spreads outward. So, a negative intrapleural pressure is created at the apex of the lung and a relatively positive intrapleural pressure (less negative than the apex) is created at the base of the lung. Hence the intraplural pressure increases from above downwards by 0·25 cm of H_2O for each centimeter of change in the height of lung. This intraplural pressure determines the regional alveolar size and the regional difference in compliance and ventilation of alveoli.

At normal resting end expiratory volume of the lung (or FRC), the gradient between the distending transpulmonary pressure and the transmural pressure is −5 cm of H_2O. This gradient of pressure make the airway patent. During inspiration this pressure gradient increases to –7 cm of H_2O which causes the patency of airway and the entry of air into alveoli. Then after inspiration, expiration starts and it is passive. During expiration the intra alveolar pressure is increased and this is due to the elastic recoil property of lungs and chestwall. So,air comes out and the gradient between the trans pulmonary and transmural pressure increases to –3 cm of H_2O. As this pressure gradient is still negative it favours the patency of small non cartilagenous airway. During forced expiration in a normal lung, this pressure gradient increases far above the atmospheric pressure and is transferred to the alveoli and the airways which causes expulsion of air and closer of airway. Actually during expiration the intra alveolar pressure is 2 cm of H_2O higher than this pressure gradient due to the addition of elastic recoil property of alveolar septa. During exhalation of air through airways intra luminal pressure gradually comes down along the length of the airways from the alveoli to the bronchi. Along the airway from alveoli to bronchi at a point where this pressure gradient becomes greater than the intraluminal pressure, the airway closes. This point is called the equal pressure point (EPP). When the EPP falls on the airways which are distal to the 11th generation and have no cartilages, then they close during expiration at certain lung volume. But, when this EPP falls on airways which are proximal to the 11th generation and have cartilages, then they are held open by these cartilages. The progressive movement of EPP from larger to smaller airways depends on the lung volumes and the force of expiration. When the lung volume decreases more and more or the expiration becomes more powerful, then the EPP moves progressively from smaller to larger airways and more and more airways close.

The closing capacity (CC) is measured by the single breath N_2-washout technique. In this process during breathing of normal air, the individual will slowly expire up to RV. Then, he will slowly takes a single breath of 100% O_2 up to maximum inhalation which will be held for few seconds and after that it will be expired slowly. During expiration the N_2 concentration and the volume of expired air is measured and recorded serially. Thus, a characteristics curve is obtained. This curve has four phases: Phase (I) dead space gas, Phase (II) mixed dead space and alveolar gas, Phase (III) mixed alveolar gas from all the alveoli and a phase (IV) at which there is sudden increase in concentration of N_2. The CC is the volume at which phase IV begins (Fig. 3.22).

The explanation is as follows. During inspiration the oxygen is preferentially distributed to the smaller alveoli at the dependent part of the lungs. This is due to the shape of the alveolar compliance curve which causes a larger change in the volume of smaller alveoli at the bottom of the lungs than the larger one at the apex of it. Therefore, N_2 will be more diluted by O_2 in the smaller alveoli at the bottom of the lung. During expiration, the initial exhaled gas (phase I) is the gas that filled the anatomical dead space and consequently contains no N_2. This is followed by a mixture of dead space and alveolar gas (phase II) which contains N_2. So, N_2 concentration will suddenly increase in this phase. Then in next phase the gas other than in dead space which has already been expelled in previous phase is expelled, containing gases coming from all the alveoli of lungs. This indicate phase III. Here, the N_2 concentration remains costant and maintains a plateau level, as the expired air is coming from all the alveoli without any closer of the airway. This phase will continue untill the point at which airway closure begins. At this moment the N_2 concentration suddenly again increases and the phase IV begins. The volume of lung at the begining of phase IV is the CC. This is because the expulsion of gases from the smaller airways ceases and exhalation is continued from those areas of lungs (i.e apex of lung) where the nitrogen concentration is higher due to the less dilution by O_2. Instead of N_2, other tracer gases such as

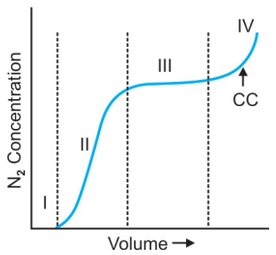


Fig. 3.22: Nitrogen washout technique for measuring the closing capacity (CC), FRC and dead space. First patient will take a deep breath of pure O_2 (100%). Then he will exhale steadily while the N_2 concentration in the expired air is continuously measured and a graph is prepared. Initially in phase I, the expired gas does not contain any N_2 as it comes from the anatomical dead space. This is followed by phase II which contain the mixture of dead space gas and alveolar gas. Here the concentration of N_2 in expired gas rises steadily as more and more alveolar gas containing N_2 is expired. Then comes the phase III where the concentration of N_2 in expired air takes a plateau level. This is because the expired gas in this phase contains only the alveolar gas which comes from all shorts of alveoli from top to the bottom of lungs and contain a average fixed concentration of N_2. Phase III terminates at closing capacity (cc) and is followed by phase IV, during which the N_2 content of the expired gas increases suddenly. CC is the lung volume (above RV) when the airways in the lower dependent parts of the lungs begin to close. The gas in the upper portion of lung is richer in N_2 than the gas in the lower dependent portion. This is because the alveoli in the upper portion of lung are more distend and less compliant at the start of the inspiration of O_2. So, they undergoes less ventilated and subsequently, the N_2 in them is less diluted by O_2. Therefore, the expired gas in phase IV comes mainly from upper part of the lungs containing more N_2 as the airways in the lower part of the lung closes. Phase III has a slight positive slope even before phase IV. This indicates that even during phase III, there is gradual increase in the portion of the expired gas which comes from the relatively N_2 rich upper part of the lung. The volume of the dead space is the volume of gas expired from begining of expiration to the mid portion of phase II

argon, helium, ^{133}xenon etc, also may be used in a similar way.

Thus, the lung volume above the residual volume (RV) at which these small airways begin to close is called the closing capacity (CC). It usually starts at the dependent part of the lungs, because the distending trans pulmonary and transmural pressure gradient is less at the base than the apex of the lung. So, it causes the four fold decrease in alveolar volume at the base than the apex of the lung. The caliber of the airways also decreases as the lung volume decreases from above downwards and make it prone to early closure.

The alveoli after closing of the airways continue to be perfused, but are no longer ventilated. Thus, it causes V_A/Q mismatch and intrapulmonary shunting.

In patients with normal lung during expiration the airways, small or large, do not close as FRC > CC, and all the airways remain open. But during forceful expiration the smaller airways (0·5 to 0·9 mm in diameter) shows a tendency to close. But the larger airways still remains open. However, it does not produce any impact on P_aO_2 or P_aCO_2. Now, if due to any reason CC increases or FRC goes much below the CC level, then more and more airways close and causes hypoxia and hypercarbia.

In patients with emphysema, bronchitis, asthma, pulmonary oedema, etc, the early airway closer occurs with mild active expiration, and at higher lung volumes. In all these conditions the airway resistance also increases. This, causes larger pressure decrease from the alveoli to the larger bronchi. Thus it creates a potential for positive intra-pulmonary and intra-airway pressure gradient which causes early closing of airways and traping of air in alveoli. Moreover, the structural integrity of airways are lost due to imflammation and scaring during the disease process. Therefore, these airways are easily collapsed or closed at higher lung volumes and low pressure gradient (Fig. 3.23).

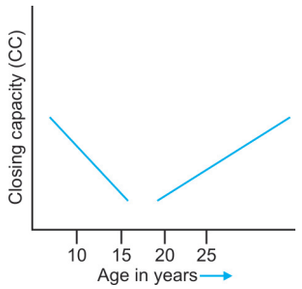


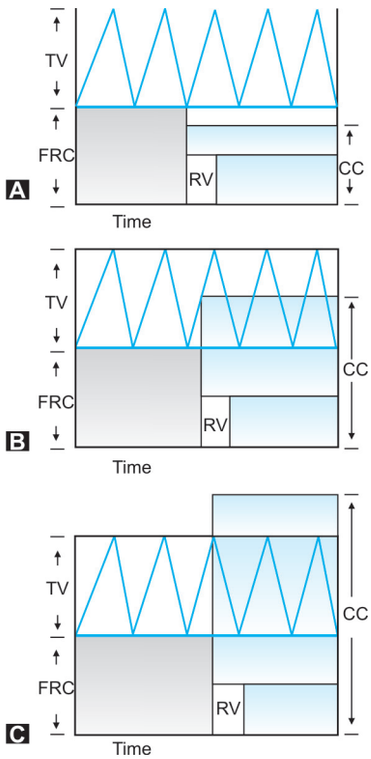
Fig. 3.23: The relationship between the age in years and the closing capacity in normal subject

In emphysema, the airways are poorly supported or stretched due to the loss of lung parenchyma and the intraluminal pressure becomes quickly negative. So, the EPP shifts close to the alveolus. Therefore, with only a mild forced expiration the airway closes early. Thus, the use of PEEP or CPAP in an emphysematous patient maintain the intraluminal pressure and prevent the airway collapse. In asthma, due to bronchospasm the middle sized airways are narrowed. During forced expiration they are further narrowed by positive intrapulmonary intraluminal pressure gradient. Thus PEEP or CPAP is also important to maintain the airway in asthma patient.

Closing capacity (CC) is also expressed as the percentage of total lung capacity (TLC). It is obtained by adding closing volume (CV) with the residual volume (RV). In healthy individual, CC is normally well below FRC. But it rises steadily with age and is the probable explanation for the normal age related decline in P_aO_2. At the age of 60, CC = FRC in upright position, but CC > FRC in supine position. On the otherhand, at the age of 40 CC < FRC in upright position but CC = FRC in supine position. Thus, in subject with normal lung CC becomes equal to FRC in age of 60 years in upright position and in the age of 40 years in supine position. CC is minimum at teenage between 15 to 20 years. Before 15 years and after 20 years CC continues to increase and tries to touch the FRC. Except age and position, smoking and obesity also affect CC. They decrease FRC and increase CC.

The Relationship between FRC and CC

The FRC and CC relationship is very important than the consideration of FRC and CC isolatedly. Becaue this relationship determines whether a given lung unit will remain in normal, atelectic or low V_A/Q ratio state. FRC is the normal resting end expiratory lung volume. Whereas CC is the expiratory lung volume when airways begin to close. In normal situation FRC > CC. It means during normal expiration when lung volume is gradually



Figs 3.24A to C: The relationship between the FRC and CC, which result in normal to low V_A/V_Q ratio (ventilation perfusion ratio) causing atelectasis. FRC is the percentage of total lung capacity (TLC) that exists at the end of expiration. Normally (Fig. A) the closing capacity remains below the FRC level and the alveoli open and empty fully before the airway closes. Increase in CC above FRC means airway closes before full exhalation during normal inspiration and expiration. When CC rises up to the mid level of tidal volume (in Fig. B) then alveoli open and closes partially and tidal volume is reduced to half. When CC level rises above the level of tidal volume (in Fig. C) then alveoli never open and atelectasis results

decreasing then FRC does not reduced to CC level where airways start to close. But this may happen even in normal lungs when the patient tries to expire forcefully and FRC goes below the CC level. So, in normal healthy patient with expiration of tidal volume small airways and alveoli remain open during both inspiratory and expiratory phase and helps in adequate gas exchange with normal V_A/Q ratio (Fig. 3.24).

In pathological condition FRC can decrease relative to CC or CC can increase relative to FRC, thus making the equation CC = FRC or CC > FRC. So, in such condition before completion of expiration upto tidal level or before reaching the FRC volume, airways start to close i.e CC volume reaches. Thus during entire period of inspiration airways open and air enter the alveoli. But during mid of the expiration when FRC goes below CC level or before reaching the full tidal volume airways start to close. This causes stoppage of ventilation and gas exchange and make these areas of lungs of low V_A/Q ratio. If the value of CC lies in between the upper and lower limit of tidal volume, then as the lung volume increases during inspiration, some previously closed airways (which occur during previous expiration) will open for a short time. Then, when during expiration lung volume recedes and FRC once again goes below the CC, the airways closes. Thus, during closing and opening of airways at expiration and inspiration, they will open for short period with less time in praticipating for fresh gas exchange, causing low V_A/Q ratio with hypoxaemia.

In severe pathological condition when the value of CC rises above the upper limit of inspiratory tidal volume then the equation will be CC >> FRC. In such situation as the CC always lies above the upper limit of tidal inspiratory volume, so no airway will open even during inspiration. Thus, all the alveoli will remain close both during inspiration and expiration. This condition is called atelectasis and will cause severe V_A/Q mismatch with severe hypoxaemia.

In condition when CC > FRC and if PEEP is applied to IPPV, then PEEP increases the FRC above the CC value and restore the normal FRC and CC relationship. Thus, no airway will close during respiration with normal tidal volume and no ventilation perfusion mismatch with hypoxaemia will occur.

4 Oxygen and Carbon Dioxide

HISTORY

William Harvey of London (1538-1657) had first described the circulation of blood in his book, named 'deMotu Cordis'. He was the pupil of Galileo. He had first observed the difference of colour between the arterial and venous blood. But he was not able to give any reason regarding this difference in colour and drew no firm conclusion about the function of the lungs. Then, between 1665 and 1675, Robert Hooke, Robert Boyle, Richard Lower and John Mayow of Oxford had made a understanding that certain components of the air was absorbed by the lungs and this process was necessary for both the maintenance of life and the burning of substances. At that time 'Phlogiston theory' was in voke for nearly 100 years. According to this theory 'phlogiston' was supposed to be a part of all the combustible substances and was liberated during their combustion or during an animal's respiration. When it is accumulated in excess as a result of combustion or by respiration in a closed containers, then it prevents further chemical activity, causing stopage of combustion or respiration resulting death.

After that, Joseph Priestly had first prepared oxygen from potassium nitrate in1771 and was first given the credit for discovering oxygen. But, instead of oxygen he called this gas as 'dephylogisticated air'. Because, he observed that this new gas was better than air for supporting respiration and combustion. He also supposed this, because it contained less phlogiston. So, he called it as 'dephylogisticated air'.

Then, Lavoisier had first clarified the use of oxygen in the process of respiration and combustion. Simultaneously, he also clarified the production of carbon-dioxide during combustion of substance and respiration. He, subsequently, demonstrated that oxygen was absorbed by the lungs and after metabolism in the body, it was eliminated as CO_2 and water. Later, he and Laplace coined the term oxygen (Oxy – acid, gene – producer) in 1779. They were also the first to compare the heat produced during respiration in animal with that produced during the combustion of carbon and showed the relationship between the oxygen used and carbon-dioxide produced. But, later Lavoisier was executed by gillotine during French revolution.

Then, Von Liebig had showed, in 1851, that carbohydrates and fats were the substrates of metabolism in cell and not carbon itself. In 1850, French chemist, Boussinggault also had first discovered that at a temperature of about 1000°C bariummonooxide absorb oxygen from air forming barium-dioxide and again release it at a more higher temperature. Then this process made charmed and was patented by his pupils, named the Brin brother, in 1880. After that they had formed a company and their company eventually then became the British Oxygen.

PROPERTIES

Oxygen is a tasteless, colourless and odourless gas. The concentration of O_2 in the atmospheric dry air at 760 mm of Hg pressure is 20.95%. The molecular weight of oxygen is 32. In atmosphere mainly O^{16} isotope of oxygen is present, but a small amount of O^{17} and O^{18} isotopes of it are also found. In one atmospheric pressure (760 mm of Hg) and at −183°C temperature, the oxygen becomes liquid (boiling point) and in same atmospheric pressure at −218°C temperature, it becomes solide (melting point). The critical temperature of oxygen is −118°C. So, at temperature greater than this, oxygen exists as gas and can not be liquified by raising the pressure. The relative density (air = 1) of oxygen is 1.105. The solubility of O_2 in plasma at 37°C temperature is 0.003 ml/100 ml of blood.

The O_2 cannot be ignited itself, but it aids combustion. So, substances often burn more vigorously or even explode in the presence of oxygen. Thus, the explosion can occur due to the presence of grease on the valves of oxygen cylinder. Due to some unpaired electrons, the oxygen molecule is attracted to the region of high flux in magnetic field and is so said the paramagnetic gas. Hence, this property of O_2 is utilized in some oxygen analysers to measure the concentration of it in a mixture of gases.

PREPARATION

Commercially, in large scale the oxygen is prepared or manufactured by the fractional distillation of liquid air. When this liquid air is gradually heated, then the more volatile nitrogen gas (boiling point at 760 mm of Hg pressure is –196°C) is separated

first followed by oxygen (boiling point is −183°C of 760 mm of Hg pressure). After that other components of air are also separated as required one after another.

STORAGE

Oxygen is usually stored at high pressure as a gas in cylinder or as a liquid in an insulated tank. For large hospitals, the storage of O_2 as liquid form in an insulated tank is much more economical. Tank with huge capacity of liquid oxygen is usually insulated by a high vacuum shell to maintain the inside temperature between −175°C to −150°C. But, still there is continuous evaporation of some liquid O_2 present within the tank. This is due to the continuous absorption of small amount of heat from the sorrounding, inspite of this vacuum insulation. So, if no oxygen is drawn off for long time from the tank, then this accumulated gas within the tank should be vented out to the atmosphere. All the O_2 tanks or cylinders are guarded with a pressure regulator valve maintaining a constant supply of oxygen at constant pressure from the tank or the cylinder into the hospital pipe line system.

The medical grade of O_2 contains 99 to 99·5% pure form of it. In most of the small hospitals, the O_2 is stored in more than two separate banks of H type of cylinders. They are connected by manifolds and valves. The number of cylinders in one bank and the number of banks depends on the anticipated daily demand of O_2 by this hospital. Only one bank is utilised at one time. The valves in the manifold connection reduces the cylinder pressure to the given pressure of the pipe line and supply gases. A bank automatically switches to another bank when one group of cylinders are emptied. In large hospitals where the liquid O_2 is used in tanks, should have a additional smaller O_2 supply system of compressed O_2 cylinders that can be used as reserve in emergency. Most of the anaesthetic machines accomodate one or two E type of O_2 cylinder in addition to pipe line connection to guard against the hospital pipe line failure. Anaesthesiologists must ensure the supply of O_2 from these cylinders before starting of any operation.

OXYGEN TRANSPORT IN BODY

The anaesthetists are mainly concerned about the transport and delivery of O_2 from the air to tissue at cellular level. The delivery of O_2 from the air to the cell at mitochondrial level is a continuous process and is occured in four phases. These are: (i) the mechanical act of breathing by which O_2 with air reaches the alveoli, (ii) the exchange of gas in alveoli by which O_2 passes from the air to the blood, (iii) the oxygenated blood, then, is transported to the tissues by circulation and finally, (iv) at the level of tissue capillaries O_2 enters into the cell and mitochondria.

Transport of Oxygen from Air to Alveoli

The mechanical act of breathing which transport O_2 from air to alveoli is fully discussed in separate chapter. But, here we will discuss only, how the PO_2 falls gradually during its transport from air to alveoli. So, when the O_2 reaches from atmosphere to the mitochondria in cell through alveoli, then the tension of O_2 (PO_2) drops in steps. This is called the oxygen cascade. The PO_2 drops in stages from 159 mm of Hg in dry air of atmosphere to the very low levels of 2 mm of Hg in the mitochondria. When the level of PO_2 in mitochondria falls below about 1 to 2 mm of Hg, which is called the Pasteur point, then the aerobic metabolism inside the cells stops. The partial pressure or tension of O_2 in the inspired air (P_1O_2) is about 159 mm of Hg (20 kpa). It is influenced by the baromatric or atmospheric pressure (P_B) and the fractional concentration of oxygen (FiO_2) in air. The normal barometric pressure at sea level is known as the one atmospheric pressure and is equivalent to 760 mm of Hg and in this condition the normal FiO_2 in air is 21% or 0.21.

So, the equation of P_1O_2 is:

$$P_1O_2 = P_B \times FiO_2$$
$$= 760 \times 21/100$$
$$= 159 \text{ mm of Hg.}$$

Then, the inspired air is saturated and diluted by water vapour, while it is passing through the air passages to reach the alveoli. It causes the reduction of PO_2, when it reaches the alveoli. The partial pressure of water vapour at 1 atmospheric pressure and body temperature (37°C) is 47 mm of Hg (Fig. 4.1).

So, when the inspired air saturated with water vapour reaches the alveoli, then the P_IO_2 comes down to 149 mm of Hg which is calculated by the following way :

$$P_1O_2 \text{ (Sat)} = (P_B - P_{H2O})\, FiO_2$$
$$= (760 - 47) \times 21/100$$
$$= 149{\cdot}73 \text{ mm of Hg}$$
$$\approx 149 \text{ mm of Hg}$$

Then, the inspired gas is further diluted by the addition of CO_2 and the removal of O_2 in the alveolus.

So, the final alveolar oxygen tension (P_AO_2) can be estimated by the 'alveolar gas equation'.

The equation is:

$$P_AO_2 = [F_IO_2\,(P_b - 47) - P_aCO_2] \times F$$
$$= [21/100\,(760 - 47) - 46] \times F$$
$$= 103{\cdot}73\ F$$
$$\approx 103 \text{ (while it is taken as 103 mm of Hg and F is ignored)}$$

Here P_AO_2 = alveolar O_2 tension, F_1O_2 = fractional inspired O_2 concentration. P_b = barometric pressure, 47 is the vapour pressure of water at body temperature (37°C), P_aCO_2 is the arterial CO_2 tension and F is the respiratory exchange ratio.

From the above equation, it is estimated that the normal value for P_AO_2 is

PO_2 in dry atmospheric air	159 (mm of Hg)
PO_2 in humidified air in airway	149 (mm of Hg)
PO_2 in alveolar air	104 (mm of Hg)
PO_2 in arterial blood	100 (mm of Hg)
PO_2 in tissue	40 (mm of Hg)
PO_2 in mitochondria	2 (mm of Hg)

Fig. 4.1: Oxygen cascade

103 mm of Hg at sea level. The normal P_AO_2 will decrease with (i) increasing altitude or decreasing P_b, (ii) increasing P_ACO_2 or (iii) with decreasing F_IO_2. So, a hypercapnic patient at high altitude would have a substantially lowered P_AO_2 .

Exchange of Gases in Alveoli

The oxygen tension of blood, entering at the arterial end of the pulmonary capillaries is 40 mm of Hg (SPO_2 75%). Whereas the PO_2 in alveolar air is 103 mm of Hg. Thus, this pressure gradient helps the O_2 to enter the blood from alveolar air across the alveolar membrane. In the blood O_2 first dissolved in plasma and then finally unite with Hb for its carriage to the tissues. Thus, at the venous end of pulmonary capillaries the PO_2 in blood is 103 mm of Hg. In the tissues, the tension of O_2 in the arterial side of the capillary blood is about 100 mm of Hg. The O_2 tension (Table 4.1)in the tissue is near about 40 mm of Hg. When the arterial blood passes through the tissues, it carries about 20 ml of O_2 as oxyhaemoglobin and about 0·3 ml of O_2 as physical solution per 100 ml of blood. As the O_2 tension in the tissue level is much lower, so the oxygen present as physical solution in plasma first passes from plasma to the tissues by diffusion. As a result the O_2 tension in the arterial plasma falls. So, the oxyhaemoglobin in the RBC being exposed to the low O_2 tension in plasma, dissociates and releases O_2 form the Hb. Then, this O_2 from RBC enters in the plasma and is carried as physically dissolved solution. Again this physically dissolved O_2 leaves the blood stream and enters the tissues. Thus, the portion of O_2 dissolved as physical solution in plasma remains always constant and this is measured as PO_2 of blood. About 30% of O_2 is liberated from blood to supply the tissues, when the tissue cells are in the resting phase. This dissociation of oxygen from oxyhaemoglobin in the RBC depends upon : the plasma O_2 tension, the plasma CO_2 tension, H^+ concentration, electrolyte content and the temperature of blood and tissues (Fig. 4.2).

The CO_2 tension and its content in the tissues are much higher than that of the capillary blood. Due to this difference of pressure, CO_2 diffuses from the tissues in the blood of capillaries. Thus, CO_2 tension in the capillary blood rises which also subsequently favours the dissociation of O_2 from oxyhaemoglobin and enters in the tissues. As the increase in PCO_2 in capillary blood favours the dissociation of O_2 from Hb, similarly the increase in PO_2 in tissues favours the dissociation of CO_2 from tissues. Hence, as a result of supply of O_2 to the tissues, the O_2 tension and O_2 content of the capillary blood fall. Thus, at the venous end of tissue capillaries O_2 tension of the blood is about 40 mm of Hg and O_2 content is about 14 to 15 ml as oxyhaemoglobin and about 0.15 ml as physical solution per 100 ml of blood. Subsequently, when this systemic venous blood with PO_2 of about 40 mm of Hg passes through the pulmonary capillaries into the lungs where in the alveoli PO_2 is about 103 mm of Hg, then O_2 again enter from alveoli into the systemic venous blood during passing through the pulmonary artery and capillaries. Therefore, O_2 tension (PO_2) rises and more oxy-Hb is formed in the red cells. Simultaneously, CO_2 diffuses out from the systemic venous blood of pulmonary artery into the alveolar air. CO_2 tension and H^+ concentration in the venous blood fall which also favour the entry of O_2 in the pulmonary capillary. The entry of O_2 in pulmonary capillary blood from alveoli also favours the exit of CO_2 from pulmonary capillary blood to alveoli.

CO_2 is much more soluble in plasma than O_2. So, hypercapnia is rarely a problem in pulmonary fibrosis which is discussed in Chapter- 3. It does occur only when the alveolar ventilation is severely inadequate and there is much V_A/Q inequality. If due to any cause the arterial PCO_2 increases other than ventilation, then by increasing the ventilation the extra CO_2 can easily be expired. But it accumulates when the ventilation is severely compromised. It is to be noted that in normal condition the difference between P_ACO_2 and P_aCO_2 is very small and alveolar ventilation (V_A) has a great impact on P_aCO_2 and P_aO_2. Doubling the alveolar ventilation (V_A) results in half of P_aCO_2 and half of V_A results in a doubling of P_aCO_2. The relationship between V_A and P_aCO_2 is exponential. If this change is entered into the 'alveolar gas equation', then we will get the relationship between the V_A and P_aO_2. It can also be seen that hypoxaemia develops rapidly than hypercarbia as V_A decreases. But, it can readily be corrected by a small increase in FiO_2 from 0.21 to 0.3.

Table 4.1: Partial pressure of gases in alveoli during normal ventilation and hypoventilation with breathing air

	Normal ventilation $PaCO_2$ = 40 mm of Hg	*Hypoventilation $PaCO_2$ =100 mm of Hg*
O_2	103 mm of Hg	43 mm of Hg
N_2	570 "	570 "
CO_2	40 "	100 "
H_2O	47 "	47 "
Total	760 mm of Hg	760 mm of Hg

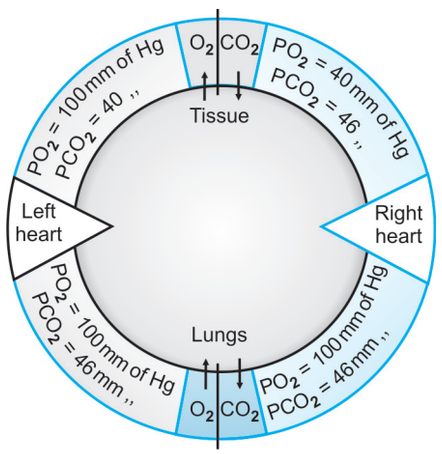


Fig. 4.2: Transport of O_2 in blood

Transport of Oxygen by Blood

The amount of O_2 transported or delivered to the tissues by blood depends on: (i) blood flow (cardiac output) and (ii) quantity of O_2 carried by blood (O_2 content). Again the O_2 content carried by blood depends on: (i) the rate of diffusion

of O_2 or oxygenation of blood in lungs (P_aO_2 and S_aO_2) and (ii) Hb content. On the otherhand, oxygenation of blood or diffusion of O_2 in blood depends on: the inspired and subsequently alveolar O_2 tension. The alveolar O_2 tension (P_AO_2), on the other hand, determines the arterial O_2 tension (P_aO_2). The alveolar and arterial O_2 tension difference (A-a) or gradient is the simplest way of quantifying the pulmonary diffusion. Other determining factors of P_aO_2: R-L shunt and pulmonary diffusion barriers. We should consider these two factors during determination of P_aO_2, only in pathological condition.

Oxygen is transported by blood: (i) by simple physical solution dissolved in plasma, and (ii) by combining with Hb.

Carriage of O_2 by simple physical solution dissolved in plasma

Very small proportion of total O_2 is carried in blood as physically dissolved solution i.e 0.3 ml/100 ml of blood/100 mm of Hg pressure (0.003 ml/100 ml of blood / 1 mm of Hg pressure). But this small quantity of O_2 is very important, because it alone reflects the tension of O_2 in blood (PO_2). First, when O_2 enters into the blood stream, it dissolves as physical solution in plasma. Then, from plasma the O_2 enter into the RBC to attach with Hb. At tissue level this plasma part of O_2 is first transferred to tissue cells and its position is rapidly taken over by O_2 liberated from Hb.

Carriage of O_2 by Hb

Except as physical solution, O_2 is also carried by combined with Hb, present in the red cells. This combination of O_2 with Hb is called oxyhaemoglobin which is loose and reversible compound. O_2 is quickly combined with Hb in the capillary of alveoli where its tension is high and then is equally quickly dissociated from Hb in the capillary of tissues where its tension is low.

Hb is a chromoprotein and has four subunits. Each sub unit (Table 4.2) contains one structure of haeme with one iron atom and is attached with the polypeptide chain of globin. So, a haemoglobin molecule contains 4 atoms of iron in ferrous form and its molecular weight is 68000. Each atom of iron can reversibly combine with one molecule of O_2. As one Hb molecule contains four haeme units and 4 iron atoms, so it reacts with 4 molecules of O_2 with formation of oxy-Hb (Hb_4O_8). Under physiological conditions, the reaction of Hb with O_2 takes place in 4 separates but simultaneous reactions, which are given below.

$Hb_4 + O_2 \rightarrow Hb_4O_2 + O_2 \rightarrow Hb_4O_4 + O_2 \rightarrow Hb_4O_6 + O_2 \rightarrow Hb_4O_8$

Table 4.2: Gradient of CO_2 and O_2 at tissue and pulmonary level

At Lungs		
A.	Venous PCO_2 = 46 mm of Hg	
	Alveolar PCO_2 = 40 mm of Hg	
	Gradient of PCO_2 = 6 mm of Hg	
B.	Venous PO_2 = 40 mm of Hg	
	Alveolar PO_2 = 103 mm of Hg	
	Gradient of PO_2 = 63 mm of Hg	
At tissue		
C.	Arterial PO_2 = 100 mm of Hg	
	Tissue PO_2 = 40 mm of Hg	
	Gradient of PO_2 = 60 mm of Hg	
D.	Arterial PCO_2 = 40 mm of Hg	
	Tissue PCO_2 = 46 mm of Hg	
	Gradient of PCO_2 = 6 mm of Hg	

Oxygen content

The oxygen content of blood is defined as the total quantity of oxygen (in millilitre) carried by 100 ml (1 dl) of blood. It is the total quantity of O_2 contained in the red cell plus the total quantity of O_2 dissolved in the plasma. 1 gm of fully oxygenated Hb contain only 1.39 ml of O_2 at 100 mm of Hg pressure. Average Hb level in an adult male is about 15 gm/100 ml. At an arterial PO_2 of 100 mm of Hg, Hb is 100% saturated.

So, the total O_2 content (CO_2) in 100 ml of arterial blood at 100 mm of Hg pressure.

$= 1.39 \times Hb \times \%$ of saturation $+ 0.003 \times P_aO_2$

$= 1.39 \times 15 \times 1 + 0.003 \times 100$

$= 20.85 + 0.3$

$= 21.15$ ml / 100 ml

Sometimes, this value is taken as average 20 ml/100 ml of arterial blood.

In the venous blood PO_2 is 40 mm of Hg and Hb is 75% saturated.

So, O_2 content (CO_2) in 100 ml of venous blood at 100 mm of Hg pressure.

$= 1.39 \times 15 \times 0.75 + 0.003 \times 40$

$= 15.63 + 0.12$

$= 15.75$ ml / 100 ml

Therefore, tissue extracts only 21.15 − 15.75 = 5.4 ml (average 5 ml) of O_2 from every 100 ml of arterial blood, while it is passing through the tissue capillaries. Thus, alternately every 100 ml of blood while passing through the lungs takes about 5 ml of O_2 (Table 4.3).

Oxygen Flux

The total amount of O_2 leaving the left ventricle per minute, when breathing air at sea level, has been termed as the oxygen flux. The normal oxygen content (CO_2) of arterial blood is 21.15 ml / 100 ml or 211.5 ml/litre. The normal cardiac output is 5 L/min.

So, oxygen flux = 5×211.5 ml/min = 1057.5 ml/min

The O_2 content of venous blood is 15.75 ml / 100 ml or 157.5 ml/L

Therefore, the total amount of O_2 leaving the right ventricle $= 5 \times 157.5 = 787.5$ ml/min

Hence, 1057.5 − 787.5 = 270 ml of O_2 is used up by the whole body during cellular metabolism in every minute and this amount of O_2 is taken up from alveolar air in every minute.

Table 4.3: Distribution of the amount of O_2 in arterial and venous blood

Oxygen	*Arterial blood*	*Venous blood*
Amount of O_2 as physical solution in plasma	0.3 ml / 100 ml	0.13 ml / 100 ml
Tension of O_2	100 mm of Hg	40 mm of Hg
Amount of O_2 combined with Hb	21 ml / 100 ml	15 ml / 100 ml
Saturation of O_2	100%	75%

Oxygen flux when Hb drops to 4 gm / 100 ml in anaemia

This can be calculated by the following way:

The O_2 content of 100 ml arterial blood with 4 gm of Hb

$= 1.39 \times 4 \times 1 + 0.003 \times 100$

$= 5.56 + 0.3$

$= 5.86$ ml / 100 ml

$= 58.6$ ml/litre

Therefore, O_2 flux = 5×58.6 ml/min = 293 ml/min. It indicates there will be no O_2 reserve.

Oxygen Delivery at Tissues

The mechanism of delivery of O_2 at the tissue level has been discussed in this chapter before. But, here we will discuss only some extra points. Previously, it was stated that the amount of O_2 delivered to the tissues depends on the cardiac output and the total oxygen content in blood. This overall flow rate of O_2 to the tissues is called the O_2 delivery. With a normal cardiac output of 5 L/min and with normal O_2 content (20 ml/100 ml of blood), the normal O_2 delivery to the tissues is 1000 ml/min.

Cardiac output varies with the size of the patient. So, cardiac output is commonly indexed to body surface area (BSA). This is called the cardiac index (CI) and can be represented as:

$CI = CO / BSA$ (L/min/m^2)

or $CO = CI \times BSA$

So, O_2 delivery can be expressed as index:

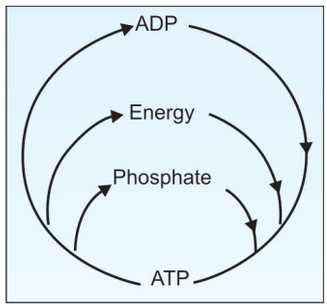
Therefore O_2 delivery (index) = $CO_2 \times CO$ (ml/min)

$= CO_2 \times CI \times BSA$ (ml/min/m^2)

In normal adult patient, the O_2 content (CO_2) = 20 ml/100 ml of blood the CI = 3 L/min/m^2 and BSA = 10 m^2. So the O_2 delivery index is 600 ml/min/m^2.

LACK OF OXYGEN OR HYPOXIA

The failure to receive adequate quantities of O_2 by the tissues is called hypoxia. Whereas, the total lack of O_2 is called anoxia and it is used in more restricted sense. In concious patient there are certain regulatory mechanism which prevents the tissue to suffer from the lack of oxygen. But, during the course of anaesthesia due to the lack of this regulatory mechanism the hypoxia has a deleterious effect (Fig. 4.3).



Light energy

$6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + 6O_2$

Fig. 4.3: Mechanism of formation of ATP

We get energy from the sun. Earth's atmosphere originally contain no O_2. But, during photosynthesis with the help of CO_2, plant absorbed this light energy in the form of glucose and release O_2 in the atmosphere.

Light energy

$$6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + 6O_2$$

But, within our cell this reaction is reverse. The solar energy which is incorporated in the glucose is released by oxidation with the help of oxygen and is used for cellular acitvity.

$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$ + Energy (Heat)

So, O_2 is very essential to maintain life. Some energy also can be obtained in absence of O_2 (anaerobic metabolism), but in terms of ATP production the anaerobic process is 1/19 as less efficient as aerobic process of metabolism. Because, during aerobic metabolism one glucose molecule produces 38 ATP, whereas in anaerobic process only 2 ATP is produced from one glucose molecule. Again lactic acid accumulation as a result of anaerobic metabolism will lead to metabolic acidosis. Then when O_2 becomes available, this lactate can further be metabolised to CO_2 and H_2O with further ATP formation.

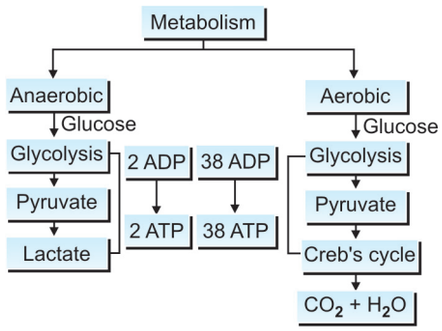


Fig. 4.4: Difference between aerobic and anaerobic metabolism

The hypoxia may result from various causes and according to the cause of hypoxia it can be classified into five types such as hypoxic hypoxia, anaemic hypoxia, stagnant hypoxia, histoxic hypoxia and conditions where P_{50} is low (Fig. 4.4).

Types of Hypoxia

Hypoxic hyopoxia

Here, the cause of hypoxia is defective oxygentation of blood or Hb in the alveoli of lungs. This results in incomplete saturation of haemoglobin by oxygen and less amount of O_2 is available in physically dissolved form, causing low oxygen tension in the arterial blood. Hypoxic hypoxia is produced in the following conditions.

(a) Decreased partial pressure of O_2 in inspired gas or air ($PIO_2\downarrow$)

This is due to:

i Fall in fractional concentration of O_2 in the inspired gas (FiO_2). This occurs during rebreathing or when the supplied gas is hypoxic in mixture,

ii Fall in barometric pressure, for example, at high altitude. At sea level, with 1 atmospheric pressure (760 mm of Hg) the air contains 20 to 21% O_2 and alveolar air contains 14% O_2. The remaining part of alveolar air is filled up by CO_2, N_2 and H_2O vapour. The total pressure exerted by these gases in alveoli is same

as the barometric pressure. So, the partial pressure of O_2 in alveoli is 14% of 760 mm of Hg or about 106 mm of Hg. At an altitude of 5500 meters or 18000 feet, the barometric pressure is only 380 mm of Hg. So, the partial pressure of O_2 in alveoli at this altitude will be 14% of 380 mm of Hg i.e. only about 50 mm of Hg. At mount Everest, where barometric pressure is only 236 mm of Hg, there alveolar PO_2 is only 40 mm of Hg (after saturated with water vapour at nasopharynx). Thus, due to diminution of partial pressure of O_2 in the alveoli which is due to the reduction of barometirc pressure at high altitude, less amount of O_2 will diffuse from the alveoli into the blood and as a result there will be reduced tension of oxygen in the blood.

(b) Fink effect or diffusion hypoxia

At the end of anaesthesia which is carried out by N_2O and O_2, when the patient breaths room air, then N_2O will diffuse out from the body tissues via venous blood into the alveoli. Subsequently the N_2 now being breathed with room air will fill the alveoli and diffuse back from the alveolar air into the tissue. Due to the higher solubility of N_2O than N_2, relatively small amount of N_2 will diffuse in from the alveolar air into the blood and restore tissue PN_2. But, much larger amount of N_2O than N_2 will diffuse out from the tissue in the alveoli and dilutes the alveolar O_2 concentration. Thus, it reduces the alveolar PO_2 and produces hypoxia which is opposite to the phenomenon occuring during the induction of anaesthesia with $N_2O : O_2$ mixture. This is called the diffusion hypoxia which is opposite to the second gas effect (Fig. 4.5).

Second gas effect

N_2O is more soluble in blood than N_2. So, during induction with N_2O, the volume of N_2O taken up by the blood is much higher than the volume of N_2 entering the alveoli from the tissue via blood. Therefore, the alveoli becomes gradually smaller and the

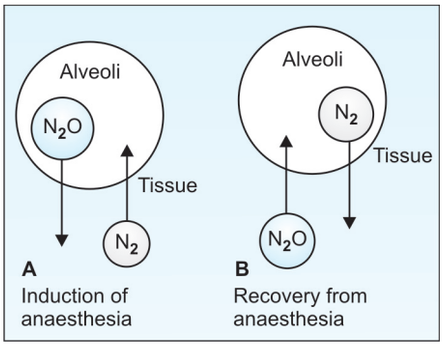


Fig. 4.5: The comparison between N_2O and N_2 regarding their speed and amount of entry and exit during induction and recovery from anaesthesia

partial concentration of the remaining gases in the alveoli increases. Now, if another inhalation anaesthetic agent (e.g. halothane) is also given with N_2O, then the fractional concentration of this anaesthetic gaseous agent will also increase. This phenomenon is called the second gas effect and increases the speed of induction by this agent. In the early part of induction, the volume of N_2O absorbed from alveoli is in the order of 1 litre/min. Although, the volume of N_2O in alveoli has decreased due to high absorbtion, the concentration of it does not reduce to the same extent, because the volume of alveoli is also decreased.

(c) Reduced alveolar ventilation

Arterial O_2 tension (PaO_2) depends on the alveolar O_2 tension (P_AO_2) which again depends on the alveolar ventilation. The relation between the alveolar ventilation (V_A) and the alveolar PO_2 (P_AO_2) is hyperbolic. It indicates (Fig. 4.6) that a reduction in ventilation of 2 litre/minute i.e. from 6 to 4 litre/minute has little effect on P_AO_2. Whereas, the reduction of ventilation from 4 to 2 litres/minute has very marked effect on P_AO_2 . Again, raising the inspired PO_2 by 64 mm of Hg (achieved by increasing the F_IO_2 from 0·21 to 0·3) results in a rise in P_AO_2 of the same amount like the reduction of ventilation from 4 litre to 2 litre/min. Raising the O_2 consumption also shifts the V_A and P_AO_2 relationship downwards and to the right. It means that what

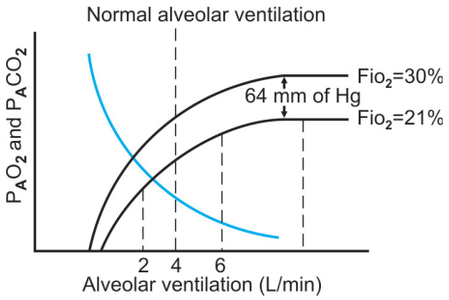


Fig. 4.6: The effect of change of alveolar ventilation on alveolar O_2 tension (P_AO_2) drawn in red line and alveolar CO_2 tension (P_ACO_2) drawn in blue line. It also shows the effect of change of FiO_2 from 21% to 30% on P_AO_2.Doubling of V_A results in halving of P_aCO_2 and vice versa. The relationship between V_A and P_aO_2 also shows that hypoxaemia develops rapidly as V_A decreases. But, it can be readily corrected by a small increase in FiO_2. On the otherhand, hyperventilation results in little increase in P_aO_2

was previously a perfect adequate alveolar ventilation may be grossly inadequate now, if the oxygen consumption increases. For example, 'halothane shake' is a common cause of increase O_2 consumption and hypoxic hypoxia which occurs in the early part of the postoperative period.

(d) Reduced diffusing capacity of O_2 across alveoli

Due to thickening of alveolar capillary membrane for any cause, there is also impairment of diffusion of O_2 from alveolar gas across the alveolar and pulmonary capillary membrane into pulmonary capillary blood, causing hypoxia. The examples of such type of hypoxia are : emphysema, pulmonary oedema, pneumonia, interstitial fibrosis, etc.

(e) Abnormalities of pulmonary mechanics

Many abnormalities in pulmonary mechanics such as asthma, emphysema, pneumothorax, collapse, obstruction in the air passages, etc, also produce hypoxic hypoxia by reducing the ventilation or decreasing the FiO_2 or changing the V_A/Q ratio.

(f) Venous admixture and shunt

This refers to some conditions when blood passes directly from the venous side of

circulation i.e. right side of the heart to the left side of heart without picking up any oxygen from lungs or passing through the zones of lung with low V_A/Q ratio, so that it is less oxygenated than normal. The examples of such direct communication between the right and left side of the heart are true shunt which is responsible for not picking up any oxygen from lungs. This takes place in PDA, patent foramen ovale or VSD etc, with pulmonary hypertension where blood flow from right to left side of the heart (true shunt).

Anaemic hypoxia

Here, the problem lies in the carrying of O_2 by blood to the tissues, but not in the oxygenation or uptake of O_2 by Hb in alveoli. The characteristic of this anaemic hypoxia is that the total O_2 content of arterial blood is reduced, but the partial pressure and the saturation of Hb by O_2 is normal. Therefore, the haemoglobin is fully saturated with O_2, but as the quantity of O_2 carrying Hb is low, so the total amount of O_2 carried by it is below normal. This is called the anaemic hypoxia. Anaemic hypoxia will result from:

(a) Anaemia

When the Hb concentration in blood becomes half, then the O_2 content of blood is also reduced to half. But the partial pressure of O_2 in blood remain the same. Thus, O_2 dissociation curve shifts to the left. But, for compensatory mechanism, anaemia causes increase in 2,3-DPG level, therefore shifting again the oxygen dissociation curve to the right at its normal position and favour the unloading of O_2 to the tissue. Shifting of the O_2 dissociation cure to the left prevents the unloading of O_2 to the tissues.

(b) Carbon monoxide (CO) poisoning or carboxyhaemoglobinaemia (Fig. 4.7)

As affinity of CO to haemoglobin is 250 times greater than that of the O_2, so a small amount of CO will replace the substantial amount of O_2 from Hb and will produce large amount of carboxyhaemoglobin. Therefore, little free haemoglobin will be available for carrying O_2. The other changes produced by carboxy-Hb is the shifting of O_2 dissociation curve to the left. The significance of this shifting of O_2 dissociation curve to the left is that it also unfavours the unloading of remaining O_2 to the tissues. Shift in the oxygen dissociation curve of Hb are usually presented mathemetically as changes in the P_{50} value. The P_{50} value is defined as the PO_2 at which Hb is 50% saturated. The normal value of P_{50} is 27 mm of Hg. It means that at 27 mm of Hg in O_2 tension Hb is only 50% saturated. A shift to the left lowers the P_{50} value i.e. it indicates that at 50% saturation of Hb the O_2 tension is less than 27 mm of Hg. Similarly a shift to the right raises the P_{50} value which indicates that at 50% saturation of Hb the O_2 tension is more than 27 mm of Hg. But the changes in P_{50} have only a modest effect on the uptake of O_2 in the lungs. The main consequence of alterations of P_{50} is on the release of O_2 in the tissues. A low P_{50} or shifting of O_2-dissociation curve to the left decreases the O_2 availability to the tissues and may therefore lead to cellular hypoxia. Similarly, a high P_{50} value or shifting of O_2 dissociation curve to the right increases the O_2 availability to the tissues. As the upper part of the O_2 dissociation curve is flat, so the changes in PO_2 at this portion have relatively little effect on the Hb saturation and therefore the blood O_2 content. Whereas, over the lower more vertical part of the curve, the changes in PO_2 have a very marked effect on the percentage of saturation of oxy-Hb, so the transfer of O_2 from Hb to the tissues. This changes in O_2 dissociation curve is also very crucial to the survival of patient, following a massive blood transfusion. Another significance of the shifting of the point P_{50} or O_2 dissociation curve is that in order to offload the same amount of O_2 to the tissues, the venous PO_2 is also reduced to a much lower level. When the Hb level is 14.4 gm/dl, the venous point is 40 mm of Hg. In anaemia (Hb = 7·2 gm/dl) the venous point is 27 mm of Hg. In 50% HbCO (Hb = 14.4 gm/dl) the venous point is 14 mm of Hg. So, although this shift of the oxyhaemoglobin dissociation curve has little effect on the arterial O_2 content, but its effect on venous PO_2 is very significant. At a cerebral venous PO_2 of 14 mm of Hg, the subject will be unconscious.

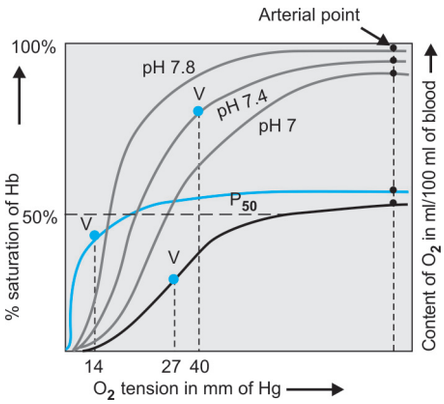


Fig. 4.7: Different O_2-Hb dissociation curves in different conditions, such as normal, acidosis and alkalosis (black curves), CO poisoning (green curve) and anaemia (red curve)

Coal gas has 10% CO as its content. Natural gas also contains trace amount of CO but does not cause CO poisoning. So, coal gas has been replaced by natural gas which contain about 90% methane, with only trace amounts of carbon monoxide. Carbonmonoxyhaemoglobin level also goes upto 10% in cigarette smoking. Car exhaust and commercial paint removal, containing methylene chloride causes also severe CO poisoning.

The treatment of CO poisoning consists of hyperbaric O_2 mixed with 5% CO_2, in order to shift the oxyhaemoglobin dissociation curve to the right towards its normal position (Table 4.4).

(c) Methaemoglobin and sulphaemoglobin

Methaemoglobinaemia is an another important, but uncommon etiology for development of cyanosis and anaemic hypoxia which demands prompt diagnosis and treatment. So, for quick evaluation the history, physical examination, bedside diagnostic

Table 4.4: Classification and causes of hypoxia

Hypoxic hypoxia	↓FiO_2, ↓Barometric pressure ↓V_A, Diffusion hypoxia, V/Q mismatch, Pulmonary diffusion defect, R → L shunt
Anaemic hypoxia	Anaemia, co-poisioning, methaemoglobinaemia, Sulphaemoglobinaemia.
Stagnant hypoxia	↓Cardiac output, MI, heart failure, dehydration
Histotoxic hypoxia	Cyanide poisoning
Low P_{50}	↓pH, ↓2,3-DPG

techniques and laboratory confirmation are all important. But, in the absence of significant history, mild cyanosis can easily be missed in dark skinned individuals during the preanaesthetic check up.

Actually methaemoglobinaemia is a condition where ferrous iron (Fe^{2+}) of the haemoglobin complex is oxidized to ferric iron (Fe^{3+}). Usually, under normal conditions methaemoglobin ($HbFe^{3+}OH$) is continuously being formed in the red blood cells of a normal individual by the process of autooxidation. But, a continuous reduction mechanism maintain the methaemoglobin levels in blood less than 1% of the total haemoglobin. The most important mechanism for converting the methaemoglobin back into the normal haemoglobin is the enzymatic reduction by NADH cytochrome-b5 reductase enzyme. Other minor alternative pathways of mathaemoglobin reduction utilizes the reduced form of NADPH which is generated by glucose-6-phosphate dehydrogenase in the pentose phosphate pathway. Glutathione and ascorbic acid also can reduce the methaemoglobin to normal haemoglobin directly, but quantitatively are not very important.

The accumulation of large amounts of the chocolate - brown, reversibly oxidised methaemoglobin in the red blood cells may be either inherited or acquired. The inherited condition producing methaemoglobinaemia is also due to two reasons: (i) a dominantly inherited abnormality in the synthesis of a special type of haemoglobin, called the haemoglobin M, in which the structural lesion prevents the reduction of methaemoglobin to haemoglobin and (ii) a recessively inherited deficiency in the synthesises of enzyme methaemoglobin reductase.

Thus in summary, the congenital causes of methemoglobin anemia include: haemoglobin M disease in which there is globin chain mutation defect (autosomal dominant) and deficiency of enzyme such as NADH cytochrome-b5 reductase (autosomal recessive). Hereditary methaemoglobinaemia, once regarded as a homogeneous clinical entity is now known that it is the result of at least 10 different mutations at three distinct gene loci : two at the locus coding for the α chain of haemoglobin, three at the locus that encodes the β chain of haemoglobin and at least five at the NADH dehydrogenase locus. The acquired methaemoglobinemia also can be caused by the exposure of haemoglobin to the coal gas, car exhaust, smoking and other oxidizing chemicals or drugs such as nitrites, xylocaine, prilocaine, phenacetin, acetanilide, sulphanilamide, etc.

The irreversible formation of another haemoglobin, causing anaemic hypoxia is sulphaemoglobin. It has distinct abnormal spectral properties and results from the administration of drugs, particularly sulphonamides. This condition is called the sulphaemoglobinaemia. The sulphaemo globinaemia also can be produced by other compounds that cause methaemoglobinaemia and these two conditions frequently coexist. Sulphaemoglobinaemia produces marked cyanosis, but disappears spontaneously as the cells containing the abnormal pigment are gradually removed from the circulation with the passing of time and further production is prevented.

As the methaemoglobinaemia results due the oxidation of iron from its ferrous (Fe^{2+}) to its ferric (Fe^{3+}) state, so the concomitant oxidation of haemoglobin protein may cause its precipitation as Heinz bodies and resulted in haemolytic anaemia. The methaemoglobin (ferric haemoglobin) can not carry oxygen and when present in excess, results in a functional anaemia. It also shifts the oxygen dissociation curve to the left and thus limits the release of oxygen to the tissues. So, the symptoms of methaemoglobinaemia are due to hypoxia and anaerobic metabolism. In many cases, there are no clinical features, other than cyanosis. But when the concentration of methaemoglobin rises to 20 to 45%, then anoxic symptoms like headache, fatigue, dysponea and lethargy may develop. There may also be alteration in the level of consciousness when methaemoglobin level rises to 44 to 55%. Cardiac arrhythmias, circulatory collapse, seizures and even death may occur at the methaemoglobin level of 70% or more.

The diagnosis of methaemoglobinaemia is based upon the presence of central cyanosis, unresponsive to oxygen therapy and decreased oxygen saturation in presence of still normal P_aO_2. Since, methaemoglobin has an absorption characteristic similar to that of deoxy haemoglobin, so its presence in the blood falsely lowers the saturation of Hb as read on the pulse oximeter. On the otherhand, oxygen saturation measured by pulse oximetry may be falsely normal. If co-oximetry is not available, methaemoglobin levels can also be estimated by the difference between the oxygen saturation calculated from the P_aO_2 and that measured directly by blood gas analysis. The saturation reported on the arterial blood gas analysis is based on the partial pressure of dissolved oxygen and assumes no abnormal haemoglobin is present. Therefore, the reported oxygen saturation from arterial blood gas analysis is higher than that measured by the pulse oximeter.

Methaemoglobinaemia induced by drugs or chemicals is spontaneously reversed when the agent is withdrawn. Most of the oxidising agents are eliminated by metabolism directly from the body, making diuresis ineffective. Supplemental O_2 should be administered.

Dialysis may be useful, depending on the specific compounds. Higher levels of pigment amounting to more than 30 to 40% of the total pigment can be life threatening and are best treated by the infusion of 1% methylene blue in the dose of 1 to 2 mg per Kg of body weight over 5 minutes. Cyanosis alone is not an indication for methylene blue therapy in methaemoglobinaemia. In patients with anaemia or cardiovascular disease where the manifestations of hypoxia are present, then methylene blue treatment may be indicated at a lower levels of methaemoglobin. After methylene blue, if clinical response is not observed within 1 hour, then the dose may be repeated. A methaemoglobin level of 40 g/L can be expected to decrease by half in 1 to 2 hour after beginning of treatment with methylene blue. However, as long as the oxidizing agent remains in the body, the methaemoglobin will be generated and additional doses of methelene blue may be necessary. This methylene blue dye helps to combine the highly efficient NADP linked methaemoglobin reducing system to methaemoglobin and thus will result in rapid reduction of methaemoglobin to haemoglobin in all patients, but not in G6PD deficient patients.

The side effects of methylene blue that occur during the treatment of methaemoglobinaemia include precordial pain, dyspnoea, restlessness, tremor, apprehension, and transiet blue colour of skin and urine. Methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, because it can cause hemolysis. Exchange transfusion for treatment of methaemoglobinaemia is indicated when: methaemoglobin level is very high, the patient is refractory to the treatment by methylene blue and the patient is deficient in glucose-6-phosphate dehydrogenase. Although methaemoglobinaemia due to methaemoglobin reductase deficiency also responds to methylene blue treatment, but this chronic disorder is best treated by the daily oral administration of 1 to 2 gm of ascorbic acid. Cyanosis due to haemoglobin M does not respond to any treatment, but is ordinarily a benign condition.

To conclude, low SPO_2 reading in the presence of normal P_aO_2 suggest the possible presence of dyshaemoglobin (methaemoglobin or other abnormal Hb) which may affect the accuracy of the pulse oximeter. This is because only two wavelengths of light are used in this device, one for oxy-Hb and another is for deoxy-Hb or reduced Hb. The role of laboratory co-oximeter which uses light of several wave lengths can identify and quantify the different types of dyshaemoglobins. Thus its role in such situations can not be overemphasized.

Stagnant hypoxia

This type of hypoxia occurs when there is decreased circulation in tissues or when the demand of O_2 at tissues level increases than the supply of it. Hence, it causes increased difference between the supply and demand of O_2 at tissue level. This hypocirculation of tissue is due to the reduced cardiac output, peripheral vasoconstriction, trauma, arterial occulation due to embolism or atheroma, etc.

Histotoxic hypoxia

Here, the diffusion of O_2 at the level of alveoli and transport of it through the blood to the tissues is alright. But the defect lies at the cellular mitochondrial level which impair the utilisation of O_2 by the cell and produce hypoxia. In mitochondria when glucose is oxidised, H^+ is removed by NAD and become NADH. Then this H^+ is passed down through the cytochrom enzymatic systems with formation of ATP and at the last react with O_2 to form H_2O. Thus poisoning of this cytochrome enzyme system by cyanide, nitropruside, etc, causes stoppage of this machine and make unable the use of O_2, delivered to the tissues causing the stoppage of aerobic metabolism and hypoxia. So, as the metabolism is stopped, CO_2 is not produced and O_2 is not utilised. Thus, reduced production of CO_2 by tissues causes fall in venous PCO_2 and subsequently reduced O_2 consumption rises mixed venous PO_2.

Condition where P_{50} is low i.e. oxygen dissociation curve is shifted to the left

P_{50} is the partial pressure of O_2 at which Hb is 50% saturated. The normal value of P_{50} is 27 mm of Hg, which means at PO_2 of 27 mm of Hg haemoglobin is 50% saturated. Low P_{50} means oxygen dissociation curve of Hb is shifted to the left which means at low partial O_2 pressure (< 27 mm of Hg) Hb is 50% saturated or in otherwords at 50% saturation of Hb it has low O_2 tension. For diffusion of O_2 at tissues, the partial pressure of O_2 at tissue level must be lower than that of the blood. But if partial pressure of O_2 at capillary level remains less, then O_2 will not flow from blood to the tissue, leading to cellular hypoxia. The example of low P_{50} value causing hypoxia are: acidosis, hypothermia, electrolyte imbalance, etc. (Table 4.5).

Effects of Hypoxia

The effects of hypoxia or anoxia vary according to the severity and the rate of occuring of it. When the supply of oxygen is cut off very rapidly, then sudden loss of consciousness will occur. But, if the hypoxia develops gradually such as in mountaineering, then the effects on the different systems of it are as follows:

Table 4.5: Effects of chronic hypoxia

1. CVS	:	↑Cardiac output, ↑BP, ↑HR, ↑sympathetic activity, Ferebral vasodilatation, ↑SVR
2. RS	:	↑Ventilation, ↑PVR
3. Metabolism	:	↓Aerobic metabolism, ↓ATP formation, ↑Anaerobic metabolism, ↑Metabolic acidosis
4. Haemoglobin	:	Polycythemia, ↑Viscosity of blood, cyanosis, reduced Hb is a better buffer
5. Organ failure	:	Depressed myocardium, unconsciousness

CVS

The hypoxia has profound effect on cardiovascular system. By direct effect it causes the systemic vasodilatation and fall of BP. This hypotension and hypoxia is compensated by ↑ sympathetic activity by peripheral baroreceptor and chemoreceptor stimulation. In the preliminary compensatory stage due to the stimulating effect of hypoxia and hypotension on vasomotor and cardioaccelerator centre, there is rise in heart rate, minute output and blood pressure. Therefore, the splanchnic and cutaneous blood vessels constrict. Thus, a large amount of blood is shifted from the non vital organs to the vital organs such as the heart and brain, so that they may be supplied by adequate amount of oxygen. In non-anaesthetized person if hypoxia continue, then hypotension will no longer be compensated and heart rate will increase further. But the force of cardiac contraction becomes gradually weaker due to the weakness of cardiac muscles caused by hypoxia and heart starts to fail. Then, CO and BP gradually goes to zero and cardiac arrest will result. In anaesthetised person, where there is no compensatory mechanism, this fall of BP and cardiac arrest will occur early. The prognosis of hypoxic cardiac arrest is extremely poor, because by the time the heart is stopped as a result of hypoxia, there is always nearly irreversible brain damage, though hypoxia increase the blood flow to most organs, especially the brain.

Respiratory system (RS)

It is seen that no alteration of respiration or breathing takes place, till the O_2 content in the inspired air is reduced to about 13 to 14%, when a slight increase of respiratory rate is seen. Later if the O_2 content in inspired air is more and more reduced, then respiration gradually more and more is stimulated. Thus, this increased ventilation try to keep the arterial O_2 tension normal, but washes out excessive amount of CO_2. This excess excretion of CO_2 also favours the better oxygenation. So, O_2 content of blood remains proportionately high, but the CO_2 tension falls. Then, gradually due to the low CO_2 tension the reflex respiration is not further stimulated and dies down, causing again less ventilation and reduced oxygenaton of blood with raised CO_2 tension. Consequently, respiration is again stimulated. In this way, respiration becomes alternately stimulated and depressed, resulting in what is known as the periodic breathing. The sequence of these events may be summarised as follows: O_2 lack stimulates breathing – washes out more CO_2 – arterial CO_2 tension is lowered – respiration is depressed – CO_2 tension in blood is again raised – breathing stimulated and so on. In this way, respiration goes on alternately waxing and waning during gradual increase in severity of hypoxia.

Thus, when the inspired O_2 concentration is reduced more and more and goes down below 15%, then cyanosis develops. The consciousness becomes dull and soon after this, the subject becomes unconscious due to the effects of hypoxia on higher centres.

But, when the lack of oxygen or hypoxia is very gradual then the results are different, because the compensatory changes are brought into play. It is best studied in subject ascending slowly to the higher altitudes. At higher altitude, the percentage of composition of air is same as over the plane. But, due to the less barometric pressure the air is more rarified or much less condensed, so that each ml of such air will contain less number of molecules of oxygen and other gases which causes less partial pressure of them than over the plane. The symptoms first appear at about 3657 metres or 12000 feet height where the barometric pressure is two third of 1 atmospheric pressure (760 mm of Hg) i.e. about 500 mm of Hg. At that height slight breathlessness and tendency to periodic breathing, especially during sleep, will appear. Nervous symptoms which closely resemble of alcohol poisoning will also appear. Gradually all the other systems will be affected and the subject will get what is called the 'altitude sickness' or 'mountain sickness'. The altitude sickness with mental depression, nausea, vomitting, etc, usually start 8 to 12 hours after the exposure to that height and may even present for few days after descent from this high altitude. But, generally these effects pass off quickly. If the oxygen lack is severe and the exposure is prolonged, then grave after effects may occur. For example, in hypoxia due to CO poisoning even when the composition of blood has been restored to normal, still the subject may not regain consciousness for many hours. He may pass into coma and may die. Even if the patient becomes conscious and apparently be normal, till there may be bouts of convulsions at intervals, owing to the irritation of nervous systems. Even the paralysis of various parts of the body may follow as a result of damage of the nerve cells. There may be complete dementia or just a temporary impairment of mind.

All these features point out that the hypoxia or anoxia devitalises and injures the whole body. From such observations Haldane has remarked that 'hypoxia or anoxia not only stops the machine, but also wrecks the machinery'. Hypoxia causes pulmonary arteriolar vasoconstriction and as a compensatory phenomenon shifts the blood from the hypoxic to the well ventilated area of lungs, keeping the P_aO_2 at normal. This is a beneficial effect for one lung intubation, lobar consolidation, etc. Chronic hypoxia due to intracardiac shunt such as ASD, VSD, PDA, etc, cause total pulmonary arteriolar vasoconstriction and increases the right sided pressure of the heart with reversal of shunt and arteriolar desaturation. This is because chronic hypoxia causes irreversible increase in PVR with pulmonary hypertension.

Metabolism

In hypoxia, anaerobic metabolic path is switched on with formation of less ATP and accumulation of lactic acid

(metabolic acidosis). The total mechanism is described below.

There is requirement of glucose for energy in all the tissues. But, in some tissues like brain and erythrocytes the requirement of glucose is substantial. Glycolysis is the (Fig. 4.8) major pathway of metabolism of glucose for energy and is found in all the cells. It is a unique pathway, because it can utilise oxygen if available (aerobic) and it can also function in the absence of O_2 (anaerobic) if it is not available. Glycolysis is the principal route of glucose metabolism leading to the production of pyruvate which undergoes further oxidation in the citric acid cycle through acetyl - CoA in the presence of O_2. Glycolysis also provides the main dependable pathway for the metabolism of fructose, galactose and other substrates derived from the diet. The crucial biological significance of glycolysis is its ability to provide ATP, still in the absence of O_2. So, it allows the skeletal muscle to perform glycolysis at very high levels when the aerobic oxidation becomes insufficient to survive anoxic episodes. Conversely, the heart muscle which is adapted only for the aerobic performance, has both the relatively poor glycolytic ability and poor survival rate under conditions of ischaemia.

Though, it has been customary to separate carbohydrate metabolism into anaerobic and aerobic phases, but this distinction is arbitrary. Because, the steps of reactions in glycolysis are the same as in the presence of oxygen or in its absence, except in extent and the end products. When the O_2 is not in supply, then reoxidation of NADH formed from NAD during glycolysis is impaired. Under these circumstances, NADH is only reoxidised during the reduction of pyruvate to lactate and the NAD so formed is used again at the step 5 of glycolytic pathway and allows further glycolysis to proceed. This reaction from pyruvate to lactate is catalysed by the lactate dehydrogenase. Thus, glycolysis also can take place under anaerobic condition. But, this has to given price for its limited action, regarding the low amount of energy liberated per mole of glucose oxidised. Consequently, to provide a given amount of energy, more glucose must undergo glycolysis under anaerobic condition as compared with aerobic conditions.

$$\text{Pyruvate} + \text{NADH} + H^+ \longleftrightarrow \text{Lactate} + NAD^+$$

The reoxidation of NADH to NAD during lactate formation allows glycolysis to continue even in the absence of oxygen by regenerating sufficient NAD^+. Thus, tissues that function under hypoxic circumstances continue the glycolysis to produce lactate. This is particularly true for skeletal muscle, where the rate at which the organs perform work is not limited by its capacity for

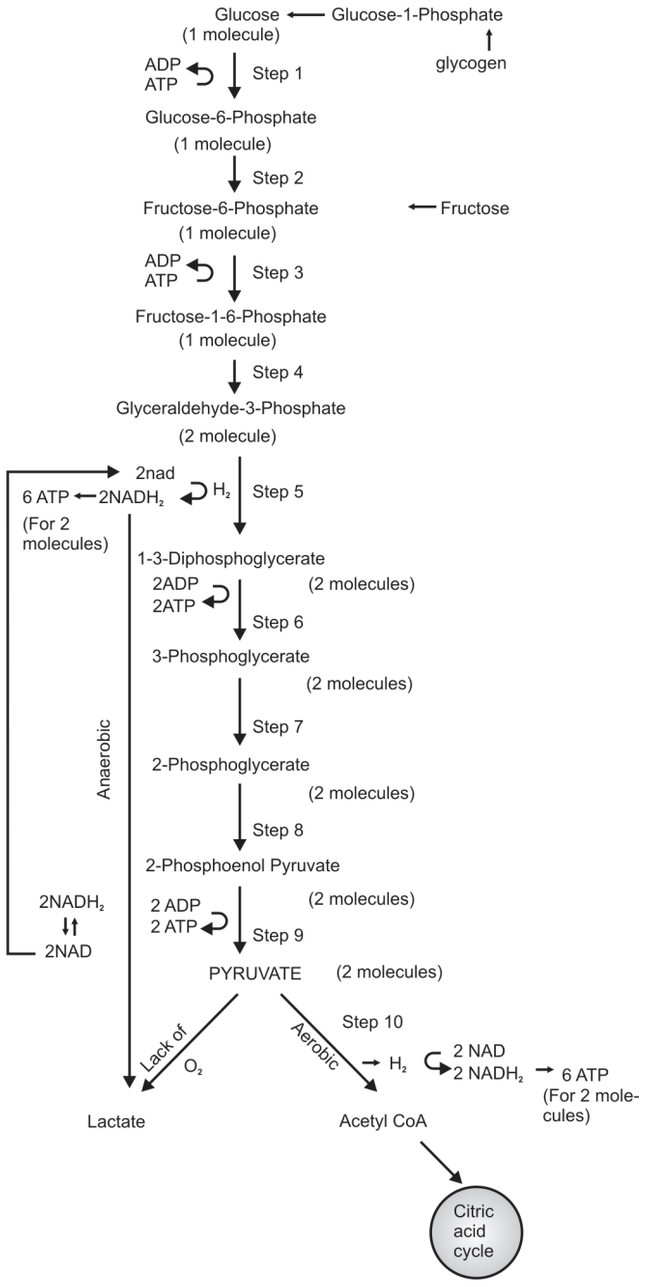


Fig. 4.8: Schematic representation of glycolysis

oxygenation. So the additional quantities of lactate thus produced may be detected in the tissues and in the blood and urine. Glycolysis which occur in erythrocytes, even under aerobic conditions always terminates in lactate. Because the mitochondrias that contain enzymatic machinery for aerobic oxidation of pyruvate through citric acid cycle are absent in RBC. The mammalian erythrocyte is unique in that about 90% of its total energy requirement is provided by only the glycolysis. Besides skeletal muscle and erythrocytes, other tissues that normally derive most of their energy from glycolysis and produce lactate include brain, GI tract, renal medulla, retina and skin. The liver, kidneys and heart usually take up this lactate and oxidise it, but will produce it only under hypoxic conditions. The overall equation for glycolysis to lactate is Glucose + 2 ADP + $2P_1 \rightarrow 2\ _L(+)$ Lactate +2 ATP + 2 H_2O All the enzymes for the glycolytic pathway are found in the extramitochondrial cytoplasm. They catalyse all the reactions involved during the glycolysis from glucose to pyruvate (in the presence of O_2) or lactate (in the absence of O_2) (Table 4.6).

In erythrocytes, the step six in glycolytic pathway from 1,3-diphosphoglycerate to 3-phosphoglycerate is bypassed. An additional enzyme, diphosphoglycerate mutase, catalyses the conversion of 1,3-diphosphoglycerate to 2,3-diphosphoglycerate (2,3-DPG). The latter is then converted to 3-phosphoglycerate. Thus, the loss of high energy phosphate as there is no net production of ATP when glycolysis takes this by pass route, may be an advantage to the function of red cell. The advantage is 2,3-diphosphoglycerate (2,3-DPG), which is present in high concentration in RBC combines with Hb and causes the decrease in affinity of Hb for O_2 with displacement of the oxyhaemoglobin dissociation curve to the right. Thus, its presence in the red cells helps oxyhaemoglobin to unload oxygen in the tissues while it is flowing through tissue capillaries.

Before the pyruvate can enter the citric acid cycle, it must be transported into the mitochondria. Within the mitochondria the pyruvate is first decarboxylated to acetyl CoA.

Pyruvate + NAD + CoA $\rightarrow$ Acetyl-CoA + NADH + H^+ + CO_2

The citric acid cycle which is also known as the Krebs cycle or tricarboxylic acid (TCA) cycle is a series of reactions in mitochondria. It brings about the catabolism of acetyl residues of acetyl-CoA liberating hydrogen ions which after oxidation while passing through cytochrome system lead to the release of most of the free energy in the form of ATP for tissue fuels. Thus the major function of this citric acid cycle is to act as the final common pathway for the oxidation of substrates including carbohydrates, lipids and proteins. This is because glucose, fatty acids and many aminoacids are all metabolised to acetyl CoA which can enter the citric acid cycle. It also plays a major role in gluconeogenesis, transamination, deamination and lipogenesis. Several of these process are carried out in many tissues, but the liver is the only tissue in which all the reactions occur to a significant extent (Table 4.7).

Essentially, the citric acid cycle starts with the combination of a molecule of acetyl-CoA with a molecule of oxaloacetate of 4 carbon atoms, resulting in the formation of a citrate with 6 carbon atoms. Then, this follows a series of reactions, in the course of which 2 molecule of CO_2 are released and again oxaloacetate is regenerated. The citric acid cycle is an integral part of the metabolic process by which huge amount of free energy in the form of ATP is liberated. During the course of oxidation of acetyl CoA in the citric acid cycle, reducing equivalents in the form of hydrogen or electrons are formed which are taken by NAD

Table 4.7: Total formation of ATP during catabolism of one molecule of glucose in anaerobic condition

Pathway	*Step*	*Method of production*	*No of ATP formed*
Glycolysis	Step 6	Substrate level	+2
	Step 9	Substrate level	+2
	Step 1	ATP consumed	−1
	Step 3	ATP consumed	−1
		Formation of net ATP	2

Formation of 2 molecules of NADH at step 5 is used for further metabolism of pyruvate to lactate in anaerobic condition.

Table 4.6: Total formation of ATP during catabolism of one molecule of glucose in aerobic condition

Pathway	*Step*	*Method of production*	*No. of ATP formed*
Glycolysis	S-5	Respiratory chain oxidation of 2 NADH	6
	S-6	Substrate level	2
	S-9	Substrate level	2
			10
	S-1	ATP consumed	−1
	S-3	ATP consumed	−1
		Formation of net ATP	8
Kreb cycle	S-11	Oxidation of 2NADH	6
or	S-15	Oxidation of 2 NADH	6
Citric acid	S-17	Oxidation of 2NADH	6
cycle	S-18	Substrate level	2
	S-19	Oxidation of FADH2	4
	S-21	Oxidation of 2NADH	6
		Formation of net ATP	30

Total formation of ATP molecules in aerobic condition from each molecules of glucose is 30 + 8 = 38

or FAD, forming NADH or FADH. These reducing equivalents then enter the respiratory chain, where large amounts of ATP are generated by the process of oxidative phosphorylation. This process is aerobic, requiring O_2 as the final oxidant of the reducing equivalents. Therefore, absence (anoxia) or partial deficiency (hypoxia) of O_2 causes total or partial inhibition of the cycle.

The enzymes of this citric acid cycle are located in the mitochondrial matrix, either free or attached to the inner surface of the mitochondrial membane. These enzymes facilitate also the transfer of reducing equivalents to the adjacent enzymes of the respiratory chain, situated also in the inner mitochondrial membrane.

When 1 mol of glucose is combusted in a calorimeter to CO_2 and H_2O, then approximately 2780 kJ are liberated as heat. But when this oxidation occurs in the tissues, then some of this energy is not lost immediately as heat, but is 'captured' as high energy phosphate in ATP. Usually 38 mol of ATP are generated per molecule of glucose when it is oxidized both by the glycolysis and citric acid cycle to CO_2 and H_2O. Assumming each high energy bond in ATP to be equivalent to 30·5 kJ, then the total energy captured as ATP per mole of glucose oxidised is 1159 kJ which is approximately 41·7% of the energy of combustion or metabolism. Most of the ATP is formed as a consequence of oxidative phosphorylation through cytochrome system, resulting from the reoxidation of reduced coenzymes such as NADH and FADH by the respiratory chain. The remainder is generated by phosphorylation directly at the substrate level.

Organ

Brain and retina is most sensitive to hypoxia. Due to the lack of O_2, the cerebral function gradually deteriorates like changes of mood to confusion to unconsciousness. If circulation stops, then the time taken for brain from stop of functioning to the extent of loss of consciouness is called the 'survival time'. Usually the survival time is 0·5 minute. Whereas the 'revival time' is defined as the time beyond which the recovery of function of brain is not possible. Usually the revival time of brain is 3 minute. Spinal cord is also very sensitive to hypoxia, for example, clamping of aorta, occlusion of anterior spinal artery, etc. Kidney has survival times of 10 minutes. More prolonged hypoxia than this causes renal tubular necrosis, renal cortial necrosis, etc. Chronic renal hypoxia causes increased synthesis of erythropoietin which subsequently causes ↑synthesis of erythrocytes from bone marrow and polycythaemia. In liver, the centrilobular cells being far remote from the systemic blood supply exhibit the first necrotic changes in response to hypoxia. In acute hypoxia the centrilobular necrosis of liver is seen.

Changes in blood (in chronic hypoxia)

In chronic hypoxia blood volume and haemoglobin concentration increases as a compensatory mechanism. Therefore, as haemoglobin content of blood rises, so the O_2 content in it is also raised. This is brought about in two ways: (i) The immediate effect is believed to be due to the contraction of spleen and the consequent pumping out of the stored red blood cells into the circulation. (ii) In the delayed effect, as the rate of multiplication of the erythrogenic tissues in the red bone marrow is stimulated by erythropoietin released from kidney in response to chronic hypoxia, so the red cell count is further raised. Therefore, many immature types of red cells (such as reticulocytes) are present in the blood during chronic hypoxia, indicating rapid erythrogenesis. This increased quantity of Hb is very helpful to carry adequate amount of O_2 in the lack of it. As for example at high altitude though Hb is not fully saturated with O_2, but as the total amount of Hb is being more, so the ultimate total O_2 supply to the tissues can be maintained. Due to chronic hypoxia as respiration is stimulated to maintain adequate oxygenation, so there is also tendency towards respiratory alkalosis due to washing out of excess CO_2. This is again combated by excretion of alkaline urine.

Changes in urine

Chronic hypoxia is associated with compensatory respiratory stimulation leading to respiratory alkalosis. Hence, in chronic hypoxia due to respiratory alkalosis kidney excretes alkaline urine as a compensatory mechanism. So, in urine the urea content is increased and ammonium salt is decreased. In other words, the ammonia coefficient of urine falls. Therefore, there is less excretion of acid in urine. All these are attempts to combat respiratory alkalosis (Fig. 4.9).

Delayed changes

The red marrow proliferates as a result of hypoxia. The yellow marrow may be transformed into red marrow. This is due to an attempt to increase the O2 carrying capacity by increasing the red cell production as a compensatory phenomenon. Vital capacity of lungs also increases in those people who live at higher altitude for long periods.

CAUSES OF POSTOPERATIVE HYPOXIA

Three types of hypoxia can occur post operatively. These are : hypoxic hypoxia, stagnant hypoxia (↓CO) and anaemic hypoxia (blood loss). The hypoxic hypoxia again may be due to diffusion problem, increased V/Q mismatch, and hypoventilation. But, whatever may be the cause of hypoxia, the O_2 flux and O_2 requirement should be matched. Otherwise, it will lead to hypoxia. The O_2 requirement also tremendously increases postoperatively due to shivering and pyrexia.

Some examples or causes of postoperative hypoxia are:

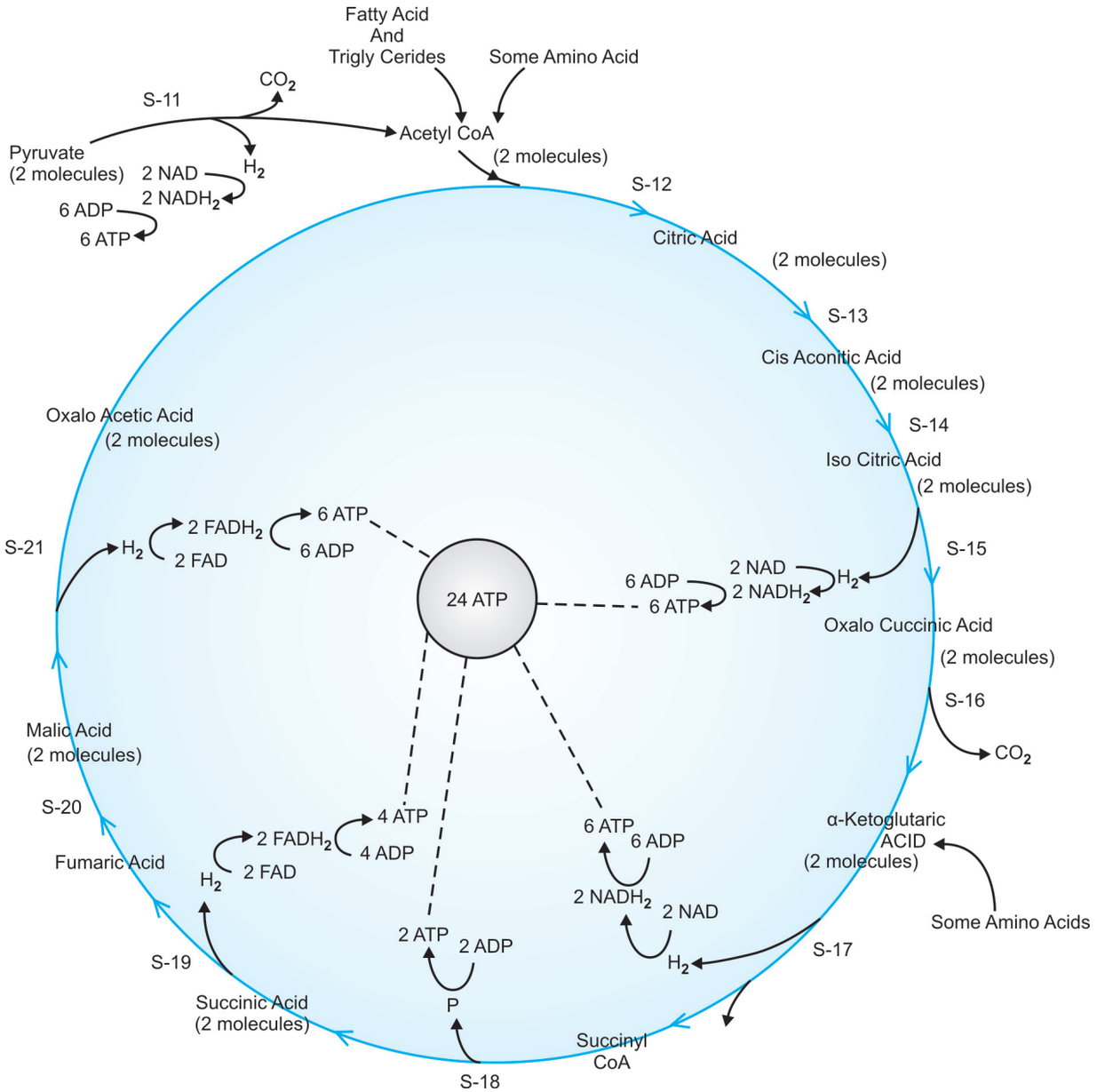


Fig. 4.9 : Schematic representation of citric acid cycle (tricarboxylic acid)

(i) Diffusion hypoxia or Fink effect

This is an example of hypoxic hypoxia.

(ii) Postoperative increased V/Q mismatch

It is also an example of hypoxic hypoxia. It is due to anaesthesia induced reduction of FRC below CC. Upper abdominal surgery causes 30% ↓FRC and increases V/Q mismatch. Elderly people, obese patients, COPD, smoking history, etc, also are more vulnerable to increased V/Q mismatch (hypoxic hypoxia).

(iii) Hypoventilation is due to:

a. drugs such as anaesthesia inducing agents, opiates, muscle relaxants, etc.
b. Obstruction of air passage by mucous plug, vomiting, blood, secretions, etc.
c. Pain preventing the free movement of thoracic and abdominal muscles.
d. Abdominal distention. It causes elevation of diaphram which contributes to hypoventilation.
e. Intra-operative hyperventilation. It causes deficit of body CO_2 reserve. So, to compensate this deficit after anaesthesia, spontaneous ventilation is reduced producing hypoxia.

(iv) Reduction of cardiac output due to any cause

It is an example of stagnant hypoxia.

So prolonged operation, thoracic and upper abdominal surgery, old age, previous lung diseases, heart diseases, huge blood loss, sickle cell disease, heavy sedation, inadequate recovery, hypotension, shivering, pyrexia, etc, where there is every possibility of hypoxia, needs post-operative O_2 therapy by masks at the rate of 3 to 4 lit/min to prevent this hypoxia. Increase in PVR by hypoxia may initiate R-L shunt through VSD, ASD or PDA, if they are patent.

HYPOXIA AND ALTITUDE

As the altitude increases, subsequently then the atmospheric pressure and then the partial pressure of O_2 in the inspired air is reduced. A list, depicted in the table, will show how the atmospheric pressure and subsequently the PO_2 in air will decrease with the increase of altitude (Table 4.8).

Normally, when a person breaths air, he becomes unconscious if SPO_2 falls to 50% or below. Usually this happens at the 23,000 feet height. But, when this person breaths only O_2 instead of air, then this height goes up to 47,000 feet at which or above unconciousness ensures inspite of inhalation of 100% O_2. The height at which the symptoms of altitude sickness actually starts or the physiological changes manifest are not common to all. Generally, within 10,000 feet height there is no necessity for additional O_2 to breathe. It has however been noticed that in most cases breathing becomes laboured at about 12,000 feet height. At about 18,000 feet heights, there is definite panting and other symptoms of altitude sickness appear. Addtional O_2 is necessary from 10,000 feet to 34,000 feet height. It has been generally observed that beyond 22,000 feet acclimatisation sometimes fails and there is a steady deterioration of condition advising to use O_2 supplementation. Pure O_2 is required from 34,000 feet to 42,000 feet height and pressure suit or pressure cabin becomes essential beyond 42,000 feet height.

Table 4.8: Partial pressure of O_2 in atmosphere at different height from sea level

Height	*Partial pressure of O_2 (PO_2)*	*Atmospheric pressure*
At sea level =	159 mm of Hg	760 mm of Hg
5,000 feet height =	130 "	–
10,000 " " =	110 "	522 "
15,000 " " =	90 "	–
20,000 " " =	73 "	346 "
30,000 " " =	48 "	–
50,000 " " =	18 "	85 "

Physiological Changes at High Altitude

At the high altitude the physiological changes occur in the following manner : High altitude − hypoxia − stimulation of periphral chemoreceptor − hyperventilation − washout of CO_2 − ↓ $PaCO_2$ − pH of CSF ↑ (alkaline) − induces renal excretion of bicarbonate − ↓ CSF bicarbonate (compensation) − normalisation of pH of CSF − allowing peripheral chemoreceptor to drive ventilation unopposed. Ventilation reaches maximum at 4th days and reaches to equilibrium over year if stays at high altitude for long time. When he again comes down to sea level, reverse reaction occurs which can be summarised as : ↑P_AO_2 − ↓peripheral chemoreceptor drive − ↓ventilation − ↑ P_aCO_2 −↑ brain PCO_2. As the pH of CSF and extracellular fluid of brain are now lower than normal (since the bicarbonate concentration is still lower than normal), so ventilation is driven by an increased central drive which gradually declines as CSF bicarbonate reaccumulates and brings back the pH of brain to normal. Other physiological changes have been described previously in hypoxia.

Sudden ascend to 10,000 feet height by an unacclimatised man leads to mountain sickness which ranges from weakness and shortness of breath to pulmonary and cerebral oedema. Prophylaxis of this can be taken by slow ascend or acetazolamide. Highest permanent habitation in the world is at about 16,000 feet height where P_AO_2 is only 45 mm of Hg, requiring 40% inspired O_2 concentration to restore the sea level condition. There are many major cities at 6,000 feet height, where PO_2 in inspired air is only 118 mm of Hg which is equivalent to 16% O_2 in air at sea level and P_AO_2 to 75 mm of Hg. At sea level, concentration and tension of O_2 in inspired air is 21% and 159 mm of Hg respectively. Alveolar O_2 tension (P_AO_2) with breathing air at sea level is 103 mm of Hg.

OXYGEN EXCESS OR TOXICITY

The oxygen toxicity is a complex phenomenon. So, inspite of much investigations over many years, still it remains an enigma. Although, it is possible that high O_2 tension could affect many, but not all the organ systems. It would also appear that certain organ systems are more susceptible than others. It is thought that the organs in body which are more susceptible to oxygen toxicity are lungs, retina, brain and cardiovascular system. Oxygen toxicity is a potential complication when FiO_2 of 0.6 or greater is given for more than 72 hours. The condition can be prevented in some cases by the use of PEEP, which allow FiO_2 values to keep below 0.6 for maintaining adequate P_aO_2 instead of higher FiO_2 while primary therapy for the underlying pathological condition is instituted. There is at present no evidence that pulmonary oxygen toxicity develops in man at an inspired O_2 concentration below 0.5, even with prolonged exposure. At inspired O_2 concentration of 0.5 (FiO_2 = 0.5), the damage occurs very slowly if it at all happens and at O_2 pressure greater than 3 ATA the pulmonary problem is overshadowed by the signs of central nervous system toxicity such as convulsions. The rate of development and the degree of damage to the lungs appears to be proportional

both to the concentration of oxygen and to the duration of exposure. Thus, O_2 is safe within a narrow spectrum of partial pressure to maintain life. It is lethal to life at partial pressure outside that ranges.

Pulmonary Effect

Prolonged inhalation of high concentration of O_2 is known to damage mainly the lungs. For the development of pulmonary O_2 toxicity, local alveolar than arterial O_2 tension is more important. Breathing 100% O_2 at 1 atmospheric pressure can cause discomfort and reduction in vital capacity after as little as 10 hours. But, recovery of this decreased vital capacity may take several days after resumption of breathing of air. So, administration of 100% O_2 for up to 10 hours at sea level with normal atmospheric pressure (760 mm of Hg) can be considered safe. But, administration of greater than 50 to 60% O_2 at sea level or 1 atmospheric pressure for more than 24 hours may lead to toxicity and is undesirable.

O_2 is irritant to the lungs and produces inflammation and congestion. This pulmonary O_2 toxicity is thought to be due to the generation of highly reactive metabolites of O_2 such as superoxide, activated hydroxyl ions, hydrogen peroxide, etc, in the cells. These metabolites of oxygen are cytotoxic and cause damage to the cellular DNA, sulfhydryl proteins and lipids of the alveolar epithelial cells. The O_2 mediated pulmonary injury produces a syndrome that is clinically and pathologically indistinguishable from ARDS. In mild cases the bronchopulmonary dysplasia and tracheobronchitis may also result.

The pulmonary oxygentoxicity shows: (i) increased capillary endothelial permeability causing accumulation of fluid in the interstitial space, (ii) depression of mucociliary transport function of airway, (iii) inhibition of phagocytosis of alveolar macrophages, (iv) changes in surfactant activity and its production. The exact highest concentration of O_2 which causes the lung damage is still not known and it varies with individual sensitivity, presence of concomitant previous lung diseases and the concentration and duration of exposure to O_2. In ICCU the FiO_2 should be kept as lower level as possible with optimum P_aO_2.

If only O_2 remains in alveoli, it is quickly absorbed by pulmonary capillary and subsequently alveoli collapses. At sea level in healthy subject, the normal ventilation is maintained by small hypoxic drive. But, in severe COPD patient the main ventilatory drive is severe hypoxia or low P_aO_2. So, therapy by high concentration of O_2 in such pathological situations remove this respiratory drive causing ↓ ventilation –↑ PCO_2 – ↓PaO_2 resulting respiratory arrest, arrhythmia and cardiac arrest. In such patient appropriate inspired O_2 concentration and ventilation is ensured by repeated blood gas analysis.

CVS Effect

The effects of increased arterial O_2 concentration or tension causing O_2 toxicity of CVS is as like as administering peripheral vasoconstrictor, producing ↑ peripheral vascular resistance, ↑BP and ↑HR.

Effect on Body N_2 Store

Inhalation of 100% O_2 causes rapid fall of arterial and body N_2 content. Blood is cleared of N_2 in few minutes, but brain tissue take 20 minutes to clear N_2 store. Whereas, the other tissues like fat, muscle, bone, etc, take few hours to clear their N_2 store. Thus, inhalation of 100% O_2 is used to remove the air and N_2 from body cavities and to prevent the air embolism. When a normal subject breath 100% O_2 the different values of tension of different gases in blood in comparison to when breath air are given in the table (Table 4.9).

From the above table we can see that PvO_2 during breathing of 100% O_2 is slightly higher than that of when breathing air. This is because of the shape of O_2-Hb dissociation curve characterised by the top part which is virtually horizontal. The amount of O_2 carried in physical solution is negligible compared with that in combination with Hb. So, the O_2 content of arterial blood during breathing of 100% O_2 is only slightly greater than that during breathing air. Therefore, there is very little difference between the mixed venous O_2 content and arterial O_2 content. This is because as we are now operating on the steep part of the curve where this small O_2 content difference is reflected by only a small PO_2 difference.

Table 4.9: Partial pressure of different gases in arterial and venous blood when breathing 100% O_2 and air

Tension of gases in arterial and venous blood	*Breathing 100% O_2 (mm of Hg)*	*Breathing of air (mm of Hg)*
$P_a O_2$	600	100
$P_a CO_2$	40	40
$P_a N_2$	0	569
PvO_2	50	40
$PvCO_2$	46	46
PvN_2	0	569

As the gases diffuse down along the gradient of their partial pressure at the level of alveoli and tissue, so the breathing of 100% O_2 containing no N_2 will enormously increase the rate of elimination of N_2 and other gases from a gas loculus within the body, such as penumothorax, emphysematous bullae, air embolism, etc.

Central Nervous System

In CNS convulsions, similar to those of grand mal epilepsy occur during oxygen toxicity.

Retrolental Fibroplasia (RLF)

The retrolental fibroplasia (RLF) is the result of O_2 toxicity in retina and is caused by retinal vasoconstriction. Due to high P_aO_2 the obliteration of most of the immature retinal vessels and subsequent new vessel formation at the site of damage is the principal pathology of this disease. So, the RLF is also called as a proliferative retinopathy. Leakage of extravascular fluid from

this new proliferation of blood vessels in retina also leads to vitreoretinal fibrosis, adhesions and subsequent retinal detachment. RLF usually occurs in infants exposed to hyperoxia in the NICU. It is related not to the FiO_2, but to an elevated retinal arterial PO_2. This is because, high FiO_2 is not always related to high P_aO_2 due to different lung pathology in neonates or prematurity which prevents the diffusion of O_2 through alveoli. It is not known the actual threshold level of P_aO_2 which is responsible for the development of this retinal damage. An umbilical arterial PO_2 of 60 to 90 mm of Hg is associated with a very low incidence of RLF. It should be noted, however, that there are also many factors which are involved in the development of RLF in addition to retinal arterial hyperoxia.

RLF is recently termed as ROP (Retinopathy of prematurity). It develops in 84% of premature infants born at ± 28 weeks of gestational period. But, fortunately it resolves in 80% of cases without any visual loss form retinal detachment and scarring. Risk of ROP increases not only with delivery at early gestational period (severity of prematurity), but also with the other comorbidities such as sepsis, ARDS, etc, which need management by ventilators with high FiO_2. In contrast to pulmonary toxicity, ROP correlates better with P_aO_2 than P_AO_2. Between 1940 to 1950s ROP had reached an epidemic lebel. This was due to the administration of high O_2 concentration ($FiO_2 > 0.5$) in incubators. So, the recommended P_aO_2 for premature infants receiving O_2 is 50 to 80 mm of Hg. But, if due to any cardiopulmonary reasons a premature infant needs arterial O_2 saturation of 96 to 99%, then it should not be withheld in the fear of ROP.

O_2 DELIVERY SYSTEM

The O_2 can be delivered at different concentration and at different atmospheric pressure by the different techniques such as nasal catheters, simple mask and pipe from oxygen cylinder, complicated anaesthetic machine, heart lung machine, O_2 pressure suit, etc. But, here only the few bed side methods of O_2 delivery system has been discussed.

Nasal Catheters or Cannulas

This is the most simplest bedside device for delivery of O_2 to the patients. It is available in all the sizes for adults, children, infants and neonates. Two types of nasal cannulas are used : one is soft, plastic, blind ended with an over the ear head -elastic adjustment and the second is dual flow with under the chin variable adjustment. The FiO_2 during the use of these cannulas is unpredictable. It is determined by: the total O_2 flow, tidal volume, respiratory rate and the nasopharyngeal volume of the patient which act as the O_2 reservoir during inspiration or during mouth breathing. Since, as the O_2 flows continuously through these catheter so 80% of the delivered O_2 is wasted during expiration which again depend on the rate of respiration. The FiO_2 increases by approximately 1 to 2% for each litre of O_2 flow during quite breathing. By the flow of 3 to 4 L/min, the FiO_2 can be increased up to 30 to 35%. Again by the flow of 5 L/min, the FiO_2 can be increased up to 40%. But the higher flow rate than 5 L/min is poorly tolerated by patient. This is due to the discomfort as the gas jets into the nasal cavity and causes dry crusting of the nasal mucosa (Table 4.10).

The advantages of nasal cannula are that it is comfortable, well tolerated and allows the patient to speak, eat, drink, etc during O_2 therapy. It is also nonclaustrophobic and allows long term use. It also can be used by cannula fixed with spectacles frame for more convenince or cosmetic purpose. To avoid the wastage of O_2 during expiration, the cannulas fitted with inlet reservoir are also used by the patients who are receiving long term O_2 therapy. This concept has resulted the development of valved reservoir device which stores the incoming O_2 during expiration till the inspiration occurs.

Table 4.10: Different O_2 delivery system, O_2 flow rate and FiO_2

Delivery system	*Flow rate (L/min)*	*FiO_2 (%)*
Nasal canula	2	25
	4	30
	6	40
Mask without reservoir	6	40
	8	50
Mask with reservoir	4	40
	6	50
Venturi mask	4	24
	6	28
	8	35
	10	40
	12	50

Cannulas providing O_2 to the patient are connected to the flow meter and cylinders or pipeline through a humidifier and a small bore tubing. Now a days, the paediatric sized nasal cannulas are also available for paediatric patient and this use has become increasingly common. During reduced minute ventilation due to any cause, the flow of O_2 through the cannulas should also be proportionately reduced. This generally requires a pressure compensated flow meter which accurately delivers the O_2 flow less than 1 to 3 L/min and will reduce the wastage. With the paediatric sized cannulas when the O_2 flows at the rate of 0.25, 0.5, 0.75 or 1 L/min, then the FiO_2 reaches 35%, 45%, 60% and 70% respectively.

Oxygen Mask with or without Reservoir

It is a simple, disposable and transparent plastic device which is placed over the face, covering both the nose and mouth. When it covers only the nose, it is called the nasal mask. The lower edge of the nasal mask rests on the upper lip surrounding the external nose only. The advantage of nasal mask over the cannula for delivery of O_2 is that it is not jetted into the nasal cavity like cannula and allows patient's comfort.

Both the nasal and the face mask are fastened to the patient's face by adjustable elastic headband. Some manufacturers provide a maleable metal nose bridge adjustment device for proper fitting of mask at the root of the nose. When the O_2 masks are used, then the patients receive the mixture of O_2 and entrained room air which enters through the leak between the mask and face. In some masks there have some small room air entrainment holes near the connection between the mask and the tubing which lead to the flow meter.

The body of the face mask actually acts as a reservoir for both the inspired O_2 and expired CO_2. So, a minimum O_2 flow of approximately 5 L/min is needed to avoid rebreathing during the use of face mask. The level of desired FiO_2 during the management of hypoxia with mask depends on the O_2 flow, mask volume, tidal volume and the respiratory rate (pattern of ventilation) of the patient. Usually, during normal breathing the FiO_2 reaches 30 to 60%, when the O_2 flow varies between 5 to 10 L/min. The FiO_2 can be higher with low respiratory rate or increased tidal volume. Masks are used for patients who need high level of FiO_2 than nasal cannula and for short period of time such as during patient transport, in the post anaesthetic care unit and in emergency department, etc. But, it is not the device of choice for delivery of O_2 in patient who is suffering from severe hypoxaemia, tachypnoea or unable to protect their airway from aspiration.

Sometimes a plastic bag is attached to the face mask, which acts as a reservoir of O_2 during inspiration. These are called the reservoir face mask. These are more scientific than the usual cannula or only face mask without reservoir. The reservoir masks are again of two types: the rebreathing reservoir mask and the nonrebreathing reservoir mask. In rebreathing reservoir mask the patient's expired air enters the bag and refill it. But usually this expired gas comes from the patient's dead space and does not cause any significant rebreathing of CO_2. In non rebreathing reservoir mask, a valve is used between the bag and the mask which prevent rebreathing. The successful use of reservoir face mask needs sufficient flow of O_2, so that the bag is atleast partially full during inspiration. Typically with O_2 flow of 5 to 10 L/min the FiO_2 reaches between 40 to 60%. With flow of 15 L/min, the FiO_2 may approach 100%. So this type of mask is indicated for severe hypoxaemia, MI or carbon monoxide poisoning, etc.

Venturi Mask

These masks are also called the air entrainment mask or high air flow with oxygen entrainment (HAFOE) system. In this system O_2 is directed by a small bore tube in jet. Then, a large amount of air is entrained through the ports which are present by the side of the small tube and mixes with the O_2. The final O_2 concentration depends on the ratio of air drawn in through the entrainment ports and the principal O_2 flow. The manufacturers have developed both the fixed and adjustable type of venturi mask, where the amount of air entrained in the mask can be adjusted or fixed. The venturi mask is used for patients whose hypoxaemia can not be controlled by nasal canula or face mask. But, it is always advised to use the minimum flow of O_2 in the ventimask. As a large amount of air entrains in the mask, so the patients get adequate amount of flow for inspiration. Hence, patients with COPD who tend to hypoventilate with moderate FiO_2 are the best condidates for the venturi mask. As low flow of O_2 is used in venti mask, so slight interruption of O_2 flow may cause serious problem resulting hypoxaemia and hypercarbia. On the otherhand, if the entrainment ports are accidentally obstructed by any means such as by bed sheet, patient's hands etc; then FiO_2 will suddenly increase due to getting pure O_2 without mixing with air.

Oxygen Hood

Many young infants and neonates do not tolerate appliances like nasal cannulas and masks over their faces, though different paediatric sizes of its are available. So, for them the oxygen hood is the best alternative for short terms O_2 therapy. Actually hood is ideal for newborns and inactive infants. While the nasal canula, face mask or ventimask provide greater acceptability for mobile paediatric group of patients. Hoods can be of different sizes for different age group of paediatric patients. Some are simple Plexiglass box. But, others have definite system for sealing the neck opening. There should be no attempt to completely seal the system which can cause the accumulation of CO_2. So, to remove CO_2 the hood needs minimum flow of O_2 greater than 7 L/min, but flows of 10 to 15 L/min are adequate for majority of patients.

HYPERBARIC OXYGEN

Hyperbaric condition is defined as the circumstances where the total enviornmental or atmospheric pressure is increased. Thus the O_2 therapy at this hyperbaric condition is known as the hyperbaric oxygen. The higher will be the atmospheric pressure, the higher will be the PO_2 in air for a fixed concentration of it in air. This is because in higher atmospheric pressure there will be increased concentration of O_2 molecule in a given volume of air which will increase the partial pressure of O_2. The higher will be the PO_2 in the inspired gas or air, the higher will be the alveolar PO_2 and arterial PO_2, provided the diffusion of O_2 through the alveolar membrane is normal. The relationship between the alveolar PO_2 and arterial PO_2 is almost linear. The higher will be the arterial PO_2, the higher will be the amount of oxygen carried as physical solution in arterial blood. This is because the amount of O_2 carried as physical solution in blood only determines the PO_2. But the amount of O_2 carried by Hb which determines the oxygen saturation will not increase.

At the sea level the fresh air contains 21% O_2, the rest being mainly nitrogen.

At the sea level the barometric pressure is of 760 mm of Hg and the partial pressure of O_2 in inspired air is thus 159 mm of Hg, which is 21% of 760 mm of Hg. When air is inspired then during its passage through respiratory tract it rapidly becomes saturated with water vapour at body temperature in the airway and on entering the alveoli it mixes with alveolar gases which contains expired CO_2. The partial pressure of water vapour and CO_2 accounts for about 47 mm of Hg and 40 mm of Hg respectively of the total alveolar gaseous pressure which is 760 mm of Hg and thus leaving pressure of 673 mm of Hg as only for the combined pressures of nitrogen and oxygen in the inspired air. At 1 atmospheric pressure air contains 78% N_2 and it comes down to 75% when reaches the alveoli. So, the partial pressure of N_2 in alveolar air is 75% of 760 mm of Hg or 569 mm of Hg. Thus, the partial pressure of O_2 in alveolar air or alveolar O_2 tension (P_AO_2) is 673 − 569 = 104 mm of Hg. Thus when 100% O_2 alone is inspired, then nitrogen is displaced from the alveoli, leaving the whole 673 mm of Hg partial pressure for only O_2. Thus, the alveolar O_2 pressure or tension can readily be calculated when breathing 100% O_2 at various ambient pressure from the following formula.

$$P_AO_2 = P_IO_2 - P_{H_2O} - PCO_2$$
$$= 760 - 47 - 40$$
$$= 673 \text{ mm of Hg}$$

P_IO_2 = Inspired partial pressure of O_2 at different atmospheric pressure.

P_ACO_2 = Alveolar partial pressure of CO_2 (usually 40 mm of Hg)

PH_2O = Alveolar pressure of water vapour (47 mm of Hg at 37°C).

Table 4.11 shows the alveolar O_2 tension or pressure at different atmospheric pressure when pure or 100% O_2 is administered.

The alveolar PO_2 is the principal determining factor of arterial PO_2. Normally the difference between the two is small (2 to 4 mm of Hg) and is mainly due to the venous admixture.

Table 4.11: Different alveolar O_2 tension in relation to different atmospheric pressure

Atmospheric pressure ATA	*Alveolar PO_2 tension (P_AO_2 in mm of Hg)*
1	673
2	1438
3	2193
4	2953
5	3713
6	4473

Oxygen is carried in blood by chemical combination with Hb and as dissolved physical solution in plasma. One gram of Hb combines with 1.34 ml of O_2 at one atmospheric pressure. Assuming haemoglobin concentration is of 14.6 grams per 100 ml of blood, the amount of O_2 which can be carried as the chemical combination with Hb will be 19.6 ml per 100 ml of blood. When breathing air at one atmospheric pressure, Hb is only 97% saturated with O_2. So only 19 ml of O_2 which is 97% of 19.6 ml is carried per 100 ml of blood. In a healthy individual when 100% O_2 is breathed at one atmospheric pressure, the Hb becomes fully saturated and carries maximum up to 19.6 ml of O_2. By increasing the atmospheric pressure this amount of O_2 carried by Hb can not be increased.

In equilibrium the amount of physically dissolved oxygen in plasma is proportional to the partial pressure of O_2 in alveolus and which again depends on the atmospheric pressure. Normally the plasma contains 0.003 ml O_2 /100 ml blood/mm of Hg arterial O_2 pressure. When breathing room air at an alveolar PO_2 of 104 mm of Hg which corresponds to the arterial O_2 tension (P_aO_2) of 100 mm of Hg at equilibrium, then the amount of dissolved O_2 as physical solution mounts to 0.3 ml O_2 per 100 ml of blood. If the P_AO_2 rose to 673 mm of Hg (when the patient breathed pure 100% oxygen at 1 atmospheric pressure) then the P_aO_2 rises to 600 mm of Hg and the amount of physically dissolved O_2 in plasma would be 1·8 ml per 100 ml of blood. If a subject breathes O_2 at 3 ATA, then the P_AO_2 will be 2193 mm of Hg and arterial PO_2 will be 2000 mm of Hg. In this situation the amount of physically dissolved O_2 would be 6 ml / 100 ml of blood. Here the dissolved O_2 would be sufficient to supply all the O_2 required for a resting man and venous blood would return to the lungs with the Hb still fully saturated.

Thus, at normal atmospheric pressure, the O_2 content of arterial blood is largely dependent on the Hb content. But when hyperbaric O_2 is given then the Hb cannot increase its O_2 load, because it is already fully saturated and in such circumstances as the P_AO_2 rises so the O_2 content of plasma carried only by the physical solution increases.

When an individual is breathing room air, his O_2 stores as the physically dissolved part in plasma are extremely limited and confined mainly to O_2 carried by Hb. However, O_2 stores in the dissolved form in plasma are considerably increased when the hyperboric O_2 is given. At 3 ATA, O_2 is physically dissolved in body water including plasma to the extent of about 6 ml / 100 ml. In a 70 Kg adult, with 50 litres body water, this would create a potential O_2 reservoir of $6 \times 500 = 3000$ ml of O_2. So, such increase in O_2 store will theoretically allow the tissues to survive temporary anoxia for much longer periods which is not possible without hyperbaric O_2 .

It was also stressed before that the tissue O_2 levels depend not only on the arterial O_2 tension, but also upon other factors which are responsible for delivery of O_2 to tissues. These include haemoglobin, cardiac output, its distribution in different tissue and some transfer factors. The hyperbaric O_2 may also cause some physiological adjustments which tend to offset the increase in tissue O_2 levels. For example, cerebral blood vessels may constrict in response to changes in CO_2 transport and thus limits the increase in cerebral tissue O_2 tension.

Today, the clinical applications of hyperbaric O_2 are only confined to some unusual

disease processes which include: carbon monoxide poisoning, gas gangrene, congenital cardiac anomalies, peripheral vascular insufficiencies and cancer therapy.

Carbonmonoxide has considerably greater affinity for Hb than O_2. So, exposure of even low concentration of carbonmonoxide (CO) to Hb rapidly leads to 'anaemic hypoxia', because this gas interfare with the ability of Hb to combine with O_2 and its transport. So, prompt institution of hyperbaric O_2 therapy has an important part to play in the management of carbon monoxide poisoning. O_2 therapy between 2 to 3 atmospheric pressure alleviates this situation in three ways: (i) it provides enough amount of physically dissolved O_2 in the plasma to keep the patient alive. (ii) It causes the shift of the O_2 dissociation curve to the right – thus enabling the remaining oxyhaemoglobin to give up more O_2 at tissue level. (iii) It accelerates the rate of dissociation of carboxyhaemoglobin twice than that achieved by conventional treatment with 5% CO_2 in 100% O_2 at normal (one) atmospheric pressure. The treatment by hyperbaric O_2 should be continued until the carboxy haemoglobin is no longer detectable in the blood by which time the consciousness will return, provided there has been no brain damage.

OXYGEN HAEMOGLOBIN DISSOCIATION CURVE

The haemoglobin is a complex molecule of haeme and globin. Again the haeme part of haemoglobin is formed by a divalent iron (Fe^{2+}, +2 charges) atom and 4 porphyrin rings. In a haemoglobin molecule there is four heme subunits. So, there is four divalent iron atom in each Hb-molecule. Only divalent Fe^{+} atom can combine with O_2 and each iron atom takes only one molecule of O_2. So, one Hb molecule can carry four O_2 molecules. The globin part of Hb consists of two α and two β subunits and these four subunits of globin are held together by weak bonds.

Each gram of Hb interacts and combines chemically with 1.39 ml of O_2. This interaction between Hb and O_2 to form oxy-Hb occurs in 4 steps. However, every step brings some conformational changes in Hb and acclerates the next step. Thus, binding of first 3 molecules of O_2 with Hb greatly accelerates the binding of last 4th molecule of O_2 and is responsible for last 75 to 100% saturation of Hb which is again responsible for the peculiar S-shaped line of oxy-Hb dissociation curve. After 90% saturation of Hb by O_2, the availiability of receptors on Hb for binding of O_2 suddenly declines. Then, O_2 combines with Hb very slowly and saturation rises gradually up to 100%. After that the oxygen saturation of Hb does not rise further as all the haemoglobin are combined with O_2 and nothing left. But, only O_2 tension of blood can be raised indefinitely without any limit as the physically dissolved amount of it in plasma which depends on atmospheric pressure and is responsible for the O_2 tension (PO_2) in blood is increased (Fig. 4.10).

The saturation of Hb by O_2 is defined as the percentage of the presence of oxy-Hb against the total amount of Hb to be oxygenated. On the otherhand, haemoglobin saturation by O_2 is the amount of O_2 expressed as percentage out of its total O_2 binding capacity. After the initial entry of O_2 in the blood stream it first partially physically dissolves in plasma and produces an O_2 tension in blood. Then, this O_2 enters in the RBC to combine with Hb producing oxyhaemoglobin. But this part of O_2 does not produce any oxygen tension in blood. Thus, Hb gradually becomes saturated by O_2 and in this phase percentage of oxy-Hb rises sharply with less increase in O_2 tension in plasma (this less increase of O_2 tension is due to the gradual mixing of O_2 in plasma from where it passes to Hb). After 100% saturation of Hb, O_2 further begins to dissolve rapidly in plasma. In that phase, the percentage of saturated oxy-Hb does not rise, but only the O_2 tension in blood increases (Fig. 4.11).

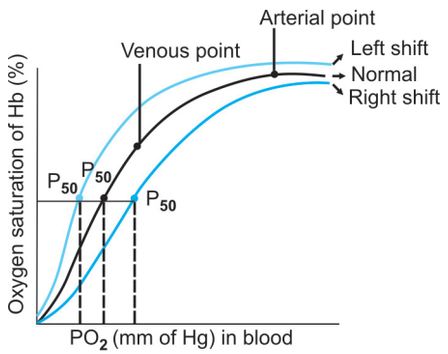


Fig. 4.10: O_2-Hb dissociation curve

Thus, the graphical representation of this whole event of relationship between the percentage of saturated oxy-Hb and the gradually developed tension of O_2 in blood forms the oxygen haemoglobin dissociation curve. Actually, the O_2-Hb dissociation curve tells us the percentage of saturation of Hb by O_2, the tension of O_2 in blood, the total content of O_2 in blood and the availability of O_2 to the tissues. The O_2-Hb dissociation curve is an elongated S-shaped line and has mainly two parts: the upper flat or near horizontal slope and the lower straight or near vertical slope. The vertical downward slope starts when the O_2 saturation of Hb or SPO_2 level comes down to 90% from 100% which corresponds to arterial O_2 tension of 60 mm of Hg. After that any slight fall of P_aO_2 causes steep fall of O_2 saturation of Hb. This is due to the large amount of O_2 uncombined from Hb for delivery to

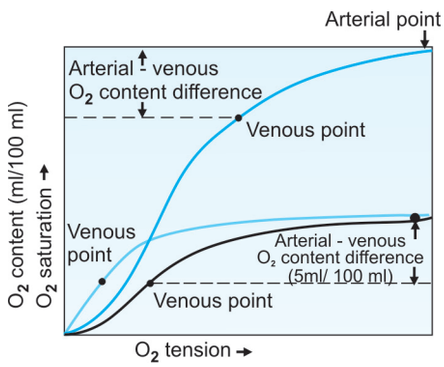


Fig. 4.11: Oxy-Hb dissociation curve of normal Hb in normal patient (red line), in anaemic patient (black line) and carbon monoxide poisoning (carboxy-Hb) (green line). The patient who has half his Hb with carbon monoixide poisoning is in much worse state than the anaemic patient who has just half Hb than normal individual

tissues which increases greatly for a given slight decrease in arterial PO_2.

There are many factors which can influence the O_2 -Hb dissociation curve. But, among them the important factors are : CO_2 tension, H^+ concentration, type of Hb, temperature and the concentration of 2,3-DPG (diphospho glycerate) level. The influences of these above factors can be expressed by P_{50}. The P_{50} is defined as the O_2 tension at which Hb is 50% saturated. Normally P_{50} value is 27 mm of Hg. It means that at 50% saturation of Hb by oxygen, the O_2 tension in blood reaches to 27 mm of Hg. Increase or decrease of P_{50} value indicats shifting of O_2-Hb dissociation curve to the right or left. The P_{50} value lower than 27 mm of Hg describes left ward shifting of the curve which means that at 50% O_2 saturation of Hb there is less tension of O_2 (< 27 mm of Hg) in blood. It also means that at this given O_2 tension Hb is more saturated than normal which also means Hb has a higher affinity for O_2, leading to less release or unloading of O_2 at the tissues, causing cellular hypoxia. The principal causes of left ward shifting of oxy-Hb dissociation curve are: alkalosis (metabolic or respiratory), hypothermia, abnormal forms of Hb (e.g foetal-Hb, methaemoglobin, carbomonoxy-Hb etc) and decrease of 2,3-DPG level.

P_{50} value higher than 27 mm of Hg describes the shifting of O_2-Hb curve to the right. It means for the same saturation of Hb, blood has higher O_2 tension (> 27 mm of Hg) or at any given PO_2, Hb is less saturated. It indicates Hb has low affinity for O_2 or more readily gives up O_2 to the tissues. The principal causes of the right wards shifting of O_2-Hb dissociation curve are : acidosis (metabolic or respiratory), hyperthermia, other haemoglobinopathies or the presence of abnormal Hb and increased 2,3-DPG level (Fig. 4.12).

Acidosis and alkalosis controls the O_2-Hb dissociation curve by controlling the CO_2 tension or H^+ concentration in blood. An increase in plasma H^+ concentration or

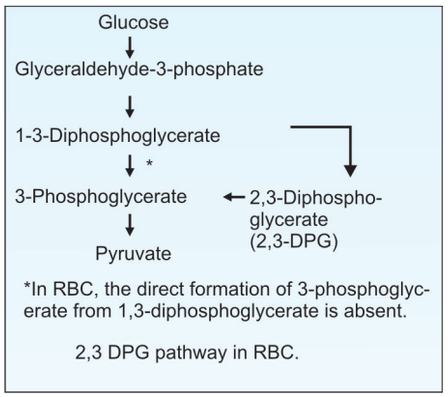


Fig. 4.12: The steps of synthesis of 2, 3-DPG in RBC

CO_2 tension decreases the affinity of O_2 to Hb and vice versa. This is called the Bohr effect. When blood flows through the tissue capillaries then the gradual increase of CO_2 tension in plasma shift the O_2-Hb dissociation curve to the right and affinity of Hb for O_2 is reduced which facilitates the release of O_2 at the tissues. Reversely, in pulmonary capillaries the lowering of CO_2 tension due to its gradual release in alveoli shifts the O_2-Hb dissociation curve to the left. Thus, the affinity of Hb for O_2 increases and facilitates the uptake of O_2 in alveoli.

Increased 2,3-DPG level in plasma shifts the O_2-Hb dissociation curve to the right and reduce the affinity of Hb for O_2 causing increased unloading of O_2 at the tissues. This plays an important compensatory role in patients with chronic hypoxia, anaemia and in blood transfusion. The 2,3-DPG is a by-product of glycolytic pathway in RBC and accumulates within it only during anaerobic metabolism. Thus, it helps in hypoxic condition by increasing the supply of O_2 to tissues through its effects on oxy-Hb dissociation curve. Under physiological condition the glycolytic pathway in RBC runs in normal pathway and less formation of 2,3-DPG through alternate pathway. So the effect of 2,3-DPG on this curve is minimum.

The use of ACD as anticoagulant during collection of blood for transfusion, there is an immediate fall of 2,3-DPG level in RBC after it is taken from the human body and dissociation curve shifts to the left. So the recently transfused blood is reluctant to give up O_2 to the tissues. Then, 2-3 days is required to recover the level of 2,3-DPG level in RBC after transfusion. Whereas the use of CPD as anticoagulant in stored blood delays the fall of 2,3-DPG level for 10 days, at which time the level is still near to normal in CPD blood (Fact file-1).

The abnormal haemoglobins which have influences on the O_2-Hb dissociation curve are methaemoglobin, suphaemoglobin, fetal haemoglobin, sickle cell haemoglobin, haemoglobin C, haemoglobin E, etc. They prevent the carrying of O_2 by Hb and have their own O_2 saturation

FACT FILE -1

2,3 DPG is very plentiful in RBC. It is formed from 3-phosphoglyceraldehyde which is a product of glycolysis via the Embden Meyerhof pathway. It is a highly charged anion that binds to the β-chain of deoxyhaemoglobin. One mole of deoxyhaemoglobin binds to one mole of 2,3 DPG.

$HbO_2 + 2,3\ DPG \longleftrightarrow Hb\text{-}2,3\ DPG + O_2$

In this equation, an increase in the concentration of 2,3 DPG shifts the reaction to the right, causing more O_2 to be liberated. Factors affecting the concentration of 2,3 DPG in RBC include pH. This is because acidosis inhibits red cell glycolysis and the formation of 2,3 DPG and vice versa. Exercise causes an increase in 2,3 DPG within 60 minutes. Therefore, much more O_2 is removed from each unit of blood flowing through active tissues which have low PO_2. Finally at low PO_2 the O_2-Hb dissociation curve is steep, and large amount of O_2 is liberated per unit drop of PO_2. Ascent to high altitude also causes a rise in 2,3 DPG level, with consequent increase in P_{50} and increase in availability of O_2 to tissues.

The affinity of foetal - Hb (Hb-F) for O_2 increase is greater than adult Hb. This facilitates the movement of O_2 from the mother to the foetus. This is due to the poor binding of 2-3 DPG by the g-polypeptide chain which is the characteristic of Hb-F. Some abnormal Hb in adults have low P_{50} values and the resulting high O_2 affinity of these Hb causes enough tissue hypoxia to stimulate increased RBC formation, with resulting polycythemia. It is because these Hb do not bind to 2,3 DPG.

The 2,3 DPG concentration in RBC is increased in anaemia and in variety of diseases where there is chronic hypoxia. This facilitates the delivery of O_2 to the tissues by raising the PO_2 at which O_2 is released in peripheral capillaries.

characteristics. The foetal - Hb has greater affinity for O_2 than the adult Hb and shifts the dissociation curve towards the left. Some chemicals like carbon monoxide, cyanide, nitric acid, etc, also combine with Hb at it O_2 binding site and prevent the O_2 to combine with Hb. Thus, they all shift the O_2 saturation curve to the left. Carbon monoxide has 200 to 300 times more affinity for Hb than O_2 and combine with it forming carboxyhaemoglobin. Thus, it decreases the O_2 carrying capacity of Hb by shifting the saturation curve to the left and impairs the release of O_2 to the tissues.

The O_2 dissociation curve is also shifted towards the right during the rise of temperature like the fall of plasma pH, showing decreased afinity of Hb for O_2 and increased unloading of it at the tissue level. Reverse effect is seen when the temperature is decreased.

Myoglobin is another iron containing pigment which resembles haemoglobin. It is present in the muscle and its affinity for O_2 is much higher than Hb. So, the O_2-Hb dissociation curve of myoglobin shifts to the left and looks like rectangular hyperbola. O_2 from myoglobin is released only when it is exposed to very low PO_2.

Coefficient of O_2 Utilisation

It indicates what percentage of arterial O_2 is used up from its total contents by a tissue. It is expressed by the following formula :

$$\text{Coefficient of } O_2 \text{ utilisation} = \frac{O_2 \text{ taken up by the tissue}}{O_2 \text{ content of arterial blood}} \times 100$$

Normally, the arterial blood contains 19 ml and venous blood contains 14 ml of O_2 per 100 ml of blood. So, usually the arteriovenous difference of O_2 content is about 5 ml. Thus the coefficient of O_2 utilisation is 5 × 100/19 or 26%. The arteriovenous O_2 difference or the utilisation coefficient of O_2 is directly proportional to the rate of tissue activity. In heavy exercise, this coefficient may increase upto 80%. Normally, in heart tissue the arteriovenous O_2 difference or O_2 taken up by myocardium is 12 ml. So, the O_2 utilisation coefficient of heart is 12 × 100/19 or 63%. During exercise it further rises. Hence, the O_2 utilisation coefficient is a true index of degree of tissue activity.

Effect of O_2-Hb saturation curve on CO_2 content and its transport

The deoxygentaed Hb has 3·5 times greater affinity for CO_2 than the O_2-Hb. So, when the blood passes through tissue capillaries, and Hb gives up O_2 becoming deoxygenated, then it helps it to carry more CO_2. As a result, venous blood contains more CO_2 than the arterial blood. Similarly, O_2-Hb has 3.5 times less affinity for CO_2 which helps it to give up CO_2 at pulmonary level. As a result, the arterial blood has less CO_2 than the venous blood. Hence, the combination of CO_2 with Hb depends on the O_2 status of it and vice versa. It is called the Haldane effect. Thus, the deoxygenation at tissue level and oxygenation at pulmonary level helps the Hb to combine with CO_2, transport of it and release of CO_2 at lung. This is indicated by that the O_2-Hb dissociation curve shifts to the right at tissue level and shifts to the left at pulmonary level.

The Haldane effect can be explained by the following way. It also explains the acid-base behaviour of Hb. At physiological pH, Hb acts as buffer due to its high content of histidine. Moreover, at tissue capillary level the removal of O_2 from Hb causes it to behave more like a base, $HbO_2 \longleftrightarrow Hb + O_2$. So, it takes up hydrogen ion which is formed from carbonic acid : $CO_2 + H_2O = H_2CO_3$. $H_2CO_3 = H^+ + HCO_3^-$, $Hb + H^+ = HbH^+$. Thus, by taking up H^+ the Hb shifts the CO_2 and bicarbonate equilibrium in favour of more bicarbonate formation.

$HbO_2 + CO_2 + H_2O \longleftrightarrow HbH^+ + HCO_3^- + O_2$.

This indicates that the deoxygenation of Hb increases the content and transport of CO_2 in venous blood as bicarbonate. Hence, the CO_2 content in venous blood increases which is reflected as an increase in bicarbonate. In the lungs the reverse occurs. Here, the combination of O_2 with Hb causes it to behave more like an acid and gives up hydrogen ion and shifts the CO_2-bicarbonate equilibrium in favour of more formation of CO_2 which is excreted through lungs.

$HbH^+ + O_2 = HbO_2 + H^+$

$H^+ + HCO_3^- = H_2CO_3$

$H_2CO_3 = CO_2 + H_2O$

$HbO_2 + CO_2 + H_2O \longleftrightarrow HbH^+ + HCO_3^- + O_2$

Hence, the total CO_2 content in blood decreases which is reflected by decrease in HCO_3^- level.

CO_2 DISSOCIATION CURVE

Under different physiological and pathological conditions the CO_2 content and its tension in blood varies. When these variations and the relationship between them is plotted in a graph, then it is called the CO_2 dissociation curve (Fig. 4.13).

Usually, the facts which can be expressed from this CO_2-dissociation curve are:

i. At any given CO_2 tension, reduced Hb takes up larger amount of CO_2 than oxygenated Hb. So, in the body the reduction of Hb in the tissue capillaries increases the degree of CO_2 uptake from the tissues.
ii. Oxygenation of Hb causes evolution of CO_2. This happens in lungs.
iii. As the CO_2 tension is increased, the total amount of CO_2 taken up by blood also rises. As the CO_2 tension falls, CO_2 content also diminishes.

The factors which influences the O_2 dissociation curve also influence the CO_2 dissociation curve, but in opposite direction. That is the factors which decrease the affinity of Hb for O_2 and shift the O_2 dissociation curve to the right also shift the CO_2 dissociation curve to the left and increases the affinity of Hb for CO_2.

CO_2 STORES

In the body always there is production, store and elimination of CO_2 which establishes

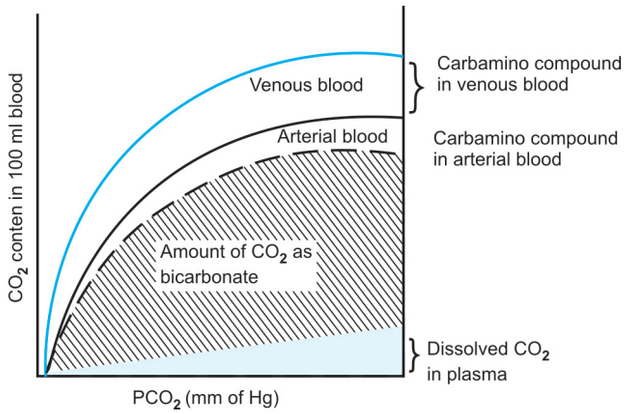


Fig. 4.13: CO_2 dissociation curve of arterial and venous blood

an equilibrium. Usually CO_2 is stored in the body in the form of dissolved CO_2 in plasma, bicarbonate and CO_2-Hb. The amount of total stored CO_2 in an adult is about 120 litres. It is stored in the body in three compartment: rapid, intermediate and slow. Rapid compartment is consist of highly vascular structures such as brain, heart, liver, kidney, etc. Intermediate compartment is mainly consist of muscle tisues and slow compartment is consist of fat and bones. When there is imbalance between the production and elimination of CO_2, then there is also change in the total amount of CO_2 stored in the body and a new equilibrium is established. This usually takes long time, near about 20 to 30 minutes (compared with O_2 which takes less than 3 to 5 minutes) and it is due to the large capacity of intermediate and slow compartment. During equilibrium, the rate of rise of CO_2 tension in arterial blood is generally slow than its fall following acute change in ventilation.

HYPERCAPNIA AND HYPOCAPNIA

Definition

Hypercapnia refers to the accumulation of CO_2 in blood. This is indicated by an arterial CO_2 tension greater than 6 kPa or end - tidal CO_2 tension greater than 60 mm of Hg. On the otherhand, hypocapnia refers to the deficit of CO_2 in blood and is indicated by an arterial CO_2 tension less than 4 kPa or end - tidal CO_2 tension less than 40 mm of Hg.

Causes of Hypercapnia

Common causes of hypercapnia during anaesthesia are inadequate CO_2 removal or excessive CO_2 production. Inadequate CO_2 removal is most commonly caused by hypoventilation or increased alveolar dead space. But it may also result from inadequate fresh gas flow or exhausted sodalime.

Hypoventilation

It is due to abnormal position of patient during surgery, increased airway resistance, decreased compliance of thorax and lungs, decreased respiratory drive due to anaesthetic agents and sedatives, and mechanical hypoventilation during IPPV. The equipmental or technical causes of hypo ventilation are obstruction, kinking, leak or disconnection, etc, at any part of the breathing circuit.

Increased Dead Space Ventilation

i. It occurs when the pulmonary artery pressure drops due to hypotension. It increases the area of pulmonary zone I. Thus, subsequently it increases the ventilation - perfusion mismatch and alveolar dead space ventilation.
ii. It also occurs when the airway pressure increases which subsequently increases the area of pulmonary zone I. Thus, subsequently it increases the ventilation - perfusion mismatch and alveolar dead space ventilation.
iii. Pulmonary embolism, thrombosis, vascular obliteration, etc, also increases the amount of lung that is ventilated, but under perfused. This also increases the dead-space ventilation by increasing the ventilation - perfusion mismatch.
iv. Rapid short inspiration may be distributed preferentially to the more compliant alveoli, causing the less compliant alveoli under ventilated. This is due to the short time constant of the less compliant alveoli. This also increases the dead space ventilation.
v. Anaesthesia apparatus also increases the total dead space by increasing the length of airway and by increasing the rebreathing of expired gas which is equivalent to dead space ventilation. The during order of increasing the rebreathing with spontaneous ventilation with Mapleson circuit is A, D, C, B and during controlled ventilation is D, B, C, A. There will be no rebreathing in circuit E (Ayre T-piece) if the patient's duration of expiration is long enough permitting the complete washout of the expired gases for a given fresh gas flow, however only if the fresh gas flow is greater than the peak inspiratory flow rate.

The effect of increased dead space can be countered by increasing the respiratory rate. Example, let minute volume of a patient is 10 L/min and V_D / V_T is 30%. Then alveolar ventilation is 7 lit/min. If due to any reason V_D / V_T is increased to 50%, then minute ventilation should be increased to 14 lit/min to maintain the alveolar ventilation at 7 lit/min.

Increased CO_2 Production

Fever, malignant hyperthermia, sepsis, shivering, hypertension, thyroid storm, increase release of catecholamines, etc, are the few of many causes of increased CO_2 production during anaesthesia. In febrile patient there is 13% increase in CO_2 production for each 1°C rise in temperature. Inadvertent or excessive CO_2 delivery from the anaesthetic machine due to exhausted sodalime and the excessive apsorption of CO_2 during laparoscopic procedure are also

other causes of hypercapnia. They indirectly increase the CO_2 production.

Causes of Hypocapnia

Causes of hypocapnia are opposite to hypercapnia. These are hyperventilation, decreased dead space ventilation (change from mask to ETT, decreased PEEP, increased pulmonary artery pressure, decreased rebreathing), decreased CO_2 production (hypothermia, deep anaesthesia) etc. Among these the mechanical passive hyperventilation is the commonest cause of hypocapnia.

Effect of Hypercapnia

In awake normal patient the progressive hypercapnia stimulates the sympathetic nervous system. It results in ↑BP, tachycardia, sweating, arrhythmias and increased cerebral blood flow. This increased cerebral blood flow is dangerous for patients with ↑ICP such as brain tumour. As anaesthesia suppresses the autonomic responses, so these signs may not occur and are masked until CO_2 tension is markedly increased. Mechanism of effect of hypercapnia on CVS is same as hypoxia. So, like hypoxia it acts both through direct effect on the myocardium which is depression and through indirect reflex (through sympathetic neural and humoral) mechanism which is stimulation. But the direct depression effect of myocardium by CO_2 is overshadowed by the indirect activation of myocardium by sympathetic nervous system. Hypercapnia, like hypoxaemia, also increase the myocardial O_2 demand (due to tachycardia, early hypertension) and decrease the myocardial O_2 supply (due to late hypotension). With moderate to severe hypercapnia hyperkinetic circulation also results. This is due to increased cardiac output and decreased SVR.

Arrhythmias due to acute hypercapnia in unanaesthetised patient have seldom been of serious problem. But, high P_aCO_2 level is more dangerous in anaesthetised patient. With halothane anaesthesia, arrhythmias will frequently occur, if P_aCO_2 goes above the arrhythmic threshold level which is often constant for a particular patient.

CO_2 is a powerful respiratory stimulant and for each mm of Hg rise of P_aCO_2 normal awake subjects increase their minute ventilation by about 2 to 3 L/minute. Maximal stimulatory respiratory effect is attained by P_aCO_2 up to about 100 mm of Hg. With higher P_aCO_2 than this, stimulation is reduced and at very high level, respiration is depressed. Later it ceases altogether. Patient with ventilatory failure, CO_2 narcosis occure when P_aCO_2 rises between 90 to 120 mm of Hg. This unconsciousness is due to the fall in CSF pH at high P_aCO_2 level. Chronic hypercapnia or respiratory acidosis results in compensatory increased resorption of bicarbonate by kidney, constituting secondary metabolic alkalosis. On the otherhand, the chronic hypocapnia causes the reverse. In each case blood pH returns to normal value, but bicarbonate concentration departs further from normal and may exceed 40 mEq/L. Hypercapnia cause leakage of Ca^{2+} and K^+ from the cells in plasma. So, it is also associated with hypercalcaemia and hyperkalaemia.

Effect of Hypocapnia

Unintentional hyperventilation in association with decreased arterial CO_2 tension is the usual cause of hypocapnia during anaesthesia. Hypocapnia produces respiratory alkalosis with decrease in serum potassium concentration. There are reductions in cerebral blood flow, cardiac output and tissue O_2 delivery. There may also be delay in onset of spontaneous ventilation at the end of anaesthesia.

Hypocapnia causes decrease in CO_2 by three mechanisms

First: Increase in intrathoracic pressure by increasing ventilation causes hypocapnia and decreased CO_2.

Second: Hypocapnia withdraws the sympathetic nervous system activity and thus decrease the ionotropic state of heart.

Third: Hypocapnia can increase pH and thus decrease the ionized Ca^{2+} and inturn the ionotropic state of heart. Hypocapnia with respiratory alkalosis shift the oxy-Hb dissociation curve to the left which increases Hb affinity for O_2 and thus impairing O_2 unloading at tissue level. Hypocapnia also increases the whole body O_2 consumption by increasing the pH mediated uncoupling of oxidation from phosphorylation. P_aCO_2 of 20 mm of Hg will increase tissue O_2 consumption by 30%. Hypocapnia cause V_A/Q abnormalities by inhibiting the compensatory HPV (hypoxic pulmonary vasoconstriction).

TRANSPORT OF CO_2

CO_2 is produced in the tissues by metabolism. Then, it enters the blood stream at tissue capillary level and is carried to the lungs where it is liberated in the alveolar air. 100 ml of venous blood carries about 52 ml of CO_2, whereas 100 ml of arterial blood carries about 48 ml of CO_2. Therefore, the average normal arteriovenous difference of CO_2 content is about 4 ml per 100 ml of blood. In other wards, each 100 ml of arterial blood, while passing through the tissues collects about 4 ml of CO_2. Similarly, each 100 ml of venous blood, while passing through lungs also releases 4 ml of CO_2. So, the blood always carries a constant amount of CO_2 which is about 48 ml per 100 ml. This constitutes the alkali reserve (as bicarbonates).

Although much CO_2 is carried in the blood, yet blood reaction does not become acid. This proves that during CO_2 transport some buffers system in blood play a very important role to maintain the acid-base balance. CO_2 is carried in the blood in following forms (Fig. 4.14).

(i) As Physical Solution

Under normal conditions of temperature and pressure only about 2.7 ml of CO_2 is carried as physical solution in plasma (i.e. as H_2CO_3) per 100 ml of venous blood. Since, this represents a very small portion of total CO_2 carried in blood, so it is evident

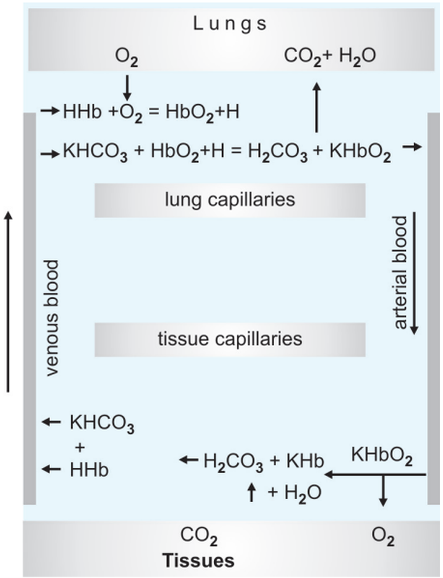


Fig. 4.14: Mechanism of entry and exit of O_2 and CO_2 at lung and tissue level

that the major portion of CO_2 is transported in some another form of chemical compounds other than the physical solution.

(ii) As Chemical Compounds

Two types of chemical compounds are formed by CO_2 in blood. These are :

1. Bicarbonates:
   a. $NaHCO_3$ in plasma: arterial blood - 33.1%,
   venous blood - 35·2%
   b. $KHCO_3$ in red cells: arterial blood - 9·8%, venous blood - 10·5%
2. Carbamino compounds:
   a. Carbamino – haemoglobin in red cells (arterial blood- 2%, venous blood - 2·6%)
   b. Carbamino – proteins (with plasma proteins) in the plasma (arterial blood- 1%, venous blood - 1·1%).

Carriage of CO_2 as Bicarbonate

A. In corpuscles

Haemoglobin remains combined with K and forms potassium bicarbonates with CO_2 in the following way:

$CO_2 + H_2O \longleftrightarrow H_2CO_3$

$KHb + H_2CO_3 = HHb + KHCO_3$

This reaction takes place at the tissue level. At the pulmonary level, the reverse reaction takes place and CO_2 is evolved out. Carbonic anhydrase which is present in the RBC helps this process as catalyst.

Carbonic anhydrase: The rate of formation and breakdown of bicarbonates depend upon the rate of this primary reversible reaction: $CO_2 + H_2O \longleftrightarrow H_2CO_3$. This reaction is catalyst by carbonic anhydrase. In absence of carbonic anhydrate when water is exposed to CO_2, a period of about 15 to 30 minutes is required for a this reaction to take place. Similarly about the same time is required for the complete dissociation of CO_2 from its water solution. But in our body, blood in the tissue capillaries becomes saturated with CO_2 in about 1 to 2 seconds only and the same time is required for the evolution of CO_2 from blood in the lungs. This is due to the existance of enzyme, called carbonic anhydrase. It is protein in nature containing Zn and its action is inhibited by cyanide and acetazolamide. In the blood, it is almost exclusively present in the red cells. So, this reaction mainly takes place in RBC. All other tissues contain it in traces. But kidney, pancreas and stomach contain considerable amounts.

B. In plasma

1. By the phosphate buffer:
   Alkaline phosphates combine with carbonic acid and form sodium bicarbonate.
   $Na_2HPO_4 + H_2CO_3 \longleftrightarrow NaH_2PO_4 + NaHCO_3$
2. By plasma proteins :
   The plasma proteins, mostly remain combined with sodium (to be represented as NaPr) and form bicarbonates in the following way.
   $NaPr + H_2CO_3 \longleftrightarrow HPr + NaHCO_3$
3. Chloride shift or Humburger Phenomenon:
   When the whole blood is saturated with CO_2, the following changes are seen:
   – The bicarbonate contents of plasma and corpuscles increase.
   – The chloride content of plasma is diminshed and that of the red cell is increased.
   – The total base (cations) of both plasma and corpuscles remain unchanged.
   – The water content and the volume of corpuscles increase (Table 4.12).

When CO_2 is removed from blood at the alveoli, reverse changes take place. From these observations it is evident that when CO_2 enters the blood, then chlorine of NaCl from plasma enters the red cells, while the base (Na^+) is left behind in plasma. When CO_2 escapes from blood, chlorine again leaves the cells, enters the plasma and combines with the base (Na^+). Due to this alternate movement of chloride ion, this phenomenon is called chloride shift or Humburger phenomenon. This can be explained by the following way.

The membrane of red cells is not permeable to basic ions (K^+, Na^+ etc), but is permeable to anions (HCO_3^-, Cl^- etc). When CO_2 enters the blood stream from the tissues, then H_2CO_3 is formed. But it is very little in amount in plasma and largely in the corpuscles, because red cells are rich in carbonic anhydrase and permeable to CO_2. The red cells contain 4 to 5 times more carbonic anhydrase than the plasma. In the RBC H_2CO_3 reacts with KHb producing $KHCO_3$ and HHB. Thus, the bicarbonate content of red cells increases and, thereby, the reaction of the cells tends to become alkaline.

So, to maintain a constant pH, either the alkali ion (K^+) is to get out of the cell or an acid ion from the plasma should enter the cell. Since, the red cell membrane is not

Table 4.12: CO_2 content in arterial and venous blood

	Venous blood (ml/100 ml)	*Arterial blood (ml/100 ml)*
Dissolved CO_2	2.7	2.4
As bicarbonate	45.7	42.9
As carbamino compound	3.7	3
Total CO_2 content	**52.1**	**48.3**

permeable to alkali ion, K^+ can not come out. So consequently, the acid ion Cl^- of NaCl from plasma, enters the red cells and combines with $KHCO_3$ forming KCl and HCO_3^- ion. The free HCO_3^- ion now tends to make the cell reaction alkali. This is prevented by the migration of HCO_3^- from the cell into the plasma. In plasma it combines with free Na^+ of NaCl which was left free by the shift of chlorine ion and forms $NaHCO_3$. All these changes takes place in the tissue capillaries. Owing to this reaction, a large amount of free Na^+ of NaCl in plasma should be made available for carriage of CO_2.

In the lungs, these changes are reversed. Chlorine comes out of the cells, reacts with $NaHCO_3$ of plasma forming NaCl and carbonic acid. Carbonic acid, thus formed is broken down into CO_2 and passes out through the lungs. In the tissue capillaries, chlorine shifts from the plasma into the cells. Thereby, the osmotic pressure of the cell will rise, water will be drawn in and the cell volume will increase. In the pulmonary capillaries, it shifts from the red cells back into the plasma. This will reudce the osmotic pressure of the red cell and the cell volume will shrink.

Carriage of CO_2 as Carbamino Compounds

CO_2 is also carried as carbamino compounds in blood. In this process, the NH_2 radicle of the globin part of haemoglobin and that of the other plasma proteins combines with one molecule of CO_2 (as free gas but not as H_2CO_3). It does not require the help of carbonic anhydrase. This reaction may be presented as: CO_2 + Pr. $NH_2 \longleftrightarrow$ Pr. NH. COOH. About 3.7 ml of CO_2 is carried in this form per 100 ml of venous blood, viz, 2.6 ml in red cells and 1.1 ml in plasma.

SUMMARY

Thus, it will be seen that CO_2 is carried in blood in three forms. 100 ml of venous blood carries about 52 ml of CO_2 as follows:

i. In physical solution (2.7 ml).
ii. As bicarbonates (45.7 ml). Bicarbonates are formed in four ways; (a) with NaPr, (b) with Na_2HPO_4, (c) with Na of NaCl helped by 'chloride shift', (d) with KHb. These are the chief forms in which CO_2 is carried in blood. It can explain about 90% of the total CO_2 transport of which the major part is carried in plasma as $NaHCO_3$. A large part of this bicarbonate remains permanently in the plasma and constitutes the so called alkali reserve of blood.
iii. As carbamino compounds (3.7). These are chiefly formed in the red cells (2.6) and only in traces in the plasma (1.1). It constitutes about 5-10% of the total CO_2 carriage and is responsible for a large part of the normal arteriovenous difference.

Interrelation between the carriage of oxygen and carriage of carbon dioxide

It has been found that reduced blood can take up more CO_2 than oxygenated blood. Also blood containing less CO_2 (Fig. 4.15) will take up relatively more O_2. In other words, these two gases tend to displace each other. This is explained by the fact that oxyhaemoglobin acts as a stronger acid (than H_2CO_3) and unites with more base. Reduced haemoglobin, on the other hand is a weaker acid (than carbonic acid) and can unite with less base. Hence, oxygenation of Hb in the lungs makes it a stronger acid and unites with more base. The latter being taken from the bicarbonates and (thus carbonic acid is formed from where CO_2 is liberated through lungs). On the otherhand, reduced haemoglobin as in the tissues being weaker acid can not hold its base and taken away by $-HCO_3$ to form bicarbonate. This $-HCO_3$ comes from carbonic acid which is formed in the red blood cells. In the RBC carbonic acid is formed from CO_2 which comes from tissues with the help of carbonic anhydrase.

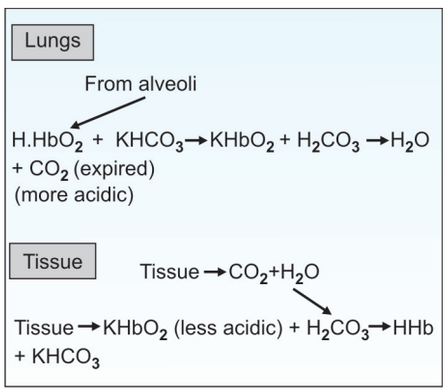


Fig. 4.15: The basic mechanism of transport of O_2 and CO_2 from lungs to tissues and tissues to lungs respectively

Factors that Determine Intake of CO_2 from the Tissues

The following factors are responsible for entry of CO_2 from the tissues into the blood stream.

1. Pressure gradient

In the tissue capillaries the CO_2 tension in arterial blood is 40 mm of Hg. The CO_2 tension in the resting tissues is about 46 mm of Hg. In the active tissues, it may be much higher (about 63 mm of Hg). Due to difference of partial pressure, CO_2 diffuses out of the tissues and enters the capillaries.

2. Reduction of Haemoglobin

Oxyhaemoglobin is reduced in the tissues, so that the base freed from the reduced haemoglobin is made available for fixing H_2CO_3. Thus more and more amount of H_2CO_3 is formed from CO_2 which diffuses from the tissues in the blood.

3. With the help of Humburger phenomenon

This is described before.

4. Carbamino compounds are formed

This is helped by increased CO_2 tension, as well as reduction of oxyhaemoglobin in the tissue capillaries.

Factors Concerned in the Liberation of CO_2 in Lungs

Since CO_2 is liberated in the lungs, it is obvious that in the pulmonary bed the factors responsible for releasing the CO_2 must be the reverse of those that are operating in the tissues.

5 Cardiovascular System (Anatomy and Physiology)

BRIEF ANATOMY OF HEART

The Greek name of heart is 'Card', from where we get the word 'cardiac' and the Latin name of heart is 'Cor', from where we get the word 'Coronary'. Heart is a hollow muscular and somewhat conical structure. It is situated in the middle of the mediastinum and covered by pericardium. It is about the size of a clenched fist of a normal adult individual. In a healthy adult individual the heart measures about 12 cm in longitudinal diameter extending from apex to base, 6 cm in antero-posterior diameter and 9 cm in widest transverse diameter. The transverse diameter of a heart should not be more than one-half of the transverse diameter of the thorax. The weight of a heart varies from 250 gm in a healthy adult female to 300 gm in a healthy adult male.

The human heart is considered as two parallel pumps and is composed of 4 chambers − right atrium, right ventricles, left atrium and left ventricles. The atria lie above and behind the ventricles. The two atria are separated from each other by inter atrial septum. Similarly, the two ventricles are separated from each other by interventricular septum. The atrium and ventricles are separated externally by coronary sulcus or atrio ventricular groove. On the otherhand, the two ventricles are also separated on the external surface by two grooves which are called as the anterior and posterior interventricular groove. The anterior interventricular groove is situated on the sternocostal surface and the posterior interventricular group is situated on the diaphragmatic or inferior surface of the heart. They meet at the apex.

The heart presents: apex, base, three surfaces and three borders. The three surfaces are: sternocostal, diaphragmatic and left surfaces. The three borders are: right, inferior and left borders.

Apex

It is a conical area of the heart and is formed only by the left ventricle. It is directed downwards, forward and to the left towards the 5th intercostal space, which is situated about 9 cm laterally from the midline and slightly below and medial to the left nipple (male). The apex is separated from the anterior thoracic wall by the anterior part of left lung and pleura. The apex beat is a forward thrust which is felt at the left 5th intercostal space, just medial to the midclavicular line or 9 cm lateral from the midsternal line, during the ventricular systole. It is due to the twisting of the heart by vortex like disposition of the ventricular muscles close to the apex. In the new born, the apex beat is usually felt at the left fourth intercostal space, just lateral to the midclavicular line. But, after about 2 years it reaches the adult position.

Base

The base or posterior surface of the heart is somewhat quadrilateral in outline and is the most fixed part of the heart. It is directed backwards and to the right. It is formed by two atria, of which 2/3 is formed by the left atrium and 1/3 is formed by the right atrium. At the base, the superior vena cava (SVC) and inferior vena cava (IVC) open in the right atrium and the four pulmonary veins, two from each lung, open in the left atrium. Between the base of the heart and the vertebral column there lies: the right and left bronchi, oesophagus and descending thoracic aorta. The distended left atrium in mitral stenosis may produce difficulty in swallowing due to the oesophageal compression. This is called the Ortner's syndrome (Fig. 5.1).

Right Border

It is rounded and convex in shape and is formed only by the right atrium. It extends from the right side of the opening of superior vena cava to that of the inferior vena cava. The right border of the heart separates the base from the sternocostal surface of it. A shallow vertical groove known as the sulcus terminals accompanies the right border of the heart. It corresponds with an internal ridge named crista terminalis in the interior of the right atrium.

Inferior Border

It is a sharp border and separates the sternocostal surface of the heart from the diaphragmatic surface of it. It extends from the opening of IVC to the apex of the heart. This border is accompanied by the right marginal branch of right coronary artery and its corresponding vein. Close to the apex, it presents a notch known as the incisura apicis cordis which gives passage to the anterior interventricular branch of the left coronary artery.

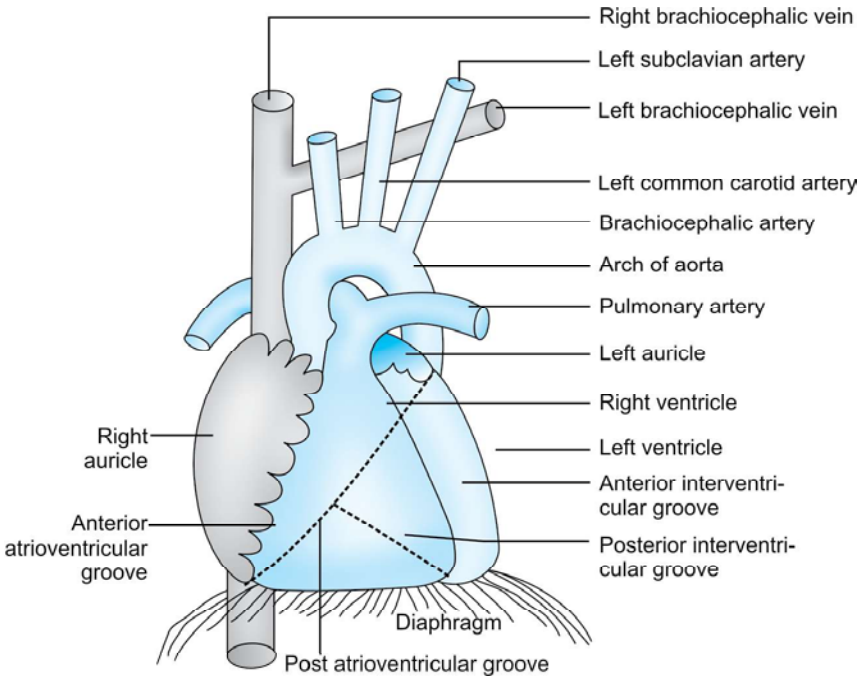


Fig. 5.1: The anterior surface of the heart

Left Border

It is an ill defined, convex border which separates the sternocostal surface of the heart from the left one. It extends from the left auricle to the apex of the heart with convexity directed upwards and to the left. This border is accompanied by the left marginal branch of left coronary artery and its corresponding vein.

Sternocostal surface

It is directed forwards, upwards and laterally towards left. It is separated from the base of the heart by the right border, from the diaphragmatic surface of the heart by the inferior border and from the left surface of the heart by the left border. It lies against the posterior surface of the body of the sternum and 3rd to 6th costal cartilages of both sides. This sternocostal surface is formed by the following parts of the heart such as:

i. The anterior surface of the right atrium and its auricle,
ii. The anterior surface of the right ventricle (2/3),
iii. A part of the anterior surface of the left auricle,
iv. The anterior surface of the left ventricle (1/3).

This sternocostal surface presents:

i. The anterior part of the atrio ventricular groove which passes downwards and to the right between the right atrium and the right ventricle. The groove holds the trunk of right coronary artery and the anterior cardiac vein.
ii. The anterior interventricular groove which passes downwards and parallel to the left border of the heart. It meets the inferior border at the apex. The groove holds the anterior interventricular branch of the left coronary artery and great cardiac vein.

Diaphragmatic or Inferior Surface

It is a flat surface and rests on the central tendon and the left part of the musculature of diaphragm. It is formed by two ventricles, of which 2/3 is formed by the left and 1/3 is formed by the right. It is separated from sternocostal surface by inferior border, from the base by the posterior part of the atrioventricular groove and from the left surface by a less defined unnamed border which is the backward continuation of the inferior border of heart. The posterior interventricular groove runs forwards along this surface and meets with the antrior interventricular groove at the apex. This posterior interventricular groove lodges the posterior interventricular branch of the right coronary artery and the middle cardiac vein (Fig. 5.2).

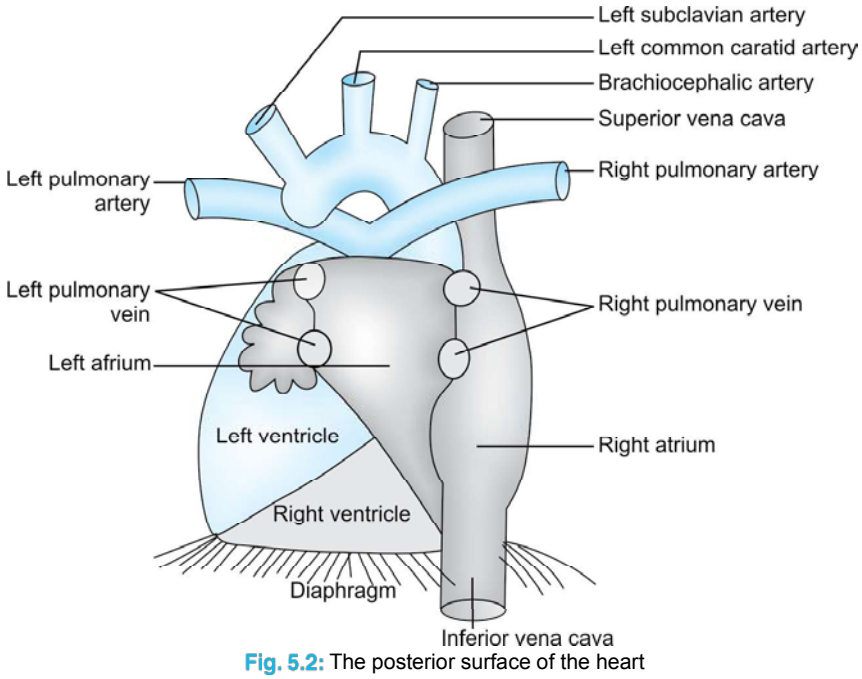


Fig. 5.2: The posterior surface of the heart

Left Surface

It is directed backwards, upwards and to the left. It is formed mainly by the left ventricle and partly by the left atrium and its auricle. This lateral surface of the heart lies against the cardiac impression of the left lung. The left part of the atrioventricular groove lies in this surface and lodges the following structures:

i. Trunk and the circumflex branch of left coronary artery,
ii. Termination of the great cardiac vein,
iii. Commencement of the coronary sinus.

Atrioventricular Groove

It is a C shaped curve and is deficient in front due to the presence of the root of pulmonary trunk and aorta. It is divided into anterior and posterior part. The anterior part is again subdivided into right and left halves. The right part of the anterior atrioventricular groove runs downwards and to the right between the right atrium and the right ventricle. It contains the trunk of right coronary artery. The left part of the anterior atrioventricular groove intervenes between the left auricle and the left ventricle. It lodges the trunk and the circumflex branch of the left coronary artery, the termination of the great cardiac vein and the commencement of the coronary sinus.

The posterior part of the atrioventricular groove intervenes between the base and the diaphragmatic surface of the heart. It contains coronary sinus and the anastonomoses between the right and left coronary arteries. The meeting point of the posterior interatrial groove, posterior interventricular groove and posterior part of the right and left atrioventricular groove from opposite direction is known as the 'crux' of the heart.

Some points to remember

1. The apex of heart is formed only by the left ventricle,
2. The base of heart is formed only by the two atria,
3. The right border of heart is formed only by the right atrium,
4. The diaphragmatic surface of heart is formed by the two ventricles.

1/3 and 2/3 features of heart

i. Base − 1/3 of the base is formed by the right atrium and 2/3 by the left atrium,
ii. Diaphragmatic surface − 1/3 of the diaphragmatic surface is formed by the right ventricle and 2/3 by the left ventricle,
iii. Sternocostal surface − 1/3 of the sternocostal surface is formed by the left ventricle and 2/3 by the right ventricle,
iv. Entire heart − 1/3 of the entire heart is right to the midline and 2/3 is left to the midline.

Right Atrium

The atria are thin walled, low pressure chambers and served as conduits of ventricle. The right atrium receives venous blood from the whole body through the SVC and IVC and pumps it out through the right atrioventricular or tricuspid opening into the right ventricle. Right atrium forms the right border, base and part of the anterior surface (or sternocostal surface) of the heart. On the outer surface along the right border of the right atrium there is a shallow vertical groove which passes from the SVC to the IVC. This groove is called the sulcus terminalis and it corresponds to an internal muscular ridge called the cristaterminalis. Cristaterminalis divides the interior of the right atrium into two parts. The posterior part is smooth and is called the sinus venaram. Whereas the anterior part is rough and is called the atrium proper which also includes the right auricle. The right auricle is a conical muscular projection which arises from the antero superior part of the atrium and extends upwards and to the left towards the ascending aorta. Multiple smooth muscular ridges arise from the crista terminalis and pass forwards, towards the right atrioventricular orifice. Some of these ridges form a network in the interior of the right auricle. These muscular ridges are called the musculi pectinati. Thus, the right auricular appendage is a potential site for the formation of thrombi, which if dislodged, can result in pulmonary embolism. Opening of the coronary sinus is situated between the opening of IVC and right atrioventricular orific, in the lower part of the interatrial septum. Just above the opening of coronary sinus lies the AV node. The SA node is situated at the upper part of the sulcus terminalis. On the external surface the right atrium is separated from the right ventricle by the right atrioventricular groove which contains the right coronary artery.

The right and left atrium is separated by a septum, called the interatrial septum. It is placed obliquely, so that the right atrium lies in front and to the right side of the left atrium. The upper part of this septum is thicker than its lower part. The right side of the interatrial septum is characterised by the presence of fossa ovalis, annulus ovalis and the AV node. The fossa ovalis is an oval depression in the lower part of the septum and the floor of the fossa is formed by the septum primum. It represents the foramen ovale during intrauterine life. The annulus ovalis is a sickle shaped fold which surrounds the upper, anterior and posterior margins of the fossa ovalis. It represents the lower free margin of the septum secundum. The AV node is situated in the lower part of the interatrial septum above the opening of the coronary sinus (Fig. 5.3).

The interatrial septum is developed from the septum primum, septum intermedium and septum seccundum. The septum primum grows as a septum from the roof and the dorsal wall of the primitive single chamber of atrium. Then like a curtain it passes downwards. During that period, another septum, named septum intermedium also grows from the below and passes upward. They do not unite and keep a gap between them. Thus, a foramen known as 'ostium primum' is formed between the upper border of the septum

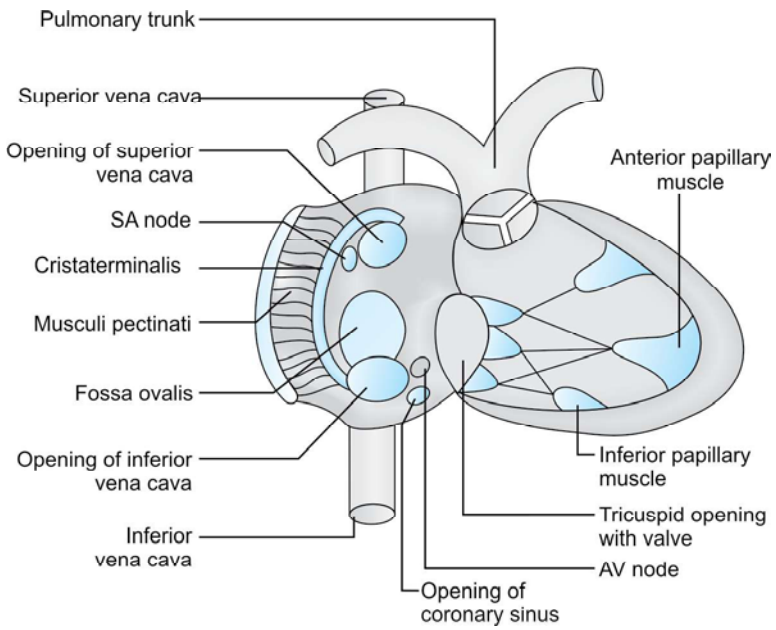


Fig. 5.3: The interior of right atrium and right ventricle

intermedium and the lower border of the septum primum. Later, ostium primum is closed by the fusion of these two septaes. Again with the closure of ostium primum, the upper part of septum primum disintegrates forming a foramen known as the 'ostium secundum'. Then another septum, called the septum secundum also grows from above and passes downwards with a sickle shaped lower free margin. The lower margin of the septum secundum grows sufficiently to overlap the ostium secondum situated on the septum primum. Thus the flap like valvular opening formed between the lower margin of the septum secundum and the upper margin of the ostium secundum of the septum primum is known as the 'foramen ovale'. The purpose of the development of septum secundum is to convert ostium secundum into a valvular foramen ovale, so as it can regulate the flow of blood from the right to the left atrium, but not in opposite direction.

After birth, the intraatrial pressure of both the sides of the atrium becomes equal and the foramen ovale is closed at first functionally and later anatomically by the fusion of the margins of septum primum and septum secundum. In about 20% of human heart, the foramen ovale is closed functionally, but anatomically it may remain patent which can be proved by passing a probe from the right to the left side of the heart.

Congenital atrial septal defect (ASD) are of the following types:

i. Probe patency of foramen ovale
   It occurs when the foramen is closed functionally, but remains patent anatomically. These subjects are considered as normal.
ii. Persistant ostium secundum:
   This is due to the incomplete development of septum secundum or extensive disintigration of the septum primum forming large ostium secundum.
iii. Persistant ostium primum:
   This may appear as single defect or associated with the patent interventricular foramen.
iv. Biventricular monoatrial heart:
   The is due to complete failure of the septation of primitive single chamber of atrium.
v. Prenatal closure of foramen ovale:
This is a rare anomaly.

The opening of IVC in the right atrium is guarded by a rudimentary valve. During intrauterine life this valve guides the inferior vena caval blood, which is oxygenated and comes from the placenta and the lower half of the body, to the left atrium through the foramen ovale. The 'intervenous tubercle of Lower' is a very small projection on the posterior wall of the atrium and situated just below the opening of SVC. During embryonic life it directs the superior vena caval blood to the right ventricle which is deoxygenated and comes from the head and neck and upper extremities.

The right atrium proper communicates with the right ventricle through the right atrioventricular orifice. This opening is oval in shape. It permits usually the tips of three fingers and is guarded by tricuspid valve. This area of right atrium proper is also known as the vestibule of the tricuspid valve. The plane of the atrioventricular orifice is almost vertical, so that blood flows almost horizontally from the right atrium to the right ventricle.

Right Ventricle

It forms the whole inferior border, larger part (2/3) of the anterior surface and a smaller part (1/3) of the inferior surface of the heart. The wall of the right ventricle is thinner than that of the left ventricle and the ratio of thickness is 1:3. But, in utero the ratio of RV : LV wall thickness is approximately 1:1. This is because the right ventricular pressure or the pressure of the right side of the heart is greater or equal to the left side of the heart. After delivery, the pulmonary vascular resistance rapidly decreases with the expantion of lungs and the SVR increases with the loss of placenta. So, the right side of the heart becomes of low pressure system than that of the left side of the heart and undergoes less muscular hyppertrophy than the left ventricle after birth. Therefore, over the 1st month of extrauterine life the RV: LV wall thickness ratio become 1:3 which is similar to that of the adult.

On cross section, the interior of the right ventricle is semilunar. Whereas, that of the left ventricle is circular. This is because the interventricular septum bulges with the convexity towards the right ventricle due to increased LV pressure than that of RV pressure. The thickness of the muscular wall of the right ventricle is 3 to 5 mm and that of the left ventricle is 8 to 12 mm.

The interior of the right ventricle consists of two parts: the inflowing rough part or inflow tract or the ventricle proper and the outflowing smooth part or outflow tract. This outflow tract is also known as the conus arteriosus or infundibulum. The inflow tract receives blood from the right atrium and the outflow tract ejects the blood from the right ventricle into the pulmonary trunk. The conus arteriosus of the right ventricle with its outflow orifice is situated in front, above and to the left side of the inflow tract. Therefore, the blood of inflow tract during ejection through the outflow tract bends roughly at an obtuse angle. The supra ventricular crest intervens between this inflow and outflow tract of the right ventricle.

The right ventricle receives blood from the right atrium through the tricuspid orifice which is guarded by tricuspid valve. Then, it ejects this blood into the pulmonary trunk or artery through the pulmonary orifice which is guarded by the pulmonary valve. The right atrioventricular or tricuspid orifice is oval in shape. It is oriented almost vertically making an angle of 40° with the sagittal plane. The orifice is directed forwards, downwards and to the left towards the apex. The tricuspid valve has three cusps − anterior, medial and pasterior and admits the tips of three fingers (8 to 11 cm^2). The chordae tendinae connect the free margins of the 3 valve cusps of the tricuspid orifice with the 3 papillary muscles and prevent the eversion of cusps to the atrium during ventricular contraction. There are three papillary muscles and each papillay muscle is connected to the contiguous halves of two cusps. Of the three papillary muscles, anterior is the largest. The tricuspid valve is closed during ventricular systole by the apposition of the atrial surfaces of the cusps near their serrated margins.

The pulmonary valve which guards the pulmonary orifice is also called the semilunar valve, because their cusps are semilunar in shape. It comprises of 3 cusps such as anterior, right and left. Normally the pulmonic valve area is 4 cm^2. Usually, the right ventricular pressure varies in the ranges between 15 to 30 mm of Hg during systole and 0 to10 mm of Hg during diastole. Whereas the pulmonary artery pressure varies in the ranges between 15 to 30 during systole and 3 to 12 mm of Hg during diastole, respectively.

Left Atrium

It forms 2/3 of the base, the greater part of the upper border, part of the anterior and lateral surfaces, and a part of the left border of the heart. The muscular wall of the left atrium is thicker than that of the right atrium and the thickness is being about 3 mm. Antero superiorly the left atrium presents a conical projection which is called the left auricle. It projects upwards and medially, towards the root of the pulmonary trunk. The most of the interior wall of the left atrium is smooth. But in certain portion a network of musculi pectinati is found within the cavity of left auricle. It receives only oxygenated blood from the lungs through 4 pulmonary veins, where orifices are not guarded by any valve and pumps it out to the left ventricle through the bicuspid or mitral orifice which is guarded by bicuspid or mitral valve. The area of mitral valve is only 6 to 8 cm^2 and admits the tip of two fingers. The mitral valve has two cusps, a larger anterior and a smaller posterior, hence it is called the bicuspid valve. The cusps of mitral valve are smaller and thicker than those of the tricuspid valve. There are two papillary muscles in the left ventricle − anterior and posterior. Chordae tendinae from both these papillary muscles are attached to both the cusps of the mitral valve. The right and left atrial pressure vary anywhere between 0 to 10 mm of Hg. The clinical importance of left auricle are:

i. It is a potential site for formation of thrombi which may dislodge at any time and can result in cerebral, renal or any systemic embolism,
ii. During mitral valvotomy operation, amputation of the left auricle may injure the circumflex branch of left coronary artery.

Left Ventricle

It forms the apex, left border, left surface and 2/3 of the inferior surface of the heart. It is conical in shape, and circular on cross section. Its musculature is three times thicker than that of the right ventricle. The muscular thickness of left ventricle is about 8 to 12 mm. The muscle of the left ventricle is thin at the apex and at the aortic vestibule the muscles of left ventricle are mostly replaced by fibrous tissue. The interior of the left ventricle is similar to that of the right ventricle. Thus, it consists of an inflow tract or ventricle proper and an outflow tract or aortic vestibule. The inflow tract of left ventricle consists of mitral valve complex and conducts blood from the left atrium to the apex of the left ventricule. The outflow tract is also called the aortic vestibule. It is smooth walled and ejects the blood into the aorta through the aortic orifice. The area of the aortic opening is only 3 to 4 cm^2 and is guarded by the aortic valve with three semilunar cusps. These are named as posterior, right and left. Opposite to the each cusp the aortic wall is dilated and form the aortic sinuses. The right and left coronary arteries arise from these right and left aortic sinuses, respectively. The opening of the coronary arteries in aortic sinuses are called coronary ostia. These aortic sinuses are significant because they prevent occlusion of the coronary ostia.

The right and left ventricles are separated by the interventricular septum. It consists of a thinner upper membranous part and a thicker lower muscular part which forms the major portion of the septum. It

is placed obliquely backwards and to the right and presents a convexity towards the right ventricle. Hence, on cross section the right ventricular cavity is semilunar and left ventricular cavity is circular in outline. The attachment of the intraventricular septum within the ventricle is indicated on the outer surface of the heart by anterior and posterior interventricular grooves. The left branch of the AV bundle first passes through the right side of the membranous part of the interventricular septum and then appear on the left side by piercing it. On the right side of the interventricular septum, the base of the septal leaflet of the tricuspid valve extends from the muscular part of the interventricular septum to the central region of the membranous part of it. As a result the part of the interventricular septum which is situated in front of the septal leaflet intervens between the two ventricles. But the portions behind the septal leaflet separates the right atrium from the aortic vestibule of the left ventricle. This portion of the interventricular septum is known as the atrio ventricular septum.

The interventricular septum develops from three sources : ventricular septum proper (septum inferior), proximal bulbar septum and septum intermedium. The primitive ventricle develops as a single cavity. It lies between the common atrium on the dorsal side and the bulbus cordis on the ventral side. From the single cavity of common atrium develops two atriums. Whereas, the bulbus cordis develop the outflow tract of the two ventricles and the root of the pulmonary and aortic trunk. Therefore, for complete separation of the ventricle, it must be done in harmony with the septation of atrium, ventricle and the proximal part of the bulbus cordis. The ventricular septum proper or septum inferior grows from below from the floor of the primitive ventricle and passed upwards. It presents a sickle shaped margin with the concavity directed upwards and backwards. Again a septum develops which divides the bulbus cordis into right and left chambers. This is called the bulbar septum which grows downwards and fuses with the upper margin of the ventricular septum proper. But still a small gap remains between these two septums. Right part of the bulbus cordis incorporates with the right ventricle and forms the infundibulum part of it. Similarly, the left part of the bulbus cordis forms the aortic vestibule of the left ventricles. The small gap which still remains after the fusion of the previous two septum is closed later by septum inter medium. Sometimes, this small gap is not closed and remains as VSD. The part of the septum formed from septum intermedium persists in adults as the membranous part of the interventricular septum.

When the intermedium septum is not developed, then it affects the membranous part of the interventricular septum and may appear as single defect (VSD). Thus it also complicates the Fallot's Tetralogy. The tetralogy of Fallot includes the pulmonary stenosis, the displacement of aortic orifice to the right to over ride the ventricular septum, the patent interventricular foramen and the hypertrophy of the right ventricle. The primary defect in fallod is tetralogy lies in the pulmonary stenosis which is due to the unequal division of the bulbus cordis, so that bulbur septum fails to fuse with the ventricular septum. Sometimes, there is complete absence of the interventricular septum. Then this condition is known as the biatrial monoventricular heart. Normally, the left ventricular pressure varies in the ranges between 100 to 140 mm of Hg during systole and 3 to 12 mm of Hg during diastole. The normal aortic pressure also varies between 100 to 140 and 60 to 40 mm of Hg during systole and diastole, respectively.

CONDUCTING SYSTEM OF THE HEART

Normally the atria and ventricles are separated by an eight shaped fibrous ring. But the fibrous tisue is not able to conduct impulses, so this ring acts as an insulator between the atrium and ventricles. Hence, a conducting system is needed for conduction of impulses from the atrium to the ventricles after its initiation in the atrium. This conducting system is actually made up of specialised fine myocardial cells. These specialised fine myocardial cells which form the conducting system of heart are completely striated and include the : SA node, AV node, junctional tissues, bundle of HIS (or AV bundle), right and left divisions of the bundle, their arborizatious under the endocardium (Purkinje fibres), and finally the terminal fibres which penetrate the ventricular musculature. Thus, this conducting system of the heart connect certain pace maker regions of heart with the ordinary working cardiac myocytes and speed up the wave of excitation to travel for synchronous action of different chamber. The intrinsic rhythmic excitation of cardiac muscle fibres are regulated by some pace maker cells in heart and the rhythmicity of these pacemaker cells in turn is regulated by the nerve impulses from the vaso motor centres of the brain stem which supply the heart (Fig. 5.4).

The conducting tissue of heart is composed of three types of specialised myocardial cells : nodal, transitional and Purkinje myocytes. The nodal and transitional myocytes posses high rates of rhythmical excitability, but their conduction velocity is slow. On the contrary, the Purkinje myocytes are blessed with maximal conduction velocity, but are less excitable. The Purkinje myocytes posses a conduction velocity of 2 to 3 meters/sec. Whereas, the nodal and transitional myocytes conduct the impulses only at the rate of 0·6 metre/sec. The SA node of the conducting system is mainly composed of highly rhythmic nodal myocyte cells, but few transitional and Purkinje myocytes are present within it. On the otherhand, the AV node is mainly composed of transitional myocytes or cell and the Purkinje fibres are mainly composed of Purkinje cells or myocytes.

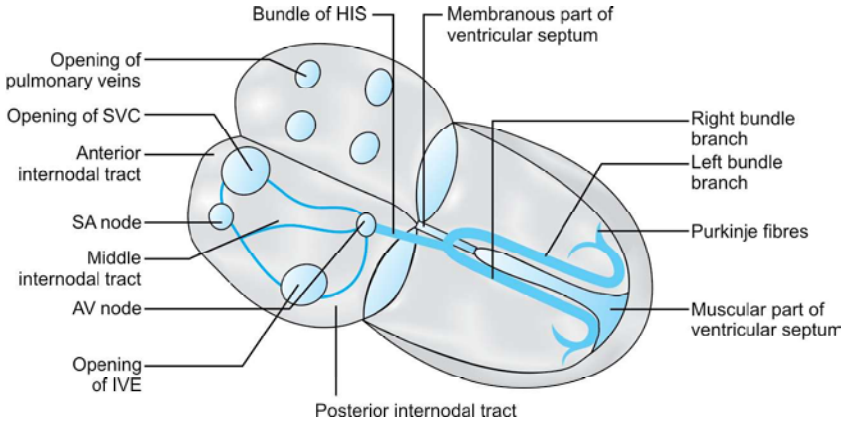


Fig. 5.4: The conducting system of the heart

SA Node

The SA node was first discovered in 1907 by Keith and Flack. It is a horse shoe shaped structure and is situated at the atriocaval juncton on the upper part of the sulcus terminalis. It extends downwards along the sulcus terminalis for a distance of about 2 cm and measures approximately 20 mm × 5 mm × 2 mm in dimensions. It is developed from the right sided embryological structure. So, there is a preponderance of the right vagal innervation on it. The parasympathetic terminal neurons of vagus are only numerous at the periphery of the SA node, whereas the excitatory postganglionic sympathetic fibres are present in the centre of it.

The discharge of impulses from the SA node passes to the AV node through atrial muscular wall via three bundles of fibres. These are the anterior internodal tract of Bachmann, the middle internodal tract of Wenckebach and the posterior internodal tract of Thorec. Of these, probably the most important is the anterior internodal pathway which also conducts impulses directly to the left atrium.

The central axis of the SA node is traversed by a nodal artery. In the majority of human population, it is derived from the right coronary artery. Possibly the thickend adventitia of this nodal artery acts as baro receptors. It monitors the aortic pressure and regulates the sinus rhythm by means of feed back. The SA node is composed of nodal myocytes (maximum quantity), transitional myocytes (less quantity) and Purkinje myocytes (least quantity). They are arranged circularly around the nodal artery from within outwards.

AV Node

Before the discovery of SA node, this node was discovered in 1906 by Tawara. It is a button shaped structure, but smaller than SA node and measures about 20 mm × 10 mm × 2 mm in three dimensions. It is situated on the lower and dorsal part of the interatrial septum, just above the opening of the coronary sinus. The AV node is embryologically originated from the left sided structure of heart and is innervated, therefore, mainly by the left vagus nerve. Impulses from the SA node converge on the AV node through three internodal tracts which are described before. Microscopically the AV node is divided into three discrete functional regions or zones. These are : (i) the AN region which joins the atrial musculature to the node; (ii) the nodal (N) or central region or the AV node proper and (iii) the NH region which joins the node to the bundle of HIS. The AN and to a lesser extent the N region is responsible for the delay that occurs during transmission of impulses from the atrium to the ventricle and allow for adequate time for filling of the later. This delay in transmission of impulse is responsible for the PR interval in ECG (Fig. 5.5).

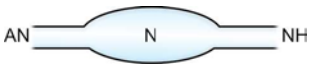


Fig. 5.5: The microscopic structure of AV node

In 80 to 90% of subjects, the AV node is supplied by the right coronary artery. In contrast to SA node, the AV node is essentially or mainly composed of slow conducting transitional myocytes, occasional nodal myocytes and covered by Perkinje myocytes which are in continuity with the AV bundle. Due to the rich population of the transitional myocytes, there is a conduction delay in the AV node.

AV Bundle (Bundle of His)

It is the only muscular (myocytes) connection between the atrium and the ventricles which are separated by 8 shaped nonconducting fibrous ring. The bundle of HIS begins at the AV node. It is enveloped by a vascular connective tissue sheath and crosses the right fibrous ring. Then, it descends along the posterior-inferior border and the right side of the membranous part of the interventricular septum (subendocardially) and reach the upper medial part of the muscular interventricular septum. At the upper border of the muscular part of the interventricular septum it divides into right and left branches. Then the left branch pierses the interventricular septum and reach the left side of it.

Right branch of the AV bundle

It passes along the right side of the interventricular septum and reaches the anterior wall of the right ventricle where it brakes into Purkinje fibres.

Left Branch of the AV bundle

It consists of two to three fascicules and passes sub endocardially along the left side of the interventricular septum in an envelope of connective tissue sheath. Then, after traversing a course of 2 to 3 cm, it splits into anterior and posterior sheets to reach the base of the corresponding

papillary muscles. Finally, it breakes into Purkinje fibres.

Sometimes the few fibres of conducting myocytes of the internodal tracts between the SA and AV node bypass the AV node and join straight with the common AV bundle. Much speculations appear about the existence of this accessory AV bundle in close proximity to the common AV bundle or around the mitral and tricuspid annuli. The presence of such accessroy conducting tissue might explain the causes of certain form of cardiac arrhythmias.

Purkinje Fibres

The purkinje fibres are composed of somewhat specialised larger cells of myocytes and forms a subendocardial plexus. The cellular outlines of these myocytes are indistinct. The central cytoplasm of these myocytes is granular and contains several nuclei. The peripheral cytoplasm of there myocytes contains myofibrillae, but these are separated by more sarcoplasm. The glycogen content of Purkinje cell is very high.

THE ARTERIES SUPPLYING THE HEART

The heart is supplied mostly by two coronary arteries such as the right and left. They arise from the root of the ascending aorta and run in the corresponding atrioventricular groove or coronary sulcus. Only the inner 100 µm of the endocardial surface of the myocardium of heart gets nutrition directly from the blood of the cardiac chambers. Anatomically, the coronary arteries are not the end arteries. Because, they anastomose with each other by their trunks, branches and subbranches, mostly at the precapillary level. But, functionally, however, they behave like end arteries, since most of the anastomoses remain impervious. Each coronary artery is actually a vasavasorum of the ascending aorta. Because the heart is developed from the fusion of two primitive endothelial tubes, from where the great vessels are developed.

Right Coronary Artery

It is smaller than the left coronary artery. It arises from the right aortic sinus of ascending aorta behind the right aortic cusp. It then passes forward and to the right and emerges on the surface of the heart between the root of the pulmonary trunk and the right auricle. It then runs downward along the right anterior atrioventricular groove or coronary sulcus up to the junction of the right and inferior border of the heart. Then, it winds round the inferior border to reach the diaphragmatic surface of the heart. After that, it runs backwards and to the left through the right posterior coronary sulcus to reach the post interventricular group where it gives a branch, named the post descending artery (in 60% population) and terminate by anastomising with the left coronary artery. In 60% subjects, the terminal part of the right coronary artery anastomoses with the circumflex branch of the left coronary artery at the 'crux of the heart' which is the meeting point of the posterior interatrial, posterior interventricular and posterior part of the atrioventricular grooves. In 20% cases, the right coronary artery traverses the entire posterior atrioventricular groove and reach the left border of the heart where it makes anastomosis with the left coronary artery. In 10% cases, it directly reaches the apex of the heart through posterior interventricular groove instead of the giving posterior descending artery and makes anastomosis with the anterior descending artery. In remaining 10% subjects, it is very short and reaches only up to the junction of the right and inferior border of the heart (Fig. 5.6).

The branches of the right coronary artery are: right conus artery, right marginal artery, posterior descending or interventricular artery and multiple muscular branches to the atrium and ventricle. The right conus artery is usually the first branch of the right coronary artery and supplies the infundibulum of the right ventricle. Sometimes, it arises directly from the anterior aortic

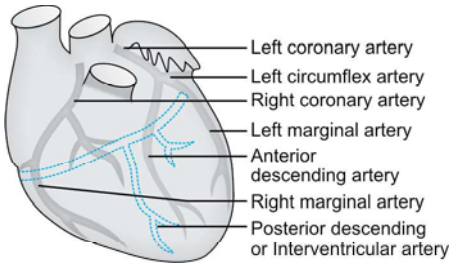


Fig. 5.6: Coronary arteries and their branches

sinus and then it is called the third coronary artery. The right conous artery sometimes anastomoses infront of the aortic root with the same type of left conus artery, derived from the circumflex branch of the left coronary artery. This anastomotic necklace, thus formed around the infundibulum, is known as the annulus of Vieussens.

The right marginal artery arises from the right coronary artery at the junction of the right border and inferior border of the heart. Then, it runs along the inferior border of the heart towards the apex and supplies the adjoining surfaces of the right ventricle. The atrial and ventricular branches or rami are the small arteries which arise from the right coronary artery at the right angles of it at fixed interval while it passes through the right half of the anterior and posterior atrioventricular group. The anterior ventricular rami or branches supply the sternocostal surface and the posterior ventricular rami or branches supply the diaphragmatic surface of the right ventricle. Atrial rami are also grouped in anterior and posterior and supply the anterior and posterior wall of the right atrium. Among the atrial rami one large artery suply the SA node which is called the 'sinoatrial nodal artery'. In 65% cases this sinoatrial nodal artery arises from the right coronary artery and in 35% subjects it arises from the circumflex branch of the left coronary aretery (Fig. 5.7).

In 60% cases the posterior descending artery or the posterior interventricular branch arises from the right coronary artery near the crux and passes downwards along the posterior interventricular

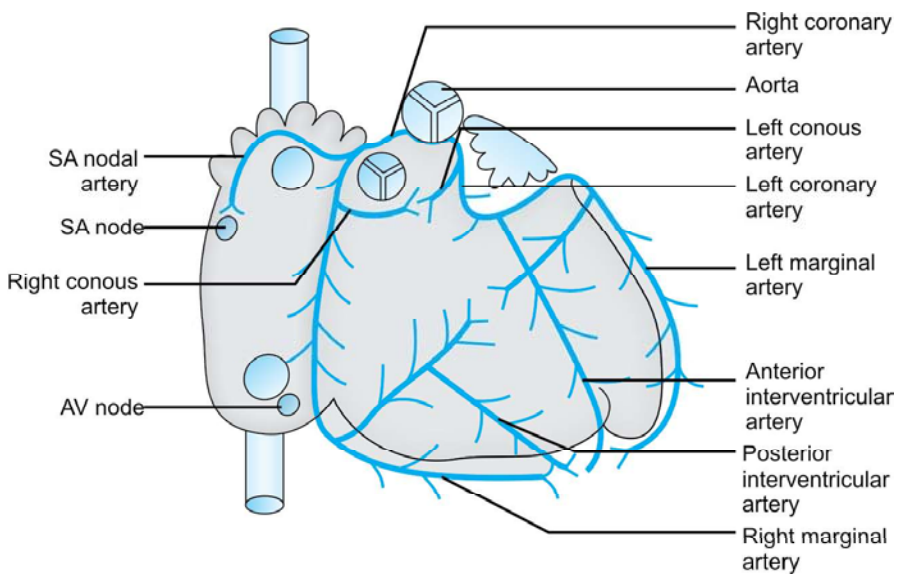


Fig. 5.7: Right and left coronary arteries with their branches

groove towards the apex. At the apex, it anastomoses with the anterior descending or anterior interventricular branch of left coronary artery. In 10% individuals, the posterior interventricular branch is derived as a continuation of the left coronary artery. So, on the basis of the origin of the posterior interventricular branch from the right or left coronary artery, the right coronary predominance' or 'the left coronary predominance of heart' is described. It supplies the diaphragmatic surface of both the right and left ventricle and postero inferior part (½) of the interventricular septum. The first septal branch of the posterior descending or posterior interventricular artery supplies the AV node. In 80 to 90% subjects the AV nodal artery is derived from right coronary artery and in 10 to 20% cases from the it is derived left coronary artery.

Left Coronary Artery

It is larger than the right coronary artery and arises from the left aortic sinus, behind the left cusp of the aortic valve. After arising from the aorta, it first runs forward and to the left between the pulmonary trunk and the left auricle. Here it gives off the anterior interventricular branch or anterior descending artery which runs downward through the anterior-interventricular groove. While passing through the anterior interventricular groove, the anterior descending artery gives off multiple branches at right angle which supplies the sternocostal surface of both the ventricles and the anterior portion of interventricular septum. One such branch of the anterior descending artery, supplying the left ventricle is large and is called the diagonal artery which arises from the junction of the anterior descending artery and the circumflex branch. In such condition the trunk of the left coronary artery actually trifurcates. The septal branches of the anterior descending artery supply the anterior 2/3 of the interventricular septum. The rest posterior 1/3 of the interventricular septum is supplied by the posterior descending artery which is the branch of the right coronary artery.

The further continuation of the left coronary artery is sometimes called as the left circumflex artery. After giving off the anterior interventricular branch, this left circumflex artery runs to the left in the left anterior ventricular groove or left coronary sulcus. Then, it winds round the left border of the heart and continues in the left coronary sulcus posteriorly. Near the posterior interventricular groove this circumflex artery terminates by anastomosing with the right coronary artery. The circumflex artery lies close to the mitral valve and may be damaged during mitral valve replacement surgery. While passing through the anterior and posterior atrio ventricular groove, the circumflex artery gives of branches supplying the adjoining surfaces of the left atrium and left ventricle. During winding round the left border of the heart, it gives a prominent branch which follows the left border of the heart towards the apex. It is called the left marginal artery. In coronary artery bypass surgery (CABG) a vascular autograft is usually anastomosed to the left marginal artery distal to the site of obstruction.Thus, the main branches of left coronary artery are: anterior interventricular (ant. descending) artery, left marginal (or obtuse marginal) artery and multiple atrial and ventricular branches or rami.

Summary of Coronary Circulation

i. The left coronary artery supplies: (a) whole of the left atrium, (b) most of the left ventricle, except a strip along the posterior and inferior surface and (c) anterior 2/3 of the interventricular septum.
ii. The right coronary artery supplies: (a) the whole of the right atrium, (b) most of the right ventricle, except a strip along the anterior interventricular groove, (c) posterior 1/3 of the interventricular septum, (d) SA node and AV node in the majority of subjects.
iii. Sometimes left coronary artery arises from the pulmonary trunk and produce left ventricular failure. Occasionally, it arises from the anterior aortic sinus and undergoes a longer course behind the pulmonary trunk, before dividing into branches. In this anomaly, the main artery may be compressed between the aorta and pulmonary trunk after severe

exercise and results in sudden cardiac death.

iv. The parasympathetic stimulation has negligible direct effect on the coronary vessels. Sympathetic α-receptors (constrictor effect) are predominant over the epicardial segment of the coronary vessels. But sympathetic β-receptors (dilatation effect) are predominant over the intramuscular segment of the coronary arteries. Therefore, sympathetic stimulation constricts the epicardial arteries and dilates the intramuscular arteries.

v. The coronary arteries are the only vessels in the body where the blood flows maximally during the diastole of cardiac cycle.

vi. Majority of people possesses 'right coronary artery predominance' where the posterior interventricular or posterior descending artery is derived from the right coronary aretery. Minority of population has 'left coronary artery predominance' where posterior descending artery extends as a continuation of the left coronary artery. These people are likely to be affected by coronary disease. This is because the entire left ventricle and the interventricular septum are under the nutritional control of left cornary artery. So, obstruction of the latter may produce output failure for systemic circulation. Sometimes, on rare occasions the posterior descending artery is derived from both the right and left coronary arteries. Individuals with such balanced type of coronary distribution are least affected by coronary disease.

vii. In the subepicardial fat, potential communication exists between the branches of the coronary arteries, the branches of the internal thoracic artery and the branches of the descending aorta such as pericardial, bronchial, phrenic and oesophageal artery. In slow obstruction of coronary arteries, these collateral channels dilate and maintain the nutrition of heart.

viii. Clinically, occlusion of the main coronary arteries and their major branches may be located within the first 2 cm of the anterior descending and/or circumflex artery or proximal distal third of right coronary artery. Average frequencies of critical narrowing of the three major arterial trunk are as follows: anterior descending branch of left coronary artery (LAD) 40 to 50%, right coronary artery (RA) 30 to 40%, (left coronary) circumflex artery 15 to 20%. Other infrequent locations of the coronary artery occlusion are : diagonal branches of the anterior descending artery, left marginal branch of the circumflex artery, trunk of left coronary artery.

ix. The total coronary circulation time is about 8 sec. The volume of coronary blood flow is about 225 ml/minute. It is about 5% of the total cardiac output in resting condition. The flow of blood through coronary capillary falls during systole and rises during diastole. Blood flow through the subendocardial arterial plexuses falls almost to zero during systole. But, in diastole blood flow through the subendocardial arteries is greater than that of the epicardial arteries. This explains why myocardial infarction in coronary occlusion involves first the subendocardial regions.

x. The incomplete and spasmodic obstruction of coronary arteries are expressed as angina pectoris where the subject complains of intense precordial pain which is occasionally referred along the left upper arm. In cardiac ischaemia due to vascular occlusion CABG operation is advocated with promising results. It is now possible to dilate the obstructed coronary arteries with a balloon, introduced percutaneously (percutaneous transluminal angioplasty - PCTA) (Fig. 5.8).

Venous Drainage of the Heart

Most of the venous blood from myocardium returns to the heart through the great (anterior) cardiac vein and the coronary sinus. Both of them drain into the right arium. The coronary sinus conveys the blood mainly from the left coronary artery

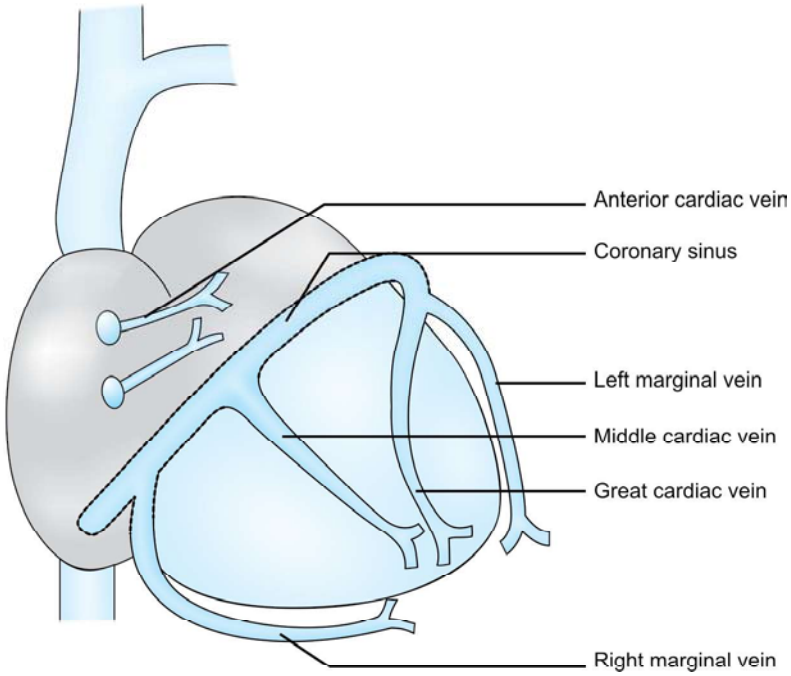


Fig. 5.8: The venous drainage of myocardium

and the anterior cardiac vein conveys the blood from the right coronary artery. The coronary sinus is a wide channel which is 2 to 3 cm long and is situated in the posterior atrioventricular groove. It receives 60% of venous blood from the myocardium. It begins in the left part of the post atrioventricular groove where it receives the great cardiac vein. Then, the sinus runs to the right and drains in the right atrium between the opening of IVC and right atrio ventricular orifice. Its main tributaries are: great cardiac vein, middle cardiac vein, right marginal vein and left marginal vein. The great cardiac vein begins at the apex of the heart and passes upwards along the anterior interventricular groove. Then, it winds with coronary sinus. The middle cardiac vein starts at the apex and runs upwards along the posterior interventricular groove to join the coronary sinus. There are also other vessels which drain directly into any of the cardiac chamber. These vessesls are: arteriosinusoidal, thebesian and arterioluminal vessels. Arteriosinusoidal vessels are capillary like sinusoidal channels which connect arterioles with the cardiac chambers. Thebesian veins are vessels that connect capilaries with the cardiac chambers. Arterioluminal vessels are small arteries which directly empty into the cardiac chambers. In addition, multiple anastomoses occur between the coronary arterioles and the extracoronary arterioles, especially around the mouth of great veins (Fig. 5.9).

CARDIAC CELLULAR ANATOMY

The cardiac muscle cells or fibres are unique in that it incoporates the characteristic features of both the skeletal and smooth muscle cells in it. They are separated from each other by the cell membrane and the connective tissues called endomysium, along with the blood vessel and lympahtics. Each cardiac muscle fibre or cell is not one straight simple cylinder, but has got short cylindrical branches in all directions. These branches are coming in contact with that of the adjacent cardiac muscle cells or fibres and ultimately forms a three dimensional network structure. Under light microscope these network of cardiac muscle cells appear as syncytium (cytoplasmic continuation in between neighbouring cells) which is also supported by the property of cardiac muscle that if one myocardial cell contracts, then all the muscle cells and the heart will contract as a whole. But, Electron Microscope reveals that the cytoplasm of each cardiac muscle cell is separated from other by intercalated disc. So, heart muscle is not a structural, but functional syncytium, because the electrical resistance offered by the intercalated disc is very low and impulse passes easily as if there is no barrier between the cytoplasm of two myocardial cells. Thus, when one cell is excited then the excitation process spreads easily and quickly across the intercalated disc to its neighbouring cells and ultimately to all the cardiac muscle cells (Fig. 5.10).

Impulse propagation in the heart depends on two factors, such as, the magnitude of the depolarizing current (usually Na^+current) and the geometry of the cell to cell electrical connection. Cardiac cells are long, thin branched and are well attached at their longitudinal end or at their branched end with the next cell through a specialised gap junction protein, called the intercalated disc. Whereas, the lateral (transverse) gap junction protein are sparser. As a result, impulses which spread along

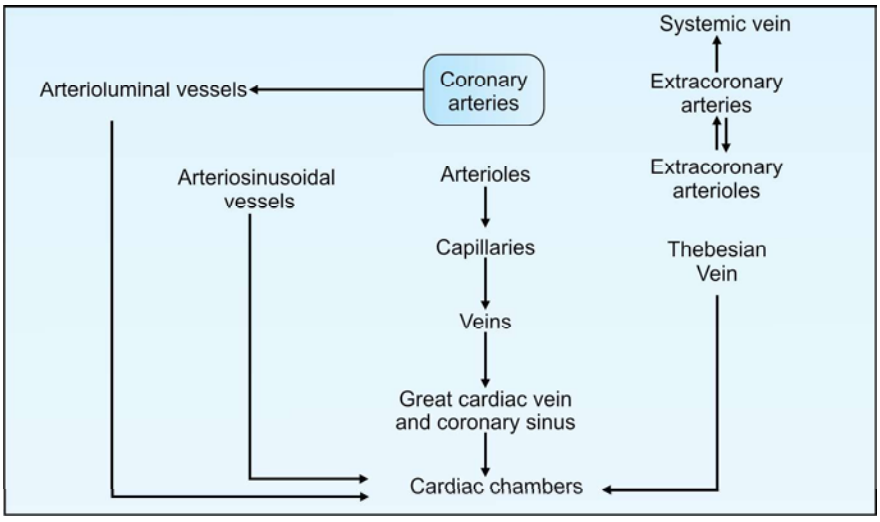


Fig. 5.9: Schematic diagram of venous drainage of heart

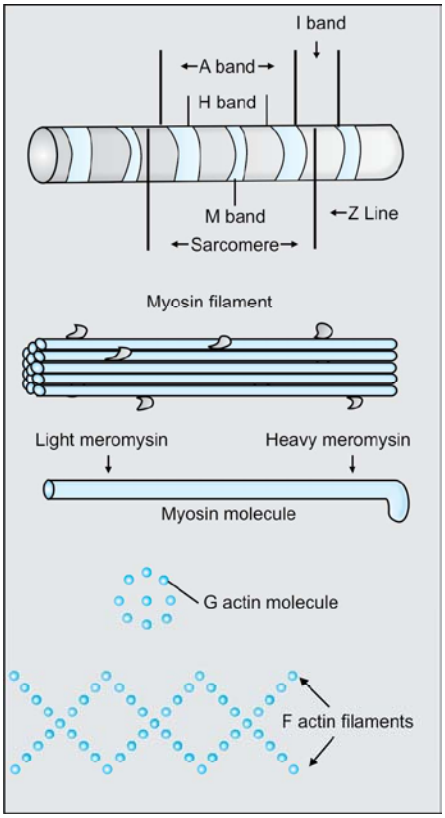


Fig. 5.10: Schematic diagram of a muscle fibre shown under polarised light, structure of myosin and actin myofilament

the longitudinal axis of the cells is 2 to 3 times faster than that of the transverse axis of the cells. This 'anisotropic' (direction-dependent) conduction may be a factor in the generation of certain arrhythmias.

Each myocardial cell or fibre is 100 µm in length and 15 µm in breadth. They are covered by an outer cell membrane, called the sarcolemma. It surrounds the numerous striated myofibrils or myofilaments which are present longitudinally in the cytoplasm of the myocardial cell. Each myofibril consists of two contractile proteins − actin and myosin. They are interrupted at intervals of 1·2 to 2·5 µm by dark lines, known as Z-lines. The portion enclosed by two adjacent Z-lines of a myofibril is considered as the contractile unit and is named as the sarcomere. It extends about 2 to 3 µm in length. During each cardiac contraction the myosin and actin filaments combine reversibly to form the actomyosin complex. This interaction is the fundamental basis of muscular contraction.

Each cardiac muscle cell or fibre consists of alternate light and dark bands. This dark band is shown as the doubly refractive (anisotropic) area when studied under polarised light. Hence, this dark band is named as the A-band. The light band is shown as monorefractive (isotropic) area under the polarised microscope. Hence it is called as the I-band. This I-band is bisected at the midpoint by the so called Z-line. At the Z-line one cardiac muscle cell or fibre ends anatomically. Here, the cell membrane (sarcolemma) contains extensive networks of interdigitating folds, and give attachment to the ends of individual actin myofibrils of two adjacent cells. These intercellular junction is called the intercalated disc and indicated by the Z-line. These intercalated discs form the tight connection with lowest resistance between the two adjacent myocardial cells and give attachment to the longitudinally arranged actin myofibrills. This also allow for tension to be transferred uniformly between the cells on that particular longitudinal axis. The Electron Microscope (EM) reveals that intercalated disc or Z-line is made up of the cell membranes of two adjacent cells. A complex pattern of ridges and papillary projection of the cell membrane at each end of the cell fit into the corresponding grooves and pits of the other cell membrane which form an elaborately interdigited junction or specialised cell to cell cohesion, with intercellular space obliteration. These areas of the intercellular space obliteration are of low electrical resistance which helps in the rapid propagation of electrical impulses from cell to cell and through out the whole mass of the heart through their branching and thus assisting the myocardium to behave as syncytium (Fig. 5.11).

The light areas adjacent to the Z-line are made up of only thin actin filaments which are anchored to the Z-line. The actin filaments, before approaching the Z-line, appear to be branched into four fine diverging filaments, called the Z-filaments which ultimately anchored with Z-line.

The dark central A-band of each cardiac muscle cell is due to the interdigitation or overlapping of thick myosin and thin actin filaments. Again the central portion of this A-band is pale in colour and called H-band. This is due only to the presence of myosin filaments and absence of actin filaments. At the mid-point of the H-band there is also a narrow dark line which is called the M-band, where the each myosin filaments are thickened maximally. This myosin and actin filaments are over lapped at the peripheral dark portion of the A-band which is named as the O-band. Transverse section of the myofibrils at different levels of the A-band and I-band will give different representations (Fig. 5.12).

Transection through the I-band will show the thin actin filaments only. Transverse section through the O-band will present both the thin actin and thick myosin filament and that at the H-band and M-band only myosin filament will be presented. In cross-section at the O-band the arrangements of the thin actin filaments appears in hexagonal shape with one myosin filament at the centre. But again when the thick myosin filaments are considered then the myosin filaments are appeared forming triangles with one central actin filaments. But in the longitudinal section, each myosin filament is followed by two actin filaments. The thin actin filaments are also connected with each other longitudinally by means of still more thinner S-filaments.

Under EM, within the myocardial cell the myofibrils or the myofilaments are seen to have surrounded by another longitudinal network of membranous-tubular structure, called the sarcoplasmic

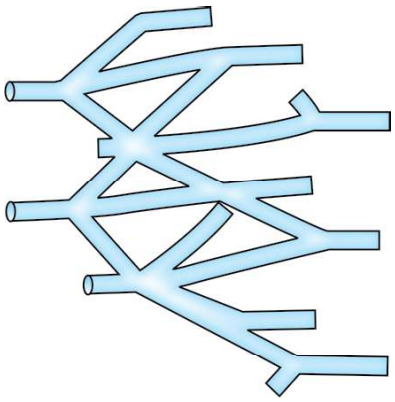


Fig. 5.11: Branched actin filaments or Z filaments at Z-line

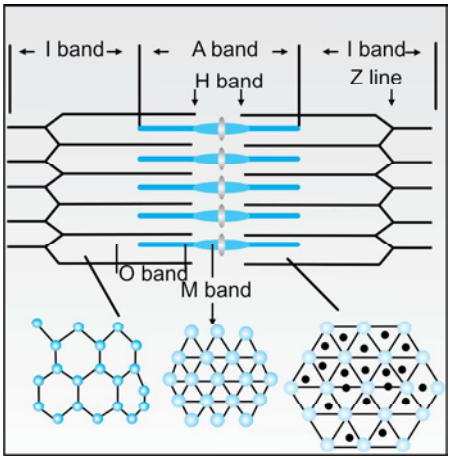


Fig. 5.12: Schematic diagram showing disposition of actin and myosin filament

reticulum (SR). This SR is identical with the endoplasmic reticulum of other cells, but with the difference that its membrane does not possess ribosomes. These longitudinal tubules of SR is dilated at their terminal end and called the 'terminal cistern'. In each myocardial cell, at the level of Z-line, a transverse invagination of the sarcolemma (plasma membrane) occurs. Thus, this results in extension of the extracellular space into the more central portion of the myocardial cells at the level of the Z-lines. These transverse invagination or tubules of sarcolemma are called T-tubules. Thus, at the level of each Z-line these T-tubules approximate with the longitudinal tubules of SR, but do not anastomose with each other. So, the term 'triad' is used to describe this arrangement of the terminal dilatation of two longitudinal tubules (terminal cisterns) from opposite direction on each side of the transverse tubule (Fig. 5.13).

The depolarization of sarcolemma causes the development of an action potential which is conducted through the transverse tubules (T-tubules) into the central portion of the cells and causes a small intracellular influx of Ca^{2+} from it. This small release of Ca^{+} from the T-tubules occurs through the L-type of calcium channel which is situated in it. Then the impulse which passes down the T-tubules causes depolarization of the adjacent cisternae of longitudinal tubule of SR. SR is the main storage site for Ca^{2+} within the cell. A large protein complex termed the Calcium Release Channel (CRC) is present within these terminal cisternae of longitudinal tubules of SR. These respond to small influx of Ca^{2+} from the T-tubules due to depolarization of cell membrane and then subsequently release the large amounts of Ca^{2+} from the stored SR into myoplasm or sarcoplasm. This results in an sudden large increase in the intracellular Ca^{2+} concentrations from 10^{-7} M to 10^{-5} M. The short distance between the L-type Ca^{2+} channel in T-tubule and the foot process of the CRC in terminal cisternae of SR allows the Ca^{2+} entry from L channel to CRC channel and immediate release of huge amount of Ca^{2+} in cytoplasm from the later.

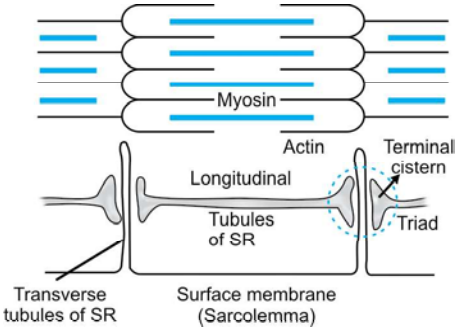


Fig. 5.13: Two dimensional diagram showing connection between the surface of muscle fibre and the endoplasmic reticulum

Ca^{2+} then diffuses from cytoplasm into the myofibrils or filaments and activates myosin. Myosin then splits ATP, yielding the necessary energy for the formation of the actomyosin complex for the contracton of muscle. After contraction, the Ca^{2+} again actively transported back into the cistern of longitudinal tubules of SR and relaxation occurs. This occurs through Ca/Mg ATPase pump which is embeded in the whole membrane of the longitudinal SR. After removal of Ca^{2+} from cytoplasm, the intracellular concentration of it is again restored to 10^{-7} M at diastole.

Like other cells, cardiac muscle cells or fibres also contain numerous mitochondria surrounded by myofibril, single nucleus, small Golgi apparatuses and abundant cytoplasm.

Mechanism of Myocardial Contraction

Myofilaments or myofibrils are the contractile units of the cardiac muscle cells. They are of two types such as the thinner ones (50 ^{o}A in diameter) are called the actin filaments and the thicker ones (100^{o}A in diameter) are called the myosin filaments.

The molecular weight of actin myofibril is 43,000. With very high magnification under electron microscope, it is found that each actin filament is consist of two strands, arranged spirally. Each strand of actin filaments which are called fibrous actin or F-actin appears as beaded and seem to consist of globular subunits, called G-actin. The two strands or F-actin are entwined in a helix. Two complex proteins such as tropomysin and troponin are interoposed between this two thin strands (F-actin) of actin filaments. Molecular weight of tropomysin is 70,000 and lies within the sulcus of two thin strands of actin filaments (F-actin). Troponin is also consists of three distinct polypeptides - Troponin T, Troponin I and Troponin C and lies within the groove of two thin strands of actin filaments (F-actin) at regular interval. Each polypeptide of troponin fulfills different functions in the regulations of muscular contractions. Troponin T binds with the tropomysin and forms a complex. Troponin I inhibits the reactions of actin with myosin filament. Troponin C binds Ca^{2+} and activates contractions by inhibiting troponin I. The binding of Ca^{2+} to Troponin C is the triggering factor that initiates the chain of reaction causing conformational changes of actin and leads to the development of mechanical activity. (Like Troponin C, calmodulin which is present in other nonmyocardial cells in place of Troponin C also binds with Ca^{2+} and initiates the different enzymatic reactions in these cells) (Fig. 5.14).

The thicker contractile element of myofibrils or myofilaments is called myosin. It consists of large asymetrical molecules, consisting of two heavy chains and four light chains. The molecular weight of heavy chain and light chain is 2,20,000 and 20,000, respectively. Each myosin molecule consists of : (i) one globular head containing the activity of enzyme ATP-ase which hydrolyses ATP to provide energy and interacts with actin to form cross - bridges, (ii) one neck area, appears to be involved in the development of tension and (iii) one tail which helps to

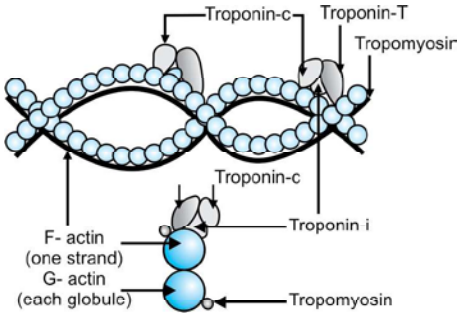


Fig. 5.14: The structure of actin filament. The backbone of each actin filament is two strands which are made up of actin monomers (G-actin). Each strand is called F-actin. Troponin complex which is made up of one molecule each of troponin-C, troponin-I and troponin-T are distributed at regular intervals along the actin filaments. Elongated tropomysin molecules, which is another protein structure and is attached to the actin filaments, lie in the grooves between the two actin strands. A cross-section of actin filaments at the level where troponin complexes are located shows the probable relationship between the actin, tropomyosin and the three components of the troponin complex. The strength of the bond linking troponin I and actin varies. It depends on whether Ca^{2+} is bound to troponin C or not

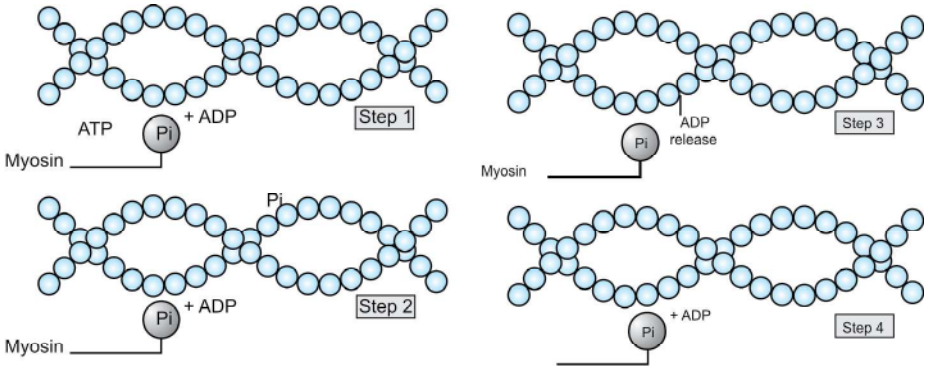


Fig. 5.15: The reaction mechanism between the actin and myosin filament is described in simplified form in four steps:
Step 1: On the head of the myosin filaments there is an ATP hydrolyzing site. After hydrolysis of myosin bound ATP at this site, energy is released. This is transferred to the myosin head and it is activated and energised. In a relaxed muscle the intracellular Ca^{2+} concentration is low and in this low Ca^{2+} concentration troponin and tropomysin complex on the actin filaments do not allow the actin filaments to intereact with the energised activted myosin head. Therefore, even though the myosin heads are energised, they can not interact with actin filament.
Step 2: After depolarization there is increased concentration of intracellular Ca^{2+}. Then, increased Ca^{2+} is attached with troponin C and make some conformational changes of actin filaments. This conformational changes of actin filament causes binding of actin with the already energised mysin filaments and formation of cross bridges.
Step 3: After the attachment of head of the mysin with the actin filament energy is released from the head which causes changes in the angle of the attachment of the head of myosin filament and the rowing motion of cross bridges. This is called the power stroke which produce muscle contraction.
Step 4: Then the muscle returns to its resting state and the cycle ends when a new molecule of ATP binds with the myosin head and dissociats the cross bidges from the actin filaments. The contraction continues until Ca^{2+} is dissociated from the troponin C of the actin filament which causes the contractile proteins to return to the resting state. Thus, (i) binding of another ATP molecule which leads to the detachment of cross bidge, (ii) the cycle of hydrolysis of ATP and (iii) reattachment of myosin head with formation of cross bridge with actin filament begin again

anchor one myosin molecule to another forming thick myosin filament. The head and neck portion of each myosin molecule is called the heavy meromysin and tail or rod like portion of it is called the light meromysin. The thickness of the myosin filament is believed to be due to the parallel arrangement of myosin molecules in such a fashion that the globular heads project outward near the surface of the myosin filaments and the rod like tail part takes its position in the smooth central portion of the myosin filament. The heads of myosin molecules are arranged in a radial pattern and each set of six head complete one revolution around the myosin filament within one 400°A segment. Each head of the myosin molecule is pointed towards a separate actin filament and make a cross bridges during actin myosin complex formation and muscular contraction.

The impulse or the wave of depolarisation is propagated from the sarcolemma (cell membrane) through the T-tubules into the interior of the cell. Then, the depolarisation of the T-tubules cause the entry of small amount of Ca^{2+} from the extracellular space into the sarcoplasm. This small entry of Ca^{2+} occurs through the L-type of Ca^{2+} channel situated on the T-tubules and acts solely as a trigger to initiate the huge release of Ca^{2+} from the longitudinal tubules of SR. The Ca^{2+} release channel on the 'terminal cisterns' of the longitudinal tubules of SR is a huge protein molecule of molecular weight of 5,65,000 with foot process which lies in close proximity to the L-type of Ca^{2+} channel. The short distance between the L-type of Ca^{2+} channel in the T-tubular membrane and the foot process of Ca^{2+} channel on terminal cistern (CRC or calcium release channel) allows the immediate entry of this small amount of Ca^{2+} in the SR and subsequent huge release of Ca^{2+} from the 'terminal cistern' of it (Fig. 5.15).

After release of Ca^{2+} and contraction of muscle, it again reaccumulates back in the longitudinal tubules of SR. This is accomplished by Ca / Mg-ATP ase pump, embedded on the membrane of the longitudinal tubule of SR. So, the removal of free intracellular Ca^{2+} from the sarcoplasm back into longitudinal tubule of SR is an active, energy consuming process. Thus, the low sarcoplasmic Ca^{2+} concentration i.e. 10^{-7} M from the high Ca^{2+} concentration i.e 10^{-5} M is restored by the tubule of the SR during diastole.

The activity of Ca^{2+} channel on the sarcoplasmic reticulum (SR) can be augmented by the cAMP dependent phosphorylation of an another SR protein called phospholamban. The β-adrenergic stimulation leads to the increase in phosphorylation of this phospholamban, causing increased Ca^{2+} channel activity and

increase in concentration of Ca^{2+} in sarcoplasm and increased force of contraction.

In the resting state, the Troponin-I exerts an inhibitory effect on the actin filaments via tropomysin and Troponin-T. But Troponin-C has an afinity for Ca^{2+} and binds calcium to its saturation point when the sarcoplasmic Ca^{2+} concentration rises to 10^{-5} M. Thus when Troponin-C is activated, it inhibits Troponin-I. As a result the inhibitory influence of the troponin-tropomysin complex on actin is removed. Simultaneously, the rise in the Ca^{2+} concentration in the sarcoplasm activates the ATP-ase enzyme situated on the myosin head. This activated ATP-ase breaks the ATP to ADP with the release of energy which energizes the myosin head and forms cross bridges with actin causing muscular contraction.

In summary, the mechanism of myocardial contraction and relaxation may be expressed as the follwoing order.

i. *Contraction:* membrane depolarization → Ca^{2+} released from the sacroplasmic reticulum (SR) → myosin ATP-ase is activated → cross bridges formed → actin slides along the myosin filaments → tension is developed.

ii. *Relaxation:* Ca^{2+} pumped back into sacroplasmic reticulum → myosin ATP-ase is depressed → cross bridges broken → actin is pulled back to its resting state → tension disappears.

CARDIAC ELECTROPHYSIOLOGY

The flow of different charged ions across the cell membrane results in the appearance of different ionic currents such as the Na^+ current, K^+ current, Ca^+ current, etc, and these make up the cardiac action potential. The action potential of a cell is a highly integrated event. Changes in the flow of one ionic current almost inevitably produces stimulatory or inhibitory secondary changes on the flow of other ionic currents. Movements of ions across the cell membrane occurs not only passively through the lipid bilayer of it, but also actively through the different specific ion channels and transporter systems, situated on it. These occur in response to either electrical or concentration gradient or both.

The contraction and relaxation of cardiac muscle are due to the event of action potential (like skeletal muscle and nerve fibres) which originates from the SA node and passes to the AV node through the atrial muscle. This initiates the atrial contraction and relaxation. It then passes through the bundle of HIS and Perkinje fibres to the ventricular muscle and initiates the ventricular contraction and relaxation. The rapid alteration of electrical potential during depolarization of cardiac muscle cell differs little from that of the nerve fibres and skeletal muscle cells which is discussed later. But, the repolarisation in cardiac muscle cell requires 400 ms. This is entirely different from the situation found in the skeletal muscle cells and nerve fibres in which the total action potential including the depolarization and repolarization is completed within few miliseconds. Because of this long duration of action potential due to the prolonged repolarisation, the cardiac muscle cells can not be further reexcited for few fraction of a second, even when the previous mechanical contraction is almost complete. Thus the heart muscle can not be tetanized like the skeletal muscle. This property of long refractory period ensues enough time for recovery of the cardiac muscle cells.

Action potential of heart is of two types. One is 'the fast response action potential' which occurs in the cells of the atrial muscle, ventricular muscle and Purkinje fibres. And second is 'the slow response action potential' which occurs in the SA and AV node and is responsible for the automaticity or pace maker activity. The myocardial cells which have the characteristic of 'fast response action potential' also posses the pace maker activity. But, it is usually suppressed by the activity of the myocardial cells which have the characteristic of 'slow response action potential'.

The differences between these two type of action potentials is discussed under different headings below:

(i) In the Resting Membrane Potential

In slow response action potential, the resting membrane potential attains rarely more negative than −60 mV. Whereas, in fast response action potential which is found in other cardiac muscle cells except the SA and AV node, the resting membrane potential approximately goes down to −80 or −90 mV. In the type of slow response action potential, during the period of phase 4, the resting membrane potential spontaneously and progressively changes from −60 mV to approximately −40 mV which is the threshold value for excitation, and thereafter a fulminant upstroke of a full action potential or depolarization occurs. This slow ascent of membrane potential to a more positive value i.e from −60 mV to −40 mV during the phase 4 of AP characterises the 'pace maker' activity of the SA or AV node. This is due to the slow inward flow of sodium current in phase 4. Initially this inward Na^+ current only slightly exceeds the outward K^+ current. But gradually the outward K^+ current stops allowing continuous inward Na^+ current to produce a progressively more positive or less negative membrane potential (Fig. 5.16).

Once the resting membrane potential achieves a threshold level of −40 mV, then there occurs a very rapid rise of inward flow of Na^+ current and the depolarisation

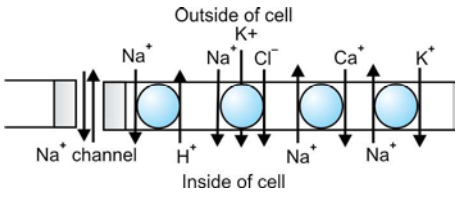


Fig. 5.16: Different types of Na+ transport systems which act during different phase of action potential. From left to right these include: The Na^+ channel, Na^+-H^+ antiport exchange. Na^+-K^+ contransport, Na^+-Ca^{2+} exchanger and the Na^+-K^+ ATPase pump

part of action potential takes off. It indicates that the threshold level for excitation is achieved earliest in the SA nodal cell and the action potential, generated there, is conducted to the other cardiac cells. As other cardiac cells are latent pace maker and the depolarisation, arising from the SA node, arrives there before their own diastolic depolarisation in phase 4 is reached to threshold level, so their automaticity is supressed.

(ii) In the Rate of Rise of Upstroke in Action Potential

In the slow response action potential of SA and AV nodal cell, there is slow depolarisation phase, slow repolarisation phase and also the slow slope of diastolic depolarisation phase (phase 4 of action potential). The peak of the action potential in case of slow response is rounded, but uninterrupted. In atrial, ventricular and Purkinje cells where the fast response action potential occurs the depolarisation phase is very sharp, the peak is mostly pointed. Besides these, there is interrupted fall of repolarisation and the upward slope of diastolic depolarisation phase is absent (actually not absent but depressed). Thus, in SA node dominated heart, the pace maker activity of the cells of atrial muscle, ventriculsr muscle and Purkinje fibres are depressed due to the higher rhythmical activity of the SA node. This is evident from the absence of the slope of slow diastolic depolarisation phase in these group of muscle fibres. But if the transmembrane potential is recorded from isolated fibres of these group of muscle cells, then the slope of slow diastolic depolarisation (phase IV) is observed (Fig. 5.17).

(iii) In the Propagation Velocity of AP

It is important to note that the conduction velocity of impulses through the AV node is slow (0·2 m/Sec). Thus, it ensures an appreciable delay between the atrial and ventricular depolarisation or contraction.

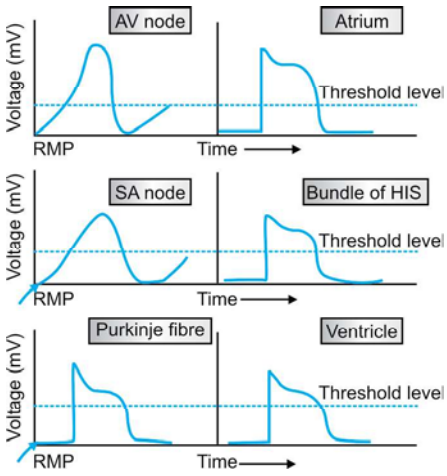


Fig. 5.17: Different configurations of action potential of different tissues of heart. The SA node has the steepest phase 4 showing rapid spontaneous depolarisation in diastole. So, it undergoes fast self excitation and acts as pacemaker. Other tissues also undergo the phase 4 slow depolarisation, but at a slower rate. So, they receive a propagated impulses from SA node, before their phase 4 of action potential reach the threshold level and remain as latent pacemakers. Two types of action potential are found in different cardiac tissues. These are slow and fast action potential. The slow action potential is characterised by: (i) shorter duration, (ii) phases 1, 2 and 3 are not clearly demarked, (iii) low amplitude, rounded overshot, initiation of action potential at lower threshold (less negative) level

This slow conduction of AV node is partly due to the small size (radius 7 µm) of the AV nodal cells compared to the Purkinje cells or fibres (radius 50 µm) which conduct the impulses at the rate of 4 m/sec. It is also partly due to the fact that the amplitude of ionic currents generated by the nodal fibres are far less than those developed by the Purkinje fibres.

There is direct relationship between the transmembrane action potential recorded from the individual cardiac muscle cells (SA node, atrium, AV node, ventricular muscle, Purkinje fibre) and ECG. But the total action potential of atrial (not SA or AV nodal) and ventricular muscles due to their increased amount of musculature dominate over the action potential of other myocardial cell present in heart and is usually recorded in clinical 12 lead ECG. The individual recording of action potential from the cells of SA node, AV node, bundle of HIS, Purkinje fibres, etc, needs special technique. The normal ECG is composed of a P wave, a QRS complex and a T wave. The QRS complex has often, but not always, three separate components : the Q wave, the R wave and the S wave. The P wave is caused by the electrical potentials when the atria depolarizes and its contraction begins. The QRS complex is also caused by the generated electrical potentials when the ventricles depolarizes and its contraction begins. Therefore both the P wave and the components of the QRS complex are deploarisation waves. The T wave is caused by the electrical potentials when the ventricles recover from the state of depolarisation. This process normally occurs in ventricular muscle 0·25 to 0·35 seconds after the depolarization. So, the T wave is known as the repolarisation wave of ventricles. The repolarisation of atrium falls within the duration of QRS complex. So, it can not be seen in usual ECG.

The cellular electrical properties of myocardium which can be assumed from the ECG are:

(a) Heart rate

It reflects the pace maker activity of the sinus node and the P wave reflects the whole atrial depolarisation and the initiation of contraction. The only depolarisation of the cells of SA node can not be recorded by the clinical ECG. The atria repolarise which lasts for about 0·15 to 0·2 second after the termination of the atrial depolarisation or P wave. This also occurs approximately when the QRS complex is being recorded in the ECG. Therefore, the atrial repolarisation wave, known as the atrial T wave, is usually obscured by the much larger QRS cmplex in ECG. For this reason, an atrial T wave seldom is observed in the ECG. Atrial depolarisation and repolarisation make atrial systole. This atrial systole is followed by atrial diastole which extend from the end of its repolarisation (it can not be seen in ECG

as it is overshadower by QRS complex) to the beginning of next P wave.

(b) PR interval

It reflects the AV nodal conduction time i.e the time taken for the wave of atrial depolarization to cross the AV node from the atrium to the ventricle. This period is also called the P-Q interval, if Q wave is present. But Q wave is likely to be absent and so it is termed as the PR interval.

(c) QRS duration

It reflects the time taken for the conduction of impulses to travel through the ventricle and the depolarisation period of the whole ventircle.

(d) QT interval (Fig. 5.18)

It is the total duration of ventricular depolarisation plus repolarisation, i.e. full period of ventricular action potential or contraction. Among this the QRS duration only implies the time taken for the initiation of depolarisation of different parts of the ventricle to full ventricular depolarisation. The ST segment implies the duration in which the whole ventricle stays in full depolarization state and T-wave implies the full repolarisation period of ventricle. Thus, the contraction of ventricle lasts almost entirely from the beginning of the Q wave (or R wave, if Q wave is absent) to the end of the T wave. The time interval in the ECG between the end of one T wave and the beginning of next QRS wave corresponds with the phase 4 of action potential and ventricular diastole.

If we corresponds the action potential graph of ventricle and ECG, then we will find that the QRS waves appear at the beginning of the action potential of ventricle (or phase 0) and T waves appear at the end of phase 3. In between these waves and also after the T waves no electrical potential difference is recorded. Thus, no movement of impulse and its corresponding graph is recorded in the ECG or oscillometer (ECG is a type of oscillometer), when the whole ventricular muscle is either completely depolarised or completely repolarised. Hence, only when the muscle is partly polarized (i.e partly depolarised or partly repolarised) then does the current flow from one part of the atrium or ventricle to another part. Therefore, current also flows on the surface of the body to produce a graph in ECG Beginning of QRS complex indicates starts of ventricular depolarisation. The QRS complex and ST segment indicates the whole duration of ventricular depolarisation. The beginning of T wafe indicates end of depolarisation and the start of ventricular repolarisation. The end of T wave indicates the end of repolarisation.

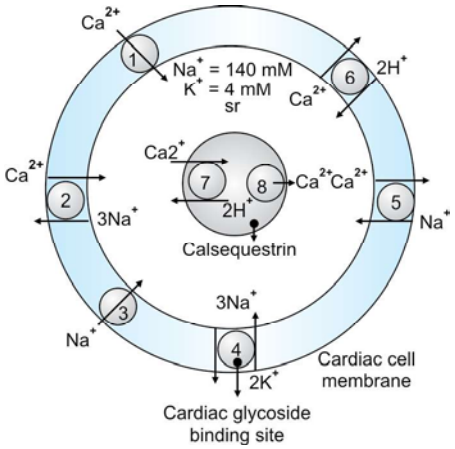
(e) Twave

It represents the ventricular repolarisation. Some ventricular muscle fibres begin to repolarise about 0.20 seconds after the begining of the depolarisation (QRS complex). But in many other fibres, it takes as long as 0.35 sec. Thus, the whole process of ventricular repolarisation extends over a long period. For this reason, the T-wave in the normal ECG is a prolonged wave. But, the voltage of the T-wave is considerably less than the voltage of the QRS complex, partly because of its prolonged length.

ECG actually represents the electrical activity of multiple cells, but not of a single cell. For this reason, the amplitude and shape of the P, R and T waves of an ECG mostly dependent upon the amount of electircal activities offered together by the group of these cells and also upon the different configuration of action potential of these cells than that of an individual one.

Cardiac Action Potential

The whole action potential of cardiac tissue is divided into two stages: depolarisation and repolarisation or more (Fig. 5.19) scientifically into stages, numbered as 0, 1, 2, 3 and 4. Among these stages 0 represents depolarisation and stages 1, 2, 3



1 = Ca^{2+} channel, 2 = Na^{+}-Ca^{2+} exchange, 3 = Na^{+} channel, 4 = Na^{+}-K^{+} ATPase pump, 5 = Na^{+}-Ca^{2+} exchanger, 6 = Ca^{2+} ATPase pump, 7 = Ca^{2+} ATPase pump, 8 = Ca^{2+} release channel

Fig. 5.18: The sarcolemmal exchange of Na^{+} and Ca^{2+} during action potential of cardiac muscle cells. Na^{+} and Ca^{2+} enter the cells during each cycle of depolarization. It triggers the release of larger amount of Ca^{2+} through Ca^{2+} release channel (8), in the sarcoplasmic reticulum (SR). The resulting tremendous increase in concentration of intracellular Ca^{2+} interacts with troponic C. This interactions is responsible for activation of the cross bridge reactions between the actin and myosin filament. Thus they form the cross bridges that result in sarcomere shortening. The electrochemical gradient for Na^{+} and K^{+} across the cell membrane is maintained by active ATP consuming Na^{+}, K^{+}ATPase pump (4). It extrudes Na^{+} out of the cell. While the Na^{+} is actively extruded by Na^{+}, K^{+}ATPase pump, the bulk of cytosolic Ca^{2+} is pumped back by Ca^{2+} ATPase pump (7) in the SR. In the SR, Ca^{2+} is bound with the protein calsequestrin. The remaining portion of intracellular Ca^{2+} is removed from the cell by either a plasma membrane bound Ca^{2+}ATPase pump (6) or by a Na^{+}-Ca^{2+} cation exchange protein (2 and 5). This cation protein exchanger (2 and 5) exchanges $3Na^{+}$ ions in for every single Ca^{2+} ion out. This direction of cation exchange is reversed briefly during depolarization. This is because when the electrical gradient across the cell membrane is transiently reversed. β-adrenergic receptor agonists and phosphodiesterase inhibitors activate the protein kinase (1) by increaseing the intracellular cAMP levels. This activated pk enhances the contractile state by phosphorylating the target proteins including phospholamban and the α-subunit of the L-type Ca^{2+} channel

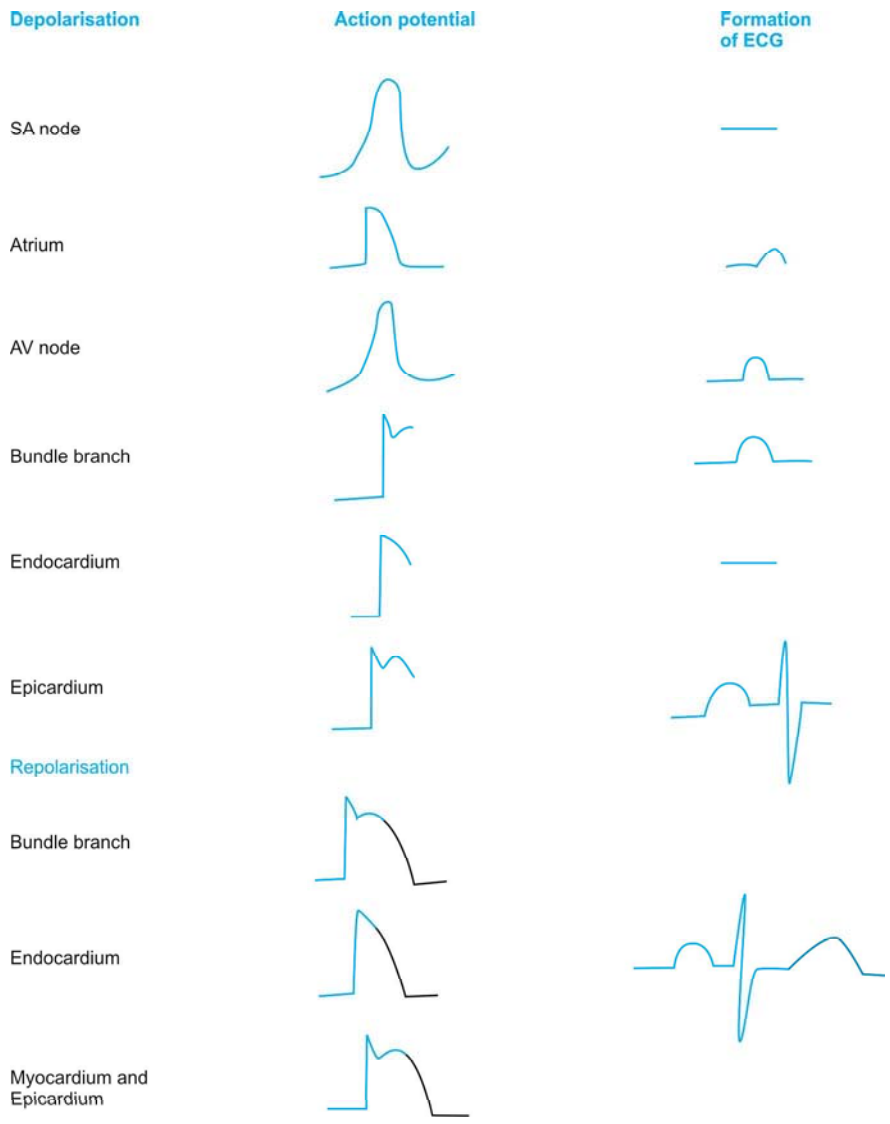


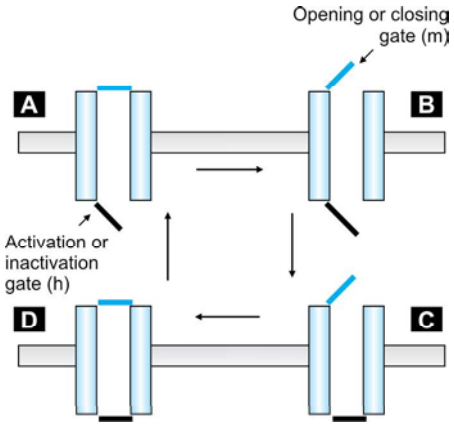
Fig. 5.19: The action potential and its subsequent ECG formation of different tissues of heart are shown. Red line indicated depolarisation and blue line repolarisation

represent repolarisation. The heart remains in systole both at the stage of depolarization and repolarisation i.e from stage 0 to stage 3. But it remains in diastole only during stage 4. After repolarisation i.e. after stage 3, in phase 4 the membrane potential comes down to the resting level. But, the ionic distribution of Na^+ and K^+ across the cell membrane remains in opposite state to that which is found in the resting state. So, in phase 4 of non pacemaking cells, the opposite ionic distribution of Na^+ and K^+ comes back to normal state without any change of the resting membrane potential which is achieved at the end of the phase 3. But this stage 4 is called the 'slow diastolic depolarisation' for the pace making cells. Because in this stage of pace making cells, the inside of the cell again starts to become slowly positive (i.e. depolarisation) from normal resting membrane potential which is achieved at the end of the stage 3, though the ionic concentration of Na^+ and K^+ is opposite to the resting condition. This slow process of depolarisation during diastole of heart is the characteristic of pacemaker activity of the SA or AV nodal cells and is absent in other cells than pace maker cells.

At rest, in the non pace making myocardial cells the membrane potential (resting membrane potential Vm) is maintained at the level of −60 mV to −70 mV, with negativity inside and positivity outside of the cell like the resting nerve and muscle cells. This resting membrane potential or the electrical gradient is established by pumps, especially the Na^+, K^+ ATPase pump which extrudes Na^+ and pushes K^+ inside the cell and some fixed anionic charges which are present within the cells. Other Na^+ channel remains closed at this negative transmembrane potential and so no Na^+ does enter inside the normal resting myocardial cell through this channel. Whereas the other specific K^+ channel (inward rectifier K^+ channel) remains in an open conformation at this negative resting membrane potential and allows the normal cardiac cells to become permeable to K^+ from outside to inside at rest. This inward rectifier K^+ channel along with the Na^+, K^+ ATPase pump maintains the intracellular K^+ concentration which is higher than the extracellular concentration. So, the concentration of K^+ in the extra cellular space is the major determinant factor for the resting membrane potential.

For each individual ion there is an equilibrium potential (Ex) after which there is no movement of ion across the cell membrane, still if the channels are open. For K^+ this value of equilibrium potential is −94 mV i.e. at this voltage there is no net force which drives the K^+ ions into or out of the cells. The Na^+ channels which allow Na^+ to move along the gradient are closed at negative transmembrane potential. So, Na^+ does not enter into the normal resting cardiac cells (Fig. 5.20).

The resting membrane potential will be maintained until the resting state is not disturbed by the propagated impulse or the slow diastolic depolarisation in phase 4. If there is any propagated impulse or the



Figs 5.20A to D: A. Closed and activated channel but no current flows. B. Open and activated channel with current flows. C. Open but inactivated channel and no current flows. D. Closed and inactivated channel − no current flows. Schematic diagram of dynamics of a voltage dependent double gated fast Na+ channel that occur during action potential of a cardiac cycle. At resting stage the channel is initially closed, but activated where upper m-gate is closed but lower h-gate is opened. Then, depolarisation causes activation of channel which opens the upper m-gate and allows the entry of Na+ ions into the cell. Subsequently the time dependent h-gate closes and inactivate the channel and prevent the ion flow where m-gate still remains open. Then, both the m-gate and h-gate is closed. This is followed by removal of inactivation, which causes opening of the h-gate and priming of the channel for voltage sensitive activation

slow diastolic depolarisation reaches the threshold level, then the resting membrane potential is changed fulminantly from −90 mV of nonpace making cells to the value of +30 mV, making the inside of the cell positive in respect to outside. This initial stage of action potential is called the depolarisation or phase 0 and this is due to the sudden influx of Na^+ into the cell from outside after the threshold level is reached and also due to some influx of Ca^{2+} into the cell. The entry of Na^+ into the cell is operated through the voltage dependent double gated fast Na^+ channel. In this channel, the outer m-gate (activation gate) remains closed and the inner h-gate remains open during resting state at the end of the repolarisation and be ready for depolarisaton (A). When the stimulus is reached, outer m-gate then opens and Na^+ is allowed to flow in the cell along its concentration and electrostatic gradient (B). As the membrane potential reaches +30 mV, then the inner h-gate (inactivation gate) closes preventing further influx of Na+ and marks the end of depolarisation or phase 0 (C).

Then when repolarisation starts, the upper m-gate closes. In this state both the m and h gate is closed and is known as the closed and inactivated state (D). During repolarisation of the cell membrane, Na^+ channel also changes its conformation from closed and inactivated state to close and activated state when the outer m-gate remains close, but the inner h-gate opens and make the Na^+ channel ready for further depolarisation. During depolarisation both the gates are again opened and Na^+ enters through this 'open and activated' sodium channel. Thus this cycle of closed and inactivated (D) → close and activated (A) → open and activated (B) → open and inactivated (C) form of Na^+ channel repeats.

After depolarisation, repolarisation occurs in several steps. These are :

i. There is an initial partial rapid repolarisation or phase I where membrane potential falls from +30 mV to +10 mV,
ii. It is followed by plateau or phase 2, in which the membrane potential falls slowly from +10 mV to −20 mV,
iii. Then it is followed by a last stage or phase 3 where a relatively more rapid drop of membranes potential to the resting value of −90 mV (for nonpace making cells) or −60 mV(for pace making cells) is achieved from −20 mV (Fig. 5.21).

After the cells are depolarised by inward Na^+ currents, the K^+ channels transiently change their conformation to open state. This results in an outward movement of K^+ or repolarisation current which contributes to phase I. The small notch of phase I is also associated with the flow of inward Ca^{2+} current which opposes the outward repolarizing K^+ current and is

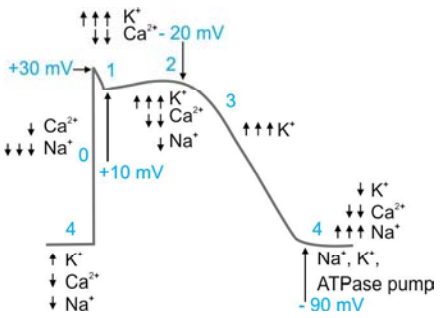


Fig. 5.21: The four phases of action potential and the movement of various ions that occur by electrostatic and / or electrochemical gradient with membrane depolarization. Na^+ current is 50 fold larger than any other current. Multiple types of Ca^{2+} current have been identified. It is likely that each represents a different channel protein and is responsible for haemostasis of Ca^{2+}. Downward arrow indicates influx of ions into the cell and upward arrow indicates eflux of ions out of the cell

responsible for the shortness of the notch. Transient outward K^+ channels, like Na^+ channels, then rapidly is inactivated. After that phase 2 starts and is dominated by the increased influx of Ca^{2+} through the L-type voltage dependent Ca^{2+} channel and to lesser extent influx of Na^+ through its slow channel (not fast channel) and balance the still outward repolarising K^+ current through the 'delayed rectifier' K^+ channel (not the previous K^+ channel). In this stage repolarising (outward) K^+ current balance the depolarising (inward) Ca^{2+} and Na^+ current and thus maintain a plateau. The entry of Ca^{2+} into the cell trigger further releases of Ca^{2+} from the intracellular SR and initiates contractile process. Catecholamines such as epinephrine and nor epinephrine increase this inward Ca^{2+} current and increase the contractile forces which is inhibited by Mg^{2+} and calcium channel blockers (dihydropyridines). After the phase 2, the phase 3 occurs as with the passing of time outward K^+ current through 'delayed rectifier K^+' channel increases, while inward Ca^{2+} current inactivated. This result in a relatively rapid repolarisation of cardiac cells (several hundred milliseconds after the initial Na^+ channel opens). Thus, the repolarising

outward K^+ current through the 'delayed rectifier' channel gradually lower the transmembrane potential to the resting state with the closure and inactivation of slow Ca^{2+} and Na^+ channels. During this period no further depolarization of cell take place and is known as the absolute refractory period. Thus, at the end of repolarisation, i.e. after phase 3 though the resting membrane potential is achieved, but the Na^+ and K^+ concentration in the intra and extracellular fluid is opposite to the normal resting condition of the cell. Thus, the restoration of concentration of Na^+ and K^+ to their pre-excitation level inside and outside of the cell occurs via an active transport system, called the Na^+/K^+ ATPase pump at a ratio of 6 Na^+ ions out for every 3 K^+ ions in. As a result the act of pumping itself generates a net outward (repolarising) current. There are also other channels through which K^+ enters the cells and maintains the pre excitational intracellular concentration of K^+, balancing the excess extrusion of Na^+ by Na^+, K^+ ATPase pump. But other Na^+ channels remain closed during the phase 4, except in the cell with the character of automaticity where few Na^+ channels open and gradually Na^+ enters the cells causing slow diastolic depolarisation.

The homeostasis of intracellular Ca^{2+} which enters the cell during phase 2 is maintained by (i) Ca/Mg ATPase pump on SR, (ii) sarcolemmal Ca-ATPase pump and (iii) Na^+ - Ca^{2+} exchange mechanism on the cell surface, which exchange three Na^+ ions in for each Ca^{2+} ion out from the cell. In phase 0, Na^+ enters and Ca^{2+} exits the cell and in phase 2 vice versa. This Na^+-Ca^{2+} exchange is not shown in the figure of action potential.

Finally, the phase 4 represents the period between the completion of repolarisation and the initiation of depolarisation of next action potential. During this period, K^+ continues to leak slowly from the cell along its concentration gradient. On reaching its most negative value after repoalrisation the membrane potential again gradually ascent to more positive value due to gradual entry of Na^+ in the cell and droping of K^+ efflux from cell. When K^+ efflux stops and due to gradual entry of Na^+, the threshold transmembrane potential of approximately −40 mV is achieved, then spike action potential again takes off and a new cycle starts.

This phase 4 or slow progressive depolarisation which occurs during diastole is called the slow diastolic depolarisation. This phase is very important for generating automaticity or pace making activity and is the characteristic of cells of nodal tissue. Normally the rate of rise of diastolic depolarisation is 15 to 20 mV/sec in SA node, whereas that of AV node and other cells are appreciably slower. In some cardiac cells this phase is flat with maintaining the resting membrane potential fixed, at −90 mV.

Acetylcholine causes a three fold inerease in the rate of loss of the positively charged K^+ from the cell with resulting more negativity of inside of the cell and thereby hyperpolarises the cell. Atropine prevents this membrane action of ACh even though it is present. Vagus stimulation, like ACh, also abolishes the slow diastolic depolarisation and indeed hyperpolarize the cell and abolishes the spontaneous rhythm. Sympathetic stimulation increases the rate of diastolic depolarisation and thus the rate of heart rate.

Different Types of Action Potential of Different Types of Cardiac Cells

In heart, there are different types of cardiac cells and therefore, there are different types of action potentials. This is due to variability in the number of different ion channel (genes expressed) in individual cells. The cells of His-Purkinje system have action potential of very long duration. The atrial cells have action potential of short duration than that of His-Purkinje system. The cells of the sinus and AV node display the phenomenon of spontaneous slow diastolic depolarisation in phase 4 and thus the RMP spontaneously reach the threshold value for regeneration of new action potentials. The cells of AV node, bundle of HIS and Purkinje system has also the slow diastolic depolarization phase in action potential and pace making activity. But the rate of spontaneous firing is usually fastest in the SA nodal cells and serves as the natural pacemaker of the heart suppressing the pace making activity of others.

Modern technique helps us to study the electrophysiological behaviour of single ion channel protein and identify the channels that may be particularly responsible for the particular pathological condition. For example, mutation in the genes which is responsible for encoding the repolarizing K^+ channel (both 'transient outward' and 'delayed rectifier' channels) is responsible for congenital long QT syndrome. Some K^+ channels remains quiescent when intracellular ATP store is normal and they become active when ATP store is depleted. Such ATP - inhibited K^+ channel also sometimes is important to produce arrhythmia in myocardial ischaemia. Most antiarrhythmic drugs affect more than one ion channels and thus usually exert multiple action which can be beneficial or harmful in individual patient (Fig. 5.22).

NERVE SUPPLY OF HEART

The heart is supplied by both the parasympathetic and sympathetic nerve with their afferent and efferent fibres and control the different cardiac functions. Both these nerves are also responsible for cardiac pain and different cardiac reflexes. To supply the heart both the afferent and efferent fibres of the sympathetic and parasympathetic nerves form the cardiac plexus from where the heart derives its nerve supply. This cardiac plexus is formed by the interlacement of nerve fibres and nerve cells and is situated at the base of the heart. This plexus is consists of

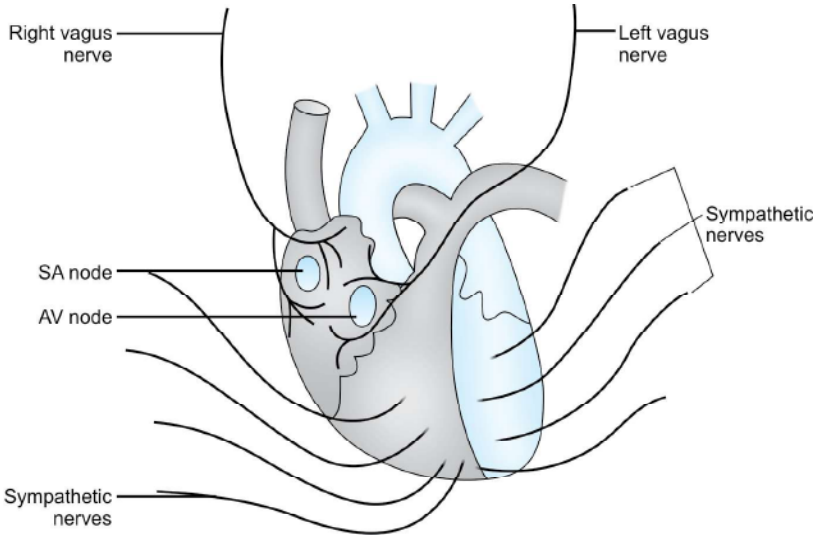


Fig. 5.22: Sympathetic and parasympathetic nerves supplying heart

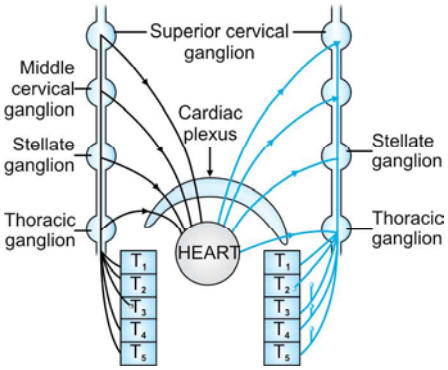


Fig. 5.23: Schematic diagram of sympathetic supply of heart. Red line indicates sympathetic motors (efferent) and green line indicates sympathetic sensory (afferent)

two parts − superficial and deep. The atria and the conducting system of the heart are innervated by both the sympathetic and parasympathetic nerves. On the otherhand, ventricular muscle is supplied only by the sympathetic nerves.

The afferent nerves from the heart passes both through the parasympathetic and sympathetic nerves as follows:

i. From the heart → through vagus, and from the aortic arch→ through aortic nerve. Both are parasympathetic.
ii. From the heart → through superior, middle, stellate and first four thoracic sympathetic ganglion → through white rami communicants → posterior nerve root and posterior dorsal ganglion → to the posterior horn cells.
iii. From the carotid sinus → through the sinus nerve, a branch of glosso pharyngeal nerve (parasympathetic). The efferent nerves supplying the heart also run through both the parasympathetic (vagus) and sympathetic nerves, as follows.

The efferent preganglionic fibres of parasympathetic nerve arise from the nucleus ambiguous and from the dorsal nuclei of vagus in the brain. They are situated on the floor of the 4th ventricle in the medulla. After their origin they descend downward as the vagus nerve. Then the cardiac fibres separate from the main trunk of vagus nerve in the neck and proceed towards the heart to from the deep and superficial cardiac plexuses with the fibres from the sympathetic nerve. After that the parasympathetic fibres finally reach the atrial muscle where they make the synaptic connections with the cells in the peripheral parasympathetic ganglion, which are situated near the SA and AV node. From the ganglion, postganglionic parasympathetic fibres arise and supply the SA and AV node and also extend between the atrial muscle fibres (Fig. 5.23).

The efferent preganglionic sympathetic fibres start from the lateral horn cells of T_1 to T_5 or T_6 thoracic segments of spinal cord. These are called the spinal sympathetic cardiac centres. Preganglionic sympathetic fibres then enter the sympathetic chain after coming out via the ventral root of the T_1 to T_5 spinal nerve and the white rami communicants. After that these preganglionic fibres make synapses with the ganglionic cells situated in the superior, middle and inferior cervical ganglia and the upper thoracic ganglia from where the postganglionic sympathetic fibres arise. In human beings the last cervical ganglion and the first thoracic ganglion fuses together to form the stellate ganglion. Then the postganglionic fibres, arising from the superior cervical, middle cervical, and stellate ganglion pass directly to the heart and form the cardiac plexus.

Cardiac branches from the superior cervical sympathetic ganglion does not contain any afferent fibres. It contains only the efferent postganglionic sympathetic fibres. Otherwise, all the cardiac branches of vagus and sympathetic nerve contain both the afferent and efferent fibres. In contrast to vagus, the exact location of the higher cardiac sympathetic centre in the brain is not yet fully known. Usually, the spinal sympathetic cardiac centres are controlled by the higher centres of brain like the cortex, thalamus, hypothalamus, etc.

The dorsal motor nucleus of vagus in the medulla is the cardioinhibitory centre and it continuously transmits tonic inhibitory vagal impulses to the heart. It is because this higher parasympathetic centre gets direct connection from the afferent fibres, coming from the peripheral baroreceptors and chemoreceptors through the sinoaortic nerves. Reflex bradycardia during the rise of systemic blood pressure is due to the stimulation of this cardioinhibitory vagus centre by the affarent impulses from baroreceptors. On the other hand, tachycardia during the fall of BP is due to

the inhibition of this cardioinhibitory centre i.e. withdrawal of vagal tone from this cardioinhibitory centre. Under such condition sympathetic cardiac centre also take the upper hand secondarily (Fig. 5.24).

As mentioned earlier, the SA node develops from the right sided embryological structure. So, it receives innervation from the right vagus nerve (parasympathetic) and the right stellate ganglion (sympathetic). Similarly also as the AV node is developed from the left sided embryological structure, so it is supplied by the left vagus nerve (which produce variable degree of nodal conduction block) and the left stellate ganglion which have a greater effect on the contractility of heart. Thus in general, the sympathetic and the parasympathetic supply via the left stellate ganglion and the left vagus nerve have a greater effect on the contractility of heart and the sympathetic and parasympathetic supply via the right stellate ganglion and the right vagus nerve have a greater effect on the heart rate.

The pain of angina pectoris or myocardial infarction is commonly felt at the retrosternal region and radiates along the inner side of the left arm. Sometimes, this pain is referred to the right arm or the both arms. Some patients experience pain of myocardial ischaemia in the neck or epigastric region. This is because the impulses of these pain are conveyed by the sensory sympathetic cardiac fibres and reach the T_1 to T_5 segment of the spinal cord, usually through the dorsal root ganglia of the left side. Hence, the pain is referred to the left arm. Sometimes, the connector neurons of the spinal cord conduct the impulses to the right side of the corresponding segments of the spinal cord. This may explain why the pain is occasionally referred to the right side or both the sides. Since, the embryonic heart is initially located in the neck and later descends in the thorax, so it is not unlikely that the pain fibres for the heart reach from the upper cervical spinal segment via the sympathetic nerve. So, sometimes the pain is also felt in the neck region.

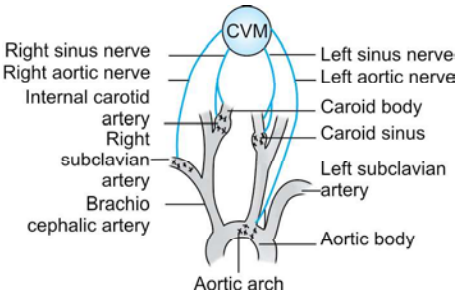


Fig. 5.24: The baroreceptors and chemoreceptors in the aorta and internal carotid artery with aortic and sinus nerves. CVM = Cardiovascular medullary centre

The parasympathetic efferent fibres work through the muscarinic (M_2) receptors and the sympathetic efferent fibres work through the β-receptors on the myocardial cells. The action of both the parasympathetic and sympathetic nerve balances each other. But, under normal resting condition in the adult, the parasympathetic tone predominates over the sympathetic tone. The efferent parasympathetic diminishes the heart rate and coronary blood flow (secondary effect). Larger branches of coronary arteries are predominantly supplied by sympathetic nerves. Whereas the smaller branches are supplied by the vagus nerves. Sympathetic efferent increases the heart rate and cardiac output. It produces vasodilatation of the intramuscular branches of the coronary artery and vasoconstriction of the epicardial arteries.

There are three types of affarent receptors through which parasympathetic reflexes work. Type A receptor is supplied by the myelinated vagal affarent fibres and is responsible for the control of heart rate. Type B receptor is also supplied by the myelinated affarent vagal fibres and is responsive to atrial stretches and changes in volume than heart rate. Type C receptors are also responsive to the changes in pressure. All the above mentioned receptors are located in the atrium. There are also receptors in the ventricle which are supplied by the myelinated vagal affarent fibres and is responsive to the changes in the rate of rise of ventricular pressure and send impulses at the onset of ventricular ejection.

The sympathetic fibres form an extensive plexus or network over the epicardium of the heart and penetrate the myocardium along the various branches of the coronary vessels. Sympathetic innervation on ventricle is more dense than atrium, where as the parasympathetic innervation is more dense on atrium than ventricle.

Sympathetic neurotransmitter or agonist work through the β-adrenergic receptors which are located on the myocardial cell surface. The attachment of sympathetic agonist with the β-receptor induces a conformational changes of this receptor and permits interaction of this receptor with the stimulatory G-proteins (Gs) at the inner site of the cell membrane. The G-protein are in the family of heterotrimeric structure, and composed of α, β, γ subunit. Binding of Gs protein with the receptor causes dissociation of the α-subunit from the remaining β − γ complex of G-protein, with the concomitant expenditure of guanosine triphosphate (GTP) to GDP. This broken α-subunit then stimulates the adenylcylase located on the cytosolic side of the membrane which hydrolysed ATP to cAMP. Thus the increase in cAMP, in turn act on certain Protein Kinases (PK_A) which phosphorylates the various intracellular proteins, especially those are related to SR and ultimately raise the intracellular Ca^{2+} concentration. The phosphorylation of many other functional proteins, including troponin and phospholamban also help to interact with Ca^{2+}, resulting in increased force of contraction (Fig. 5.25A).

The parasympathetic stimulation works through the neurotransmitter named acetylcholine (ACh) which binds with muscarinic M_2 receptor, located on the myocardial cell membrane. The binding of ACh with M_2 receptor causes conformational changes of this receptor and in turn allow the binding of receptor

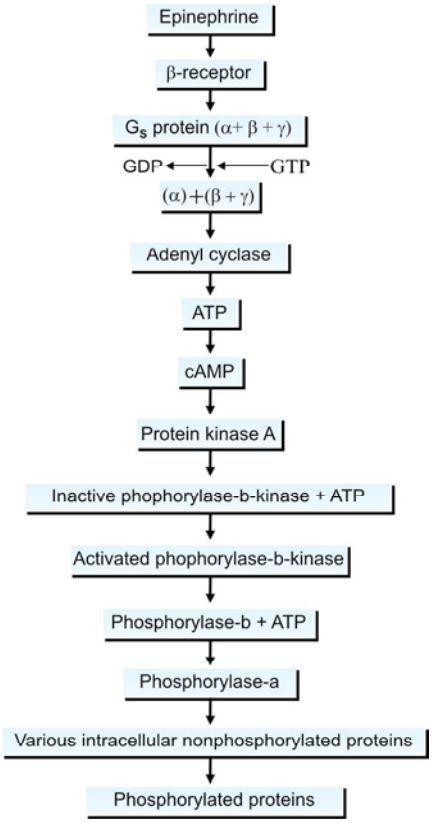


Fig. 5.25A: Schematic diagram showing the mechanism of action of sympathetic agonist through beta-receptor

with the inhibitory Gi protein. This activates the Gi protein by dissociating the α-subunit from it. The activated Gi protein inhibits adenyl cyclase leading to decrease in cAMP synthesis and in turn inhibition of PK_A and its sequelae described above.

Finally, the ACh released from the parasympathetic postganglionic nerve terminals that lie in close proximity to sympathetic postganglionic nerve terminals may also inhibit the release of norepinephrine and this in turn decrease the β-receptor stimulation and ultimately cAMP levels.

CORONARY BLOOD FLOW AND VARIATIONS OF IT DURING DIFFERENT PHASES OF CARDIAC CYCLE

The heart muscle is rich in blood supply. The predominance of supply of heart by right coronary artery is seen in about 50% of cases. Whereas, in about 20% of human heart the predominance is by the left coronary artery. But, in about 30% of cases both the coronary arteries predominate. The last group in which the nature of supply is not made predominantly by either right or left coronary artery is least vulnerable to the cardiovascular disorder.

Anatomically the coronary arteries are not the end arteries. But functionally the coronary arteries are the end arteries, though anatomical anastomoses are present and become active under the pathological state. In adult human heart each cardiac muscle fibre receives one capillary twig, whereas in foetal life one capillary twig supplies 4 to 6 muscle fibres. During rest, for each 100 gm of left ventricular musculature the left coronary inflow is 65 to 85 ml/min and the total coronary blood flow is 250 ml/min. This is about 5% of the total cardiac output. While during heavy exercise this coronary inflow rises to 5 folds than that of the rest, i.e. 300 to 400 ml/100 gm/min or 800 to 1000 ml/min. The myocardial arteriovenous differences of O_2 content at rest is also very high and is about 10 to 15 ml per 100 ml of blood (desaturation is 70%). This signifies that the extraction of O_2 from arterial blood by the cardiac muscle is very high. Normally, the myocardial tissue extracts about 65 to 70% of O_2 supplied by the myocardial arterial blood. Thus, if the arterial O_2 content is 20 ml per 100 ml, then the blood in the coronary sinus which drains the left ventricle contains only 6 to 7 ml of O_2 per 100 ml, even when the individual is at rest. The ratio of systolic coronary blood flow to diastolic coronary blood flow is approximately 0.22 at rest which is increased to 0·9 during exercise (Fig. 5.25B).

Cardiac Cycle

The two atriums of the heart contract and relax simultaneously in a cyclical fashion like the two ventricles. But when the atria contract, the ventricles dialate and vice versa. The duration of systole

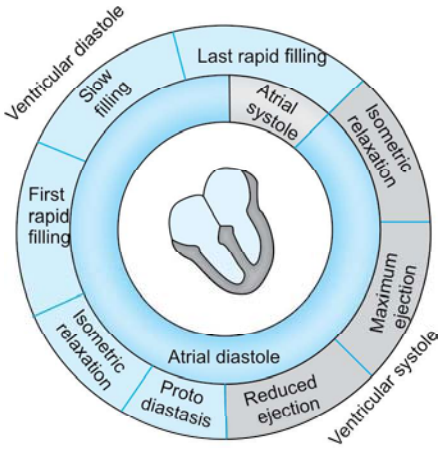


Fig. 5.25B: The cardiac (atrial and ventricular) cycle

and diastole of atrium is 0.1 sec and 0.7 sec, respectively. Whereas, the duration of systole and diastole of ventricle is 0·3 sec and 0.5 sec, respectively. However, though the atrium and ventricle have the separate cycle of function, but mainly the ventricular cycle will be considered here as the cardiac cycle and will determine the variations of coronary blood flow during the different phases of it. It starts at point A and signifies the later half of ventricualr diastole with filling of blood from atrium. This blood comes to the atrium at its phase of diastole during the time of previous ventricular systole. In the middle of ventricular diastole when the ventricular pressure goes below the atrium or atrial pressure exceeds than that of the ventricle then the atrioventricular valves (tricuspid and mitral) open (point A) and blood enters the ventricular chamber. At this stage both the atrium and the ventricle is in diastole and blood flows passively to ventricle from atrium which accounts for roughly 75% of the total ventricular filling. The rest of the ventricular filling is contributed by the active atrial contraction or atrial systole (point A′) which begins with the depolarisation of the SA node and corresponds to the P wave of ECG. Thus, the curve of the ventricular filling, shown in figure by the AB segment, depends on the compliance of ventricle and the venous

return to atrium. Passive ventricular filling will be hampered if the ventricle and its wall becomes less compliant (such as muscular hypertrophy, fibrosis and many other causes) and if there is hypovolaemia. In these circumstances atrial systole is very important to maintain the adequate ventricular filling (Fig. 5.26).

After the ventricular filling at its diastole, ventricular systole starts with the closure of the tricuspid and mitral valve and corresponds to the R-wave on ECG and point B on the picture. The first part of the ventricular systole is called isovolumic or isometric contraction (shown in figure by BC segment), where all the valves are closed and the intraventricular pressure rises sharply without any change in the intraventricular volume. In the 2nd part of the ventricular systole at the point when the developed pressure within the two ventricles exceed than that of the pulmonary artery and aorta (point C), then the pulmonic and aortic valves open and allow the blood to flow into their respective circulations. This second portion of the ventricular systole is called the ventricular ejection phase (shown in figure as CE segment). It has an initial rapid phase (point C to D) or maximum ejection phase, characterised by maximal forward flow of blood. Then, it gradually tapers, because as the systole progresses (point D to E) the ejection phase is slowly reduces.

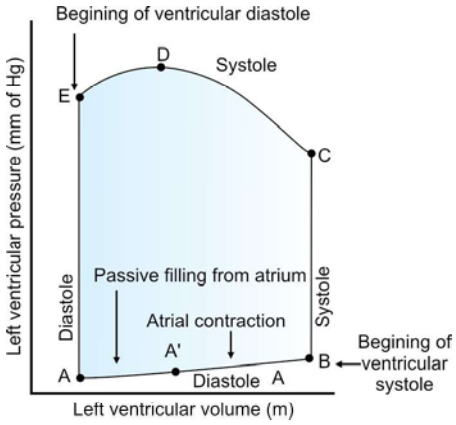


Fig. 5.26: The changes of left ventricular volume and pressure during different phases of cardiac cycle. AB = Ventricular diastole, AA′ = Atrial diastole, A′B = Atrial systole

After systole, the ventricular diastole begins at the point E with the closure of the pulmonic and aortic valve. This is due to the fall of intraventricular pressure below that of the aorta and pulmonary artery. The EA segment of ventricular diastole is called the isovolumetric or isometric relaxation phase, because during this period the pulmonary and aortic valve closes, but the atrioventricular valve does not open and no flow of blood occurs into the ventricle from atrium. After beginning of ventricular diastole as point E. The ventricular pressure continues to drop until they fall below that of the right or left atria. At the point A during ventricular diastolic period the atrioventricular valve (tricuspid and mitral) opens and blood starts to flow from the atrium to the ventricle. Thus, the ventricular filling commences and the cycles repeat themself. This point E corresponds to the end of the T wave on the ECG.

During systole the peak left ventricular pressure is about 120 mm of Hg and the peak right ventricular pressure is about 25 mm of Hg. At the end of the diastole the volume of the ventricles is 130 ml and it is called the 'end diastolic ventricular volume' (EDVV). About 50 ml of blood always remains in each ventricle after ejection at the end of the systole. This is called the 'end systolic ventricular volume' (ESVV). The percent of end diastolic ventricular volume which is ejected with each stroke is called the ejection fraction and is about 65 to 85% in a normal healthy individual.

The cardiac muscle has unique property of depolarisation and repolarisation which is faster than that of any other muscles of the body. This is more prominent when the heart rate increases. The duration of ventricular systole decreases from 0·3 sec at the heart rate of 75/ minute to 0·2 sec at the heart rate of 200/ min. This shortening is mainly due to the decrease in duration of systolic ejection period. However, the duration of systole is much more fixed than that of diastole. So, when the heart rate is increased then the duration of diastole is shortened to a much greater extend than that of the systole. For example, at a heart rate of 75/min, the duration of diastole is 0·5 sec. Whereas at a heart rate of 200/min, it is only 0·1 sec. This fact has important physiologic and clinical implications. This is because it is only during diastole that the heart muscle rests and coronary blood flow to the subendocardial portions (which is most vulnerable to infarction) occur. Furthermore, most of the ventricular filling occurs in diastole. Thus up to the heart rates of about 180 per minute, the ventricular filling and (Fig. 5.27) cardiac output is adequate, but as long as there is ample venous return. However, at very high heart rates (>180) ventricular filling may be compromised to such a degree even with adequate venous return that CO falls and symptoms of heart failure develop.

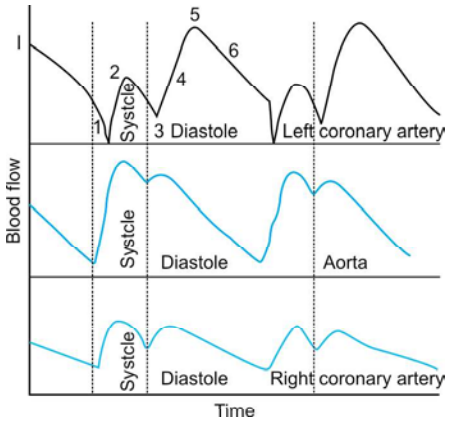


Fig. 5.27: The blood flow in the aorta, left coronary artery and right coronary artery during various phases of the cardiac cycle
1 = Isometric ventricular contraction (BC segment),
2 = Maximum ejection phase (CD segment),
3 = Reduced ejection phase (DE segment),
4 = Isometric relaxation phase (EA segment),
5 = Rapid ventricular filling phase (1st part of AB segment),
6 = Later part of diastole (2nd part of AB segment)

Variation of Coronary Inflow with Cardiac Cycle

The ventricular contraction affects the coronary circulation in two ways: (a) by altering the aortic pressure which produces the pressure head for coronary circulation and (b) by exerting a variable degree of compression on the coronary vessels by myocardium. Thus, the following variations of coronary inflow are seen during the ventricular contraction and relaxation.

i. During the phase of isometric ventricular contraction (BC segment), the coronary flow sharply falls and reaches minimum or even falls below the level of zero due to the back flow. This is because at this stage the aortic pressure is minimum and this is due to no flow of blood in the aorta and the subsequent compression on the coronary vessels by myocardium is maximum.

ii. During the maximum ejection phase (CD segment) coronary inflow rises sharply due to the sudden rise of aortic pressure. This is again due to the high aortic inflow which reaches its maximum.

iii. During the reduced ejection phase (DE segment) the coronary inflow again falls below the previous level. This is because gradually the aortic pressure is falling, but the compression on coronary vessel by myocardium is still continued.

iv. During the phase of isometric relaxation (EA segment) the coronary inflow again sharply rises. This is because the aortic pressure in this phase is still fairly high, though no extra blood flows into the aorta or pulmonary artery from ventricle but the compression of myocardium on coronary vessel is minimum. Maximum coronary filling takes place during this phase due to the maximum fall of coronary vascular resistance or compression in this period.

v. During the rapid ventricular filling phase (1st part of AB segment or the AA′ segment) the coronary inflow again continues to rise, but slowly. This is because the relaxation of the myocardium continues and the vessels begin to open.

vi. During the later part of diastole (i.e. later part of AB segment or the A′B segment) the coronary inflow again slowly diminishes. This is because the aortic pressure is failing and the coronary vessels are stretched due to the gradual filling of heart and the consequent elongation of the cardiac muscles (Fact file-I).

Neverthless, from the above discussion the conclusion can be drawn that about 80% of the total coronay blood flow occurs in diastole and this is because though during this period the mean aortic pressure head is low, than systole, but the true coronary vascular resistance caused by the myocardial compression on the vessels is still even lower.

During the ventricular isometric contraction phase the blood flow through the right coronary artery sharply falls and then rapidly rises again in the maximum ejection phase. Then, it again falls during the reduced ejection phase. During the isometric relaxation phase the right coronary inflow rises again, but not so steeply high like the left coronary inflow.

In conclusion, it is said that the coronary blood flow is dependent on the pressure gradient which is principally guided by the difference between the mean aortic pressure and the resistance of coronary arteries due to the compression by the ventricular musculature. The coronary blood flow through the left ventricle is maximal during the early diastole, corresponding to the period of isovolumic relaxation which accompanied by the minimal coronary vascular compresson by the myocardium. However, the coronary blood flow through the right coronary artery is maximal during the period of peak systole. This is because the developed right intramyocardial pressure and consequently the vascular compression by the right ventricle are considerably less than the pulmonary arterial pressure and thus allowes for anterograde flow through right coronary artery during both systole and diastole of right ventricle (Table 5.1).

Although the blood flow through the left coronary arteries supplying the subendocardial portion of the left ventricle occurs only during diastole, but as the contractile force during systole is sufficiently dissipated in the more superficial portions of the left ventricular myocardium, i.e. epicardium, so some blood flow

FACT FILE - I

So, greater coronary inflow takes place in diastole than systole due to less compression of the coronary vessels during relaxation of the cardiac muscle and diminution of the intramural tension. The left coronary inflow during systole is affected much as the pressure difference between the aorta and the left ventricle becomes −2 mm of Hg. But the right coronary inflow during systole is not so much affected as the pressure difference between the aorta and the right ventricle is 95 mm of Hg.

Table 5.1: Pressure in aorta, left coronary artery (LCA) and right coronary artery (RCA)

	Pressure in aorta (mm of Hg)	*Pressure in LV and LCA (mm of Hg)*	*Pressure difference between aorta and LCA (mm of Hg)*
Systole	120	122	−2
Diastole	80	0	80
	Pressure in aorta (mm of Hg)	*Pressure in RV and RCA (mm of Hg)*	*Pressure difference between aorta and RCA (mm of Hg)*
Systole	120	25	95
Diastole	80	0	80

LV = Left ventricle, LCA = Left coronary artery, RCA = Right coronary artery

in this region also occurs during systole through out the cardiac cycle. Since the ventricular diastole is more shorter, when the heart rate is high, so the left ventricular coronary flow is further reduced during tachycardia. Thus, as during both the systole and diastole no blood flow occurs through the myocardium and the subendocardial portion of the left ventricle during tachycardia, so this region is maximally prone to ischaemic damage and is the most common site of myocardial infarction. Blood flow to the left ventricular musculature is further decreased in patients with stenotic aortic valves. This is because in aortic stenosis the pressure in the cavity of left ventricle must be much higher than that of the aorta to eject the blood. Consequently, the coronary vessels are severly compressed during systole and there is less development of pressure (Fact file- II) head in the aorta for coronary flow due to less ejection of blood in the aorta. So, patients with this disease are particularly prone to develop symptoms of myocardial ischaemic, in part because of the compression of the coronary arteries, in part because of the myocardium requires more O_2 to expel blood through the stenotic aortic valve and in part because of the less coronary flow due to less ejection of blood in the aorta. Coronary flow is also reduced when the aortic diastolic pressure is low. The rise in venous pressure in condition such as congestive heart failure also reduces the coronary flow because it decreases the effective coronary perfusion pressure.

The difference between the minimum (resting) and the maximal coronary blood flow is termed as the 'coronary flow reserve'. Under normal circumstances the myocardial wall pressure is highest near the endocardium and lowest near the epicardium. Thus, a gradual negative gradient of coronary blood flow was seen to exist during the ventricular systole from epicardium to endocardium. So, the outer layers of ventricular wall receives a larger share of blood flow and innermost wall presumbly receives no flow of blood at the peak of systole and thus make the endocardium relatively more sensitive to ischaemia. Thus, the endocardial blood flow is greatly influenced by ventricular relaxation during diastole which decreases the myocardial wall pressure and enhances the coronary flow from epicardium to endocardiaum. So, the endocardium is more sensitive to pathological changes like hypotension, coronary occlusion, hypertrophy, aortic stenosis, etc. (Fig. 5.28).

Regulation of Coronary Blood Flow

Like renal and cerebral arteries, coronary arteries also have the autoregulation. This autoregulation maintains constant coronary blood flow within perfusion pressure ranging between 50 to 120 mm of Hg and is independent of myocardial O_2 demand. Coronary perfusion pressure is defined as

FACT FILE - II

Factors influencing the coronary circulation

1. Mean aortic pressure:
   It is the chief motive force for driving blood into the coronary vessels. Any alteration of aortic pressure will, therefore, cause parallel changes in coronary circulation.
2. Cardiac output :
   Obviously, the coronary inflow is directly proportional to the cardiac output. Increased output raises the coronary flow in two ways : (a) raising the aortic pressure, (b) by reflex inhibition of the vagal vasoconstrictor tone.
3. Metabolic factors:
   With increased metabolism of the heart, the O_2 requirement and subsequently the coronary circulation is also increased. There is a casual relationship between the myocardial metabolic activity, O_2 consumption and coronary blood flow.
4. CO_2 and O_2:
   If O_2 supply to the heart muscle is decreased, then the coronary flow is increased. But, if the supply of O_2 is more than requirement, then the coronary circulation is decreased. Similarly, CO_2 stimulates the coronary flow. When the CO_2 concentration in the blood is increased, then coronary flow is also increased in first stage in order to maintain the total O_2 requirement of the cardiac muscle. If this state prevails further, the coronary flow is decreased abruptly and the heart stops in diastole.
5. Effects of ions :
   K+ in low concentration dilates the coronary vessels, whereas K+ in higher concentration constricts. Ca^{2+} in therapeutic doses increases the flow and O_2 consumption of the cardiac muscle.
6. Polypeptides :
   Angiotensin II is an active octapeptide which causes arteriolar constrction of the skin, kidney, brain and also in coronary vessels. Bradykinin is claimed to cause coronary vasodilatation but still its physiogical role is not proved.
7. Adenine neucleotides :
   It is discussed in the test.
8. Cardiac sympathetic and parasympathetic nerves :
   Stimulation of the cardiac sympathetic fibres from the stellate ganglion produces increased coronary flow. This is mainly due to the release of norepinephrine which causes coronary dilatation and increased coronary flow.
9. Heart rate :
   When the heart rate is increased minute cardiac output and aortic blood pressure is increased, but the stroke volume decreases. The phasic coronary blood flow and O_2 consumption per beat decrease, but the minute coronary flow and O_2 consumption per minute are increased. With the increase of heart rate, O_2 consumption of the heart muscle is increased and is maintained normally through increase of minute flow.
10. Pitressin or vasopressin :
    It causes increased coronary resistance and diminution of coronary flow.
11. Temperature :
    With rise of body temperature, body metabolism and O_2 requirement is increased. Therefore, to meet this O_2 demand coronary flow also increases.
12. Viscerocardiac reflex :
    The coronary flow is markedly decreased during visceral distension and it is often encountered in a patient with ischaemic heart disease.
13. Anaemia :
    In anaemia, the coronary flow is increased sharply in order to maintain the normal O_2 need of the cardiac muscle.

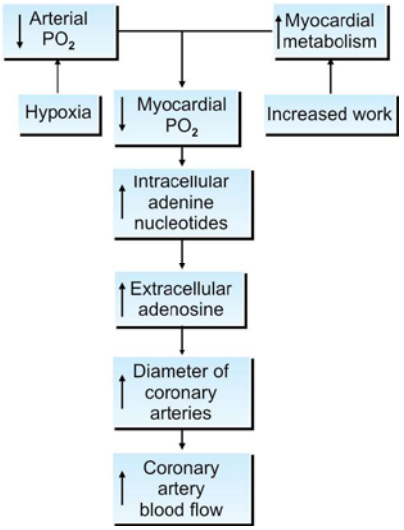


Fig. 5.28: The local mechanism of control of myocardial blood flow

the difference between the diastolic aortic pressure and the LV end diastolic pressure. Sympathetic adrenergic stimulation causes the coronary artery dilation. This can be explained by the following way. Unopposed α_1-adrenergic stimulation produce coronary vasoconstriction and unopposed β-adrenergic stimulation cause coronary vasodilation. But, when the both act at the same time, then the β-receptor's vasodilating properties predominates over the α-receptor's vasoconstricting properties.

Sympathetic stimulation also increases the coronary blood flow due to their stimulant effect on the both cardiac contractile force and metabolism. But the increase in coronary blood flow secondary to metabollic changes in heart is of far less quantitative significance than that caused by the increased discharge of impulse from the sympathetic nerves and receptor stimulation which occur simultaneously.

The stimulation of parasympathetic muscarinic receptor also produce coronary vasodilation. Though vagi are not proven to supply the coronary vessels, but vagal stimulation, sufficient to cause cardiac arrest, does increase coronary flow. This effect is probably due to the lessened intramural tissue pressure and lessened extravascular resistance, caused by the reduction of force of contraction. There are other various chemical mediators which control the coronary vascular tone. These are O_2, CO_2, K^+, histamine, prostagladins and adenosine. Among these adenosine is the most important chemical mediator which couples the coronary blood flow to the O_2 consumption and demand.

Adenosine arises from the adenine nucleotides (ATP, ADP) of myocardial cells which are disrupted by hypoxia. This nucleoside, adenosine, does traverse the myocardial cell membrane and gain access to the resistance vessels including the precapillary sphineters of the coronary vascular system and causes dilation. Like adenosine the ATP, ADP are equally potent vasodilator, but is not permeable to cell membrane. In the blood, adenosine is destructed by adenosine deaminase to inosine and hypoxanthine which have no vasodilating properties. Like cerebral circulation coronary circulation (like brain) is also conspicuous in manifesting self control on vascular resistance which is effected by chemical rather than by nervous influences. Thus with increase metabolism of heart the O_2 requirement is increased and the circulation is greatly increased. Similarly, CO_2 also stimualtes the coronary blood flow. For the increased coronary blood flow this increased O_2 requirement acts through hypoxia and adenosine mechanism (Fig. 5.29).

Study of Coronary Blood Flow

The coronary blood flow has been viewed by angiography. It also can be measured by inserting a catheter into the coronary sinus, and by taking sample and applying the Kety method on the heart. A number of techniques, utilising radionuclides, radioactive tracers, etc, that can be detected with radiation detectors over the chest, also have been used to study the regional blood flow in the heart. It detect the areas of ischaemia and infarction as well as evaluate the ventricular function.

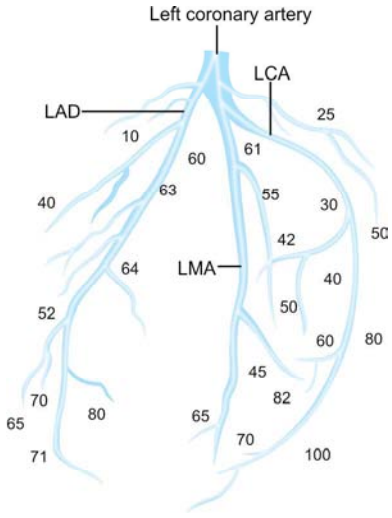


Fig. 5.29: The myocardial perfusion pattern following injection of 133Xe into the left main coronary artery. The numbers indicates the flow values in ml/100 gm/minute, measured by scintillation detector.
LAD = Left anterior descending artery,
LCA = Left circumflex artery,
LMA = Left marginal artery.

When radio nuclides such as thallium 201 (^{201}TI) is used, it is forced into the cardiac muscle cells by Na^+-K^+ ATPase pump and equilibrate with the intracellular K^+ pool. For the first 10 to 15 minutes after IV injection, thallium 201 distribution is directly proportional to the myocardial blood flow. Then, the areas of ischaemia can be detected by their low uptake of thalium 201 in the myocardial tissues by special instrument. The uptake of this isotope by heart is often determined soon after exercise and again several hours later to bring out areas in which exertion leads to compromised flow. Conversely, radiopharmaceutical agent such as technetium 99 m pyrophosphate (^{99m}Tc - PyP) also can be used which is selectively taken up by the infarcted tissue by an incompletely understood mechanism and make the infarct area to stand out as 'hot spots'on CT scans of the chest. The coronary angiography also can be combined with measurement of ^{133}Xe washout technique to provide the detailed analysis of the coronary blood

flow. Radiopaque contrast medium is first injected into the coronary arteries and X-rays are used to outline their distribution. The angiographic camera is then replaced with a multiple crystal scintillation camera and ^{133}Xe washout is measured. An example of normal flow distribution after injection in a left coronary artery is shown in figure.

Myocardial Metabolism

To maintain the cell integrity by controlling the Na^+, K^+ ionic gradients across the cell membrane and for contraction of myocardium, energy is needed. Heart uses ATP and creatine phosphate as the source of this energy to perform this mechanical and chemical work such as contraction and ion transport. Substrates like glucose, lactate, fatty acids are usually used by the heart muscle to get its metabolic energy source of ATP. During fasting, the free fatty acids are the main substrate for the energy source of heart. When carbohydrates is used as energy source the myocardial respiratory quotient (RQ) exceeds 0·9. But, fasting lowers the RQ to 0·7. This characterises that fat is metabolised during fasting.

When cardiac muscles contract, the ATP is broken down to ADP and inorganic phosphate (Pin) is produced. But, ATP is again rapidly synthesized by the Lohmann reaction from creatine phosphate.

Lohman reaction

$$ATP \xrightarrow{\text{Actomycin}} ADP + Pin \text{ (energy)}$$

$$ADP + CP \xrightarrow{\text{Creatine phosphotransferase}} ATP + C \text{ (creatine)}$$

When the heart is subjected to hypoxia, then the creatine phosphate concentration drops strikingly and the ATP/ADP (Fig. 5.30) ratio of the myocardium falls precipitously. The myocardial cells contain phosphorylase in an inactive form, i.e. phosphorylase-b. This inactive form can be activated by the cAMP to phosphorylase-a. The cAMP is formed from ATP by the enzyme adenyl cyclase which is again activated by adrenaline. Phosphorylase-a breaks down the glycogen to yield glucose-1-phosphate which is converted to glucose-6-phosphate. This compound is then broken down in myocardium by glycolysis to give pyruvic acid (in aerobic metabolism) which again enter the citric acid cycle to yield further energy by the synthesis of ATP (aerobic metabolism).

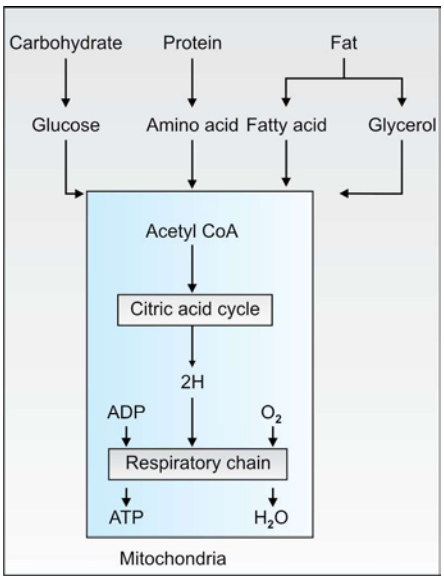


Fig. 5.30: The myocardial metabolism

The inner membrane of mitochondria consists of multiple folds and contain multiple enzymes which are needed for the aerobic metabolism or the citric acid cycle. The mitochondria also contains cytochrome system which are involved in the electron transport and ATP formation. Thus, mitochondria and O_2 become the sources of continuous supply of energy in the form of ATP for continuous cardiac function (Fact file - III).

Glucose is metabolised by the glycolytic pathway to yield pyruvate. Then pyruvate is metabolized to lactate when O_2 supply is inadequate. But if the supply of O_2 is adequate then pyruvate enter into the mitochondria for citric acid cycle. In the first step of citric acid cycle pyruvate is enzymatically transformed to acetyl-co-A and NADH. The enzyme responsible for this transformation of pyruvate to acetyl-coA is pyruvate dehyogenase which is a highly step limiting regulated

FACT FILE - III

The net production of ATP during the metabolism of glucose or glycogen to pyruvate depends on whether the metabolism occurs aerobically or anaerobically. During oxidation of glucose through Embden-Meyerhof pathway, the conversion of 1 mol of phosphoglyceraldehyde (PGD) to phosphoglycerate (PG) generates 1 mol of ATP, and the conversion of 1 mol of phosphoenolpyruvate to pyruvate generates another 1 mol of ATP. Therefore, as 1 mol of glucose produces the 2 mol of puruvate during its metabolism through E-M pathway, so 4 mol of ATP is generated. All these reactions occur in the absence of O_2. On the otherhand, 1 mol of ATP each is used during the conversion of fructose-6-phosphate to fructose-1-6-diphosphate and phosphorylation of glucose when it enters the cell. Since, when the puruvate is formed from glucose through E-M pathway the net gain of ATP is only 2 mol.

In E-M pathway of glucose metabolism during conversion of phosphoglyceraldehyde (PGD) to phosphoglycerate (PG) 1 mol of NAD^+ is converted to 1 mol of NADH. In the presence of O_2 this H^+ of NADH is transferred to cytochrome system. While in the absence of O_2, pyruvate accepts this hydrogen from NADH, forming NAD^+ and lactate where this NAD^+ is again used for the conversion of PGD to PG. Thus, in absence of O_2 pyruvate can not enter the citric acid cycle.

Pyruvate + NADH $\rightleftharpoons$ Lactate + NAD^+

In this way, glucose metabolism with production of lactate and energy may continue for a while without O_2.

During aerobic glucose metabolism (glycolysis) the net production of ATP is 19 times more than the two ATPs, formed under anaerobic conditions. Six ATPs are formed from two NADH (3 ATPs from one NADH) by oxidation through flavoprotein - cytochrome system. These NADHs are formed when 2 mol of PGD is converted to PG. Then, six ATPs are formed from the two NADHs which are produced when 2 mol of pyruvate is converted to acetyl-CoA for the pyruvate to enter into the citric acid cycle. After that 24 ATPs are formed from the citric acid cycle. Of these, 18 are formed from oxidation of six NADH, 4 from oxidation of two FADH, and 2 from succinyl-CoA when it is converted to succinate. This succinyl-CoA to succinate reaction actually produces GTP, but the GTP is converted to ATP. Thus the net production of ATP per mol of glucose metabolism aerobically by the E-M pathway and the citric acid cycle is 2 + (2 × 3) + (2 × 3) + (2 × 12) = 38.

enzyme found in the inner mitochondrial membrane. Then acetyl-CoA in citric acid cycle is ultimately broken down to CO_2 and H_2O yielding NADH, $FADH_2$ and 2ATP. These NADH and $FADH_2$ then enter in the respiratory chain (cytochrome system) where they are oxidised by giving up H^+. This hydrogen atom is carried out by the cytochrome system or respiratory chain and at the end of the cytochrome system in the presence of O_2, this H^+ form water (aerobic metabolism). Thus, during the oxidation of one molecule of reduced coenzyme (NADH) via the respiratory chain (cytochrome system), metabolic energy equivalent to 3ATP molecule is generated.

$$\text{NAD, 2H} + \tfrac{1}{2}\,O_2 \xrightarrow{\text{Many steps}} \text{NAD} + H_2O + \text{Pi}$$

$$3\ \text{ADP} + 3\ \text{Pi} \longrightarrow 3\ \text{ATP}$$

Thus, from each hydrogenated NAD molecule (i.e. NADH) three molecules of ATP are formed. In the absence of O_2 , the transport of H^+ or electron will proceed only until all the coenzymes/cytochrome has been exhausted.

CARDIAC OUTPUT

The cardiac output (CO) is defined as the total amount of blood pumped out by each ventricle per minute. This is also called the minute volume. The stroke volume means the amount of blood pumped out by each ventricle during each stroke or beat. So, the minute volume or cardiac output is the stroke volume multiplied by the heart rate. As the volume of blood pumped out by both sides of the heart is same, so the cardiac output is to be multiplied by 2 to calculate the total quantity of blood pumped out by the whole heart in a minute (Fig. 5.31).

The ejection fraction of left ventricle is defined as the stroke volume divided by the left ventricular end diastolic volume. It indicates the percentage of blood, ejected per ventricle per beat during the systole. The typical value for ejection fraction in a healthy adult male ranges from 60 to 70%. Values less than 40% represent severe ventricular contractile dysfunction or severe reduction of ventricular preload.

In adults, the average stroke volume is about 70 ml and the minute volume or cardiac output is about 5 to 6 litres/minute. In other words, the total volume of blood present in the body is expelled by each ventricle in every minute. Cardiac output is not the same in all individuals in all the ages. It is shown that CO increases approximately in proportion to the surface area of the body. So, the CO is frequently stated in terms of cardiac index. Thus, the Cardiac Index (CI) is defined as the CO per minute per square meter of body surface area. The average value of CI in healthy adult male is about 3·3 litres/min/m^2 (the surface area of an average sized adult male is about 1·7 m^2). Similarly, the stroke volume per square meter of body surface area is also known as the stroke volume index (SI). The average value of SI in a healthy adult male is about 47 ml/min/m^2.

Since, the venous return to the heart per minute should be the same as the minute output or cardiac output, so it follows that blood flow through all the tissues together

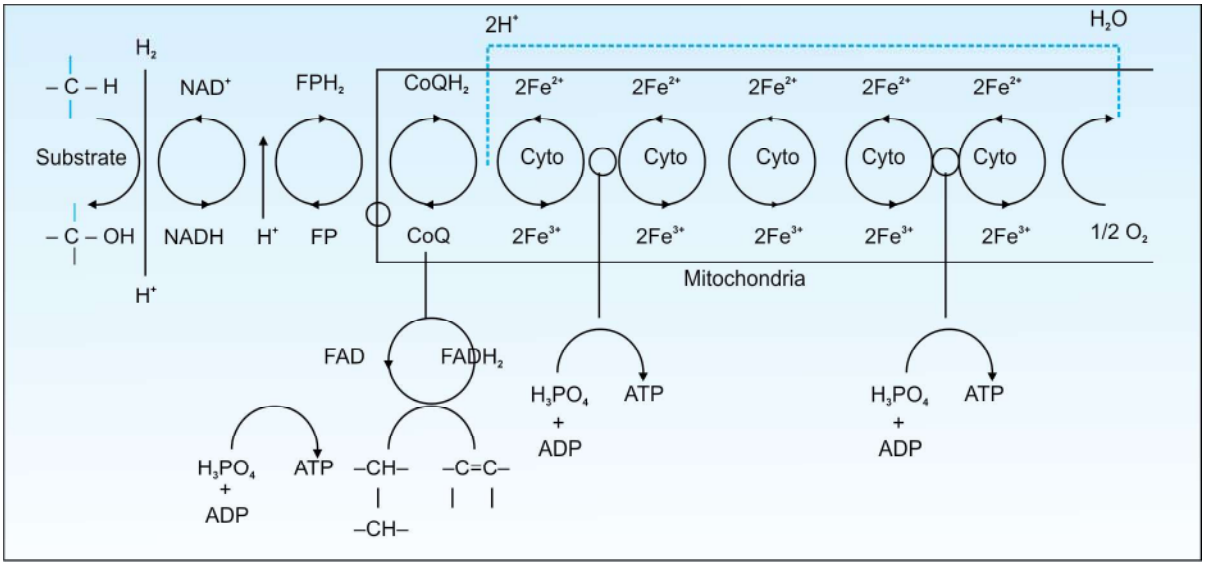


Fig. 5.31: Model of electron transport chain which is found within the mitochondrial matrix. Reducing substances such as $NADH_2$ or $FADH_2$ usually enter at the two points of the respiratory chain. But synthesis of ATP occurs at three separate sites. At the end O_2 accepts electron (H^+) from chytochrome (chy) and yields H_2O. Hydrogen (H^+) or electron flows through the chain in steps from the more electronegative components to the more electropositive oxygen. When substrates are oxidized via NAD linked dehydrogenase and the respiratory chain, 3 molecules of inorganic phosphate are incorporated into 3 molecules of ADP to form 3 molecules of ATP per 1/2 molecule of O_2 consumed. For $FADH_2$ only 2 molecules of ATP are formed. This reaction is called as oxidative phosphorylation

per minute must also be the same as the cardiac output. In other words, 5 litres of blood passes out per ventricle per minute, 5 litres of blood flows through all the tissues per minute and the same 5 litres of blood comes back to the heart to be distributed again to the different tissues per minute, such as Kidney - 1300 ml/min; Brain - 700 to 800 ml/min; Coronary - 200 ml/min; Muscle - 600 to 900 ml/min; Liver - 1500 ml/min, etc. The total quantity of blood distributed in these organs does not exceed 4500 ml/min. So, the remaining amount of blood is distributed to the skin, bones, GI tract and other less perfused tissues.

Cardiac reserve is defined as the capacity of heart which helps to generate the sufficient amount energy to expel a large quantity of blood above the basal level during emergency. Generally, the normal hearts expel about 5 to 6 litres of blood per minute per ventricle. But during exercise this amount may increase up to 30 to 40 litres/minute/ventricle (Fig. 5.32).

Determinants of Cardiac Output

Cardiac output mainly depends on the following four factors. These are: preload, force of cardiac contraction, after load and heart rate.

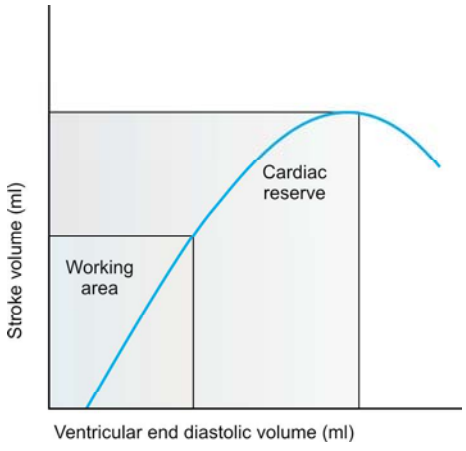


Fig. 5.32: Graphical representation of Starling's law of heart. When end diastolic volume (or the myocardial fibre length) increases, ventricles contract more vigorously and stroke volume increases. The pink area shows the cardiac reserve area and the blue area is the normal functioning area. When the function of heart goes beyond the reserve range, the stroke volume decreases and the relationship is reversed

Preload or venous return

The relationship between the length and tension of cardiac muscle is similar to that of the skeletal muscle. When the muscle is stretched or the length is increased, then the resultant developed tension for next contraction in the muscle fibre also increases. But this is up to a limit, because the developed tension for subsequent contraction declines as the stretch becomes more extreme. This is called the length tension relationship of muscle. On the otherhand, the developed increased tension after the length is increased is proportional to the subsequent force of contraction of the muscle fibre. Then, Starling stated that the energy or force of contraction is proportional to the initial length of the cardiac muscle fibre. This pronouncement has come to be known as the Starling's law or the Frank Starling law, in honour of Frank and Starling who were the two great physiologists of a century ago. So, basically the Frank Starling mechanism means that the greater the heart muscle is stretched during diastolic filling (or muscle fibre length is increased due to increased end diastolic volume) the greater will be the subsequent force of ventricular contraction and the greater will be the quantity of blood pumped out into the aorta or pulmonary trunk. Thus, the relationship between the ventricular stroke volume and the end diastolic volume is called as the Frank Starling curve (Fig. 5.33).

When the force of ventricular contraction is increased without an increase in fibre length or end diastolic volume due to sympathetic stimulation, then more blood that normally remains in the ventricles is also expelled without applying the Starling's law. It means that ejection fraction increases without increasing the preload, venous return or end diastolic volume or applying the Frank-Starling law. Thus the end systolic ventricular blood volume falls. The best example of this phenomenon is compensated hypovolaemia when the venous return falls, but the cardiac output is maintained up to a certain extent by increasing the inherent ability of contraction (contractility) and heart rate which is the function of the sympathetic system. This will be discussed more in detail below. So when there is both sympathetic stimulation and increased end diastolic volume due to good venous return, then there is tremendous increase in cardiac output. This is simply due to application of both Starling law and sympathetic stimulation (Fig. 5.34).

Thus, the preload is defined as the end diastolic fibre length or end-diastolic volume of the ventricle. But preload actually

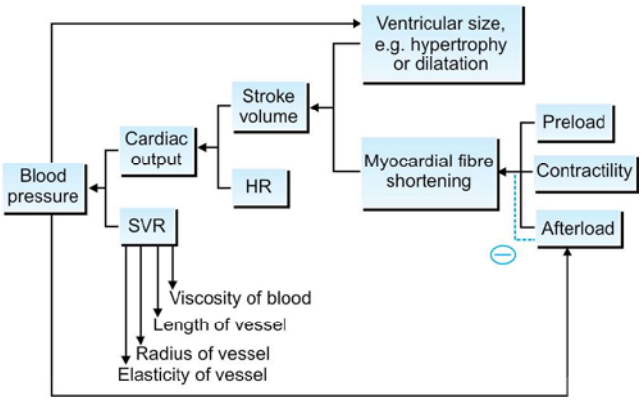


Fig. 5.33: The interactions between the components that regulate the cardiac output and the blood pressure. Solid arrows indicate increase and the red dashed line indicates a decrease

Contractile state of myocardium is influenced by

- Hypoxia
- Hypercarbia
- Acidosis
- Circulating catecholamines
- Sympathetic / parasympathetic nerve impulse
- Intrinsic depression
- Loss of myocardium
- Force frequency relation
- Pharmacologic depression
- Digitalis and other inotropics

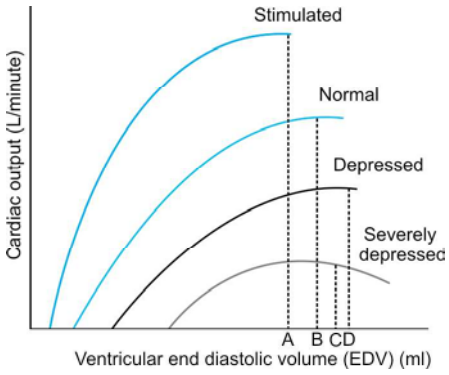
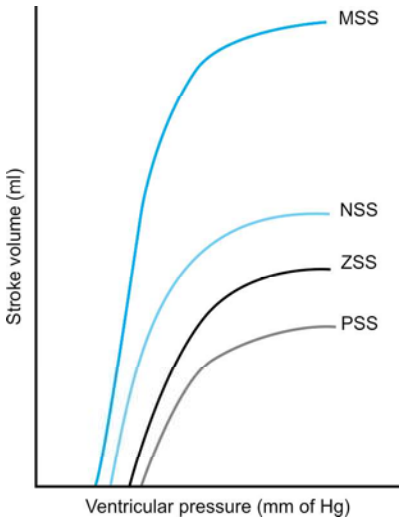


Fig. 5.34: The Frank Starling curve and the effects of changes in myocardial contractility on this curve. The curve shifts downward and to the right (green and black line) as contractility is depressed. The factors influencing the myocardial contractility are summarised in the table. The vertical dashed line ABCD indicates the portion of the ventricular function curve where maximum contractility has been exceeded and correponds with the point on the descending limb of the Frank Starling curve

means the pressure within the ventricle at the end of the diastole for a given volume of blood which depends on the venous return or ventricular filling during diastole. Anything that increases or diminshes the venous return will also increase or decrease the preload and the cardiac output accordingly. These are: intravascular volume status, capacitance of venous system and ventricular compliance.

There is pressure difference between the arterioles, capillaries and venules. At the level of the heart, pressure at the arteriolar end of a capillary loop is 32 mm of Hg and at the venous end of the loop is 12 mm of Hg. So mean capillary pressure is 25 mm of Hg. Pressure in the great veins may vary from positive to negative. Venous dilation without arteriolar dilation or without fall of general BP will increase venous return and CO. But the resultant effect may show no increase in BP due to different reflex mechanism which try to maintain the BP at normal level. On the otherhand, arteriolar dilation definitely show the decrease of BP or afterload even though the CO increases. On the contrary arterial dilatation without venous dilatation will cause decrease in venous return and ↓CO and ↓BP. During both the arterial and venous dilatation, there is tremendous reduction of CO and fall of BP which is seen in spinal and epidural anaesthesia (Fig. 5.35).

Vasomotor system control the pump, the lumens of arterioles, the lumens of venules and thereby control the preload, CO and after load. In shock the intravascular volume status is altered definitely or relatively, affecting the preload, CO and after load.

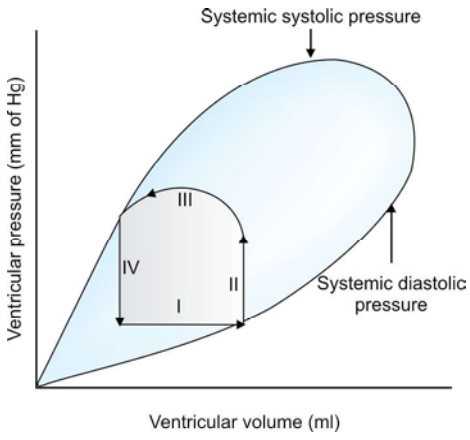


MSS = Maximum sympathetic stimulation
NSS = Normal sympathetic stimulation
ZSS = Zero sympathetic stimulation
PSS = parasympathetic stimulation

Fig. 5.35: The effect of different degree of sympathetic stimulation on the stroke volume

Force of cardiac contraction (contractility)

Within the physiological limits, the heart pumps 70 to 80% of the total blood that returns to it by the way of veins. The amount of blood that returns to the heart accounts for the preload and is estimated by the end diastolic ventricular volume or the initial length of muscle fibres of ventricle before contraction. Cardiac output not only depends on this preload, but also on the inherent pumping action or contractility of the ventricle. So, this pumping action or the force of cardiac contraction is defined as the inherent isotropic or contractile ability of the heart. This is due to the balance between the parasympathetic and sympathetic activity on it. The contractility of myocardium will also exert a major influence on the stroke volume other than preload. This intrinsic contractile ability of heart can not be explained by the Frank Starling mechanism which relates best the intial length of the muscle fibre or end diastolic volume with the subsequent force of contraction. So, it is described previously under the heading of preload (Fig. 5.36).



I = Period of filling, II = Isovolumic contraction, III = Period of ejection, IV = Isovolumic relaxation.

Fig. 5.36: The central square shaped figure represents the relationship between the left ventricular volume and the left intraventricular pressure during diastole and systole. The outer shaded area represents the work performed by the heart

The best way to express the functional or contractile ability of the ventricles is 'ventricular function curve'. It describes that as the intra ventricular pressure increase by ventricular contraction due to sympathetic activity the respective ventricular output also increases.

Thus, the ultimate force of cardiac contraction depends on the following factors:

i. The initial length of the cardiac muscle fibre: Within the physiological limits, greater the initial length, stronger will be the force of contraction (Starling's law). It is an inherent self-regulating mechanism that permits heart to adjust the changing end-diastolic volumes. It is obvious that the initial length of ventricle muscle fibre is proportional to the degree of filling which again depends on the venous return.
ii. The length of ventricular diastolic pause → Filling, rest and recovery of the heart muscle usually takes place during diastole. Hence, with shorter diastolic period which is inadequate for filling, rest, and recovery, the force of cardiac contraction will also diminish.
iii. Ventricular compliance: It determines the ability of the ventricle to be relaxed and dilated and thus the filling capacity.
iv. Nutrition and O_2 supply: An adequate supply of nutrition and O_2 to the myocardium is essential for the efficient cardiac activity. In addition to this, an optimum H^+ concentration, intracellular Ca^{2+} concentration, a proper balance of inorganic ions and appropriate temperature are needed for better cardiac contraction.
v. The pumping effectiveness or contractility of the heart is also controlled by the sympathetic and parasympathetic nerves. By sympathetic stimulation the cardiac output often can be increased more than 100% (both by increasing the heart rate and force of contraction). By contrast, the cardiac output can be decreased to as low as zero by parasympathetic (vagal) stimulation. When the sympathetic nerve to the heart is stimulated, the whole length tension curve of Starling law shifts upward and to the left. This is due to the positive inotropic effect of both norepinephrine and epinephrine.

Under normal condition, the sympathetic nerve fibres, supplying the heart, discharge continuously at a slow rate that maintains the pumping action at about 30% above that when there is no sympathetic stimulation. Therefore, when the activity of sympathetic nervous system is depressed, then this decreases both the heart rate and the strength of ventricular contraction which is as much as 30% below the normal.

The vagal fibres are distributed mainly to the atria and not so much to the ventricles, where the main power of contractions of heart occurs. This explains the effect of vagal stimulation which mainly to decreases the heart rate rather than greatly to decreases the strength of cardiac contraction. Neverthless, the great decrease in heart rate combined with a slight decrease in contractile strength can decrease the ventricular pumping ability or cardiac output to 50% or more (Fig. 5.37).

Afterload

The afterload of the ventricle is defined as the pressure in the principal arteries which are coming out from the ventricle and opposes its ejection. This afterload closely, but not exactly corresponds to the systolic pressure, described by the phase III curve of the volume pressure diagram. Sometimes, the afterload is loosely considered as the resistance in the vessels of circulation rather than the pressure. But it is incorrect. So, only the mean arterial blood pressure is equivalent to the afterload and therefore, it may be defined as the force or pressure opposing the ventricular ejection (the unit of force is dyne or mm of Hg whereas the unit of pressure is dyne/cm^2 or mm of Hg/cm^2).

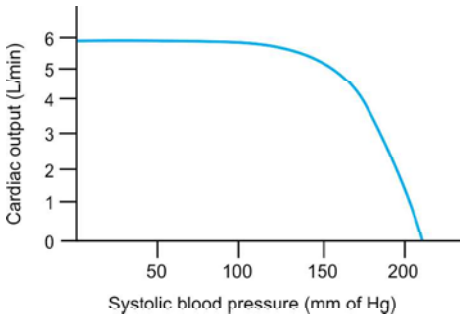


Fig. 5.37: The relationship between the systolic blood pressure and the cardiac output. When the blood pressure rises above 150 mm of Hg the cardiac output falls significantly

The importance of the concept of preload and afterload is that in many abnormal functional states of the heart or circulation, the intraventricular pressure during filling of it (i.e. the end diastolic ventricular pressure or the preload which closely corresponds with end diastolic volume) and the arterial pressure against which the ventricle must contract (i.e. the afterload) or the both are severely altered from the normal.

Increasing the arterial pressure in aorta or after load does not decrease the cardiac output, until the mean arterial pressure rises above the approximately 160 mm of Hg. In other words, during the normal function of heart at normal systolic arterial pressure (80 to 140 mm of Hg), the cardiac output is determined almost entirely by the ease of flow of blood through the tissues which in turn controls the venous return of blood to the heart and cardiac contractility (Fig. 5.38).

Total Peripheral Resistance

It is also an extremely important or principal factor for controlling the cardiac output. We know that the arterial pressure is equal to the cardiac output multiplied by the total peripheral systemic resistance. On the otherhand, we can say that the cardiac output is equal to the arterial pressure divided by the total peripheral systemic resistance. Thus, under most normal circumstances, the cardiac output varies reciprocally with the changes in total

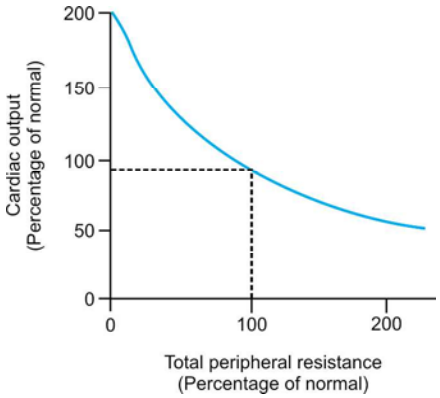


Fig. 5.38: The relationship between the total peripheral systemic resistance and the cardiac output which is reciprocal in nature. Here 100% is taken as normal

peripheral resistance. In the figure when the peripheral resistance is exactly normal i.e. at the 100% mark, the cardiac output is also normal. Then, when the systemic resistance increases above the normal, the cardiac output gradually falls. Conversely, when the resistance decreases, the cardiac output increases.

Thus, one can easily understood this relationship by reconsidering one of the forms of Ohm's law as expressed by:

$$\text{Cardiac output (or flow of current)} = \frac{\text{Arterial pressure (or electromotive force)}}{\text{Total peripheral resistance (electrical resistance)}}$$

Heart rate

Heart rate affects both the stroke volume and the minute volume. It affects the stroke volume by altering the period of diastole and there by altering the degree of ventricular filling (preload) and subsequently the force of contraction. Minute volume is equal to the heart rate multiplied by the stroke volume. So, the heart rate also affects the minute volume by altering one of the determinants of it. It should be noted that blood pressure depends upon the minute volume or cardiac output but not on the stroke volume (BP = CO × SVR) though there are also many other factors which determine the BP.

Venous return remaining constant, the rise of heart rate will reduce the diastolic pause and, therefore, the stroke volume. But the product of stroke volume multiplied by heart rate (i.e. cardiac output - CO) may not fall, even it may rise above the resting value. Thus, minute volume (CO) and therefore, BP may rise even if the stroke volume falls, provided the venous return is maintained. This happens with a moderate rise of the heart rate, i.e. up to 160 per minute. If the heart rate becomes too high, then ventricular filling and the stroke volumes become so low that the minute output (CO) falls far below the normal, though venous return is maintained. Thus, blood pressure may drop and the subject may become unconscious. This happens in paroxysmal tachycardia, when the frequency of heart beat suddenly rises to 150 to 200 per minute. But, muscular exercise is an exception. Here, both the frequency of heart beat and the rate of venous return increases. Therefore, cardiac filling becomes more than normal even during the short diastolic period during exercise. Hence, both the stroke volume and the minute volume increases.

On the other hand, when the heart rate becomes very low (as in heart block or due to any other causes), then although the stroke volume is much higher than normal, yet due to the same reason the total minute volume may fall. This is because the product of heart rate and stroke volume which determine the cardiac output may be less than normal. But, with the moderate slowing of heart rate, the minute volume may not fall at all. In some instances it may rise. Thus, alteration of the heart rate, on either side i.e. not too high or not too low will generally raise the minute volume up to a certain extent. Beyond that limit, the minute volume or cardiac output will fall.

Measurement of Cardiac Output (CO)

In animal experiments, one can cannulate the aorta, pulmonary artery or any other great veins or arteries entering or exiting from the heart and thus can measure the cardiac output directly by using any type of flowmeter (invasive method). But, non-invasively cardiac output can be measured in experimental animal only by an electromagnetic flow meter placed on the root of the aorta or pulmonary artery. In human beings the methods which are used to measure the cardiac output are : Doppler combined with echocardiography method, direct Fick principle method and indicator dilution method (a popular indicator dilution method is thermodilution method where the heat is used as an indicator).

(i) Doppler and echocardiography combined technique:

The wall movement of cardiac chambers and also the other aspects of cardiac function can be evaluated by the echo cardiography. It is a non-invasive technique and thus does not involve injections or insertion of catheter into the any cardiac chambers or in any great vessels. In echo cardiography, pulses of ultrasonic sound waves, commonly at a frequency of 2·25 MHz are made emitted from a transducer. This transducer also functions as a receiver to detect ultrasonic waves which is reflected back from the various parts of the heart. This reflections always changes whenever the acoustic impedance changes. Thus, when this recording of the changing echoes is placed against time on an oscilloscope, it provides a record of the movements of the wall, septum and valves of different cardiac chambers during different phases of cardiac cycle. When this echo cardiography is combined with Doppler principle, then this combined method, can be used to measure the velocity and the volume of flow through the valves and thus cardiac output.

(ii) Fick Principle

Normally, 200 ml of O_2 is absorbed from the alveoli of lungs into the pulmonary blood in each minute. It is found that blood

entering the right side of the heart has an O_2 content of 160 ml per litre. Whereas the blood leaving the left side of the heart has an O_2 content of 200 ml/litre. From these data we can calculate that each litre of blood passing through the lungs absorbs 40 ml of O_2. Therefore, dividing the total quantity of O_2 absorbed into the blood from the lungs i.e. 200 ml by the O_2 absorbed by per litre of blood (which is obtained by the atrio venous O_2 difference) i.e. 40 ml, we can get the total amount of blood passing through the pulmonary circulation per minute which absorb this total amount of O_2. Therefore, the total quantity of blood flowing through the lungs each minute is 200 ml/40 ml = 5 litres. Thus, the cardiac output can be calculated by the following formula : Cardiac output (L/min) = Total O_2 absorbed by the lungs (ml/min) /arteriovenous O_2 difference (ml/L of blood). This is the Fick principle.

In applying this Fick principle for measuring the cardiac output in the human being, mixed venous blood is usually obtained by a catheter which is inserted through the brachial vein of the forearm, passed and through the subclavion vein, and then down the right atrium into the right ventricle or pulmonary artery finally. Systemic arterial blood can be obtained from any systemic artery of the body. The rate of O_2 absorption by the lungs is measured by the rate of disapearance of O_2 from the respired air i.e. from the difference in O_2 concentration in the inspired and expired air, using any type of oxygen meter.

(iii) Indicator dilution technique

In this technique a known amount of any substance, such as a dye or more commonly a radioactive isotope is injected into any vein of a arm and then the concentration of this indicator from the serial samples of arterial blood is determined. The output of the heart (i.e. cardiac output) is equal to the amount of indicator injected divided by its average concentration in arterial blood after a single circulation through the heart. The indicator must of course be a substance that stays in the blood stream during the test and has no harmful hemodynamics effects. A popular indicator dilution technique is a thermodilution technique, in which the cold saline is used as an indicator.

Vascular Resistance (VR)

Blood flows through the vessels primarily because of the forward forces, imparted by the pumping action of the heart. But the elastic recoil property of the walls of the arteries (Fig. 5.39) during diastole, compression of the veins by the contraction of skeletal muscle during exercise and the negative suction pressure in the thorax through venous system during inspiration also help to move the blood forward through arterial system. This flow of blood (F) in a long tube like vessel depends on multiple factors such as the length of the tube (L), radius of the tube (r), viscocity of blood (η) and the pressure difference ($P_A - P_B$) between the two end of the tube, which follows the Poiseuille Hagen formula.

So, according to this formula:

$$F = (P_A - P_B) \times \frac{\pi}{8} \times \frac{1}{\eta} \times \frac{r^4}{L}$$

But, we know from Ohm's law that flow is equal to the pressure difference ($P_A - P_B$) divided by resistance (R).

Current (I) or flow (F) =

$$\frac{\text{Electromotive force (E) or pressure difference}}{\text{Resistance (R)}}$$

So, from here we can calculate the resistance (R) as:

$$R = \frac{8\,\eta\,L}{\pi\,r^4}$$

The resistance to the flow of blood depends very slightly on the viscosity of blood, but mostly on the radius or diameter and the length of the vessels (principally of the arterioles, because they are more in length) (Fig. 5.40).

Plasma is about 1.8 times more viscous than water. Whereas the whole blood is 3 to 4 times more viscous than water. Thus viscosity depends mainly on the hematocrit value i.e. percentage of the volume of blood occupied by the red blood cells. In large vessels, the increase in hematocrit causes appreciable increase in viscosity and therefore the resistance. However, in vessels smaller than 100 µm in diameter, i.e. arterioles, capillaries and venules, etc. the change of viscosity due to per unit change of hematocrit has much less effect on resistance than it is in the large

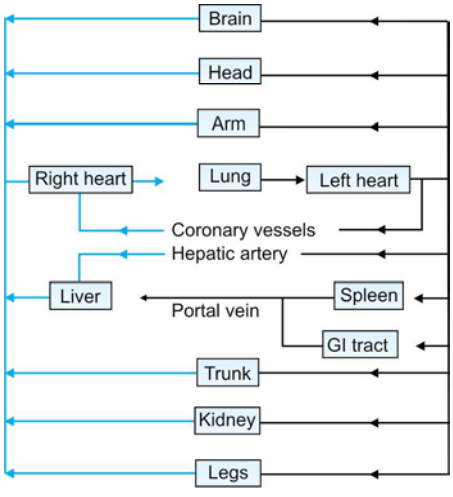


Fig. 5.39: Schematic diagram of different parallel circuits of circulation

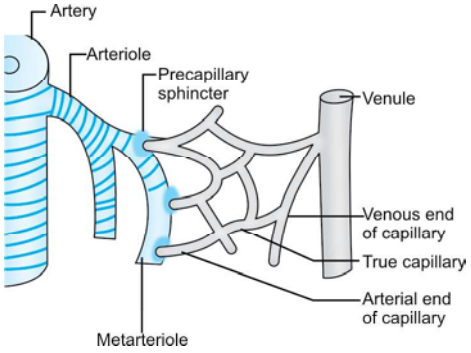


Fig. 5.40: The microcirculation. Arterioles give rise to metaarterioles which give rise to capillary. The capillary drains into the venule. The walls of artery, arteriole and venule contain relatively large amounts of smooth muscles. But the wall of meta arteriole contain few smooth muscle and capillaries have no. The opening of the capillaries are guarded by muscular precapillary sphincters

bore vessels of large diameter. This is due to the difference in nature of flow through the small vessels. Therefore, the net change in viscosity due to per unit change in hematocrit and its subsequent effect on total resistance is considerably smaller in the body as the smaller vessels occupy the larger portion of the total length of blood vessels. This is why the changes in hematocrit value have relatively little effect on the SVR, except when the changes are larger.

The flow of blood through each tissue or organ is regulated by the local chemical and/or the general neural and humoral mechanisms which causes dilatation and constriction of the vessels. The blood flows through the lungs without any change of the circuit. But, the systemic circulation is made up of numerous different circuits which are arranged in parallel. These arrangements permit wide variation in regional blood flow without changing the total systemic flow and resistance.

The walls of the aorta and other arteries of large diameter contain less amount of smooth muscles, but contain a relatively large amount of elastic tissues which are primarily located in the inner and external elastic laminas. They are stretched during systole and recoil on the blood column during diastole which is responsible for the forward motion and circulation of blood. On the other hand, the walls of the vessels of smaller diameter or arterioles contain less elastic tissue, but much more smooth muscle. These muscles are innervated by noradrenergic nerve fibers which function as constrictors, but in some instances they are innervated by cholinergic fibers which dilate the vessels. The arterioles are the major site of the resistance to blood flow and thus is the main determinant of the afterload. Because this after load is the blood pressure which is obtained by multiplying the cardiac output with the resistance imparted by these arterioles i.e. afterload or blood pressure = CO × SVR.

The arterioles divide into smaller vessels which are sometimes called the metarterioles and these in turn feed into capillaries. In some vascular bed these metarterioles are connected directly with venules through fare vessels. The true capillaries are an anastomosing network of side branches of this throughfare vessel. The opening of the true capillaries are surrounded on their upstream side by some smooth muscles sphincter which are called the precapillary sphincters.

The true capillaries are about 5 µm in diameter at the arterial end and 9 µm in diameter at the venous end. When the sphincters are dilated then the diamter of the capillaries is just sufficient to permit a squeezed red blood cells through it. The total surface area of all the capillary walls in the body is near about 6300 m^2 in an adult.

The walls of the venules are only slightly thicker than those of the capillaries. The walls of the large veins are also thin and easily distended. They contain relatively little smooth muscle than the metaterioles. But, considerable venoconstriction can be produced by the activity of the noradrenergic nerves on the veins or by circulating vasoconstrictors such as endothelins, epinephrine, norepinephrine, etc. Variations in venous tone are very important in circulatory adjustments.

Blood always flows from the areas of high pressure to the areas of low pressure. The relationship between the mean flow, mean pressure and the resistance in the blood vessels is analogous to the relationship between the flow of current (I), electromotive force (E) and the resistance (R) in an electrical circuit which is expressed as Ohm's law described before as I = E / R or the flow = Pressure / Resistance.

Thus, the flow of blood in any portion of the vascular system is equal to the effective perfusion pressure in that portion divided by the resistance. The effective perfusion pressure is the mean intraluminal pressure at the arterial end minus the mean intraluminal pressure at the venous end. The unit of resistance (pressure divided by flow) is expressed as dynes/s/cm^5. But to avoid the dealing of such complex units, resistance in the cardiovascular system is sometimes expressed as R units. This is obtained by dividing the pressure in mm of Hg by flow in ml/sec. Thus, for example, when the mean aortic pressure is 90 mm of Hg and the flow is 90 ml/sec, then the resistance is 90 mm of Hg / 90 ml per sec = 1 R units.

When the blood is poured into any segment of the vena cava or other large distensible veins, then the pressure does not rise rapidly until the very large volumes of fluid are injected. So, the veins are called as the blood reservoir. Normally veins remain in partially collapsed state. A large amount of blood can be added to the venous system before the veins become fully distended to the point where further increments in volume produce a large rise in venous pressure. The veins are, therefore, also called the capacitance vessels. On the otherhand, the walls of the arterial system is not distensible. Therefore, the addition of little amount of blood in this system causes precipitous increase in pressure. So, the small arteries and the arterioles are referred to as the resistance vessels, because they are the principal site of producing blood pressure and the peripheral resistance (Fig. 5.41).

At rest, atleast about 50% of the total circulating blood volume remains in the systemic veins, 12% is in the cavities of heart and 28% is in the low pressure pulmonary circulation. However, only 2% is in the aorta, 8% in the arteries, 1% in the

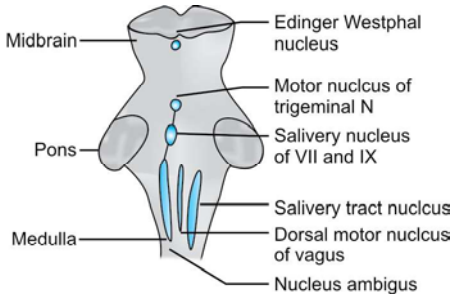


Fig. 5.41: Different nuclei of cranial nerves on the dorsal aspect of the brain stem, with nucleuses of vagus nerve

arterioles and 5% in the capillaries. When extra blood is administered by transfusion, then less than 1% of it is distributed in the arterial system (the high pressure system) and all of the rest is found in the systemic vein, pulmonary circulation and the cardiac chambers of low pressure system (i.e right side of the heart) other than the left ventricle.

CARDIAC REFLEXES

Cardiac reflexes are carried out by afferent pathways, vasomotor centre (VMC) and effarent pathways, lying within the sympathetic and parasympathetic nervous system, whose activities are further modified by the thalamus, hypothalamus and some other higher centers.

Vasomotor Centre

It is situated on the floor of the 4th ventricle in the reticular formation. There are practically two areas in the vasomotor centre. These are pressure centre and depressor centre. The pressure centre situated laterally and rostrally which causes the rise of BP. Whereas the depressor centre is situated medially and caudally which causes the fall of BP. These are the completely physiological areas as there is no clear cut anatomical separation between the presure and depressor areas. In the intermediate region they overlap (Fig. 5.42).

Sometimes it is appropriate to use the term 'medullary cardiovascular centre' instead of vasomotor centre, because it is recognised that the area contains both the neurons which excite and inhibit the thoracolumbar sympathetic centre supplying the heart and blood vessels. Within the VMC lies (i) the nucleus of tractus solitarius which receives the sensory fibres carrying general visceral sensations through the vagus and glossopharyngeal nerve, (ii) the dorsal motor nucleus of vagus which supply motor to the heart, lungs, esophagus, stomach, small intestine and large intestine up to the right two-thirds of the transverse colon and (iii) the nucleus ambigus which contributes fibres to the glossopharyngeal and vagus nerves.

The depressor centre is not the direct vasodilator centre. This centre causes inhibition of the sympathetic vasoconstrictor tone and thus indirectly dilates the vessel. The depressor centre relays the inhibitory impulses to the pressor centre. Pressor and depressor centres form the one functional physiological unit and it is defined as the VMC. The VMC discharges impulses which pass down the lateral white column of the spinal cord through the cervical, thoracic and lumbar segments and form synaptic connection with the lateral horn cells of the spinal cord (spinal sympathetic centre) (Fig. 5.43).

When BP rises, signals from the baroreceptors of carotid sinuses and aortic arch goes to the depressor centre which relays inhibiting impulses to the pressor centre causing slowing of the heart rate and dilatation of arterioles. Thus, vasodilatation and fall of BP is due to inhibition of the vasoconstrictor effect of the sympathetic (depressor reflex) system. On the otherhand, diminuation of blood

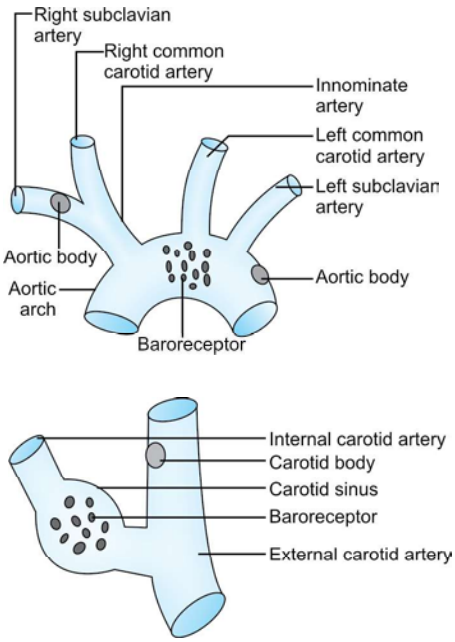


Fig. 5.43: The baroreceptors and chemoreceptors in the carotid sinus and aortic arch

presure fails to stimulate the baroreceptor of the carotid sinuses and aortic arch. Thus, the inhibitory impulses over the pressure centre is withdrawn and BP is raised reflexly through the overactivity of the sympathetic system.

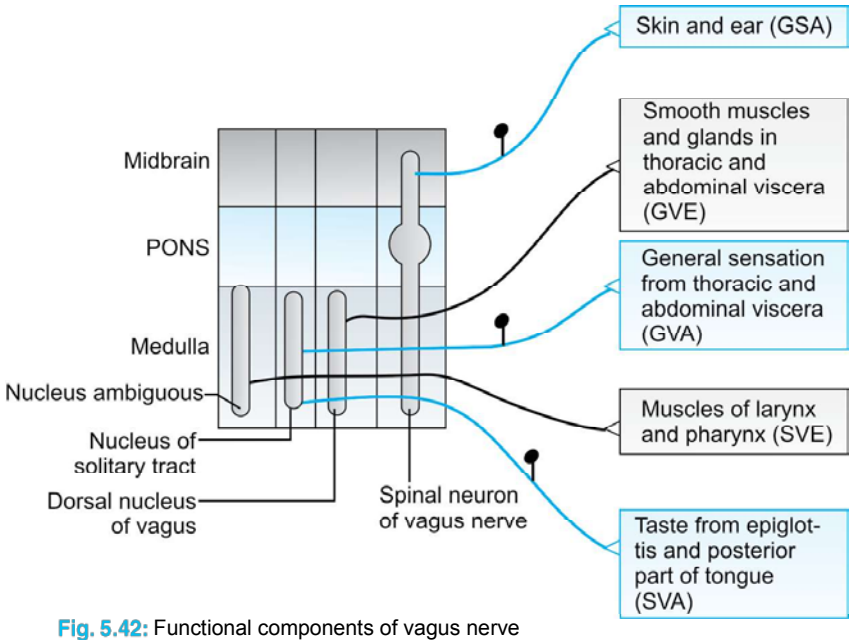


Fig. 5.42: Functional components of vagus nerve
GSA = General somatic afferent, GVE = General visceral efferent, GVA = General visceral afferent, SVE = Special visceral efferent, SVA = Special visceral afferent

Afferent Pathways

The afferent pathways, lying in the nerve fibres, starts from the two sets of receptors that continuously carry information regarding the peripheral circulatory status to the VMC. These sensory receptors are baroreceptors and chemoreceptors. The baroreceptors include the carotid sinus and aoritc arch, whereas the chemoreceptors include the carotid body and aortic body.

Carotid sinus

It is a dilatation at the root of the internal carotid artery, often involving the common carotid artery. The wall of the sinus is thin and is due to the less amount muscle fibres in the tunica media. In the deeper part of the adventitia, an extensive network of afferent nerve fibres is present. The nerve fibres end as the free terminals. These are the pressor receptors and are sensitive to stretch, being stimulated by rise of BP. The nerve arising from the carotid sinuses (baroreceptor) and carotid body (chemoreceptor) is purely afferent and is called the sinus nerve. It passes along the glossopharyngeal nerve and ends in the medulla.

Aortic arch

The stretch receptor and affarent nerves, similar to those of the carotid sinuses, are also present in the adventitia of the aortic arch, the roots of the great vessel arising from aorta and even in the adjoining parts of the left ventricle. They serve the same function as the carotid sinus. The nerve arising from the aortic arch (baroreceptor) and aortic body (chemoreceptor) is called the aortic nerve. It is purely afferent nerve and passes through the vagus to end in the medulla.

Carotid body

It is a small nodular structure situated close to the carotid sinus. It consists of clumps of large polyhedral cells and richly supplied with blood vessel and nerves. Numerous afferent nerve fibres surround these clumps of cells and even the individual cells and terminate in special chemoreceptor. Afferent pathways from these chemoreceptor areas are lying in the sinus nerve.

Aortic body

Like the carotid body, it is also a nodular structure and supplied richly by the blood vessels and the nerve fibres. Affarent pathways from these chemoreceptor areas lie in the aortic nerve and vagus. Their structure, nerve ending and functions are similar to those of carotid body.

Except these above mentined baro and chemoreceptors there are also other baroreceptors and chemoreceptors which are distributed throughout the whole body. These baroreceptors are located in the right atrium, left ventricle, left atrium, at the junction of the superior thyroid artery and common carotid artery, at the junction of the subclavian artery and common carotid artery, throughout the common carotid artery, in between the superior thyroid artery and subclavian artery, thoracic arch of aorta and in the central vein. The chemoreceptor are also located in the ventricular cavity and throughout the whole blood vessel's wall.

Efferent Pathways

Efferent pathways passes through the vagus and the sympathetic nerves which control the cardiovascular system by modifying the cardiac activity and the lumen of the blood vessels. These efferent pathways are divided into vasoconstrictor and vasodilatios fibres, carried by the different nerves.

Vasoconstrictor fibres

These fibres pass mainly through the sympathetic outflow, extending from the lateral horn cells of the first thoracic to the 2nd lumbar segments of the spinal cord and distributed in the following way.

i. To the skin and muscle: pass out through the gray rami communicantes as the postganglionic sympathetic fibres from all the ganglion of the sympathetic chain - to the mixed spinal nerves and finally distributed over the whole body through the somatic motor and sensory nerves. The distribution is strictly unilateral and stops sharply at the midline.
ii. To the head and neck: preganglionic fibres come from the lateral horn cells of the first to the fourth thoracic spinal segments - enter the superior cervical ganglion from which postganglionic fibres arise and pass along the carotid artery and its branches and along the spinal nerves of cervical plexus.
iii. To the fore limbs: preganglionic fibres arise from the lateral horn cells of the 4th to the 10th thoracic spinal segments - enter the stellate ganglion from which the postganglionic fibres arise and pass along the spinal nerves and the blood vessels going to superior extremity.
iv. To the hind limbs: preganglionic fibres arise from the lateral horn cells of the 11th thoracic to the 2nd lumbar spinal segments - relay in the lower lumbar and upper sacral ganglia of the sympathetic chain from where the postganglionic fibres arises and accompany the nerves of the lumbar and sacral plexus.
v. To the abdominal viscera: preganglionic fibres arise from the lateral horn cells of the lower thoracic and upper two lumbar spinal segments pass through the splanchnic nerves to coeliac ganglion - the postganglionic fibres pass along the blood vessels.
vi. To the thoracic viscera: Heart receives the accelerator fibres from the lateral horn cells of the T_1 to T_4 spinal segments through the cardiac plexus. Lungs also receives sympathetic bronchodilator fibres from these segments of spinal cord (Fig. 5.44).

Vasodilator fibres

There are three types of vasodilator fibres: parasympathetic, sympathetic and the antidromic fibres of the posterior spinal root. Among these parasympathetic

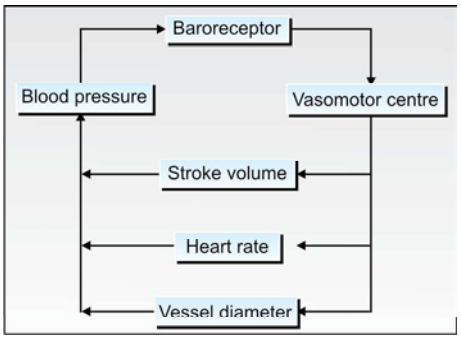


Fig. 5.44 : The feedback control of BP through baroreceptor

efferent is the vagus and control the cardiovascular system. The action of parasympathetic efferent is opposite to the sympathetic efferent. The sympathetic fibres are mostly vasoconstrictor in nature. But some sympathetic vasodilator fibres are also present. For instance, (i) the dilator fibres of the coronary vessels come through the sympathetic nerves, (ii) some sympatheitc dilator fibres also have been demonstrated in the peripheral nerves in human beings, (iii) stimulation of the last anterior thoracic root produces dilatation of the vessels of kidney, (iv) stimulation of the right splanchnic nerve sometimes causes vasodilatation and fall of blood pressure.

Some Common Cardiac Reflexes

Baroreceptor Reflex

This reflex controls the blood pressure via the circumferential and longitudinal stretching of the baroreceptor present in the carotid sinus and aortic arch. Increase in blood pressure stimulates these two receptors and send impulses along the glossopharyngeal and vagus nerve to the depressor centre, containing the nucleus of tractus solitarius, situated in the medullary cardiovascular centre (MVC). Inhibitory impulse then moves from the depressor centre to the pressor centre. Therefore, the response is decreased sympathetic activity and increased parasympathetic activity causing lowering of BP and decrease in heart rate. Typically this reflex works in the range varying between the systolic BP of 170 to 50 mm of Hg. When the systolic pressure falls below 50 mm of Hg then this compensatory mechanism fell. In chronic or poorly controlled hypertensive patients the upper set point of this reflex shifts upward.

Chemoreceptor reflex

This reflex control the arterial PO_2 and PCO_2 (pH status) via the chemoreceptors, present in the carotid and aortic bodies. Increased H^+ ($\uparrow PCO_2$) and hypoxia ($\downarrow PO_2$) stimulates these chemoreceptors and send impulses along the glossopharyngeal (nerve of Hering) and vagus nerve to the chemosensitive area of the medulla. This area then stimulate the respiratory centre and increase ventilation.

Bainbridge reflex

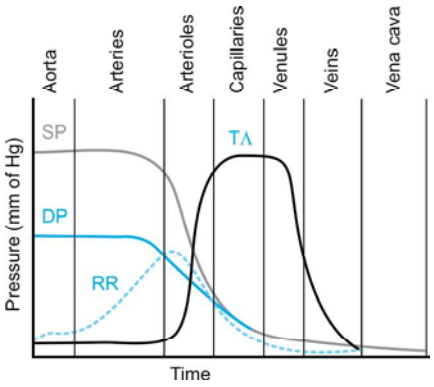
This is actually a baroreflex which involves the stretch receptors, located in the right atrial wall and cavoatrial junction. Increase in right sided filling pressure due to the increased intravascular volume stimulate these receptors and send impulses through the vagal afferent to inhibit the parasympathetic activity and increase the heart rate.

Bezold-Jarisch reflex

Here, the mechanoreceptors present in the left ventricular wall respond to the noxious ventricular stimuli and send impulses along the unmyelinated vagal afferent fibres. Thus, it increases the parasympathetic tone, leading to bradycardia, hypotension and coronary artery vasodilatation.

Valsalva Maneuver

If forced expiration against closed glottis is done - it increases the intrathoracic pressure - decreases venous return to heart - decreases CO - $\downarrow$BP - stimulation of baroreceptor - sympathetic stimulation - $\uparrow$HR. When glottis opens the reverse phenomenon occur and heart rate decrease (Fig. 5.45).



SP = Systolic pressure, DP = Diastolic pressure, TA = Total cross sectional area, RR = Relative resistance

Fig. 5.45: The changes in systolic pressure (SP), diastolic pressure (DP), total cross sectional area (TA) and resistance (RR) as the blood flows through the systemic circulation

Cushing's reflex

This reflex is manifested by increased HR, cardiac contractility and BP in response to increase intracranial pressure. It is the initial response of the reflex in an effort to increase the cerebral perfusion pressure. This is followed by reflex bradycardia mediated by baroreceptor within carotid sinus and aortic arch as a result of the increased peripheral vascular tone.

Oculo Cardiac reflex

This is discussed in the ophthalmic anaesthesia chapter.

CIRCULATION

An average adult has a blood volume of about 5 to 6 litres in his circulation and it is more or less equal to the resting cardiac output. But during heavy exercise this cardiac output may increase up to 25 litres per minute which indicates the increased circulation. The main purpose of this circulation is to supply adequate O_2, carbohydrate, fats, amino acids, hormones, immunological agents etc. to tissues and

to remove the waste products of its metabolism. But for this circulation only a little heart weighing about 300 gm acts as a pump and is highly adequate. Still no engineers has yet been able to develop such a pump with long term performance like it (Table 5.2).

Heart provides energy for circulation. Its phasic ejection of blood into the aorta produces the blood pressure and subsequently the pressure head. This pressure-head may be regarded as the cause of flow of blood or may be regarded as the potential energy for circulation.

During spinal or epidural anaesthesia, in the anaesthetized portion of the body both the pressure gradient (E) and the resistance (R) is reduced. But the ultimate flow (F) which depends on the relative ratio of E and R (according to the Ohm's law) is adequate even though the mean arterial pressure is low. Whereas in the unanaesthetized segment (i.e in the upper part of the body during lumbar spinal or epidural anaesthesia) resistance does not fall, even increases due to the compensatory elevated sympathetic activity in this portion of the body for the fall of systemic BP. Thus, the pressure head responsible for circulation in the unanaesthetized segment severly falls due to the fall of mean arterial pressure and thus blood flow (I) in this segment is tremendously jeopardised. So, BP should not be reduced below 20 to 25% of MAP to maintain adequate supply to the vital organs during central neuroaxial block.

There is different value of resistance in the different parts of the body. But to counter this variable resistance, exhibited in the different parts of the body, the pressure gradient must be adequate to maintain the circulation. Again as the cardiac output is pulsatile, so the pressure head and the flow into the arteries from the heart is also pulsatile. This means that the peripheral arterial system at the capillary level should possess a system of low impedence which will convert the pulsatile flow into the continuous flow. This is because the tissues themselves require a steady flow of blood through the capillaries, so as to benefit maximaly from the diffusion between the blood and the tissues.

On the otherhand, the resistance and subsequently the cardiac work can be lessened by increasing the radius of the vessels into which the blood is delivered. But this reduces the presure gradient. While, on the otherhand, adequate pressure gradient is required to provide an adequate flow. Alternatively, the cardiac work also can be reduced by considerably increasing the distensibility or stretching of the vascular system and this would decrease the pulsatile pressure and hence the impedence. However, such an increase in the distensibility of the vascular tree would prevent the immediate increase in CO and arterial pressure which is needed in biological emergencies and may be of imense important for survival of life. If the system took long time to inflate, then the urgent requirement for blood supply to the brain and the myocardium by increasing BP in emergencies circumstances could not be achieved, because for the pressure head available to such organs would rise too slowly, due to increased distensibility (Fig. 5.46).

So, some compromise should then have to be arrived. The arteries are distensible, but the arterioles convert the pulsatile ejection of heart into a steady flow to the tissue capillaries. The arterioles also offer resistance and step down the hydrostatic pressure within the capillaries. Veins have been equipped to serve as capacitance vessels. This is because by appropriate variation of their diameter the mobilization of blood to the heart are controlled in various circumstances.

The blood enters the right and left atrium at a pressure near about zero. The left ventricle pumps the blood into the aorta when the intraventricular pressure reaches a peak value during the cardiac contraction phase (systole) which is about 120 mm of Hg or so. During diastole the aortic pressure subsides to some 80 mm of Hg. This is due to the some elastic recoil property of the arterial system and due to the resistance to the outflow, offered by the peripheral arterioles. This combination of the elasticity and the resistance converts the pulsatile ejection flow of the heart into a steady outflow at the capillary level.

Table 5.2: Factors affecting the diameter of blood vessels

Factors	*Constriction*	*Dilatation*
Circulating hormone	1. Norepinephrine	1. Epinephrine (skin, muscle)
	2. Epinephrine (except skin and skeletal muscle)	2. Histamine
	3. Angiotensin - II	3. Substance - P
	4. Vasopressin	4. Vasoactive intestinal peptide (VIP)
	5. Neuropeptide - Y	5. Atrial natriuretic peptide (ANP)
	6. Na+ - K+ - ATPase inhibitor	
Local factors	1. Autoregulation	1. ↑CO_2, ↓O_2
	2. Cold	2. ↓pH
		3. ↑K+, ↑Lactate
		4. ↑Adenosine
		5. Heat
Neural factors	1. Sympathetic stimulation	1. Sympathetic inhibition
		2. Activation of cholinergic Vasodilator fibres to skeletal muscle (sympathetic and parasympathetic)
Endothelial factors	1. Endothelin	1. Kinius
	2. Thromboxane A2	2. NO
	3. Serotonin	3. Prostacyclin

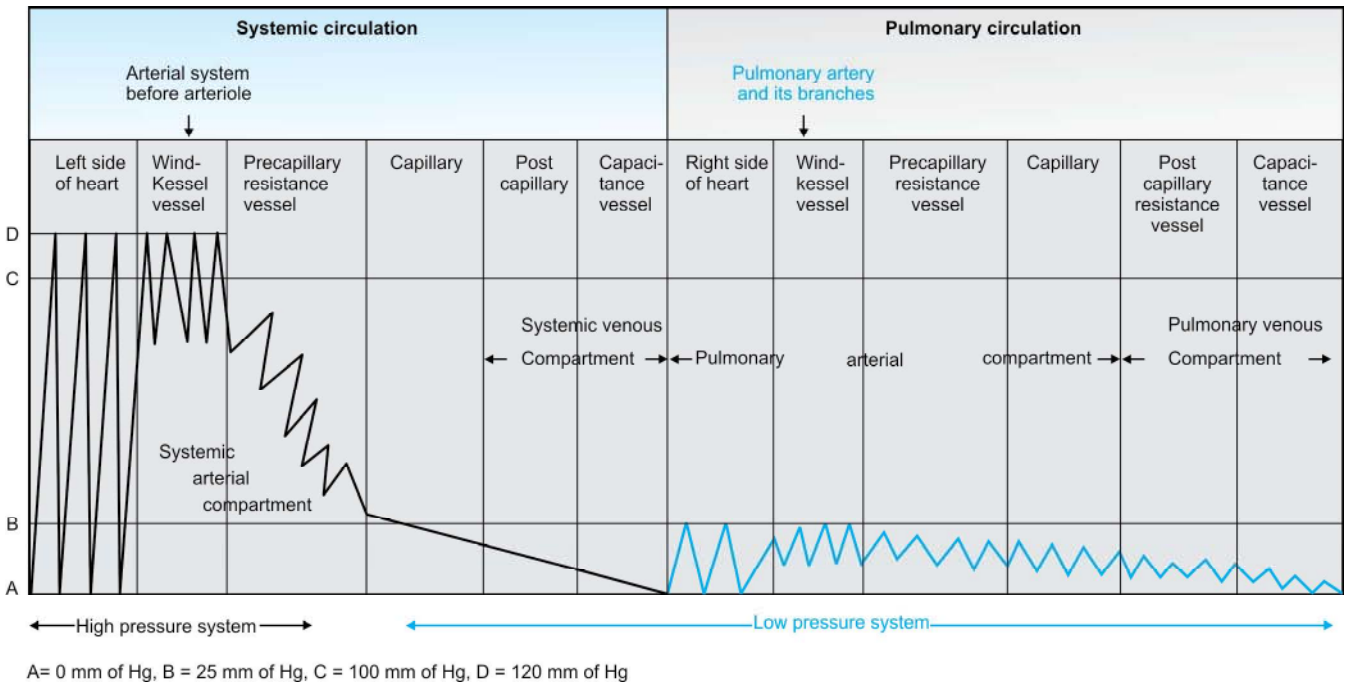


Fig. 5.46: Differential level of pressure in different systemic and pulmonary vessels

So the vascular system can be described as consisiting of

i. Wind Kessel vessels,
ii. Precapillary resistance vessels,
iii. Precapillary sphincters,
iv. Capillary,
v. Postcapillary resistance vessels,
vi. Capacitance vessels.

The concept of Wind Kessel vessels is represented by the aorta and its large branches which are highly elastic. Systolic ejection distends these vessels and during diastole the elastic recoil of these vessels substains the pressure gradient and renders the blood to flow foreward continuously to the periphery. The potential energy, stored during cardiac contraction in the elastic tissue of the aorta and its branches is reconverted into kinetic energy for the circulation during the diastolic phase. In disease process the degenerative changes in the media of the large vessels causes a loss of this arterial elasticity. Thus a high pulse pressure results owing to the lack of this Wind Kessel effect.

The precapillary resistance vessels (arterioles) provide the majority of the systemic vascular resistance. It exibits an efficient local myogenic control of their own vascular radius and on this local myogenic tone is superimposed an extrinsic neural control, effected by the sympathetic constrictor nerves and the parasympathetic vasodilator nerve. Normally these nerves discharge impulse at the frequence of 1 imp s^{-1}, but the rate of discharge may be increased to 10-16 imp s^{-1} in emergency circumstances (e.g. haemorrhage) and entirely suspended (e.g. in the skin vessels) during heat stress.

Blood vessels in the muscles represent by far the most important site for the peripheral resistance. This is due to the high degree of basal sympathetic myogenic tone in the vessels of the muscles. The blood flow in the muscle in resting man is only 2·7 ml/100gm/min. However, during exercise this flow may increase up to 50 to70 ml/100gm/min. This enormous increase in blood flow in the muscles is achieved by vasodilation of the arterioles and the precapillary sphincters, caused by local metabolites produced by the active tissue. But, it is not due to the neural factors. In resting muscle, however, the influence of sympathetic constrictor nerves on the precapillary sphincter is partly responsible for keeping the muscle blood flow at low values. In resting circumstances the skin vessels also manifest a high regional resistance.

The precapillary sphincters which are also themselves of a part of the precapillary resistance vessels, are particularly important in determining the size of the total capillary area. For example, any increase in the patency of the sphincters causes an increase in the number of capillaries open. The radius of the precapillary sphincters is controlled both by the neurogenic factors (sympathetic and parasympathetic) and by the local concentration of tissue metabolites.

Capillaries are consist of single layer of endothelial cells. This allows the exchange of substances across it's wall at the tissue level. Capillaries are not controlled by either nervous or metabolic factors. It is the alteration of the precapillay sphincter tone which determines the number of capillaries patent and hence the surface area, available for exchange between the blood and the interstitial fluid. In resting tissues

only some 20 to 25% of the total capillaries are patent. The onset of tissue activity is attened by relaxation of the sphincters and perhaps maximal opening of the capillary exchange bed.

The capacitance vessels are represented by the venular end of the capillary and the venous compartments. These contribute little to the over all resistance of the vascular circuit, but are important sites for the total capacity of the vascular system. Changes in the luminal configuration (from elliptical to circular cross-sectional profiles) and changes in myogenic tone of the veins, induced by sympathetic constrictor nerves, are of great importance in adjusting of the total capacity of the venous system.

Shunting of vessels occur only in few tissues - most notably in the skin. Such vessels bypass the capillaries and if patent they permit a rapid flow of blood. Their patency is controlled entirely by the sympathetic vasoconstrictor discharge. Thermal stress causes, via central nervous system, abolition of such discharge and the tremendous increase of the cutaneous blood flow which allows dissipation of heat from the body surface.

Wind Kessel concept

The arterial system is a very complex net work of elastic tubes which at the one end accepts the intermittent spurts of blood from the left ventricle of the heart and at the other end through its myriad of termination passes the blood by a steady stream into the resistance vessels, which perfuse the organs and tissues of the body. Thus, the arterial system acts both as conduit and as cushion when delivering the blood with a minimum fall in pressure to peripheral tissue (conduit function) and by reducing the flactuations of pressure imposed by intermittent ventricular action (cushioning function). Thus, this complex network of tubes can be viewed as a simple system, at least as first approximation. This simple idea is the Wind Kessel concept. This concept is based on the elastic property of the blood vessels. During systole the elasticity of the great vessels causes dilatation. This dilatation reduces the BP, resistance and the cardiac work. It also tries to reduce the pulsetality of the blood flow by absorbing the energy. But during diastole, the recoiling property of the elastic tissue helps for the forward movement of the blood during diastole and maintain the diastolic pressure. Thus, a continuous flow of blood is maintained in the tissues. This recoil effect is sometimes called the 'Windkessel effect' and the vessels are called the Windkessel vessels. The Windkessel is a German word which is used for an elastic reservoir. This elastic reservoir is responsible for continuous flow both during systole and diastole which appears to maintain a optimal function of the tissues. If an organ is perfused with a pump that delivers a pulsatile flow, then there would be gradual rise in vascular resistance and tissue perfusion fails.

The blood, forced into the aorta during systole not only moves the blood in the vessels forward, but also sets up a pressure wave on the wall of the vessel due to elastic property of it that travels along the arterial wall. This pressure wave expands the arterial wall and as it travels periphery along the wall of the large vessels, then this expansion is palpated as the pulse. The rate at which the pulse wave travels along the vessel wall is independent and of much higher than the velocity of the flow of blood. The velocity of pulse wave along the arterial wall is about 4 m/s in the aorta, 8 m/s in the large arteries and 16 m/s in the small arteries. Whereas, the velocity of the flow of blood in aorta is 40 cm/s. Actually the velocity of blood flow in aorta ranges from 120 cm/s during systole to negative value during diastole.

ARTERIAL BLOOD PRESSURE

The blood pressure is defined as the lateral pressure which is exerted by blood on the wall of the vessels, while flowing through it. There are four common terms regarding the blood pressure.

i. Systolic pressure - maximum pressure in artery during the systole of cardiac cycle.
ii. Diastolic pressure - minimum pressure in artery during the diastole of cardiac cycle.
iii. Pulse pressure: the difference between the systolic and diastolic pressure.
iv. Mean arterial pressure (MAP): It is the average pressure throughout a single cardiac cycle, i.e. during both systole and diastole. So, it depends on the duration of the cardiac cycle and indicates the arithmetic mean of the systolic and diastolic pressure throughout the cycle. Thus, as the systole is shorter than the diastole, so the mean pressure is slightly less than the value which is halfway between the systolic and diastolic pressure. It can actually be determined by integrating the area of pressure curve which is shown in the figure by the shaded area. However, a close approximation to the mean arterial pressure may be obtained by adding the diastolic pressure with one third of the pulse pressure (Fig. 5.47).

The blood pressure falls very slightly in the large and medium sized arteries though their resistance is small. This is because the flow of blood is high in these vessels due to low resistance. But it falls rapidly in the small arteries and arteriols though they are the main sites of the SVR against which the heart has to pump. Here, yet the resistance is high, but still the pressure is low. This is becuase due to high resistance, flow of blood is low. The mean pressure at the end of the arterioles is 30 to 38 mm of Hg. Pulse pressure also declines rapidly to about 5 mm of Hg at the end of the arterioles. The magnitude of the drop of pressure along the arterioles also varies considerably depending on whether they are constricted or dilated.

Thus, in summary, it is stated that the pressure in the aorta, brachial and other large arteries in a young human adult rises to a peak value (systolic pressure) of about 120 mm of Hg and falls to a minimum value (diastolic pressure) of about 70 mm of Hg during each cardiac diastole. So, the arterial pressure is conventionally written as systolic pressure over diastolic pressure e.g 120/70 mm of Hg. In SI unit, one millimeter of mercury equals 0·133 kPa. So in this unit system, the value of arterial pressure is 16/9·3 kPa.

The height of the systolic pressure indicates :

i. The cardiac output,
ii. The degree of pressure which the arterial walls have to withstand. Diastolic pressure is the measure of peripheral resiatance. It indicates the constant load against which heart has to work.
iii. The extent of work done by the heart.

The height of the diastolic pressure indicates:

i. The constant load against which heart has to work,
ii. The measure of peripheral resistance.

Factors controlling the blood pressure:

There are two main determining factors which can control the blood pressure. These are cardiac output (CO) and systemic vascular resistance (SVR). So, any alteration of CO and SVR will alter the BP according to Ohm's law. Cardiac output again depends on the venous return to heart, force of myocardial contraction or contractility (pumping action of the heart), frequency of contraction or heart rate and ventricular size. Venous return (preload) again depends on the blood volume and the venoconstriction or dilatation. Cardiac output depnding on the factors such as cardiac contractility and the frequency of contraction or heart rate is already discussed previously under the heading of cardiac output. Ventricular size also determines the cardiac output. For example a hypertrophied heart prevents proper diastolic filling and reduces the cardiac output. SVR is also an important determining factor of blood pressure. The chief seat of SVR is the arterioles. SVR depends on : (i) the velocity of blood, (ii) the viscosity of blood, (iii) the elasticity of arterial walls, (iv) the radius of the lumen and (v) the length of the vessel. For a given elasticity of the arterial wall and velocity of blood, the other factors responsible for SVR can be represented by Poiseuille's law.

According to Poiseuille's law the resistance in any blood vessels varies directly with the viscosity of the blood and the length of the blood vessel and inversely with the fourth power of the radius of the blood vessel. Thus it can be represented by the formula :

$$R = \frac{8\eta L}{\pi r^4}$$

Here R stands for the resistance to blood flow, η for the viscocity of blood, l for the length of blood vessel, r for the radius of the blood vessel. The value of π is 3·14 and 8 is the Hagen's integration factor.

According to Ohm's law the relationship between peripheral resistance (PR), cardiac output (CO) and blood pressure is

$BP \propto CO \times PR$

$CO \propto BP / PR$

$PR \propto BP / XO$

6 Electrocardiogram

INTRODUCTION

During each contraction of heart an impulse is generated in the SA node. It is then simultaneously transmitted to the AV node, bundle of His, two bundle branches, Purkinje fibres, ventricular muscle fibres and lastly to the surrounding body tissues in which the heart is bathed in. Thus, an electrical impulse that is initiated in the cardiac muscle is ultimately transmitted throughout the whole body tissues. So, if two suitable electrodes (or leads) are placed on the surface of the body, opposite to the heart and are connected to a very sensitive galvanometer with a recording device, then this electrical potential can easily be recorded. This record is called the electrocardiogram and the machine by which the electrocardiogram is recorded is called the electrocardiograph. However, the process of making graphic records of the variations in electrical potential, caused by the electrical activity of the heart muscles on the body surface is called the Electrocardiography. Practically the electrocardiograph is a sophisticated galvanometer where a sensitive electromagnet detects and records the changes of electrical potential which is generated in the heart and transmitted throughout the whole body. Thus, for detection of changes in the cardiac electrical potential, two electrodes or leads (one +ve and another –ve) are needed. So, the theoretical straight line joining the two electrodes or leads is called the lead axis. However, this should not be confused with the electrical axis of the heart or the cardiac axis.

ECG PAPER (FIG. 6.1)

The electrocardiographic paper is divided into 1 mm small and 5 mm large squares, both horizontally and vertically. Therefore, within one large square there are 5 small squares accomodated both horizontally and vertically. Hence, every large square is 5 mm in length, both vertically and horizontally.

After every 15 large squares, there is a vertical line at the upper border of the ECG paper. Horizontally, the squares measure the time in seconds and vertically they measure the amplitude of deflection in millivolt. Conventionally, the electrocardiogram is always recorded at a paper speed of 5 large squares or 25 mm (25 small squares) per second. So, every small square of 1 mm measures a time of 1/25 seconds or 0.04 seconds and one large square is 0.2 seconds ($0.4 \times 5 = 0.2$). Vertically, one small square measures a deflection of 1 millivolt.

ELECTROCARDIOGRAPHIC LEADS

An electrocardiographic lead can be placed on the body in respect to any three dimensional relationship of the heart, such as frontal (coronal), sagittal and horizontal plane. But, practically we use only 12 conventional leads in frontal and horizontal planes (6 leads in the frontal plane and 6 leads in the horizontal plane). Other different types of leads which are used in different planes in special conditions are discussed later (Fig. 6.2).

So, the leads can be classifed according to the planes where they are situated. These are frontal plane leads, horizontal plane leads and sagittal plane leads. (Fig. 6.3).

Frontal or Coronal Plane Leads

The frontal plane leads consist of standard leads I, II, III and the leads aVR, aVL, aVF.

These leads are oriented or situated on the frontal or coronal plane of the body and looks at the heart from its sides (Fig. 6.4).

The sides or the angles from which it looks at the heart depends upon the lead in question. Thus, the lead aVR looks at the cavity of the heart from patient's right shoulder. Whereas, the lead aVL looks at the cavity of the heart from the left shoulder and the lead aVF looks directly up towards the heart from the foot end of the patient (Fig. 6.5).

In the standard lead I the lead is derived from the placement of positive electrode on the left arm and negative electrode on the right arm. In the standard lead II,

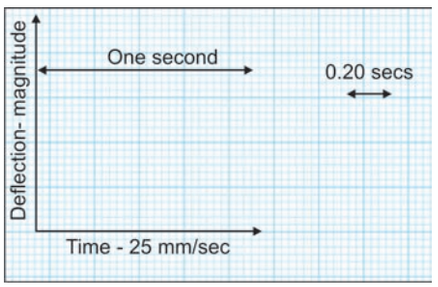


Fig. 6.1: An electrocardiograph paper with a time scale at a recording speed of 25 mm per second

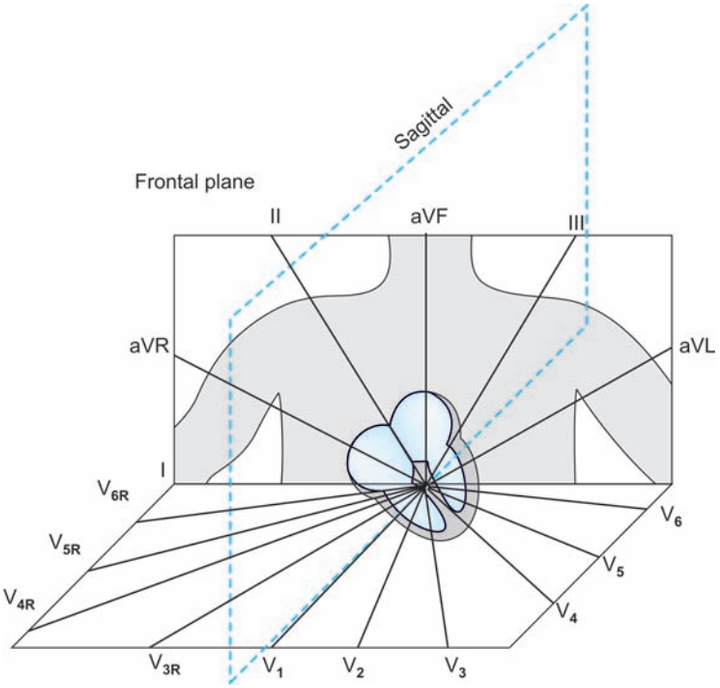


Fig. 6.2: The frontal (coronal) and the horizontal plane leads

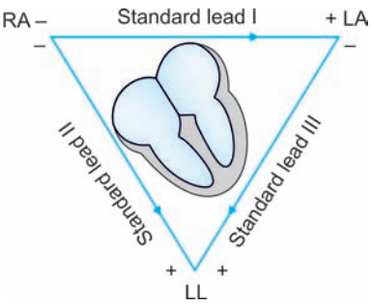


Fig. 6.5: Einthoven's triangle

also called the bipolar leads and are the original leads described by Einthoven. All the ECG machines also have a connection with right leg by electrode and this acts as a ground wire and plays no role in the production of ECG.

Horizontal Plane Leads

These leads are situated or oriented on the horizontal or the transverse plane of the heart and consists of all the precordial chest leads, such as: leads V_1-V_9,V_{3R-9R}, $3V_{1-9}$, $2V_{1-9}$.

Sagittal Plane Leads

These leads are situated on the sagittal plane of the heart and measure the electrical potential of cardiac activity in the sagittal plane. An example of the sagittal plane lead is the oesophageal lead.

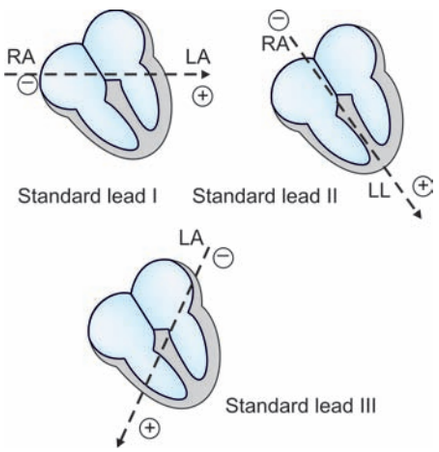


Fig. 6.3: The different electrode placements in standard leads I, II and III. The positive poles in standard leads I,II and III are located respectively at the left arm (LA), left leg (LL) and right leg (LL).The three axes formed by these three leads form a triangle.As the electrodes are situated at equidistant from the heart, so it is also considered that the axes are also situated equidistant from the heart and the heart is located at the centre of the triangle formed by these three axes. This equilateral triangle formed by these three axes is called the Einthoven's triangle

the lead is derived from the placement of positive electrode on the left foot and negative electrode on the right arm. In the standard lead III, the lead is derived from the placement of negative electrode on the left arm and positive electrode on the left foot. These standard I, II and III leads are

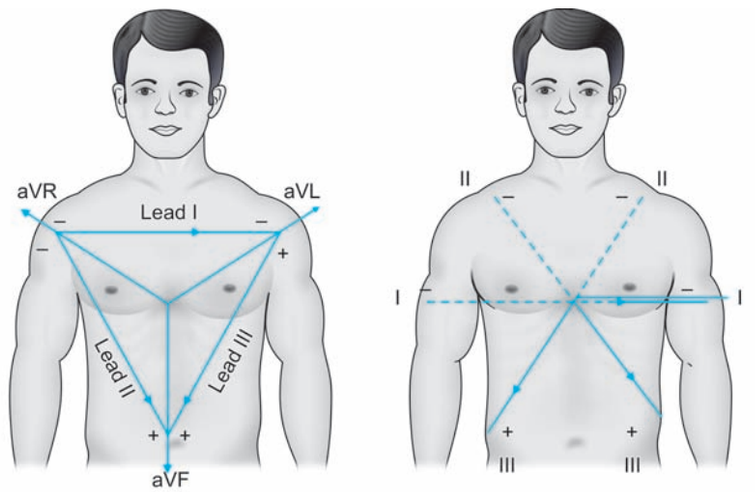


Fig. 6.4: Einthoven's triangle and the frontal plane bipolar leads

According to the polarity the leads can also be classified into two groups: (i) Bipolar leads and (ii) Unipolar leads (Fig. 6.6A and B).

Bipolar leads

The bipolar leads are the original standard leads, selected by Einthoven to record the electrical potential of heart and are situated in the frontal plane. These are leads I, II and III. Actually, the bipolar leads represent the difference of electrical potential between 2 selected sites. Lead I gives the difference of electrical potential between the left arm and the right arm (LA-RA) and the lead axis is directed from RA to LA. Lead II gives the electrical potential difference between the left leg and the right arm (LL-RA) and the lead axis is directed from RA to LL. Lead III shows the potential difference between the left leg and the left arm (LL-LA) and the lead axis is directed from the LA to LL.

The relationship of electrical potential between these 3 bipolar leads is expressed algebraically by the Einthoven's equation. The equation states that:

Lead II = Lead I + Lead III

i.e. amplitude of any deflection in lead II is equivalent to the sum of the amplitude of deflections in lead I and II.

Unipolar leads

The use of unipolar leads in clinical practice was introduced by Wilson in 1932.

The examples of unipolar leads are:

i. Unipolar extremity or limb leads: VR, VL, VF
ii. Unipolar chest leads: V_1 , V_2 , V_3 , V_4, V_5 , V_6 , V_7 , V_8 ,V_9 , $V_{3R–9R}$, $3V_{1–9}$, $2V_{1–9}$, $6V_{1–9}$, $3V_{3R–9R}$.
iii. Oesophageal leads.
iv. Unipolar intracardiac leads.

All the unipolar extremity or limb leads and chest leads are designated as V and unipolar oesophageal leads are designated as E.

Unipolar extremity or limb leads

There are three unipolar limb leads. These are: (i) Right arm (VR) lead, (ii) Left arm (VL) lead, (iii) Left foot (VF) lead, where V denotes unipolarity. In these unipolar limb leads among the two electrodes, one is an exploring electrode and acts as a positive end. The negative end of that lead is not actually negative, but is at the '0' potential. So, these leads are called the unipolar leads and they actually measure or represent the amount of potential at that point of heart for a given lead and not the difference of electrical potential (where as the bipolar leads measure the potential difference) between the two electrodes of the lead. But, technically we may call this unipolar lead as bipolar one, because it has two poles (Fig. 6.7).

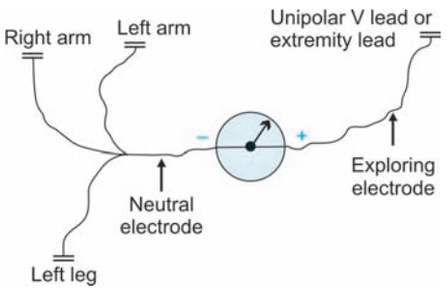


Fig. 6.7: The derivation of the unipolar (chest and extrimity) leads. The neutral limb is connected to the negative pole of the galvanometer. The exploring electrode is connected to the positive pole of the galvanometer

The mechanism by which the unipolar limb lead works is described below. It is considered that the heart lies at the centre of an equilateral triangle, called the Einthoven's triangle which is formed by the three standard limb leads I, II and III. According to Einthoven, the sum of the potential differences of these three leads at any instant is zero (Fig. 6.8).

Therefore, RA + LA + LL = 0

Hence, when these three leads are at first connected together and then finally to one end of a galvanometer and the other end of the galvanometer is attached to the exploring electrode, (now this is how the

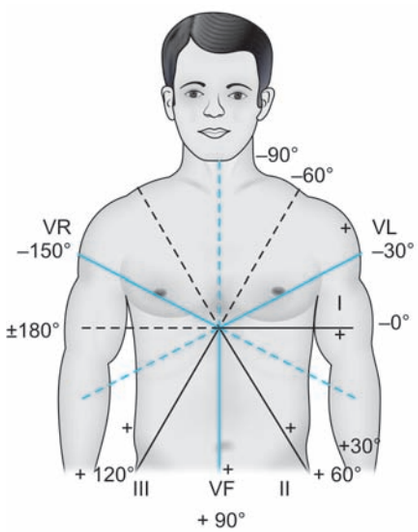


Fig. 6.6A: Total frontal (Coronal) plane leads-both bipolar and unipolar limb leads

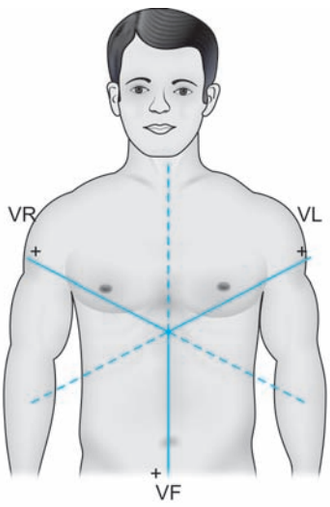


Fig. 6.6B: Only frontal plane unipolar leads

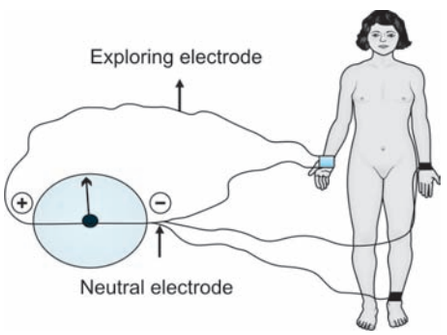


Fig. 6.8: The derivation of the lead aVR. Here the right arm has connections from both the neutral and the exploring electrodes

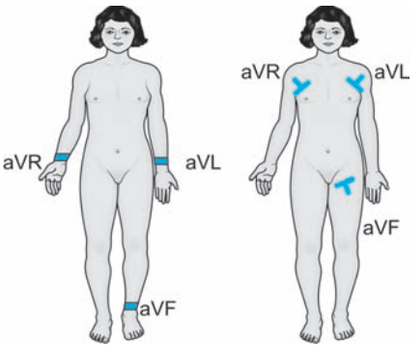


Fig. 6.9: Diagrammatic representation of the unipolar extremity leads

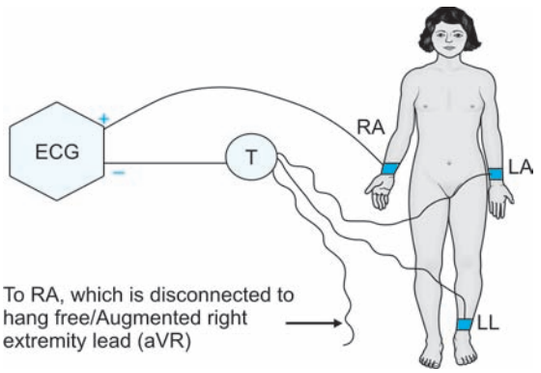


Fig. 6.10: The principle of augmented extremity leads. All modern ECG machines are so designed that the augmented extremity leads can be taken with the same electrode attachment on the body which are used for the standard leads and chest leads by just turning the selector dial to aVR, aVL and aVF. Unipolar chest leads are also taken by applying the electrodes on the chest to any desired position and turning the selector dial of the ECG machine to the V position. If a modern ECG machine is not available, an ECG machine that can record standard leads like I, II, III can also be used to obtain augmented extre- mity leads satisfactorily. To get this, one first constructs an indifferent electrode T by attaching RA, LA and LL electrodes together and then to the negative pole of the machine. Then the connection of the neutral terminal to the limb which is being tested, is disconnected and is allowed to hang free and the exploring positive side of the machine is attached to that limb. This will produce an augmented version of the unipolar limb leads

unipolar lead is formed), then unipolar limb lead will be formed and the machine will record the true potential of body tissue under that exploring electrode (Fig. 6.9).

However, using the above technique the potential obtained by the exploring electrode of unipolar limb lead is of low voltage. This low voltage can be augmented by omiting the connection of the neutral terminal to the limb which is being tested and allowing it to hang free. Then, the unipolar limb lead is called as an augmented limb lead and designated as aVR, aVL and aVF (where 'a' stands for the word augmented) (Fig. 6.10).

Lead aVR (or AVR) is the augmented ('a' or 'A') unipolar (V) right arm (R) lead, and is usually oriented towards the cavity of the heart from the right shoulder. So all the deflections, such as: the P, QRS and T are normally negative in this lead. This is because the vector of electrical current making all these waves pass away from this lead. The aVL (AVL) is the augmented unipolar left arm lead, and is oriented to the anterolateral or superior surface of the heart from the left shoulder. Lead aVF (AVF) is the augmented unipolar left leg lead and is oriented to the inferior surface of the heart from the left leg.

Unipolar oesophageal leads

The unipolar oesophageal leads are taken from within the oesophagus. A nasal catheter which is threaded with a wire and having an electrode attached to its tip is passed through the nares into the oesophagus. Using this as exploring terminal and the zero potential at the other terminal, an unipolar oesophageal lead can be obtained. This is designated as the E lead. The nomenclature of the different types of oesophageal lead is derived as the distance from the tip of the nares to the position of electrode in oesophagus in centimetres. Thus, E_{50} represents an unipolar oesophageal lead at a distance of 50 cm from the nares. Lead $E_{40\text{-}50}$ usually reflects the posterior surface of the left ventricle. The $E_{15\text{-}25}$ reflects the atrial area and $E_{25\text{-}35}$ reflects the region of the atrioventricular groove.

The oesophageal leads are especially useful in recording the atrial complexes which are greatly magnified at this location and also in exploring the posterior surface of the left ventricle.

Unipolar chest leads

The unipolar chest leads are also called the precordial leads and constitute the horizontal plane leads. It is designated as 'V' due to the unipolarity. The landmarks for placement of precordial electrodes are:

V_1: Fourth intercostal space at the right sternal border.

V_2: Fourth intercostal space at the left sternal border

V_3: Equidistant between V_2 and V_4.

V_4: Fifth intercostal space in the left midclavicular line.

All subsequent chest leads ($V_{5\text{-}9}$) are taken in the same horizontal plane as V_4.

V_5: Anterior axillary line.

V_6: Midaxillary line.

V_7: Posterior axillary line.

V_8: Posterior scapular line.

V_9: Left border of the spine.

$V_{3R\text{-}9R}$: Taken on the right side of the chest in the same location as the left sided leads $V_{3\text{-}9}$. V_{2R} is therefore the same as V_1.

$3V_{1\text{-}9}$: Taken as the left $V_{1\text{-}9}$ lead but in the 3rd intercostal space. The same terminology can be applied to leads taken in other intercostal spaces e.g., $2V_{1\text{-}9}$, $6V_{1\text{-}9}$, etc (Fig. 6.11).

Unipolar intracardiac leads

This can be constituted by an electrode, contained in a cardiac catheter and the ECG can then be recorded from the various intracardiac chambers, such as: right atrium and right ventricle. But use of this

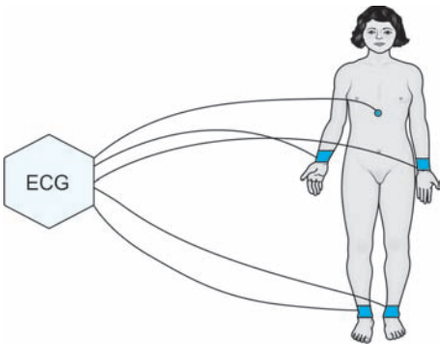


Fig. 6.11: Unipolar chest (precordial) leads in a modern ECG equipment. It records the potential difference in horizontal plane, without being influenced by the actual potential from an indifferent electrode. The unipolar precordial lead does not record only the electrical potential from a small area of the underlying myocardium, but also records all the electrical events of the entire cardiac cycle, as viewed from the selected lead site

technique is limited to cardiac laboratories only.

BASIC MECHANISM OF ACTION OF AN ELECTROCARDIOGRAPH (FIG. 6.12)

In resting state like all other cells of the body, the cardiac muscle cells are also in a polarised state, i.e, the outer surface of the cell is + vely charged and the inner surface of the cell is –vely charged. If the two electrodes of a galvanometer are attached at the opposite ends on the outer surface of a resting cell, then no deflection will occur. This is because the entire outer surface of the muscle cell has the same charge and the measured potential difference will be zero.

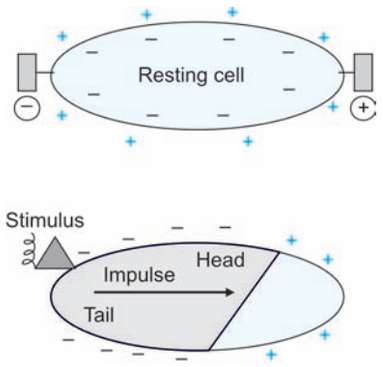


Fig. 6.12: Electrical potential of a resting and a stimulated muscle

But, when the muscle cell is stimulated or activated, then the surface of the stimulated portion of the cell becomes electrically negative (as the positive charges pass into the cell). This process is termed as depolarisation. Then, an impulse of this negative charge will progress along the outer surface towards the other end of the muscle cell which is still positive (Fig. 6.13).

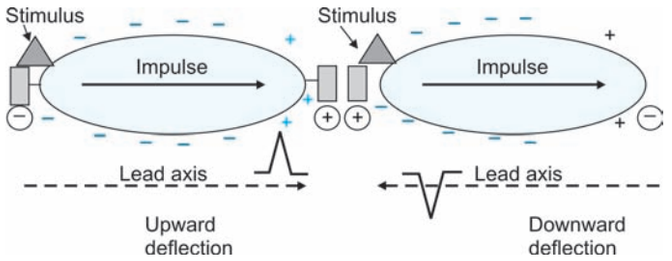


Fig. 6.13: Process of depolarisation

When this impulse passes through many resting (polarized) cells of an organ, then those cells which are initially activated or depolarised will have negative charges on their surface, while those not yet activated will have positive charges on their surface. Therefore, a sum-up potential difference of electrical charges will exist between the surface of the excitable cells and the surface of the adjacent resting cells of the same organ. So, a current will flow from the depolarised area to the polarized area of the organ.

Now, this flow of current will have a positive head and a negative tail. So the positive pole of a bipolar lead or a unipolar lead, oriented towards the oncoming head, will record a positive or upward deflection.

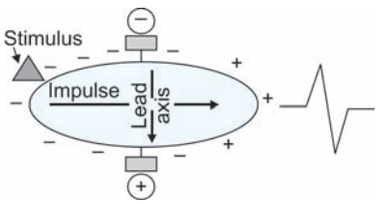


Fig. 6.14: Process of downward deflection

On the otherhand if the positive pole of a bipolar lead or a unipolar lead is oriented towards the receeding tail-end of the flow of curent then it will record a negative or downward deflection in ECG (Fig. 6.14).

Therefore, the direction in which a impulse spreads through the muscle and the position of the positive electrode of a lead in relation to the direction of the spread of the impulse will determine the positive or negative deflection of the ECG tracing. Thus, for example, an upright QRS complex in any particular lead means the flow of current during ventricular depolarisation (i.e. the QRS vector) is directed towards the positive pole of that particular lead. Alternatively, if the QRS is inverted in any particular lead, it means that the QRS vector is directed away from the positive pole of that particular lead. This principle is also applied to all the electrocardiographic deflections, such as: P, T, U and the ST segment (if it is deviated).

If the electrodes of a lead is placed on the mid portion of the path or passage of the current, then the deflection will be biphasic. Because, the initial positive deflection will be upward due to the advancing head of the flow of current and the second negative deflection will be downward due to its receeding tail.

If the two muscle mass is stimulated in the middle with the positive electrodes at either end of the muscle, then both the electrodes will show a positive deflection of depolarisation of equal magnitude. This is because both the electrodes recognise the head of the passing current (Figs 6.15 and 6.16).

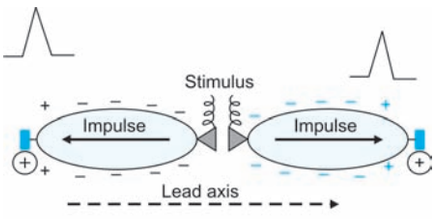


Fig. 6.15: Two muscle masses of equal size

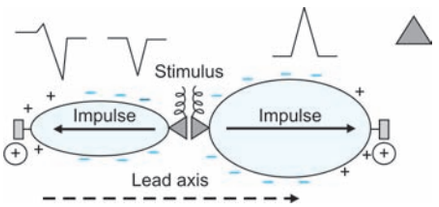


Fig. 6.16: Two muscle masses of different sizes

If the two muscle masses are of markedly different sizes (analogous to the right and left ventricle) and are stimulated at a central point, then a large positive deflection will be produced by the positive electrode over the larger muscle mass and a small positive deflection, followed by a deep negative deflection or a entirely negative deflection will be produced by the electrode over the smaller muscle mass.

This is because depolarization of the smaller muscle mass will be masked by the larger muscle mass and the electrode over the smaller muscle mass will partially or fully recognise the larger muscle mass (Fig. 6.17).

The return of the stimulated muscle mass to the resting state is known as repolarisation. If repolarisation occurs in the same direction as that of depolarisation, then deflection on the galvanometer will be opposite to that of depolarization. But, if the repolarisation occurs in the opposite direction to that of depolarisation, then the deflection will be same as that of depolarization. Since this flow of current is electromagnetic in nature like depolarisation, so it has also a vector. Thus, it also possesses both magnitude and direction (Fig. 6.18).

It must be emphasized that since the electrical activity usually occurs synchronously in more than one region of the heart, so the electrocardiograph at any given moment senses or reflects the net or resultant force of several small synchronous electrical activity, travelling in different directions.

GENESIS OF P WAVE

The P wave is the deflection produced by atrial depolarisation. The initial depolarisation in heart begins in the SA node. But, this initial depolarisation of the SA node cannot be recorded in the clinical ECG. Then the impulse generated from the SA node traverses to the AV node through three internodal pathways (Bachmann, Wenckebach, Thorel) and depolarises the whole atrium, producing the whole atrial contraction and P wave. As the SA node is situated in the right atrium, so the right atrial activation begins first which is followed by the left atrial activation. Hence the P wave is a composit deflection of both the right and left atrial activation. The right atrial activation constitutes the ascending limb and the left atrial activation constitutes the descending limb of the P wave (Fig. 6.19).

There is no clear and normal range for P wave height, but any P wave over 2.5 mm (2.5 small squares) in height should arouse suspicion.

Normally, the width of the P wave is < 0.08 seconds (2 small squares). But, the maximum duration of the P wave is 0.11 seconds (Fig. 6.20).

Normally, the vector of the P wave (the direction of the current flowing from

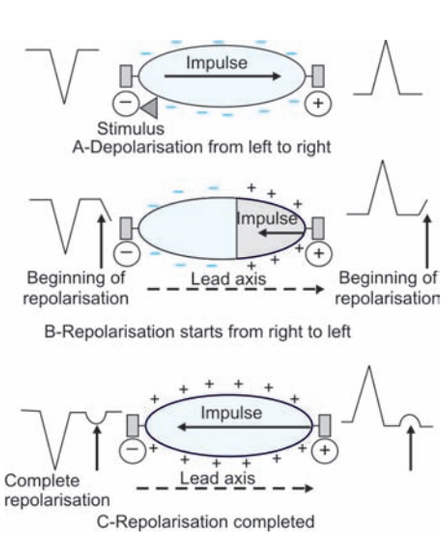


Fig. 6.17: Repolarisation in the direction opposite to that of depolarisation

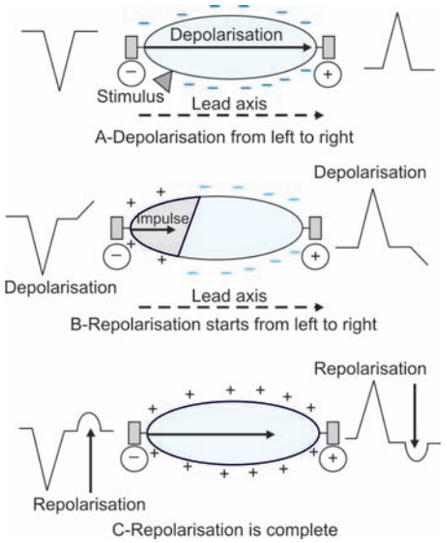
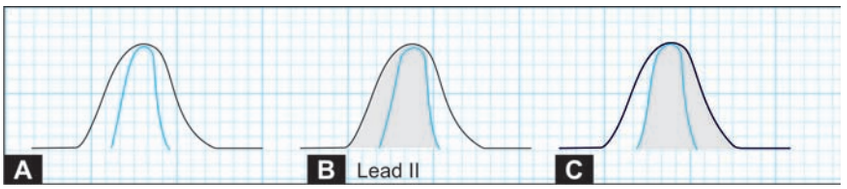
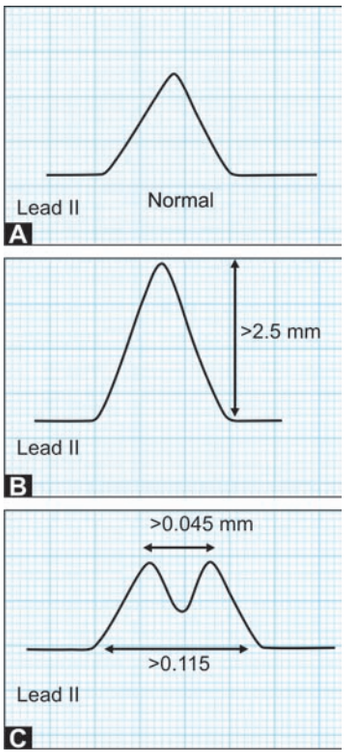


Fig. 6.18: Repolarisation occurs in the same plane as depolarisation



Figs 6.19A to C: The formation of P wave in lead II ECG: **A.** A normal composite P wave. **B.** Contribution of right atrial activation(shaded part) **C.** Contribution of left atrial activation (shaded part)



Figs 6.20A to C: The picture shows-
A- Normal P wave in lead II.
B- P wave due to right atrial enlargement in lead II.
C- P wave due to left atrial enlargement in lead II

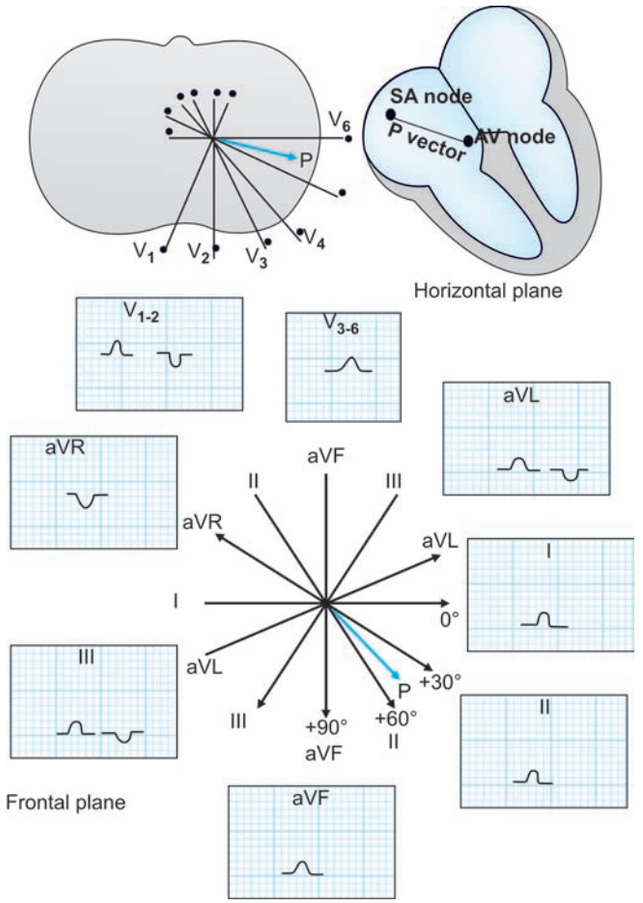


Fig. 6.21: The direction of the normal P vector in the frontal and horizontal planes. The normal P vector in the frontal plane is between 0° and +90°. So, a P vector between 0° and +30° will produce an inverted P wave in lead III and a P vector past +60° will produce an inverted P wave in lead aVL. The amount of clockwise or anticlockwise orientation of the P vector in the horizontal plane will also determine whether the P wave will be upright or inverted in lead V_1 to V_6

the SA node to the AV node) is oriented inferiorly (in the frontal plane) and to the left and slightly anterior (in the horizontal plane). Therefore, the polarity of P wave in any given lead will depend on the relation of positive electrode of that lead to the direction of this vector. In the frontal plane, the P wave vector is usually aligned or parallel to the standard lead II. So, the P wave is best seen and studied in standard lead II (Fig. 6.21).

In other leads of the frontal plane, such as in lead I and aVF and in some leads of the horizontal planes, such as in: V_3-V_6 leads (in the horizontal plane, the P vector is directed leftwards and anteriorly) the P vector is directed toward the positive pole of these leads. So, in the above mentioned leads the P wave is upright. The normal P wave axis is directed between +45° to +65° , clockwise. Hence, a P wave axis of less than +45° is reflected as left axis deviation and a P wave axis of greater than +70° is reflected as right axis deviation. In left axis deviation when the P wave is directed towards the 0°, then it will be best aligned to the standard lead I and is best evaluated in this lead.

Alternatively, during right axis deviation of the P wave when it is directed to the region of +80° to +90° , it is most aligned to the lead aVF and so in this circumstances it is best evaluated in this lead. In lead aVR the P wave is always inverted, as the direction of the vector of P wave is always away from this unipolar lead. In lead III, aVL,V_1 and V_2 the P wave may be upright, biphasic, flat or inverted, according to the direction of the P wave (Fig. 6.22).

The P wave in lead V_1 is usually biphasic, having an initial positive and terminal negative deflection. The explanation for this biphasic P wave in lead I is as follows: The right atrium with the SA node which is activated first is situated anteriorly and to the right of the left atrium. So, the vector of right atrial activation is directed towards the lead V_1. Whereas, the vector of left atrial activation which is situated to the left and is posterior to the right atrium is directed away from the axis of lead V_1.Thus, the P wave in lead V_1 shows the initial upward deflection due to right atrial activation and later downward deflection due to left atrial activation. The P wave in lead V_1 is thus a composite deflection

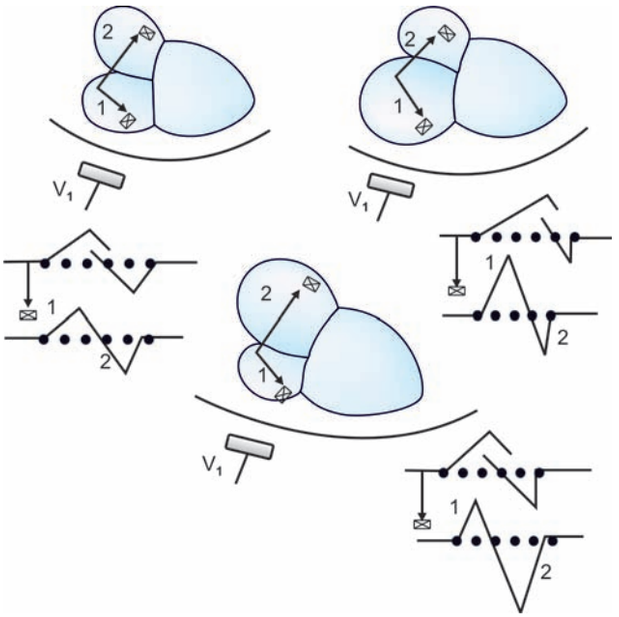
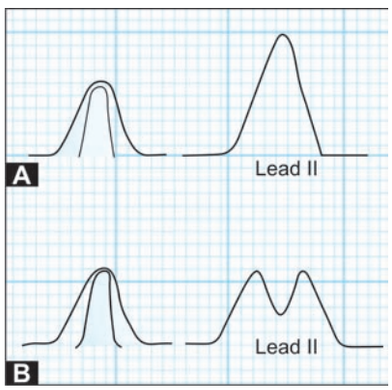


Fig. 6.22: A. Illustrates the normal activation of both the atria, (when they are normal in size), the P vector and its effects on V_1. B. The effect of right atrial enlargement in lead V_1. C. The effect of left atrial enlargement in lead V_1.

of both the right and left atrial activation, making it biphasic.

The P waves in the oesophageal leads have greater amplitude than any other lead of the conventional 12 lead ECG. As the P vector is directed inferiorly in the frontal plane, so the P wave will be inverted in high oesophageal leads (E_{10-25}) i.e, above the AV groove. In lower oesophageal leads (E_{35-50}), the P wave will be upright. In the region of AV groove (E_{25-35}), the P wave will be large, sharply peaked, a biphasic complex, simulating a RS complex of ventricular depolarisation.



Figs 6.23A and B: The change of a P wave in standard lead II
A. Right atrial enlargement
B. Left atrial enlargement

P Wave in Atrial Hypertrophy

The P wave in left atrial hypertrophy is called the 'P-mitrale'. It is characterised by a broad and notched wave. Normally it is best seen in lead II, when the P wave axis is directed to +50°. But if P wave axis is deviated towards 0° or further leftwards (a not uncommon occurence in the left atrial enlargement), it will then be mostly aligned with the standard lead I and the lead aVL, and 'P mitrale' will be seen in these leads (Fig. 6.23).

The broad P wave in left atrial hypertrophy is due to the delayed activation of the hypertrophied or enlarged left atrium (separation of right and left atrial component in the genesis of P wave). In lead V_1 a wide, slurred, biphasic P wave is characteristically seen in left atrial hypertrophy where the downward component of the P wave is most prominent. Clinically, the left atrial enlargement is found in systemic hypertension concomitant with left ventricular hypertrophy, mitral stenosis, mitral incompetence, etc.

The right atrial hypertrophy is characterised by tall, slender, peaked P waves called 'P-pulmonalae' and is found in lead II, III and lead aVF. Right atrial hypertrophy is found in chronic obstructive pulmonary diseases.

Completely Absent P Wave

There are two reasons for the P waves to be absent from ECG. The first is when there is not a single coordinated full atrial activity, regulated by the SA node. So, as the P waves are not being formed are completely absent. The second is when the P waves are present but are just not clearly seen. (Fig. 6.24).

The lack of SA node regulated and a co-ordinated full atrial activity occurs in atrial fibrillation, and this is the commonest reason for the absence of P waves in ECG. In such situation instead of a definite P wave, chaotic atrial activity produces a low amplitude oscillatory or fibrillatory waves in the ECG. These are called the fibrillatory or 'f' waves. So the atrial fibrillation can be recognised by the absence of P wave, presence of fibrillatory waves and the erratic formation of the QRS complexes. On the otherhand the configuration of QRS complexes is normal, unless there is concomitant bundle branch block. The ECG manifestation of atrial fibrillation is best seen in the frontal plane leads, especially standard leads II, III and aVF. The fibrillatory or 'f' waves are usually of negative deflection in these leads, reflecting caudal to cranial atrial activation. In the horizontal lead V_1, in contrast to the

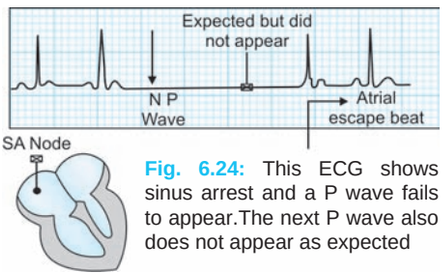
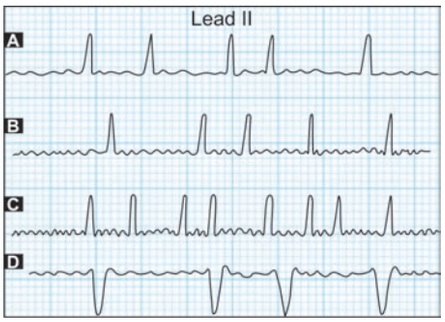


Fig. 6.24: This ECG shows sinus arrest and a P wave fails to appear.The next P wave also does not appear as expected



Figs 6.25A to D: ECG tracings in lead II shows the various manifestations of atrial fibrillation
A. Long standing atrial fibrillation, with a smooth slightly undulating baseline and slow irregular ventricular response.
B. Coarser and more recent fibrillation with relatively slow ventricular response. Here, the baseline is irregular and ragged.
C. The same features as B, but with a rapid ventricular response.
C. Atrial fibrillation with complete AV block

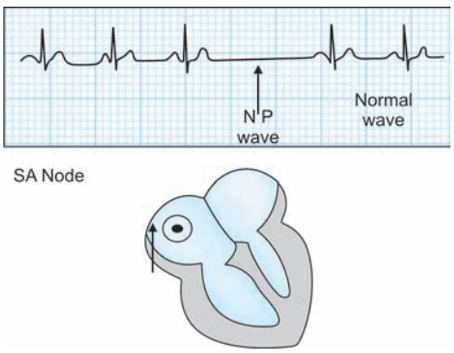


Fig. 6.26: This ECG shows sinoatrial block. P wave fails to appear, but next wave appears where expected

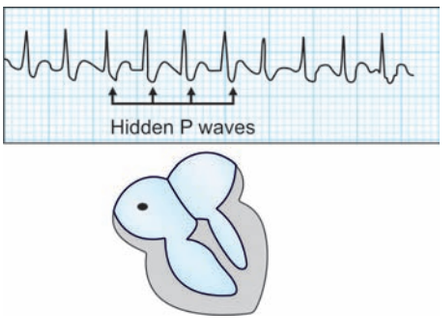


Fig. 6.28: This ECG shows AV junctional tachycardia. Heart rate is 130/min with narrow QRS complexes. These narrow QRS complexes are due to AV conduction through the His-Purkinje system. P waves are hidden within the ST segments

frontal plane leads, the P wave usually shows an isoelectric feature or are usually masked by the f waves.

The P waves will also be completely absent if there is prolonged period of sinus arrest or sino-atrial block. In these conditions the atrial activation does not occur, because SA node either fails to depolarise (sinus arrest) or fails to transmit the depolarisation from the SA node to the atrial musculature (sino-atrial block). Either condition may cause ventricular asystole, but more commonly an escape AV junctional or escape ventricular rhythm occurs. (Fig. 6.25).

During a sinus arrest in ECG, the P wave will suddenly fail to appear at the expected place, and there is a gap of variable length, until the sinus node fires again and a P wave appears or an escape ventricular beat takes over the responsibility. On the other hand, in sino-atrial block the sinus node depolarises normally (which cannot be recorded in the ECG). But this impulse fails to reach the atria. So, it is also called an exit block. However, like the sinus arrest the P wave in exit block also fails to appear at the expected place, but the next one usually appears exactly where it is expected (Fig. 6.26).

Rarely the sino-atrial exit block may occur at regular intervals e.g. 2:1 ratio. This resembles the slow regular rhythm of sinus bradycardia. But the diagnosis can only be established, when in contrast to the gradual acceleration of sinus bradycardia, the rate suddenly doubles with the effect of atropine (Fig. 6.27).

In SA block neither the P wave nor the QRS complex is recorded at the moment of the block. Whereas, in AV block all the P waves are recorded but the P waves of the blocked beat is not followed by a QRS complex. SA exit block is found in the same condition as in sinus bradycardia and is the result of an increased vagal tone. It occurs in normal high vagotonic persons e.g. athletes. It can also be produced by pressure on the carotid sinus or eyeball (during eye surgery) or other vagal reflexes (Fig. 6.28).

It is very mandatory for the P waves to be present except in certain conditions, but sometimes is not evident in many ECG tracings. So, an ECG should be searched carefully for evidence of P wave, before concluding that they are absent. This is because the P waves are often hidden by QRS complexes in any rapid tachycardia. For example, in AV junctional tachycardia (shown in the figure) with a heart rate of 130/min, at a first glance the P waves appear to be absent. On close inspection they can just be seen, buried within the ST segment. Even in sinus tachycardia at high rates the P wave may be overlapped with the T wave of the previous beat, making it hard to identify (Fig. 6.29).

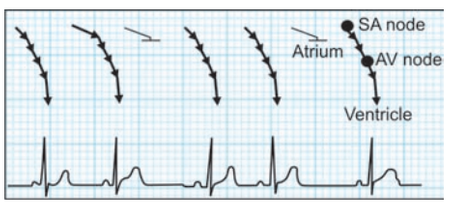


Fig. 6.27: SA node exit block.This is a 3:2 Wenckebach type of block. It is characterised by two repetative sinus conducted beats, followed by a pause. All P wa es are of the same form. The PR inter- val is constant and no AV block or atrial premature beats are evident. In this case the sinus node is firing regularly, but sometimes cannot be seen in the ECG. There is progressive SA exit block, as a result of which every third discharge from the SA node is not conducted to the atrium

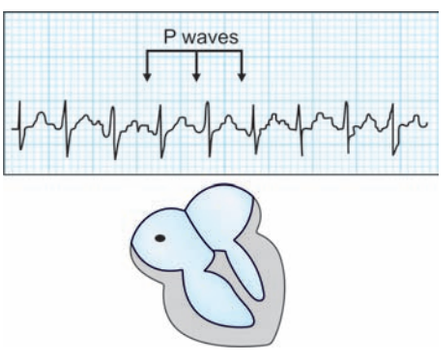


Fig. 6.29: This ECG shows sinus tachycardia with heart rate of 130/min with narrow QRS complexes. All QRS complexes are followed by a P wave and all the P waves are upright. But these P waves are hidden within the previous T waves

In ventricular tachycardia, the retrograde (backward) conduction of ventricular impulses through the AV node may cause each ventricular complex to be followed by an abnormal P wave which may not be immediately obvious and may also be inverted. Even more importantly the independent atrial activity from SA node can occur during ventricular tachycardia and these P waves can be buried anywhere within the QRS complex. So the evidences of independent atrial activity is a very useful clue in the differentiation of the ventricular and supraventricular tachycardia.

Premature Atrial Depolarisation (Atrial Extrasystole) and P Wave

The waves of depolarisation of atrial activity normally spreads from SA node to AV node through atria. If any extra-atrial depolarisation is initiated by a secondary stimulus, arising from any ectopic focus situated anywhere in either right or left atrium except at the SA node, then it is called the premature atrial beat. This depolarisation wave travels in the opposite (retrograde) direction through the atria, if it arises in the lower part of the atria. But, it travels like a normal P wave, i.e. from above downwards, if it arises in the upper part of the atria. However, both of these will cause premature atrial excitation and a P′ wave in ECG. Simultaneously, it will also initiate a ventricular complex with a normal QRS configuration (Fig. 6.30).

From the view point, in most of the positive electrodes of different leads this abnormal P wave which is originating from the lower part of the atrium, will show to move away from them rather than to flow towards them, and thus an inverted P′ waves (instead of an upright P wave) will be produced in most of the leads. However in the aVR lead this retrograde P′ wave will produce a positive deflection as it is moved towards the positive pole of this lead from lower part of atrium. Many abnormal sources of atrial activation which can thus cause retrograde depolarisation and inverted P′ waves includes atrial ectopics, AV junctional rhythm, ventricular tachycardia, ventricular ectopics, etc. (Fig. 6.31).

If an ectopic atrial stimulus arises from the upper end of the atrium, then the resulting abnormal P′ wave will have the same normal direction and configuration like the P wave. However, this premature atrial depolarisation will usually depolarise the SA node, upsetting its rhythmicity. The next normal sinus impulse, therefore, will not occur as scheduled, because the SA node needs to pass through a complete recovery cycle, before it can discharge again. The basic rhythm of the SA node is thus disturbed and a pause will follow the ectopic atrial beat. This is called the compensatory pause of the SA node. This pause is usually incomplete, i.e. it does not fully compensate for the prematurity of the extrasystole. This means that, the sum of the pre and postectopic intervals (Y-Z) is less than the sum of two consecutive normal intervals (X-Y). We should compare these events with those occasioned by a ventricular extrasystole, when the sinus rhythm is not disturbed and where the compensatory pause is subsequently complete (Fig. 6.32).

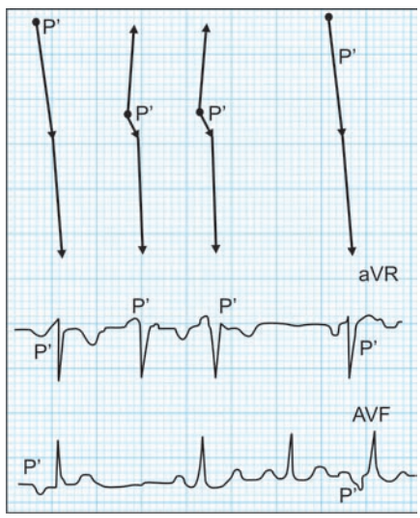
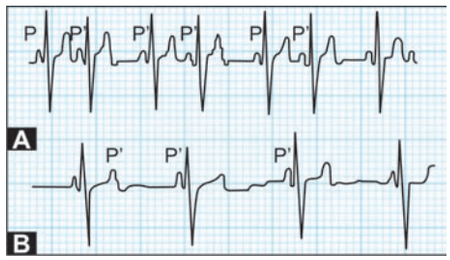


Fig. 6.30: Atrial premature beats with low atrial ectopic focus. The prominant feature is a regular sinus rhythm. The P′ waves occur prematurely. The P′ is upright in aVR and inverted in aVF. This is the reverse of the normal P wave and indicates a low atrial ectopic focus.The QRS complexes are normal



Figs 6.31A and B: This ECG shows alternate atrial extrasystoles
A: Here the ECG shows alternate atrial extrasystole indicated by a P' wave and a sinus P wave. All the atrial extrasystoles are conducted to the ventricle like a normal P wave, causing ventricular bigeminal rhythm. Here the P' wave is of upward direction, which indicates that it originates at the upper part of the atrium
B: Here the atrial extrasystole is indicated by P'. It is superimposed on the T wave and has distorted it. Here any atrial extrasystole is not conducted up to the ventricle, due to their extreme prematurity causing a slow and regular ventricular rhythm

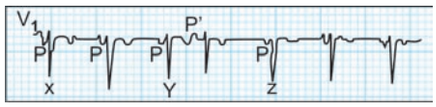


Fig. 6.32: This is an ECG of atrial extrasystole. The fourth P wave, marked as P′, is the atrial ectopic, which is conducted to the ventricle. This P′ is different from the other P waves and is characterised by a positive narrow and pointed wave.The sum of the pre and post ectopic intervals, i.e. Y to Z is less than the sum of the two consecutive normal sinus interval, i.e. X to Y

The unifocal atrial extrasystole tends to have a fixed coupling interval i.e, the interval between the extrasystole and the preceeding beat tends to be the same for all unifocal extrasystoles. This fixed coupling with atrial extrasystoles, however, is usually not as constant as that which occurs with ventricular extrasystoles. If an atrial extrasystole (which is conducted to the ventricle) occurs after every sinus impulse, then it will result in ventricular extrasystolic bigeminal rhythm. If an atrial extrasystole is not conducted to the ventricle and occurs after every conducted sinus impulse, then it will result in an atrial

bigeminal rhythm and a slow regular ventricular rhythm. Three or more consecutive atrial extrasystoles constitute a paroxysmal atrial tachycardia (Fig. 6.33).

Atrial premature beats may frequently occur in normal individuals. At times, it may occur secondary to stimulation due to emotional disturbances, tobacco, tea, coffee,etc. Digitalis may also produce such an arrhythmia. Almost any form of organic heart disease e.g. rheumatic heart disease, chronic coronary artery disease, hyperthyroidism, viral infection, etc, may be responsible for premature atrial beats and in such instances the atrial arrhythmia may be the precursor of paroxysmal atrial tachycardia and atrial fibrillation.

Wandering Atrial Pacemaker

In this type of atrial arrhythmia normally some impulses arise from the SA node, whereas the other ectopic impulses arise from the different ectopic sites of the atrium. It may even be from the AV node. As a result there will be variation of atrial rhythm, changing configuration of the P′ wave (due to atrial activation from different ectopic foci) and changing in P′R interval (Fig. 6.34).

Normally, an inverted P waves in aVR and an upright P waves in aVF will be found from impulses arising in the SA node or from the ectopic focus (P') arising in the upper portion of the atrium. Whereas an upright P′ wave in aVR and inverted P′

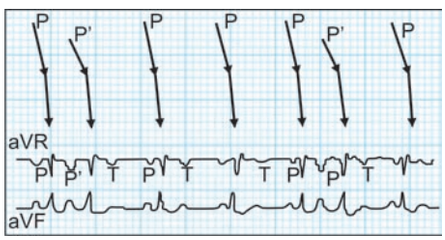


Fig. 6.33: This is an ECG of high atrial extrasystole.The P'R interval is longer than the PR interval. In lead aVR inverted P' indicates that the atrial ectopic focus is high enough. The P' wave is followed by a normal QRS complex, which indicates that the conduction is through the AV node and the Purkinje fibres of ventricle

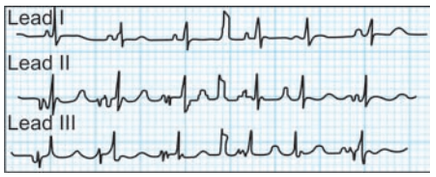


Fig. 6.34: This is an ECG of a wandering atrial pace maker. The rhythm is irregular and each QRS complex is preceeded by a P wave. But there is a marked variation in the morphology of the P wave. Some are tall and upright (sinus origin), while others are inverted and biphasic (ectopic origin). The above is indicative of varying atrial pacemakers

wave in aVF will be found from impulses arising from an ectopic focus situated in the lower portion of the atrium or AV junction.

This type of atrial arrhythmia (wandering atrial pacemaker) may also occur in a normal individuals with increased vagal tone. Digitalis may be the another important aetiological factor for this. Various forms of organic heart diseases, e.g. acute rheumatic disease can also produce this type of arrhythmia.

Paroxysmal Supraventricular (Atrial) Tachycardia (PSVT)

It is due to the rapid electrical discharge from an ectopic atrial focus, causing regular and consecutive atrial extrasystoles. It is characterised by regular atrial rhythm at rate of 160 to 220/min. Atrial tachycardia differs from sinus tachycardia, as the impulses are generated from an ectopic focus, somewhere, within the atrial myocardium rather than the sinus node (Fig. 6.35).

Some claim that re-entry mechanism is mainly responsible for this PSVT, rather

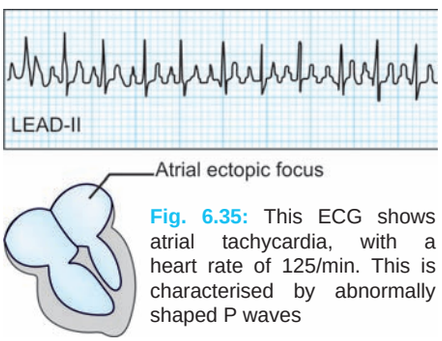


Fig. 6.35: This ECG shows atrial tachycardia, with a heart rate of 125/min. This is characterised by abnormally shaped P waves

than the ectopic focus which simply fire repeatedly on its own. The re-entry mechanism may be localised in the sinus node, atrial muscle or the AV node, involving conduction in an anterograde direction through the AV node or a retrograde conduction through the AV bypass tract. Such a bypass tract may also conduct anterogradely, in which case the WPW syndrome is said to be present. When the bypass tract conducts only retrogradely, then it is termed 'concealed by-pass tract' and in this case QRS complex is normal without any delta waves. In the absence of WPW syndrome (i.e. anterograde conduction through the bypass tract), the re-entry of impulses through the AV node or through a concealed bypass tract constitutes for more than 90% of all the PSVTs. This results in atrial rhythm with the following characteristic features: heart rate greater than 100/min and abnormally shaped P or P waves.

In most instances there is 1:1 AV conduction. But, when the atrial rate goes above 200/min, then the AV node struggles to keep up with the impulse conduction and an AV block may occur. On reaching the AV node,the atrial impulse may be conducted as follows:

i. With a normal AV conduction, resulting in normal P′R interval.
ii. With 1st degree AV block.
iii. With 2nd degree AV block—the passing of impulses through the AV node is so rapid that its cycle is shorter than the AV nodal refractory period. Thus when this occurs, then every alternate impulse is blocked, resulting in a 2:1 AV block.

The atrial tachycardia may also be associated with more complex form of 2nd degree AV block, e.g. 3:2 block. On reaching the ventricles, the atrial impulses may be conducted like normal intraventricular conduction which is manifested as rapid regular or irregular QRS complexes (if block is present) or with aberrant ventricular conduction in the presence of LBBB or RBBB, resulting in broad and rapid QRS

complexes, simulating ventricular tachycardia. The combination of atrial tachycardia and AV block is very common in digitalis toxicity. If the patient is not taking digitalis, then the probable causes of PSVT are: rheumatic heart disease, IHD, SSS, cardiomyopathy etc. (Fig. 6.36).

In atrial premature beats the direction of P′ wave in leads aVR, aVF and the oesophageal leads will indicate the site of origin (high or low) of the atrial ectopic focus. However, the identification of P′ wave is very difficult and the P′ to QRS relationship cannot be established with certainty. So, this rhythm is termed as supraventricular tachycardia, because the exact site of origin of atrial ectopic focus is not diagnosed and whatever may be the site of origin of ectopic focus it is above the ventricle. In this type of arrhythmia, the impulse spreads through the atrial muscle more slowly than a normal sinus beat. Thus P′R interval is often prolonged. The P′ wave may, therefore, be buried in the preceeding ventricular QRS complex, simulating an AV junctional tachycardia (Fig. 6.37).

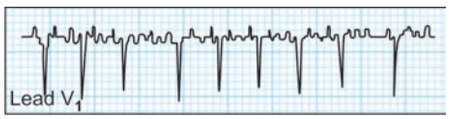


Fig. 6.36: This ECG shows extrasystolic atrial tachycardia. This is characterised by varying second degree AV block. The P' waves are bizarre and the P'-P' interval measures 0.24 sec, which represents an atrial rate of 250/min. The AV conduction ratio varies between 2:1 and 3:1

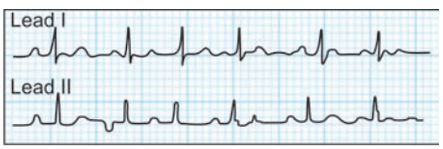


Fig. 6.37: This ECG shows multifocal atrial tachycardia, where the ventricular rhythm is irregular. Each QRS is preceeded by a P wave which varies in configuration and direction. PR interval varies from beat to beat, and some of the P waves do not activate the ventricles (blocked atrial beats) The tracing represents an atrial tachycardia, resulting from multiple atrial foci (wandering atrial pacemakers)

When a paroxysmal atrial tachycardia, arises from an ectopic focus which is high in the atrium, then it produces normally directed P waves. This may be indistinguishable from a sinus tachycardia arising from the SA node at rates of approximately 140 to 160/m in one single ECG. A constant RR interval without any change with respiration will favour the diagnosis of paroxysmal atrial tachycardia. The response to carotid sinus pressure may also help in the diagnosis. In PSVT this manoeuvre may abruptly terminate the attack. Whereas in sinus tachycardia there may be slow, gradual and slight slowing of the heart rate. If there is no response to carotid sinus pressure, then one must compare the pattern of the P or (P′) waves of the tachycardia to the pattern present during the previous regular sinus rhythm. If there is difference in configuration of the atrial complexes in these two tracings, then the diagnosis of paroxysmal atrial tachycardia is justified.

PSVT occurs most commonly in normal individuals. It may show no clinical evidence of heart disease. It may occur even in relation to emotional trauma. The lesser common aetiological factors of PSVT are rheumatic valvular disease, pulmonary embolism,cardiac surgery, thyrotoxicosis, coronary arterial disease, etc. It is the most common arrythmia associated with WPW syndrome. Atrial tachycardia with AV block is a common manifestation of digitalis toxicity.

Mechanism of PSVT

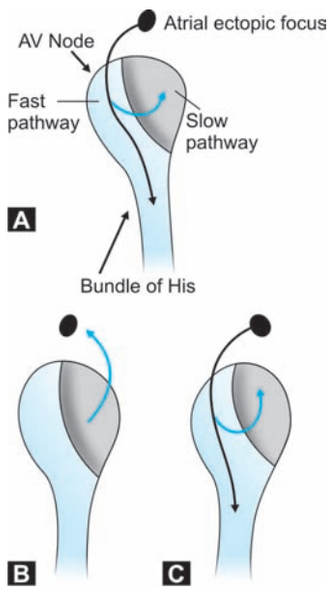
Several mechanisms are responsible for the production of paroxysmal supraventricular tachycrdia or atrial tachycardia. These are explained below.

1. *AV nodal re-entry tachycardia*

This is the most frequent mechanism of PSVT. In this circumstance, there is functional longitudinal dissociation of the AV node which results in dual AV nodal pathways with different functional properties. This dual AV nodal pathway is designated each as 'slow' and 'fast' pathways.The 'slow' pathway has a longer refractory period, and allows anterograde conduction of atrial impulse. The 'fast' pathway has a shorter refractory period and prevents anterograde conduction (Fig. 6.38).

Thus atrial tachycardia is produced sequentially by:

i. An ectopic atrial depolarisation.
ii. An anterograde conduction in one pathway (usually the 'slow' one) which results in ventricular capture, because of an unidirectional anterograde block



Figs 6.38A to C: The mechanism of AV nodal re-entry tachycardia. In such situation the AV node is divided into two parts (Shaded and unshaded in the picture),according to the conducting and refractory characteristics of the nodal tissues

A: An impulse comes from the atrial ectopic beat and tries to pass both through the shaded and unshaded areas. But due to the faster conduction property of the unshaded part,impulse first passes through it and depolarises the ventricle. Passage of impulse through the shaded part is blocked.

B: After a few milliseconds when this shaded area is no more refractory, few impulses from the unshaded area enter the shaded portion and pass back (retrograde conduction) to the atrium,resulting in another atrial depolarisation. Impulses from this second atrial depolarisation again pass through the shaded and the unshaded areas and depolarise the ventricle (antegrade) and atrium (retrograde) like the previous manner.

C: Thus repeat re-entry of impulses in atria causes atrial tachycardia.

in the other pathway (usually the 'fast' one).

iii. A retrograde conduction then occurs through the previously blocked (fast) pathway, resulting in another atrial depolarisation, which in turn again activates the ventricle, like the previous one, which passes through the slower pathway.

iv. Thus there is continuation of this re-entry circuit within the AV node producing tachycardia. Less commonly the anterograde conduction ocurrs via the faster pathway and retrograde conduction through the slower pathway. But, to differentiate between this slow and fast AV nodal re-entry pathways, special electrophysical studies are required.

2. AV re-entry tachycardia with the accessory pathway

The AV re-entry tachycardia is not the same as the AV nodal tachycardia where the defect lies within the AV node itself. In addition to the normal route of conduction via the AV node and the bundle of His, when there is an accessory connection between the atria and ventricles, then also AV re-entry tachycardia arises. By any one of the two routes the impulse travels down (anterograde conduction) and then backs (retrograde conduction) by the other route. In this way the impulse is continuously cycled and causes into repeated activity of firing the atria and the ventricle in rapid succession.

The classic examples of PSVT with this mechanism are the pre-excitation syndrome,WPW syndrome and Lown-Ganong-Levine syndrome.

Wolf-Parkinson-White syndrome

In this condition there is a strip of accessory conducting tissue that allows the electrical impulse to bypass the AV node and spread from the atria to the ventricle rapidly without any delay which occurs in AV node. When the ventricle is depolarised through the AV node though there is presence of accessory pathway, then the ECG shows normal without any delta wave. But, when the ventricles are depolarised through the accessory conducting pathway, then the ECG shows a very short PR interval, delta wave and a broad QRS complex. This is because the accessory pathway has high conduction velocity rate than the AV node. The ECG manifestation of the WPW syndrome may differ in the following ways (Fig. 6.39).

(a) Sinus rhythm

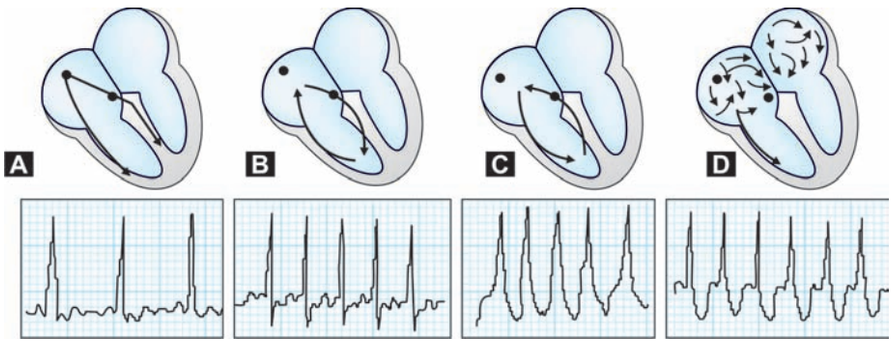
In sinus rhythm with an accessory conducting system, the ventricles are partly depolarised through the AV node and partly through the accessory pathway. Thus, it produces an ECG with a short PR interval and a slurred, broad QRS complex. The characteristic slurring of the upstroke of the QRS complex is known as the delta wave. The ECG depends on the degree of the proportion of electricity passing down the accessory pathway (i.e pre-excitation) and therefore the ECG appearances may vary a lot. Sometimes the ECG may also look normal.

(b) Orthodromic tachycardia

This the most common form of tachycardia in WPW Syndrome. Here the re-entry circuit passes anterogradely from the atrium to the ventricle, through the AV node and then comes back retrogradely through the accessory pathway. The ventricles are therefore depolarised in the normal way and produces a narrow complex tachycardia, that is not distinguishable from other forms of supraventricular tachycardia.

(c) Antidromic tachycardia

Here the re-entry circuit passes anterogradely from the atrium to the ventricle through the accessory pathway, and then comes back retrogradely through the AV



Figs 6.39A to D: The mechanism of WPW syndrome

A. Here the cardiac rhythm is sinus without any tachycardia and the impulse passes through both the pathways. The ventricle is depolarized by impulses which pass partly through the accessory pathway and partly through the AV node. The accessory path way has faster conduction rate than the AV node and is responsible for short PR interval and also delta wave. The next part of the QRS complex (after the delta wave) is as usual, and formed by the impulse coming through the AV node. The ultimate configuration of the QRS complex depends upon the degree of pre-excitation, i.e. the proportion of impulse passing through the accessory pathway and normal AV node. Therefore, the appearance of ECG may vary a lot and it may look normal or abnormal.

B. This shows tachycardia with WPW syndrome. Here, the re-entry circuit passes through the AV node (anterograde) and comes back through the accessory pathway(retrograde or orthodormic). Thus ventricles are depolarised by normal AV nodal path and produces narrow complex tahycardia without delta wave which is indistinguishable from other causes of SVT.

C. This also shows tachycardia with WPW syndrome. But here the impulse first passes through the accessory pathway and then comes back through the AV node(retrograde or antidormic),after depolarising the ventricle. As the ventricle is depolarised first by the accessory pathway,so it produces broad complex tachycardia.

D. This shows atrial fibrillation associated with WPW syndrome where the ventricle is depolarised by impulses passing through the accessory pathway producing broad complex tachycardia.

node. The ventricles are then depolarised through the accessory pathway, producing a broad complex tachycardia.

(d) Atrial fibrillation

In this rhythm the ventricles are largely depolarised through the accessory pathway, producing an irregular broad complex tachycardia (Fact file-I).

Bradycardia Tachycardia (Brady-Tachy) Syndrome

It is one of the presentations of a disease with wide (potential) spectrum of disorder of rhythm, such as: Sick-Sinus Syndrome. It is apparently an paradoxial association of depressed conduction activity with hyperexcitability. But, the precise mechanism of this syndrome is not known.

There is an abnormality of impulse formation and impulse conduction, involving both the SA node, AV node and its appendages, such as: the bundle of His, the right and left bundle branches and the Purkinje fibres. Bradycardia part of this syndrome is due to sinus bradycardia, sinus arrest or sinus block. This bradycardia may or may not be associated with conduction defects in the AV node and its appendages and with or without adequate escape rhythm. The supraventricular tachyarrhythmia often emerges as an adequate escape rhythm in response to an episode of severe bradycardia due to sinus arrest or sinus block.. The supraventricular tachyarrhythmias may also be paroxysmal atrial tachycardia, atrial flutter or atrial fibrillation. This tachyarrhythmias may manifest first or may precipitate as a compensatory response to a long pause due to the sinus arrest or block. The diagnosis of sick sinus syndrome is suspected when following the termination of tachyarrhythmias, there is a period of exceptionally very slow sinus rate manifested as bradycardia which may be as slow as 25 to 35 beats per minute for a short period. This tachyarrhythmia may ultimately establish as atrial fibrillation. The abnormal AV nodal conduction often become apparent when a patient with brady-tachy syndrome develops AF with AV nodal failure to conduct all the atrial impulses leading to slow ventricular response.

The commonest cause of brady-tachy syndrome or sick-sinus syndrome is the degeneration and fibrosis of the sinus node, AV node and the conducting system. Other causes are IHD, drugs (digoxin, quinidine, beta blockers), cardiomyopathy, amyloidosis, etc. The symptoms of brady-tachy syndrome are dizziness, fainting or even syncope due to low cardiac output, caused by severe bradycardia. In addition to symptoms of bradycardia, patients may also experience episodes of supraventricular tachycardia.

The asymptomatic patients of brady-tachy syndrome do not require any treatment. Symptomatic patients may be considered for permanent pacemaker implantation. Medical therapy for tachycardia require anti-arrhythmic drugs which again worsens the phase of bradycardia. Therefore, pacing is also helpful to prevent this serious bradycardia and also permits medical therapy for tachycardia. Paroxysmal tachycardia which arises as an escape rhythm to episodes of bradycardia may also improve as a consequence of pacing.

FACT FILE- I

AV re-entry tachycardia

The accessory pathway is an extra connection between the atria and the ventricles, which is anatomically separated from the AV node. Accessory pathways make the patient susceptible to the episodes of AV re-entry tachycardia, with anterograde conduction via the AV node and retrograde conduction via the accessory pathway. In such circumstances, Delta wave is not seen in the ECG. In variety of re-entry tachycardia, where the impulses take the opposite route i.e, anterograde flow down the accessory pathway and retrograde flow up the AV node, which is very rare, then delta waves are seen (delta waves are seen when anterograde impulse passes through the accessory pathway). The AV nodal re-entry tachycardia is called when the accessory pathway lies within the AV node, in which anterograde conduction usually occurs down the normal AV nodal tissue and returns retrogradely via the abnormal AV nodal tissue.

Both the AV re-entry and AV nodal re-entry tachycardia have the following characteristics :

i. Heart rate is 120 to 240 beats per minute.

ii. There is one P wave for every QRS complex but P waves are not always seen clearly.

iii. QRS complexes are regular if there is no AV block.

iv. QRS complexes are narrow if there is no conduction defect or bundle branch block

If there is a pre-existing bundle branch block, QRS complex will be broad and re-entry tachycardia will be mistaken for VT. So, a previous ECG will be helpful in determining whether a bundle branch block existed before the tachycardia or not. In AV re-entry tachycardia, the inverted P waves are often seen halfway between QRS complexes. Whereas in AV nodal re-entry tachycardia the inverted P waves are impossible to see as they buried within the QRS complexes. Although the position of the P waves may help to distinguish between AV re-entry and AV nodal re-entry tachycardia, still an ECG in sinus rhythm is more helpful, as it may reveal a short PR interval or delta wave, suggesting WPW syndrome. Still, a definite diagnosis is very difficult and sometimes require electrophysiological studies.

Atrial Flutter (AF)

Atrial flutter is the manifestation of rapid and regular extrasystolic atrial excitation. It shares the same mechanism as paroxysmal atrial tachycardia, arising from an ectopic atrial focus or results from a continuous depolarization encircling the atrium through accessory pathway, i.e. the re-entry mechanism.

The ectopic atrial focus producing AF causes rapid discharge from the ectopic site, similar to atrial extrasystole or PSVT (atrial tachycardia). But, this is not a well accepted concept for atrial flutter. However the re-entry mechanism can be described by the re-entry pathway which is situated within the atrium and does not involve the AV node. This is the most acceptable explanation for atrial flutter (Fig. 6.40).

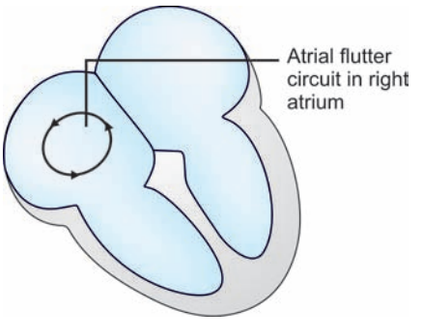


Fig. 6.40: The atrial flutter circuit.It's key point is the circuit of activity, which circles in the right atrium continuously

Except for the mechanism of origin, the atrial-flutter also differs from the atrial tachycardia by the atrial rate (P wave) which is higher in AF and usually 250 to 350/min. The ventricular response to this rapid atrial activity depends upon the efficacy of conduction of impulses through the AV node. AV node cannot keep up with such a high atrial rate, and AV block occurs. Most commonly there is 2:1 block, where only alternate atrial impulses get through the AV node to initiate a QRS complex. Though, 3:1, 4:1, 6:1 or variable other degrees of blocks are also seen. Thus, the ventricular rate is less than the atrial rate and is often 150, 100 or 75/min according to the Av block, but is regular.

We should always suspect atrial flutter with 2:1 block when a patient has a tachycardia with a regular ventricular rate around 150/min. Occasionally, every atrial impulse is conducted to the ventricles with a 1:1 response (i.e. without any block), resulting in a very fast, but regular ventricular rate (Fig. 6.41).

The cardinal sign of atrial flutter in ECG is the presence of regular undulating waves, resulting in the characteristic 'saw tooth' appearance with prominent negative deflection in tracing. These manifestations are usually best seen in standard leads I, II and aVF and chest lead V_1. The T wave is usually masked or deformed by the flutter waves. The QRS complexes are normal, unless there is a coincidental bundle branch block (Fig. 6.42).

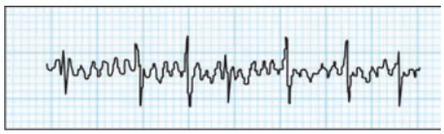
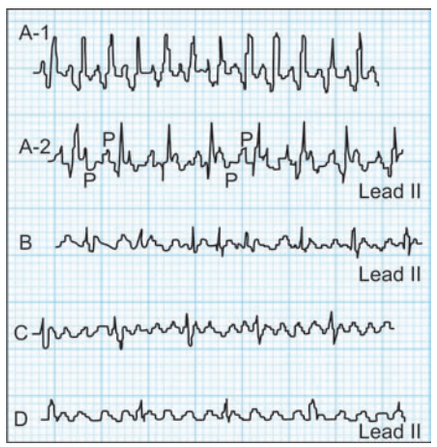


Fig. 6.41: ECG showing atrial flutter associated with fibrillation. So, this is called flutter fibrillation It is still doubtful whether this type of arrhythmia has a definite entity or not. The so-called atrial flutter-fibrillation may probably be a case of a lesser degree of atrial fibrillation. Digitalis can convert atrial flutter into fibrillation. This is due to the shortening of the refractory period of atrium by digitalis. When digitalis is stopped the fibrillation may convert to normal rhythm

The basic difference between the atrial tachycardia and the atrial flutter are the atrial rate, site of re-entry, presence and degree of AV block, and responses to therapy.

Sometimes, atrial flutter with 2:1 AV block may be mistaken as atrial tachycardia with 1:1 conduction (i.e., no block) or even regular sinus rhythm, because one of the P' wave is buried in the QRS complex. Atrial flutter may also be mistaken the basic difference between the atrial flutter and fibrillation is that in fibrillation due to rapid atrial rates many leads of the ECG



Figs 6.42A to D: This ECG shows various forms of atrial flutter. The key points of atrial fibrillation are - rapid atrial rate, wide saw-tooth deflection in the place of the P wave, and absent or barely noticeable baseline
A-1: This shows atrial flutter with a 1:1 response.
A-2: This shows 2:1 response of atrial flutter after treatment with digitalis in the same patient.
B: This shows atrial flutter with 2:1 response but without treatment with digitalis
C and D: This shows atrial flutter with 4:1 response

will not clearly show the regularly recurring P′ waves. Whereas in atrial flutter P′ waves are regularly and clearly seen. If the ventricular response is irregular, then it will simulate an atrial fibrillation (Fig. 6.43).

Atrial Fibrillation

Atrial fibrillation is much commoner than atrial flutter, affecting 5 to 10% of all the elderly people. It may be permanent or paroxysmal, particularly in younger people. In atrial fibrillation no P waves are seen and the ECG base line consists of low amplitude fibrillatory waves. In atrial fibrillation, the excitation and recovery processes of the atria are completely disorganised and chaotic. The whole atrium is functionally divided into numerous islands of tissue which are in a different chaotic electrical state and in various stages of excitation and recovery. These numerous excitatory wavelets or stimuli pass irregularly through the whole atria without any effectful atrial contraction. Normally, the human atrium can respond and contract regularly to stimulus, only up to a certain rate. This is usually in the range of 350/min. But at a rate faster than this, the atrium can no longer respond completely to each stimulus. So, a chaotic electrical disturbance with asynchronous atrial depolarization and ineffective atrial contractions results in atrial fibrillation.

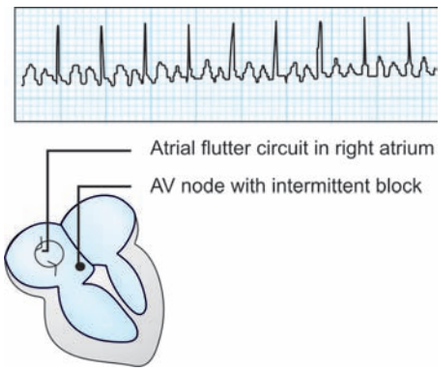


Fig. 6.43: ECG shows atrial flutter with 3:1 AV block. Flutter waves are at a rate of 300/min and QRS complexes at a rate of 100/min. Therefore 3:1 AV block is present

In atrial fibrillation, the atrial activation is manifested in ECG by an undulating baseline or by a more sharply inscribed atrial deflection of varying amplitude and frequency, ranging from 350 to 600 beats per minute (Fig. 6.44).

The ventricular rhythm is totally irregular because the majority of the atrial impulses reaching the AV node are blocked and it is because of the refractoriness of the AV node. There is no fixed 2:1 or 3:1 or 4:1 AV block like the atrial flutter. The AV node can only conduct some of these stimuli, because following conduction of one such stimulus it is refractory for a short period and impulses reaching the AV node during this period are blocked. Only occasional impulses meet during the nonrefractory period of the AV node and are conducted distally to activate the ventricles. This is called 'concealed conduction'. Although around 350 to 600 impulses reach the AV node every minute, but only 120 to 180 of these will reach the ventricles to produce normal QRS complexes provided there is no bundle brunch block.

In ECG the atrial deflections are recorded as irregular, chaotic, fibrillatory waves (F-wave) resulting in a ragged baseline. No P waves and irregularly-irregular ventricular rhythm will be seen. In long standing cases of atrial fibrillation, the deflection may be of a low amplitude and the base line may be found almost straight with minimum and smooth undulation of low amplitude. At times, the rhythm may alternate between the flutter and fibrillation in a single tracing. These are the borderline cases in which a precise differentiation can not be made. In such instances the term 'flutter-fibrillation' may be used. However, it is better to reserve the term 'flutter' for those records, which have perfectly regular atrial depolarisation and fibrillation for all those that are irregular.

A rapid atrial fibrillation with ventricular rate of 200/m may simulate an atrial tachycardia. But, it can be differentiated easily as the ventricular rhythm in atrial fibrillation will show variations whereas the ventricular rhythm in later will be perfectly regular.

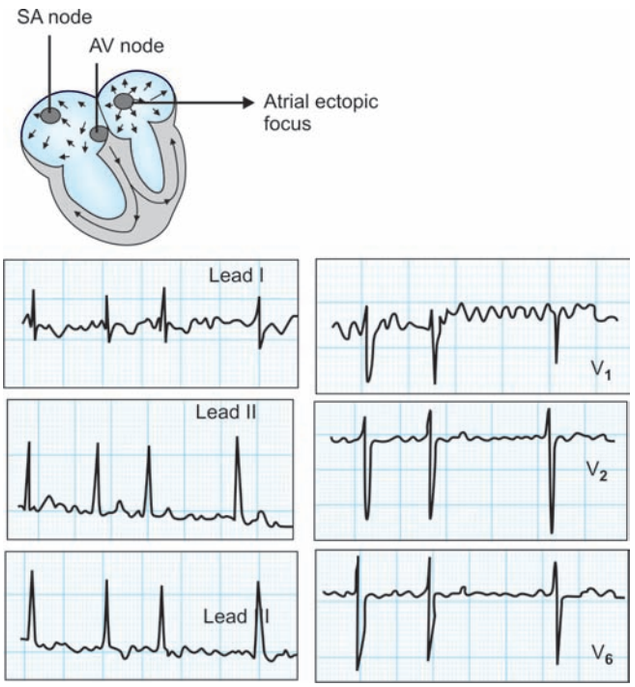


Fig. 6.44: Atrial fibrillation activity is manifested by small rapid irregular fibrillatory waves. The ventricular rhythm is completely irregular

THE GENESIS OF PR INTERVAL

After flowing through the atria from SA node, the electrical impulses reach the AV node which is normally the only entry route of an electrical impulse to the ventricle from the atrium. This is because the rest of the atrial myocardium is separated from the ventricles by a non-conducting ring of fibrous tissue. Activation of the AV node does not produce any obvious wave in the ECG like SA node, but it does contribute to the time interval between the P wave (atrial contraction) and the subsequent Q or R wave heralding the beginning of ventricular contraction. So, sometimes the PR interval is referred to as the PQ interval. By delaying the conduction from atrium to ventricle, the AV node acts as a safety mechanism which prevents the rapid atrial impulses from spreading to the ventricles at the same rate (Fig. 6.45).

So, the time taken for the depolarisation wave to pass from its origin in the SA node, across the atria and through the AV node to the ventricle is called the PR interval. This is measured from the begining of the P wave to the beginning of R wave and is normally between 0.12 to 0.2 seconds (maximally up to 0.22 seconds) or 3 to 5 small squares. Thus it includes (i) the time required for the atrial depolarization to travel from the SA node to the AV node (usually 0.03 sec), (ii) normal conduction delay in AV node (approximately 0.07 sec)

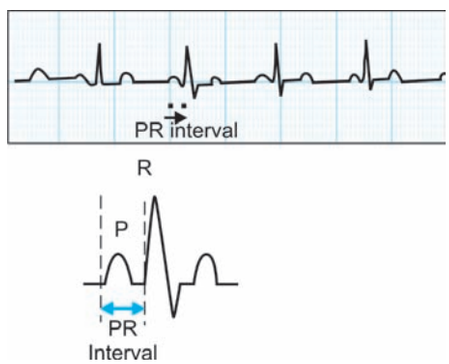


Fig. 6.45: The PR interval.The normal interval is 0.12 - 0.20 seconds

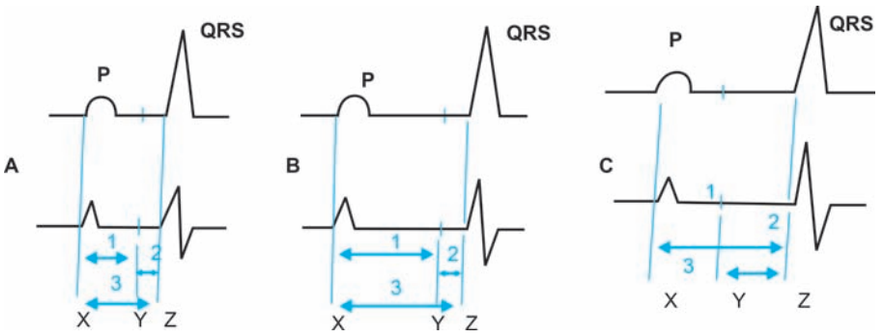
and (iii) the passage of impulse through the bundle of His and the bundle branches to the ventricle.

The PR interval should be correlated with the heart rate (HR). Normally slower the HR, longer the PR interval. A PR interval of 0.2 seconds may be of no clinical significance with a HR of 60/min. But it may be well significant with a HR of 100/min. Though, the interval between the P waves and the QRS complexes changes, but it is approximately constant between 0.12 to 0.2 seconds (Fig. 6.46 and Fact file -II).

Atrioventricular Block

The atrioventricular block is characterised by a delay or interruption in the conduction of atrial impulses to the ventricle through the specialised AV conduction system such as the AV node, bundle of His or bundle branches (right and left bundle branches). The atrio-ventricular (AV) block can be classified into three degrees.

i. In first degree block there is delay in conduction of impulses more than 0.2 sec through the AV node.
ii. In second degree block there is intermittent or incomplete interruption of conduction of impulses through the AV node.
iii. In third degree block there is permanent or complete interruption of conduction of impulses through the AV conduction system. The first and second degree heart block is called the partial or incomplete heart block and the third degree heart block is called the complete AV block or complete heart block.



Figs 6.46A to C: A: This shows normal AV conduction
B: This shows first degree AV block. Here 1 is prolonged but 2 isnormal. So 3 is also prolonged. Therefore the block is proximal to the Bundle of His in the AV node
C: This also shows first degree AV block. Here 1 is normal but 2 is prolonged. So 3 is again prolonged Therefore the block is distal to the Bundle of His in the intraventricular conduction system. The QRS interval is prolonged when there is a block distal to the Bundle of His.

FACT FILE- II

Mechanism and site of AV block

The AV block results either from a functional or pathological defect in the atria, AV node, bundle of His or bundle branches, causing delay in the relay or conduction of impulses through the AV node.The functional block of AV node can occur as a result of increased vagal tone.The AV block produced by digitalis toxicity is also partly due to the vagal stimulation. The PR interval can be subdivided into two segments.

(i) The time from the beginning of the P wave to the end of depolarization of AV node. This is represented in the figure as XY interval.

(ii) The time from the end of AV node depolarization to the beginning of the ventricular depolarization.This is represented in the figure as YZ interval. These measurements are of major clinical significance.

In the presence of first degree AV block (prolonged PR interval) the block may be at the following sites:

(i) Above the bundle of His (therefore in the AV node), giving a prolonged XY interval and a normal YZ interval.

(ii) Below the bundle of His (therefore in the intraventricular conduction system), giving a normal XY interval and a prolonged YZ interval.

(iii) A combination of both (i)and (ii) with prolonged XY and YZ intervals. Even in the presence of a normal PR interval, either the XY or the YZ interval may be prolonged.

The bundle of His recordings, although not available as a routine clinical tool, have resulted in more clarification of the mechanism and sites of first, second and third degree AV block.

First degree AV or heart block

In this condition there is a disturbance or delay in conduction through the AV node and bundle of His. This results in prolongation of the PR interval above the upper limit of normal range (> 0.2 sec), constituting the first degree AV or heart block.

In first degree AV block, all the P waves are followed by QRS complexes. It is usually asymptomatic and in general does not progress to other degrees of heart block. No specific treatment is necessary for first degree AV block in its own right, but needs close observation. It is not an indication for pacemaker implantation (Fig. 6.47).

Second degree AV or heart block

Second degree AV or heart block is again classified into Mobitz type I (Wenckebach phenomenon) and Mobitz type II block.

Mobitz type I of 2nd degree AV block

Here, the PR interval gradually lengthens with each successive beat, until after several, usually 3 to 6 beats when an atrial depolarisation fails to pass and initiate a ventricular response due to a complete block of AV node and thus this beat is

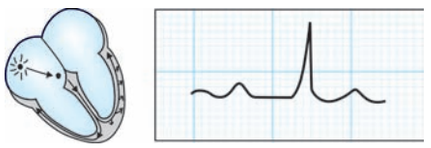


Fig. 6.47: First degree AV block-Delay in conduction through AV node, Bundle of His or atria.This produces length ening of the PR interval

dropped. Hence, a long diastolic pause results. The pause caused by this dropped beat allows the conducting system to recover. The PR interval again resets back to normal and now allows the atrial depolarisation to be further conducted to the ventricle. The sequence is then repeated. Here, the defect lies with in the AV node (Fig. 6.48).

The Mobitz type I AV block is thought to be as the result of abnormal conduction through the AV node itself and can result simply from high vagal activity. So, it sometimes occurs even during sleep. It may also occur in any generalised disease of the conducting system or tissue. It is regarded as a relatively benign form of AV block and permanent pacemaker is not required, unless the frequency of the dropped ventricular beats causes any symptomatic bradycardia. Patients found to have the Mobitz type I of 2nd degree AV block prior to surgery will usually require temporary pacing perioperatively

Mobitz type II of 2nd degree AV block (Fig. 6.49)

Here, there is no gradual progression or prolongation of the PR interval, like Mobitz type I AV block. The PR intervals of all the conducted impulses are constant. But, periodically the ventricles fail to respond to the atrial stimulations and this may occur at any interval. For example, for every 6 atrial complexes there are only 5 ventricular complexes and will be termed as 6:5 AV block. Again it may be of any combination, such as: 3:2, 2:1, 4:3, or 2:1 AV Mobitz Type II block (Fig. 6.50).

The lesion in this form of Mobitz type II of 2nd degree AV block is actually situated in the bundle of His i.e. below the AV node and is always organic or pathological. It carries an adverse prognosis, since it frequently progresses to 3rd degree or complete AV block. So Mobitz type II is more serious than Mobitz type I AV block. It is also an indication for perioperative pacing (Fig. 6.51).

2:1 AV block is a special form of 2nd degree heart block (also termed as '2nd degree constant block') in which alternate P waves are not followed by QRS complexes. Regular sinus rhythm complicated by 3:2 AV block will result in a ventricular bigeminal rhythm (Fig. 6.52).

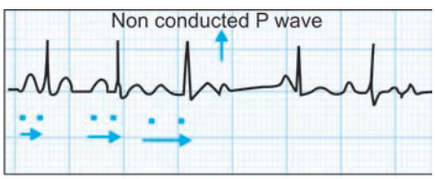
Third degree AV or complete heart block

The third degree AV block is characterised by the complete or permanent interruption of AV conduction. All the supraventricular impulses (sinus rhythm, atrial tachycardia, atrial fibrillation, etc.) are blocked to pass to ventricle at the level of AV conducting system. The ventricles are then activated by a subsidiary ectopic foci acting as a pacemaker for escape rhythm, situated on the AV node but below the level of block or within the ventricles (Fig. 6.53).

The atrium is thus activated by one pacemaker (usually sinus or may be ectopic) and ventricle by another idioventricular pacemaker. Hence the two rhythms—atrial and ventricular run independently and asynchronously.

The features of complete AV block are:

i. P wave has no relationship with the QRS complex and if it is sinus in origin, then the rate is 60 to 80/min. Any



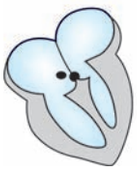


Fig. 6.48: The ECG shows Mobitz type I variety of 2nd degree AV block (Wenckebach phenomena). There is progressive lengthening of PR interval with intermittent failure of P wave to be conducted. Then PR interval again resets and cycle repeats

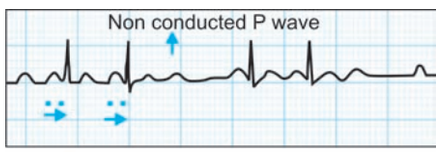


Fig. 6.49: This is an ECG of Mobitz type II variety of 2nd degree AV block. It is characterised by a normal and constant PR interval, but occasional P wave fails to be conducted

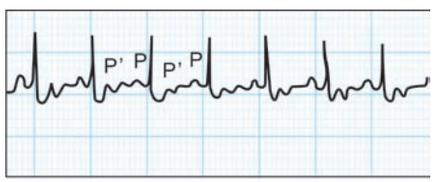


Fig. 6.50: This ECG shows 2:1 AV block,where alternate P waves fail to be conducted

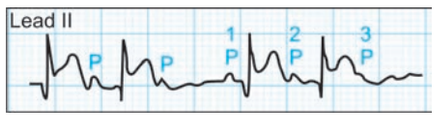


Fig. 6.51: ECG of inferior wall MI in hyperactive phase, with 3:2 second degree AV block of Wenckebach type. This is evidenced by tall R wave, ST segment elevation and tall-wide T wave. The first PR interval is normal,the second PR interval widens and the third P wave is not followed bt a QRS complex

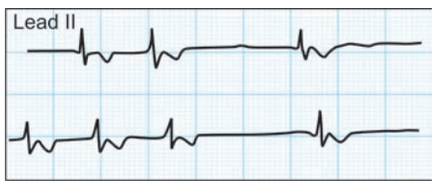


Fig. 6.52: This ECG shows Mobitz type II AV block. This is evidenced by irregularly dropped P waves resulting in successive 3:2, 2:1, 4:3 and 2:1 AV block. The PR interval is prolonged but is same for all the conducted beats

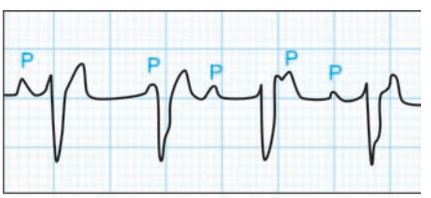


Fig. 6.53: This ECG shows third degree AV or complete heart block.This is characterised by (i) no relation between P waves and QRS complexes, (ii) broad QRS complexes (iii) P wave(atrial rate) is 86/min and QRS complex (ventricular rate) is 50/min

abnormal atrial rhythm can coexist with the third degree heart block and so the P wave may be abnormal or even absent.

ii. There is slow ventricular rate or QRS complex, usually in the range of 35 to 40/min and it is not under vagal influence (since ventricles have no parasympathetic activity). It is thus not usually affected by exercise, emotions or atropine.

iii. If the subsidiary pacemaker arises from the AV node below the block or bundle of His, then the configuration of the QRS complex is normal or near normal in shape.

iv. If the pacemaker is situated peripherally in the Purkinje fibres or in the ventricular musculature, then the QRS complex will be abnormal and broad. Sometimes, the ventricle may be under the control of 2 or 3 alternative pacemakers, resulting in QRS complexes of different configurations.

A combination of bradycardia and broad QRS complexes should alert a suspicion of third degree heart block. For the management of this type of complete block temporary pacing is always indicated, regardless of the patient's symptom or haemodynamic state. Pacing is also necessary perioperatively for patients who are waiting for surgery.

Atrioventricular Junctional Rhythm (Fig. 6.54)

This type of rhythm is also called the AV nodal rhythm, because here the impulse arises from the AV node as an ectopic focus. The impulse then spreads upward into the atrium and downward into the ventricle. This usually produces an upright P′ wave in aVR and in high oesophageal leads and an inverted P′ wave in lead II, aVF and low oesophageal leads. Thus P′ wave is inverted in leads where it is normally upright and vice-versa (Fig. 6.55).

The QRS complex is of normal configuration, as it arises from the AV node

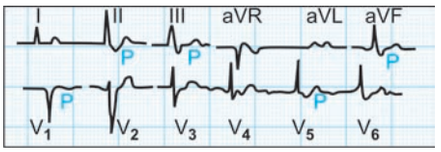


Fig. 6.54: ECG shows AV nodal junctional rhythm with late retrograde conduction and activation of atria. Here P waves follow each QRS complex and are inverted. This inverted P wave is seen in Lead II, III, aVF, V4 and V5

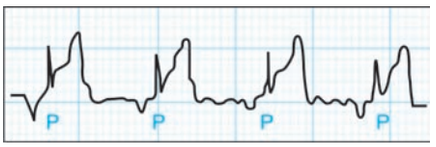


Fig. 6.55: This ECG illustrates the AV nodal rhythm with retrograde conduction to atria. So an inverted P wave precedes each QRS complex

and passes through the normal conducting pathway. If the retrograde conduction to the atria is faster than the anterograde conduction to the ventricles, then P′ wave will precede the QRS complex. But if the opposite occurs, then the P′ wave will follow the QRS complex. If conduction to the atria and ventricles occurs at the same rate, then the P′ wave will be hidden within the QRS complex (Fig. 6.56).

These junctional beats may appear as escape beats when the sinus rate is very slow or as premature beats when an increased automaticity of the AV junction site develops. This increased automaticity of AV junction may be due to digitalis toxicity. The transient or permanent AV junctional rhythm may result from organic heart diseases like IHD, myocarditis,

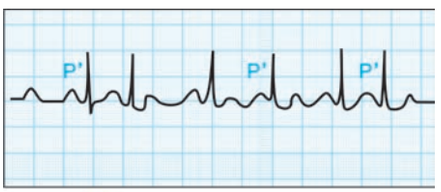


Fig. 6.56: This ECG shows atrial ectopic beats.The key points are (i) P waves are earlier than expected, and (ii) P waves are abnormally shaped

rheumatic heart disease, etc. The significance of these junctional beats or rhythm is similar to that of atrial premature beats. The escape beats are protective in nature as they represent a secondary pacemaker (to SA node) and takes over the responsibility, when the primary pacemaker slows or fails (Fig. 6.57).

AV Junctional Tachycardia (Fig. 6.58)

It is defined as the successive three or more AV nodal extrasystoles. Like PSVT it has an abrupt onset and termination. It is relatively uncommon and the rate can vary from 120 to 200/min. The ventricular rhythm associated with AV junctional or nodal tachycardia is regular. The P′ waves originating from the AV junctional tissue may precede, be buried in, or follow the QRS complexes. The pattern of each QRS complex is identical to that of a junctional premature beat. With a rapid rate during tachycardia it is impossible to identify any single P′ wave. Practically, one cannot

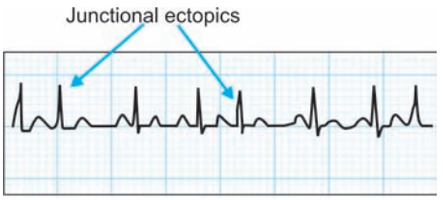


Fig. 6.57: The ECG shows AV junctional ectopic beats. It is characterised by (i) QRS complexes are earlier than expected (ii) QRS complexes are not preceded by P wave, and (iii) QRS complexes are narrow

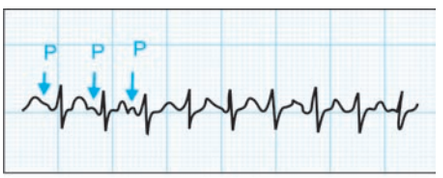


Fig. 6.58: ECG of sinus tachycardia.It is evidenced by narrow QRS complexes and P waves arehidden within the previous T waves

differentiate the ECG pattern produced by AV junctional tachycardia from that produced by atrial tachycardia arisig from a low atrial ectopic focus. Therefore, the appropriate term such as supraventricular tachycardia is more applicable to AV junctional tachycardia and atrial tachycardia. The clinical significance of AV junctional tachycardia is similar to that of atrial tachycardia (supraventricular tachycardia) (Fig. 6.59).

GENESIS OF QRS COMPLEX

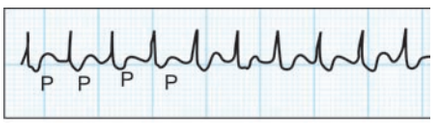
The activation or depolarization of ventricle is reflected by a QRS complex in an ECG tracing. The normal QRS complexes have different appearances in each of the 12 ECG leads (Fig. 6.60).

The activation of ventricle starts at the left side of interventricular septum in the bundle of His and then it spreads from the left to the right. This is called the septal force or the septal vector of QRS complex, producing septal activation and is responsible for small positive deflections or r waves in V_1, V_2 leads and small negative deflections or q waves in leads I, V_5, V_6 and aVL. As the amount of electrical activation is little at the septum, so the amplitude of deflection is very small.

The activation of septum is then followed by activation of free walls of both the ventricles. This can be represented by a large right to left force through the thick free walls of the left ventricle, which occur simultaneously with a smaller opposing force directed from the left to the right through the thinner free wall of the right ventricle. The larger right to left force of the left ventricle dominates and counteracts the smaller left to right force of the right ventricle. This results in an effective or net resultant vector which is directed from the right to the left through the left ventricle and produces a large negative deflection i.e. S wave in leads V_1, V_2, aVR (negative deflection because the flow of current is away from these leads) and large positive deflection i.e. R wave in leads I, II, V_5, V_6 (positive deflection because the flow of current is towards these leads) (Fig. 6.61).

The last portion of the ventricular muscle to be activated is the posterobasal portion of the left ventricle, followed by the region of pulmonary conus and lastly the upper most portion of the interventricular septum. The vector of the force of this last part of activation is directed rightwards and anteriorly. So, a small positive deflection will be recorded in lead $V_{1\text{-}2}$, and a small negative deflection S will be recorded in leads I and $V_{5\text{-}6}$. Thus, the right oriented leads (V_1 ,V_2) will therefore, normally reflect an rS or rSr complex, and the left oriented leads (V_5 ,V_6) will reflect an qR or qRs complex. Lead V_3 and V_4 are the transitional leads and reflect the transition from rS complex to qR complex. The transition pattern is usually a RS complex. But, at times the pattern may be relatively bizarre and depends on the presence of clockwise or counter clockwise rotation of the heart. So, the transition pattern should be ignored (Fig. 6.62).

An initial downward deflection after the P wave is called the Q wave (small q is for a small downward deflection) and an initial upward deflection after the P wave is called the R wave (small r for a small upward deflection). After Q and / or R, the next downward deflection is called the S wave. After the S wave the next positive deflection (second positive deflection of the QRS complex) is called the R′ or r′ (r′ for a small amplitude). These different nomenclatures of a QRS complex are given in the picture. The QRS interval is the measurement of total ventricular depolarization time. It is measured from the onset of Q wave or R wave (if there is no



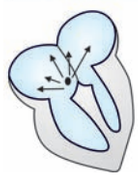


Fig. 6.59: ECG of AV junctional tachycardia. The key points are (i) tachycardia (ii) narrow QRS complexes (iii)P waves follow QRS complexes (iv) P waves are inverted in lead II

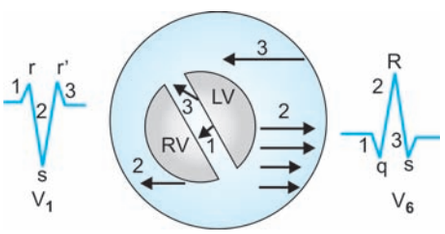


Fig. 6.60: The basic vector of ven tricular depolarisation and its effects on leads V_1 and V_6: LV- Left Ventricle, RV- Right Ventricle

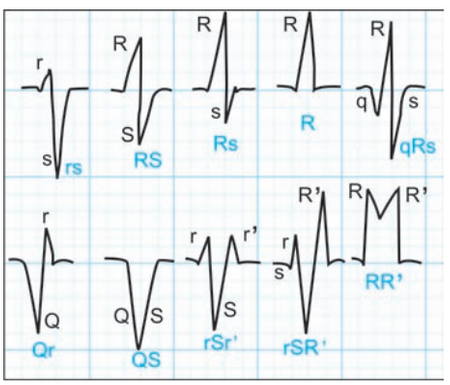


Fig. 6.61: The various forms of the QRS complexes and their nomenclatures

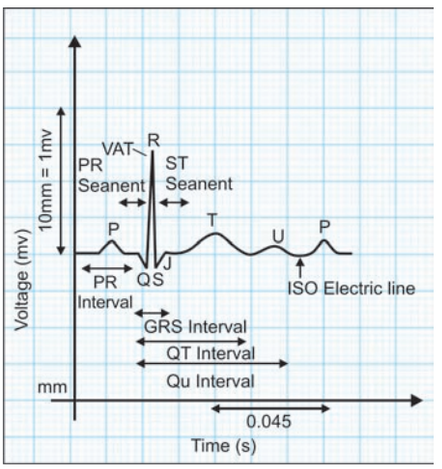


Fig. 6.62: A schematic diagram of ECG complexes, intervals and segments. The graph is magnified for clarity and better understanding

Q wave) to the termination of S wave or r′ wave. The upper limit of QRS interval is 0.12 secs.

The ventricular activation time (VAT) is an indirect measurement of the time which is taken for an impulse to traverse the whole thickness of the left ventricular wall. It is measured from the beginning of the QRS complex (or the beginning of the Q or r wave) to the peak of the R or S wave. The upper limit of VAT is 0.04 secs.

Intraventricular Conduction Defects

The intraventricular conduction defect is the result of conduction abnormality through one or more divisions of the ventricular conduction system which are distal to the bundle of His. The anatomical structures for normal intraventricular conduction are (from the bundle of His to the ventricular muscle fibres): (i) right bundle branch, (ii) left bundle branch, (iii) left anterior fascicle, (iv) left posterior fascicle, (v) septal fibres from the left bundle branch that enter the left septal myocardium and (vi) peripheral Purkinje fibres (Fig. 6.63).

The conduction defect may be a delayed conduction through the conducting pathway or even a total block. But, as the ECG cannot distinguish between the two, so it is better to use the term 'conduction defect'. The conduction defect is only an ECG diagnosis, but not a clinical diagnosis.

The ECG criterias for conduction defects or blocks are:

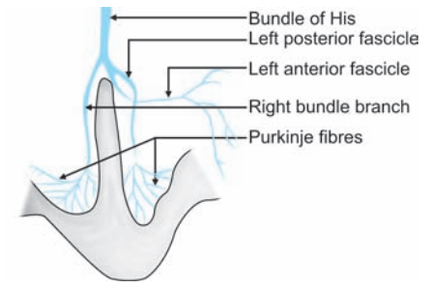


Fig. 6.63: The intraventricular conduction system

i. Abnormal QRS configuration due to abnormal spread of conduction through the conducting system of ventricle
ii. Prolongation of the QRS interval, i.e, more than 0.12 sec
iii. Prolonged VAT
iv. The ST segment is depressed and the T wave is inverted in leads that record abnormal R′ wave

In an incomplete block all the above criteria should be present, except the QRS interval which is not more than 0.12 sec.

Right Bundle Branch Block (RBBB)

It is a very common ECG finding and is not pathognomonic of any organic heart disease. It may be present in association with any type of heart disease and may also be found in normal individuals with an incidence of 1.5 per thousand, between ages of 20 to 40 years and 2.9 per thousand over the age of 40 years. It may also be associated with different types of cardiomyopathies, ASD, coronary artery disease, pulmonary embolism, Ebstein's anamoly, etc (Fact file-III).

Mechanism

Here, the spread of excitation from the SA node to the AV node and then up to the bundle of His is normal. After that the septal activation occurs normally from left to right through the bundle of His. In leads V_1 and V_2 as a result of normal septal activation which is oriented to the right and anteriorly, a small r wave will be recorded. Since, the right bundle branch is blocked, so the excitation wave will next spread down the left bundle branch and through the left ventricular myocardium, resulting in a S wave in leads $V_1$and V_2. The impulse will then pass around the apex of the heart, bypassing the blocked right bundle into the right ventricular myocardium, producing a R′ wave. Thus, a typical pattern of rsR′ will be found in leads V_1 and V_2 in RBBBs. If the S wave is small or absent, then the pattern will be RR′. The ST segment will be depressed and so the T wave is inverted (Fig. 6.64).

The T wave is opposite in direction to the terminal QRS deflection. Thus, if the terminal deflection is R′, for example, in lead V_1, then the T wave will be inverted. However, the associated ST segment will show deflection which is slightly convex upwards or sometimes minimally depressed. If, on the other hand, the terminal deflection is an S wave, for example, in lead V_6 then the T wave will be upright. The associated ST segment will be slightly

FACT FILE - III

Common causes of bundle branch block

RBBB	**Normal variant**
	Coronary artery disease, Congenital heart disease (e.g. ASD)
	Right ventricular hypertrophy or strain
	(e.g. pulmonary embolism)
	Cardiomyopathy
	Ebstein's anamoly
LBBB	Coronary artery disease
	Hypertension
	Coarctation of aorta
	Hypertrophic cardiomegaly
	Aortic valve disease
	Cardiomyopathy
	Fibrosis of the conduction system

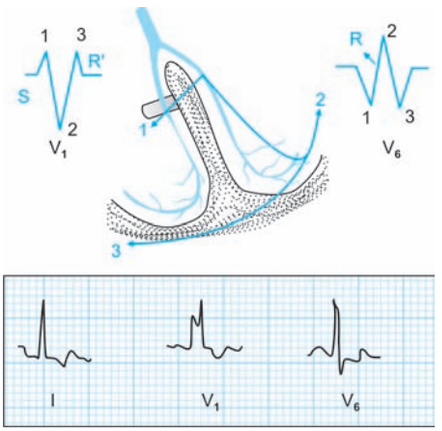


Fig. 6.64: The ECG shows RBBB. The key points are:
i. Broad QRS complexes
ii. R' wave in lead V1
iii. S wave in lead V6.
In RBBB, the QRS looks like 'M' in lead V_1 and W' in lead V_6. In 'M' and 'W'.
1. due to septal activation
2. due to left ventricular activation
3. due to right ventriculae activation

concave downwards and at times is minimally elevated.

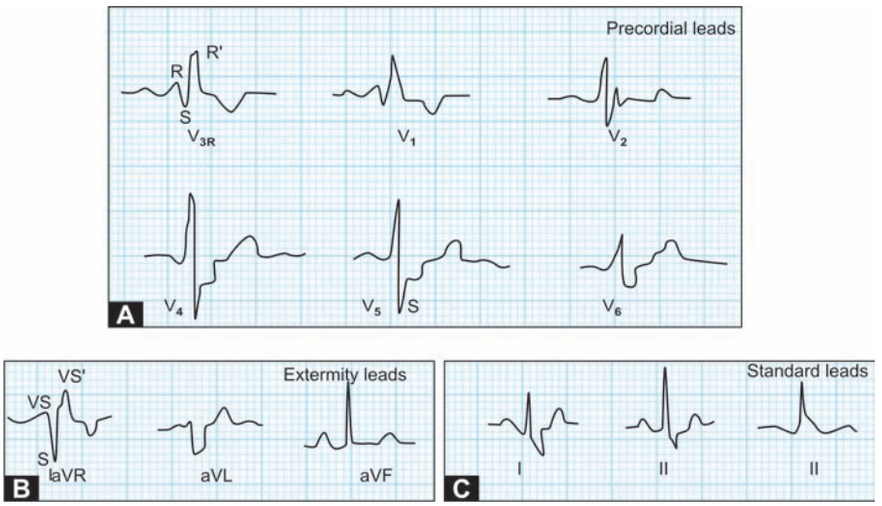
In lead V_5 and V_6 an initial small q wave will be formed as a result of normal left to right septal activation. This will be followed by a R wave, resulting from a large left ventricular activation. Then this R wave will be followed by a S wave which results from the delayed large activation of the right ventricle. The ST segment is isoelectric and the T is upright.

So, in RBBB the QRS will look like 'M' in V_{1-2} and 'W' in lead V_{5-6}. The characteristic feature of RBBB is a delayed electrical force of right ventricular depolarisation, oriented to the right and anteriorly. This late right vector force produces a wide S wave in lead-I, V_{5-6} and a wide R or R′ (RSR′ pattern) in lead aVR and V_{1-2}. The ST and T are opposite in direction to this late force of ventricular depolarisation (R or R′ wave) in the precordial leads. An initial q wave will never be present in V_{1-2} leads in RBBB or an initial q wave in V_{1-2} lead indicates it is not RBBB. Alternatively, an initial q wave in V_{1-2} leads always indicates LBBB (Fig. 6.65).

Incomplete RBBB

A delay, but not a complete stoppage of conduction of impulses through the right or left bundle branches manifests as an incomplete bundle branch block. In case of incomplete RBBB conduction through the right bundle branch is still possible, but is delayed. It is now increasingly clear that this slowed down conduction of impulses is not the only cause for the genesis of an incomplete RBBB. But the increased length of the right bundle branch may also play a significant role for relative delay where conduction itself is not delayed. For example, an increased length of the right bundle branch is responsible for the longer time of conduction producing relative delay and incomplete RBBB. This anatomical factor (increase in length) responsible for the cause of incomplete RBBB is clearly significant when there is dilatation of the right ventricle due to volume or diastolic overload. The causes of this right ventricular dilatation are: ASD, tricuspid insufficiency, chronic corpulmonale, right ventricular hypertrophy, etc.

The pattern of ECG in incomplete RBBB is similar to that of complete RBBB, except that the QRS interval is not greater than 0.12secs. Sometimes, it is impossible to differentiate between the incomplete RBBB and normal QRS pattern in lead V_1.



Figs 6.65A to C: Summary of RBBB-
A: Depicts precordial leads, characterised by
1. RSR1 or rsR_1 complexes in V3R and V_{1-2}. An initial 'q' wave is never present in these leads unless there is associated infarction, right ventricular hypertrophy or dilatation ,or additional left ventricular fascicular block
2. Wide S wave in V_{5-6}
3. QRS interval >0.12s
4. ST depression and T wave inversion in V_{1-3}

B: Depicts extremity leads,characterised by
1. Wide rsr1 complex in aVR
2. Patterns in aVL and aVF will depend on heart position.

C: Depicts standard leads, characterised by wide S wave which is invariably present in lead I Among these many findings are common but are not essential for the diagnosis. So,minimum criteria for RBBB diagnosis is rsR_1 complex in right precordial leads(V3R and V_{1-2}) with QRS interval >0.12 sec and a wide S wave in lead I

Left Bundle Branch Block (LBBB)

Complete LBBB always indicates some form of organic heart disease. It is commonly associated with an ischaemic heart, left ventricular hypertrophy due to a hypertensive heart, and aortic valvular diseases. But, it may occur with almost any form of heart disease. It is rarely seen in individuals, with no clinical evidence of an organic heart disease.

Mechanism

Here, the spread of excitation from SA node to the AV node and the bundle of His is normal. Then as due to the block the impulse cannot enter the left bundle system (left side of the septum), so septal activation starts on the right side and follows to the left, resulting in an initial vector oriented from the right to the left (opposite to normal) (Fig. 6.66).

Therefore, in leads V_{1-2} an initial q wave will (does not normally present in lead V_{1-2}) result which is due to septal activation from right to left. Since the left bundle branch is blocked, so the excitation wave next spreads down the right bundle branch to the right ventricular myocardium, resulting in a r wave in the V_{1-2} leads. Because of the relative thinness of the right ventricular wall, the amplitude of this r wave may or may

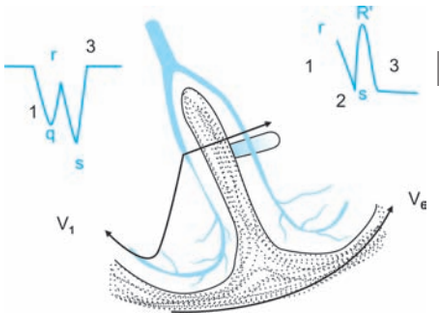


Fig. 6.66: ECG of a fully evolved LBBB

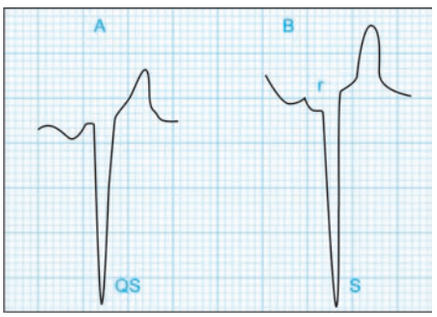
not pass above the isoelectric line or may produce a notch in the qS wave in these V_{1-2} precordial leads. The impulse then passes from the right ventricular myocardium around the blocked left bundle branch into the left ventricular myocardium and produces a deep wide S wave. Thus, a typical W-pattern QRS complex will be developed in leads V_{1-2}. Occasionally, either a small q or r wave cannot be recorded. Therefore, the pattern looks like a rs or QS complex. The ST segment may be elevated and T will be upright (Fig. 6.67).

In leads V_{5-6} as a result of septal activation from the right to the left a small initial r wave will be recorded. Q wave will not be formed (in normal ECG Q wave is a must in V_{5-6} lead). This is followed by activation of the right ventricle and anegative deflection S wave. Because of the thinness of the right ventricle this S wave may not go below the isoelectric line, but may merely produce a notch in the R wave. The impulse then passes around the blocked left bundle branch into the left ventricle through the myocardium and produces a R′ wave. Thus, a typical pattern of rsR′ or RsR′ or a slurred and widened R wave will be formed. The ST segments are usually depressed and T waves are inverted (opposite the direction of the last wave). So, in LBBB the QRS looks like 'W' in V_{1-2} leads and like 'M' in V_{5-6} leads (Fig. 6.68).

Thus, the characteristic feature of LBBB is the absence of normal septal q wave in lead I and in left precordial leads V_{5-6}. Conduction delay is present through most of QRS vector, producing a broad and slurred R wave or rsR′ or RSR′ complexes in lead I and V_{5-6}. The QRS interval is > 0.12 secs.

Significance of LBBB is that it may be permanent or transient. Transient LBBB may occur during the course of MI, heart failure, acute myocarditis and as a result of drug therapy (quinidine, procainamide, amiodarone, etc.). However, the permanent LBBB is always the result of some organic heart disease.

In the right ventricular cavity complex the LBBB will produce a wide QS complex.This is because the septal activation is from the right to the left and the cavity will be negative throughout the ventricular depolarization. In left ventricular cavity complex the initial septal depolarization from the right to the left produces an initial small r wave. Then ventricular depolarization, proceeding from the endocardial to the epicardial surfaces results in a larger negative deflection S wave. The left ventricular cavity complex is therefore rS.



Figs 6.67A and B: A. ECG changes of LBBB in right ventricular cavity complex. B. ECG changes of LBBB in left ventricular cavity complex

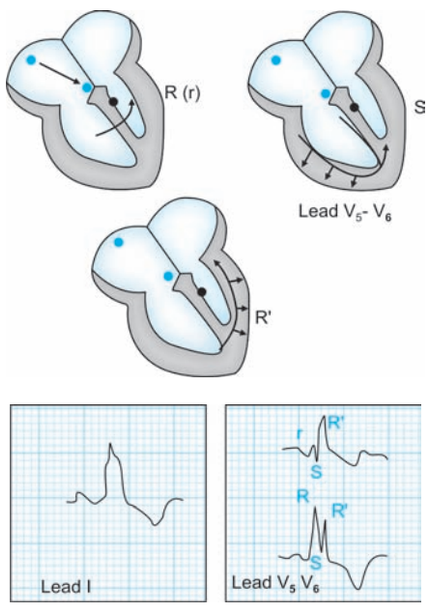


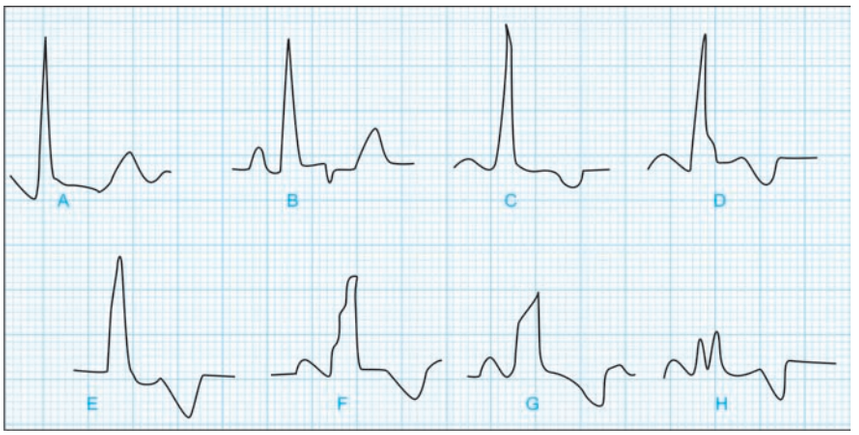
Fig. 6.68: ECG of LBBB in left epicardial complex

Incomplete LBBB

In case of incomplete LBBB the conduction of impulses through the left bundle branch and its ramifications is still posible. But this is delayed. The type of ECG manifestation which occurs with incomplete LBBB will depend upon the degree of delay of conduction of impulses within the left bundle branch. Progressively increasing delay of conduction within the left bundle branch will result in a progressive sequence of ECG manifestations, leading to a complete block. All grades of incomplete LBBB are illustrated in the picture (Fig. 6.69).

The initial manifestations of an incomplete LBBB are the following:

i. The small initial q wave (due to normal septal activation) of the normal qR complex in the left oriented leads, i.e. V_{5-6} and I disappears. This results in a single tall R wave.
ii. The small initial r wave (due to normal septal activation) of the normal rS complex in lead V_{1-2} disappears. This results in a QS complex.
iii. With further progression a slur appears on the upstroke of QRS complex. This slur becomes increasingly prominent and is accompanied by widening and an eventual notching of the QRS complex, until the fully developed manifestation of complete LBBB is attained. Such a manifestation is due to the increasing dominance of the right ventricular factors due to the increasing delay of conduction within the left bundle branch.



Figs 6.69A to H: This ECG in lead V_{5-6} shows the progression from normal intraventricular conduction through var ious phases of incomplete LBBB to complete LBBB
A: Normal intraventricular conduction, where the small initial normal q wave is still visible
B: Earliest stage of incomplete LBBB. Here the initial q wave has disappeared and there is the beginning of a small initial slur QRS complex
C to G: Reflect progressive increase in the degree of complete LBBB. These are: increasing prominence of the initial slur, progressive widening of the QRS complex,development of a notch in the QRS complex,an increase in secondary ST segment and T wave changes.
H: Complete LBBB

Fascicular Block (Hemiblock)

It is defined as a delay or interruption of conduction within one of the two major divisions or fasciculi of the left bundle branch. The left bundle branch after its origin from the bundle of His divides immediately into 2 major divisions.

i. The anterosuperior division: passes anteriorly and superiorly.
ii. The posteroinferior division: passes posteriorly and inferiorly.

The anterosuperior division of the left bundle branch is more vulnerable to interruption of activity than the posteroinferior division. The reasons are:

i. The anterosuperior division is long and thin, whereas the posteroinferior division is short and thick.
ii. The posteroinferior division has double blood supply, whereas the anterosuperior division has a single blood supply by the septal branch of the anterior descending coronary artery which also supplies the right bundle branch.

Thus, the anterosuperior division is more vulnerable to injury (ischaemia, fibrosis, etc) and interruption of activity than the posteroinferior division.

This also explains the frequent association of RBBB with left anterior fasciculi or hemiblock.

Left anterior fascicular or hemiblock (LAHB)

It is the delay or interruption of conduction through the anterosuperior division of the left bundle branch. It may be due to fibrosis or infarction. The fibrosis may be due to coronary artery disease, cardiomyopathy, longstanding hypertension, long standing chronic heart failure, etc.

When there is an interruption in conduction through the anterosuperior division of left bundle branch, then the entire conduction from the left bundle branch passes through the posteroinferior division, resulting in a mean QRS axis or vector in the frontal plane which is directed superiorly and to the left, i.e. left axis deviation (greater than –30°). Thus, the left-axis deviation is the diagnostic criteria of left anterior hemiblock in ECG. There is no appreciable widening of the QRS complex (Fig. 6.70).

In LAHB the first part of the ventricle to be activated is the inferior septal region and the posterior region of the free left ventricular wall, i.e. the posteroinferior region of the left ventricle. Therefore, it results in initial QRS forces to be directed to the right (q in lead I) and inferiorly (r in II and III and aVF). This initial activation is followed by a delayed activation of the anterosuperior lateral region of the free left ventricular wall by the anterior fascicle via

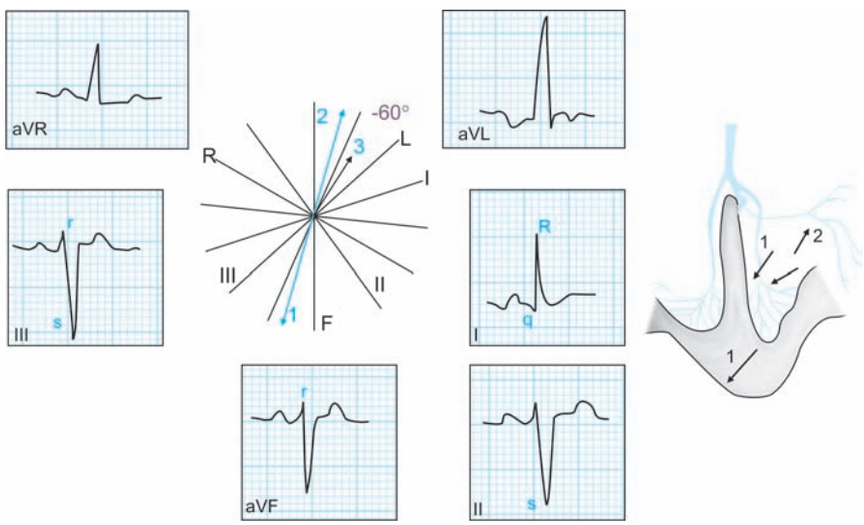


Fig. 6.70: The left anterior fascicular or hemiblock. The initial QRS vector (1) is directed to the right causing q in 1 and inferiorly causing r in II, III and aVF. The terminal QRS vector (2) is directed to the left causing R in I and superiorly causing s in II,III and aVF. Thus, the resultant QRS frontal plane vector (3) is oriented to –60°

the interconnecting Purkinje fibres distal to the site of the block. This results in a QRS vector oriented to the left (R wave in I) and superiorly (S in II, III and aVF). Thus, qR in lead I and rS in lead II diagnose the left axis deviation and left anterior hemiblock. But, other causes mimicking the left axis deviation should be excluded.

Therefore, LAHB causes the following modifications of the QRS complex:

i. A prominent QRS vector which is directed towards the right,
ii. Left QRS axis deviation,
iii. Slight increase in QRS duration,
iv. Increased magnitude of the QRS deflection,

Other causes of left axis deviation are:

i. Myocardial Infarction—inferior wall.
ii. Pacing, arising from the apex of the right ventricle (right or left).
iii. WPW syndrome (some presentation).
iv. Ventricular ectopic beats arising from the apex.
v. Some congenital heart diseases.
vi. Coronary artery disease.
vii. Left ventricular hypertrophy.
viii. Pulmonary emphysema.

Left anterior hemiblock is the commonest cause of left axis deviation and is most frequently due to fibrosis. This fibrosis may be due to chronic cardiac failure, chronic coronary insufficiency or chronic left ventricular decompensation which occur with chronic cardiomyopathy and long standing systemic hypertension. In elderly patients the left anterior hemiblock may be due to the subclinical coronary artery disease. When the left anterior hemiblock is associated with congestive heart failure, then it usually indicates a long standing heart disease.

The isolated left anterior hemiblock in the absence of any overt cardiac disease does not necessarily imply an adverse prognosis or constitute a great risk factor. When LAHB is associated with RBBB (bifasicular block), then it usually indicates an adverse prognosis and may precede to complete heart block.

Bifascicular block in a patient with syncopal attacks is often a sufficient indication for permanent pacemaker implantation. Asymptomatic bifascicular block is not necessarily an indication for pacing.

Left posterior fascicular or hemiblock (LPHB)

It is a very rare occurance and results from a lesion in the posterior fascicle of the left bundle branch. Left ventricular conduction initially spreads through the anterior fascicle, resulting in a QRS vector oriented to the left (r in lead I) and superiorly (q in lead II, III and aVF). So, last part of the anterior hemiblock is manifested first here. Then, the posterior fascicule is activated via the interconnecting purkinje fibres distal to the site of the block. This results in a vector oriented to the right (S in lead I) and inferiorly (R in lead II, III and aVF). First part of the anterior hemiblock is manifested later here. Hence, the mean frontal plane QRS axis is deviated to the right (right axis deviation) (Fig. 6.71).

There are other causes of right axis deviation, such as: right ventricular hypertrophy, lateral myocardial infarction, etc, which can be excluded from the left posterior hemiblock. Therefore, an ECG diagnosis of the left posterior hemiblock can be made only by excluding the possibility of right ventricular hypertrophy and MI.

An easy workout for determination of cardiac axis

i. A predominatly positive QRS complex in both lead I and lead II indicates a normal axis.
ii. A predominantly positive QRS complex in lead I and predominantly negative QRS complex in lead II indicates a left axis deviation.
iii. A predominantly negative QRS complex in lead I and a predominantly positive QRS complex in lead II indicates a right axis deviation.

Bilateral Bundle Branch Block

It indicates conduction defects in both the right and the left bundle branch systems in different combinations. According to this combination they are classified as:

i. RBBB with left anterior hemiblock or fascicular block.

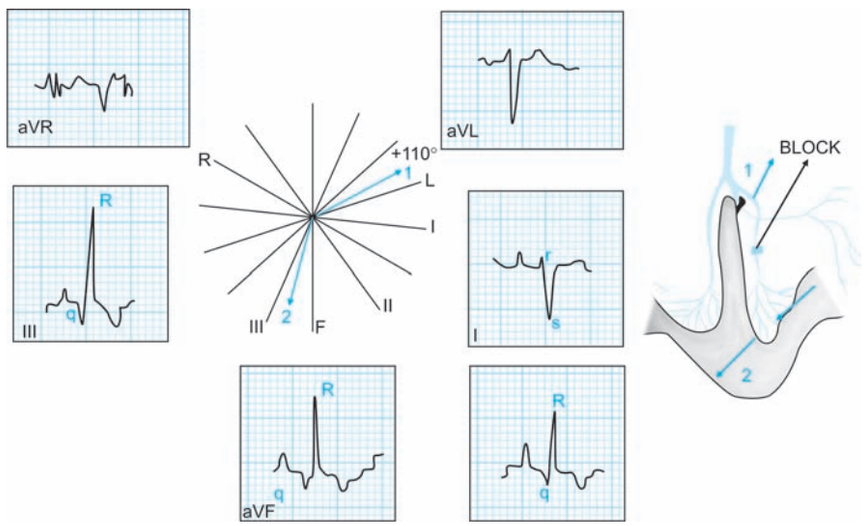


Fig. 6.71: The left posterior fascicular or hemiblock. The initial QRS vector (1) is directed to the left causing r in I and superiorly causing q in II, III and aVF. The terminal QRS vector(2) is directed rightwards causing S in I and inferiorly causing R in II,III and aVF. Thus, the resultant QRS frontal plane vector is oriented to +110°

ii. RBBB with left posterior hemiblock or fascicular block.
iii. Right or left bundle branch block with prolonged AV conduction (PR interval > 0.20 secs).
iv. RBBB with left anterior fasicular block and left posterior fasicular block. This means RBBB with complete LBBB or a complete heart block.

The bilateral bundle branch block is prognostically significant. Because, they greatly increase the probability of complete heart block. The most common cause of bilateral bundle branch block is a degenerative process that involves the upper part of the intraventricular septum and the annulus structure of mitral and/or aortic valve, leading to fibrosis and calcification. The next common cause of this type of block is coronary artery disease. When bilateral bundle branch block is associoated with MI, the prognosis is very poor. When RBBB is combined with left anterior or posterior hemiblock, it is termed as bifascicular block. It means two of the three main conducting pathways to the ventricles are blocked. Again if bifascicular block is combined with a first degree AV block (long PR interval), it is called the trifascicular block. Actually, trifascicular block means all the 3 fascicules (right bundle branch, left anterior and left posterior fascicules) of the interventricular conducting system are blocked and it is not possible for a supraventricular impulse to activate the ventricle. So, it is a situation equivalent to third degree or complete heart block with idioventricular rhythm. But, the term trifascicular block is not used as a nomenclature for complete heart block.

RBBB with LAHB

This condition can be recognised easily in ECG by (i) typical finding of complete RBBB and (ii) left axis deviation of the QRS vector greater than −30° in frontal plane. It is one of the most common types of bilateral bundle branch block or bifasicular block. There is a combination of both the features of RBBB and LAHB, i.e. (i) delayed terminal QRS forces, oriented to the right and anteriorly producing wide S waves in lead I, V_{5-6} and wide R S R′ waves in V_1, V_2 and W in V_{5-6}, (ii) left axis deviation i.e. QRS vector in the frontal plane is greater than −30° (Fig. 6.72).

RBBB with LPHB

This condition can be recognized in ECG by (i) typical findings of complete RBBB and (ii) right axis deviation of the QRS vector greater than +110° in the frontal plane. RBBB alone does not produce such a degree of rightward axis deviation. As in isolated left posterior hemiblock, the right ventricular hypertrophy must be excluded, which is also responsible for right axis deviation (Fig. 6.73).

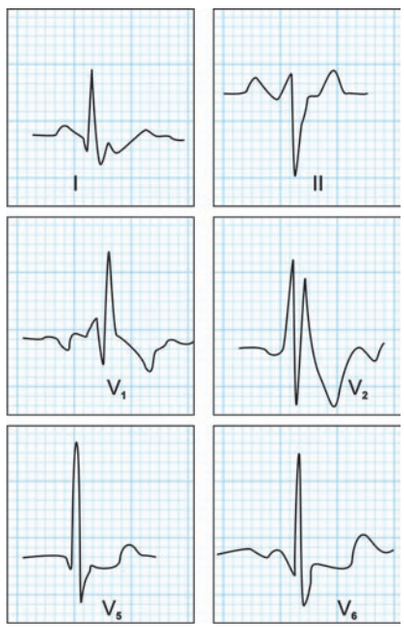


Fig. 6.72: This is an ECG of bifascicular block(RBBB withleft anterior hemiblock-LAHB). Here the QRS pattern in V_{1-2} is rsR' (M pattern) which indicates RBBB.There is also left axis deviation because there is a predominant positive QRS complex in lead I and a predominant negative QRS complex in lead II

Right or left bundle branch block with left anterior hemiblock with prolonged PR interval

This is also termed as trifasicular block, but the term is not appropriate (actual meaning of trifascicular block has been explained previously). Again, this condition should not be included in bifascicular block, because only one bundle branch is affected and the prolonged PR interval is not due to the defect in bundle branch, but due to the defect in AV node.

Ventricular Arrhythmias

There are different forms of ventricular arrhythmias .They are:
i. Ventricular premature or extrasystole or ectopic beats.
ii. Ventricular tachycardia.
iii. Ventricular flutter and fibrillation.
iv. Ventricular escape beat.

Ventricular Extrasystoles

This is due to the premature depolarization and subsequent contraction of ventricles due to the discharge of impulses from an

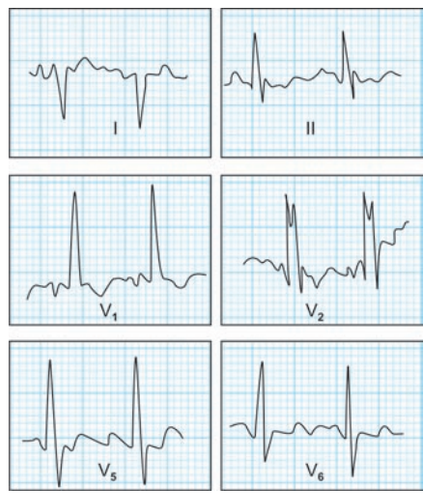


Fig. 6.73: ECG of RBBB, with left posterior hemiblock (LPHB)-Bifascicular block.The RBBB is evidenced by M-pattern or positive QRS complexes in lead V_1-V_2. Left posterior fascicular (hemi)block is evidenced by right axis deviation, because there is predominant negative QRS complex in lead I and predominant positive QRS complex in Lead II

FACT FILE- IV

Classification of heart block

i. First degree AV heart block.
ii. Second degree AV heart block.
   Mobitz type I (Wenckebach)
   Mobitz type II
iii. Right bundle branch block.
   Incomplete
   Complete
iv. Left bundle branch block.
   a. Incomplete
      Complete
   b. Left anterior hemiblock
      Left posterior hemiblock
v. Bifascicular heart block
   a. Right bundle branch block plus left anterior hemiblock
   b. Right bundle branch block plus left posterior hemiblock
   c. Right or left bundle branch block with prolonged AV conduction
vi. Third degree (complete) heart block.
   Nodal
   Infranodal (Table 6.1)

ectopic focus situated at any portion of the ventricular myocardium. It is less common than supraventricular ectopics, but like it ventricular extrasystoles may occur even in normal individuals. Though ventricular premature beats are commonly seen in association with any form of organic heart disease, but is most common in IHD, infarction, myocarditis, digitalis toxicity, etc. Ventricular extrasystoles may also result from the effect of some drugs, e.g. catecholamines, halothane, digitalis, etc.

Mechanism or pathophysiology

As the ventricular extrasystole results from an irritable extra focus, situated at any portion of the ventricular myocardium,so these impulse does not travel through the normal specialised conductive tissue, i.e. purkinje fibres. Contrarily, the impulse travels through the ordinary ventricular muscle tissue which is a poor conducting medium. As a result the QRS complex is bizarre, widened and slurred, or notched. This premature impulse activates both the ventricles and a premature contraction occurs (Fig. 6.74).

The regular SA nodal rhythm is not disturbed, as the ectopic ventricular impulse does not penetrate the AV node and activates the atria or depolarises the SA node. Again the regular sinus impulse following the premature beat will usually not be able to activate the ventricles, since the latter is still in refractory state from the previous premature contraction.

Thus, the next sinus impulse will activate the ventricles only when the refractory period is over, provided another ventricular extrasystole does not occur (Fig. 6.75).

Therefore, the interval between the two successive sinus beat preceeding and following the premature beat will be exactly twice of the regular sinus interval. The ventricular extrasystole is premature. It arises in the ventricular diastolic period caused by the preceeding sinus beat. It is therefore recorded earlier, than the next anticipated sinus beat.

This ventricular extrasystole fails to penetrate the AV node retrogradely. Thus, the SA node is protected from the ectopic ventricular impulse and is not diturbed from its rhythmic function. Following an extrasystole, as the ventricles remain in a refractory stage, so the regular normal incoming impulses from the SA node fails to initiate regular ventricular contraction. Hence, following an extrasystole, there is a time gap, during which the ventricle is waiting for impulses from the SA node in normal a rhythm. This time gap following the extrasystole is called the compensatory pause. The interval between the ectopic beat and the previous sinus beat is called the coupling interval. It is constant for all the extrasystoles arising from the same focus. This is because the extrasystole is anyway related to or forced by or precipitated by the previous sinus beat.

Table 6.1: Causes of complete heart block

(i)	**Congenital**
(ii)	**Acquired**
	Idiopathic fibrosis
	Myocardial ischaemia/infarction
	Inflammation (carditis)
	Trauma (cardiac surgery)
	Drugs-digoxin, β-blockers

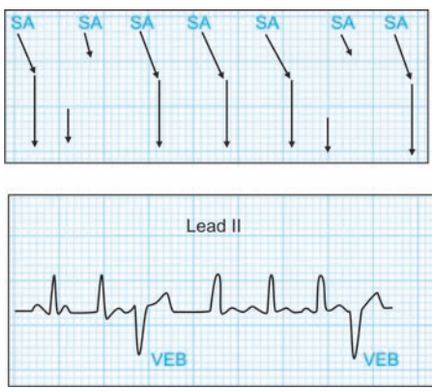


Fig. 6.74: Unifocal ventricular ectopic beats (VEB). Two VEB's are seen in association with a regular sinus ventricular rhythm. Both VEB's are of the same configuration and direction which indicates a single focus of origin

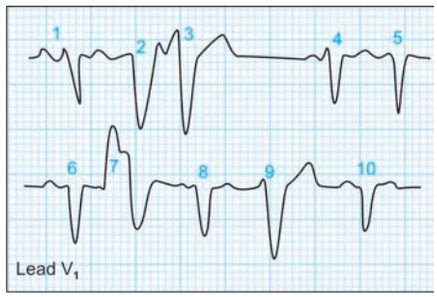


Fig. 6.75: Multifocal VEBs in lead V_1. Here QRS complexes (1, 4, 5, 6, 8 and 10) are sinus conducted. Ectopic QRS complexes (2, 3 and 9) are oriented towards the left (deep S wave in V_1), which indicates right ventricular origin. Ectopic QRS complex (7) is oriented toward right (tall R wave in V_1) which indicates left ventricular origin

ECG pattern

The QRS complexes of ventricular extrasystoles are broad, bizarre, slurred and notched in appearance. The ST segment and T wave is directed opposite to the main deflection of ectopic QRS complex. When the ventricular extrasystoles arise from multiple ectopic foci, then the configuration of extra QRS complexes are

different, even in the same lead. Couplet and triplet terms are used to describe two or three successive ventricular ectopic beats, whereas a run of alternate sinus and ectopic beat is called bigeminy. But, when this arises from a single focus, the configuration is same in one lead. Depending upon the relationship of timing between a ventricular premature beat and a P wave, the later may precede or be hidden or even follow the QRS complex (Fig. 6.76).

Since the normal sinus beat is usually not disturbed, a full compensatory pause follows the ventricular premature beat. If the sinus rhythm is very slow, then a ventricular premature beat can occur between two normal sinus beats without altering the RR interval and without producing a compensatory pause. This is known as the 'interpolated beat' (Fig. 6.77).

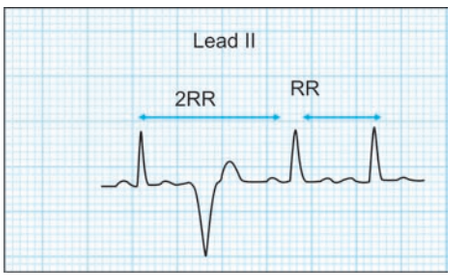


Fig. 6.76: A VEB with a compensatory pause. VEB is seen after the 1st sinus beat. The RR interval between the 2nd and 3rd sinus conducted QRS complex is 0.8 sec. The RR interval between the 1st and 2nd sinus conducted QRS complex is double than the RR interval between the second and third sinus conducted beats. This indicates full compensatory pause

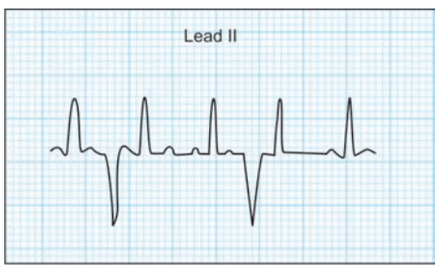


Fig. 6.77: Interpolated ventricular ectopic beats (VEB). This VEB is seen after the 1st and 3rd sinus beats, without any compensatory pause

If the extra QRS deflection is upright, in the right precordial leads (V_{1-2}) and downwards in the left precordial leads (V_{5-6}), then one can safely distinguish that this ectopic focus is situated in the left ventricle. The reverse is true for the right ventricular premature beats. Thus, the left ventricular extrasystole mimics the QRS pattern of complete RBBB and right ventricular extrasystole mimics the QRS pattern of complete LBBB. The ventricular premature beats may occur in association with other arrhythmias also (Fig. 6.78).

The premature ventricular contraction by ectopic beats produce a low stroke volume, because this ventricular contraction is ineffective. The pulse is therefore irregular with weak or missed beats. Patients are often asymptomatic, but may complain of an irregular heartbeat, missed beats or abnormally strong beats. The significance of ventricular ectopic beats (VEBs) depends on the nature of the underlying heart disease.

VEBs may frequently found in normal people and their prevalance increases with age.VEBs are more prominent at rest in patients with otherwise normal hearts and tend to disappear with exercise. The outlook of these type of VEB is excellent and so treatment is unnecessary. Although a low dose β-blocker treatment is sometimes used to suppress the anxiety and palpitation. VEBs are sometimes a manifestation of subclinical heart disease. There is no evidence that such patients are merited by anti-arrythmic therapy. But the discovery of frequent VEBs may prompt some general cardiac investigations (Fig. 6.79).

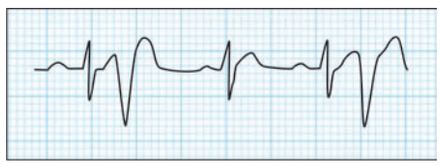


Fig. 6.78: This ECG shows ventricular premature contractions during a vulnerable period i.e. before completion of the T wave of the preceeding beat (R on T phenomenon)

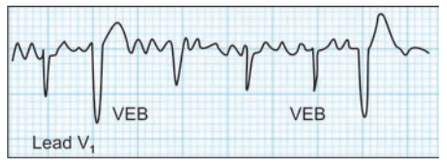


Fig. 6.79: Ventricular ectopic beats (VEB) in association with atrial fibrillation

Frequent VEBs are often observed during acute MI. But, they are of no prognostic significance and require no special treatment. However, persistent and frequent VEBs in patients, who have survived the acute phase of MI are indicative of a poor outcome. Unfortunately, antiarrythmic therapy doesnot improve and may even worsen the prognosis in these patients (Figs 6.80 and 6.81).

VEBs are common in patients with heart failure and are associated with an adverse prognosis. But again, the outlook is not better if they are suppressed

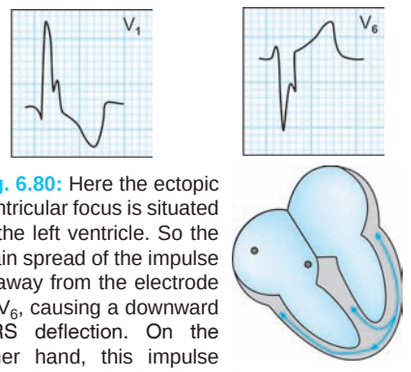


Fig. 6.80: Here the ectopic ventricular focus is situated in the left ventricle. So the main spread of the impulse is away from the electrode at V_6, causing a downward QRS deflection. On the other hand, this impulse spreads towards the electrode at V_1, causing an upward QRS deflection

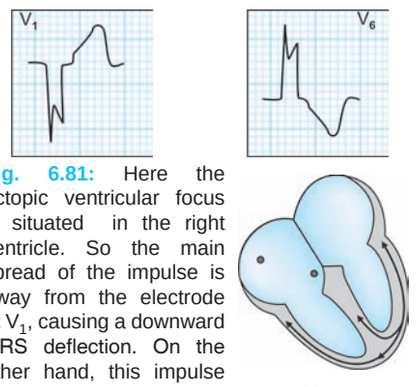


Fig. 6.81: Here the ectopic ventricular focus is situated in the right ventricle. So the main spread of the impulse is away from the electrode at V_1, causing a downward QRS deflection. On the other hand, this impulse spre- ads towards the electrode at V_6, causing an upward QRS deflection

with anti-arrythmic drugs. Effective treatment of the heart failure may suppress the ectopic beats. VEBs are also the feature of digoxin toxicity and may occur as escape beats in the presence of an underlying bradycardia. Treatment should be directed at the underlying causes.

R on T phenomenon

The QT interval approximates the refractory period of the action potential of cardiac myocytes. Ventricular extrasystoles usually occur after the T waves of the previous beat and before the next beat.

Sometimes, the ventricular extrasystole starts at the upstroke or downstroke of the T wave of the previous beat (Fig. 6.82).

This portion of the T wave coincides with the supernormal excitability period of the action potential of cardiac myocyte and is very vulnerable for repetitive firing. So such an ectopic beat is prone to initiate repetitive discharges, i.e. ventricular tachycardia or ventricular fibrillation. This phenomenon is called the R on T phenomenon and has serious clinical significance.

Supernormal excitability

The time period in the action potential curve during which no stimulus will propagate another action potential is known as the absolute refractory period.

This period includes phases 0, 1, 2 and part of the phase 3. Following this, there is a time period when only a strong stimulus can evoke a response. This is called the relative (or effective) refractory period. It begins when the transmembrane potential in phase 3 reaches the threshold potential level (about –60 mV) and ends just before the termination of phase 3. This is followed by a period of supernormal excitability (terminal part of phase 3 and beginning of phase 4) when even a relatively weak stimulus can evoke a response.

Ventricular bigeminy

When a regular sinus beat controlled normal ventricular contraction and a ventricular premature beat (or extrasystole) occurs alternately, then it is called the ventricular bigeminy. Here there is a fixed coupling i.e. there is a constant interval between a sinus beat controlled ventricular beat and a premature ventricular beat. This fixed coupling indicates that the sinus beat controls the VEB by re-entry mechanism, present in the ventricular myocardium (Fig. 6.83).

Significance of Ventricular Extrasystole

Although, ventricular extrasystoles may occasionally occur in normal individuals, still their presence should always be viewed with suspicion. VEB is always significant when it is associated with some myocardial disease. The ventricular extrasystoles from multiple foci with or without chest pain always indicate serious myocardial disease. Unifocal ventricular extrasystoles are usually indicative of cardiac diseases if (i) they occur in persons over 40 years of age, (ii) they occur frequently, i.e in crops or showers, (iii) they occur in association with other cardiac diseases, (iv) they occur in bigeminal rhythm and (v) they are precipated by exercise.

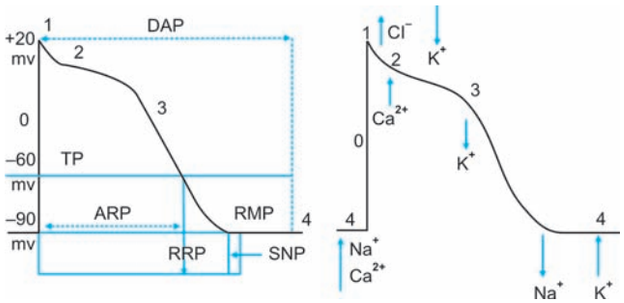


Fig. 6.82: Action potential (AP) of a cell of ventricular muscle
TP= Threshold potential, RMP= Resting membrane potential, DAP = Duration of action potential, ARP = Absolute refractory period, RRP = Relative refractory period, SNP = Super normal period, 0 = Depolarisation phase, 1, 2, 3 = Repolarisation phase, 4 = Diastolic phase
Depolarisation + repolarisation = ventricular systole.
Action potential (AP) occuring cyclically is described below--
Phase 4 = Resting condition or diastole where the resting membrane potential (RMP) is -70 to -90 mv. This mainly depends on the K^+ concentration, as it is more permeable than the Na^+.
Phase 0 = Rapid depolarisation phase due to Na+ and Ca^{2+} influx.
Phase 1 = Initial repolarisation phase. It is due to influx of Cl^- and coming out of K^+
Phase 2 = Plateau phase of repolarisation with slow influx of $Ca^{2+}$and coming out of K^+ from cells. The amount of entry of Ca^{2+} and exit of K^+ is same and balance each other. So a plateau of electrical potential is maintained.
Phase 3 = Rapid repolarisation it is due to the efflux of K^+ causing rapid return of intracellular potential to-70 or -90 mv. It estalishes the normal negative resting potential. But inside of the cell is left with excess Na^+ and deficit of K^+.
Phase 4 = The Na^+ goes out of the cell in exchange of K+, which enters the cell, maintaining the RMP. In the resting state, the outside of the cell is positive while the inside is negative.This is called the polarised state (phase 4). When the outside of the cell becomes negative and the inside is positive, the condition is called the depolarised state(phase 0). Again when the out side of the cell becomes positive and the inside becomes negative, but the intracllular and extracellular concentration of Na^+ and K^+ is opposite to normal. It is called the repolarised state (phases1,2and3). When the polarisation of the cell remains same as repolarisation, but the Na^+ and K^+ concentration becomes normal, it is called the polarised state.

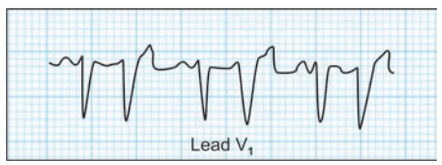


Fig. 6.83: ECG of ventricular bigeminy.It is characterised by regular sinus rhythm followed by a VEB, a pause, a sinus ventricular beat and then repetation of this sequence.The time interval between the sinus beat and the VEB is perfectly constant. This is called fixed coupling. The P waves of the sinus beat are buried in the QRS complex of each VEB

The following classification of ventricular premature beats is commonly used as a clinical guide to indicate the severity:

Grade 0: No ectopic
Grade 1: < 30/hour
Grade 2: > 30/hour
Grade 3: Multiformed complexes
Grade 4: Couplets of 3 or more (ventricular tachycardia)
Grade 5: R on T phenomenon

Ventricular Tachycardia

The ventricular tachycardia is due to the rapid and successive discharge of impulses from an ectopic ventricular pacemaking focus. It may be defined as a series of four or more consecutive ventricular ectopic beats which are recorded in rapid succession. The rate of ventricular tachycardia usually varies between 140 to 220 beats per minute. There are two principal forms of VT. They are (i) idio ventricular tachycardia and (ii) extrasystolic ventricular tachycardia (Fig. 6.84).

The basic principle of idioventricular tachycardia is the idio ventricular rhythm, where there is complete heart block and an increased escape ventricular rate. Actually it is a severe form of accelerated ventricular rhythm. On the contrary, the extrasystolic ventricular tachycardia is not associated with a complete heart block and impulses from the SA node comes to ventricular regularly. But, there is an increased automacity of any ventricular tissue, making ectopic focus.

The ventricular tachycardia is also the result of re-entry mechanism within the ventricular myocardium. It is most commonly associated with a recently manifested acute MI. It may also occur in association with hypertensive and atherosclerotic heart diseases and certain drug (digitalis, quinidine, etc) intoxication. It also occurs in association with WPW syndrome. Ventricular tachycardia is a very serious condition and always indicates a serious heart disease. It should be treated successfully, otherwise mortality rate is very high.

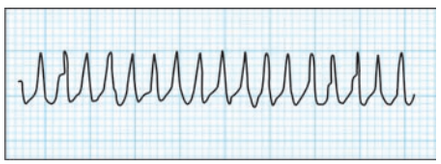


Fig. 6.84: ECG of ventricular tachycardia, characterised by repeated broad QRS complexes (broad complex tachycardia.)

ECG pattern

The ECG tracing of ventricular tachycardia is constituted by a rapid succession of ventricular premature beats, where it may be impossible to separate the QRS complexes from the ST segments and T waves. The abnormal ventricular complexes are regular, and the tracing has the appearance of a series of regular wide and large undulations.

The normal sinus rhythm usually continues independently with the ventricular tachycardia. But, the P waves cannot be seen within the images of ventricular complexes. Ventricular tachycardia may occur independently with sinus rhythm or also in the presence of any atrial arrhythmia. But, it cannot be diagnosed without the use of oesophageal leads or intracardiac monitoring. It has been assumed that ventricular tachycardia originating from the left ventricle would result in ventricular complexes simulating RBBB and that ventricular tachycardia originating in the right ventricle would simulate LBBB.

The ventricular tachycardia differs from ventricular fibrillation by its uniformity, constancy and deflections of relatively large amplitude. The deflections of ventricular fibrillation are small, completely chaotic and irregular.

Torsades De Pointes

This is also called 'the multiform ventricular tachycardia or flutter'. As the name signifies, it is polymorphic type of origin where the QRS complexes arise from multiventricular ectopic foci. Therefore, the QRS complexes vary from upright to inverted in direction and come in a cyclic fashion. The sharp points of the QRS complexes may for a short period be directed upwards which is followed for a short period by a change in QRS contour where the sharp points are directed downwards. Hence, the term 'torsades de pointes' which means twisting or torsion of points is applied. The most common cause of this situation is prolongation of ventricular repolarisation and this is due to drug toxicity such as quinidine, amiodarone, etc. (Fig. 6.85).

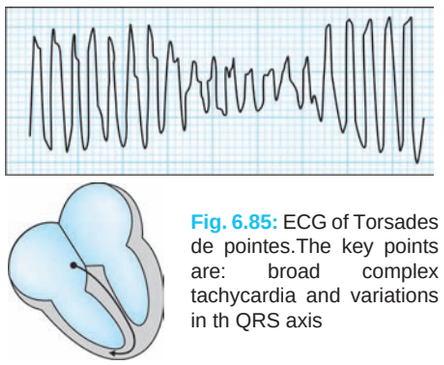


Fig. 6.85: ECG of Torsades de pointes.The key points are: broad complex tachycardia and variations in th QRS axis

Accelerated idioventricular rhythm

The heart has many potential pacemaking cells or tissues such as the SA node, AV node, atrial muscle, ventricular myocardium and special conducting tissues. But, among these only one pacemaking cell which has the highest rate of automacity controls the heart rate. This is because the impulses arising from the tissues with higher automaticity reach the other potential pacemaker cells and abolish their discharge, before they have the time to mature and fire (Fig. 6.86).

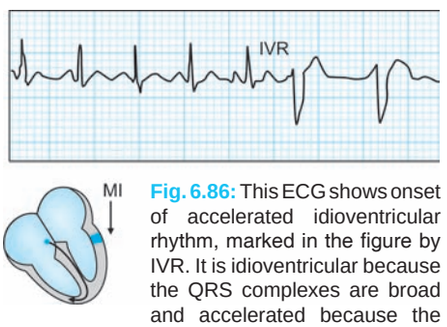


Fig. 6.86: This ECG shows onset of accelerated idioventricular rhythm, marked in the figure by IVR. It is idioventricular because the QRS complexes are broad and accelerated because the rate is ± 88/min

Therefore, the subsidiary pacemaker area gets some protection from the impulses of the fastest pacemaker area. Under certain circumstances the automaticity of these subsidiary pacemakers area becomes enhanced. For example, when the AV nodal discharge rate exceeds the sinus rate, then the AV nodal rhythm manifests as AV nodal tachycardia. Similarly, in a complete heart block when the ventricular myocardium acts as a pacemaker and beats 30 to 40 times per minute, then it is called the idioventricular rhythm.When this idioventricular rhythm is enhanced due to any cause, it is called the idioventricular tachycardia whose rate is usually 150 to 200/min. The accelerated idioventricular rhythm is in between these two conditions (idioventricular rhythm and idioventricular tachycardia) where heart rate varies between 60 to 100/min. Here the term tachycardia is not used, because the heart rate remains below 100/min.

This condition is most commonly seen in association with acute MI. It is usually transient and may not require any therapy at all, especially if the haemodynamic status is stable. It is a much more benign abnormal ventricular rhythm than the slow idioventricular rhythm with complete heart block, or ventricular tachycardia with sinus activity. Therapy is not indicated initially, but close observation is needed for any clinical deterioration and then management is started.

Ventricular Fibrillation

It is the expression of uncoordinated, chaotic, ventricular depolarisation. Electrophysiologically the ventricular myocardium is fragmented into multiple islets of tissues which are in various stages of excitation and recovery. As the coordinated ventricular activation and muscular contractions is lost and the ventricular myocardium starts fibrillating, therefore the haemodynamic pumping action of the heart ceases and death ensues, unless defibrillation is instituted immediately. The diagnosis of ventricular fibrillation must be made electrophysiologically, since the peripheral pulses are not palpable and the heart sound is inaudible (Fig. 6.87).

As the ventricular activation and contractions are completely irregular and chaotic, so the ECG shows completely irregular and bizarre QRS complexes with varying size and configuration. The atria may continue to respond to the sinus rhythm, but the P waves are not visible without the aid of oesophageal leads.

The factors that give rise to ventricular tachycardia may also be responsible for ventricular fibrillation. Among them, the most important factor is MI and this explains many sudden deaths in this disease. It may also occur as the terminal manifestation of many organic heart diseases and hypokalaemia. It may also occur during surgical procedures performed under GA where hypoxia is the commonest precipitating factor. It occurs characteristically with hypothermia, when the body temperature drops below 28°C. The electrical shock may also produce ventricular fibrillation. The ventricular fibrillation can be classified into: (i) primary ventricular fibrillation and (ii) secondary ventricular fibrillation (Fig. 6.88).

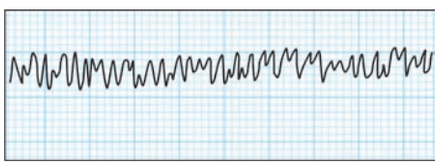


Fig. 6.87: This is an ECG of ventricular fibrillation, characterised by chaotic ventricular activity

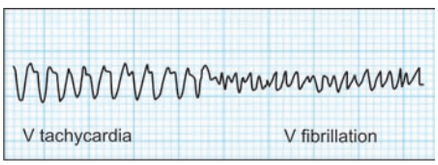


Fig. 6.88: This is an ECG of ventricular fibrillation after a ventricular tachycardia.The QRS complexes are more bizarre during the period of ventricular fibrillation and vary in size and configuration from beat to beat

The primary ventricular fibrillation is defined as the ventricular fibrillation that occurs in patients without any preexisting cardiac diseases e.g. hypotension, (systolic pressure < 80 mm of Hg, due to blood loss), hypokalaemia, heart failure, etc. It responds relatively well to electrical defibrillation and resuscitation is usually successful. The secondary ventricular fibrillation is defined as the ventricular fibrillation which occurs in patients with serious medical disorders in the presence of previous cardiac diseases (e.g. severe uncorrected hypotension, respiratory failure, cardiac failure, liver diseases, electrolyte imbalance, etc). Resuscitation is usually unsuccessful in secondary ventricular fibrillation.

Aetiopathology

Development of VF (Ventricular Fibrillation) is usually caused by the coincidence of following two fundamental events.

1. Development of advanced physiological asymmetry between two ventricular areas, as there is a nonhomogeneous state of myocardial refractoriness. Such asymmetrical refractory state of the ventricular myocardium is due to severe disease processes, e.g. M1 which results in local O_2 lack, local glucose deficiency and local ionic changes such as: Ca^{2+}, Na^{+}, K^{+} etc.
2. Premature repetitive stimulation of the ventricular myocardium which aggravates the out of phase state and precipitates fibrillation. The source of such premature rapid stimulation is ventricular extrasystoles with very short coupling interval. Ventricular extrasystoles with R on T phenomenon represent the most vulnerable type of ventricular excitability and precipitates VF.

Clinical significance and prognosis

VF is the most serious among all the cardiac arrythmias and should be treated promptly. The prompt treatment of patients

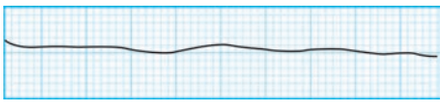


Fig. 6.89: ECG of an asystole, characterised by a 'flat line' with no spontaneous atrial or ventricular activity

with VF which is commonly associated with MI in coronary care units has largely reduced its mortality rate by its immediate recognition and treatment.

VF may occur in transient paroxysms and may be the cause of the Stokes-Adams Syndrome. Prognosis is very poor for such VF and recovery is rare, if arrhythmia continues for over 5 minutes. Prognosis is better when this arrhythmia occurs in the operating room or in the intensive care unit where immediate resuscitative measures including electrical defibrillation can be instituted immediately (Fig. 6.89).

Clinically, VF can not be differentiated from a ventricular standstill, because in both the conditions there is no palpable or auscultatory evidence of cardiac action. So, it is essential to differentiate these two conditions electrocardiographically, since their treatment differs considerably. For example, ventricular standstill may respond to epinephrine, isoproterenol, atropine or even electrical pacing, whereas VF requires immediate electrical defibrillation.

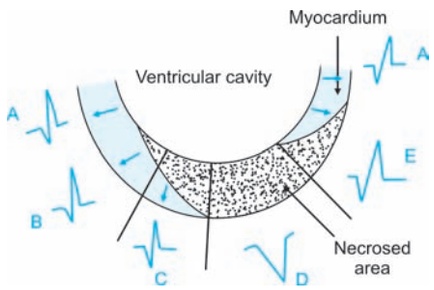
GENESIS OF ST SEGMENT AND T WAVE

In the ECG tracing, the point at which the QRS complex ends and the ST segment begins is called the J point or J junction. The portion of tracing from the J junction to the onset of the T wave is called the ST segment. The ST segment is usually an isoelectric line, but may vary from 0.5 to +2 mm in the precordial leads. It is elevated or depressed in comparison to that portion of the baseline which is situated between the termination of the T wave and the beginning of the next P wave. The ST segment usually merges smoothly and imperceptibly with the proximal limb of the T wave (Fig. 6.90).

The ST segment and the T wave represents the ventricular repolarization. As the normal ST segment is isoelectric, so it does not manifest the axis. Only in abnormal conditions when the ST segment is deviated above or below the baseline, then it produces a measurable axis.

The deviation of the axis of ST segment is based on the same principles as those used for the P, QRS and T wave axes. The first step is to look out for the lead in which the ST segment is more or less isoelectric or equiphasic. Then, it is obvious that the axis of the ST segment in this particular tracing is perpendicular to that lead. For example, if the ST segment is isoelectric i.e. no deviation in the lead aVR, then the ST segment axis is perpendicular to the lead aVR and / or parallel to lead III, where it is maximally deviated from the isoelectric line. Thus, the ST segment is parallel to the positive pole of that lead which is perpendicular to the isoelctric lead.

When the ST segment is deviated above or below the baseline, as a result of coronary artery disease, in both horizontal and frontal plane it is directed towards the surface of the injury (Fig. 6.91).



Figs 6.90A to E: This diagram illustrates-

A. Normal endocardial to epicardial QRS activation.
B. Minimal subendocardial necrosis with slight change or unchanged QRS activation.
C. Significant subendocardial necrosis with dimini shed QRS activation, and a pathological Q-wave
D. Total transmural necrosis with absent QRS activation and presence of Q wave.
E. Subepicardial necrosis with diminished QRS activation

CORONARY INSUFFICIENCY

The impaired coronary blood flow may be an established case (i.e. inadequate coronary blood flow both during rest and increased demand) or may be a relative one (i.e. blood flow being adequate at rest but inadequate when the myocardial demand is increased such as in exercise) or may even be due to some additional transient factors (i.e. coronary vasospasm). In ECG coronary artery disease may be reflected as changes in the QRS complexes, ST segment, T wave and the U wave. Like before, these changes may be present at rest or may be precipitated by factors which induce transient myocardial ischaemia, e.g. exercise.

ECG Effects

The QRS complexes represent the phase of depolarisation of the ventricles, while the ST segment and the T wave represents the repolarisation process of the ventricles. The effects of coronary insufficiency is reflected in both the depolarisation and repolarization processes. But, the earliest changes are usually evident during repolarisation, i.e. on the ST segment and T wave. As a rule the changes in depolarisation due to ischaemia tend to be

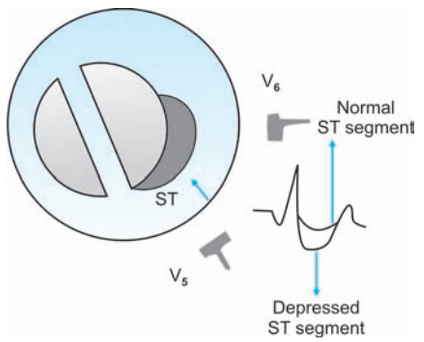


Fig. 6.91: The basic principles of ECG changes in subendocardial and subepicardial injury in angina pectoris. The subendocardial ischaemia results in a ST shift towards the injured surface i.e. the left ventricular cavity in aVR and away from the precordial leads in V_1 to V_6. Thus, it results in ST segment depression in leads V_1 to V_6 and elevation in leads aVR

permanent, whereas the initial changes in repolarisation tend to be temporary.

A. Effects on QRS complex

The effects of coronary insufficiency on QRS complexes are like changes during depolarisation and are permanent e.g LBBB, left axis deviation, etc.

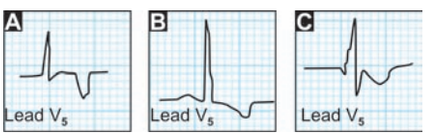
B. Effects on ST segment

Coronary insufficiency may depress and alter the shape of ST segment. Occasionally, it may also present with transient elevation of ST segment. This is the manifestation of variant forms of angina pectoris, such as : Prinzmetal Angina.

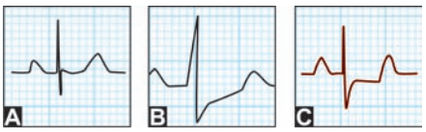
C. Effects on T wave

The T wave is the most unstable, but a significant component of an ECG recording. Certain nonspecific changes of this deflection may occur with hyperventilation, heavy meals, anxiety, etc. (Fig. 6.92).

Despite this, there are certain specific T wave changes that are frequently suggestive of coronary insufficiency. The T wave associated with coronary insufficiency has symmetrical limbs and a sharp pointed arrow-head vertex. The changes of T wave configuration from other causes usually show asymmetrical limbs with a relatively blunt vertex or nadir. As a result of ST segment depression, the T wave may be dragged downwards, giving an appearance of inversion. This T wave inversion is of slight to moderate degree. Occasionally, one may see a very deep T wave inversion, simulating that seen in myocardial infarction (Fig. 6.93).



Figs 6.92A to C: ECG shows the ST segment and T wave changes
A: Coronary insufficiency.
B: The "strain" pattern, associated with ventricular hypertrophy.
C: The effect of digitalis



Figs 6.93A to C: This ECG shows—
A: Normal ST segment
B: Junctional ST segment depression
C: Plain ST segment depression

Depression and Significance of the Shape of ST Segment

Normally the ST segment merges gradually, smoothly and imperceptibly with the ascending limb of T wave, so that a separation between the two is difficult or impossible (Fig. 6.94).

One of the earliest signs of coronary insufficiency is an alteration in the shape of ST segment, resulting in a sharp-angled ST-T junction. This produces a horizontal appearance in the ST segment. A further evaluation of this effect is depression of the ST segment. The depression of the horizontal ST segment gives the appearance of plane depression. The ST segment may also have a sagging depression.

ST Segment Depression

The most significant criteria of ST segment change in coronary insufficiency is depression of 1 mm or more at a point, 0.08 seconds after the onset of the ST segment (J point). Clinically the character of the ST depression has major significance. The various types of ST segment depression are:

i. Down sloping ST segment: There is a ST depression of 1mm or more at the J point. This finding has the highest specificity for the diagnosis of myocardial ischaemia. The false positive incidence is less than 1 to 2%.
ii. Horizontal ST segment: There is a ST depression of 1 mm or more at the J point and then the ST segment continues horizontally in a depressed condition, for 0.8 seconds. Although such a finding has been considered diagnostic of myocardial ischaemia, but the false positive incidence is approximately 15 to 20%.
iii. Slow upstroke of the ST segment: This is defined as ST depression of 1 mm or more at the 'J' point, with an upward sloping of the ST segment, which is not greater than 1 mV/sec. Thefalse positive incidence exceeds 40 %.
iv. Rapid upstroke of the ST segment: There is 1 mm or more ST depression at the 'J' point, but the ST segment goes rapidly upwards and the slope exceeds 1 mV/sec (Fig. 6.95).

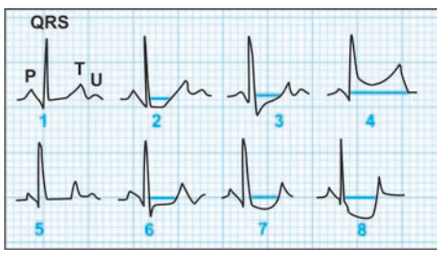
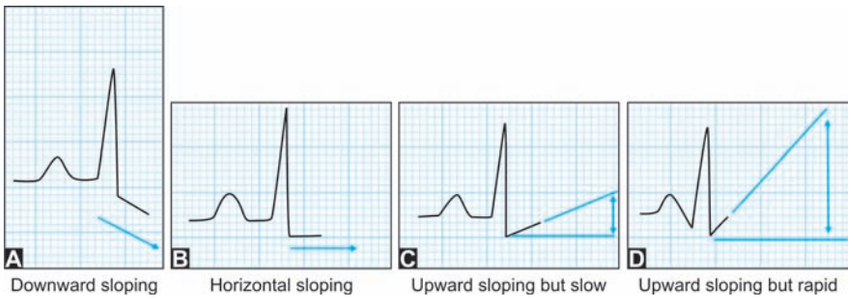


Fig. 6.94: This diagram illustrates-
1. Normal P-QRS-T-U complex.
2. Junctional depression.
3. Depression with upward sloping
4. Elevation of ST segment and increase in T wave amplitude
5. Horizontal ST segment with sharp-angled ST-T junction.
6. Plain depression with U wave inversion.
7. Sagging depression.
8. Depression with downward sloping

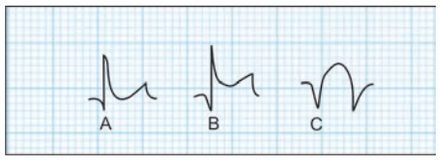
Mechanism of depression of ST segment

Transient myocardial ischaemia, as manifested clinically by the classic form of angina pectoris, results in temporary subendocardial ischaemia at the apical region of left ventricle. This injured surface faces the left ventricular cavity.

The basic principles for the determination of ST segment deviation is that the ST segment vector is always directed towards the surface of the injury. Thus, a lead oriented to the injured surface, (in this case the left ventricular cavity) e.g. lead aVR will reflect the ischaemia by a raised ST segment and an inverted T wave. Leads facing the external surface, mainly leads V_5 and V_6 will reflect a reciprocal ST segment depression.



Figs 6.95A to D: Different types of ST segment depression



Figs 6.96A to C: This diagram illustrates
A. Normal QRST complex.
B. Hyperactive or acute phase of myocardial infarction (MI).
C. Fully evolved phase of MI

ST Segment Elevation

Uncommonly in response to ischaemia, ST segment elevation of more than1 mm can develop. This is generally an evidence of severe transmural ischaemia.

This variant form of angina pectoris is due to the transient subepicardial ischaemic injury. This condition manifests characteristically with transient elevation of the ST segment in leads oriented to the injured surface. This type of angina pectoris was first described by Prinzmetal and his associates, so it is named as 'Printmetal angina'.

Computer Analysis

Recently computers are frequently used to measure accurately the amount of depression and elevation of the ST segment and its slope in ECG records. It is definitely more correct than visual interpretation of an individual. Nowadays, a newer and better computer programs are being developed, which measure the ST segment depression in multiple leads and integrade it with the changes in voltage of R wave, heart rate at which these abnormalities appear, effect of exercise and the duration of such changes. The computer analysis improves the specificity and sensitivity of the ECG recordings.

MYOCARDIAL INFARCTION AND ECG CHANGES

The site of myocardial infarction is actually constituted by three pathological conditions such as necrosis, injury and ischaemia. So the different electrical charges in these three pathological areas are reflected at a time in the ECG and help to constitute a composite ECG picture of MI. Again the myocardial infarction passes through three phases and has different sites of occurrence. So, according to these two factors (different phases of evolution and various sites) the ECG graph also changes. The ECG of MI also changes with the presence of concomitant arrhythmias e.g LBBB, VT, etc. The three phases through which the myocardial infarction passes are: hyperacute phase, fully evolved phase and phase of resolution.

Hyperacute Phase

This hyperacute phase of MI occurs just after its acute onset and it should be distinguished from the next phase, i.e the fully evolved phase. This hyperacute phase of MI is most important because it is very critical from the prognostic point of view and also for the occurance of complications such as: primary ventricular fibrillation and death which is most likely to occur in this phase. So, the manifestation of hyperacute phase is an indication for intense vigilence and proper coronary care monitoring.

ECG Pattern

During the hyperacute phase of MI the ECG is characterised by the following three principal changes in leads, oriented to the infarcted surface (Fig. 6.96).

(i) Slope elevation of the ST segment

The ST segment is markedly elevated up to the apex of the T wave, which becomes widened and tall. The ST segment and the proximal limb of the T wave blends in such a smooth and imperceptible way that they cannot be identified separately. The leads oriented to the uninjured surface opposite to the injured surface, usually reflect marked reciprocal ST segment depression.

(ii) Tall and widened T wave

The T wave becomes widened and is taller (height may even exceed that of the R wave). Its proximal limb blends with the elevated ST segment and the two components cannot be distinguished separately. The classical and pathological diagnostic Q wave of MI does not develop until the large amplitude of T wave regresses.

(iii) Increased ventricular activation time (VAT)

This is due to the delay in onset of intrinsicoid deflection i.e. the time from the beginning of QRS complex to the apex of R wave (X-Y interval in the picture). This delay is due to the activation process of ventricular myocardium which takes a longer time to travel through the injured, but still viable infarcted region.

This hyperacute phase of MI is analogous to the manifestations of a variant form of angina pectoris. But in angina it is transient and in MI it proceeds to the next fully evolved phase of MI.

The Fully Evolved Phase of Acute MI

A fully evolved site of MI has usually three pathological areas—necrosis, injury

and ischaemia. Each area has separate distinguishable reflection in the ECG which is discussed below under the separate headings.

ECG Manifestations of Myocardial Necrosis

Myocardial necrosis is reflected by a deep and wide Q wave in electrodes oriented towards the necrotic area.

Mechanism

Dead tissue cannot be activated or depolarised, because it is electrically inert. Hence, when the dead or necrotic tissue involves the full thickness of the muscle, it produces an electrical sense of a hole or window in the muscle wall. So, an electrode placed over or oriented to this electrical hole (necrotic area) reflects the activity of distant healthy muscle as seen through the window (hole) (Fig. 6.97).

Thus, an electrode placed over an area of dead muscle tissue of left ventricular wall, i.e. left precordial leads (V_{5-6}) reflects the initial septal depolarisation which is passing from the left to the right. So, as this electrical impulse passes away from the lead V_{5-6}, so this is reflected as a negative deflection in these leads. Then, this left precordial lead senses only the distant right ventricular depolarization which is again from the left to the right due to the electrical impulses passing through the right ventricle in the absence of electrically active left ventricular tissue. Thus,

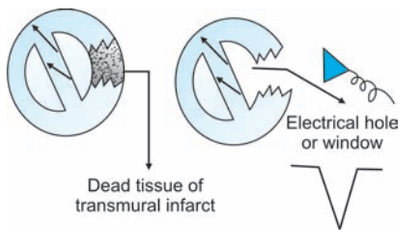


Fig. 6.97: The transmural dead tissue, representing the electrical hole or window. The electrode placed on this electrical hole will sense only the electrical impulse of the interventricular septum and right ventricular wall through the window which is running away from the electrode and producing a Q wave

it produces a further negative deflection. Hence, this results in a broad deep Q wave which is called the pathological Q wave of MI. As there is no R wave, so this Q wave can be termed as the QS wave.

ECG Manifestation of Myocardial Injury

In ECG the myocardial injury is reflected by a deviation (raised or depressed) of the ST segment and this deviation is towards the surface of injured tissue. This is because as discussed previously the current will flow from the uninjured tissue to the injured tissue, so the ST segment will be deviated towards the surface of injured tissue. Thus, if the injury is present dominantly on the left epicardial surface then the ST segment is deviated towards the injured left epicardial surface. It means the current will pass from the uninjured tissue of the right side of the heart to the injured tissue on the left and leads oriented towards this epicardial surface (e.g. lead V_6 in the diagram) will reflect a raised ST segment. On the contrary a lead oriented towards the uninjured surface (e.g. lead aVR in the diagram A) will reflect a depressed ST segment. With a dominant subendocardial injury a lead oriented to the injured subendocardial surface e.g. lead aVR will reflect an elevated ST segment. Whereas in a subendocardial injury a lead oriented to the uninjured surface e.g. lead V_6 will reflect a depressed ST segment. (Fig. 6.98).

Since, as the myocardial injury in most MI is predominantly epicardial with some subendocardial 'sparing' effect, so the manifestation presented electrocardiographically is an elevated ST segment in leads oriented to the epicardial surface. Thus, the ST segment in the leads oriented over the injured epicardial surface in a fully evolved phase of infarction is coved or convex-shaped (Fig. 6.99).

ECG Manifestation of Myocardial Ischaemia

The myocardial ischaemia is reflected by an inverted T wave (in reverse to the acute

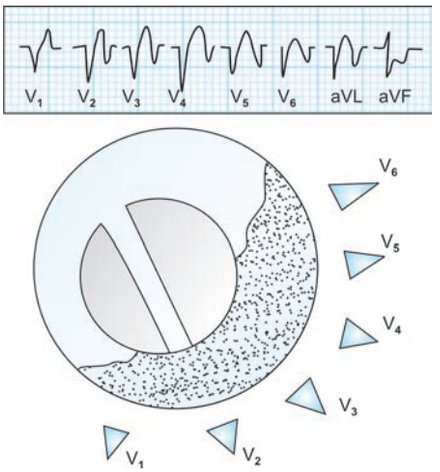
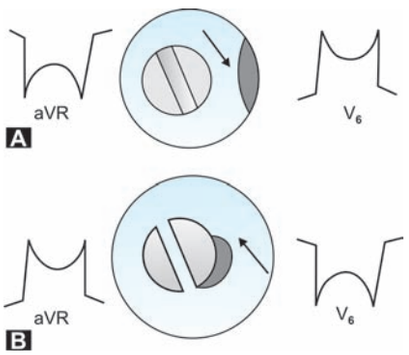


Fig. 6.98: ECG changes in acute extensive myocardial infarction

phase of MI where the T wave is upright and tall) in leads oriented to the ischaemic surface. This T wave becomes inverted when Q wave appears in the fully evolved phase of MI. This T wave inversion may be due to many conditions. But, in myocardial ischaemia it has certain characteristics, which tend to reflect their 'ischaemic' origin. These are usually 'arrow headed,' being peaked and symmetrical in appearance.

Total QRS Pattern of The Fully Evolved Phase of MI

As mentioned previously an infarcted area consists of a centrally situated necrotic



Figs 6.99A and B: The deviation of the ST segment in—
A. Subepicardial injury
B. Subendocardial injury

tissue, surrounded by a zone of injured tissue which again is surrounded by a zone of ischaemic myocardial tissue. So, a conventional electrode placed over the heart cannot pin point the individual injured tissue and so cannot reflect the electrical activity of the individual tissue of the infarcted area. Again, as the leads are situated on the body surface i.e. some distance away from the heart and subserves a relatively large area, so such electrodes shall reflect all the three electrical patterns of the three types of tissues such as pathological Q wave (for the necrosed tissue), raised and coved ST segment (for the injured tissue) and pointed inverted-symmetrical T wave (for the ischaemic tissue). This is referred to as the typical infarction pattern (Fig. 6.100).

When an electrode is oriented towards the injured and ischaemic tissue only but not on the necrotic tissue, then it will record only the coved and raised ST segment and an inverted T wave. The pathological Q wave will be absent or insignificant.

On the contrary, the reciprocal depression of the ST segment will occur in leads which are oriented towards the uninjured and healthy surface, opposite to the infarction. However, the diagnosis of infarction must not be based on the depression of the ST segment only. Because, this may also occur in conditions like angina pectoris. The diagnosis of MI must be based on the presence of pathological Q waves and / or a typically raised and coved ST segment, and/or inverted T wave.

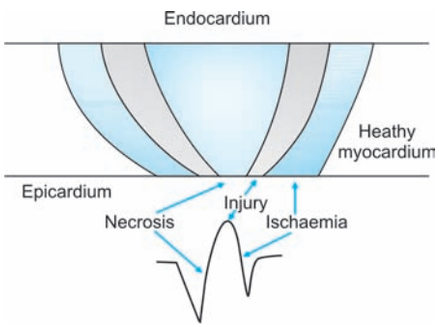
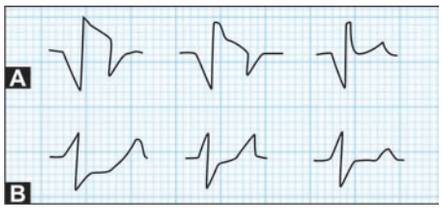


Fig. 6.100: An ideal representation of the fully evolved phase of acute myocardial infarction. The infarct is pyramidal in shape.Its broad base is oriented towards the endocardium



Figs 6.101A and B: The resolution of MI
A. When lead is oriented to the injured surface.
B. When lead is oriented to the uninjured surface

The Phase of Resolution

During the phase of resolution of an acute MI the following ECG changes occur progressively.

i. There is a gradual return of the elevated ST segment to its baseline, over a few weeks.
ii. Simultaneously, there is an appearance of a tall symmetrical T wave in leads oriented to the uninjured surface.
iii. Then, over a few weeks the abnormal T waves gradually return to their normal configuration.
iv. The pattern then stabilises into a residual state. In this state the only evidence of the previous MI is recognised by an abnormal Q wave in leads oriented to the infarcted area (Fig. 6.101).

SUMMARY

i. Acute infarction or the hyperactive phase: Slope elevation of the ST segment, tall widened T wave, Increased VAT.
ii. Fully evolved phase: Pathological Q wave, coved and raised ST segment, inverted symmetrical T wave.
iii. Old infarction: Pathological Q wave, ST segment and T wave may be normal or equivocal.

Significance of Q Waves

Normal Q waves (q)

The small 'q' waves which indicates initial activation of the interventricular septum are normally present in the left precordial leads (V_{4-6}), lead aVL and the standard lead I with the horizontal heart position and in left axis deviation. It is also present in standard leads II, III and lead aVF with the vertical heart position or right axis deviation.

The normal deep wide Q wave or QS complex may normally be present in the lead aVR and in lead V_1. This is because the positive poles of these leads are oriented towards the cavity or the basal region of the heart, so that the ventricular activation process moves away from these leads.

Pathological Q waves

The pathological Q wave which is designated as a capital letter have certain characteristics.

i. It should be wide > 0.04 secs in duration i.e. one small square.
ii. It should be deep > 4 mm i.e. more than 4 small squares.
iii. Pathological Q wave is associated with a great loss of height of the subsequent R wave and the Q: R ratio will be 25% or greater.
iv. Pathological Q wave may appear in several leads where normal q waves are not found. As for example, with anterolateral infarction, the pathological Q waves will be present in standard lead I, lead aVL and the lateral precordial leads V_{5-6}. With inferior infarction Q waves will be present in standard leads II, III and aVF.
v. The above mentioned characteristics of the Q wave must appear in leads which do not normally have deep and wide Q wave (i.e deep Q wave does not indicates infarction if it appear in lead aVR and possibly in lead V_1.)

Q Waves and bundle branch block

In the presence of LBBB the normal septal activation representing q waves is absent in leads oriented to the left precordial leads i.e V_{5-6}. Thus, in the presence of LBBB the manifestations of any small q wave in these leads no matter how small,

is always pathological and usually signifies MI. Alternatively, in the presence of LBBB a deep Q or a QS complex in lead V_1 resembling a pathological Q wave does not necessarily signify an infarction.The significance of the appearance of q or s waves in the presence of RBBB is same as in normal individuals.

Significance of Q wave in standard lead III

It is common for lead III to record a Q wave of 0.04 sec duration and a Q: R ratio greater than 25%. This is especially seen in normal ECG with a mean frontal QRS axis between +30° to 0° (horizontal heart position). When this is seen as normal finding, lead aVF will not record an abnormal Q wave. Therefore, the diagnosis of infarction must never be made on the basis of lead III tracings alone.

Further, pathological Q waves are also present in lead III in conditions other than MI. These are acute pulmonary embolism, left posterior hemiblock, etc. The presence of a Q wave in lead III is suggestive of MI, only if it carries the following criteria. They are:

i. The duration of the Q wave must be minimum 0.04 seconds
ii. The presence of any small q wave in leads aVF and II, along with lead III. The normal q wave present in lead III sometimes disappear when the patient takes a deep inspiration. So, it is always suggested to take a deep inspiration while recording a standard lead III ECG.

Localisation of Infarcted Areas

Myocardial infarction occurs predominantly at the anterior, inferior and posterior walls of the left ventricle, according to the rate of incidence (Fig. 6.102).

Anterior wall infarction (Fig. 6.103)

The anterior wall of the left ventricle is oriented towards all the precordial leads, aVL and standard lead I. Thus, an anterior wall infarction will be reflected by the presence of a typical infarction pattern like pathological Q wave, raised ST segment and inverted T wave in standard lead I, aVL and all the precordial leads. (Fig. 6.104).

The anterior wall infarction is further subdivided into:

i. Extensive anterior wall infarction: It is reflected by the typical infarction pattern in all the precordial leads, standard lead I and lead aVL
ii. Anteroseptal wall infarction: This indicates infarction across the interventricular septum. This is reflected by the infarction pattern in leads V_{1-4}.
iii. Anterolateral wall infarction: It is reflected by the typical infarction pattern in leads V_{4-6}, leads I and aVL (Fig. 6.105).

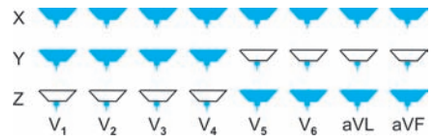


Fig. 6.102: The classification according to the extension of infarction. The black leads indicate the areas of infection
X. Extensive anterior infarction
Y. Anteroseptal infarction
Z. Anterolateral infarction

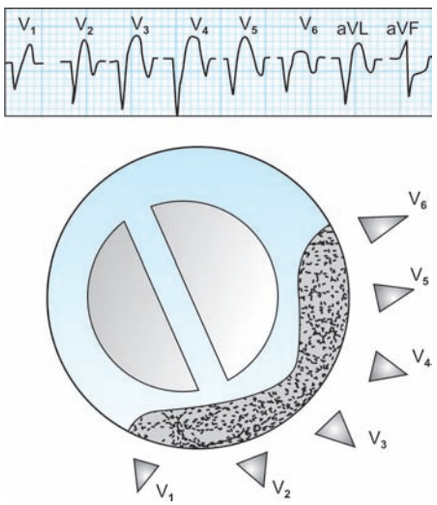


Fig. 6.103: Massive acute MI (extensive as all the leads are involved)All leads from V_1 to V_6 show the fully evolved phase of MI, which indicates acute and extensive anterior myocardial infarction

Inferior wall infarction (Fig. 6.106).

Lead aVF, standard lead II and III are oriented to the inferior surface of the heart. Thus, inferior infarction will be reflected by the presence of a typical infarction pattern in leads II, III and aVF (Fig. 6.107).

Posterior wall infarction

None of the conventional leads are oriented towards the true posterior surface of the heart. So, the diagnosis of true posterior wall infarction is made from reciprocal inverse changes in leads, which are

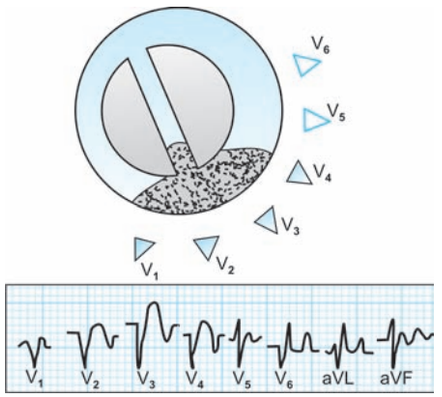


Fig. 6.104: Acute anteroseptal myocardial infarction

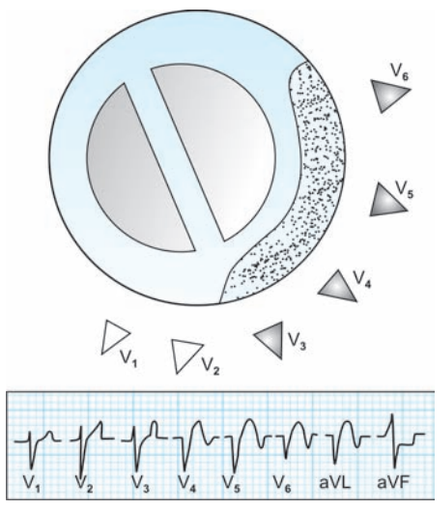


Fig. 6.105: Acute anterolateral myocardial infarction

directed towards the uninjured anterior surface of the heart, i.e. lead V_{1-2}. (Fig. 6.108).

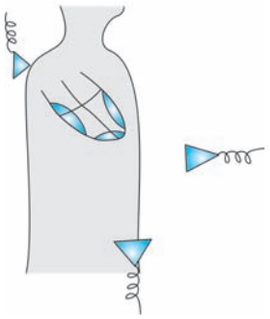


Fig. 6.106: The location of the inferior, anterior and posterior acute myocardial infarction and the corresponding leads by which it can be diagnosed better

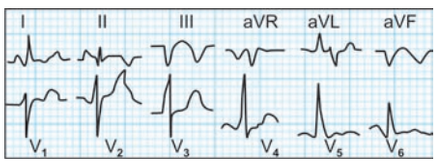
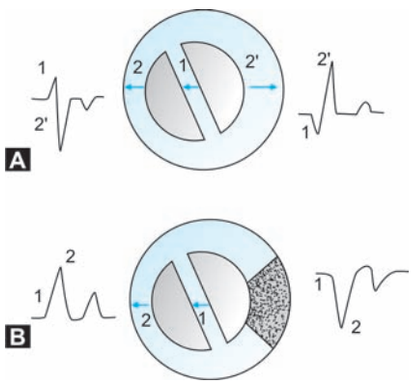


Fig. 6.107: A fully evolved acute inferior MI. A typical infarction pattern in standard lead III and lead aVF indicatethe infarction is situated at the inferior wall of the ventricle



Figs 6.108A and B:

A. The electrode is placed on left and right ventricle and there is no infarction. The subsequent normal ECG shows the pattern which should be formed.

B. There is infarction in the left ventricle ,and the second component (2') of the left ventricular electrical impulse is absent. The subsequent ECG shows how it is formed in the respective electrodes

CARDIAC AXIS AND NORMAL ECG

What is Cardiac Axis?

In simple term the cardiac axis is defined as the general direction, according to which the vector of a wave of any depolarisation and repolarisation of different cardiac activity flows through the atria and the ventricles during different cardiac cycles. The axis is, therefore conventionally referred to the angle of direction of flow of different electrical current, through the atria and the ventricles and is measured in degree. The reference or zero point for the measurement of this angle of direction is taken as the horizontal line which looks at the heart from left. The angle of direction of flow of electrical current which is situated below the horizontal (Figs 6.109 to 6.114) line is expressed as a positive number, i.e. clockwise measurements are positive. When the direction of flow is above the horizontal line, the angle is expressed as negative number, i.e. anticlockwise measurements are negative. Hence, the cardiac axis may be either +1° to +180° (clockwise) or –1° to –180° (anticlockwise).

The six limb leads (three bipolar standard limb leads and 3 unipolar augmented limb leads) look at the heart from six different sides or view points with different angles in the frontal plane.

The different angles from which the different limb leads look at the heart in the frontal plane are given in the table below. The six conventional precordial leads look at the heart from six different view points from anterior side of the heart with different angles in the horizontal plane. Thus, the axes or vectors of different depolarisation and repolarisation waves of heart in both the frontal and horizontal planes give an idea of formation or configuration of different ECG complexes, in all the 12 conventional leads (Table 6.2).

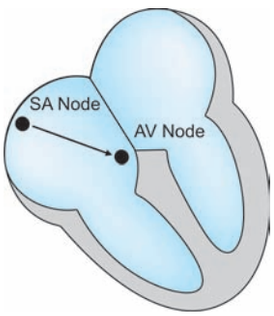


Fig. 6.109: Atrial activation

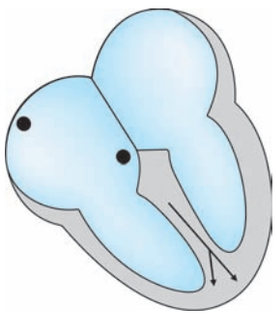


Fig. 6.111: Activation of the anteroseptal region of ventricular myocardium

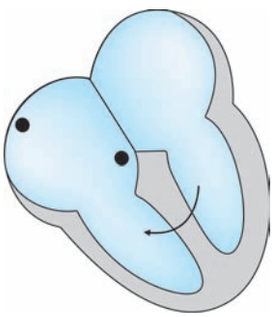


Fig. 6.110: Septal activation from left to right

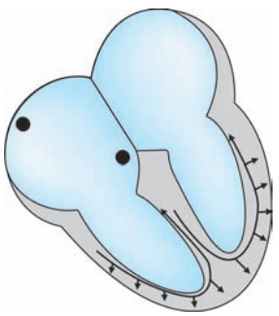


Fig. 6.112: Activation of major portion of ventricular myocardium from endocardium to epicardial surface

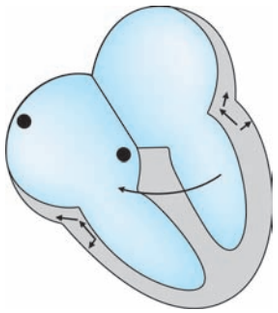


Fig. 6.113: Late activation of posterobasal portion of the left ventricle,the pulmonary conus, and the uppermost portion of the interventricular septum

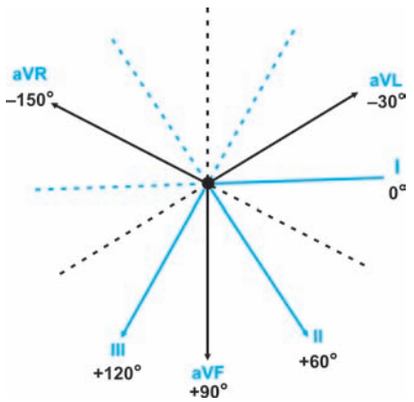


Fig. 6.114: The view points of six limb leads such as bipolar I, II, III and unipolar aVR, aVF, aVL. Each lead looks at the heart from different angles

Table 6.2: Limb leads and their angles of view

Limb leads	*The angles of view*
I	0
II	+60
aVF	+90
III	+120
aVR	–150
aVL	–30

What is Normal Axis of Heart?

The angle of mean QRS vector in the frontal plane determines its frontal axis of heart (I, II, III, aVR, aVL, aVF) and in horizontal plane determines its horizontal axis of heart ($V_{1\text{-}6}$). (Fig. 6.115).

In the frontal plane the normal axis of the heart lies between –30° and +110°.

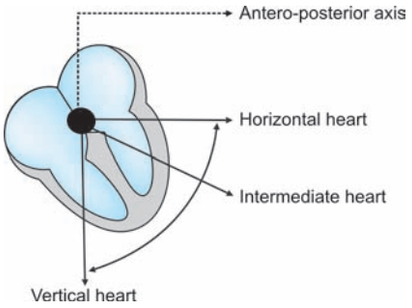


Fig. 6.115: Different position of the heart after rotation in anteroposterior axis

Therefore, the left axis deviation is defined as when the QRS vector lies between –30° and –90° and right axis deviation is defined as when the QRS vector lies between +110° and +/–180° (Fig. 6.116).

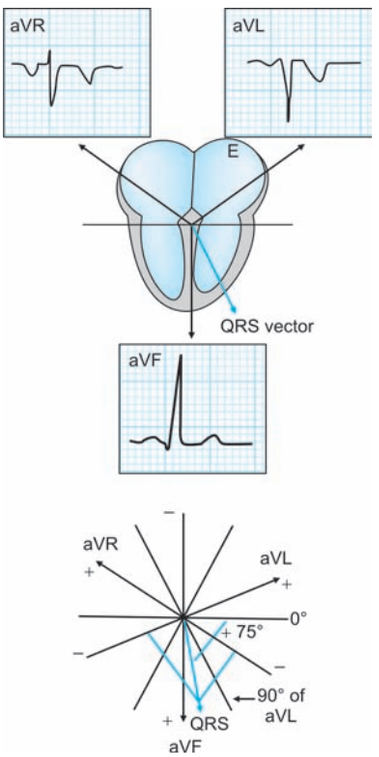


Fig. 6.116: The vertical position of the heart. The mean QRS vector is oriented at +75° left and inferiorly. So it will produce a positive QRS deflection in aVF, because the vector is situated with in 90° of the positive pole of this lead. But it will produce a negative deflection in aVL lead because the QRS vector is situated beyond the 90° of the positie pole of aVL lead. Due to the same reason it will also produce negative deflection in aVR

Rotation of the heart may occur either around the anteroposterior axis, i.e. in the frontal plane, such as: vertical, horizontal, intermediate or around the the long axis, i.e. in the horizontal plane, such as: clockwise or counterclockwise. With clockwise rotation, the transitional zone (V3, V4) is displaced to the left, so the typical left ventricular precordial pattern does not appear until V7-9 lead (Figs 6.117 and 6.118).

The term clockwise rotation is defined by persistant S waves in lead $V_{5\text{-}6}$, i.e. the lead $V_{1\text{-}2}$ configuration is seen in lead $V_{5\text{-}6}$. In counterclockwise rotation, the transitional zone is displaced to the right, resulting in a left ventricular epicardial complex, as early as in lead V_2 (Figs 6.119 and 6.120).

Within the normal axis deviation in the frontal plane, the axis between 0° to –30° represents a normal horizontal heart position and the axis between +75° and +110° represents a normal vertical position of the heart (Fig. 6.121).

Principles

Electrical flow through the myocardium towards the positive pole of a lead causes a positive deflection in this lead in ECG. Similarly a cardiac electrical flow away from the positive pole of lead causes a negative deflection in this lead in ECG (Fig. 6.122).

Using this principle, now we will consider how lead II records ventricular depolarisation. From lead II's point of view, the flow of current in the atria and the ventricles is entirely directed towards the positive pole of it and so the P and QRS complexes are entirely positive in this lead. The lead aVL, however, will see the same flow of current at right angles to lead II and record an isoelectric QRS complex. Because, if the current of the heart flows at right angles to a given lead, then the ECG complex which is analysed by this lead will be isoelectric, i.e. the positive and negative deflections will be equal in magnitude and will cancel each other (Fig. 6.123).

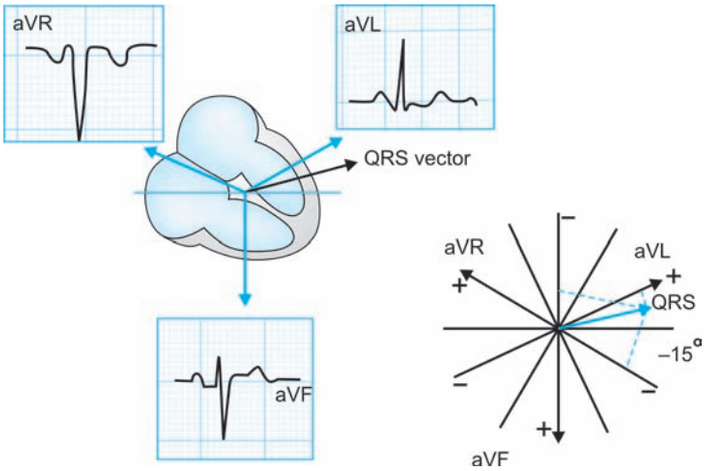


Fig. 6.117: The horizontal position of the heart. The QRS vector is situated at –15°. Thus it is oriented left and superiorly,more towards the positive pole of the aVL leads. Due to the same reasons described in the vertical position of the heart,this orientation of the QRS vector will produce positive deflection in aVL and negative deflection in aVF and aVR leads

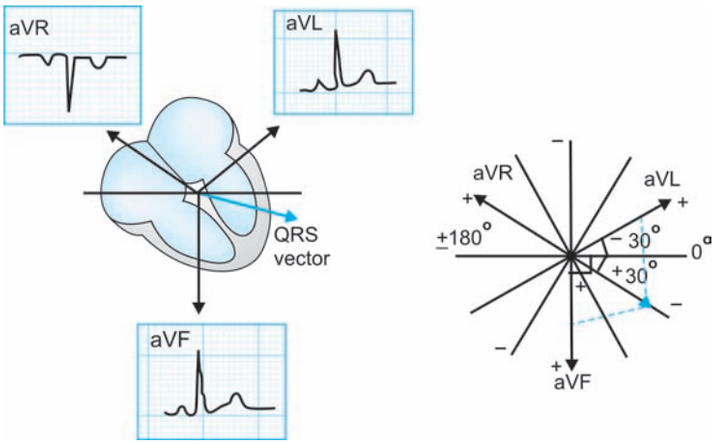


Fig. 6.118: The mean QRS vector is oriented towards the left and inferior at +30o. So it is 60° away from both leads aVF and aVL, that is midway between the positive poles of these two axes. Thus, it will produce a positive QRS deflection of equal magnitude in bothaVL and aVF leads. The QRS deflection is positive in these two leads because it lies within 90° of the positive poles of these two leads (aVL, aVF). Equal magnitude of deflection in aVL and aVF leads indicates that the heart is in intermediate position. Since the QRS vector is situated beyond the 90° of the positive pole of aVR lead, it will produce a downward deflection in this lead

Any lead situated between lead II and aVL will record a QRS complex that becomes increasingly positive. The closer it is to lead II, the greater is the positive deflection. Similarly this principle can be followed in other leads also. For example, lead I and aVF which are at right angle to each other and lead III and aVR which are also at right angle. But these pairs are not taken in normal situation (Fig. 6.124).

Determination of cardiac axis

The two ways of calculating the cardiac axis are:

i. A quick but less precise way
ii. A slow but more precise way

Quick but less precise way to work out cardiac axis

This technique helps us to decide within a moment, if the cardiac axis is normal or abnormal. For this, we will have to look only at the two limb leads that is lead I and II. If the QRS complex in lead I is mainly positive, it indicates that the axis or the main direction of flow of impulse of ventricular depolarisation lies anywhere between –90°

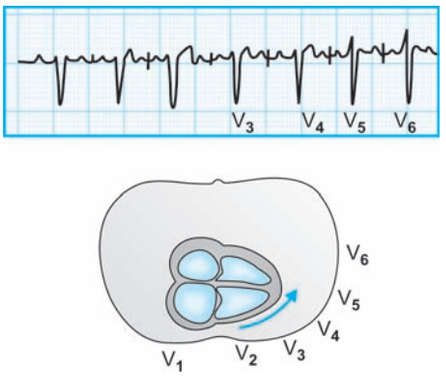


Fig. 6.119: Clockwise rotation-In precordial leads RS complex is still present in V_6,indicating that a left ventricular epicardial complex has not yet been reached and clockwise rotation of heart

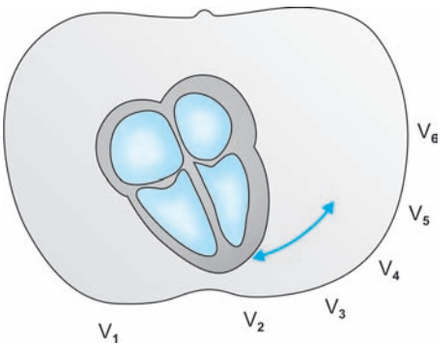


Fig. 6.120: Counterclockwise rotation—A left ventricular epicardial complex is seen in V_2 indicating counterclockwise rotation of the heart

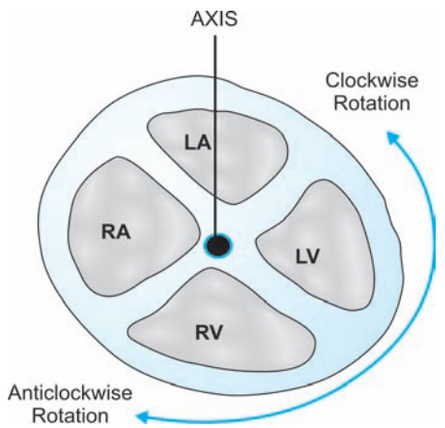


Fig. 6.121: Rotation of the heart around the long axis

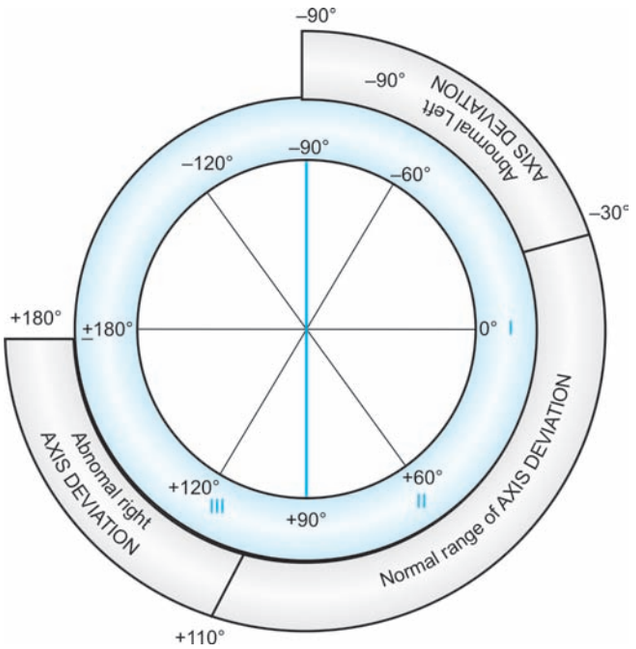


Fig. 6.122: Normal and abnormal axes

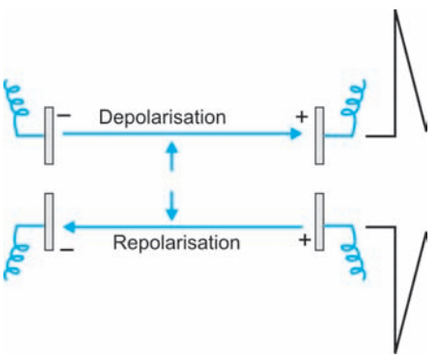


Fig. 6.123: Fundamental vectrial principle which govern ECG

and +90°. An cardiac axis situated exactly at –90° or +90° would produce a precisely isoelectric QRS complex in lead I. Hence, a predominantly positive QRS complex found in lead I rules out right axis deviation (beyond +110°). Because, if the axis goes beyond +90° (see the picture) the deflection in lead I will become negative. But positive deflection in lead I does not exclude left axis deviation (an axis beyond –30°) (Fig. 6.125).

On the otherhand if the QRS complex in lead II is mainly positive, then it confirms

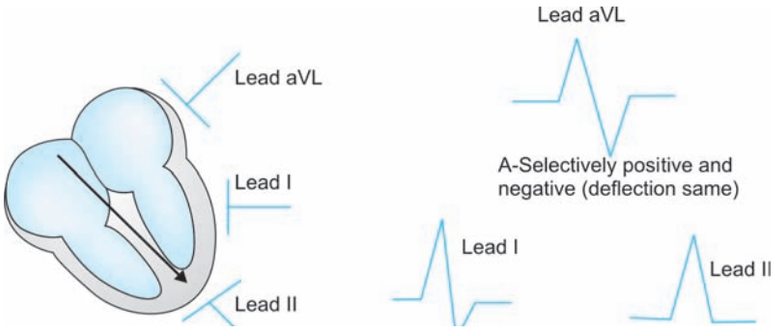


Fig. 6.124: If a current flows at right angles to a lead, the generated ECG complex will be isoelectric because positive and negative deflections cancel each other. Here in this picture it is applicable in the aVL lead. So it can be explained how lead II records ventricular depolarisation. As the flow of the current in the ventricle is entirely towards it, the QRS complex is entirely positive in this lead. Any lead looking towards the heart, between leads II and aVL will record a complex that becomes increasengly positive, the closer it is to lead II

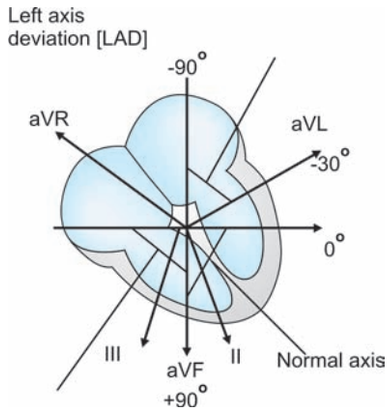


Fig. 6.125: A predominantly positive QRS in lead I puts the axis between -90° and +90°. So, a predominantly positive QRS complex in lead I excludes right axis deviation

that the axis lies anywhere between –30° and +150° (see the picture). Thus a positive deflection of QRS complex in lead II rules out left axis deviation (beyond –30°). Because if the axis is beyond –30° then the deflection in lead II will be negative. But, positive deflection in lead II does not rule out right axis deviation (beyond +110°). Because, if there is a right axis deviation i.e. beyond +90°, there will also be positive deflection in lead II. (Fig. 6.126).

So, now depending on whether the QRS complex is positive or negative in

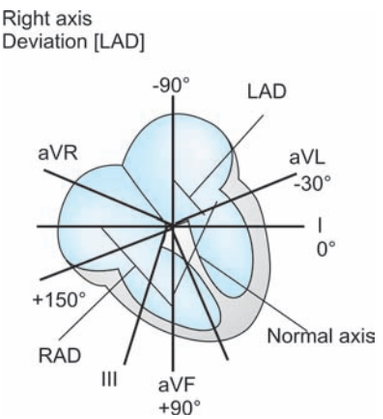


Fig. 6.126: A predominantly positive QRS in lead II puts the axis between -30° and +150°. So a predominantly positive QRS complex in lead II excludes left axis deviation

these two standard limb leads I and II, we are able to say immediately whether the axis is normal or deviated to the left or right (abnormal).

SUMMARY

i. A mainly positive QRS complex in both standard limb leads I and II means the axis is normal.
ii. A mainly positive QRS complex in lead I and mainly negative QRS complex in lead II indicates there is left axis deviation.
iii. A mainly negative QRS complex in lead I and mainly positive QRS complex in lead II indicates a right axis deviation (Table 6.3).

A slow but more precise way to calculate the cardiac axis

For more practical purposes it is sometimes very necessary to determine accurately the axis of heart. Because it is not always sufficient to know simply whether the axis is normal or abnormal. Contrarily, calculation of cardiac axis precisely is not difficult. But, it does take a little time.

The principle for precise calculation of axis is that the net amplitude and direction of the QRS complex in any two of the frontal plane leads that look at the heart at right angles to each other are plotted along the axis of these two leads. For example, we usually take lead I and lead aVF for calculation of the cardiac axis as they are at right angles to each other. The overall size and polarity of the QRS complexes in these two leads should be worked out by substracting the depth of the S wave from the height of the R wave.The polarity (positive or negative) tells us whether the impulse is moving towards or away from the lead. The two QRS vectors should then be plotted according to their amplitude and direction in the lead axes of these two leads (see the picture). Perpendicular lines are next drawn at these two locations. A line is then drawn from the centre of the reference system to the intersection of these two perpendiculars and this represents the approximate mean QRS vector. Its angle is the frontal plane axis. We can thus finally derive an angle in degrees that determines the cardiac axis. The axis in this patient (in the picture) is, therefore, +132° (90° + 42°) and he or she has right axis deviation (Fig. 6.127).

So far, we have concentrated only on the axis of ventricular depolarisation (QRS complex). Because, it flows through the ventricles. This is generaly referred to as the main cardiac axis. However, it is also possible to workout the axis of atrial depolarisation (using P waves) and ventricular repolarisation (using the T waves). But, these measurements are seldom necessary, except where a more detailed analysis of the ECG is required.

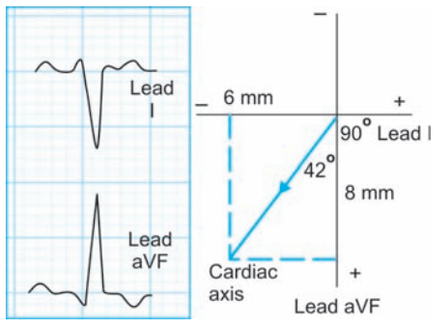


Fig. 6.127: The method of construction of axis from the ECG. First the overall size and polarity of QRS complexes in lead I and aVF is determined. Here the overall QRS height is -6 mm with negative polarity in lead I. On the other hand, the over all QRS height is +8 mm with positive polarity in lead aVF

Table 6.3: Determination of cardiac axis

Lead I	*Lead II*	*Cardiac axis*
Positive QRS deflection	Positive QRS deflection	Normal axis
Positive QRS deflection	Negative QRS deflection	Left axis deviation
Negative QRS delection	Positive QRS deflection	Right axis deviation

ELECTROPHYSIOLOGY OF NORMAL HEART AND PRODUCTION OF NORMAL ECG

Atrial Complex

The initial impulse in the cardiac cycle begins at the SA node due to its depolarisation. This depolarisation of SA node can not be recorded in the clinical ECG. But, it can be recorded by a special electrode placed within the right atrium. The impulse arising from the SA node, then, traverses through the internodal pathways to depolarise the whole atria, producing this P wave and then reaches the AV node. Normally, the impulse is delayed in the AV node by 0.07s econds and then passes on to the bundle of His (Fig. 6.128).

So, the P wave represents the atrial depolarisation and its vector (P vector) is directed leftwards, inferiorly in frontal plane and slightly anteriorly in horizontal plane. The polarity (negative or positive deflection) of P wave in any given lead will, therefore, depend on the relation between the direction of the P vector and the positive pole of the respective lead.

P-wave in frontal plane leads (I, II, III, aVR, aVL, aVF)

Normally, the P vector is oriented inferiorly and leftwards in the frontal plane between 0° and +90°. Therefore, the P vectors are upright in leads I, II, aVF and inverted in aVR. The P vector is upright in lead III, when its axis is greater than +30°. It is inverted when its axis is lesser than +30°. In lead aVL, the P vector is upright if its axis is lesser than +60° and inverted if its axis is greater than +60°.

P wave in horizontal plane leads (precordial leads V_1 to V_6)

In the horizontal plane, the normal P vector is directed leftwards and anteriorly. Depending upon the degree of anterior or leftward orientation, the P wave may be upright, biphasic or inverted in lead V_{1-2}. But it is always upright in leads V_{3-6}.

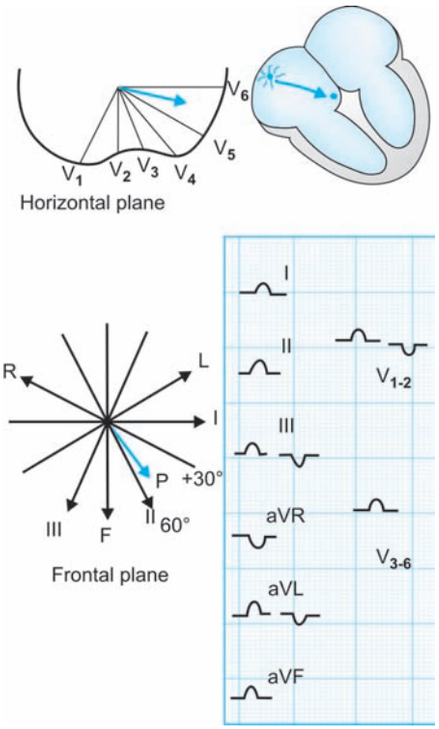


Fig. 6.128: The vectors of P wave in both frontal and horizontal planes,in a 12-lead ECG. Normally the P vector remains in the frontal plane between 0o and +90°. If the P vector lies between 0o and +30° then it will produce an inverted wave in lead III.If it lies beyond +30°, then it will produce a positive P wave(upright) in ECG. AP- vector lying past +60° will produce a negative P wave in aVL.Alternatively if it lies within +60°, it will produce a positive P wave in the same lead. On the otherhand the amount of anterior and right or left orientation or direction of the P vector in horizontal plane will determine the positive or negative deflection in V_1 and V_2 leads

After the impulse reaches the AV node from the SA node, it is normally delayed for 0.07 seconds before the impulse passes on to the bundle of His. This delay of impulse at AV node produces an isoelectric PR segment in all the leads.

Ventricular Complex (Initial)

The initial conduction of impulses from the AV node and bundle of His via the septal fibres of left bundle branch results in primary depolarisation of the left side of interventricular septum which next spread to the right side of it. This produces septal depolarisation from left to right. This vector is, therefore, oriented rightwards in horizontal. Due to the anatomical disposition of the septum, the septal depolarisation force is oriented anteriorly and superiorly or sometimes even inferiorly in frontal plane. It is of a small magnitude.

Initial ventricular complex in frontal plane leads

This initial left to right septal vector records a small negative deflection as q in lead I. Its recording and deflection in ECG in the other frontal plane leads will also depend on its relationship with the other frontal plane axes. Lead II will record an upright deflection r if it lies inferiorly between –30° and +150° and a negative deflection if it lies superiorly between –30° and +150°. Lead aVF will record an upright deflection 'r', if the septal vector lies inferiorly between 0° and +180° and a negative deflection if the septal vector lies superiorly between 0° and –180°. In other leads like aVL, aVR and lead III the same principle is applied (Fig. 6.129).

Initial ventricular complex in horizontal plane leads

The left to right and anterior septal vectors will record a small positive deflection as r in leads V_{1-2}. Reciprocally, it records a small negative deflection as q in leads V_{5-6}.

Ventricular Complex (Major)

After depolarisation of the interventricular septum, the impulse goes down the right and left bundle branches. Then, it passes through the purkinje system and activates the right and left ventricles. After that, the impulses traverse through the ventricular myocardium from the endocardial to the epicardial surfaces.

Vectors of the major ventricular QRS complex in frontal plane leads (Fig. 6.130)

The axis of major QRS vector is directed leftwards between –30° and +90° in frontal

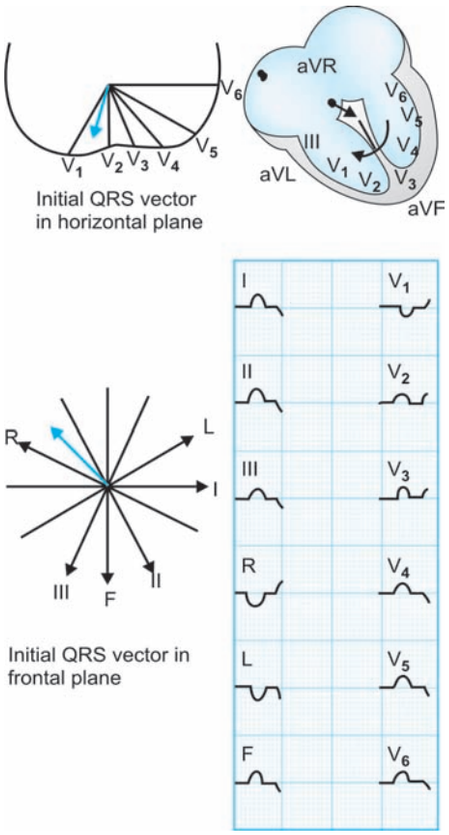


Fig. 6.129: Septal activation which is the beginning of ventricular QRS complex.This force is normally oriented to the right and anteriorly in horizontal plane. It may also be directed superiorly (shown in picture)or inferiorly in frontal plane

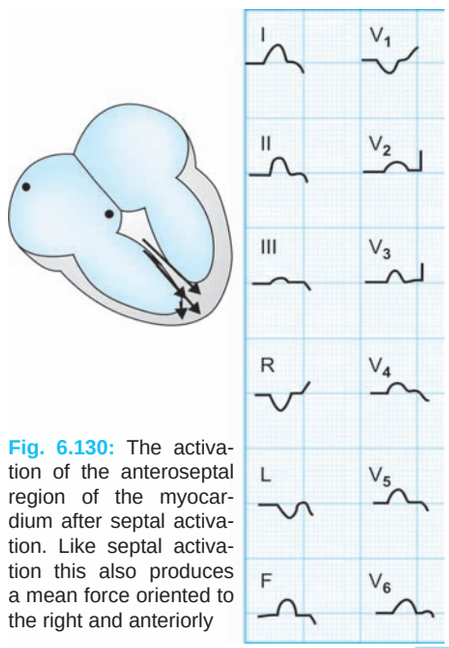


Fig. 6.130: The activation of the anteroseptal region of the myocardium after septal activation. Like septal activation this also produces a mean force oriented to the right and anteriorly

plane, and results in an upright deflection (R wave) in leads I and II. On the contrary, it produces a negative deflection (S wave) in the lead aVR. The recording in other frontal plane leads will depend on the relation between the axis of the frontal plane lead and the axis of this major ventricular vector. Lead aVF will record an upright deflection R, if the axis of the major ventricular vector lies between 0° and +90°. It will record a RS or a rs complex, if the mean axis is 0°. It will also record a negative deflection S, if the axis of QRS vector is directed between 0° and –30°. Lead III will record an upright deflection R, if the axis of major QRS vector lies between +30° and +90°, and a negative deflection S if the same vector lies between +30° and –30°. Lead aVL will record an upright deflection R, if the axis of QRS vector lies between –30° and +60° and a negative deflection S, if it lies between +60° and +90° (Fig. 6.131).

Major ventricular complex in horizontal plane leads

The axis of mean QRS vector in the horizontal plane is directed to the left and posteriorly. So, it produces predominantly negative deflection (S wave) in lead V_{1-2} and predominantly positive deflection (R wave) in lead V_{4-6}.

Ventricular Complex (Late)

The last portion of the ventricular myocardium to be depolarised is the posterobasal portion of the left ventricle and the region of the pulmonary conus. The mean vector of this activation is oriented in many directions. If it is directed rightwards, then a small negative deflection S will be recorded in leads I and V_{5-6}. If it is directed superiorly, then a small negative deflection s will be recorded in lead aVF. If it is oriented anteriorly, a small positive deflection r′ will be recorded in the leads V_{1-2} (Fig. 6.132).

Repolarisation

The sequence of events of ventricular repolarisation is very complex. Simply, it can be said that both the right and left ventricular cavities are negative during ventricular repolarisation.

The epicardial surface of the left ventricle is positive. That of the right ventricle may be positive or negative. The ST segment will be isoelectric in all leads. The usual normal axis of mean T vector is oriented to the left and inferiorly (between 0° and +90°). So the frontal plane leads will record upright T waves in leads I and II and inverted T (Fig. 6.133) waves in lead aVR.

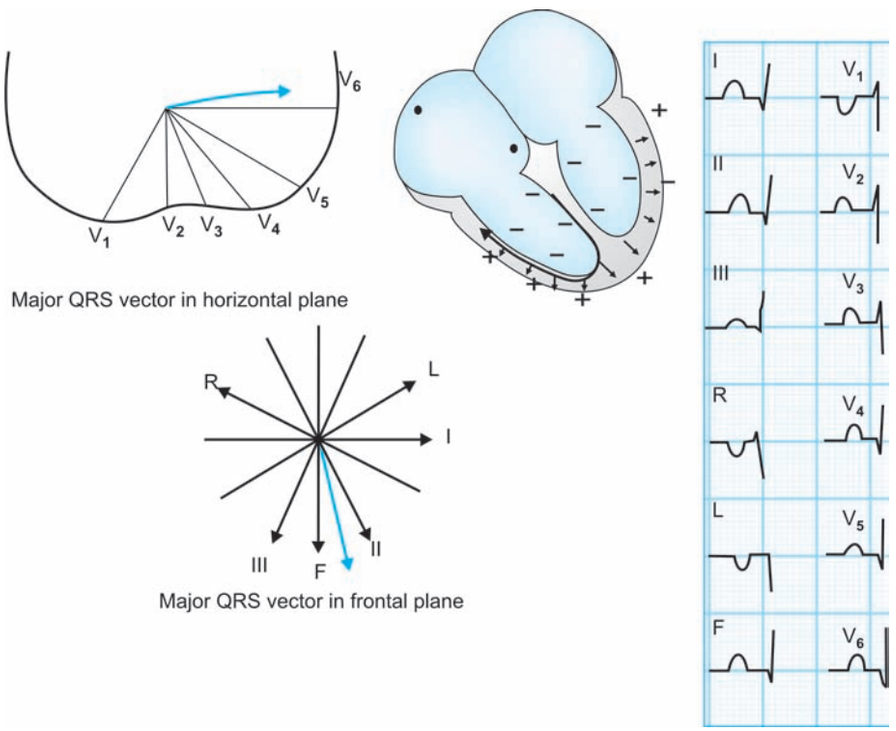


Fig. 6.131 : Right and left ventricular activation.The mean vector of the force is direc ted to the left in the horizontal plane and inferiorly and posteriorly in the frontal plane

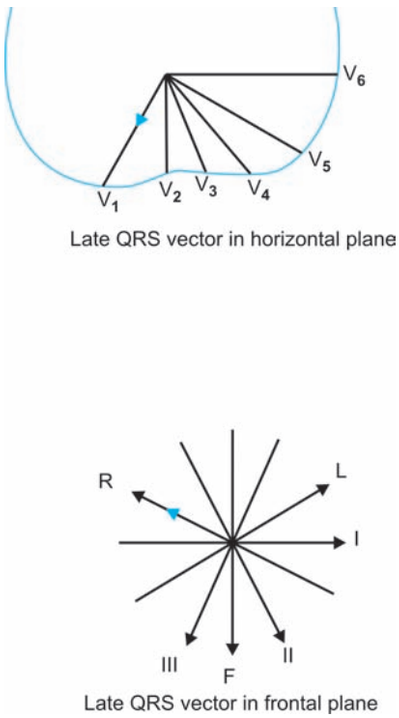
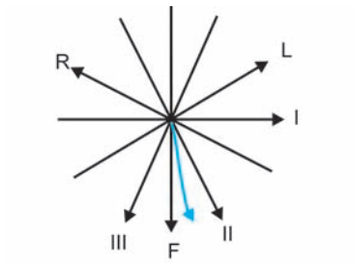
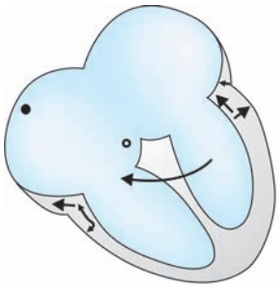
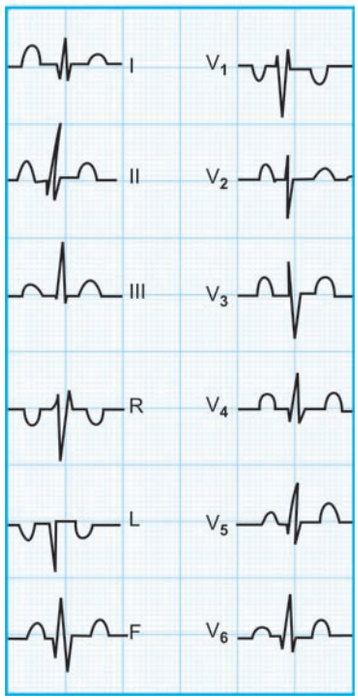


Fig. 6.132 : Late major QRS vector is due to the activation of posterobasal portion of the left ventri-cle,pulmonary conus and the uppermost portion of interventricular septum. This picture illustrates the mean vector of this force which is oriented rightward, superiorly and anteriorly



In frontal plane the mean vector of T





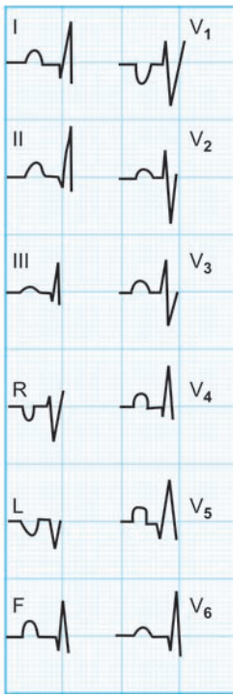


Fig. 6.133: Repolarisation– The mean T vector is oriented left wards (in horizontal plane) and inferiorly and anteriorly (in frontal plane)

The polarity of the T wave in other frontal plane leads (aVL, aVF, II) will depend on the relation between the axis of the vector of the T wave with the axis of this frontal plane, like the P and QRS axes, described before. In horizontal plane leads the mean T vector is oriented anteriorly. Depending on the degree of anterior orientation, the T wave may be inverted, biphasic or upright in lead V_1 and upright in leads V_{3-6}.

7 Neuromuscular Physiology Related to Muscle Relaxants

MORPHOLOGY

A single myelinated axon or nerve fibre after arising from the body of a motor nerve cell, which is situated at the ventral horn of the gray matter of spinal cord runs uninterruptedly through the spinal nerves to supply the muscles. There it branches and ultimately end into several expanded complicated structures which are known as the axon terminals or sole feet. These axon terminals ultimately end on each muscle cell or fibre as neuromuscular junction or motor end plate. Actually the motor end plate is a small depression on the muscle cell where a branch of the nerve terminal ends. It contains many nicotinic cholinergic receptors which are sensitive to acetylcholine. The diameter of this typically discoid or oval shaped neuromuscular junction or motor end plate is 20 to 30 µm. The number of muscle cells supplied by the terminal branches of a single axon or nerve fibre together form one motor unit. In single motor unit there may be 5 to 2000 muscle fibres. Synchronous contraction of all these muscle cells of a motor unit is called fasciculation. Fasciculation usually can not be seen by the naked eye, but sometimes it is often vigorous enough to be observed through the skin when the muscle is very superficial and the patient is lean and thin.

The axon carries electrical signal from the spinal cord to the muscle. At the neuromuscular junction this electrical signal is converted into the chemical signal by the release of neurotransmitter (acetylcholine - ACh) from the presynaptic membrane (which is nothing but the cell membrane of nerve fibre) and this chemical signal is again converted to the electrial signal by the binding of ACh with the nicotinic receptor at the postsynaptic membrane (which is nothing but the cell membrane of muscle fibre), leading to muscular contraction. All the enzymes, proteins, (Fig. 7.1) macromoleculaes and the membrane of vesicles, needed for the nerve ending to synthesise, store and release the acetylcholine for chemical signal are made in the nerve cell body and are then transmitted to the nerve ending by axonal transport. Only the chemical substances such as the choline and acetate are obtained locally at the nerve ending to synthesise ACh. The nerve ending is itself nonmyelinated, because myelin sheath ends before the nerve terminal touches the end plate of the muscle cell. But it is covered with the cytoplasm of Schwann cell with its nucleus. The axoplasm of axon at its terminal end is filled with numerous mitochondrias, endoplasmic reticulum and other materials which are required for chemical synthesis of neurotransmitter, and numerous vesicles to store it (Fig. 7.2).

The gap between the nerve cell membrane (presynaptic membrane) and the muscle cell membrane (postsynaptic membrane) at the neuromuscular junction is called the junctional cleft or synaptic cleft which is measured about 20 nm. The synaptic cleft is filled with extra cellular fluid. This is also called the gap substance. The synaptic cleft, separated by the basal membrane of both the nerve (presynaptic membrane) and muscle cell (postsynaptic membrane) also contains many fibrous strands linking the nerve and muscle cell membrane and enzyme called the cholinesterase (ChE). Multiple secondary cleft arise from the postsynaptic membrane of the muscle cell membrane from the main junctional cleft and thus the total postsynaptic surface area of the end-plate increases many fold. The branched and expanded nerve terminal which come in contact with muscle fibre lie within this corrugated sarcolemma (muscle cell membrane) of the end plate and the corrugation is due to this formation of multiple secondary cleft from the main synaptic cleft. Numerous nuclei and mitochondria are also seen in the sarcoplasm (cytoplasm) of the muscle cell near the nerve terminal or synapse. It is claimed that mitochondria present in the axoplasm take part in the

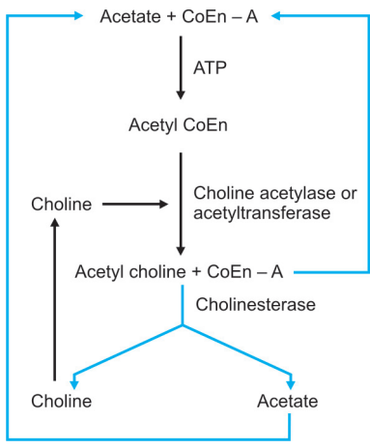


Fig. 7.1: Acetylcholine is broken down locally into acetate and choline which are available locally to synthesise further acetylcholine at the nerve endings

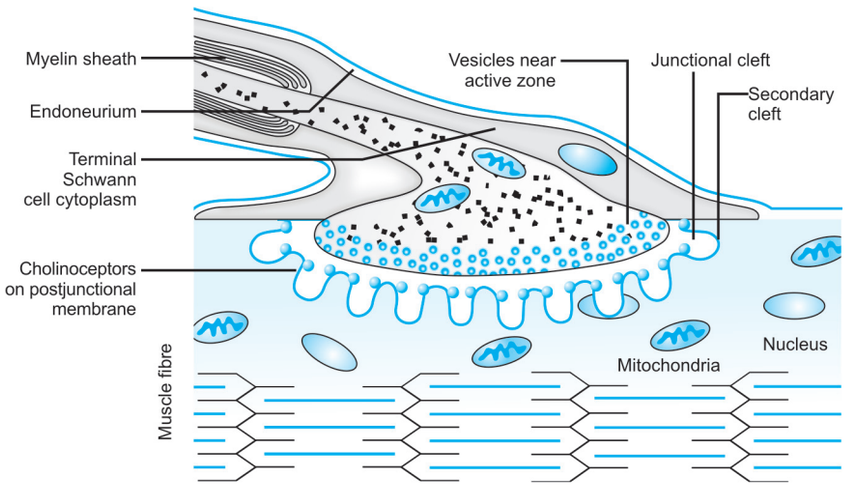


Fig. 7.2: Neuromuscular junction or motor end plate with an axon terminal containing vesicles of acetylcholine. The neurotransmitter is released on arrival of an action potential and crosses the junctional cleft to stimulate the postjunctional receptors on the shoulders of the secondary clefts

synthesis of acetylcholine which is then subsequently stored in the synaptic vesicle of the nerve terminal and released when the propagated impulse through the nerve fibre reaches the terminal. (Fact file-I)

There is only one neuromuscular junction for each muscle cell or fibre except some of extraocular muscles and internal laryngeal muscles which have several neuromuscular junctions or end plates for each muscle cell, locating at short distance from each other and maintain a steady contraction in response to stimulus. These muscles are important to anaesthetists, because instead of causing brief contraction and followed by paralysis, the depolarising muscle realxants cause long lasting contractions in these type of muscles and contribute to a rise in intraocular pressure. Virtually all human muscles (except extraocular and possibly some laryngeal muscles), however, contract in all-or-none principle. On the contrary, short muscle fibres have only one end plate, but long muscle fibres may have 2 to 6 endplates, separated by long distances, typically 100 mm. However, these long muscles also have all-or-none principle of action (Fig 7.3).

The peripheral area of the muscle cell membrane around the neuromuscular junction is called the perijunctional area. It actually indicates the transitional area between the postsynaptic membrane of end-plate and the true cell membrane of muscle fibre. It is very critical for the function of the neuromuscular junction. This is because it is here where the electrical or action potential, developed at the end plate is converted to an electrical impulse that sweeps along the whole muscle cell membrane and initiate muscular contractions. It contains a mixture of smaller number of ACh or nicotinic receptor and higher number of Na^+ channel. The perijunctional area also participates actively in the modulation of neuromuscular transmission and controls the individual's response to muscle relaxant. Moreover some special variants (isomer) of nicotinic receptor and Na^+ channel can appear in this area at different stages of live which are responsible for abnormal decrease or increase in nerve muscle activity. This variability seems to contribute to the quantitative and qualitative differences in response to muscle relaxants that are seen in patient at different clinical status and age. Congenital abnormalities regarding the number and morphology in the ACh receptor and Na^+ channel are also known.

There are many vesicles at the nerve ending which are arranged or congregated towards the presynaptic membrance of neuromuscular junction. On the other hand microtubules, mitochondria and other structures of the nerve terminal are located on the opposite side of the junctional surface of the nerve ending. Vesicles are arranged in a pattern of triangular arrays, with the apex of each triangle directing towards a small, thickened electron dense patch of presynaptic axonal membrane which is referred to as an active zone. This thickened area (or active zone) in a cross section shows many bands running across the width of the synaptic surface of the nerve ending. Vesicles are attached to the active zone before they rupture into the junctional cleft. The attachment sites of the vesicles lie on the sides rather than in the centre of the active zone. Many small particles are also seen along the active zone between the vesicles. Actually

FACT FILE- I

The shoulder of secondary cleft is densely populated with acetylcholine (ACh) receptor. But the depth of the secondary fold is populated with Na^+ channel, which transform the depolarisation (electrical signal) produced by ACh-receptor into the muscle action potential (electrical signal) and triggers contraction of muscle. Muscle cell membrane surrounding the end plate at the periphery is also rich in Na^+ channel and functions as the same i.e. end plate depolarisation into muscle action potential.

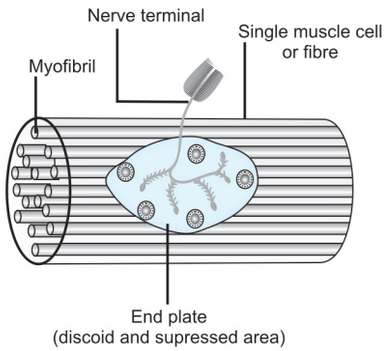


Fig. 7.3: Motor end plate in relation to a muscle fibre— surface view

these particles are the special voltage gated calcium channel that allow the Ca^{2+} to enter the nerve ending from the extracellular space and cause the release of vesicles (Fig. 7.4).

The end plate area of the muscle cell membrane which is a part of the neuromuscular junction forming post synaptic membrance is very convoluted and is due to the presence of multiple secondary cleft or folds which is already discussed. Thus, the muscle cell membrane which is a part of the neuromuscular junction exposes a very large area to the nerve terminal for better transmission of impulses. The crests or shoulders of these folds are aligned opposite to the vesicle release site or active zones of the nerve terminal and contain a high density of ACh receptors (nicotinic receptor channel). But deep in these folds, the endplate membrane contains a high density of sodium channels. There are about 5 million nicotinic receptor at the each neuromuscular junction.

The stimulus or electrical impulse reaching at the nerve ending allows the Ca^{2+} to enter the nerve terminal through the special voltage gated calcium channels situated on the presynaptic membrane and causes the vesicles to migrate to the active zone. Then the membrane of the vesicles fuse with the neural membrane of nerve terminal and discharge their contents of ACh into the synaptic cleft. Since the release sites of ACh are located along the sides of the active zones and immediately opposite to the nicotinic receptors on the postjunctional surface, so normally little transmitter is wasted and the response of the muscle is coupled very directly with the signal from the nerve (Fig. 7.5).

Normally the end plate potential that is produced continuously at rest by the continuous release of uniformly sized packages or quantas of transmitters is called the miniature end plate potential (MEPP). This is 1/100th of the amplitude of the evoked endplate potential when the motor nerve is stimulated and muscle contraction occurs. But this is too big to be produced by a single molecule of ACh.

For each nerve impulse 200 quanta or vesicles containing 5000 ACh molecules in each vesicle is released. Thus, the number of ACh molecules released by each impulse is 10,00,000. Each acetylcholine or nicotinic receptor needs two ACh molecules for its activation. Thus the number of receptors activated by the neurotransmitter (ACh) released by a nerve impulse is also large and is about 5,00,000. But actually each impulse activate only 3,00,000 receptors, requiring only 6,00,000 molecules of ACh (each vesicle activate 1500 receptors requiring 3000 ACh molecule but they have extra amount). Thus the rest of the ACh molecule is either destroyed by acetylcholinesterase or binding solo instead

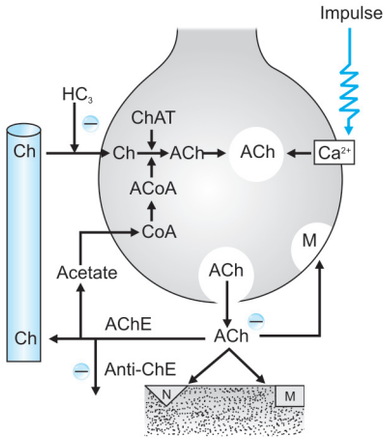


Fig. 7.5: The process involved in synthesis, release and deposit of acetylcholine at cholinergic nerve terminals and receptor site during transmission of nerve impulse
ACh = Acetylcholine, Ch = Choline
ChAT = Choline acetyl transferase
ACh E = Acetylcholinesterase
Anti-Ch E = Anticholinesterase
M = Muscarinic receptor, N = Nicotinic receptor
HC_3 = Hemicholinium, BoT = Botulinus toxin
ACoA = Acetyl coenzyme A

of pairs to a receptor. After coupling of neurotransmitter such as ACh with the postjunctional acetylcholine or nicotinic receptor, the Na^+ ions that flow through the channel of the activated receptor cause maximum depolarisation of the end plate, which in turn causes a full end plate action potential that is greater than the threshold for stimulation of the muscle fibre. Entry of Ca^{2+} inside the nerve ending is most important step for the release of neurotransmitter. Neither only Na^+ in flux, nor only depolarisation of nerve membrane will produce the release of neurotransmitter from the nerve ending if Ca^{2+} is not entered. The introduction of Ca^{2+} into nerve ending by micropippet will also release the neurotransmitter even if the nerve is not depolarised (Table 7.1). Ca^{2+} enter the nerve terminal from extracellular fluid via a special type of protein channels which are called the Ca^{2+} channel. Among the several types of these calcium channels only P and L channels are most important for the release of neurotransmitter from

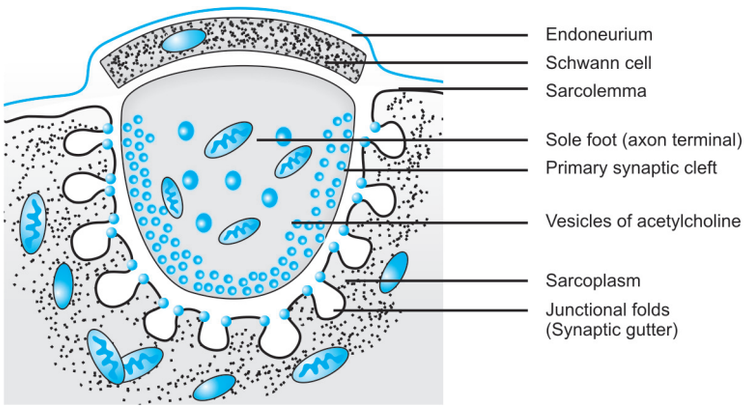


Fig. 7.4: Electron microscopic appearance of myoneural junction at the region of an axon terminal (sole foot) ending in the motor end plate

Table 7.1: Differences between two types of cholinesterases

		True cholinesterase (Acetyl cholinesterase)	*Pseudo (butyryl) or plasma cholinesterase*
1.	Distribution	All cholinergic sites and RBC	Plasma, liver, GI
2.	Hydrolysis of ACh	Very fast	Very slow or nil
3.	Hydrolysis of butyryl-choline	Not hydrolysed	Hydrolysed
4.	Inhibition	More sensitive to physostigmine	More sensitive to organophosphates
5.	Function	Termination of action of ACh	Hydrolysis of synthetic esters such as succinylcholine

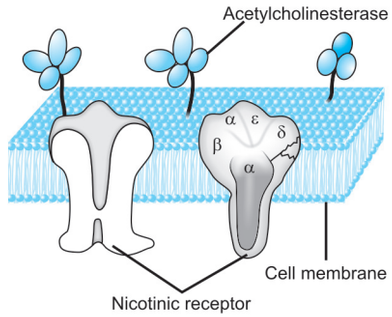


Fig. 7.6: This is a schematic diagram of the postsynaptic membrane. The picture shows two structures in the centre which represent nicotinic acetylcholine receptors. Each is made up of five subunits arranged in a ring around a channel. The three balloon like structures represent acetylcholinesterase (ACh E)

the presynaptic membrane. Again among the P and L channels, P channels are found only in motor nerve ending adjacent to the active zones of the nerve terminals and is responsible (not L type of Ca^{2+} channel) for Ca^{2+} entry and subsequent transmitter release for neuromuscular transmission. They are voltage dependent which means they are opened and closed by the changes in membrane voltage caused by the propagated nerve action potential. On the otherhand, many bivalent organic cations such as Mg^{2+}, cadmium, Mn^{+}, etc, can also block this Ca^{2+} channel and thus profoundly impair the neuromuscular transmission. This is the mechanism for muscle weakness in mother and the foetus when magnesium sulfate is administered to treat the pre-eclampsia. Eaton-Lamber myasthenic syndrome is an another acquired autoimmune disease in which antibodies are detected against this voltage gated calcium protein channel at the nerve ending. Patient with this myasthenic syndrome exhibit an increased sensitivity to the depolarising and non-depolarising muscle relaxant. Normally calcium P channel cannot be blocked by organic calcium channel blocking drugs such as verapamil, diltiasem, nifedipine, etc. Because these drugs have only profound effects on the slower L type of Ca^{2+} channel present in the CVS. So, L-type calcium channel blockers at therapeutic doses have no significant effect on the normal release of ACh from the nerve terminal or on the strength of the normal neuromuscular transmision.

The exact mechanism by which the Ca^{2+} causes the release of neurotransmitter from nerve terminals is not yet known. But its entry into the nerve terminal seems to trigger a series of phosphorylation reaction which disrupt the resting state of nerve terminal and causes the release of neurotransmitter. An effect of the increasing level of calcium at the nerve ending is also seen clinically important in post tetanic potentiation which occurs when a nerve of paralysed patient paralysed with non-depolarising muscle relaxants is stimulated by the current of high tetanic frequencies. During tetanic stimulation calcium enters the nerve ending with every stimulus, but it can not be excreted out as quickly as the nerve is stimulated and Ca^{2+} enters. Thus, it is gradually accumulated during tetanic period. So, when a strong stimulus is applied post-tetanically, then the nerve ending causes the releases of more than the normal amount of ACh due to more availability of Ca^{2+}. This abnormally large amount of released ACh antagonises the effect of muscle relaxant and causes the characteristic increase in the size of post tetanic twitch which is known as posttetanic potentiation (Fig. 7.6).

Two types of vesicles are found at the nerve ending. One is readily releasable smaller vesicles, called VP_2. They are situated very close to the synaptic cleft in the nerve terminal, attaching to the active zones and are ready to release the neurotransmitter present within them. Another is large reserve or store vesicles, called VP_1. They are majority in number and are firmly tethered to the cytoskeleton by proteins, called the synapsins. Some of these vesicles have been recycled after their use by releasing transmitter. But most of the vesicles are new and are formed in the cell body and transported to the nerve ending. The release of neurotransmitter from the vesicles involves many steps, all of which are regulated by the vesicular or synaptic membrane proteins. First the vesicle has to unbind from the storage position and then it binds to a docking protein which is situated on the innerside of the presynaptic membrane. There then fusion occurs between the vesicular and synaptic neural membrane. Next Ca^{2+} enter the nerve ending through the P type of Ca^{2+} channel which is lined up on the sides of the active zone and activate a protein, called synaptophysin, which is situated on the vesicle wall. The activated vesicle wall protein then react with the nerve membrane to form a pore through which the vesicles discharge its contents. Thus, acetylcholine is poured into the synaptic cleft. Hence there is delay in propagation of impulse from nerve fibre to muscle fibre through synaptic cleft. This delay of propagation of depolarisation between the nerve ending and that of the end-plate of the muscle cell is called synaptic delay which is about 0.1 ms. When the nerve is called upon to work (Table 7.2) hard due

Table 7.2: Cholinergic receptors and its sites and action of relaxants

Receptors	*Location*	*Function*	*Relaxant - interactions*
Nicotinic	Postsynaptic neuromuscular junction	Depolarisation of end plate – muscle contraction	Succinylcholine — stimulates, Non-depolariser – block
Nicotinic	Presynaptic neuromuscular junction	Helps in release of ACh	Succinylcholine — stimulates Non-depolarisers – block
Nicotinic	Autonomic ganglion	Depolarisation of ganglionic cell	Succinylcholine — stimulates Non-depolariser – block
Nicotinic	Post-ganglionic neuron terminal	Positive feed back for transmitter release	Succinylcholine — stimulates Non-depolariser – block
Muscarinic	SA node of heart	↓ heart rate	Succinylcholine stimulate — ↓ HR Non-depolariser block — ↑ HR
Muscarinic (M_1)	Autonomic ganglionic interneuron cell bodies	Inhibition of depolarisation	Non-depolariser block
Muscarinic (M_2)	Autonomic ganglia : Ganglion cell bodies	Depolarisation	Atropine blocks, Non-depolarisers do not act

to repeated stimulation at high frequencies, then this reserved VP_1 vessicles replaces the wornout VP_2 vesicles and participate in transmission of impulse. Under such circumstances calcium enter the nerve terminal more deeply also through the L type of Ca^{2+} channel in addition to the P-channel and activate calcium dependent enzymes. These enzymes then phosphorylate and cause the breakage of synapsin links that hold the vesicles to the cytoskeleton, and thereby allow the vesicles to be moved to the release sites.

After discharge of the neurotransmitter into the synaptic cleft, vesicular membrane temporarily becomes the part of the nerve cell membrane. Then a special protein that is present in the vesicular membrane, detaches it from the nerve cell membrane and make it return back again into the cytoplasm of the nerve terminal as a rudimentary vesicle. This rudimentary vesicle then again becomes filled with ACh neurotransmitter and moves into the previous position for release. Thus, these membranes of vesicles are used again and again until finally worn out and transported back to the nerve's cell body for complete destruction. The complex molecules, such as enzymes, proteins and new membrane which are used for the synthesis and storage of ACh in vesicle are made in the nerve's cell body and transported back through the axon to the nerve terminal. For the synthesis of acetylcholine (ACh) the simple molecule, choline, is only obtained by the nerve cell body from the extracellular fluid and is transported to the cytoplasm of nerve ending by a special system.

But the acetate for synthesis of acetylcholine is available from acetylcoenzyme A (acetyl CoA) which is present in the mitochondria of nerve ending and is obtained during the metabolism of glucose, fat and amino acid. Choline and acetate then react with the help of enzyme choline acetyl transferase or cathecol-o-methyltransferase (COMT) to form acetylcholine which is then stored in the cytoplasm and transported into the vesicles. At rest, as the lipid bilayer of the cell membrane is more permeable to K^+ than Na^+, so more K^+ leaks out of the cell than Na^+ gets in. Thus, it creates a slight excess of positive charges on the outside and a negative charges on the inside of the cell membrane, leading to resting membrane potential of about −70 to −90 mV. During the action potential of nerve fibre, Na^+ flows inside of the cell and thus resulting depolarisation opens the voltage gated Ca^{2+} channel. This allows the entry of Ca^{2+} ion into the nerve ending and cause release of acetylcholine from the vesicles.

In resting situation, the concentration of Ca^{2+} ion is many times greater at the outside than the inside of the neural cell membrane, which facilitate the influx of it from extracellular fluid after depolarisation reach the nerve ending. This concentration gradient of Ca^{2+} ion between the intracellular and extracellular fluid of nerve ending is maintained by:

i. A very efficient system, which transports the Ca^{2+} ion from inside to outside of the cell,
ii Sequestrating a huge amount of Ca^{2+} inside the intracellular organelles,
iii. Binding of Ca^{2+} with intracellular proteins (Fact file-II).

After the release of ACh, it reacts with the acetylcholine receptor protein (or nicotinic receptor) on the endplate to initiate muscular contraction. Acetylcholinesterase enzyme remain attached to the endplate by thin stalks of collagen fibres, like bundles of balloon attached to stringes. So, most of the acetylcholine molecule after its release

FACT FILE-II

Depolarisation or opening of Na^+ channel of nerve cell membrane activates Ca^{2+} channel and causes transient and localised rise of intracellular Ca^{2+} concentration in nerve terminal. This inward Ca^{2+} current persists until the membrane potential is returned to normal by outward fluxes of K^+ from the nerve cell. Thus, calcium current can be prolonged by potassium channel blockers (e.g. 4-aminopyridine) which slow or prevent K^+ efflux out of the nerve. Thus prolongation of action potential causes increase in quantal discharge.

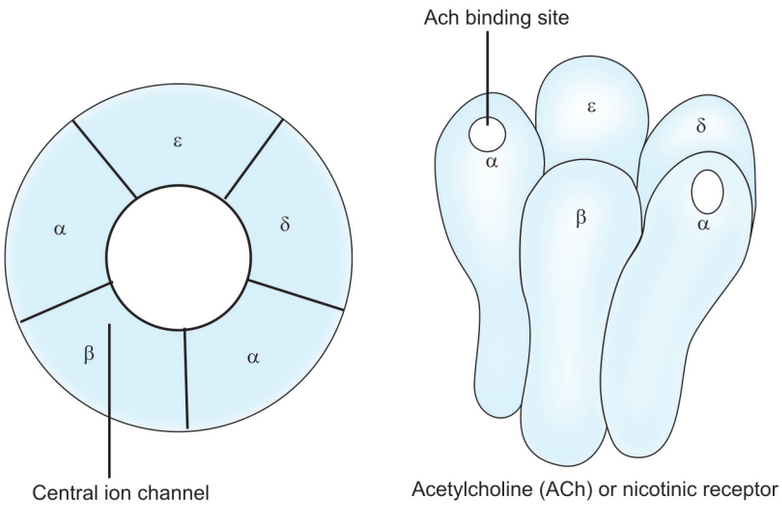


Fig. 7.7: This is a schematic diagram of cholinergic nicotinic receptor

from the nerve terminal pass between the esterase enzymes to reach the post junctional nicotinic receptor. Hence, they are hydrolysed by enzyme acetylcholinesterase during their passage through the synaptic cleft. ACh molecule that is not hydrolysed during their passage through the synaptic cleft react with receptor and are later hydrolysed by cholinesterase. So the action of acetylcholine is very short lived and is destroyed in less than 1 millisecond. Two ACh molecule react with one receptor only for function of the later (Fig 7.7).

Acetylcholine or nicotinic receptors are synthesised at the end plate of muscle cell membrane under the guidance of mRNA. After synthesis, each receptor is inserted into the cell membrane at end plate and held firmly there by 43Kd protein in such way that each receptor crosses from one side of the cell membrane to the other. Each ACh-receptor is made up of 5 protein subunits and are assembled like a cylinder with a channel within it. Each of these protein subunit consists of 400 to 500 amino acids. Normally, the receptors looked like cylinder and the channels within it are closed. But if acetylcholine reacts on the specific sites at the extracellular end of the receptor, then the protein subunits undergo in conformational changes and opens the channel in the centre of the receptor. When the channel is opened then Na^+ and Ca^{2+} flow from outside to inside and K^+ flow from inside to outside of the cell, resulting in an end plate potential that stimulates the muscle to contract. The current that passes through the each opened channel is very minimal, and only of few picoampere. However, burst of each vesicle from the nerve terminal liberating acetylcholine neurotrammitter normally opens about 5,00,000 ACh receptor channels. Hence, the produced total current is more than adequate to cause depolarisation of the end plate and helps its subsequent spread over through the whole muscle cell membrane with contraction. The channel in the receptor is large enough to accomodate many cations other than Na^+, K^+, Ca^{2+} and also electrically neutral molecules. But it excludes anions (e.g. Cl^-) for their passage through this channel.

These nicotinic or ACh receptors are found in pair. Molecular weight of each receptor is 2,50,000 Da and is made up of about total 2000 to 2500 amino acids. Each receptor has five protein subunit (as described before) and is designated as α, β, δ and ε. There are two α subunits and one for each of the rest. The α-subunit is the smallest of the five and is made up of 437 amino acids adding up to a weight of 40000 Da to the receptor. The molecular weight of other subunits range between 50 to 70,000 Da. One of the likely configuration of nicotinic receptor, looking clockwise from the outside of the endplate membrane, is α, ε, α, δ and β.

All the five subunits of the receptor have four membrane spanning domains. It means their string of aminoacids traverse the cell membrane four times and both the end is being on the extracellular side. The channel in the receptor is funnel shaped and is only lined by the 2nd membrane domain of each subunit. Length of each receptor is 11 nm of which half protrudes in the extracellular space and only 2 nm protrudes in the cytoplasm. The larger end of the funnel shaped channel of the receptor is on the outside of the cell. The ACh binding site of the receptor is situated only on both the α-subunit. They are also the site for binding of both the agonist and antagonist. When only both the α-subunit is occupied by agonist, then the protein molecule or subunit of the receptor undergoes conformational changes and the channel opens. On the other hand if only one of them is occupied then channel remains closed. At rest, the channel is closed because the membrane spanning domains of subunits lining the channel in the centre touch each other at one point. Non-depolarising relaxants act by binding with one or both α-subunit of the nicotinic receptor and prevent ACh to bind. So the channel of the receptor remains closed and thus prevent depolarisation and muscular contraction. The interaction between the agonist and antagonist on the receptor site is competitive in nature and the final outcome depends on the relative concentration and binding characteristic of these agents (agonist and antagonist) involved. There is also acetylcholine receptors on the presynaptic membrane which play role in mobilizing the vesicles containing neurotransmitter from its reserve to the immediately releasable position. These receptors are also of nicotinic cholinergic type and are blocked by small doses of non

depolarising agents. Presynaptic receptors also bind agonists such as succinylcholine. This presynaptic action of succinylcholine accounts for fasciculations and the effectiveness of pretreatment with small doses of non-depolarising agents.

Summary of Mechanism of Muscular Contraction by Neuromuscular Transmission

Contraction

When an impulse reaches the nerve terminals or sole feet, then depolarisation of end plate takes place by the help of liberation of acetylcholine (ACh) from the vescicle, with the participation of entry of Ca^{2+} from outside within the nerve terminal. By the propagated impulse along the axon, Ca^{2+} from the extracellular fluid enters into the vesicles of sole feet or nerve terminal and causes the ACh to come out from the vesicles. The acetylcholine (ACh) thus liberated diffuses across the synaptic cleft and reacts with the acetylcholine or nicotinic receptor on the post junctional membrane (PJM), forming the acetylcholine-receptor complex. The acetylcholine-receptor complex at the end plate thus increases the permeability of the PJM to Na^+ and K^+ (Fig. 7.8).

Due to enough release of ACh, a large number of nicotinic receptors in PJM are activated and this state facilitates the entry of enough Na^+ producing depolarisation of the post-junctional membrane. If the depolarisaing potential of PJM attains a threshold level, then an impulse of action potential is propagated in both directions along the sarcolemma (the cell membrane of muscle cell). After that the released acetylcholine at the end plate is rapidly destroyed and its concentration is declined either by the true cholinesterase which is present in high concentration at the rim of the synaptic gutter or by simple diffusion out in the surrounding tissues. From the sarcolemma the action potential is then propagated through a triad system, into the contractile units of the muscle cell. The pair of terminal transverse cisternae and the central T-tubles are collectively called as the triad system. In mammalian muscle cell, the each triad system is present at the junction of A-band with the adjacent I-band of contractile unit of muscle cells. Thus, there are two sets of triad system in each segment of sarcomere and plays an important role in quick transmission of impulses from the cell surface to the whole triad system and contractile unit inside the muscle cell. Depolarisation of the muscle cell membrane causes release of Ca^{2+} from the triad system or sarcoplasmic reticulum which in turn bind with troponin. Then troponin activate the myosin ATPase and helps in the cross-bridging of myosin and actin filaments with the developments of muscle contraction. Troponin is a protein which in resting state prevents actin and myosin filaments from cross bridging (Fact file-III).

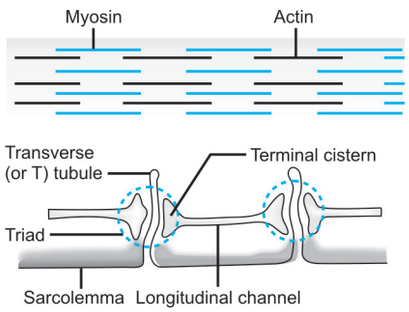


Fig. 7.8: The logitudinal channel, transverse tubule and triad. This tirad is the connection between the surface of the muscle fibre and the endoplasmic reticulum

Relaxation

After contraction when the action potential is over → Ca^{2+} is pumped back again into the sarcoplasmic reticulum → myosin ATPase is depressed→ cross−bridges are broken → myosin is pulled back to its resting site.

Under normal condition, the impulses may be excitatory or inhibitory. When there is preponderence of the excitatory impulses over the inhibitory impulses, then there will be depolarisation of the postsynaptic motorneurone membrane and the discharge of the action potential will be of EPSP (excitatory postsynaptic potential) type. But, when there is predominance of the inhibitory impulses over the excitatory impulses, then there will be hyperpolarisation of the postsynaptic motorneurone membrane. Thus, inhibitory postsynaptic potential (IPSP) will be developed and this will inhibit the discharge of any impulses.

FACT FILE- III

Propagated action potential along the axon → depolarisation of the neurone terminals → ACh is released from synaptic vesicles with the help of Ca^{2+} entry → released ACh diffuses across the synaptic cleft → ACh forms a ACh−receptor−complex with the nicotinic receptor on PJM → opening of the channel of the receptor → increased permeability of Na^+ and K^+ of the PJM → depolarization of end plate → depolarization of Na^+ channel at the perijunctional zone which is a very critical area where potential developed at the end plate is converted to an action potential which sweeps along the muscle sarcolemma cell membrane → transmission of such action potential from sarcolemma to the triads (sarcotubular system – T system + sarcoplasmic reticulum) → release of Ca^{2+} from sarcoplasmic reticulum → binding of Ca^{2+} with troponin → troponin with Ca^{2+} activate myosin ATPase → myosin ATPase is activated → cross−bridges are formed → myosin slides along actin → contraction of muscle is developed.

End plate potential

It can be defined as the potential changes at the motor end plate induced by activation of the acetylcholine receptors which cause the increase in end plate permeability to Na^+ and K^+. End plate potential can be recorded by inserting microelectrode into the motor end plate. When an impulse reaches the neuromuscular junction through an axon, ACh is liberated from the terminal nerve endings and then depolarises the motor end plate of the muscle cell membrane. When this local depolarisation exceedes −30 mV to −40 mV (threshold level), then a spike potential in the muscle cell is initiated with an amplitude of +35 mV and the muscle contracts.

At rest, the neurotransmitter substances are continuously liberated from the vesicles at a very slow rate from the nerve

terminal which is incapable of producing any depolarisation up to the threshold level and failed to initiate a full action potential with any propagated impulse and contraction of muscle. This small end plate potential is called the miniature end plate potential (MEPP) and it is not more than 0.5 mV. However, when the nerve action potential reaches axon terminals, then there is synchronous release of several vesicles full of transmitter substance, causing a threshold end plate potential and muscle contraction.

ACTIONS OF DRUGS ON NEUROMUSCULAR TRANSMISSION

Neuromuscular transmission can be blocked by two ways: (i) by inhibiting the release of acetylcholine (ACh) or (ii) by inhibiting the action of ACh on its receptor at the motor end plate through (a) competitive inhibition or (b) by persistent depolarisation of nicotinic receptor (Fig. 7.9).

Botulinus toxin blocks the neuromuscular transmissions by inhibiting the release of ACh from nerve terminals through its action on presynaptic membrane. Whereas curare muscle relaxants such as tubocuranine, pancuronium, atracurium, etc. blocks the neuromuscular transmissions by competitive inhibition of acetylcholine at the level of nicotinic receptor. It means, the curare competes with ACh for binding on the nicotinic receptor, but does not prevent the release of it from the presynaptic nerve terminal. These curares are called the non-depolarising muscle relaxants.

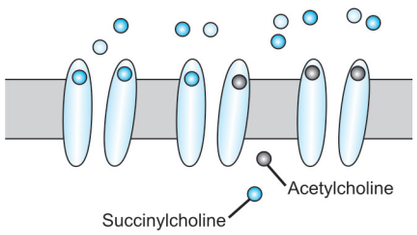


Fig. 7. 9: The classical action of agonists (acetylcholine and succinylcholine) on end plate nicotinic acetylcholine receptors. Any combination of the two agonists molecules causes the channel to open. But different agonists cause action potential of different durations, depending upon the duration of binding of agonist to the receptors. ACh causes few millisecond of binding with depolarization and paralysis. Succinylcholine causes long duration of binding with depolarization (better to say prevent repolarization) and paralysis than ACh

The drugs which block the neuromuscular transmission and produce muscular paralysis by persistent depolarisation are decamethonium and succinylcholine. These act on the nicotinic receptor like ACh, and cause prolonged depolarisation of the motor end plate. Thus, they prevent the further action of ACh and produce muscular relaxation, because ACh can not act on the already depolarised nicotinic receptor. So, they are called the depolarising muscle relaxant. The prolonged depolarisation produced by succinylcholine or decamethonium is because these drugs are metabolized and eliminated very slowly in comparison to ACh. The ACh which is found in normal neuromuscular transmission cannot produce prolonged depolarisation and muscular paralysis because the elimination of it is very rapid (fraction of second) as the true cholinesterase present in the synaptic cleft destroys it.

Non-depolarising Muscle Relaxants and Receptor

Non-depolarising muscle relaxants prevent the depolarisation of the endplate because they bind to the ACh recognition site of α-subunit of the nicotinic receptor. Thus, it prevents the ACh from its binding to the α-subunit of the receptor and cause the ion channel within the receptor not to open. Cholinesterase enzyme present in the synaptic cleft destroys the ACh and removes it from the competition with the non-depolarizing muscle relaxants molecule. Thus, the neuromuscular transmission and subsequently the muscular contraction is prevented. If anticholinesterase is added then cholinesterase enzyme is destroyed and it can not destroy the acetylcholine further. Thus, the concentration of ACh gradually increases in the synaptic cleft and shifts the competition between the ACh and the muscle relaxants (non-depolarising) in favour of ACh, though the nondepolarizing muscle relaxants is still present in the enviornment. Hence, the neuromuscular transmission is improved and muscle contracts (Table 7.3).

Nicotinic receptor channels will not open unless the ACh is attached to the binding sites of the two α-subunit of receptor, i.e. two molecules of ACh per receptor is needed. Whereas binding of single molecule of non-depolarising muscle relaxant to the binding site of single α-subunit of receptor is adequate to prevent the opening of channel. So, the competition between the agonist (ACh) and antagonist (relaxants) is biased in favour of antagonist. Mathematically this bias ness is equivalent to the second power effect of the number of molecule of antagonist (i.e. for 2 molecule of relaxants 4 molecule of ACh is needed). All these explanations indicate that the block produced by high concentration of nondepolarising muscle relaxants is difficult to reverse than the low concentration of it and sometimes impossible (Fig. 7.10).

There are typical features of non-depolarising and depolarising block or muscular relaxation by which we can

Table 7.3: Characteristics of depolarising and non-depolarising block

Feature	*Depolarising or (phase I) block*	*Nondepolarising and phase II block*
Effect on single twitch height	Reduced	Reduced
TOF fade	Not found	Found
Tetanic fade	Not found	Found
Post tetanic facilitation	Not found	Found
Effect of Anti-ChE agent	Potentiation	Reverse
Effect of non-depolarising agent	Reduction of block	Potentiation

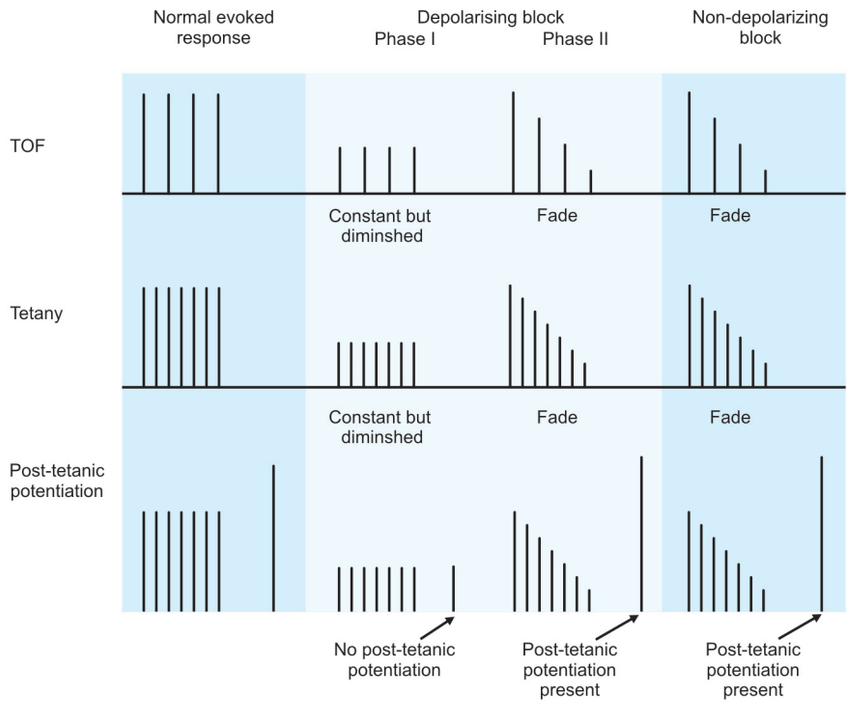


Fig. 7.10: Evoked responses during depolarising (phase I and phase II) and non-depolarising block

differentiate them. The characteristic features of non-depolarising and depolarising block or muscular relaxation are:

i. Generally, in the normal neuromuscular physiology at least 10 seconds must be allowed to elapse between the two successive single twitch stimulus (or pulse) for complete recovery of the motor end plate and subsequent contraction. Therefore, if the interval of two pulses is more than 10 seconds i.e. if the frequency of impulses is < 0.1 Hz, then there is full recovery of motor end plate and no depression or fade on successive impulses will be found. On the other hand, if frequency of impulses is more than 0.1 Hz, i.e. the interval between two successive impulses is <10 seconds, and the end plate does not get adequate time to recover completely then fades appears after successive impulses. Fade increases with frequency up to 2 Hz, when a plateau is reached. This plateau is maintained upto 50 Hz. Fade reaches its maximum value by the fourth impulse from where the idea of train of four (TOF) has come. In non-depolarising and depolarising block, when the block is very intense i.e. one hundred percent (100%) then there is no response to any type of stimulus. This is called the period of no response. Thereafter, with the passing of time when the intensity of block declines then the response to different types of stimulus starts to appear (responsive phase). Then if the frequency of stimulus is < 0.1 Hz, then in the response against the stimulus there is no fade, but only the depression of all the height of response will occur. But if the stimulus is > 0.1 Hz, then gradual depression of the response, i.e. gradual decrease in the height of response or fade appears in non-depolarising type of block, but not in the depolarising type. Clinically in surgical state of anaesthesia, patients usually stay in responsive phase because the intensity of block is not so high that any stimulus will not respond. So, in the therapeutic clinical dose of relaxants for the surgical stage of anaesthesia any single twitch stimulus will produce response, but of low amplitude in both depolarising and nondepolarising block but will so fade in nondepolarising relaxant and no fade in depolarising relaxant provided the stimulus is > 0.1 Hz. (NB 1 Hz = 10 impulses in 10 seconds. 0.1 Hz = 1 impulse in 10 seconds. 2 Hz = 20 impulses in 10 seconds).

ii. In train of four (TOF), the frequency of impulse is 2 Hz and is consists of four impulses separated by 0.5 seconds. With non-depolarising relaxants, fade is seen with TOF stimulus after the first response and is maximum at fourth. In contrast, with depolarising relaxants there is no fade after TOF stimulus but all the responses are low in amplitude than the previous non block one. (2 Hz = 20 impulses in every 10 seconds. So interval between two impulses is 0.5 sec).

iii. Tetanic stimulation (30 to 100 Hz) is also characterised by fade in non-depolarisation relaxation. However, in depolarising relaxation, the response to tetanic stimulation is sustained like normal muscle, but with low amplitude.

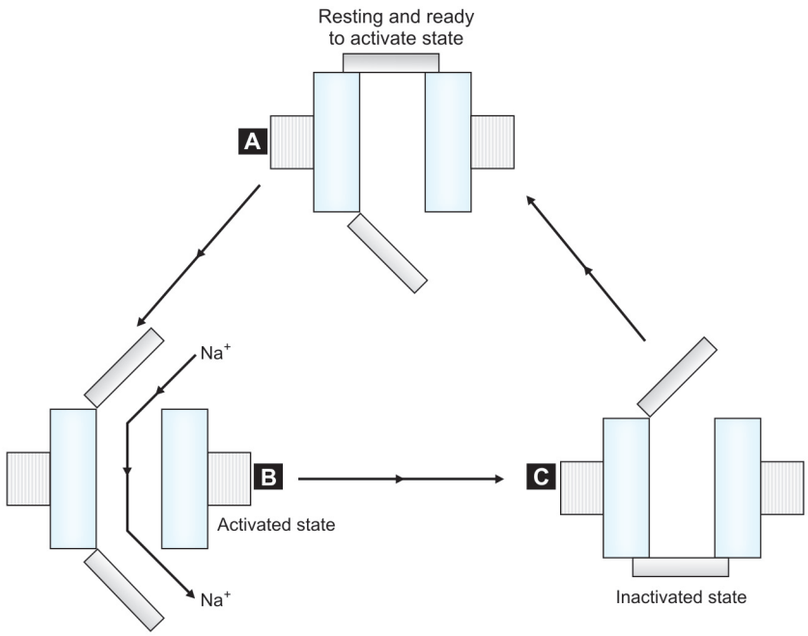
iv. When a single twitch or train-of -four stimulus is applied after a tetanic stimulation, then the response in non-depolarising block is exaggerated or facilitated. This is called the post-tetanic facilitation and the probable explanation is the displacement of non-depolarising muscle relaxant molecules from the motor end-plate by the acetyl-choline which is released maximally during the tetanic stimulation. This post-tetanic facilitation is absent in depolarising block like normal muscle. This post-tetanic facilitation should not be confused with post tetanic potentiation, applied in post-tetanic count (PTC) which is an augmented stimulus of single twitch or T-O-F stimulation after a tetanic stimulation.

v. Non-depolarising block is reversed by anticholinesterase agents, but depolarizing block becomes intense due to potentiation of depolarisation by increased acetylcholine level by these agents. Depolarising agents also antagonize the nondepolarising block or relaxation, provided the dose of depolarising agent is small enough not to produce block in its own right and blockade by non-depolarising agent is intense enough. On the other hand, non-depolarising agents also antagonize the relaxation produced by depolarising block.

Depolarising Muscle Relaxants and Receptors

The depolarising muscle relaxants act in the same way as ACh. They act by attaching on the same binding site of ACh on the α-subunit of nicotinic receptor to open the receptor channel and initiates depolarisation. Like ACh, succinylcholine is not attaches to the receptor very briefly. So, each opening of channel is not so of very short duration, i.e. 1 millisecond or less like ACh. But in contrast to ACh, depolarising relaxant's (succinylcholine) action lasts longer extending from minutes to hours (ACh action lasts only for millisecond) and have a biphasic action on muscle causing it to contract initially and then to relax the explanation of which is discussed below. The difference between the duration of action of ACh and succinylcholine (structurally which is actually two molecules of acetylcholine) is because ACh is rapidly destroyed by true acetylcholinesterase and is cleared from the synaptic cleft very quickly. Whereas succinylcholine is not destroyed by the true choline esterase enzyme present in the cleft. On the other hand, it is eliminated through hydrolysis by plasma or pseudocholine esterase circulating in plasma. So, the rate of clearance of succinylcholine from the whole body will determine how long it will last in the cleft and repeatedly react to open the receptor channels and continuously depolarise the endplate. (Some author's view is that binding of receptor to succinylcholine is prolonged and this produces desensitisation i.e. unresponsiveness of the nicotinic receptor to the further action of ACh). But here, it is explained that the prolonged action of succinylcholine is not due to the prolonged duration of binding with receptor, but due to repeated binding, with sustained depolarisation of end plate (not desentisation or unresponsiveness) that causes the adjacent Na^+ channels of perijunctional area to remain in inactivated state by sustained depolarisation and not getting time for repolarisation and rest which normally help further transmission of impulses causing muscular contraction. So, after first muscle contraction (fasciculation) paralysis prevails (Fig. 7.11A to C). In case of succinylcholine there is quick shift from brief muscle contraction which is seen as fasciculation to relaxation. This is because at the edge of the motor endplate, i.e. at the perijunctional area two different kinds of membrane such as the endplate membrane and the true muscle membrane with their different types of channel come in contact. End plate membrane contain ACh receptor channel that open by ACh or succinylcholine and muscle membrane contain Na^+ channel that do not respond to chemicals such as ACh or succinylcholine but open when they are exposed to postsynaptic transmembrane voltage change due to depolarisation of nicotinic receptor of end plate. Thus the channels on the two parts of membrane (end plate area responds to chemical stimuli) respond to two different type of stimuli i.e. chemical and electrical. End plate area responds to chemical stimuli such as ACh and perijunctional area respond to electrical stimuli, such as depolarisation of end plate created by the previous chemical stimuli.

Na^+ channel like ACh receptor is also a cylindrical protein tube across the



Figs 7.11A to C: This is a schematic diagram of sodium (Na^+) channel. The bright red bars represent the gate of the channel. The upper one is voltage dependent. But the lower one is time dependent:
A. Represents the resting state of the Na^+ channel. With upper gate is closed and lower gate is opened
B. Represents the activated state with both the gates open
C. Represents the inactivated state with upper gate open and lower gate closed. Then it again passes to the resting state where upper gate is closed and lower gate is opened. Thus, the cycle repeats and becomes ready for next impulse

membrane. It responses only to the sharply changing electrical voltage due to the opening of adjacent nicotinic receptor by ACh but not due to the direct responses to chemical like ACh. The Na^+ channel is made up of three protein subunits called α, β_1 and β_2. The α-subunit has the shape of a doughnut and is thicker than the membrane itself. The intracellular portion of the channel is larger than the extracellular portion. The β_1 and β_2 subunit, each lie on the outside of the α-subunit. They are smaller than the α-subunit and occupy only the external half of the cell membrane. The overall size of the Na^+ channel is approximately 13.5 nm in thickness and 10 nm in its largest diameter. The molecular weight of Na^+ channel is 30,000 da.

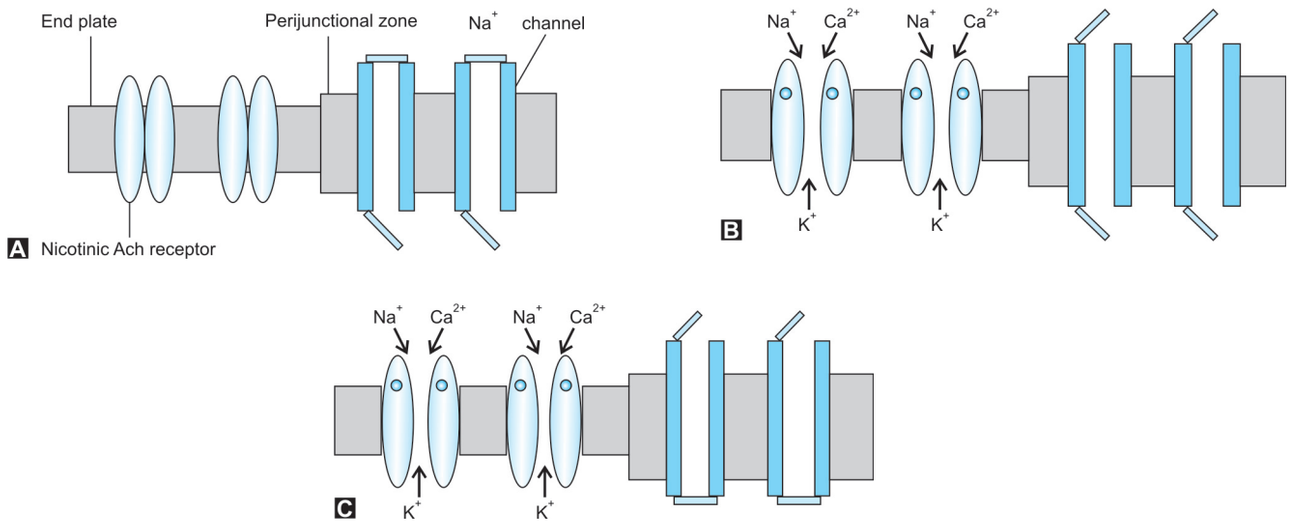
It has two gates which act sequentially. Upper gate is voltage dependant and responses only to voltage changes. Lower gate is time dependant and closes or opens for a fixed time period (1 to 2 millisecond). In resting state, the upper gate remains closed and the lower gate remains opened. So, sodium (Na^+) can not pass through this incompletely opened Na^+ channel. When the Na^+ channel of the perijunctional area is subjected to sudden voltage changes by depolarisation of the adjacent endplate membrane by the activation of ACh or nicotinic receptor channel, then the top gate of Na^+ channel opens. Therefore, since the lower gate is still open, so Na^+ starts to flow through this Na^+ channel driven by the favourable high extracellular concentration and electrical gradients. This state of Na^+ channel is called the activated state. Thus, this entry of Na^+ in the muscle cell fibre from outside initiates the depolarisations of the muscle cell membrane and spread from one Na^+ channel to the next. In that way a wave of depolarisation moves along the whole muscle cell membrane and triggers the muscle contraction which is seen as fasciculation shortly after administration of succinylcholine. Shortly after that the time dependant lower gate closes with still the upper gate open after a fixed time, i.e. after 1 to 2 millisecond and cuts off the flow of Na^+ ions. This state of the Na^+ channel is called the inactivated state. When the activation of the ACh or nicotinic receptor and the depolarisation of end-plate stops and end-plate membrane potential is brought back to its resting value, then the Na^+ channel again comes to the previous resting and ready to activate state from inactivated state with voltage dependant upper gate closes and lower gate opens. But during continuous depolarisation of end plate by succinylcholine, the perijunctienal Na^+ channels remain in this inactivated state (as the lower time dependent gate must closes after a first time under any condition) after the first activated state for which muscle contraction (that is seen as fasciculation) occurs and does not reach the resting and ready to activated state. This prevents the further spread of depolarisation from the end plate which is still now in depolarised state to the other part of the muscle cell membrane causing muscle relaxation.

During depolarization of end plate by ACh the activation of Na^+ channel of perijunctional area also causes activation of the adjacent K^+ channel and opening of it as the inside of the cell becomes electrically positive (due to influx of Na^+). These channels are selective only for K^+ ions and it exit the cell, driven by the high intra cellular concentration of it and electrical gradient. Thus, the waves of action potential spread along the muscle cell membane. So the excitability of the resting cell can also be modified by the K^+ channels. For example, continuous opening of K^+ channel produces a hyperpolarisation state (inside of the cell is more negative) and the cell becomes less excitable (Fact file-IV).

When depolarising muscle relaxants such as succinylcholine is administered, then the initial response of it on the nicotinic receptor at the end plate and causing depolarisation and subsequently the response of depolarisation of end plate on the Na^+ channel at the perijunctional area causing muscular contraction which is seen as fasciculation resembles like ACh. But as this muscle relaxant (succinylcholine) is not hydrolysed by the true choline esterase at the synaptic cleft, so depolarisation of the end plate continues and muscle fasciculates. After that since, Na^+ channel immediately adjacent to the endplate in perijunctional area are influenced by the continuous depolarisation of the end plate, so their voltage dependent upper gates stay open, but consequently their time dependent lower gates stay closed which is called inactivated state and remains in this inactivated state. This inactivated state of Na^+ channel persists until the voltage dependent upper gate closes and lower gate opens. Thus, the sodium channel can not complete its cycle (i.e. untill the end plate comes back its resting state). Since the Na^+ can not flow through a channel that has a closed lower gate in perijunctional area, so the adjacent Na^+ channel in muscle membrane is not further depolarised and due to that the other down stream channels on muscle cell membrane are freed of depolarising influence. So, the muscle remains paralysed as long as the end plate remains depolarised by succinylcholine and Na^+ channel of perijunctional area stay in inactivated state. Infact in junctional zone the first line of Na^+ channels act as buffer which shields the rest of the Na^+ channel of the muscle membrane from the events of the motor end plate (Figs 7.12A to C).

FACT FILE- IV

Normally, ACh is hydrolysed quickly within the synaptic cleft and so depolarisation of endplate is very short. But this acetylcholine induced depolarisation of the end plate causes the Na^+ channel in the adjacent muscle membrane (perijunctional area) to open which subsequently activate the adjacent K^+ channel and depolarise the muscle membrane. This depolarisation on the muscle membrane spreads from one Na^+ channel to another Na^+ channel and like waves spread all over the muscle. Upon the hydrolysis of ACh, end-plate repolarises and the adjacent Na^+ channels quickly complete their cycles. Then it returns to their resting state and muscle relaxes.



Figs 7.12A to C: This is a schematic diagram of nicotinic acetylcholine receptors (red) in the end plate, perijunctional zone and Na^+ channel (blue) in the muscle membrane. Red ACh receptors are chemically sensitive, but voltage insensitive. Blue Na^+ channels are chemically insensitive, but voltage sensitive. Red appendages within Na^+ channel represent gates. The top gates remain closed. But it opens when voltage is applied across the membrane. This top gate of Na^+ channel is called activation gate. The lower gate is called the inactivation gate and normally it remains open. But it closes spontaneously after the voltage dependent upper gate opens and after a fixed time. So, it is called the time dependent gate. To flow Na^+ through the sodium channel both the gates must be opened:

A. Shows resting membrane. Here no current flows through any ACh or Na^+ channel, as they remain in resting state
B. Activation of chemically sensitive ACh-receptor of end plate by acetylcholine or succinylcholine (red dot) by nerve impulse or applied. Thus, the voltage potential which is developed by the flow of current through the ACh receptor channel causes the upper gate of the adjacent voltage sensitive Na^+ channel in the perijunctional zone to open. Therefore, the first Na^+ channel is activated and current (ions) starts to flow through this Na^+ channel. This causes subsequent voltage changes and opens the next Na^+ channel. Thus a wave of depolarisation spreads along the surface of the muscle cell membrane which starts first at the end plate and then by Na^+ channel at the perijunctional zone.
C. The ACh receptors in the endplate are still in depolarized state. So, the voltage dependent upper gate of the Na^+ channel in the perijunction zone next to the end plate remains open. But, the time dependent inactivation lower gate closes spontaneously after a fixed time interval. So, no ion flows through this Na^+ channel situated in the first row of the prijunctional zone. Therefore, there will be no change of voltage potential in the muscle membrane around the end plate. Thus, the gates of the next 2nd, 3rd, 4th and subsequent rows of Na^+ channel return to their resting state. So, the inability of the Na^+ channels which are situated just by the side of end plate, in the perijunction zone to pass sodium current due to continuous depolarisation of the ACh receptor causes blockade of neuromuscular transmission

Thus, during the action of depolarsing muscle relaxant such as succinylcholine the muscle membrane is divided into 3 zones: (i) the motor end plate with nicotinic receptor which is depolarised by succinylcholine, (ii) junctional zone where Na^+ channels are frozen in inactivated state after a brief depolarisation and muscular contraction, and (iii) rest of the muscle membrane where Na^+ channels are in resting state after passing an impulse and producing fasciculation. Since a further burst of acetylcholine from the nerve terminal cannot produce depolarisation of end plate due to the still presence of succinylcholine at the end plate and can not overcome the inactivated state of Na^+ channel in perijunctional area due to continuous depolarisation of end plate. So, neuromuscular transmission is blocked. This phenomenon is called accommodation. During accommodation when the synapse is inexcitable via the nerve, then direct electrical stimulation of muscle will cause muscle contraction. This is because since the sodium channel beyond the perijunctional area are in the resting excitable state.

However, the extraocular muscles are tonic muscles which are multiply innervated with numerous motor end plates. So, most of its surface is chemically excitable with no resting and relaxation zone. Thus, accommodation does not occur. So, these muscles undergo sustained contraction in the presence of succinylcholine and causes increased intraocular pressure. There is also evidence that extraocular muscles contain a special type of receptor which does not become desensitised in the continued presence of succinylcholine or other depolarising agent.

Succinylcholine also has presynaptic action. Binding of succinylcholine to this presynaptic nicotine receptors depolarises the nerve terminals and action potential may be generated which travel backwards retrogradely along the nerve terminals to invade the neighbouring branches and thus produce contraction of a whole motor unit. Fasciculation is probably (some school thought) due to this mechanism rather than the transient depolarisation of the motor end-plate receptors, because small doses of non-depolarising agents are effective in preventing this phenomenon. Another probable explanation of fasciculation is the special sensitivity of muscle spindles (intrafusal fibres) to succinylcholine

which may produce muscular contractions via gamma affarents.

There are many drugs which acts on the nicotinic receptor, but not classically as competitive of ACh like succinylcholine. Because they can not be antagonised by increased level of ACh by anti-cholinesterase. They act by desensitisation of the nicotinic receptor molecule and blockade of ion channel. These drugs react with the ACh-receptors directly or via its lipid environment to change their functional integrity and impair transmission, but not acting via the acetylcholine binding site of the receptors. This reaction between the drugs and the receptor causes changes in the dynamics of the nicotinic receptor, so that the modified receptor channels instead of opening and closing sharply, become fixed or sluggish. They open more slowly and stay open longer or they close slowly in several steps or both. This effect of drugs on nicotinic receptor causes corresponding changes in the flow of ions and distortion of end plate potential. Procaine, ketamine, inhaled anaesthetic agents and other drugs which dissolve in the membrane lipid acts in that way. If the channel is prevented from the opening, then transmission is weakened. On the other hand, if the channel is prevented from the slowed in closing, transmission may be enhanced. Such drugs can be involved in two clinically important reaction: receptor desensitisation and channel blockade.

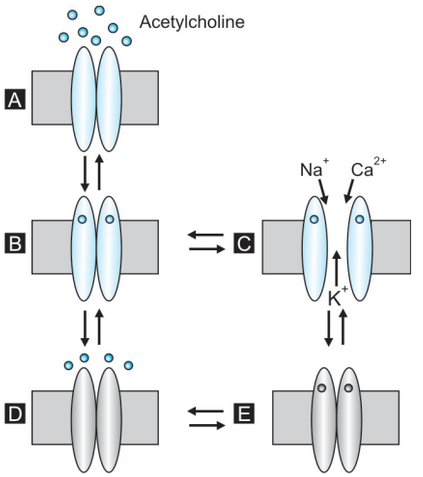
Desensitisation

The ACh or nicotinic receptors are macromolecules. They are not rigid static and fixed. Actually they are flexible dynamic and set in a fluid lipid content of muscle cell membrane and be in a many states. One of these states is desensitized state. In this state agonist bind with the receptor with exceptional avidity and it does not undergo any conformational changes that opens the channel. The mechanism by which the desensitization of nicotinic receptor occurs are not known. Some evidence suggest that densitisation is accompanied by the phosphorylation of tyrosin unit present in the receptor protein. Indeed, normally the receptor molecules undergoes spontaneously in and out of the transformation of the desensitised state and at a particular time the sensitized and desensitised receptors remain in a certain proportion at motor end plate. Therefore, at a certain time, the intensity of neuromuscular transmission depends on the ratio of these sensitized (resting normal) and desensitized (abnormal) receptor concentration. This is because desensitized receptors are not able to take part in neuromuscular transmission. If only few receptor are desensitized, then the system will be more susceptible to blockade of neuromuscular transmission by antagonist (non depolarising relaxants) and vice versa (Fig 7.13A to E).

Agonist such as acetylcholine or succinylcholine binds tightly with the nicotinic receptor and promotes the transition from sensitised to desensitised state. Antagonist also binds tightly to desensitised receptor and its action is augmented by ACh. Many drugs such as halothane, alcohol, pentothal, succinylcholine, neostigmine, local anaesthetic, chlorpromazine etc; promote the shift of the receptor from normal sensitised to abnormal desensitised state and reduce the neuromuscular transmission, augmenting non-depolarising agent's action. These drugs also can weaken the neuromuscular transmission by reducing the margin of safety that normally exists at the neuromuscular junction or they can cause an apparent increase in the sensitivity of the non-depolarising agents to block neuromuscular transmission. As these actions are not based on a competition between the drug and ACh and based on the making more desensitized receptor from sensitized one, so it can not be reversed by anti cholinesterase (Table 7.4).

Channel blockade

The molecules of many drugs (like local anaesthetics and Ca^{2+} channel blockers)



Figs 7.13A to E: Here the picture shows the different states of end plate nicotinic acetylcholine receptors.

A. resting receptor,
B. resting receptor with agonist (acetylcholine) bound to the recognition site. But the channel not yet opened,
C. active receptor with opened channel which allows the flow of ion,
D. desensitised receptor without agonist bound to the recognition site,
E. desensitised receptor with agonist bound to the recognition site. Both D and E are nonconducting. All states of the receptors are in dynamic equilibrium.

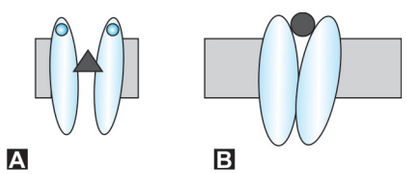
Table 7.4: Some drugs that can cause desensitisation of nicotinic cholinergic receptors

1.	AChE inhibitors
	Neostigmine, pyridostigmine, edrophonium, physostigmine, organophosphorus compounds.
2.	Agonists
	Acetylcholine, succinylcholine, decamethonium, carbachol.
3.	Volatile anaesthetics
	Halothane, isoflurane, methoxyflurane.
4.	Antibiotics
	Polymyxin - B
5.	Alcohols
	Ethanol, butanol, propanol.
6.	Barbiturates
	Thiopental, pentobarbital.
7.	Local anaesthetics
	Lignocaine, dibucaine, prilocaine, etidocaine.
8.	Phenothiazines
	Chlorpromazine, trifluoperazine prochlorperazine.
9.	Ca^{2+} channel blocker
	Verapamil

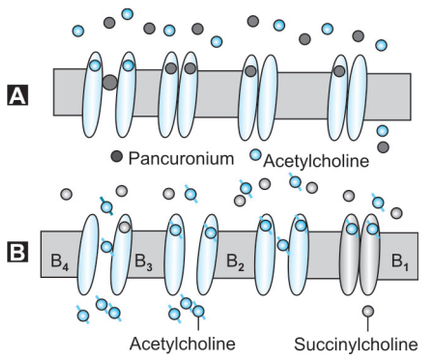
may enter the nicotinic receptor channel and block the flow of ions preventing depolarisation. These are called the channel blockers. There are two types of channel blockade: open channel blockade and close channel blockade. In both opened and closed channel blockade, the normal flow of ions through the nicotinic receptor is impaired resulting in prevention of depolarisation of the motor end plate and a weak or no neuromuscular transmission. However, since the action of these agents is not at the acetylcholine recognition site of receptor, so it is not a competitive antagonist of ACh and is not relieved by the action of anticholinesterase that increases the concentration of ACh (Figs 7.14A and B).

Open channel blockade

Some drugs like muscle relaxant also enter up to the middle of the channel while it is opened by ACh and block it. So, it impedes the flow of ion through it. Thus, it prevents the depolarisation of the end plate. The non-depolarising muscle relaxant is the best example of it. Even though they act at the ACh recognition site, they also block the nicotinic receptor channel directly or physically by this way. A given drug may act preferentially at one or the other site. Pancuronium acts preferentially at ACh recognition site. Gallamine acts equally at two sites. Tubocurarine at low dose purely acts at recognition site and at higher dose at both the sites (recognition site and enter the receptor to block the channel). Increasing the concentration of ACh may cause the channel to open more and it make more susceptible to open channel blockade. So neostigmine and other cholinesterase inhibitors also can act as open channel blocking drug. Decamethonium and succinylcholine act as agonist and open the channels by binding at the selective site of α-subunit of nicotinic receptor. They also enter the channel and block them as open channel blocker. But decamethonium and some other drugs also can penetrate all the way through the open channel and enter the muscle cytoplasm where they interfere the intracellular process and prevent depolarization. Whether prolonged administration of nondepolarizers, as in the intensive care unit, can result in the entry of relaxant in channel and blockade of it or finally entry of drug into the cytosol is unknown. This effect may partially explain the muscle weakness associated with prolonged relaxant therapy in the intensive care unit. In such situation neuromuscular block is complex. At the end, we can conclude that some drug molecules cause depolarisation due to action on the recognition site, while others cause: channel blockade, promote desensitization of the receptor, or interfere with the intracellular process (Figs 7.15A and B).



Figs 7.14A and B: Nicotinic receptor channel blockade. A. Open, B. Closed



Figs 7.15A and B: A. shows some effects of prolonged exposure of ACh receptor to high concentrations of antagonists (pancuronium). The three receptors at the right have recognition site blockade by pancuronium. The single receptor at the left has open channel blockade. B. shows some effects of prolonged exposure of ACh receptor to high concentrations of agonists (succinylcholine). The right most single receptor (B_1) is desensitized (blue). While that to the right of centre (B_2) has open channel blockade. At left (B_3, B_4) succinylcholine has penetrated the open channels of two ACh receptor and entered the cytoplasm

Close channel blockade

In closed channel blockade, drug block the mouth of channel while it is closed. Thus, by their (drug) presence it prevents physiological ions from passing through the channel to depolarise the end plate. This process can take place even when the channel is not open. This type of blocked is the part of action of cocaine, quinidine, tricyclic antidepressants etc.

Phase II Blockade

This is a complex phenomenon which occurs if neuromuscular junction is continuously exposed to a depolarising agent. The characteristic features of this phase II block is similar to the nondepolarising block, but can not be reversed by anticholinesterase agent. Normally the neuromuscular transmission usually remains blocked through out the period of exposure with a depolarising agent by continuous opening of the receptor channel. But, continuous and repeated opening of the receptor channels by large doses of depolarising agent allows the continuous efflux of potassium and influx of sodium. This results in abnormal electrolyte balance of the motor end plate which distorts the function of the perijunctional membrane and Na^+ channel and thus explain the mechanism of phase II block. Ca^{2+} entering the muscle fibre via open channel also cause the disruption of the function of receptor and sub end plate element. This also contribute to the mechanism of phase II block. On the other hand, the activity of the Na^+- K^+-ATPase pump on the muscle membrane increases due to increased intracellular Na^+ and extracellular K^+ concentration. Thus by pumping more Na^+ out of the cell and more K^+ into it, it works hard to restore the normal ionic balance and membrane potential as a compensatory mechanism. Return of the ratio of Na^+ and K^+ to normal level restore the membrane potential toward normal level even though the channel remains open. If depolarising muscle relaxant is applied in

Table 7.5: Difference between phase I and phase II block by succinylcholine

Features	*Phase I*	*Transition*	*Phase II*
Tetanic stimulation	No fade	Slight fade	Fade
Train - off - four	No fade	Slight fade	Fade
TOF ratio	> 0.7	0.4 - 0.7	< 0.4
Post-tetanic facilitation	Nil	Slight	Yes
Anti ChE	Potentiate	Little effect	Antagonise
Recovery	Rapid	Rapid	Prolonged
Dose requirement (mg/kg)	± 2	± 4	≥ 6

high concentration and allowed to remain at the neuromuscular junction for a long time, other things also occur which further explain the mechanism of phase II block. These are that the drug itself enter into the channel to obstruct it, and pass through the channel into the cytoplasm like open and close channel blockade. Similar actions also occur on the (Table 7.5) prejunctional structure. Thus the combination of the pre and post junctional effects plus the secondary changes on muscle and nerve homeostasis results in the complicated phenomenon, known as the phase II blockade. Phase II block is a complex and everchanging phenomenon. Though phase II block shows response to tetanic or TOF stimulation like nondepolarising agent, still it is best not to take any attempt to reverse this type of block by anticholinesterase. Development of phase II block depends on the type of depolarising drug, duration of exposure, concentration of drug and the type of muscle.

Atypical Receptors

In contrast to other cells, muscle cells have hundreds of nuclei. Each of these nuclei have genes which direct to make two types of ACh (nicotinic) receptors at the motor end plate – mature or junctional and immature or foetal or extrajunctional. Other than gene, multiple other factors such as electrical signal coming to muscle (innervation), growth factor, etc, also determine which type of receptor will be formed on the muscle fibre in every individual (Figs 7.16A and B).

The difference in the structure of these two types of receptors cause significant qualitative variations in the response among the individual patient to muscle relaxants and also seem to be responsible for some of the abnormal results to muscle relaxants. At molecular level, these two types of nicotinic receptor differ at ε-subunit of junctional receptor which is replaced by γ-subunit in extrajunctional receptor. This difference is of great enough to affect the physiology and pharmacology of nicotinic receptor and ion channel within it. Although the names of the receptors are junctional and extrajunctional, which imply that each is located in the junctional and extrajunctional area respectively, but this is not strictly correct. Because junctional receptor are always confined to the motor end plate of the muscle membrane. But immature or extrajunctional receptor may be expressed any where in the muscle membrane including motor end plate. When muscle cells loose its nerve connection due to avulsion, stroke, burn or before innervation (foetal life), it produces extrajunctional or immature or fetal form of receptor in place of normal or junctional receptor.

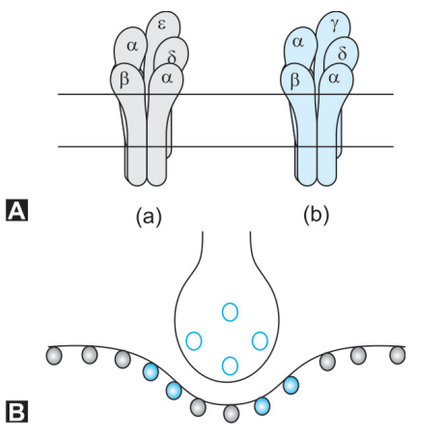


Fig. 7.16A and B: A. Shows junctional (a) and extrajunctional (b) ACh-receptors. Junctional receptors contain ε and extra junctional receptors contain γ subunits.
B. Neuromuscular junction with deficient activity. Muscle membrane contains extrajunctional receptors (blue circle). End plate contains both junctional (red circle) and extrajunctional receptors.

In foetus, before innervation, muscle cells only synthesize the extrajunctional receptors through out the whole muscle membrane including the motor end plate. Then as the fetus develops, muscle becomes innervated and begin to manufacture junctional receptor at the motor end plate and over the whole muscle. In this stage, at the end plate there is mixture of both the junctional and extrajunctional receptor. In a child of about 2 year old, before nerve muscle units are matured both types of receptors are found. Then as the child grows and nerve muscle unit matures, extra junctional receptor diminishes in concentration and disappear, both from the periphery of the muscle and the end plate. Process of making and removing the extrajunctional receptor is very fast. They appear within an hour after diminution of neuromuscular activity and are removed within half-life of 18 hours when activity returns to normal.

Although ACh does not binds with the γ or ε-subunit of receptor, still these subunits influence the ways in which these two kinds of receptors respond to the drug. Extra-junctional receptor are activated by lower concentration of agonist (succinylcholine) than are junctional receptor. So, extrajunctional receptors are more sensitive to depolarising agents. In contrast, extra junctional receptors are less sensitive than junctional to the non-depolarising drugs. In some circumstances, the non-depolarising muscle relaxants act as partial agonist and muscle contracts.

As extrajunctional receptors develop within few hours of stoppage of muscle

activity, so due to denervation or paralysis, patient becomes resistant to non-depolarising agents and then it is become more difficult to block them than ususal. So, the patient with deficient neural activity, demand more than usual dose of non-depolarising agent. On the other hand, as the extrajunctional receptor is sensitive to depolarising agent, so less amount of agonist such as succinylcholine is needed. Patient's receptor mixture and sensitivity to relaxants can began to change with in a day after an nerve injury or hospitalisation. Well built heavy muscular person who exercise vigorously are resistant to non-depolarising agent. This is because their nerve secret more ACh than normal and so transmission is more vigorous and hardened to block.

Patient with muscular paralysis due to denervation are more prone to succinylcholine induced hyperkalaemia. This is because in these patients, extrajunctional receptors predominate over the muscle cell membrane which are sensitive to depolarising agent. So, they remain open for long time by the agonist succinylcholine and allow more K^+ to escape from the muscle and enter the blood.

In infant and children, neuromuscular junctions are not mature. So, there are mixture of junctional and extra junctional receptor at the motor end plate. Their ratio varies with chronological age (with increasing age extrajunctional receptors disappear), muscular activity, health, vigor of child and from one group of muscle to another. Since, the junctional and extrajunctional receptor differ in their sensitivity to depolarising and non-depolarising agent, so, the amount of relaxant needed to produce muscle paralysis differs from one children to another, but in poorly predictable ways. Muscular paralysis produced by succinylcholine is not due to continuous depolarization of the whole muscle. But it is due to inactivated Na^+ channel ring at the perijunctional zone due to continuous depolarisation of endplate which insulate the depolarised motor end plate from rest of the muscle. Therefore, in infant and children as the insulating Na^+ channel ring is not developed properly, so the effect of depolarising relaxant may not be the same in thame as that of an adult.

ANTAGONISM OF NEUROMUSCULAR BLOCK

The competitive neuromuscular block caused by the action of (antagonist) non-depolarising muscle relaxants on nicotinic receptor is overcomed by increasing the concentration of competitor i.e. ACh (agonist). Increasing the number of molecules of ACh in the synaptic junctional cleft changes the agonist / antagonist ratio and increases the probability of agonist molecules such as ACh to bind with the unoccupied recognition site of it on it on nicotinic receptor. Normally, only about 5,00,000 out of 5 million available receptors are activated by a single nerve impulse. So, a large number of receptors are in reserve and could be occupied by a competitor agonist. Actually ACh can not displace from the nicotinic receptor the already bound molecule of non-depolarising agent and has to wait for the antagonist (non-depolarising muscle relaxant) to dissociate spontaneously from the receptor before it can compete with antagonist for free site. So, the length of time for which the nondepolarising agents presents in the synaptic cleft is also important. Non-depolarising relaxants bind to receptor for longer period than the life span of ACh. It indicates that most of the ACh is destroyed before any significant number of antagonist molecules have dissociated. So, prolonging the time for which ACh remain in junction, allows the time for dissociation of antagonist and for receptor to be freed and made available to ACh.

Neuromuscular block can be antagonised by two classes of drugs such as: K^+ blocking agents and acetylcholinesterase inhibitors. K^+ blocking agent such as 4-aminopyridine acts on the prejunction area. By impeding the efflux of K^+, it also prolongs the action potential of nerve ending. So, the duration of depolarisation of nerve axon is prolonged. Thus, indirectly prolonged action potential increases the influx of Ca^{2+} into nerve ending. Therefore, the nerve releases more ACh and for longer time than usual causing antagonism of neuromuscular blockade produced by nondepolarsing agents. As K^+ blocking agent acts only prejunctionally, so it also antagonizes the blockade produced by some antibiotics that act on prejunctional nerve endings such as polymyxin. So, 4-aminopyridine and this class of drugs are used very restrictedly to antagonize some specific neuromuscular block. However these drugs are not specific and act on all nerve endings including motor nerves, autonomic nerves, CNS etc, and is so associated with many side effects. So, this group of drugs is not used routinely to antagonise the neuromuscular block produced by non-depolarising agents.

Acetylcholine is inhibited or hydrolysed by an enzyme called true acetylcholinesterase or cholinesterase (chE) which is present is synaptic cleft. So, acetylcholinesterase inhibitors or anti-cholinesterases such as, neostigmine, pyridostigmine, edrophonium, etc, increase the level of ACh and improve the neuromuscular transmissions by inhibiting the acetylcholinesterase enzyme. Anticholinesterases or acetylcholinesterase inhibitors are ester of carbamic acid. So, they are also called carbamates. ACh is inactivated by its combination with the enzyme, cholinesterase, at its two sites: (i) an anionic site, bearing a negative charge which attracts the quaternary nitrogen atom (N^+) of acetylcholine and (ii) an esteric site which attracts the carboxyl group (COO) of the ACh molecule. As a result of the union of ACh molecule with the cholinesterase enzyme, the esteric site of the enzyme is acetylated by the acetylcholine molecule and this results in splitting of this molecule. Then, the acetyl group from the esteric site of the enzyme is immediately removed

(in nano second) as a result of combination with water, forming acetic acid. Thus, this sets the esteric site of the enzyme (cholinesterase) free for further inactivation of an other acetylcholine molecule. Anticholinesterase or cholinesterase inhibitors such as neostigmine, pyridostigmine, etc, act in the same way as acetylcholine with the cholinesterase enzyme, sparing the acetylcholine. Anticholinesterases are usually of two types: reversible and irreversible. Once irreversible anticholinesterase combines with the cholinesterase enzyme then this binding is not reversed until the whole complex of cholinesterase and anticholinesterase molecule is metabolised. The examples of these irreversible anticholinesterases are organophosphorous compounds.

Reversible anticholinesterase are also capable of combining with the anionic and esteric sites of cholinesterase enzyme like ACh, but does not form fixed cholinesterase and anticholinesterase complex like irreversible anticholinesterase. So, they are called reversible anticholinesterase. The complex which anticholinesterase form with the esteric site of cholinesterase enzyme is hydrolysed, but much less readily (Fig. 7.17) (after many minutes) than the acetyl-esteratic site complex formed with acetylcholine. Thus, this produces a temporary inhibition of the cholinesterase enzyme and prevent the breakdown of ACh and increase its concentration in synaptic cleft. Like ACh, both the reversible and irreversible anticholinesterases also can directly act on the ACh-receptor and may produce muscle relaxation like depolarizing agents, but it needs higher doses. In contrast to other reversible anticholinesterase, edrophonium forms reversible complex only with the anionic site of cholinesterase enzyme and hence has a shorter duration of action.

Organophosphorous compound (irreversible anticholinesterase) combine only with the esteric site of cholinesterase enzyme and consequently the esteric site is phosphorylated. Then the hydrolysis of this phosphorylated esteric site of cholinesterase enzyme is extremely slow and in certain cases does not occur at all. This produces an almost irreversible permanent inhibition or destruction of cholinesterase enzyme. So, they are called irreversible anticholinesterase or cholinesterase inhibitors. Echothiophate (irreversible anticholinesterase) forms complexes with

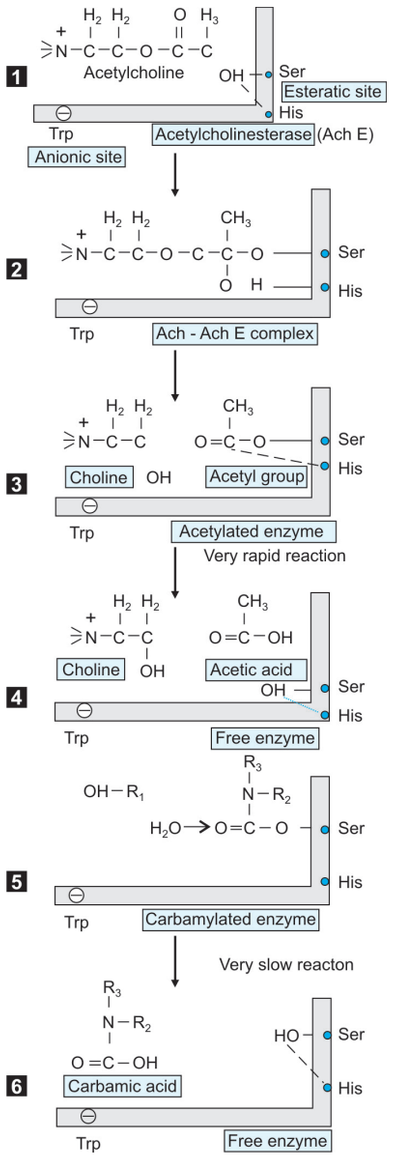


Fig. 7.17: Schematic representation of breakdown of ACh (1 to 4) and mechanism of action of carbamate anticholinesterase (3, 4). Ser = Serine, His = Histidine, Trp = Tryptophan

both anionic and esteratic site of the cholinesterase enzyme and hence is much more potent than other organophosphorus compounds. Thus, organophosphorus compounds permanently inhibiting the cholinesterase enzyme gradually raises the body ACh level which causes prolonged depolarisation of motor end plate, skeletal muscle paralysis, respiratory arrest, cardiac arrest and death.

Edrophonium (reversible anticholine esterase) is neither an ester, nor a carbamate compound. It is attracted and only bound to the anionic site of the cholinesterase enzyme by the electrostatic attraction between the positively charged nitrogen in the drug (edrophonium) and the negatively charged site of the enyme without any hydrolysis of edrophonium. It is removed from the enzyme molecule as in fact form and excreted through kidney. Other than inhibition of cholivesterare enzyme edrophonium also enhances the release of acetylcholine from the prejunctional site and so helps in the reversal from the deep neuromuscular block. The blockade of cholinesterase enzyme by edrophonium is very short lived and departs the enzyme in very short time. So, for decades edrophonium was considered to have short duration of action and to be useful in anaesthesia. But, now it is understood that the duration of action of any anticholinesterase is not determined by the duration of molecular reaction with the cholinesterase enzyme, but by the existence of drug (cholinesterase inhibitor or anticholinesterase) in body which depends on renal clearance. One edrophonium molecule attaches with enzyme (cholinesterase) for short time but as one molecule departs, it is immediately replaced by another edrophonium molecules, so that the cholinesterase enzyme remains inhibited for as long as the drug edrophonium is in the body. Elimination of edrophonium from body is same as neostigmine and pyridostigmine. So the duration of acetylcholinesterase inhibition and blockade reversal is same for all the three drugs.

However, as the patient has normal serumcholine esterase enzyme, so the pharmacokinetic properties of anticholinesterase are the principle determinant factor of the reversal of blockade. Activity of serum or plasma cholinesterase or the lack of it plays a minor role in the recovery of non depolarizing agent. Of the three commonly used anticholinesterase, edrophonium shows by far the greatest selectivity between the true acetylcholinesterase and butyryl or plasma cholinesterase. Butyryl cholinesterase is the serum esterase that hydrolyzes only succinylcholine and mivacurium but not ACh. Edrophonium greatly favours the true cholinesterase enzyme and the most desirable agent to reverse mivacurium. If patient has atypical esterase that does not destroy mivacurium, inhibition of true cholinesterase by neostigmine has no result till mivacurium will be present in the body. Mivacurium, like succinylcholine, is metabolized by pseudocholinesterase. It is only minimally metabolized by true cholinesterase. This introduces the possibility of prolonged action in patients with low pseudocholinesterase levels or variants of the pseudocholinesterase gene. In fact, patients who are heterozygous for the atypical gene will experience a block approximately twice the normal duration. Whereas atypical homozygous patients will remain paralysed for several hours. As atypical homozygotes can not metabolise mivacurium, the neuromuscular blockade may last for 3 to 4 hours. In contrast to succinylcholine induced paralysis, in these patients pharmacological antagonism with cholinesterase inhibitors will quicken reversal of mivacurium blockade once some response to nerve stimulation becomes apparent. Edrophonium more effectively reverses mivacurium blockade than neostigmine because it inhibits true cholinesterase activity only. Again there is no reason to choose one anticholinesterase over another.

Neostigmine, pyridostigmine and edrophonium does not cross the blood brain barrier as they are the quarternary ammonium compound. So, they have less CNS effects. Similarly, quarternary ammonium derivative of atropine such as glycopyrrolate also can not cross the blood-brain barrier. So, frequently glycopyrolate is used to limit the cholinergic effects of anticholin esterase agents on the periphery. Atropine cross blood-brain barrier and may cause CNS problems.

Anticholinesterases are not only selective for the neuromuscular junction, producing the nicotinic action of ACh which causes removal of neuromuscular blockade. But it also acts on cholinesterase in other sites of the body producing muscarinic action of ACh. So, atropine or glycopyrrolate like drug is used to counter the muscarinic effects of acetylcholine that accumulates in the synapses of gut, bronchi, salivary gland, and CVS, etc. Anticholinesterase such as physostigmine, tacrine are not quaternary ammonium compound. So, they cross blood-brain barier and have profound CNS effect. Anticholin esterase like physostigmine, tacrine also inhibit phosphodiesterase enzyme in addition to cholinesterase enzyme which plays important role in transmitter release at many synapses in CNS. This action is used in the treatment of Alzheimer's dementia.

Many anticholinesterase agents have methyl group on its positively charged nitrogen atom. So, it also acts as agonist like ACh on the nicotinic receptor channel, initiating ion flow and enhancing neuromuscular transmission. Mixing of different anti-ChEs (neostigmine, edrophonium etc) is not advisable. Because they do not potentiate each other. Therefore, when additional doses of anti-ChE is needed for treatment of incomplete reversal, then it is better to continue the original drug.

ANTICHOLINESTERASES OR CHOLINESTERASE INHIBITORS

Though discussion under this heading has already been discussed under the previous heading, still it lacks some points which are elaborated here. Anticholinesterases (anti-ChEs) are agents which inhibit the cholinesterases (ChEs) enzyme from destroying the acetylcholine and thus they protect ACh and promote neuromuscular transmission. Except increasing the level of acetylcholine (ACh) at the motor end plate, anti-ChEs have additional direct action on cholinergic nicotinic and muscarinic receptors situated on other places. So, the actions of anti-ChEs are qualitatively similar to that of acetylcholine (ACh) and other directly acting cholinoreceptor stimulants. Hence the action of anti ChEs which is mediated by ACh are divided into two groups – muscarinic action and nicotinic actions like ACh. However, the relative intensities of action of anti-ChEs mediated by ACh on muscarinic (smooth muscle, GI, respiratory tract, urinary system, glands glands) and nicotinic (autonomic ganglion, skeletal muscle, CNS) receptors varies among the different agents.

Classification of Anti-ChEs

Anti-ChEs are primarily grouped into two groups such as reversible and irreversible anticholinesterase.

Reversible anti-ChEs

Carbamates
- Neostigmine
- Pyridostigmine
- Physostigmine
- Edrophonium

Acridine
- Tacrine

Irreversible anti-ChEs

Carbamates
- Carbaryl (sevin)
- Propoxur (Baygon)

Organophosphates
- Parathion
- Malathion
- Diazinon(TIK-20)

Echothiophate
- Tabun
- Sarin
- Soman

- Insectisides
- Nerve gases for chemical warfare

Chemistry

Anti-ChEs are either esters of carbamic acid (carbametes) or derivatives of phosphoric acid (organophosphates) (Fig. 7.18).

In carbamates, R_1 may have a nonpolar tertiary amino N (e.g. in physostigmine), and render the compound lipid soluble. In other reversible inhibitors, R_1 has a quaternary N^+ and render them lipid insoluble. All organophosphates are highly lipid soluble except echothiophate which is water soluble.

Mechanism of Action

The main mechanism of action of anticholinesterases (anti-ChEs) are the reaction (inhibition) with cholinesterases enzyme which destroy the acetylcholine. This results in an increased concentration of acetylcholine at synaptic cleft and thereby increase the likelihood of ACh, occupying the unblocked nicotinic receptors and improve the neuromuscular transmission. The reaction between the anti-ChE and ChE (cholinesterase) differs from the reaction between the ACh (acetylcholine) and ChE in that at the previous reaction the complex molecules (formed by anti-ChE and ChE) have a longer dissociation half-life and is about 7 minute, as the complex molecules are hydrolysed at very slow rate. Whereas the ACh and ChE complex molecule breaks down by hydrolysis within a fraction of second and ChE is freed for further action on ACh molecule. Thus, it quickly breaks all the ACh. In the reversible group of anti-ChE, the ChE is freed after a long time during which period the level of ACh is increased sufficiently to produce muscular contraction. Then free ChE again hydrolyse the ACh. In the irreversible group, the complex formed by anti-ChE and ChE is permanent and is not freed by hydrolysis (so they are called irreversible anti-ChE) So the ChE does not become free and gradually excessive ACh accumulates and death occurs.

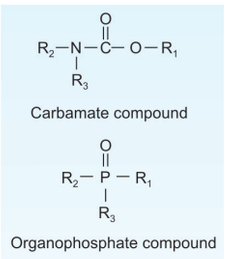


Fig. 7.18: Basic structure of anticholinesterase

The active region of ChE enzyme (such as acetylcholinesterase) makes a groove which contains an aromatic anionic site near trytophan 86 and an esteric site near serine 203 and histidine 447. The quaternary nitrogen atom (N^+) of ACh is attached with the negatively charged anionic site of ChE enzyme and the carboxyl group (COO) of ACh is attached with the esteric site of ChE enzyme. As soon as the carboxyl group of ACh is attached with ChE enzyme at the esteric site, then choline is splitted out from ACh forming actylated enzyme complex. Then acetylated enzyme complex reacts with water exremely rapidly and the esteric site is freed in a fraction of millisecond forming acetic acid and free cholinesterase enzyme (cholinesterase is here known as acetylcholinesterase). Thus, at the end of the reaction we get choline, acetic acid and free cholinesterase enzyme (ChE).

Neostigmine and pyridostigmine (carbamated compound) combines with the both sides of the ChE enzyme in almost the same way as acetylcholine, but with a longer dissociation half-life of about 7 minutes. The carbamate and the ChE complex (carbamylated enzyme) hydrolysed very slowly, so it is reversible. Whereas, organophosphate and ChE complex (phosphorylated enzyme) hydrolyze not at all, (irreversible). It is noteworthy that edrophonium (carbamate) in difference with neostigmine attaches only to the anionic site of the enzyme, while organophosphates attach only to the esteric site of the ChE enzyme. Dissociation of edrophonium from ChE enzyme (reactivation of the inhibited enzyme) does not involve hydrolysis of edrophonium, but involve only its detachment from the ChE. Dissociation of edrophonium from enzyme occurs more readily with much shorter dissociation half-life of about 20 seconds.

Anticholinesterase (anti-ChE) agents, such as neostigmine, pyridostigmine and edrophonium, may also have a direct stimulating effect on the nicotinic receptor, facilitating neuromuscular transmission. Another action of these agents is at the presynaptic level, involving direct enhanced liberation of acetylcholine (ACh). This effect is particularly marked with edrophonium which is thought to act mostly by increasing the liberation of ACh, rather than by inhibition of acetylcholinesterase (AChE).

If anti-ChE agents are administered in large doses or in the absence of muscle relaxants, they produce fasciculations and even a depolarising type of block, similar to that produced by succinylcholine. However, this is unlikely to occur if a nondepolarising muscle relaxant is used, even if almost complete recovery appears to have occured. The likely explanation of it is that a large proportion of the receptors are still occupied by the muscle relaxant.

After treatment with anti-ChEs, the acetylcholine (ACh) released by a single nerve impulse, is not immediately destroyed but rebinds to the same recptor, diffuses to act on neighbouring receptors and activates prejunctional fibres causing repetitive firing, twitching and fasciculations. Force of contraction in particularly curarized and myasthenic muscles are increased. Higher doses of anti-ChE cause persistent depolarisation of end plates resulting in blockade of neuromuscular tranmission with weakness and paralysis.

Pharmacokinetics

Neostigmine and its congenrs are poorly absorbed orally. Oral dose of them is 20 to 30 times higher than their parenteral dose. They do not penetrate the blood-brain barrier. They are partially hydrolysed and partially excreted unchanged through urine. Elderly patients show reduced rate

of clearance of all these three agents with prolongation of half-life. Dose-response curves of these three anti-ChE agents show that pyridostigmine is five times and edrophonium is 10 times less potent than neostigmine. It has also been shown that the dose response curves of neostigmine and edrophonium are not parallel which indicate that edrophonium has a different mode of action. The elderly require a larger dose of neostigmine to attain the same rate of recovery, while the dose should be reduced in children.

Doses

The commonly recommended doses for neostigmine is 0.3 to 0.5 mg/Kg (30 to 50 µg/Kg), for pyridostigmine is 0.2 to 0.25 mg/Kg, and for edrophonium is 0.5 to 1 mg/Kg. Among these three antiChE agents, edrophonium is the most rapid acting with peak effect between 2 and 4 minutes after its administration. While the peak effect of neostigmine is 10 minutes and pyridostigmine is 15 minutes after their administration. Pyridostigmine is, therefore, too slow for routine use. On the other hand, although the edrophonium is faster acting, but it is not always effective in antagonising a relatively deep block. It is also true that higher doses of anti-ChE is required to antagonize the higher depth of block more rapidly and more completely than smaller doses. But this is true upto a limit. Beyond which the increase in dose of anti-ChE does not produce any greater antagonism. Thus the maximum dose of neostigmine and pyridostigmine is 60 to 80 µg/Kg and 1 to 15 mg/Kg, respectively.

Other effects

It is previously stated that the actions of anti-ChEs are qualitatively similar to that of directly acting cholinoreceptor stimulants i.e. acetylcholine (ACh) which is classified as muscarinic, nicotinic and CNS effects. The muscarinic actions are consists of actions on heart, blood vessels, smooth muscles, glands and eye. Nicotinic actions are consist of actions on autonomic ganglia and skeletal muscles. The effects of neostigmine (also other anti-ChEs) on the cardiovascular system are variable and depend upon the prevailing autonomic tone. The drug may cause bradycardia, leading to a fall in cardiac output. It decreases the effective refractory period of cardiac muscles and decreases the conduction time in conducting tissue. In higher doses, neostigmine may cause hypotension secondary to a central effect. Actually cardiovascular effects of neostigmine are complex. This is because muscarinic action of it would produce bradycardia and hypotension, while ganglionic stimulating effect of neostigmine would tend to increase the heart rate and BP. Action of neostigmine on medullary centres further complicates the picture, so does ganglionic blockade with high doses. Thus the overall effects of anti-ChE are often unpredictable and depend on the agent and its dose.

Neostigmine increases the bronchial secretion and may cause bronchoconstriction. The drug also increases the salivation, lower oesophageal and gastric tone, increases gastric acid output and increases gastrointestinal tract motility. So, nausea and vomiting may occur.

In therapeutic doses, the drug has action on skeletal muscle, leading to muscular contaction. But in higher doses, neostigmine may block the neuromuscular transmission by the combination of a direct effect on nicotinic receptor and by allowing the excessive accumulation of ACh.

Lipid soluble antiChE agents such as physostigmine and organo phosphates have more marked muscarinic and CNS effects. They also stimulate ganglia but action on skeletal muscles is less prominent. Whereas the lipid insoluble agents such as neostigmine and other quarternary ammonium compounds have more nicotinic effects producing more marked action on skeletal muscles (direct action on muscle end plate cholino receptors as well) and autonomic ganglia, with less muscarinic effects. They do not penetrate CNS and have no central effects.

In ganglion, local hydrolysis of ACh is less important. But inactivation of acetylcholine is ganglia occurs partly by diffusion and partly by hydrolysis in plasma. Anti-ChEs stimulate ganglia primarily through nicotinic receptors, present there. High doses of anti-ChEs cause persistent depolarization of the ganglionic nicotinic receptors and blockade of transmission.

Muscarinic actions of anti-ChE agents result in bradycardia, hypotension, increased secretions and increased smooth muscle contractions. These effects (muscarinic actions of anti-ChEs) can be prevented by the simultaneous or prior administration of antimuscarinic (anticholinergic) agents such as atropine (20 to 30 µg/Kg or 0.02 to 0.03 mg/Kg) or glycopyrolate (10 µg/Kg or 0.01 mg/Kg). These anticholinergic agents only have antimuscarinic actions (so called antimuscarinic agent) without any antinicotinic actions. Nicotinic antagonists are generally referred as 'ganglion blockers' and 'neuromuscular blockers'.

Atropine and glycopyrrolate is highly selective for muscarinic receptors. But some of its synthetic substitutes do possess significant nicotinic blocking property in addition to antimuscarinic property. Atropine and glycopyrrolate only block ACh induced muscarinic actions but not the actions evoked by histamine, 5 HT. The use of glycopyrrolate is associated with greater stability of the heart rate when neostigmine is used. But, atropine is the preferred agent with edrophonium because of their similar speed of onset of effect. Edrophonium requires a lower dose of the anticholinergics agent as its muscarinic effects are less. Glycopyrrolate has distinct advantages over atropine as it does not cross the blood-brain barrier.

Neostigmine and pyridostigmine but not edrophonium causes prolongation of the effect of subsequently administered succinylcholine and mivacurium, by inhibiting plasmacholinesterase activity. Administration of neostigmine also may be associated with increased incidence of PONV.

8 Acid-Base Balance

INTRODUCTION

In our body, the amount of H^+ (Hydrogen ion) is very small in comparison to other common physiologically important cations and anions such as Na^+, K^+, HCO_3^-, Cl^-, etc. In normal plasma, their concentrations are respectively 140, 4, 24 and 100 mmol/L. Whereas the H^+ concentration in normal plasma is only 0.00004 mmol/L or 0.00000004 mol/L. So this small number of H^+ concentration is commonly expressed either as pH (–ve logarithm of H^+ concentration) or as nmol/L. The concentration of H^+ in normal arterial blood is 40 nmol/L or pH is 7.4 which is considerably an easier expression to write than 0.00004 mmol/L or 0.00000004 mol/L.

Life is an acidogenic process. Because for continuation of life, during production of energy by catabolism of glucose, fatty acids, amino acids, etc. different acids are produced. For example during metabolism of glucose, amino acids and fatty acids through the citric acid cycle, CO_2 and water are produced. This again form carbonic acid ($CO_2 + H_2O \leftrightarrows H_2CO_3$ $H_2CO_3 = H^+ + HCO_3^-$) giving H^+. At the alveolar level, this H_2CO_3 is then broken down and CO_2 is excreted though the lungs. Thus, lung is the main channel of excretion of carbonic or nonmetabolic acids. During metabolism of amino acids through other cycles, different noncarbonic or metabolic acids, such as H_2SO_4, H_3PO_4, etc. are also produced. These also produce H^+ and are mainly excreted through the kidneys. Diet also contains large amount of H^+ ion normally in the form of sulphur containing amino acids in protein. Urine is the main channel of excretion of these noncarbonic or metabolic acid, whereas lung is the main channel of excretion of nonmetabolic or carbonic acid such as CO_2. In a normal (Table 8.1) adult, the average daily oral H^+ intake is 50 to 80 mmol/day. In the resting subject the catabolism of carbohydrates and fats produce an acid load (volatile acids $\rightarrow H_2CO_3$) of approximately 18,000 to 20,000 mmol/day, which is excreted by the lungs as CO_2. Protein catabolism also leads to additional production of 60 to 80 mmol/day of nonvolatile acids, mostly in the form of sulphuric and phosphoric acids, which are excreted by kidney. Again oxidation of carbohydrates and fats in a diseased state or in anaerobic metabolic state leads to the production of more nonvolatile acids, such as, lactic acid (in anaerobic metabolism) and ketoacids (in diabetes mellitus) (Table 8.2).

During intracellular metabolism the various acids, produced from catabolism of different substrates flow into the alkaline extracellular fluid and thus maintains the normal intracellular H^+ concentration. Then this H^+ is excreted through urine as titrable acid or through lungs as CO_2.

Table 8.1: Daily normal input and output of acids and bases through body

	Input (mmol/day)		*Output (mmol/day)*
A. Non volatile acids			
Lactate	1500	Liver, kidney,	1500
Protein	50-80	by titrable	30
Phospholipid	30	Acids	40
Other	12		
B. Volatile acids	13,000		13,000
Carbon dioxide		Lungs	

Table 8.2: The mechanism by which the primary acid-base changes are compensated. If the pH has been fully returned to normal the primary change is said to be fully compensated. Otherwise organic acid base .... it is said to be partially compensated

Respiratory acidosis	Kidney	Metabolic alkalosis with further rise in plasma [HCO_3^-] by increasing its absorption through kidney or with further fall in plasma [H^+] by increasing its excretion through kidney.
Respiratory alkalosis	Kidney	Metabolic acidosis with further fall in plasma [HCO_3^-] by increasing its excretion through kidney or with further rise in plasma [H^+] by decreasing its excretion through kidney.
Metabolic acidosis	Lungs	Respiratory alkalosis with further fall in plasma [H^+] by eliminating more CO_2 through lungs.
Metabolic alkalosis	Lungs	Respiratory acidosis with further rise in plasma [H^+] by decreasing the excretion of CO_2 through lungs.

Hence, body constantly balances this H^+ input with the H^+ output. Small changes in normal H^+ concentration can produce significant alteration in body enzymatic activity. This presents clinically, then, as organ dysfunction. As metabolic process leads to changes in H^+ concentration, similarly the changes in H^+ concentration or acid-base balance is also an indicator of status of current metabolic process, occuring in human body and a real time predictor of the utility of critical therapy. So, the complete understanding of acid-base balance is very important. But, unfortunatley most anaesthetists avoid this chapter. This is because pH is defined complicatedly as the negative logarithm (−log) of the H^+ ion concentration and there is wide spread use of multiple, complex, overlapping, irrelevant terms such as 'standard bicarbonate', 'negative base excess', 'alkali reserve' etc. to describe the acid base status.

Various buffer systems in the cells and in the extracellular fluid work against this accumulation of H^+ or when there is disruption of balance between the amount of intake and output of H^+. The buffer capacity capable of absorbing the H^+ is up to 10 mmol per Kg of body weight, i.e. 500 to 700 mmol in an adult. Tissue hypoxia, starvation, diminished ventilation, diabetes, heart failure, renal failure, etc, which cause increased input of H^+ in body cause strain to this buffer capacity of the body. Therefore, it is important that all this should be brought under control before any surgery as far as possible, with least possible encroachment on the buffer capacity. This is because to deal by buffer system in future with acute rises of H^+ concentration due to any cause, during surgery.

The normal arterial H^+ concentration is 40 nM/L, yielding pH of 7.4. This arterial H^+ concentration reflects the present dynamic balance between the input (from ingestion and metabolism of food) and the output (through lungs as CO_2 and through kidney as nonvolatile acids) of it. Thus when an imbalance between this input and output occurs, then the H^+ concentration in blood will deviate from the normal to the range of viable variability, roughly 160 to 20 nM/L (pH 6.8 to 7.7) beyond which life is not possible.

Table 8.3: Sets of pH – PCO_2 acid-base data forming CO_2 – titration curve

SL	*$PaCO_2$ (mm of Hg)*	*pH*	*Metabolic status*	*Respiratory status*	*Overall status*
N	40	7.4	Normal	Normal	Normal
M	70	7.1	Acidosis	Acidosis	Acidaemia
O	70	7.4	Alkalosis	Acidosis	Normal
P	30	7.3	Acidosis	Alkalosis	Acidaemia
Q	30	7.6	Alkalosis	Alkalosis	Alkalaemia

Two types of acids are produced during metabolism of substrates in the body:

(i) Volatile or carbonic or respiratory acids

This is carbonic acid (H_2CO_3) which is formed by the hydration of CO_2.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrows H^+ + HCO_3^-$$

CO_2 is produced by metabolism of glucose, fatty acids and amino acids through TCA cycle in mitochondria. CO_2 is produced at an average rate of about 200 ml/min or 288 L/day. This gas is eliminated via the lungs and, so, is referred to as the 'volatile' or 'respiratory' acid.

(ii) Nonvolatile or noncarbonic or metabolic acids

These are lactic acid, pyruvic acid, acetoacetic acid, β-hydroxybutyric acid, phosphoric acid, sulphuric acid, hydrochloric acid, keto acids and variety of other organic acids. The lactic acid is produced from pyruvic acid during glycolysis in the absence of O_2. So, lactic acid is often used as a clinical marker of anaerobic metabolism from hypoxia, poor perfusion of tissues or other disturbances of tissue oxygenation. Also, it is important to realise that about 1400 mmol of lactic acid is normally produced each day, principally by skeletal muscles, RBCs and the skin. This lactic acid is then converted in liver to form CO_2 and H_2O. A smaller amount of lactate is also cleared through renal excretion or by conversion through gluconeogenesis in liver.

Keto acids are produced in diabetes mellitus. Phosphoric, hydrochloric and sulphuric acids are produced during the metabolism of amino acids. Hydrochloric acid (HCl) is produced during the metabolism of lysine, arginine and histidine amino acids. Sulfuric acid (H_2SO_4) is the product of cysteine and methionine amino acid metabolism. Phosphoric acid (H_3PO_4) is derived from the normal metabolism of dietary phosphate (Fig. 8.1 and Table 8.3)..

Part of these load of metabolic acid is balanced by the production of bicarbonate (HCO_3^-) from the metabolism of aspartate, glutamate and citrate, and part is excreted through kidney. The sum of these addition and loses of metabolic acids and bases results in a net positive balance of H^+ of about 70 mmol/day or approximately 1 mmol/Kg/day. Metabolic acids are either further metabolised in liver or excreted primarily through kidney. Pyruvic acid, acetoacetic acid and β-hydroxybutyric

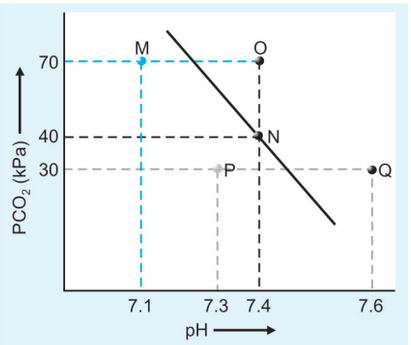


Fig. 8.1: CO_2 titration curve formed by sets of pH – PCO_2 acid-base data

acids which are also obtained from other sources are further degraded to CO_2 and H_2O in liver.

Changes in the carbonic acid component in blood reflect an imbalance between the CO_2 production and its elimination by alveolar ventilation. It is represented by the changes in P_aCO_2 and is termed as the respiratory or carbonic acid-base abnormalities (respiratory acidosis or alkalosis). Whereas, the changes in handling of metabolic acid or alkali result in metabolic or noncarbonic acid-base abnormalities (metabolic acidosis or alkalosis) and is represented by the HCO_3^- level in blood.

The goals of the assessment of acid-base balance

i. To define the types of acid-base imbalance, whether respiratory (carbonic) and/or metabolic (noncarbonic).
ii. To quantify the magnitude of respiratory abnormality by measurement of P_aCO_2.
iii. To quantify the magnitude of metabolic acid-base abnormality by estimation of plasma HCO_3^- level or the extracellular fluid base excess.
iv. To quantify the buffer capacity.

TERMINOLOGY

Chemically, the acidity of a substance is defined by its ability to ionise in the solution and to give the amount of H^+ and base (A^-). Thus, the relationship between the acid and base can be written by the equation as:

$HA\ (acid) = H^+ + A^-\ (base)$

In this reaction HA is termed as the acid or H^+ (proton) donor and the anion A^- is termed as the H^+ (proton) acceptor or conjugate base.

The acid which dissociates more in aqueous solution is called the strong acid e.g. HCl. The stronger is the acid, the weaker is its conjugate base, that is, the less ability of the base to accept H^+, e.g. $HCl \rightarrow H^+ + Cl^-$.

The acid which dissociates to lesser extent in aqueous solution is called the weak acid. The weaker is the acid, the stronger is its base.

For example, lactic acid:

$CH_3CHOHCOOH \rightarrow CH_3CHOHCOO^- + H^+$

Other examples of weaker acids are:

$H_2CO_3 \rightarrow H^+ + HCO_3^-$

$H_3PO_4 \rightarrow H^+ + H_2PO_4^-$ etc.

In our body, only 1/100 of the lactic acid remain in ionised form, while 99/100 remain in unionized form.

The equation of acid base balance follows the Law of Mass Action which states that the product of reaction on one side are proportional to the products of the reaction on the other side. The degree to which a certain acid will remain in dissociated condition in solution is constant for that specific acid and is known as the dissociation constant. This Law of Mass Action can be expressed in the following formula:

$$HA \underset{k_1}{\overset{k}{\leftrightarrows}} H^+ \times A^-$$

Here, the dissociation constant (k or k_1) determines the point at which equilibrium is reached in a specific equation. If k is larger than k_1, then the reaction will proceed preferentially toward the right and will result in more H^+ and A^- ions than HA. This means HA is more acidic in nature. Reversely, if k_1 is larger than k, then there will be more HA than the amount of H^+ and A^- is formed. This means HA is less acidic in nature.

Acidity of a solution is also defined by the H^+ concentration in that solution or more precisely the actibity of H^+ in that solution which is measured by pH electrode. The normal value of arterial plasma pH is 7·4 at $PaCO_2$ of 40 mm of Hg which usually varies within the range between 7.35 to 7.45. Range of pH of venous blood is 7.32 to 7.42. Acidaemia occurs when the arterial blood pH is less than 7.35 or H^+ ion concentration is greater than 44 nM/L. Alkalaemia occurs when the arterial blood pH is greater than 7.45 or H^+ ion concentration is less than 36 nM/L.

Acidosis or alkalosis are abnormal conditions which cause acidaemia and alkalaemia in blood respectively, provided if no secondary changes occur to compensate for the primary changes. Usually, the acidosis or alkalosis of one system (e.g respiratory system) is compensated by alkalosis or acidosis of other system (metabolic system), so that the resulting pH still lies within the normal ranges. But, the actual acid-base status should be known by its primary cause such as the respiratory or metabolic acidosis or alkalosis and by its compensatory phenomenon such as the metabolic or respiratory alkalosis or acidosis and vice versa. That is, though the pH is normal, still the acid-base status should be talked as primary respiratory or metabolic acidosis or alkalosis and compensatory metabolic or respiratory acidosis or alkalosis with their different combination and vice versa.

A respiratory acidosis or alkalosis is said to present when P_aCO_2 is above 45 mm of Hg (6 KPa) or below 35 mm of Hg (4.7 PKa) respectively. Also if the set of pH and PCO_2 value produces a point to the left or right of the normal CO_2 titration curve (in figure) then a respiratory acidosis or alkalosis, respectively is present. But, one has to keep in mind that there is no specific centre for H^+ ion regulation in CNS.

Though the concentration of H^+ in aqueous body solution is very low, still the range of concentration of it that varies normally is large enough which extends from 10^{-1} to 10^{-15} mol/L. So for convenience, these H^+ concentration or $[H^+]$ is expressed by the way of exponential arithmtic method such as:

$[H^+] = 10^{-P} = 1/10^P$

As pH is the negative logarithm of H^+ concentration (as P means —log)

So $pH = -\log [H^+] = -\log [10^{-P}] = P$

(Negative logarithm of $10^{-P} = P$)

The term pH was introduced by Sorensen, in 1909. It is the more convenient way of expression of H^+ concentration than molar expression of it in m.mol/L or nmol/L. Here, the exponent of H^+ concentration, i.e. p, stands for the initial letter of the ward 'potenz' or 'puissance' or 'power'.

The hydrogen ion concentration of pure water is 10^{-7} mmol/L. Using the pH notation, the pH of pure water is 7, because $pH = -\log [H^+] = -\log (10^{-7}) = 7$. The negative log of 10^{-7} is 7. For various reasons, the H^+ concentration of our body is conventionally expressed as the pH which is the negative logarithm of concentration of H^+ ion in mmol/L. Thus, this pH scale indicates the number of H^+ in mmol/L logarithmically.

According to the System of International (SI) nomenclature, the acidity is expressed as H^+ concentration in nmol/L, instead of mmol/L or pH unit. But, such expression of H^+ concentration in favour of nmol/L is sometimes criticised. This is because:

i. the biological activity of a solution is related to the chemical potential of it which is exerted by the activity of H^+ ion and this is logarithmic in nature,
ii. the measurement of H^+ concentration is made according to a standard, operational pH scale,
iii. the blood pH values in the population are probably evenly distributed, but the distribution of H^+ concentration in $nmol^{-1}$/L in population is distorted.

Thus, ideally, the H^+ concentration should be converted to pH units before any statistical analysis for easy and correct result. But, the pH system has a great source of confusion. Because unlike the direct concentration of H^+ in n.mol or mmol/L which is usually expressed as a linear, positive numerical scale, the pH scale is logarithmic which is not linear. On the other hand, the number used to express the pH becomes smaller as the H^+ concentration becomes greater. So, this counter molar system makes the clinician awkard. But once understood, the concept of molar system, expressed as nmol/L is quite workable in the clinical setting. (Table 8.4).

Some important points regarding the pH scale are:

i. As pH scale is expressed as the negative logarithmic of base 10, so it means there is tenfold change of H^+ ion concentration expressed in nmol/L for every one unit change in pH. For example, a solution with pH of 4 has 10 times more H^+ ion concentration in nmol/L than a solution with pH of 5 and 100 times more than a solution with pH of 6.
ii. The changes in H^+ concentration in nmol/L differ vastly at different points of the pH scale, depending upon at which point of the scale these changes occur.
iii. Though the H^+ concentration in nmol/L scale is easier to visualise, still the pH scale is deeply infixed in our mind and is the standard with which we can function.

INTERCONVERSION OF H^+ CONCENTRATION AND pH

This can best be shown by two examples:

i. If the normal pH of whole blood is 7·4, then what will be the H^+ concentration or $[H^+]$

$[\ ]$ is the symbol of concentration.

$pH = 7.4$

$\text{or } -\log H^+ = -\log 10^{-7.4}$

$\text{or } H^+ = 10^{-7.4}$

$\text{So } [H^+] = 10^{-7.4} \text{ mol/L}$

$= 10^{-7.4} \times 10^9 \text{ nmol/L}$

$= 10^{1.6} \text{ nmol/L}$

$= 40 \text{ nmol/L}$

ii. If the hydrogen ion concentration is 100 n.mol, what is the pH ?

$100 \text{ nmol/L} = 100 \times 10^{-9} \text{ mol/L}$

$\therefore [H^+] = 100 \times 10^{-9} \text{ mol/L}$

$\therefore pH = -\log [H^+]$

$= -\log (100 \times 10^{-9})$

$= -\log [1/100^{-1} \times 1/10^9]$

$= -\log [1/10^{-2} \times 1/10^9]$

$= -\log [1/10^7]$

$= -\log [10^{-7}]$

$= 7$

In other simple way, it can also be calculated by

$[H^+] = 100 \text{ nmol/L}$

$= 100 \times 10^{-9} \text{ mol/L}$

$\therefore pH = -\log [H^+]$

$= -\log (100 \times 10^{-9})$

$= -\log 100 - \log^{-9}$

$= -2 + 9$

$= 7$

[The negative log of 100 is –2 and the negative log of 10^{-9} is 9. Thus taking the advantage of log we can add instead of multiplication] (Table 8.5).

Another way of interconvertion between pH and $[H^+]$ is:

i. If the $[H^+]$ of a solution is 2.86×10^{-4} mol/L, then the pH can be calculated as follows:

$[H^+] = 2.86 \times 10^{-4}$

$pH = -\log H^+$

Table 8.4: Conversion of H^+ concentration in mol / Lit and nmol / Lit to pH units

1 nanomole (nmol) = 10^{-9} mole or 10^{-6} mmole
1 mole = 109 nanomole

H^+ (mol / Lit)	*pH*	*H^+ (nmol / Lit)*
$0.001 = 10^{-3}$	3	1000,000
$0.0001 = 10^{-4}$	4	100,000
$0.00001 = 10^{-5}$	5	10,000
$0.000001 = 10^{-6}$	6	1000
$0.000,000,1 = 10^{-7}$	7	100
$0.000,000,01 = 10^{-8}$	8	10
$0.000,000,001 = 10^{-9}$	9	1
$0.000,000,000,000,001 = 10^{-15}$	15	0.000,001

Table 8.5: Relation between H^+ concentration and pH

$[H^+]$ nmol/L	pH	
10	8	
15	7.8	
20	7.7	Alkalosis
25	7.6	
30	7.5	
40	7.4	Normal
50	7.3	
65	7.2	
80	7.1	Acidosis
100	7	
160	6.8	

$$= \log 1/[H^+]$$
$$= \log [1/(2.86 \times 10^{-4})]$$
$$= \log [1/(10^{0.456} \times 10^{-4})]$$
$$= \log (1/10^{-3.544})$$
$$= \log 10^{3.544}$$
$$= -\log 10^{-3.544}$$
$$= 3.544$$

or,

$$pH = -\log [H^+]$$
$$= -\log (2.86 \times 10^{-4})$$
$$= -\log (10^{0.456} \times 10^{-4})$$
$$= -\log 10^{-3.544}$$
$$= 3.544$$

ii. For calculation of $[H^+]$ from a known pH value, the calculation will be reversed. Suppose the pH value of a solution is 3.544 then the $[H^+]$ will be:

$$pH\ 3.544 = \log 10^{3.544}$$
$$= \log (1/10^{-3.544})$$
$$= \log (1/10^{0.456} \times 10^{-4})$$
$$= \log (1/2.86 \times 10^{-4}),$$

Antilog of 0.456 = 2.86

$\therefore$ H^+ concentration of $[H^+]$
$= 2.86 \times 10^{-4}$ mol/L
= 286000 nmol/L

Calculation of pH of Neutral Pure Water

According to the law of mass action the equilibrium, governing the ionisation of water, is as follows:

$H_2O \leftrightarrows [H^+] \times [OH^-]$, or
$K[H_2O] = [H^+] \times [OH^-]$

[ ] is the symbol of concentration.

At a particular temperature (23°C) the product of the number of hydrogen ions multiplied by the number of hydroxyl ions is constant for pure neutral water and this is known as dissociation constant. The dissociation constant of water can be denoted as K_W (w stands for water) and its value in case of pure water is 10^{-14}. Thus, by the law of mass action :

$$[H^+] \times [OH^-] = K_W = 10^{-14}$$

In pure water the concentration of H^+ ions is equal to the concentration of OH^-. Hence,

$[H^+] = 1 \times 10^{-7}$, $[OH^-] = 1 \times 10^{-7}$

Therefore, pH of the pure neutral water will be

$$pH = -\log [H^+]$$
$$= \log [1/H^+]$$
$$= \log (1/1 \times 10^{-7})$$
$$= 7$$

So, pure water having equal number of $[H^+]$ and $[OH^-]$ ions is neutral with pH 7.0.

Here, one thing is to notice that the reduction of pH of 0.3 units represents a doubling of $[H^+]$ and vice versa.

One basic difficulty during the measurement of pH *in vivo* is that it is not possible to measure either the actual H^+ concentration or its activity in biological system. On the other hand, the pH numbers which is produced by electrometric measurement *in vitro*, are defined by an operational scale which is based upon the standard buffer solution and fixed temperature. They do not relate precisely to H^+ concentration and its activity.

ACID-BASE HOMEOSTASIS

The acid base homeostasis means the addition or elimination of acid to compensate the elimination or addition of base and vice versa. But, as life is an acidogenic process, so there is continuous formation of acids. Hence, in normal situation, acid base homeostasis means elimination of acid and addition or recovery of base to balance that small portion of acid that is normally not eliminated or added. In pathological state this normal homeostasis may be failed causing alkalosis (metabolic or respiratory) or moves in opposite direction causing acidosis (metabolic or respiratory). Despite the regulating mechanisms, the H^+ concentration in the tissue varies upto 10 fold from 16 nmol/L to 160 nmol/L (pH 6.8 to 7.8) which is compatible to life. Beyond that range life is not compatible. However, usually the normal range of H^+ concentration in blood is 36 to 44 nmol/L (ph 7.35 to 7.45) after homeostasis. No other ion in the tissue has such a wide range of variablility within which life can exist.

There are three mechanisms that maintain this pH homeostasis. These are: (i) buffering, (ii) compensation and (iii) correction. Buffering is the process in which chemical or buffer agent is used by the body to immediately neutralise or minimize the change in pH or H^+ concentration. Compensation is a process where other systems are acitvated to restore the HCO_3^-/H_2CO_3 ratio to normal. For example, when there is retention of CO_2 or H_2CO_3 due to the downward adjustment of ventilation, then there is excessive loss of H^+ or retention of HCO_3^- by kidney and maintain the normal acid base ratio. Correction refers to the exogenous medical management of the primary metabolic derangement responsible for the abnormality in pH.

Buffer System

Buffer system is composed of weak acid and their salt as strong base or a strong acid and their salt as weak base. It resists the changes of H^+ concentration in a solution after addition of a stronger acid or base in this solution. Stronger acids which are added in the solution are buffered by the base part of the buffer system to form weak acids. Similarly stronger bases which are added in the solution are buffered by the acid part of the buffer system to produce weak bases. For example, HCl is a strong acid which is largely dissociated as H^+ and Cl^-. This H^+ combines with

$NaHCO_3$ (base part of the bicarbonate buffer system) to produce H_2CO_3, which is a weaker acid than HCl. It is less dissociated and, therefore, less H^+ is released by its dissociation than if the HCl was present alone in the solution without a buffer. Similarly, a strong base such as NaOH is buffered by the acid part of bicarbonate buffer system to produce a weak base. For example $NaOH + H_2CO_3 = NaHCO_3 + H_2O$. If NaOH is not buffered, then the large amount of dissociated OH^- from the strong base of NaOH would combine with large amount of H^+ and will decrease the huge concentration of it. Thus, it will raise the pH much. On the otherhand, after buffering as the $NaHCO_3$ is a weaker base than NaOH, it is less dissociated and thereby causes less change in the H^+ concentration. To be maximally effective, a buffering system must be adequate enough to be able to buffer a large amount of acid or alkali which is eliminated or added and have a pK value which is close to the initial pH of the solution to be buffered. It is known that weaker acids and their salts (Na-salts of acids are base) as strong base are more effective buffers than the buffer system which is composed of strong acid and their salts as weak base.

About 3/4 of the chemical buffering power of our body lies within the cells. It is due to the high concentration of intracellular proteins, phosphate, haemoglobin (in RBC) and other inorganic compound. So, protein, phosphate and haemoglobin buffer systems are more important intracellularly. On the other hand, the remaining 1/4th of the buffering power of our body lies in the extracellular fluid. The acid base disturbances due to the respiratory causes is buffered mainly by the intracellular buffers. Whereas the acid base disturbances due to metabolic causes is buffered mainly by the extracellular buffers. The preferential utilisation of extracellular buffer occurs in the initial phase of metabolic acidosis with the contribution of intracellular buffer which is becoming gradually greater as the acidosis increases in severity. The buffer pair of greatest important in the extracellular fluid is carbonic acid (H_2CO_3) and bicarbonate ($NaHCO_3$ or $KHCO_3$), i.e. bicarbonate buffer system. In both the intracellular and extracellular environment the power of action of a buffering system depends on: the pK value of this buffer system, pH at which it is working and on the concentration of the buffer elements.

Although, both the carbonic and non-carbonic buffer systems are located through out the body in both the intracellular and extracellular fluid, but blood is the only window through which we can view the acid-base derangements. So, the pH and PCO_2 electrodes only measure the plasma pH and P_aCO_2, but can not tell anything about inside of the cell. On the other hand, plasma is in close equilibrium with interstitial fluid as far as pH, PCO_2 and $[HCO_3^-]$ are concerned. Thus, measurement of acid-base status of blood gives a reasonable assesment of the acid-base status of extracellular fluid, but offers only indirect insight of the intracellular status from which the actual acid-base disorder is originating.

The tendency of an acid to dissociate in water may be described quantitatively by the law of mass action.

Thus, [HA] (acid) $\propto [H^+] \times [A^-]$, A^- is the base

or $K [HA] = [H^+] \times [A^-]$

Here, K is the dissociation constant which describes the tendency of an acid to dissociate. Large K means stronger acid and vice versa. This equation is called the Henderson equation.

So, $[H^+] = K [HA]$ (acid) / $[A^-]$ (base) (Fact file -I).

The negative logarithmic expression of this equation is:

$-\log [H^+] = -\log k [HA]$ (acid) / $[A^-]$ (base)

or $pH = p^K + \log [A^-]$ (base)/[HA] (acid) ($p = -\log$)

Here, p^K is the negative logarithm of K and also reflects the strength of an acid.

Therefore, $pH = p^K + \text{Log base / acid}$

This is called the Henderson Hasselbalch equation. This equation is used for the determination of pH of a buffer solution or for the determination of relative concentration of the salt (base) and acid which is required to achieve the normal pH. For example, the pH of a buffer solution prepared by mixing 35 ml of (N/10) acetic acid with 15 ml of (N/10) NaOH can be determined by the Henderson-Hasselbalch equation:

$pH = p^K + \log$ (salt A^- / acid HA) where p^K is log (1/k), k is the dissociation constant of acid.

When these two solutions are mixed up, then 15 ml of (N/10) NaOH will neutralise 15 ml of (N/10) acetic acid to form 15 ml of the salt, Na-acetate. So, 20 ml of acetic acid will remain unneutralised. Thus, in the buffer solution, the salt and unneutralised acid ratio will be (15/20). The dissociation constant (k) of acetic acid is (1.86×10^{-5}) and so the p^K will be log (1/k), that is 4.73. So, in Henderson-Hasselbalch equation

$pH = 4.73 + \log (15/20)$

$= 4.73 + \log 0{\cdot}75$

$= 4.73$

$= 4.6$

FACT FILE - I

From the Henderson equation such as, $[H^+] = K[HA]/A^-$, we can calculate any one factor, if other two factors are known. This is as follows:

For bicarbonate buffer system, the Henderson equation can be written as: $[H^+] = K(P_aCO_2$ mm of Hg) / HCO_3^-.

If P_aCO_2 = 50 mm of Hg, HCO_3^- = 24 m.Eq/L, and K = 24 (dissociation constant of carbonic acid),

then $[H^+] = (24 \times 50) / 24 = 50$.

Therefore, the $[H^+]$ concentration is 50 nmol/L. Now from the table we can read the pH as 7.3.

When the pH is 7.4 and the P_aCO_2 is 50 mm of Hg, the HCO_3^- level can be calculated like this:

$H^+ = K(P_aCO_2) / HCO_3^-$

or HCO3– = K (PaCO2) / H^+

or HCO_3^- = (24 × 50) / 40 (H^+ concentration at pH 7.4 = 40 nmol/L).

or HCO_3^- = 30 mEq/L.

If the ratio of salt and unneutralised acid ratio becomes 1:1, then the pH value of the buffer mixture will be equal to p^K of the acid. As for example, if 30 ml of (N/10) acetic acid and 15 ml of (N/10) NaOH are mixed up then 15 ml of salt Na - acetate will be formed and 15 ml of acetic acid will remain as unneutralised acid. So, the salt and acid ratio will be (15/15) = 1. So, interpolating the value in the Henderson - Hasselbalch equation the result will be

$pH = p^K + \log (salt / acid)$
$= 4.73 + \log (15/15)$
$= 4.73 + \log 1$
$= 4.73 + 0$
$= 4.73$

So, the buffering action in this case is at its maximum and can react either as acid or as base.

Each unit change in pH represents a 10 fold change in $[H^+]$. So, when the pH number decreases, the $[H^+]$ increases and vice versa. For any given buffer system, the p^K is constant, so the pH will depend on the log of the ratio of [base]/[acid]. If acid or alkali is added, then the smallest change in this ratio and therefore the smallest change in pH will result if (initially [base] is equal to [acid]) or base = acid.

Under these circumstances, $pH = p^K$ [since base/acid = 1 and log1 = 0]

So, a buffer system resists the pH changes best when it is operating at a pH close to its p^K value.

In the plasma, tissue fluids and in the cells many buffer systems exist. These important buffer systems are: bicarbonate, phosphate, protein and haemoglobin. The buffering of H^+ in extracellular compartment can also be accomplished by the exchange of H^+ for Na^+ and Ca^{2+} from bone. Thus acid loads demineralize the bone and release alkaline compounds such as $CaCO_3$ and $CaHPO_4$. Contrary, alkaline loads increase the deposition of carbonate in bone. The buffering in plasma by bicarbonate is immediate. Whereas the buffering in interstitial fluid compartment by bicarbonate takes 15 to 20 minutes and buffering by intracellular proteins and bone takes 2 to 4 hours. Upto 50 to 60% acid loads may ultimately be buffered by intracellular buffers and bone.

(i) Bicarbonate buffer system (HCO_3^- / H_2CO_3)

$H^+ + HCO_3^- \leftrightarrows H_2CO_3 \leftrightarrows CO_2 + H_2O$ I

This is the main buffer system in blood and interstitial fluid. This system consists of a mixture of H_2CO_3 (weak acid) and its salt $NaHCO_3$ (strong base). Usually $NaHCO_3$ remains in the extracellular fluid and $KHCO_3$ or $Mg(HCO_3)_2$ present in the intracellular fluid. The relationship between the concentration of carbonic acid and their salt (bicarbonate buffer system) and the pH can be described by Henderson-Hasselbalch equation:

$pH = p^K + \log [HCO_3^-] / [H_2CO_3]$
$= 6.1 + \log [HCO_3^-] / P_aCO_2 \times 0.03$

(0.03 is the solubility coefficient of CO_2 and 6.1 is the negative log of dissociation constant of H_2CO_3 or p^K value of the bicarbonate buffer system).

So, the pH of blood is determined by the ratio of $[HCO_3^-]$ / $[H_2CO_3]$. The reaction curve of the bicarbonate buffer system, i.e. the relation between the relative concentration of HCO_3^- and H_2CO_3 with pH is S-shaped. The buffering power of this system is greatest where the slope of the curve is steepest. This is because addition of a certain amount of acid or base cause smallest change of pH to occur in this part. This buffer system is most efficient when the concentration of HCO_3^- and H_2CO_3 are equal or when $pH = p^K$ or $\log [HCO_3^-] / [H_2CO_3] = 0$.

The p^K value of bicarbonate buffer system is 6.1, therefore it is most effective at pH 6.1. Its chemical buffering capacity at pH 7.4 (which is its usual working pH) is poor, but its efficiency increases when the pH of blood decreases (Fig. 8.2). Normally, when this buffer system functions at a pH of around 7.4, then the ratio of bicarbonate to carbonic acid is 20:1 which is well outside its optional working range (once the relative concentration of bicarbonate and carbonic acid exceed about 8:1 in either direction, then the buffering power of the system falls rapidly).

But, on the other hand, at physiological pH of 7.4 the importance of this bicarbonate buffer system lies in the ability of carbonic acid to produce CO_2 which is excreted via lungs. Addition of H^+ and elimination of CO_2 drives the equation-I to the right and compensate the acidosis.

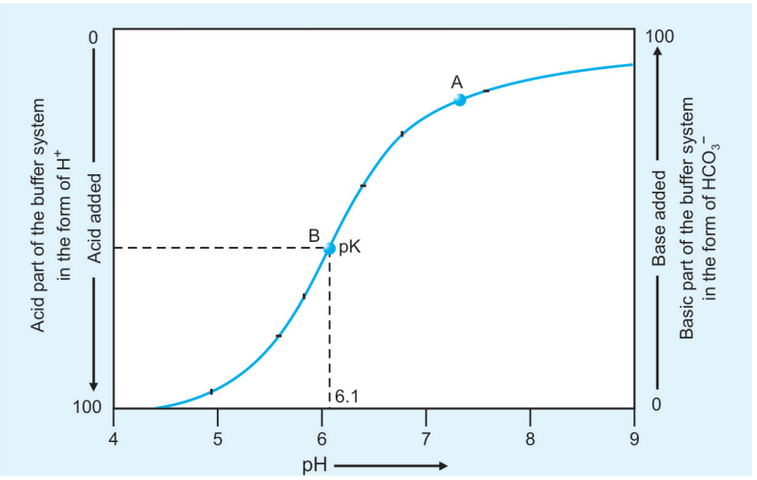


Fig. 8.2: Reaction curve of the bicarbonate buffer system. Point A indicates the normal operating condition where this bicarbonate buffer system works in the body. Point B indicates pK value of this buffer system at which it works maximally

The bicarbonate-carbonic acid buffer system, i.e. the bicarbonate buffer system forms the corner stone of acid-base balance. This is because carbonic acid (H_2CO_3) can be formed by the addition of nonvolatile acids (metabolic or nonrespiratory load), as seen in equation-II. This H_2CO_3 ultimately converts to CO_2 which is then eliminated by ventilation through lungs. CO_2 remains in equilibrium with the HCO_3^-. More H^+ leads more consumption of HCO_3^- and more excretion of CO_2 through stimulated ventilation. It is clinically important to note that the change in HCO_3^- in the body resonably reflects the amount of H^+ added to or removed from the system (in a short time at least until other slower buffer systems have had time to compensate).

Mechanism of Action

Carbonic acid and its salt, primarily $NaHCO_3$ [other salts are $KHCO_3$, $Mg(HCO_3)_3$] which is present in extracellular fluid constitutes the bicarbonate buffer system. It buffers only the metabolic (noncarbonnic) acid or alkali. This system does not function to buffer the respiratory acid load that is CO_2 or H_2CO_3 load.

Excreted through lungs $\leftarrow CO_2 + H_2O$

$$\downarrow\uparrow$$

$$HCl + NaHCO_3 \leftrightarrows H_2CO_3 + NaCl \quad \text{..... II}$$

$$\downarrow\uparrow$$

$$H^+ + HCO_3^-$$

The resulting carbonic acid is weaker acid than the hydrochloric acid which is added in the system of our body. The carbonic acid thus formed, escapes from the blood as CO_2, causing constant P_aCO_2 of 40 mm of Hg. The changes in HCO_3^- level or the amount of consumed HCO_3^- in the form of $NaHCO_3$ to neutralise the acid equals to the amount of acid added. Thus, for bicarbonate buffer system, the change in $[HCO_3^-]$ provides a good measure to know the quantity of H^+ added or removed from the plasma. The major buffering capacity of this system at body pH is physiological, rather than physicochemical. This is an open ended system, because CO_2 can be adjusted immediately by ventilation through normal lungs and HCO_3^- by kidney in long term. The larger amount of plasma HCO_3^-, available in bocarbonate buffer (24·28 m.mol/L), makes this system especially important. In the first instances the strong acid is 'swapped' for a weak acid (H_2CO_3) which is called the chemical buffering. Then, the carbonic acid dissociates into water and CO_2 and the latter is excreted by lungs. This is called the physiological buffering. It is the only buffer system which can be physiologically adjusted to maintain a normal pH. A strong base such as NaOH may also be buffered by carbonic acid (H_2CO_3) of this bicarbonate buffer system.

$NaOH + H_2CO_3 \leftrightarrows NaHCO_3 + H_2O$

$NaHCO_3$ is a weaker base than NaOH. So, it will less dissociate, causing less change in H^+ and OH^- concentration (explained before).

The bicarbonate buffer system functions to neutralise the metabolic acid and base only. It does not buffer the respiratory acids such as H_2CO_3. This is because if carbonic acid is added to a bicarbonate buffer solution, then the H^+ and HCO_3^- level does not change. They are produced in equal amounts.

$CO_2 + H_2O + NaHCO_3 = H^+ + HCO_3^- + NaHCO_3$

Changes in the absolute value of $[HCO_3^-]$ from normal indicate the amount of metabolic (noncarbonic) acid or H^+ is added to or removed from the solution. But, the changes in P_aCO_2 do not cause any measurable alteration in the bicarbonate $[HCO_3^-]$ level in plasma.

A working formula of Henderson - Hasselbalch equation for bicarbonate buffer system is: $H^+ = 24 \times P_aCO_2 / [HCO_3^-]$

Another simple theory is that below 7.4 pH, for every 0·01 unit decrease in pH there is 1.25 n.mol/L increase of H^+ concentration and above 7.4 pH for every 0.01 increase in pH there is 0.8 nmol/L decrease of H^+ concentration. These two theories are very helpful clinically because H^+, pH, P_aCO_2 and HCO_3^- concentration, all can be calculated easily from the above. For example: if pH of arterial blood is 7.26, then the $[H^+] = 40 + [(40 - 26) \times 1.25] = 57.5$ n.mol/L. If P_aCO_2 in the arterial sample is 30 mm of Hg, then

$57.5 = 24 \times 30 / [HCO_3^-]$ or $[HCO_3^-] = (24 \times 30) / 57.5 = 12.52$ mEq/L

(ii) Phosphate buffer system (HPO_4^{2-}/ $H_2PO_4^-$)

$H^+ + HPO_4^- \leftrightarrow H_2PO_4$

This buffer system consists of NaH_2PO_4 (weak acid) and Na_2HPO_4 (strong base). This system work in exactly the same way as the bicarbonate buffer system. p^K value of this buffer system is 6.8. It means this buffer system has the highest working capability at the pH near about 6.8. It is the largest inorganic chemical buffer system in the body. Its concentration in plasma is much lower and, therefore, its capacity as a buffer in blood is also much less. Its importance predominantly lies in the intracellular enviornment and in the urine. Unlike bicarbonate buffer system, this system neutralises both the carbonic (respiratory) and noncarbonic (metabolic) acid or alkali. Thus, this phosphate buffer system neutralises strong acids and alkalis as seen in the following reactions.

$HCl + Na_2HPO_4 \leftrightarrows NaH_2PO_4 + NaCl$

$NaOH + NaH_2PO_4 \leftrightarrows Na_2HPO_4 + H_2O$

Here, NaH_2PO_4 and Na_2HPO_4 are the weak acid and weak base, respectively. These conversions of strong acids and bases to weaker ones result in the liberation of less H^+ and OH^- and therefore smaller changes in pH.

This buffer system has little effect in the extracellular environment. This is because the concentration of this system is less than 10% of the bicarbonate buffer system in the extracellular fluid. The concentration of this system is highest within the cell. Furthermore, its p^K value is about the same as the intracellular pH (intracellular pH is 6.9) which increases its buffering

power in the cell (explained before). For the similar reasons, this buffer system is very important in the renal tubular fluid. In renal tubular fluid, the phosphate buffer is greatly concentrated and the pH of renal tubular fluid is closer to the p^K value of this buffer system which increases its efficacy.

Formation of Urinary Titrable Acidity (TA)

At pH 7.4, the 80% of circulating phosphate is in the monohydrogen form and 20% is in the dihydrogen form. The majority of urinary TA is produced by the conversion of monohydrogen to dihydrogen phosphate ($Na_2HPO_4 \rightarrow NaH_2PO_4$). This occurs throughout the nephron. At maximum urinary acidity, i.e. pH 4.5, all most 99% of the filtered phosphate is in the dihydrogen form (as the pKa of this system is 6.8). At this highest urinary pH, 70% of filtered creatine and 90% of uric acid are in unionized form and may account for 20% of the urinary TA.

Normally 20 to 40 mmol of H^+ is excreted per day as TA. In diabatic ketoacidosis the rate of excretion of nonionised beta hydroxybutyric is 60%. In this condition it produces a large component of urinary TA. Acetoacetic acid is excreted, but forms a lesser component of urinary TA. Almost all of the urinary ketone excretion is in the form of beta hydroxybutyric acid. Excretion of nonionized lactic acid in lactic acidosis is also low. Normally, the urinary excretion of phosphate is determined by the need to maintain phosphate balance rather than acid base homeostasis. Thus, TA appears to play a supportive rather than an active role in H^+ balance.

(iii) Proteins as buffer (Pr− / PrH)

$H^+ + Prot^- \leftrightarrows H\ Prot$

Like haemoglobin, plasma proteins also act as an effective buffer. This is because of the large total concentration of it in the body and the p^K of some proteins approximates 7.4 at which they are likely to work. Proteins are the most important buffers in side of the cells. They contain both acidic group (–COOH) and basic group ($–NH_2$) in one molecule to make up the buffer pairs.

Acidic group dissociate into $−COO^− + H^+$ and donate H^+ to buffer excess base:

$− COOH + OH^− \leftrightarrows − COO^− + H_2O.$

Basic group, commonly in the form of $− NH_2$ buffers excess acid by accepting H^+ to form $–NH_3^+$.

$− NH_2 + H^+ \leftrightarrow − NH_3^+$

As p^K value of most of the protein buffer systems are around 7·4, so at normal condition they work best. They buffer both carbonic (respiratory) and noncarbonic (metabolic) acid or alkali.

(iv) Haemoglobin as buffer (Hb− / HbH)

Hb is responsible for 50% buffering power of the blood. It is an effective buffer between pH of 5.7 to 7.7, because its p^K value is 6.8. It buffers respiratory and metabolic acids only. It does not buffer any alkali. It acts as a buffer, because it is a protein in nature and more importantly due to the ability of the imidazole group (within the histidine molecules which dissociates less in oxygenated than deoxygenated blood) to accept H^+. This H^+ for neutralisation comes from two sources. One, from dissociation of metabolic acids and another from CO_2which is available from metabolism of substrates through TCA cycle. At tissue level O_2 is liberated from Hb and CO_2 enters in the erythrocyte. Erythrocyte is rich in carbonic anhydrase which help in the formation of H_2CO_3 from CO_2 by the reaction:

$CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$

When H^+ of H_2CO_3 is buffered by Hb it exists within the erythrocyte as a weak acid (HHb) than carbonic acid (because p^K value of HHb is 6.8 whereas p^K value of H_2CO_3 is 6.1). After buffering of H^+ by Hb, HCO_3^- within RBC is increased proportionally.

The corresponding increase in HCO_3^- in erythrocyte causes a diffusion back of HCO_3^- into the plasma along the concentration gradient. This results in exchange (Fig. 8.3) or shifting of Cl^- in the erythrocyte from plasma which is called the chloride shift. Therefore, while most of the H^+ is buffered within the cell (RBC) most of the change in HCO_3^- is seen in the plasma. After entering into the erythrocyte, CO_2 is also carried as carbino compound after combining directly with the terminal amino acids of the globin part of haemoglobin molecule. The acidity of these imidazole group (or deoxygenation) is influenced by the oxygenation and reduction of Hb. Haemoglobin is a weaker acid in reduced form than when it is oxygenated and increases the availability of buffer sites for H^+. When oxygenated Hb gives up O_2 to the tissue it becomes reduced and is therefore more able to accept CO_2 in the form of H^+. In the lungs reverse effects occur. Upon reaching the lung and

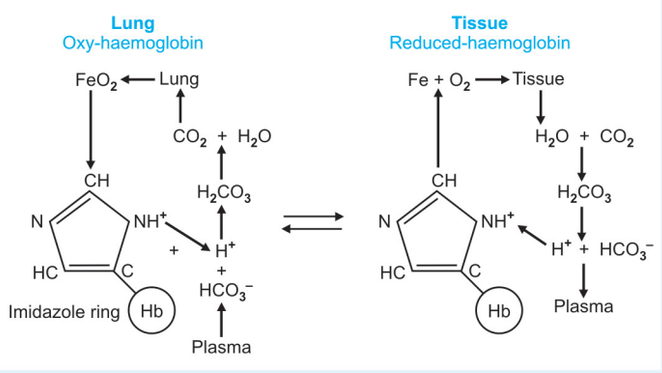


Fig. 8.3: Reduced (or deoxygenated)— Hb is a better buffer than oxygenated Hb

becoming oxygenated, the Hb becomes a stronger acid and buffering capacity is reduced. So, H^+ is released from the Hb to react with $KHCO_3$ and CO_2 is released from the carbamino groups.

$HHb + O_2 + KHCO_3 \leftrightarrows KHbO_2 + H_2O + CO_2$

This effect explains that reduction or deoxygenation of Hb makes it weaker acid and increases its buffering capacity to accept H^+. Whereas oxygenation makes Hb a stronger acid and decreases its buffering capacity to accept H^+. This is known as Haldane effect. Reduced Hb is better buffer than O_2-Hb. Haemoglobin has three times better buffering capacity than plasma proteins in gram for gram comparison and is twice the concentration in blood than plasma protein. Therefore, Hb has six times the total buffering capacity than plasma protein (Figs 8.4A and B).

Thus, the buffers in order of importance are:

i. In blood: Hb, bicarbonate, plasma protein, and phosphate.
ii. In interstitial fluid : Bicarbonate, phosphate, and interstitial protein.
iii. In cells: Proteins, phosphate, ammonia and other inorganic substances. Phosphates and ammonia are also important urinary buffers.

As nonvolatile acids are released from the cellular metabolism, their effect is mainly buffered by the action of bicarbonate buffer system in the extracelular fluid (ECF) and by bicarbonate (50%), Hb (35%), plasma protein (6%) and phosphate buffer system in the plasma.

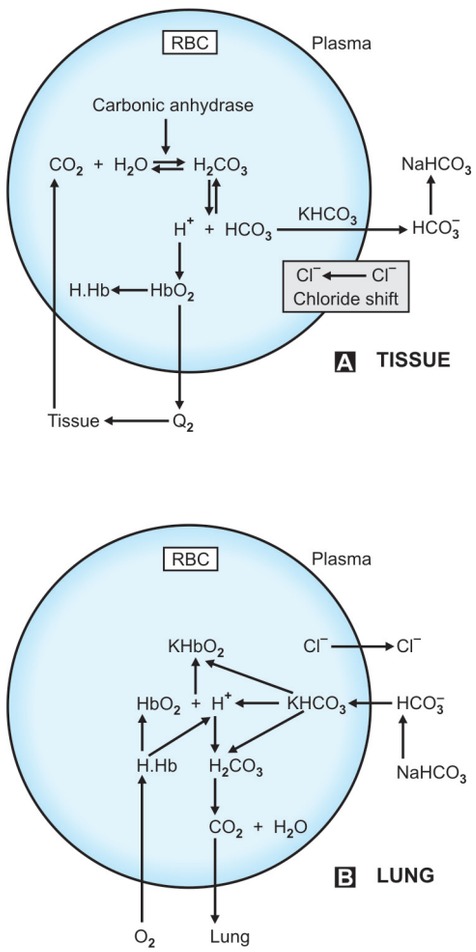
In summary, buffering is the mechanism by which an influx of H^+ is initially dealt with by the body and limits the change in pH. Thereafter, respiratory mechanism becomes activated to elimainte CO_2 and later renal regulation of acid and alkali secretion increases to increase the buffer capacity.

Compensation

The alteration of H^+ concentration also stimulates the compensatory part of the pH homeostatic mechanism and maintain the normal pH by restoring the HCO_3^- / P_aCO_2 or HCO_3^- / H_2CO_3 ratio. So in addition to the buffering mechanism, the homeostasis of acid-base disturbance is also maintained by compensation, played by the pulmonary and renal excretion or retention of acids or bases.

Pulmonary Compensation

Pulmonary compensation is made by increasing or decreasing the ventilation and is only limited to CO_2 excretion by the lungs ($CO_2 \leftarrow H_2O + CO_2 \leftarrow H_2CO_3 \leftarrow H^+ + HCO_3^-$). So the pulmonary compensation is active only during metabolic acidosis or alkalosis, because the respiratory acidosis or alkalosis is caused by the diseases of pulmonary system itself which can not work now as the compensatory organ. Ventilation is controlled by chemoreceptor areas of medulla, and carotid and aortic bodies. Among them the medulla plays the primary role and H^+ is the predominant mediator effecting the chemoreceptors of it. Changes in blood PCO_2 cause rapid changes in PCO_2 of CSF. This is because the blood-brain barrier is highly permeable to CO_2, but not to H^+. Thus, rapid increase in CO_2 concentration and subesquently its tension in CSF is associated with rapid increase in H_2CO_3 in CSF which in turn dissociate into large amount of H^+. But, the buffering capacity of CSF to neutralise the H^+ is limited. So, increase of H^+ in CSF is greater than it would be



Figs 8.4A and B: Schematic diagram of chloride shift in tissue (A) and in lung (B)

in the tissue and stimulate the medullary chemoreceptor centre increasing ventilation and washing out CO_2. Minute ventilation increases 1 to 4 L/min for every 1 mm of Hg increase in P_aCO_2. Usually, lungs are responsible for eliminating approximately 15 mEq of CO_2, produced every day as a byproduct of carbohydrate and fat metabolism.

Metabolic acid-base disturbances are only compensated by ventilation. Among this the metabolic acidosis or alkalosis, caused by the increase or decrease of H^+ from metabolic acid is best compensated by the pulmonary mechanism. The metabolic acidosis or alkalosis caused by the increase or decrease of HCO_3^- concentration is also compensated by pulmonary mechanism. This is described now. Decrease in plasma HCO_3^- level with its concomitant decrease in pH, due to any metabolic causes, will stimulate the ventilation and will excrete more CO_2 and will reduce H_2CO_3 level, despite normal or low PCO_2 in blood. This is only to maintain the ratio of HCO_3^- / H_2CO_3. Conversely, an increase in plasma HCO_3^- concentration with its concomitant increase in pH, due to any metabolic causes will depress the ventilation and retain CO_2. This will increase H_2CO_3 level and maintain the ratio of HCO_3^-/H_2CO_3 and thus pH, though PCO_2 is high. If the decrease of ventilatory drive is very strong to cause hypoxia, ventilatory centre will be stimulated by the effects of hypoxia on carotid bodies.

Renal compensation

Unlike, the pulmonary compensation which is only limited to the metabolic acidosis and alkalosis, the renal compensation extends to both the respiratory and metabolic acidosis and alkalosis. However, the renal compensation is 3 times more active in acidosis than alkalosis. It is performed by three ways: increasing reabsorption or excretion of filtered HCO_3^-, increasing or decreasing the secretion of H^+ from tubular cells in tubular fluid, increasing excretion of $H_2PO_4^-$ as titrable acids, and increasing producion of ammonia. These mechanisms of acid-base balance are probably activated immediately. But their effects are generally not appreciated for 12 to 24 hours and becomes maximum at 5th day.

The amount of HCO_3^- filtered by the kidney is approximately 24 m.mol/L and virtually all are reabsorbed. HCO_3^- is not permeable to cell membrane. So, it can not be reabsorbed directly through the tubular cell membrane. The mechanism of reabsorbtion of filtered HCO_3^- is: H^+ is passed into the tubular fluid through the tubular cells of proximal tubule and react with HCO_3^- to form H_2CO_3 which further dissociates into $H_2O + CO_2$. This reaction is catalysed by carbonic anhydrase present in large amount in the brush border of tubular cells. Then CO_2 is rapidly reabsorbed into the tubular cell. Again carbonic anhydrase within the tubular cell converts the CO_2 back into HCO_3^-. The proximal tubules usually reabsorb 80 to 90% of the filtered HCO_3^- along with Na^+. Whereas the remaining 10 to 20% of HCO_3^- is absorbed in the distal tubules. Unlike the secretion of H^+ in proximal tubules, the secretion of H^+ in distal tubules is not necessarily linked to absorption of Na^+. The secretion of H^+ in distal tubules is capable of generating steep gradient of H^+ between the tubular fluid and tubular cells. Thus, urinary pH can decrease to as low as 4.4 compared to pH of 7.4 in plasma (Fig. 8.5).

Instead of reabsorbtion of HCO_3^- which are filtered through glomerulus, kidneys also generate new HCO_3^- during metabolism of glutamine in proximal tubules to compensate acidosis. The mechanism is: metabolism of glutamine produces CO_2 and NH_3. This ammonia constitutes 60% of urinary ammonia, whereas another 40% comes from blood. Acidosis increases markedly the renal production of NH_3 from glutamine. This NH_3 is secreted into the tubular fluid. It buffers the H^+ of the tubular fluid by forming NH_4^+ which is nondiffusible (NH_3 is diffusible) and excreted through

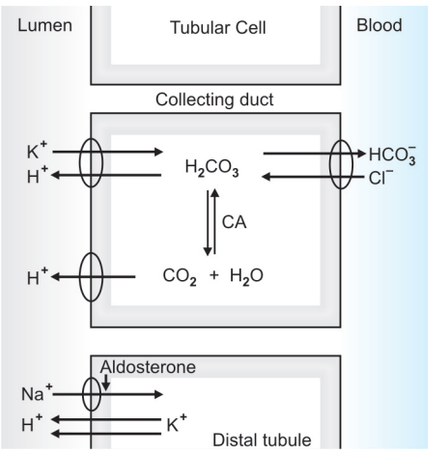


Fig. 8.5: In collecting duct, some H^+ secretion occurs in exchange for K^+. Whereas in distal tubule aldosterone helps in absorption of Na^+ in exchange of K^+ and H^+

urine. Then CO_2 which is produced by the metabolism of glutamine also diffuses in tubular fluid and combines with H_2O to form HCO_3^- which is then absorbed. If the kidneys are unable to excrete NH_4^+ through urine, the retention of NH_4^+ negates the benefit of the new HCO_3^- generation. Systemic acidosis, hypokalaemia, mineralocorticoids increase ammonia production and thus try to combat acidosis.

In addition to recovering of HCO_3^-, the kidneys also excrete an amount of acid (H^+) equal to its daily production. It is approximately 70 mmol/day. This may increase to 300 mmol/day in severe acidosis. These acids (H^+) are not excreted directly through urine. Before being excreted directly through urine, these free acids are first buffered by the weaker acids such as ammonia (NH_3^+ / NH_4^+) and phosphate (HPO_4^{2-} / $H_2PO_4^-$) in renal tubular fluid. These, NH_4^+ and $H_2PO_4^-$ can not be absorbed due to its charge and excreted through urine. Therefore, the net result is: H^+ is excreted as $H_2PO_4^-$ and NH_4^+ from body and the HCO_3^- that is generated in the process of formation of CO_2 from H^+ enter the blood stream. With p^K value of 6.8, this $HPO_4^{2-}/H_2PO_4^-$ buffer pair is normally present in urine. However, when urinary pH reaches 4.4, then all the phosphates reaching the distal tubule is in the form of

$H_2PO_4^-$. In such condition HPO_4^{2-} are no longer available for elimination of more H^+. After complete reabsorption of HCO_3^- and consumption of phosphate buffer, the NH_3/NH_4^+ buffer pair becomes the most important urinary buffer system. However, both the reabsorbtion of HCO_3^- from tubular fluid and secretion of H^+ in it depends on the active secretion of H^+ which in turn is regulated by the changes in plasma HCO_3^-, plasma pH and plasma PCO_2.

During metabolic or respiratory acidosis, due to increase in H^+ concentration or decrease in HCO_3^- concentration, there is direct or indirect increase in concentration of H^+ in tubular cell which in turn stimulates the release of H^+ into the tubular fluids. Increase availability of H^+ in tubular fluid increases the recovery of HCO_3^- ($H^+ + HCO_3^- = H_2CO_3 = CO_2 + H_2O$, $CO_2 \rightarrow$ passed in the tubular cell. Then $CO_2 + H_2O = H_2CO_3 = HCO_3^- + H^+$) and thus try to compensate the acidosis. In acidosis metabolism of glutamine is also stimulated by increasing the availability of H^+ in tubular fluid. But this glutamine mechanism takes up to several days for complete adaptation, because it requires more times for synthesis of new enzymes for more metabolism of glutamine.

Conversely during metabolic and respiratory alkalosis, there is inhibition of reabsorption of HCO_3^- from the tubular fluid due to reduction of the availability of H^+ in tubular fluid and thus compensate alkalosis.

Since, the renal H^+ excretion from tubular cells occurs simultaneously with Na^+ reabsorption for electrical balance, but the process is also affected by aldosterone. Increased aldosterone stimulates reabsorption of Na^+ and simultaneous excretion of H^+ into the tubular fluid, causing an increased reabsorption of HCO_3^-, alkalosis and acidic urine. Thus, Na^+ deficiency and excess of mineralocorticoid is associated with metabolic alkalosis. Na^+ depletion decreases ECF volume and enhances the absorption of Na^+ in the proximal tubule. To maintain neutrality, increased Na^+ absorption causes increased absorption of Cl^-. So, as Cl^- ion decreases in number (< 10 m.mol/L) reabsorption of HCO_3^- must be increased. Thus, metabolic alkalosis is frequently associated with less urinary Cl^- excretion. The opposite effect occurs with decreased levels of aldosterone.

The excretion of H^+ in proximal tubule is a low gradient, but a high capacity system. The proximal H^+ secretion is increased with hypokalaemia, hypercapnia, increased luminal HCO_3^- level, increased tubular Na^+ reabsorption, the presence of nonabsorbable anions (e.g NO_3^-, SO_4^{2-} etc) and increased carbonic anhydrase activity. In the presence of extracellular fluid depletion or metabolic acidosis the Na^+/H^+ exchange mechanism exaggerated, maintaining the extracellular fluid volume at the expense of pH homeostasis. Thus, the maximum HCO_3^- reabsorption capacity of the kidney is not a fixed value and varies in response to the above factors.

Contrary to proximal tubules the secretion of H^+ in distal tubule is a high gradient, but a low capacity system. Unlike proximal tubule, it is influenced by mineralocorticoid acitivity. In hyperaldosteronism distal Na^+ reabsorption and in exchange excretion of H^+ and K^+ are increased. In the presence of hypokalaemia, H^+ loss is further increased due to maintain electroneutrality in tubular fluid. In secondary hyperaldosteronism, the loss of K^+ and H^+ may be less than in primary hyperaldosteronism. This is due to reduction in distal luminal Na^+ flow induced by avid proximal reabsorption of it. Thus an increase in distal H^+ or K^+ urinary secretion may only become evident when distal Na^+ delivery is increased. The example of it is use of diuretics.

CARRIAGE OF CO_2

The discussion of transport of CO_2 in blood is important in this chapter, because it is carried in blood as H^+ and HCO_3^- form which are the important determinants of acid-base balance. Near about, 120 litres of CO_2 is contained in the body at any moment. This CO_2 store can be divided into three compartments depending on the possible rate of exchange of gas between the compartments. These are fast, medium and slow compartment. The fast compartment is consists of brain, heart, and kidney with high blood flow, (Table 8.6) where the tissue PCO_2 levels match with the alveolar PCO_2 very closely. Medium compartment consists mainly of skeletal muscle and slow compartment consists mainly of fatty tissues. The blood flow in these compartments varies from medium to low and also PCO_2 of these compartment do not match well with the alveolar PCO_2. Though, the volume of these three compartments are different, still the slow compartment have the greatest capacity for storing CO_2 and the fast one has the smallest.

Due to the enormous volume of CO_2 storing capacity in the body, the changes in the arterial PCO_2 will not be sudden due to sudden changes of ventilation or other causes. It will take much time for a new equilibrium to be attained. But contrary, following a sudden increase in ventilation a new equilibrium is reached after about 20 minutes (the half time is 3 to 4 minutes). Following a sudden decrease in ventilation the half time for the new equilibrium to reach is 15 to 20 minutes (i.e. delayed).

After CO_2 is produced in the tissues by metabolism, it enters the blood stream through the tissue capillaries and is carried to the lungs where it is liberated. 100

Table 8.6: Differences between venous and arterial blood sample

	Venous sample	*Arterial sample*
PO_2	38-42 mm of Hg	80-100 mm of Hg
PCO_2	44-48 mm of Hg	36-44 mm of Hg
pH	7.36 - 7.39	7.38-7.42
SO_2	75%	95-100%
HCO_3^-	20 -24 mEq/L	22 -26 mEq/L
Na^+	135-145 mEq/L	Same
K^+	3.5-5.5	Same
Cl^-	95-105 mEq/L	Same

ml of venous blood carries about 52 ml of CO_2. Whereas, 100 ml of arterial blood carries 48 ml of CO_2. Therefore, the average normal arterio-venous difference of CO_2 content is about 4 ml. In other words, each 100 ml of arterial blood, while passing through the tissues, takes up 4 ml of CO_2. Similarly, each 100 ml of venous blood, while passing through lungs, also releases 4 ml of CO_2. So that, blood carries a constant volume of CO_2 amounting to about 48 ml per 100 ml of blood. This constitutes the 'alkali reserve', because most of the bicarbonate is obtained from it during equilibrium. Although, much CO_2 is carried in the blood, yet blood reaction does not become acid. This proves that, during CO_2 transport, the blood buffers play a very important role.

After CO_2 is produced by metabolism in the cell, it comes out through the interstitial fluid and enters the plasma. Then, it passes into the red cells to reach lungs. PCO_2 of the venous blood reaching the pulmonary capillary is 46 mm of Hg whereas pCO_2 in alveoli is 40 mm of Hg. Therefore, a pressure gradient of 6 mm of Hg drives CO_2 across the alveolar membrane from venous end of capillary into the alveoli.

CO_2 is Carried by Blood to Lungs

(i) As physical solutions in the plasma

Though, only a small quantity of total CO_2 (5%) is carried in this manner, but it forms a very important portion. Because this portion is responsible for CO_2 tension in plasma and acts intermediatory between alveolar air and the inside of red cell. The solubility coefficient of CO_2 in plasma is 0.03 mmol/L/mm of Hg. Therefore, at P_aCO_2 of 40 mm of Hg and at 37°C only $0.03 \times 40 = 1.2$ m.mol/L of CO_2 is carried by plasma in this physical form. CO_2 is also carried in plasma by H_2CO_3 form. But, the concentration of H_2CO_3 in plasma by which form CO_2 can be carried is only 1/1000 of total CO_2 content, due to the lack of carbonic anhydrase (CA) in plasma.

(ii) As bicarbonate

Most part of the total CO_2 (90%) content in blood is carried in this manner i.e. in bicarbonate form. Bicarbonates are formed in blood by the following ways (Fig. 8.6):

A. In RBC

Hb remains combined with K and forms bicarbonates in the following way:

$CO_2 + H_2O = H_2CO_3$

$KHb + H_2CO_3 = HHb + KHCO_3$

In RBC carbonic anhydrase helps in this process. In the absence of carbonic anhydrase the reaction between CO_2 and H_2O to form H_2CO_3 take 15 to 30 minutes. But, in our body RBC in the tissue capillaries becomes saturated with CO_2 within 1 to 2 seconds and the same time is required for the excretion of CO_2 through lungs. This is only possible due to the presence of carbonic anhydrase. In the blood, it is almost exclusively present in the red cells. All other tissues contain it in traces. But, pancreas and stomach contain it in considerable amounts.

B. In plasma

i. By the phosphate buffers
   Alkaline phosphates combine with carbonic acid and form sodium bicarbonate.
   $Na_2HPO_4 + H_2CO_3 = NaH_2PO_4 + NaHCO_3$
ii. By plasma proteins
   The plasma proteins mostly remain combined with sodium (to be presented as NaPr) and form bicarbonates in the following way.
   $NaPr + H_2CO_3 = HPr + NaHCO_3$
iii. Chloride shift or Hamburger phenomenon.This can be described by the following way.

After entering into the plasma from tissue, CO_2 enters the red cell where with the help of enzyme, carbonic anhydrase (CA), CO_2 react with H_2O to form H_2CO_3. This is because RBC is rich in this enzyme. The

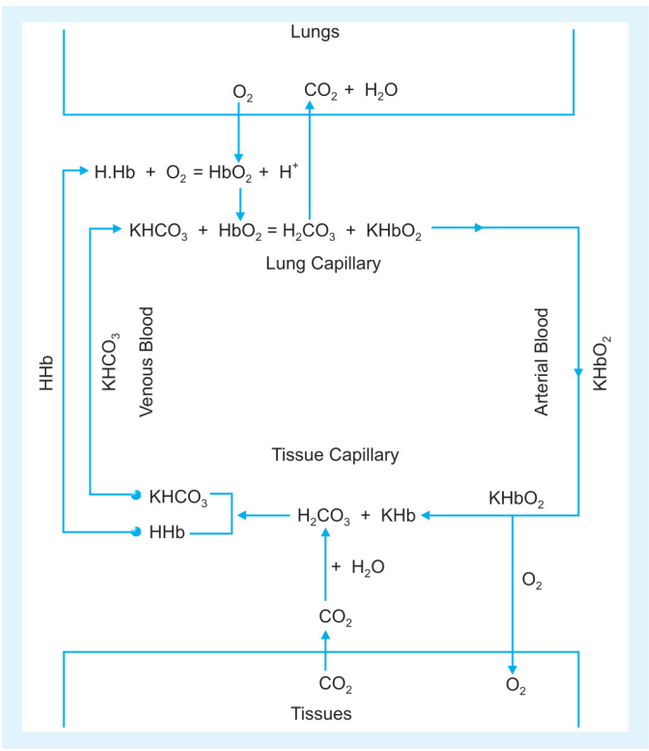


Fig. 8.6: Schematic representation showing inter relation between the carriage of O_2 and CO_2

enzyme carbonic anhydrase is not found in plasma. So, the formation of H_2CO_3 and subsequent bicarbonate can not take place in plasma or in very little amount. Within the RBC, H_2CO_3 is formed and dissociates into H^+ and HCO_3^- ($H_2CO_3 \leftrightarrows H^+ + HCO_3^-$).

At the tissues within red cells O_2Hb after giving up the O_2 combine with this H^+ which comes from the dissociation of H_2CO_3 ($Hb + H^+ \leftrightarrows HHb$) and favour the formation of HCO_3^- by displacing the equilibrium (of the bicarbonate forming equation) to the right according to the law of mass action ($H_2CO_3 \leftrightarrows H^+ + HCO_3^-$). Then, bicarbonate ($HCO_3^-$) diffuses out of the red cell into the plasma and to maintain the ionic equilibrium chloride ions (Cl^-) diffuse back in the opposite direction from plasma into the red cells. This is called the chloride shift or Hamburger effect (phenomenon). Thus, CO_2 is carried to the lungs as bicarbonate (HCO_3^-).

When blood reaches the lung capillaries then all the reactions occur in reverse direction. Due to pressure gradient of CO_2 of 6 mm of Hg (plasma pCO_2 = 46 mm of Hg and alveolar pCO_2 = 40 mm of Hg) CO_2 dissolved in physical state in plasma, diffuses out across the alveolar membrane from plasma. So the physically dissolved CO_2 concentration in plasma falls. Then, the pressure gradient of dissolved CO_2 between RBC and plasma widens. So, CO_2 leaves the red cells and is excreted through the lungs. To produce more CO_2 in red cells, HCO_3^- again enter the red cells in exchange of Cl^- (Cl^- come out of red cell $\rightarrow$ opposite to the chloride shift or Hamburger effect). In the red cell HCO_3^- combine with H^+ to form CO_2. Here, the equation $CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$ is shifted to left. H^+ is obtained from Hb, which take O_2 from alveoli and release H^+. This explains how CO_2 comes out of red cells and excreted through lungs.

Plasma bicarbonate (HCO_3^-), therefore, plays a very important role as the principal store house of CO_2 and carries of it in the blood.

(iii) As a carbamino compound

5% of the total body CO_2 is carried within the plasma in this manner. Here, CO_2 combine with the amino group of globin (protein) part of Hb to form carbamino-haemoglobin. In this process, the NH_2 radicle of the globin part of Hb combines with one molecule of CO_2 as free gas, but not as H_2CO_3. It does not require the help of carbonic anhydrase.

$Hb.NH_2 + CO_2 \leftrightarrows Hb.NH.COOH$

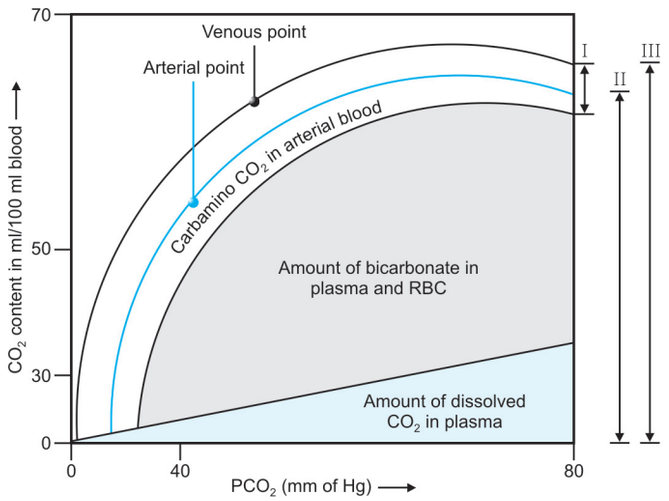
Smaller amount of CO_2 also combines with the amino group of plasma protein in similar fashion, like globin (protein) part of the haemoglobin to form the carbamino compound. The combination between CO_2 and plasma protein also takes place directly and no enzyme is required.

Thus, it will be seen that the CO_2 is carried out in the blood in three forms and 100 ml of venous blood carries about 52 ml of CO_2 as follows:

a. In physical solution (2.7 ml)
b. As bicarbonate (45.7 ml) – Bicarbonates are formed in four ways: (i) with NaPr, (ii) with Na_2HPO_4, (iii) with Na of NaCl helped by 'chloride shift', (iv) with KHb. These are the chief forms in which CO_2 is carried. A large part of this bicarbonate remains permanently in the plasma and constitutes the so-called alkali reserve.
c. As carbamino compounds (3.7 ml) – These are chiefly formed in the red cells (2.6 ml) with the protein of Hb and only in traces in the plasma (1.1 ml) with plasma protein. It constitutes about 5 to 10% of the total CO_2 carriage and is responsible for a large part of the normal arterio-venous difference.

CO_2 DISSOCIATION CURVE (Fig. 8.7)

The relationship between the CO_2 concentration and the CO_2 tension (PCO_2) in blood is depicted by this curve. Oxygenation of blood is the main determitant of position of this curve. Because the more deoxygenated the blood will be the more CO_2 it will carry at a given pCO_2 and change the curve. This is called the Haldane effect. The upper portion of the curve is for the fully deoxygenated blood and the lower portion of the curve



I = Carbamino CO_2 in venous blood
II = Total CO_2 content in arterial blood
III = Total CO_2 content in venous blood

Fig. 8.7: This is a CO_2 dissociation curve of whole blood

is for the fully oxygenated blood. The major part of the Haldane effect is due to the increased carriage of CO_2 by reduced haemoglobin as carbamino compound. In addition, carriage of CO_2 as bicarbonate is also increased.

$CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$

Reduced or deoxygenated haemoglobin buffers the H^+. Thus by absorbing H^+ the reduced Hb displaces the equilibrium of this equation to the right and increases the concentration of bicarbonate (HCO_3^-) and produces the chloride shift (Hamburger effect). Thus due to Haldane effect, at the capillary level CO_2 uptake and at the lung level CO_2 elimination is facilitated by shifting the equation once to the right (at capillary level) and then to the left (at lung level) respectively.

ELIMINATION OF H^+

(i) Rapid Elimination by Respiration

CO_2 produced by the oxidation of substrates, produces H^+ load in the body which is excreted again as CO_2 through the lungs, leaving H_2O.

$CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$

After production in the cell, CO_2 readily diffuses across the cell membrane and produce changes of pH in both ICF and ECF. H^+ directly can not diffuse through the cell membrane. So, it passes through the cell membrane in disguish of CO_2. Thus increased CO_2 production in normal situation stimulates respiration and balance H^+ concentration (in turn CO_2 concentration) rapidly. The carbonic acid and bicarbonate chemical buffer or the bicarbonate buffer system is ineffective here. Carbonic acid remains in equilibrium with the dissolved CO_2 content of body fluids and can therefore be eliminated through the lungs. Addition of H^+ from the metabolic acids also increases H_2CO_3 at the expense of a reduction in bicarbonate and is eliminated as CO_2.

H^+(metabolic origin) + HCO_3^- = H_2CO_3 = $H_2O + CO_2 \rightarrow$ lungs

(ii) Slow Elimination by Kidney

Slow and long-term control of H^+ elimination by kidney depends on three mechanism.

A. Reabsorption of filtered bicarbonate

Presence of carbonic anhydrase in renal tubular cells facilitate the production of H^+ from CO_2 load.

$CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$

This H^+ passes in the luman of the proximal tubule. Normally daily 5000 nmol HCO_3^- is filtered at glomerulus. This HCO_3^- react with H^+ and CO_2 is produced which diffuses back in the tubular cells. Thus no net H^+ excretion results from this action but prevents loss of filtered base. Smaller amount of H^+ is secreted in the distal and collecting ducts to make the urine acidic with pH of 4.6.

During acidosis the excess H^+ passes in the proximal tubular lumen and after preserving all the filtered HCO_3^-, extra H^+ is excreted. This secondary response is slow to develop and take 5 days for full compensation to occur. In the absence of CA or when acetazolamide is used then non availability of H^+ causes HCO_3^- to be excreted as $NaHCO_3$ and plasma HCO_3^- falls. So, in acidosis acetazolamide should never be used.

B. Buffers

20 to 30 mmol of H^+ which is excreted daily through urine as titrable acid, is combined to monohydrogen phosphate and excreted as dihydrogen phosphate (titrable acid).

$H^+ + HPO_4^{2-} \leftrightarrows H_2PO_4^-$

C. Formation of Ammonia

NH_3^+ is formed in the renal tubular epithelium throughout the nephron. Among this 60% is formed from glutamine by deamination and 30 to 35% comes from artery as free NH_3^+. This NH_3^+ diffuses into the renal tubular lumen and binds to neutralise H^+ by producing non-diffusible ammonium ion (NH_4^+). This is excreted daily and may rise to 700 mmol per day in severe acidosis. Thus, the maximum renal acid secretion as in diabetic ketoacidosis is approximately 700-750 mmol per day of which two-third is NH_4^+ and one third is titrable acid.

MEASUREMENT OF ACID-BASE BALANCE

The acid base disturbances in the body occur when the disease processes cause disruption of the normal pH homeostatic mechanisms or when the acid or alkali burden (more rarely) exceeds the adaptive capacity of compensatory mechanisms.

- The normal arterial pH usually ranges from 7.36 to 7.42. It is maintained by intracellular and extracellular buffers. These buffers work through the renal and respiratory regulatory mechanisms.
- The intracellular pH ranges from 6.4 to 7.35.
- pH is −log of the hydrogen ion concentration expressed in mol/L.
- pH of 7.4 represents [H^+] of 40 nmol/L.
- pH rising to 7.5 represents a drop in [H^+] to 32 nmol/L.
- pH of 7 is equal to [H^+] of 100 nmol/L.
- The centre of the understanding of acid-base disturbance is the understanding of carbonic acid and bicarbonate buffer pairing. This is expressed by Henderson - Hasselbalch equation such as $[H^+] = 181 \times P_aCO_2 / [HCO_3^-]$, 181 is the dissociation constant or coefficient of carbonic acid in the presence of carbonic anhydrase. This buffer pairing system is ubiquitous. It is also the dominant physiological buffer system in man and most importantly it is in equilibrium with all other buffer systems of body.
- A combination of both the respiratory and metabolic acidosis or alkalosis may present at the same time with normal pH value compensating with each other.

The dissociation constant (K) is affected by the changes in temperature. For example, the pH of water at 25°C is 7, whereas it is changed to 6.8 at 37°C. So,

during the measurement of pH the temperature should be taken into consideration.

The respiratory acidosis or alkalosis is the change or a potential change in pH, resulting from alteration in the PCO_2. The metabolic acidosis or alkalosis is the change or a potential change in pH, resulting from alterations in the nonvolatile acids in the blood such as lactic acid, keto acid, β-hydroxybutyric acid, sulphuric acid, phosphoric acid, pyruvic acid, etc or when the primary disturbance is in the control of plasma bicarbonate concentration. Though, all the types of combination is possible, so the PCO_2 measurement quantify the respiratory component and the 'base excess' or base deficit measurement quantify the metabolic component of acid-base balance.

Despite the presence of buffer and other compensatory mechanisms, the acid-base disturbances do occur in the body. So, to determine the primary cause of acid-base imbalance, the degree of buffering, the degree of compensation and the ultimate pH, PCO_2 and HCO_3^- level should be measured. There are several methods to measure these parameters. But, due to the presence of complex inter relationships between the buffer systems and the compensatory mechanisms, the measurement of the above parameters are not sometimes correct, indicating the primary cause, the degree of buffering and the degree of compensation. Again, there is loss of precision which is inherent in the simplification of the complex processes of measurement.

The Hendersons-Hasselbalch equation is usually used to measure the bicarbonate buffer system. But several other different methods are also utilised to correct for the presence of other buffer system, by allowing one to evaluate the entire system as bicarbonate buffer. These include alkali reserve, standard bicarbonate, base excess, and buffer base. The alkali reserve and the standard bicarbonate are no longer in use for clinical practice. Base excess and buffer base are still in use and act by compensating the buffering capacity of nonbicarbonic buffer system. In this compensation, other buffer systems are converted to the equivalent of bicarbonate buffer in which the change in HCO_3^- level directly reflects a change in H^+ of the system.

The acid-base disorders also can be evaluated from the CO_2 titration curves, derived from the present values of pH, PCO_2 and HCO_3^- concentration. Clinical values are then compared with the normal human values and the deviation is quantified for both the acute and chronic disorders. This *in vivo* method (titration curve) is superior to the *in vitro* methods (measurement of pH, PCO_2 and HCO_3^-), because it recognises the changes in pH due to specific causes and thus present a very dynamic scenario.

PCO_2

The PCO_2 of a gas mixture, saturated with water vapour at 37°C is given by the equation.

$PCO_2 = FCO_2 \times (P_B - 47)$ mm of Hg

FCO_2 is the fractional concentration of CO_2 in the mixture, P_B is the barometric pressure (760 mm of Hg) and 47 mm of Hg is the saturated vapour pressure of water at 37°C. The PCO_2 in plasma is best understood by considering a gas-liquid system which is in equilibrium. The CO_2 tension in a liquid is equal to that in the gas when no net exchange of CO_2 occurs between these two-phases. At any given equilibrium, the CO_2 content of plasma is a reflection of the PCO_2 of the gas phase. The PCO_2 of blood is thus defined as that PCO_2 in a gas mixture which, when in contact with the blood results in no net exchange of CO_2 between the two phases. The normal value of P_aCO_2 is 35 to 42 mm of Hg.

CO_2 Titration Curve

The consideration and the application of Henderson-Hasselbalch equation is the core to the understanding of acid-base balance. Both the metabolic and respiratory factors are represented in this unique equation. This equation also linked pH to the molar concentration of bicarbonate and carbonic acid in plasma. But, the constants in the equation can not be predicted accurately (Fig. 8.8A).

This equation also says us that any alteration of the PCO_2 will be associated with a predictable change in pH. If the PCO_2 is either increased or decreased and time is allowed for a steady state or an equilibrium to be reached, then CO_2 titration curve (straight line using a pH and PCO_2 plot) is obtained (Fig. 8.7A). When a titration is performed adding deliberately varying amounts of acid, then a family of curves, approximately parallel to and to the left of the normal curve is found. The more acid is added, the further is the curve shifted to the left. Thus, a non-respiratory (metabolic) acidosis produces curves shifted to the left and a non respiratory (metabolic) alkalosis produces curves to the right. With increasing metabolic acidosis, the buffering capabilities will also increase, which causes the left shifted curves to be more vertical and the right shifted curves to be more horizontal (Fig 8.8B).

During the construction of CO_2 titration curve, arterial blood is tonometered with CO_2 gases of two known, but

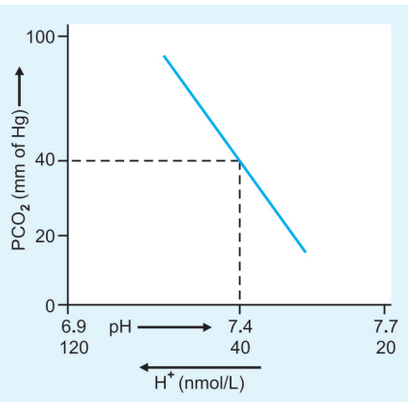


Fig. 8.8A: *In vivo* CO_2 titration curve

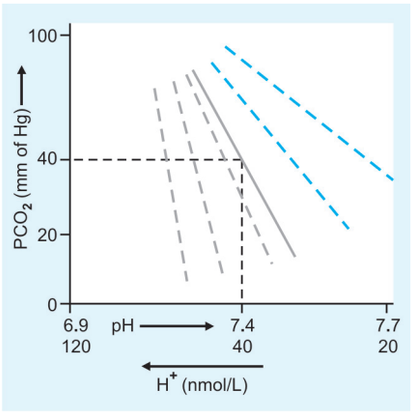


Fig. 8.8B: Family of *in vivo* CO_2 titration curves in non respiratory (metabolic) acidosis (red lines) and alkalosis (green lines)

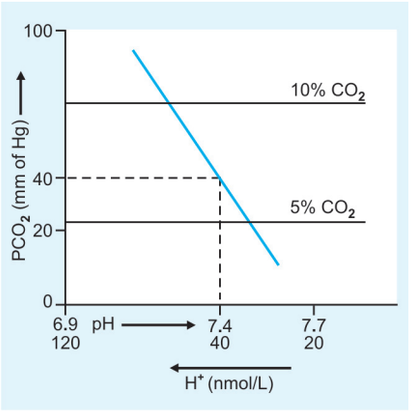


Fig. 8.8C: Measurement of PCO_2 and construction of in vitro CO_2 titration curve

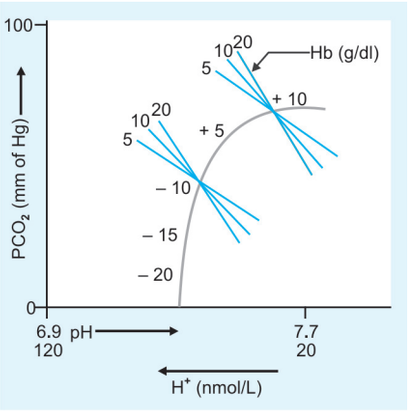


Fig. 8.8D: Construction of 'base excess' curve

different concentration. If pH is measured after tonometry, then an *in vitro* blood CO_2 titration curve could be constructed (Fig. 8.8C). Next the actual PCO_2 of any original blood sample can be determined by interpolation, if its pH is measured. In general, it is realized that the titration curve of blood from acidotic patients lay to the left of this curve and from alkalotic patients lay to the right. But, it was appreciated that the Hb concentration altered the slope of the curve and induces errors. Thus, a number of parameters were used to get rid of these errors. These are base excess, buffer base, and standard bicarbonate (Fig. 8.8C).

When the normal blood is diluted to different Hb concentration and thereafter is equlibrated with gas mixutres of different PCO_2, then this yields a family of PCO_2/pH curves intersecting at pH of 7.4 and PCO_2 of 40 mm of Hg. After that if a strong acid or alkali is added, then different families of curves are produced (Fig. 8.8D). Now, if the intersections of each family are joined, then a base excess curve is produced. The value of this base excess curve is thus independent of Hb concentration and is a useful index of only patient's metabolic acid-base status (not the patient's respiratory acid-base status). It was found emperically that the correction of metabolic acidosis could often be obtained by the infusion of sodium bicarbonate in m.mol/L which can be determined by the formula: 0.3 + base excess × weight in Kg (Fig. 8.8D).

In acute respiratory acidosis, the arterial pH falls according to the CO_2 titration curve. Acute respiratory acidosis follows titration line from N to x in Figure 8.8E. Then, in long standing conditions the kidney excretes an increasing proportion of the acid load producing a shift to the right of the titration curve from x to y in Figure 8.8E. In acute respiratory alkalosis, the pH also increases according to the CO_2 titration curve. Acute respiratory alkalosis follows tritation line from N to O. Then, renal compensation causes a shift to the left of the titration curve from O to P (Fig. 8.8E).

In metabolic acidosis, the CO_2 titration curve is shifted to the left in figure F. In metabolic acidosis, the ventilation is stimulated by the peripheral chemoreceptor drive, so that the CSF and arterial PCO_2 and HCO_3^- concentration are lowered until the pH returns almost to normal. If the pH is corrected rapidly by the administration of bicarbonate, then the PCO_2 of CSF will rise and pH will fall stimulating the central chemoreceptors and replacing the arterial metabolic acidosis with a respiratory alkalosis. In metabolic alkalosis the CO_2 titration curve is shifted to the right in Figure 8.8G (Fig. 8.8F).

There is usually the same respiratory compensation, but less than in a metabolic acidosis. So the PCO_2 is elevated, which reduces the pH of CSF and leads to an increase in CSF the concentration of HCO_3^- (Fig. 8.8G).

Standard Bicarbonate

It is the bicarbonate concentration (HCO_3^- in mmol/L) in fully oxygenated blood which has been equilibrated at 37°C with gas mixture having a PCO_2 of 40 mm Hg. The normal range of standard bicarbonate (HCO_3^-) concentration is 22 to 26 mmol/L. It is an effective evaluation of only the metabolic status of

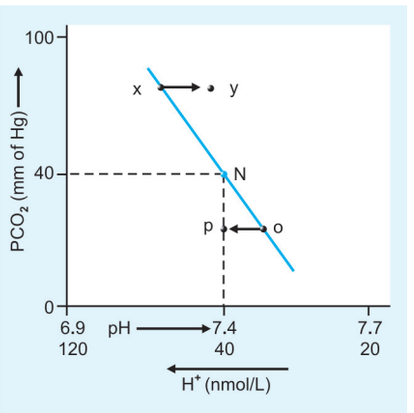


Fig. 8.8E: pH - PCO_2 changes during respiratory disturbances. Acute respiratory acidosis follows titration line N → x and alkalosis N → o. Renal compensation is slow and causes pH change x → y and o → p

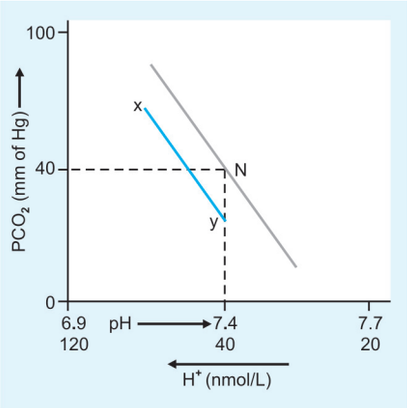


Fig. 8.8F: Acid-base change during non respiratory (or metabolic) acidosis. Respiratory stimulation allows pH to move N → x. In the absence of respiratory compensation, pH would be yF

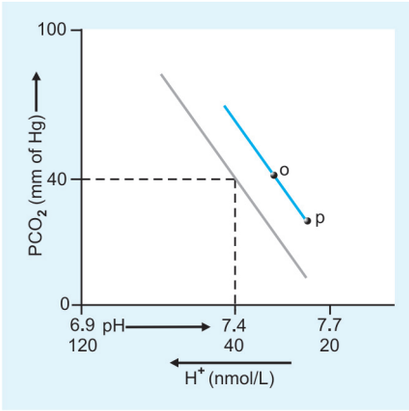


Fig. 8.8G: Acid base changes during metabolic alkalosis. Respiratory compensation allows pH to move N → o. In the absence of respiratory compensation pH would be p

acid-base balance. A standard bicarbonate level in excess of 26 mEq/L (in case of HCO_3^- the numerical value in mmol/L and mEq/L is same as valency of HCO_3^- is one. This is discussed in elecrolyte chapter) is a sign of the presence of a metabolic alkalosis. A standard HCO_3^- level less than 22 mEq/L is a sign of metabolic acidosis. To determine the metabolic acid-base status among the parameters such as the base excess, buffer base and standard bicarbonate, the first one is most useful and widely used. This can be calculated by extrapolation from the pH and PCO_2 value, using Siggaard- Andersen (SA) nomogram. (A nomogram is a graph with several scales line laid on the graph intersects the scale at related values of the variables. The values of any two variables can be used to find the values of the others).

SA Nomogram: $pH = p^K + \log [HCO_3^-]/[H_2CO_3]$

As H_2CO_3 concentration is directly proportional to PCO_2, therefore H_2CO_3 in the above equation for bicarbonate buffering system can be replaced by $\alpha\ PCO_2$. α is the solubility coefficient for CO_2 (0.03 mmol/L/mm of Hg).

The equation then becomes:

$pH = p^K + \log [HCO_3^-] / \alpha\ PCO_2$

The value of p^K for bicarbonate buffer system is 6.1at 37°C. Again at PCO_2 of 40 mm of Hg. the plasma bicarbonate concentration is about 25 mmol/L .

So, $pH = 6.1 + \log 25 / (0.03 \times 40) = 7.4$

Numerous graphic representations of this Henderson-Hasselbalch equation have been suggested. The important graphic representation is a pH − bicarbonate plot and the pH − log PCO_2 plot.

Siggaard-Anderson nomogram is the graphic representation of Henderson-Hasselbalch equation in which pH is plotted against log P_aCO_2 .

Lines can be plotted on this nomogram showing the changes in pH which occur when a sample with normal Hb is equilibrated with various concentration of CO_2. An arterial blood sample is taken and equilibrated with two gas mixture containing different but known concentration of CO_2 and then pH of the sample is measured. Two points are therefore plotted on the nomogram and joined by a straight line. This is called the buffer line and it describes the relationship between pH and P_aCO_2 in that particular blood sample. The pH of the patient's blood is measured anaerobically in the sample. Using this pH value and the buffer line, the CO_2 of the sample can be interpolated from the nomogram. The buffer line will cross the horizontal plasma bicarbonate line at a P_aCO_2 of 40 mm of Hg , where the bicarbonate value can be read. This is the standard bicarbonate.

Base Excess (BE)

It is not uncommon that there may be mixed respiratory and metabolic acid-base disturbance. Thus, the base excess measurement is one way of quantifying the metabolic component, when there is presence of mixed acid-base disturbance. The two examples will best illustrate this term-base excess.

First example

Let the initial measurements of an arterial blood sample are: pH is 7.6, P_aCO_2 is 55 mm of Hg, and Hb is 15 mg/dl. Then the blood sample is kept at 37°C, and equilibrated with CO_2 gas mixture to make the PCO_2 40 mm of Hg. Therefore, it will remove the respiratory component of the acid base abnormality. The pH is now 7.7. Next a strong acid is added to titrate the pH back to 7.4. The amount of acid required is found to be 20 mmol/L. Therefore, the base excess of the original sample is 20 mmol/L

Second example

Let the initial measurement of an arterial blood sample are: pH is 7.3, and P_aCO_2 is 20 mm of Hg, and Hb is 15 gm/dl. Then the blood sample is kept at 37°C and equilibrated with CO_2 gas mixture to make the P_aCO_2 40 mm of Hg. Now the pH is 7. Then a strong alkali is added to bring the pH to 7.4. The amount of alkali required is 15 mmol/L. Therefore, the base excess is −15 mmol/L. This also can be expressed as base deficit which is 15 mmol/L. Both the expressions such as base excess with –ve value or deficit with +ve value are commonly used. Usually, there should normally be neither a base excess nor deficit. So, the normal valve for base excess or deficit is zero.

Therefore, it is defined as a titrable base which can be titrated to pH 7.4 at PCO_2 of 40 mm of Hg and at temperature of 37°C. This is the base concentration of whole blood measured by titration against a strong acid or base to pH 7.4, at PCO_2 of 40 mm of Hg, and at 37°C. For acidosis (base deficit) titration is carried out with a strong base and for alkalosis titration is carried out by strong acid (base excess). Base excess is measured in mmol/L and is an attempt to quantify the excess or deficit of HCO_3^-. The normal range of base excess varies between −2 to +2 mmol/L (or 12 mEq/L). It represents residual buffering capacity.

The BE less than −2 signifies the presence of metabolic acidosis. Whereas, BE more than +2 signifies the presence of metabolic alkalosis. Nowadays, it is not necessary to perform this time consuming titration to measure the base excess. In practice, the base excess is derived from: (a) Siggaard-Anderson nomogram, (b) acid-base slide rule (Severinghans) or (c) mathematically as in many automatic blood gas analysers.

The base excess (unlike buffer base) measurement is independent of Hb concentration. Altering the Hb concentration of a blood sample would result in a change in pH and PCO_2 but no change in base excess.

Buffer Base

It is the sum of concentration of all the buffer anions in the blood such as HCO_3^-, phosphate, protein, Hb, etc. The normal values of buffer base depends on the Hb concentration. So, it is reduced in anaemia. Apart from the changes in Hb concentration, it is increased in metabolic alkalosis and decreased in metabolic acidosis. A rise in PCO_2 in respiratory acidosis does not affect it. Because although $[HCO_3^-]$ increases, the extra $[H^+]$ combine with Hb, so that the concentration of this ion is correspondingly reduced (Table 8.7).

Table 8.7: Uncompensated changes in acid-base status

	Acid-base state	*pH*	*Plasma bicarbonate*	*PCO_2*
	Normal	7.35 - 7.45	22 - 28 m.mol/L	36-46 mm of Hg
1.	Meta acidosis	Low	Low	Normal
2.	Meta alkalosis	High	High	Normal
3.	Res acidosis	Low	High	High
4.	Res alkalosis	High	Low	Low

$$CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$$
$$\downarrow\uparrow$$
$$H^+ + Hb^- \leftrightarrows H.Hb$$

pH Measurement

H^+ concentration is measured directly by a glass electrode with a membrane which is only permeable to H^+ ions. Then, derived pH is displayed on a meter. PCO_2 is measured by the Seveinghaus electrode which incorporates a modification of the technique where a CO_2 permeable membrane is used. PO_2 is measured by Clark polarographic electrode (Table 8.8).

Our concept regarding acid-base balance is now changing. In the past, we concentrate on the concentration of the H^+, pH, PCO_2, standard bicarbonate, base excess/base deficit, etc. But, now the world is thinking on: strong ion difference (SID), PCO_2, total weak acid concentration (A_{TOT}), etc. to explain in best way the acid-base balance in physiological system. SID is the sum of all strong, completely dissociated cations such as Na^+, K^+, Ca^{2+}, Mg^{2+} minus the sum of all strong anions such as Cl^-, lactate, HCO_3^-, etc. When we calculate the SID, it indicates some unmeasured ions. PCO_2 is important because it is independent variable as respiration is going on.

TECHNIQUE FOR ARTERIAL BLOOD-GAS SAMPLING

The acid-base status of the most body tissues is reflected in that tissue's venous blood. But the brain is an important exception to this rule, as lactate produced by anaerobic metabolism is confined by the blood-brain barrier ion, the brain cells and CSF. Thus, the assessment of whole body acid-base status may be determined by analysis of mixed venous blood and this can only be achieved by pulmonary artery or at least, right ventricular sampling which is very difficult. So, most investigators use arterial blood as 'oxygenated mixed venous blood' to measure the different parameter of acid-base balance. This has the additional advantage that the arterial PO_2 may be determined from the same sample.

An alternative, which is particularly useful in small childen, is to use a sample of capillary blood. If this is taken from a warm, vasodilated part of the periphery, usually the hand or heel, then it has been shown that the PCO_2 is within 0.5 mm of Hg and the pH is within 0.005 units of simultaneously obtained arterial samples. But this capillary sampling is unsuitable for PO_2 determination.

Table 8.8: Acid-base status

Acid-base state	*Standard bicarbonate in mmol/L*	*Base excess in mmol/L*	*Total buffer base in mnol/L*
Normal	22-26	0 ± 3	44-48
1. Meta acidosis	Low	Negative	Low
2. Meta alkalosis	High	Positive	High
3. Res acidosis	Normal	Normal	Normal
4. Res alkalosis	Normal	Normal	Normal

Samples for arterial blood gas analysis is taken into a syringe whose potential dead space is filled with heparin in concentration of 1000 units/ml. There must not be any air bubble in the syringe and the blood should be well mixed with heparin. Excess heparin reduces the value of measured pH by virtue of its own acidity. Blood should be taken by direct arterial puncture from brachial, radial or femoral artery or withdrawn from an indwelling arterial cannula, taking care to avoid air bubbles.

Measurements should be done immediately after drawing of blood sample because metabolism will continue within the blood cells at room temperature and this will increase PCO_2 and decrease PO_2. Alternatively sample should be capped and stored in crushed ice. Temperature of the patient and the inspired O_2 concentration should be noted. Diffusion of CO_2 across the wall of plastic syringes does not produce a change in CO_2 tension within the first three hours of storage.

Capillary samples are often used in babies and are taken into special preheparinised glass capillary tubes. The PCO_2 and pH of capillary blood are close to those of arterial blood, taken at the same time. The PO_2 is less reliable.

DISTURBANCES OF ACID-BASE BALANCE

During the management of a patient with severe acid-base disturbances, it is very essential to keep in mind the clinical condition of the patient, while evaluating the laboratory results. An isolated pH measurement is totally valueless without an arterial PCO_2, and in the case of respiratory disease without an arterial PO_2, as well. Free H^+ are constantly being produced by the body, but changes in the H^+ concentration are kept to minimum by different buffering mechanisms of the body. Respiratory and renal compensatory mechanism come into play, when plasma buffering capacity is exceeded, in an attempt to achieve a normal plasma pH.

Classically, disturbances of acid base balance are divided into respiratory and metabolic acidosis or alkalosis and should be considered in relation to the Henderson-Hasselbalch equation which normally works in the following manner.

$pH = p^K + \log [HCO_3^- / H_2CO_3]$ I

$= p^K + \log 24 / 1.2$ (Normal plasma $[HCO_3^-]$ is 24 m.mol/L and $[H_2CO_3]$ is 1·2m.mol/L)

$= p^K + \log 20$

$= 6.1 + \log 20$ (p^K of bicarbonate system is 6.1)

$= 6.1 + 1.301$ (log 20 = 1.301)

$= 7.4$ (Fig. 8.8H).

Despite the apparent clear cut disturbances of acid-base balance, in practice there are often a mixed disorders. In such situations, when we are confronted with an estimation of blood gases, then it is important to isolate the most abnormal parameter, since other abnormalities are possibly secondary to this or of a compensatory in nature. So, in these circumstances an acid-base diagram may be very helpful. The Flenley acid-base diagram is an alternative way of looking at the acid-base disturbances and is infact a modification of the Siggard-Anderson nomogram in which bicarbonate buffer system only is considered. In it the linear relationship between the H^+ ion activity and P_aCO_2 is plotted on a graph in which isopleths of equal HCO_3^- concentration radiate out as a fan shapped manner from the origin or centre. The fan shaped radiation represents 95% confidence limits which are shown on the diagram. During acid-base disturbances serial values of blood gases are plotted on it to define the nature of the disturbance and its progress.

On this acid-base diagram, a point to the left of the normal pH of 7.4 implies an acidosis and a point to the right of the normal pH implies an alkalosis. The plasma bicarbonate can be read directly. This diagram is of great value during therapy, to monitor the changes in response to treatment.

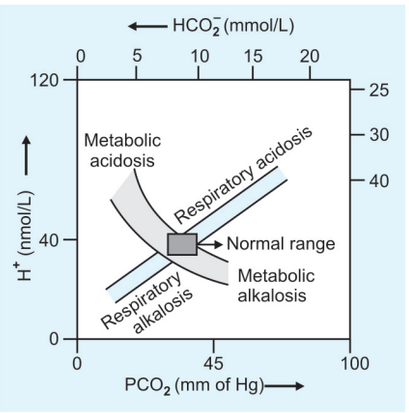


Fig. 8.8H: This is a Flenley acid-base diagram, which shows changes in blood H^+ concentration, PCO_2, HCO_3^- level in stable compensated acid base disorders. The rectangle at the centre indicates limits of normal ranges for H^+ concentration and PCO_2. The bands extending from the central rectangle represent 90% confidence limits for single disturbance of acid base balance. When the point is obtained by plotting H^+ concentration against PCO_2 and it does not fall within one of the bands, then compensation is incomplete or a mixed disorder is present

Siggaard-Andersen Nomogram

This nomogram is very useful to plot the acid-base characteristics of a sample of arterial blood. This nomogram has a vertical axis which indicates PCO_2 and a horizontal axis which indicates pH. Thus, any point to the right of a vertical line through pH 7.4 indicates alkalosis and any point to the left indicates acidosis. Similarly, the position of a point below or above the horizontal line through PCO_2 of 40 mm of Hg indicates the degree of hyper or hypoventilation, respectively (Fig. 8.9).

If a solution containing $NaHCO_3$ and no buffer is equilibrated with a blood sample containing gas mixture of various amount of CO_2, then at equilibrium the pH and PCO_2 value would fall along the line A or a line parallel to it. If buffers are not present, the steepness of the line will be greater and if buffers are present, the slope of the line will be greater. For normal blood containing 15 gm of Hb, the CO_2 titration line will pass through the 15 gm/dl mark on the haemoglobin

scale (point B) which is situated on the underside of the upper curved scale. This line will also pass through the point where the PCO_2 = 40 mm of Hg and pH = 74 lines will interact. When the Hb content of the blood is low, then there is significant loss of buffering capacity. It will cause the diminished slope of the CO_2 titration line. However, blood always contains some buffer in addition to Hb. So, the line drawn from the zero point on the Hb scale and through the normal PCO_2- pH intercept is steeper than the line for a solutions containing no buffers.

For clinical use, the arterial blood is drawn anaerobically and its pH is measured. The pH of same blood is again measured after equilibration with two gas mixtures containing different known amount of CO_2. This pH value at known CO_2 concentration are plotted and connected to provide the CO_2 titration line for the blood sample. The pH of the blood sample before equilibrium is plotted on this line and the PCO_2 of the sample is read from the vertical scale.

The standard bicarbonate content of the sample is indicated by the point at which the CO_2 titration line intersects the bicarbonate scale on the PCO_2 = 40 mm of Hg line. The standard bicarbonate is not the actual bicarbonate concentration. Rather, it indicates the remaining portion of bicarbonate which is present after elimination of any respiratory component. Actually, it is a measure of the alkali reserve of blood and like it, it is also an index of the degree of metabolic acidosis or alkalosis. But the difference is that standard bicarbonate is measured by determining the pH, rather than the total CO_2 content of the sample after equilibration.

The buffer base also can be measured from the additional graduations on the upper curved scale of the nomogram. The point where the CO_2 titration line of the arterial blood sample intersects this scale shows the buffer base in meq/L. The normal value of it in an individual with 15 gm/dl of Hb is 48 meq/L. The buffer base is equal to the total number of buffer anions such as protein, HCO_3^-, Hb^-, etc, which can accept H in blood.

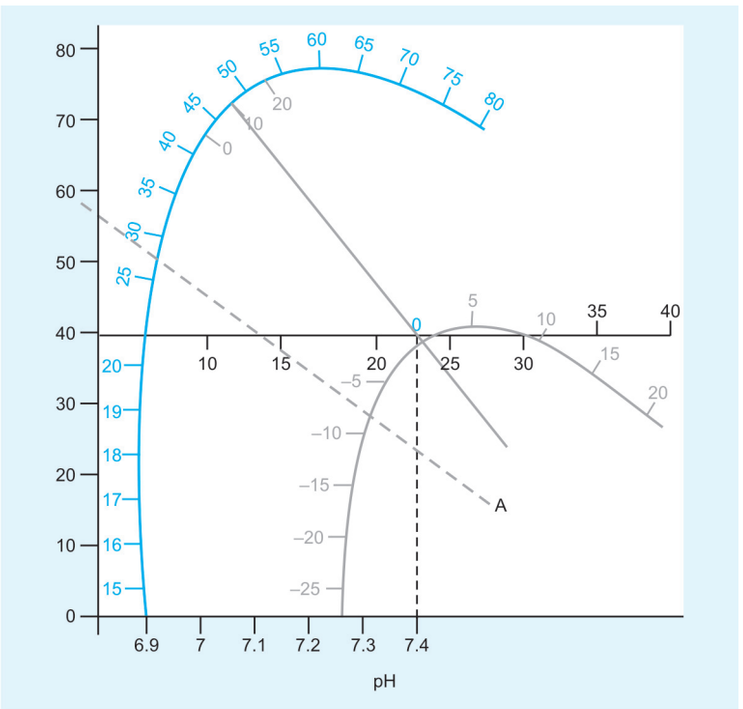


Fig. 8.9: Siggaard -Andersen nomogram (schematic diagram)

Base excess also can be calculated from this nomogram. The point at which the CO_2 titration line intersects the lower curved scale indicates the base excess. It is defined as the amount of acid or base that would restore one litre of blood to normal acid base composition at a PCO_2 of 40 mm of Hg. It is positive in alkalosis and negative in acidosis.

RESPIRATORY ACIDOSIS (TABLE 8.9)

The typical blood picture of pure respiratory acidosis will be like that pH < 7.40, Pa CO_2 > 40 mm of Hg and H CO_3^- > 24 mEq/L. This is due to the the excess of of CO_2 in blood. This excess of CO_2 in respiratory acidosis is due to the the lack of excretion through lungs or excess production from hypermetabolism or excess inhalation of CO_2. It may be acute or chronic in nature. But the compensatory response to acute elevation of PCO_2 in respiratory acidosis is limited. This is because ventilation can not be increased to excrete excess CO_2 as the pathology is within the lungs. Buffering is primarily provided by Hb and the exchange of H^+ (produced by reaction of CO_2 with H_2O) for Na^+ and K^+ from bone and intracellular fluid. The renal response to retain more HCO_3^- as a compensatory process is also very limited in acute condition. Latter slowly renal compensation occurs. The normal arterial CO_2 tension in blood is 35 to 45 mm of Hg. The term 'respiratory acidosis' means that P_aCO_2 is higher than this normal value and this CO_2 becomes hydrated to H_2CO_3, so that the value of log $[HCO_3^-]$ / $[H_2CO_3]$ in equation I falls with a fall in pH. The kidney compensates this respiratory acidosis by retaining more HCO_3^- and excreting more H^+ and thus tries to reduce or compensate the fall in pH. Thus, renal compensation causes to increase in plasma and CSF bicarbonate (HCO_3^-) level, so as to return pH towards normal. But, an acute increase in P_aCO_2 results in acute increase in H_2CO_3 which does not get anytime for

Table 8.9: Causes of respiratory acidosis

1. Parenchymal lung diseases
   Pneumonia, collapse, aspiration, pulmonary emboli, pulmonary oedema, interstitial lung disease, etc.
2. Airway obstruction
   Asthma, foreign body, tumour, laryngospasm, COPD, etc.
3. Skeletal abnormalities
   Myopathies, neuropathies, flail chest, kyphoscoliosis, poliomyelitis, myasthenia gravis, tetanus, etc.
4. Pleural abnormalities
   Pleural effusion, pneumothorax.
5. CNS depression
   Drug overdose, trauma, tumour, CVA, Obesity hypoventilation (Pickwickian syndrome).
6. Ventilator malfunction Increased CO_2 production

Thyroid storm, malignant hyperpyrexia, severe shivering, thermal injury, etc.

compensation by kidney. For every 10 mm of Hg rise of PCO_2, there is 8 nmol/L rise of H^+ but only 0.08 m.mol/L rise of HCO_3^- and the relation between PCO_2 and H^+ concentration is linear. But the relation between the logarithmic scale of H^+ concentration (pH) and PCO_2 is not linear. The approximate relation between pH and PCO_2 is: for every rise of 10 mm of Hg of PCO_2, there is decrease of 0.07 unit of pH within 30 to 60 mm of Hg range of PCO_2. Beyond this range the decrease of pH is more faster. In chronic respiratory acidosis with renal compensation, as the ratio of HCO_3^- to H_2CO_3 (or PCO_2) approaches to normal by the retention of HCO_3^-, so the changes in HCO_3^- is greater and the changes in pH is less than for an acute disturbance. So, in chronic hypercapnia with renal compensation, every 10 mm of Hg increase of PCO_2 results in 4 mmol/L increase of HCO_3^- and 3.2 n.mol/L rise of H^+ with 0.03 unit decrease of pH. The upper limit of HCO_3^- for compensation in acute respiratory acidosis is 30mEq/L and in chronic respiratory acidosis is 50 mEq/L. If the measured HCO_3^- is higher than expected HCO_3^- level, then metabolic alkalosis is also present. On the other hand, if measured HCO_3^- is below the expected HCO_3^- level, then associated metabolic acidosis is present. The expected HCO_3^- after compensation is acute resp. acidosis: $HCO_3^- = (PCO_2 - 40) \times 0.1 + 24$. In chronic resp. acidosis this formula is: $HCO_3^- = (pCO_2 - 40) \times .35 + 24$.

This secondary renal compensatory change in response to respiratory acidosis is slow to develop, and it may take many days for full compensation to occur. The compensatory response to a chronic respiratory acidosis is therefore a metabolic alkalosis (retention of HCO_3^- by kidney) which tends to return the pH to normal. In the presence of acute hypercapnia which happens during GA, there is no time for any appreciable renal compensation to occur. During apnoea the arterial PCO_2 rises about 3 to 6 mm of Hg per minute and H^+ accumulate at a rate of 10 nmol/min. This is 20 times faster than the kidney to excrete them.

The high arterial PCO_2 in respiratory acidosis can be produced by:

i. If CO_2 production remains constant, but alveolar ventilation (V_A) is reduced e.g. COPD, parenchymal lung disease, lung injury, acute respiratory depression by narcotics, impaired neuromuscular function such as relaxant drugs, myasthenia gravis, poliomyelitis, peripheral neuritis etc.
ii. If CO_2 production is raised but V_A does not rise sufficiently to excrete the extra CO_2 e.g. fever.
iii. If CO_2 tension in inspired air ($FiCO_2$) is raised, e.g. rebreathing of CO_2 from expired air due to malfunctioning of anaesthetic apparatus.

Systemic Effects of Respiratory Acidosis (Hypercapnia)

The respiratory acidosis or hypercapnia has multiple systemic effects. The central nervous system effects include: impairment of mental activity, loss of consciousnes, ↑central blood flow due to cerebral vasodilation, ↑CSF pressure, and stimulation of respiration followed by depression if PCO_2 rises gradually.

The general sympathetic over activity also occurs due to hypercapnia. If high inspired O_2 concentration is not delivered during hypercapnia, then hypoxaemia also follows hypercapnia and there after profound effects of these both (i.e hypoxia and hypercapnia) are seen on the CVS. The heart muscles are depressed by high blood CO_2 level. However, this effect is partly offset by the increased sympathetic activity due to hypercapnia. This increased sympathetic activity, accompanied by peripheral vasodilation cause rise in CO but causes pulmonary vasoconstriction. As the arterial PCO_2 rises due to hypo ventilation from low to high values then the cardiac output (CO) increases at first gradually only due to the (Table 8.10) increase in stroke volume. Later, the increase in cardiac output is due to the increase in both the stroke volume and the heart rate. These changes are accompanied by a rise in mean arterial pressure and a fall in peripheral vascular resistance (due to vasodilatation). Thus, the gradual rise of CO_2 tension in blood causes tachycardia. This is followed by bradycardia and depressed conduction in heart, particularly in the bundle of His, when plasma pCO_2 rises to very high. So, in severe hypercapnia the heart block and a slow ventricular rhythm is commonly observed, with an increased myocardial irritability. A rise in the CO_2 tension in blood increases the secretion of catecholamines (mainly epinephrine) from the sympathetic nerve ending within the myocardium. There is also an increase in plasma epinephrine and norepinephrine level due to secretion from the adrenal glands due to high CO_2 level. At the same time during anaesthesia the sensitivity of a target organs to catecholamines by volatile anaesthetics is increased by high plasma PCO_2. So, many anaesthetic agents, primarily halothane, cause arrhythmia in presence of high CO_2 level. Thus, both increased catecholamine level and increased sensitivity make the halothane responsible for frequent arrhythmia during hypercapnia. In such situation, improving

Table 8.10: Characteristic changes in arterial H^+ concentration, PCO_2 and HCO_3^- level in different acid-base disturbances

Disorder	*H^+*	*nmol/L*	*P_aCO_2*	*mm of Hg*	*HCO_3^-*	*nmol/L*
Resoiratory acidosis						
Acute	+	60	+ +	70	WNR	28
Compensated (by renal retention of HCO_3^-)	Slight ↑ or WNR	44	+ +	66	+ +	40
Respiratory alkalosis						
Acute	–	22	– –	20	WNR	22
Compensated (by renal excretion of HCO_3^-)	Slight ↓ or WNR	36	–	30	–	15
Metabolic acidosis						
Acute	+	60	WNR	40	– –	12
Compensated (by ↑ ven)	Slight ↑ or WNR	48	–	30	– –	13
Metabolic alkalosis						
Acute	–	26	WNR	40	+ +	42
Compensated (by ↓ ven)	Slight ↓ or WNR	35	+	60	+ +	40

Normal H^+ concentration = 35 to 45 nmol/L, P_aCO_2 = 35 to 45 mm of Hg, HCO_3^- = 21 to 28 mmol/L, WNR = within normal range, + = increased, – = decreased.

ventilation and reducing the dose of halothane will help to restore the normal rhythm.

During hypercapnia, the blood pressure rises due to sympathetic stimulation. So increased bleeding is seen through surgical wounds. The patient presents with warm skin, dilated veins and bounding pulse. There is also small rise in plasma potassium level. Oxyhaemoglobin dissociation curve is shifted to the right in any acidosis. But it is important to mention that under anaesthesia many of the above signs may be masked.

It is important to emphasise that during anaesthesia the anaesthesists are largely responsible for controlling the arterial PCO_2 at about the normal level. The main difficulty for the anaesthesist is to recognise the minor degrees of hypoventilation clinically. The time-honoured custom of looking only at the reservoir bag and thinking that ventilation is adequate is often grossly erroneous, especially for high risk patients. Fluctuation of P_aCO_2 between 40 and 60 mm of Hg is probably of little consequence in normal, healthy patient. But, when the arterial PCO_2 rises to around 80 mm of Hg, it denotes a severe and dangerous hypoventilation. When CO_2 level rises to 110 mm of Hg, then CO_2 narcosis occurs. In such situation, the patient will not regain consciousness, even when the anaesthetic drugs are withdrawn. If, at this moment, the patient is allowed to breath room air, simply because the operation is over then he will be with the disadvantage, because alveoli filled with anaesthetic gases (usually N_2O) escaping from circulation will cause diffusion hypoxia. This hypoxia will again increase due to the uneven ventilation-perfusion ratio, which normally follows anaesthesia and also due to the reduced quantity of available oxygen from the lungs due to high CO_2 tension. Thus, hypoxia will occur definitely.

Treatment

The treatment of respiratory acidosis is aimed at the underlying causes, for example improving ventilation by using intermittent positive pressure ventilation, if respiration is depressed or totally absent. Rebreathing of CO_2 should be avoided. Dead space of the anaesthetic apparatus should be reduced. Alkali therapy has no place in chronic respiratory acidosis. In COPD, the aim of treatment of respiratory acidosis should be to lessen the H^+ activity just less than 56 nmol/L (pH > 7.25), rather than to normalise completely. This is because the acidity of the blood which is important to maintain the ventilation through the chemoreceptor mediated ventilatory drive by CO_2 in COPD patient and this is modified by renal compensatory HCO_3^- retention. It is too difficult to assess the P_aCO_2 simply by clinical examination. So, repeated blood gas monitoring is of course mandatory. If IPPV is used to produce normal P_aCO_2 then the patient will be left with variant HCO_3^- level and metabolic alkalosis.

The typical blood gases level in acute situation of respiratory depression and acidosis without any compensation are like this:

pH → 7.2,
P_aCO_2 → 70 mm of Hg,
HCO_3^- → 29 mmol/L.

In the more common COPD, where renal compensation has occured, typical blood gases findings are like this:

pH → 7.3,
P_aCO_2 → 60 mm of Hg,
HCO_3^- → 35 mmol/L,
P_aO_2 → 70 mm of Hg.

The alveolar gas equation in a case of respiratory acidosis always predicts that hypoxia is must accompanied with ↑ $PaCO_2$ due to poor ventilation. The resultant fall in PaO_2 limits hypercapnia

to approximately 100–110 mm of Hg. Higher $PaCO_2$ imposes PaO_2 so low that it is incompatible to life. Under such circumstances it is hypoxia, but not hypercapnia which poses the principal threat to life. So, administration of O_2 along with ventilation is the most critical part of the management of respiratory acidosis.

Naloxone and flumazenil is important to treat hypercapnia if it is due to opioid or benzodiazepine overdose. During mechanical ventilation minute ventilation should be gradually raised in such a fashion that $PaCO_2$ will gradually return to higher side of normal base level. Rapid reduction of $PaCO_2$ risks the development of posthypercapnic alkalosis with potential serious consequences. If posthypercapnic alkalosis is developed, then it should be treated with chloride, usually as its K-salt and administering bicarbonate wasting diuretic such as acetazolamide at the doze of 250–350 mg once or twice daily.

Differentiation between primary respiratory acidosis and compensated respiratory and metabolic alkalosis

	pH	*$PaCO_2$*	*HCO_3^-*
Primary respiratory acidosis	7.30	55	24
Compensated respiratory acidosis	7.38	50	30
Compensated metabolic alkalosis	7.42	50	32

Explanation

In primary resp. acidosis HCO_3^- is in normal value. So no renal compensation. In compensated resp. acidosis HCO_3^- elevated, pH is on the acidotic side of normal range compensated metabolic alkalosis looks like compensated respiratory acidosis but diagnostic point is pH is on alkali side.

RESPIRATORY ALKALOSIS

Respiratory alkalosis is the most frequently found acid-base disorder. Because it occurs in normal pregnancy and high altitude dwellers. It is also particularly prevalent among the critically ill patients. In this group of patient it carries band prognosis, because mortality increases in direct proportion to the severity of hypocapnia. The usual blood picture of primary respiratory alkalosis is pH > 7.40, $PaCO_2$ < 40 mm of Hg, HCO_3^- < 24 mEq/L. In most of the cases pH does not exceed 7.55 and severe manifestation of alkalaemia is usually absent.

$pH = p^k + \log [HCO_3^-] / [H_2CO_3]$.

In this situation, CO_2 is washed out due to hyperventilation and this reaction:

$CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$

is shifted to the left leaving HCO_3^- in excess in respect to H^+ concentration in plasma. Thus, plasma H_2CO_3 level is reduced in respect to H^+ and log $[HCO_3^-] / [H_2CO_3]$ value is increased with an increase in pH. Compensatory changes occur if the disturbance is prolonged. The kidney compensates for this rise in pH by excreting more HCO_3^- (Table 8.11) and retaining more H^+ and thus restore pH to normal by reducing the log $[HCO_3^-] / [H_2CO_3]$ ratio. By reabsorbing less HCO_3^- and secreting less H^+ it produces an alkaline urine. The secondary response to a respiratory alkalosis is therefore a metabolic acidosis (retention of H^+). But, this secondary compensatory response is reduced in anaesthetised person due to fall in renal blood flow. So it is not uncommon to find mild metabolic acidosis in anaesthetised hyperventilated patient with mild respiratory alkalosis.

An uncompensated respiratory alkalosis leads to the following changes in blood such as low P_aCO_2, low plasma bicarbonate, high pH but normal buffer base, base excess and standard bicarbonate level. In acute respiratory alkalosis or hypocapnia there is decreased level of PCO_2, H^+ and HCO_3^-. But decrease of H^+ in comparison to HCO_3^- is more (reverse of the respiratory acidosis). An acute decrease of 10 mm of Hg of PCO_2 results in decrease of 2 mmol/L of HCO_3^- against 8 nmol/L decrease of H^+. The pH increases by 0.08 unit for every 10 mm of Hg decrease of PCO_2. Renal compensation for chronic respiratory alkalosis causes a decrease in tubular H^+ secretion and diminished HCO_3^- reabsorption. So, plasma HCO_3^- level decreases and the ratio of HCO_3^- to H_2CO_3 (pCO_2) approaches to normal by compensation. In chronic compensated respiratory alkalosis, each 10 mm of Hg decrease in PCO_2 is associated with 6 nmol/L decrease in H^+ and 0.03 unit increase of pH. After compensation, if the measured HCO_3^- is higher than the expected level, then metabolic alkalosis is present along with respiratory alkalosis. On the other hand, if the measured HCO_3^- is lower than the expected level, then associated metabolic acidosis is present along with respiratory alkalosis. The expected HCO_3^- after compensation in acute resp. alkalosis is HCO_3^- = 25 – (40–$PaCO_2$) × .25. In chronic resp. alkalosis this formula is HCO_3^- = 25 – (40 Pa CO_2) × .5.

The main danger of respiratory alkalosis under anaesthesia is cerebral vasoconstriction. This is because it is known that arterial PCO_2 largely controls the diameter of these cerebral vessels. Thus, a severe alkalosis may produce intense cerebral vasoconstriction and decreases intracranial pressure by decreasing CBF. The cerebral effects of hyperventilation or hypocapnia such as euphoria and analgesia also have been demonstrated. But, whether they are only due to cerebral vasoconstriction or due to direct action of low CO_2 tension on the brain cells is not definitely known. However, the latter seems to be much

Table 8.11: Causes of respiratory alkalosis

CNS stimulation causing hyperventilation

Anxiety, pain, fever, infection, drug induced (salicylates), stroke, tumour, hysteria etc.

Peripheral stimulation causing hyperventilation

Hypoxaemia, anaemia, high altitude, shock, pregnancy, pulmonary diseases, etc.

Iatrogenic

IPPV

more likely. It is also true that long periods of severe respiratory alkalosis leading to cerebral damage is still lacking. So most clinicians believe that a mild respiratory alkalosis is more beneficial for the patient, rather than a mild respiratory acidosis.

Other features of respiratory alkalosis are hypokalaemia, increased neuromuscular excitability producing tetany due to decreased ionic Ca^{2+} concentration, a tendency towards increased ventricular irritability and a shift to the left of Hb-O_2 dissociation curve. This causes increased O_2 affinity to Hb and less unloading of it to tissues which is again prevented by rise in 2-3 DPG level by alkalosis. Decrease in the level of 2-3 DPG tries to shift the Hb-O_2 dissociation curve to right and help in unloading of O_2 to tissues.

Alkalaemia reduces the original threshold and predisposes the patient to refractory supraventricular and ventricular arrhythmias. This cardiac effect is more evident in patients with underlying heart disease. Alkalosis also depresses respiration. This effect is of little consequence in healthy patient. But this effect is very prominent in a patient who is on ventilator. In such patient even mild alkalaemia can frustrate the efforts to wean from ventilator.

Hypokalaemia is a almost constant feature of any alkalaemic disorder. But it is more prominent in those of metabolic origin. Translocation of K^+ into cells, and renal losses of it are the cause of hypokalaemia in alkalosis. This hypokalaemia has several adverse effects. These are: neuromuscular weakness, polyuria, increased ammonia production (that can highten the risk of hepatic encephalopathy), digitalis induced arrhythmia, etc. Alkalosis stimulates anaerobic glycolysis and increases the production of lactic acid and ketoacids.

Respiratory alkalosis in commonly associated with hyponatraemia, hypokalaemia, hypocalcaemia (ionised Ca^{2+}) and hyperchloraemia.

During anaesthesia with controlled ventilation the low PCO_2 causes the cardiac output to fall. This is because the main determinants of the cardiac output during anaesthesia is the arterial PCO_2 level.

Causes of Respiratory Alkalosis

The causes of respiratory alkalosis are:

i. Cortical stimulation causing hyperventilation due to pain, fear, anxiety, analeptic drugs, salicylate poisoning, head injury, hepatic failure, pregnancy, labour pain, etc.
ii. Hyperventilation by hypoxic drive due to high altitude, haemorrhagic shock or any other shock. A hypoxic drive from peripheral chemoreceptor occurs at high altitude and probably explain the cause of hyperventilation and respiratory alkalosis.
iii. Cardiopulmonary diseases: asthma, pulmonary oedema, pulmonary embolism, etc. All these factors may also cause respiratory acidosis, but will depend on the degree of stimulation of respiration causing hyperventilation and the lung condition causing the retention of CO_2.
iv. Excessive IPPV during long-term ventilatory support.
v. Hysterical overbreathing.

An important and serious clinical hazard of acute hyperventilation or respiratory alkalosis occurs, when it is super imposed upon pre-existing metabolic alkalosis. Because it may result in severe hypokalaemia, especially in the presence of digitalis leading to severe ventricular arrhythmias. In such situation, severe depletions of body's CO_2 store occurs. When hyperventilation ceases, then the stores of CO_2 are gradually replaced during the period of hypo ventilation. The O_2 consumption is unchanged and the respiratory quotient RQ (CO output/O_2 consumption) is decreased during respiratory alkalosis. The reduction in RQ in respiratory alkalosis causes a decrease in P_aO_2 and is thus another reason why patient should receive additional O_2 during weaning from mechanical ventilation, if there is hyperventilation.

Treatment

Whenever possible the management of respiratory alkalosis must be directed correcting the underlying cause. In most cases, especially chronic cases pose little risk to health and produce few or no symptoms. So in such circumstances measures to treat the deranged acid-base status is not required. In anxiety hyperventilation syndrome sedation and psychotherapy is very helpful. Rebreathing into a paper bag on through any closed system provides prompt relief, but it is short lived.

Differentiation between primary respiratory alkalosis and compensated resp. alkalosis and compensated metabolic acidosis

	pH	*$PaCO_2$*	*HCO_3^-*
Primary respiratory alkalosis	7.55	30	24
Compensated respiratory alkalosis	7.45	28	15
Compensated metabolic acidosis	7.35	30	17

Explanation

In primary respiratory alkalosis as there is no compensation, so HCO_3^- is in normal range. In its compensated form pH comes down, but on slightly alkali side and HCO_3^- falls. In compensated metabolic acidosis $PaCO_2$ falls for compensation and pH is slightly on acidic side after compensation.

Correction of respiratory alkalosis can be made by preventing the increased central or peripheral respiratory drive, if this is appropriate. Mechanical ventilation should be controlled by monitoring the arterial or end-tidal pCO_2.

METABOLIC ACIDOSIS

This occurs when an abnormal amount of metabolic acids (noncarbonic acid) are formed and accumulate or an abnormal loss of base occurs. So, as a compensatory mechanism the level of PCO_2 (marker of respiratory acid base status) in blood is reduced. This is manifested

secondarily by hyperventilation which try to mitigate the ratio of HCO_3^- /H_2CO_3 to normal level (compensatory respiratory alkalosis). Here, the sources of H^+ are nonvolatile acids or fixed acids and not the H_2CO_3, coming from reaction of CO_2 with water. Normally, the different types of nonvolatile acids such as lactate, acetoacetic acid, hydroxybutyric acid, acetone free fatty acids, etc, are produced in variable amounts during metabolism of different substrates (discussed before) and have relatively little renal excretion. They are normally removed by metabolism in the liver with regeneration of bicarbonate. However, fixed acids including HCl, H_2SO_4 and H_3PO_4 can only be eliminated by renal excretion. If uncompensated, then the changes due to metabolic acidosis seen in blood are: low pH, low plasma bicarbonate, normal PCO_2, a negative base excess, and a low standard bicarbonate. But, typical values after compensation are: pH less than 7.36 (H^+ concentration is more than 44 n.mol/L) P_aCO_2 less than 35 mm of Hg (compensated), HCO_3^- less than 18 mmol/L (compensated).

In metabolic acidosis an increase in anion gap may occur and an insight of the overall buffering capacity of the body during this acid base disturbance may be available by calculating this anion gap. These represents those negative ions which is not normally measured in clinical practice, including phosphate, sulphate, lactate, ketoacids and albumin. The working formula is: anion gap = plasma Na^+ − (plasma Cl^- + plasma HCO_3^-). Normally the value of anion gap varies between 8 to 14 mmol/L. Where excessive acid is added to the plasma, either by metabolic disorder or by addition of exogenous acid or there is failure of acid excretion, then this anion gap is increased. In metabolic acidosis, the value of log HCO_3^- / H_2CO_3 will be reduced due to low HCO_3^- or high H_2CO_3 level and hence pH falls. In metabolic acidosis though CO_2 does not accumulate excessively to form much H_2CO_3, but it is formed excessively by the reaction of $H^+ + HCO_3^- = H_2CO_3$ where the equation is shifted to the right and further reduces the HCO_3^- level. This H^+ comes from metabolic acids, such as lactic acid, keto acids, pyruvic acid etc. This H^+ stimulates chemoreceptors and increases ventilatory drive to washout CO_2 for compensation (compensatory respiratory alkalosis). Thus, CO_2 is excreted ($H_2CO_3 \leftrightarrows H_2O + CO_2$) from H_2CO_3 through lungs as a compensatory process, resulting in decrease in PCO_2 or H_2CO_3 level and attenuation of the fall in pH. Although the reduction in PCO_2 is rapid, still the respiratory response is only capable of 50 to (Fact file- II) 70% compensation for the metabolic acidosis. In other word, an uncorrected metabolic acidosis which would reduce the pH to 7 is normally compensated to a pH of 7.2 to 7.3.

The typical blood picture of a metabolic acidosis is pH < 7.40, $PaCO_2$ < 40 mm of Hg, and HCO_3^- < 24 mEq/L. If the measured $PaCO_2$ from a blood sample is higher than the expected $PaCO_2$ (which should be reduced), then it should be thought that additional respiratory acidosis is present. On the other hand, if the measured $PaCO_2$ is less than the expected $PaCO_2$, then an additional respiratory alkalosis is present. There are the mixed disorders. In a compensated metabolic acidosis the expected $PaCO_2$ is calculated as: $(1.5 \times HCO_3^-) + 8 \pm 2$.

Profound derangements of K^+ level occur in metabolic acidosis. For every decrease in 0.1 pH, there is equivalent 0.8 increase in K^+ level. Correction of it usually not required, unless there is threat to life. Because correction of acidosis will correct it.

Causes of Metabolic Acidosis

The causes of metabolic acidosis are:

A. *Accumulation of acid:*

a. Diabetic ketoacidosis where blood levels of lactic acid, aceto-acetic acid,

FACT FILE - II

Anion Gap (AG)

It is a very useful clinical tool for (i) narrowing the differential diagnosis of metabolic acidosis, (ii) identifying the variety of acids originated in metabolic disorder and (iii) recognising certain mixed acid base disturbances. The anion gap is generally measured from the concentration of four common electrolytes such as Na^+, K^+, Cl^- and HCO_3^-. Sometimes K^+ is excluded from the calculation. Then the calculation will be:

$Na^+ = Cl^- + HCO_3^- + AG$

or $AG = Na^+ - [Cl^- + HCO_3^-]$

Otherwise, the usual formula is (if K^+ included in the calculation):

Na^+ (140) + K^+ (5) = Cl^- (105) + HCO_3^- (25) + AG (15)

or $AG = [Na^+ + K^+] - [Cl^- + HCO_3^-]$

The normal range of AG is 12 ± 4 mEq.

Some causes of metabolic acidosis release anions in extracellular fluid which are not normally measured. But, when this occurs there will be an unexpected discrepeancy between the sums of the principal cations and anions. When there is some additional unmeasured anions, they become part of the gap which will be the larger. A anion gap larger than 30 mEq suggests that there is an increase in the concentration of the unmeasured anions. An increased AG is the only clue that metabolic acidosis is present isolatedly or in a mixed acid base disorder. The AG indicates the quantity of added acids. The fall in HCO_3^- also equals the rise in AG. It is useful in following the response of patient treating for diabetic ketoacidosis or other metaboic disorder.

In anion gap metabolic acidosis (AG > 12 mEq), there is decrease in HCO_3^- level. This is due to buffering of an acid whose anion is other than Cl^- (such as H_2SO_4, lactic acid etc). Hence, it is called normochloraemic acidosis. These acids may be endogenous (lactic acid, keto acid, uraemic acid) or exogenous (salicylates) or the endogenous metabolic products of exogenous toxins (such as methanol, ethanol, etc). Other unmeasured anions are proteins, phosphates, sulphates etc.

There is another metabolic acidosis where there is no anion gap (AG = 8 to 12 mEq), but decrease in HCO_3^- level. This is due to buffering of an acid whose anion is Cl^- (such as HCl acid). So, this is called hyperchloraemic acidosis.

betahydroxybutyric acid, α-ketoglutaric acid, and acetone are increased.

b. Lactic acidosis due to starvation. C. Administration of large volume of stored blood, where ACD is used as an anticoagulant. It produces an acute acidosis, although hepatic metabolism of the citrate in the next 2 to 3 days will convert this to a non-respiratory alkalosis.

c. Renal tubular acidosis (RTA) – The RTA is a type of metabolic acidosis where the cause is in renal tubule. It results either from a defect in reabsorption of bicarbonate in the proximal tubule or from a defect in failure of secretion of H^+ (failure of acidification of urine) from collecting tubules. Decreased reabsorption of bicarbonate causes large amount of losses of HCO_3^- in urine and marked reduction in plasma HCO_3^-. In failure of secretion of H^+, there is also failure of secretion of Cl^-. So there is persistant hyperchloraemic acidosis. It is also associated with hypercalciuria, hyperphosphaturia and loss of Na^+ in urine.

d. Salicylate over dose.

e. Hypoxia – It causes acidosis by metabolising pyruvate to lactic acid, but not to acetyl CoA which is the gateway of pyruvate to TCA cycle in the presence of O_2.

f. Low cardiac output (CO) − producing tissue hypoxia.

g. Following cardiac arrest − Anaerobic metabolism and acidosis occurs in cardiac arrest.

Substances such as paraldehyde, methyl alcohol, ethylene glycol, fructose, sorbitol, xylitol, ethanol, etc, may also cause metabolic acidosis. There may also be an increase in H^+ concentration from accumulated HCl which is released during the metabolism of arginine and lysine present in synthetic amino acid solution and following the therapeutic use of NH_4Cl.

An uncommon, (but probably over emphasised), form of metabolic acidosis also occurs when sometimes extracellular bicarbonate is diluted with saline which is used excessively during over enthusiastic replacement therapy. Such administration of excessive NaCl only occurs during the resuscitation of a severly hypovolaemic patient, in whom the restoration of circulatory volume by an isotonic fluid is an urgent requirement to restore the tissue perfusion and aerobic metabolism. A mild metabolic acidosis occurs in GA. It is also commonly observed after a period of extra corporeal perfusion, after circulating arrest, after hypothermia, following temporary occlusion of a major vessel such as aorta, massive blood transfusion, etc.

B. *Loss of Bicarbonate:*

i. From GI Tract
   a. fistula of small intestine, pancreatic fistula or biliary fistula.
   b. diarrhoea.
   c. uretero enterostomy.
   d. cholestyramine.

ii. From Kidney
   a. renal tubular acidosis.
   b. Use ofcarbonic anhydrase inhibitor (CAI) such as acetazolamide (explained before).

In metabolic acidosis, the body will try to compensate this fall of pH by stimulation of respiration, leading to fall in P_aCO_2 which will try to return the pH towards normal by reduction the H_2CO_3 level in blood. Although the fall in pH is modified but it does not return completely to normal (Table 8.12).

Effects of Metabolic Acidosis

The effects of metabolic acidosis are :

i. Initially, the acidosis stimulates the CVS and increases CO and BP. But later the heart muscles are depressed and CO falls. The cardiovascular responses to sympathetic activity or sympathomimetic drugs are initially increased and then reduced. Intense peripheral vasoconstriction occurs initially. These changes further tend to intense the acidosis, so that a vicious cycle is set up.

ii. Increase in circulating catecholamines.

iii. Increased H^+ will tend to displace K^+ from the intracellular fluid which result in hyper kalaemia.

iv. Cardiac arrhythmias and arrest.

v. Pulmonary hypertension.

vi. Mental changes.

vii. Metabolic acidosis stimulates the peripheral and central chemoreceptors by increased H^+. Thus, ventilation is increased and arterial and CSF PCO_2 and HCO_3^- are lowered, untill the pH returns almost to normal. If the pH is corrected rapidly by $NaHCO_3$, then the blood and CSF pCO_2 will rise and pH will fall stimulating central chemoreceptor and replacing metabolic acidosis with respiratory alkalosis.

viii. Hb-O_2-dissociation curve will shift to the right.

Management

The treatment of metabolic acidosis is directed towards the underlying causes.

Table 8.12: Causes of metabolic acidosis

With increased anion gap (AG)	
A.	Increased production of acid
	Starvation, diabetic ketoacidosis, lactic acidosis, inborn errors of metabolism, alcohol, etc.
B.	Reduced excretion of acid
	Renal failure.
C.	Administration from outside
	Salicylates, para-aldehyde, ethylene glycol, methanol.
With normal anion gap	
A.	Loss of bicarbonate
	i. Renal—Renal tubular acidosis, carbonic anhydrase inhibitors, hypoaldosteronism, etc.
	ii. Extrarenal — Diarrhoea, fistula (biliary, pancreatic, small bowel), ileostomy, ureterosigmoidostomy, etc.
B.	Addition of acids (chloride containing)
	Administration of NH_4Cl, HCl, lysine hydrochloride, arginine hydrochloride, total parenteral nutrition (Cl^- salts of amino acid), etc.

It is generally more serious than respiratory acidosis, because aetiology of metabolic acidosis is more life threatening. Treatment of metabolic acidosis is also very difficult and more complex than treating respiratory acidosis. Therefore, therapy with $NaHCO_3$ should be reserved for fairly severe disorders, since it is not without hazards.

If the pH is very low (< 7.2), then the metabolic acidosis itself becomes life threatening, because of its serious effects on the heart. Therefore, in such circumstances $NaHCO_3$ should be given IV without delay. If the acidosis is less severe, then the management depends upon: the diagnosis of the causes, associated disorder of electrolyte and fluid balance, and whether the acidosis is still developing or not. Thus, for example, a patient with diabetic ketoacidosis and base excess of –12 mmol/L (base deficit 12 mmol/L) will correct his own acidosis if only saline and insulin is given. It probably does not require any bicarbonate. But, patient with a base excess of –8 mmol/L during any major surgery probably requires bicarbonate, because they can not tolerate the depressant effect of the slight decrease of pH on the myocardium. On the other hand, it is important not to give too much $NaHCO_3$, as this may have several undesirable effects.

Sodium Bicarbonate ($NaHCO_3$)

$NaHCO_3$ solution is available in a variety of concentration. The concentration of $NaHCO_3$ that commonly used clinically for resuscitation is 8·4% which contains 1 mmol of Na^+ and HCO_3^-. Therefore, there is a danger of high Na load, precipitating heart failure. The sodium bicarbonate solution of this concentration is hypertonic and irritating to veins. Thus, it may also result in extensive skin necrosis, if the solution leaks from the vein into the tissues. Sometimes a hyperosmolality syndrome may be precipitated by 8.4% $NaHCO_3$ solution. Therefore, 8.4% $NaHCO_3$ should be reserved for acute situations such as cardiac arrest and should preferably be given via a central line.

Disadvantages of $NaHCO_3$

The disadvantages of IV administration of $NaHCO_3$ are the following:

i. Administration of 8·4% $NaHCO_3$ causes excess of sodium load which is especially dangerous in patients with heart disease. The administration of 50 ml of 8.4% $NaHCO_3$ will increase the serum osmolarity by 3 mmol/L in the normal adult (Fact file- III).

ii. During cardiac arrest there is both respiratory and metabolic acidosis which develop rapidly in the tissues. In such situation of complete absence of circulation and respiration, administration of $NaHCO_3$ evolves large amount of CO_2. This huge amount of CO_2 can not get its exit through lungs due to absence of circulation and respiration (if circulation and ventilation is not started). Then it leads to more severe hypercapnia and acidosis and more and more depression of myocardium. Thus a vicious cycle will set up.

$$NaHCO_3 + H^+ \leftrightarrows H_2CO_3 \leftrightarrows CO_2 + H_2O$$

During cardiac arrest lactic acidosis results from anaerobic metabolism and there is no formation of CO_2 due to stoppage of TCA cycle in the absence of O_2. Therefore, sudden increase in CO_2 level in blood after administration of $NaHCO_3$ reverses the diffusion gradient and CO_2 will easily enter the cell, causing intracellular acidosis. This intracellular hypercapnia will compound the existing intracellular lactic acidosis which will further reduce the intracellular pH and will decrease the myocardial contractility. Thus, it will exacerbate an already compromised low cardiac output state. The CO_2, thus, produced in the blood will also easily cross the blood-brain barrier and will cause a disproportionate acidosis of CSF. Infact, 50 ml of 8.4% $NaHCO_3$ will be converted to 200 ml of CO_2 which is equivalent to the production of it by the basal metabolism of a normal adult in 1 minute.

iii. $NaHCO_3$ administration causes an extracellular alkalosis and movement of oxyhaemoglobin dissociation curve towards the left. This will impair O_2 delivery to the tissues. In uncontrolled diabetes mellitus, the acidosis exists with high level of 2, 3 DPG level. Acidosis itself shifts the O_2 dissociation curve to the right and on the other hand high 2, 3 DPG shifts it to the left, so that the net effect of oxygen delivery to the tissue remains normal. If $NaHCO_3$ is administered in these circumstances

FACT FILE- III

High anion gap metabolic acidosis (HAGMA)

Ketoacidosis is one of the example of HAGMA. It is found in starvation, alcoholism and insulin dependent diabetics. It is characterised by elevated level of β-hydroxybutyric acid and acetoacetic acid. The elevation of level of these two acids are due to:

(i) An increased hepatic synthesis caused by an increase in free fatty acid (FFA) which is liberated from adipose tissue due to reduced insulin and increased catecholamine level.

(ii) An altered hepatic metabolism due to reduction in insulin, promoting ketogenesis rather than triglyceride synthesis.

Betahydroxybutyrate, acetoacetate and acetone are together called as ketone bodies. Among these acetoacetate undergoes spontaneous decarboxylation and yields CO_2 and acetone. Acetone is not an acid and excreted largely through lungs like CO_2. Acetoacetate and betahydroxybutyrate remain in equilibrium in plasma and the normal ratio is 3:1 (vary between 1:1 to 10:1). This level increases during hypoxia. The normal fasting level of betahydroxybutyrate is < 1.2 mEq/L. In prolonged fasting it may rise to 2 to 5 mEq/L. Normally, the FFA concentration in plasma ranges between 0.4 to 0.8 mEq/L and seldom rises more than 1 mEq/L. But, in diabetic ketoacidosis, the FFA level may rise upto 2 to 4 mEq/L and ketoacids may increase upto 10 to 15 mEq/L.

then the pH will rise, leaving the unopposed effect of high 2, 3 DPG level and further shifting the O_2 dissociation curve to the left. This will cause service impairment of delivery of O_2 to the tissues. The 2, 3 DPG level takes several days to return to normal and it is important in this respect to ensure a normal plasma phosphate.

iv. In diabetes acidosis, $NaHCO_3$ may precipitate the disequilibrium syndrome.

v. Rebound alkalosis may occur, if excessive dose of $NaHCO_3$ are used. This alkalosis will also reduce serum ionised Ca^{2+} level by 25% and can further decrease the myocardial contractility.

vi. Administration of $NaHCO_3$ results in rise of P_aCO_2. If the patient is able to hyperventilate, then this excess CO_2 will be excreted via lungs. But, in a patient with an impaired consciousness, mechanical ventilation at high minute volume may be required to washout this excess CO_2 with repeated measurement of blood gas tension.

vii. In hypokalaemic patients $NaHCO_3$ administration will increase pH. This will promote further K^+ uptake by the cell and thus lethal hypokalaemia may occur.

In summary, $NaHCO_3$ is a dangerous drug, but may be very essential after cardiac arrest for the successful action of inotropic agents, only if the circulation and ventilation is established.

Doses of bicarbonate

The doses of bicarbonate for the acute management of metabolic acidosis can be calculated from the base excess, assuming that the equilibrium will occur throughout the extracellular fluid which is about 20% of the total body weight or lean body mass (LBM).

So, the dose of $NaHCO_3$ (mmol) = [Base excess × Body weight (Kg)] / 3

It is often recommended that at the initial phase about half of the total calculated dose of $NaHCO_3$ is given. After that blood gases must be checked again. It is much better to undercorrect the acidosis than to overcorrect it. The results, after administering the total dose of bicarbonate as suggested above, are not always predictable. This is due to the possible development of further acidosis and because the original blood sample which was taken during altered equilibrium, does not indicate the actual base excess level. Also it will have to keep in mind that measurement of the acid-base state of the blood may give a very inaccurate index of the actual metabolic state of the whole body, as the measurement of intracellular pH by a clinical procedure is not yet possible. For this reason it is essential to reassess the acid-base status of the arterial blood after half of the recommended dose of bicarbonate has been given and to correct further, if it is necessary only. Sodium bicarbonate is a poor buffer in its own right (as explained previously) and acts mainly by combining with H^+ ions to form CO_2 and H_2O. Administration of bicarbonate to correct a metabolic acidosis, therefore, presents a CO_2 load on the lungs. So, the efficient buffering of metabolic acidosis by $NaHCO_3$ depends mainly on the adequate pulmonary ventilation.

Trihydroxymethyl amino methane (THAM)

It is a non-sodium containing buffer which has been used in some parts of the world, with a variable degree of success, to treat metabolic acidosis instead of $NaHCO_3$ (Fig. 8.10).

Lactic Acidosis

Glycolysis is the process of breakdown of glycogen or glucose into pyruvic or lactic acid through Embden-Meyerhof or glycolytic pathway. Glycogen may leave the liver in the form of glucose, but it leaves the muscles in the form of pyruvic or lactic acids only, and not in the form of glucose. This difference is probably due to the fact that the enzyme systems and the chemical reaction responsible for metabolism of glucose in the liver and muscle are

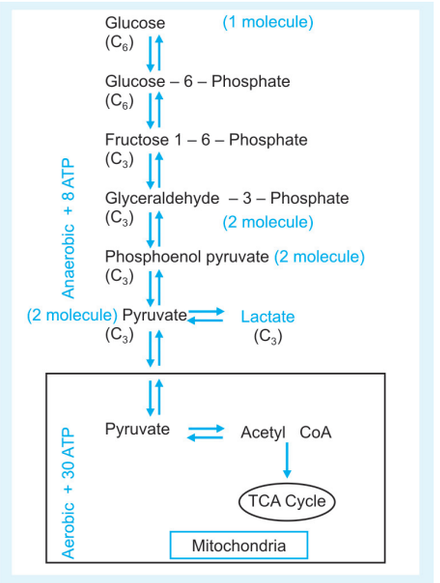


Fig. 8.10: Pyruvate and lactate metabolism.

not the same. Pyruvic or lactic acid that emerges from the muscles is carried to the liver through the blood stream where it is reconverted into glycogen. This glycogen in liver is again remobilised to form glucose which enters into the blood stream. Muscles take up this glucose from the blood stream and recovers its lost glycogen from where again pyruvic or lactic acid is produced due to metabolism. This cyclic process of circulation of carbohydrate in different forms in different tissues is known as Cori cycle, through which muscle lactic acid and liver glycogens become readily interchangeable. In normal condition, 1/5th of the muscle lactate is broken down to CO_2 and H_2O and 4/5th is reconverted into glycogen in the liver (Fig. 8.11).

In the skeletal muscles, the pyruvic acid but not the lactic acid is the end product of the glucose metabolism. It is converted into lactic acid only in anaerobic conditions. Lactic acid from muscles also enters the blood stream during heavy muscular excercise when O_2 supply is inadequate. In the muscle pyruvic acid is also finally oxidised into CO_2 and H_2O through citric acid or TCA cycle in the presence

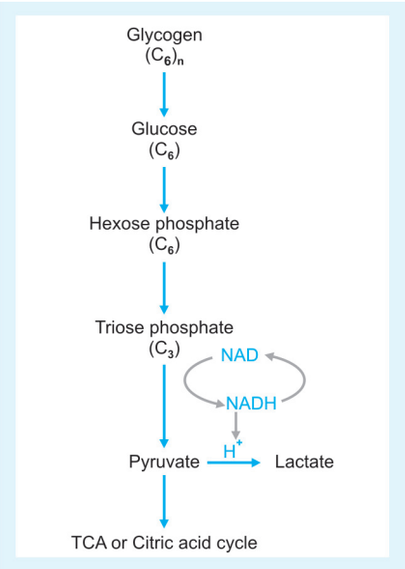


Fig. 8.11: Mechanism of formation of lactate in anaerobic metabolism. H^+ which is formed in step 3 is used for conversion by pyruvate to lactate

FACT FILE- IV

Lactic acidosis may be caused by an increased lactate production due to hypoxia or due to decrease in rate of lactate utilisation by liver and kidney. Normal arterial lactate level is < 2 m.mol/L. Lactate level between 2 to 4 m.mol/L are abnormal, but of uncertain clinical significance. Plasma lactate level greater than 5 m.mol/L is used to diagnose lactic acidosis. But in most cases of lactic acidosis the lactate level runs between 10 to 30 m.mol/L. Plasma lactate is measured in a heparinised arterial blood sample, stored in ice. It should be assayed within 1 hour, after sample is drawn. Lactate level can also be measured from blood, collected in a fluoride oxalate tube which is normally used for glucose estimation. Though lactic acidosis is classified into type A and type B, still some believe that there is little utility in this division, as both types often share mechanisms of over production or under utilisation.

of O_2. Cardiac muscle utilises lactic acid directly and completely in preference to glucose. Glucose utilisation by the heart of a diabetic person is less than normal, but as regards lactate, the diabetic heart uses it almost as readily as the normal heart. On the other hand, there is very little glycogen store in the brain. It uses sugar in the form of galactose only which is locally synthesized from the blood glucose. In the brain galactose is also metabolised to lactic acid. It is also interesting to note that the brain tissue is very rich in fat, but it derives its energy from sugar. The RBC also readily form lactic acid from sugar.

Lactic acidosis is best defined as the acidotic condition when pH is less than 7.25 and the blood lactate concentration is more than 5 mmol/L. But, the care must be taken to exclude other conditions which are responsible for acidosis with increased level of lactic acid such as renal failure, ketoacidosis, and other conditions where the elevation of lactic acid is not alone responsible for the acidosis.

Lactic acid is formed from pyruvic acid and is the (Fact file- IV) final product of the glycolytic pathway in the absence of O_2. Thus, glycolysis unlike the citric acid cycle can continue in anaerobic condition also. But, normally further metabolism of pyruvate requires its entry in the presence of O_2 into the oxidative tricarboxylic acid (TCA) cycle which is present within the mitochondria. In the absence of O_2, the TCA cycle stops and pyruvate accumulates. In hypoxia, this accumulation of H^+ and pyruvate would allow transformation of pyruvate to lactate with production of energy which will allow to continue the reaction (Embden-Meyerhof) for some period. Thus lactate accumulation occurs during anaerobic metabolism (i) by increased production or (ii) by decreased gluconeogenesis from lactate in the liver and kidney or (iii) by the failure of pyruvate to enter the tricarboxylic acid (TCA) cycle. Hepatic utilization of lactate usually acounts for 1500 m.mol/day with the ability to rise it to 3400 mmol/day.

Aetiology of lactic acidosis

Lactic acidosis is classified into two types– type A and type B. Type A is due to tissue hypoxia and anaerobic metabolism. Type B is due to other causes which will be described later. (Fig. 8.12).

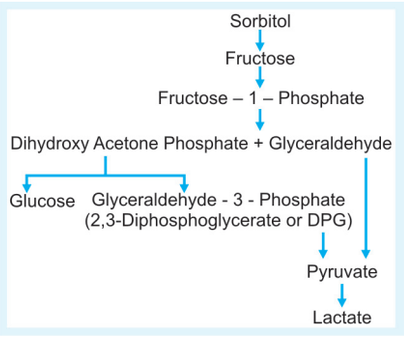


Fig. 8.12: Metabolism of fructose and sorbitol

(i) Type A lactic acidosis

The association between the metabolic acidosis, circulatory collapse and hypoxia is well recognised. The impaired tissue perfusion from circulatory collapse causing tissue hypoxia is the result of any form of shock. Tissue oxygenation is further compromised by added severe hypoxaemia (low P_aO_2) and anaemia. So, the blood lactate concentration, although seldom measured, closely correlates with mortality rate. There is a mortality rate of about 75% in patients with blood lactate concentration which rises from 4.4 to 8.9 mmol/L. But, there is only 10% mortality rate with lactate concentration which rises from 1.3 to 4.4 mmol/L. However, the treatment of type A lactic acidosis entails the removal of causes and the subsequent O_2 and alkali therapy.

(ii) Type B lactic acidosis

The causes of type B lactic acidosis are:

a. Common Disorders—diabetes mellitus, renal failure, hepatic failure, severe infection, leukaemia.
b. Drugs—phenformin, metformin, salicylates, paracetamol.
c. Parenteral nutrition - fructose, sorbitol, xylitol.
d. Inherited—glycogen storage disease, fructose 1-6 diphosphate deficiency, leigh's syndrome, methylmalonic acid aemia.
e. Toxins – ethanol, methanol.

The commonest cause of acute and serious Type B lactic acidosis is biguanide

therapy for diabetes mellitus. Among the biguanides, phenformin is ten times more likely to produce an attack of lactic acidosis than metformin. The mortality of Type B lactic acidosis is 50%. Biguanides produce hypoglycaemia by (a) reducing the alimentary absorption of glucose and amino acids, (b) decreasing the hepatic gluconeogenesis and (c) increasing the glycolysis. Thus, lactic acidosis by biguanides is inherent and is produced by the hypoglycaemic actions of it mentioned in (b) and (c). Usually during biguanide therapy blood lactate is less than 2 mmol/L, but impaired renal excretion, hepatic dysfunction or cardiovascular disease may easily induce lactic acidosis.

Fructose, sorbitol, xylitol, etc, have been used as energy substrates instead of glucose in diabetic patient. Because they all can be metabolised without insulin. This is of particular importance in very sick patients who are insulin resistant. In addition, these agents are less irritant to veins than glucose. However, all these agents result in the increased production of lactate. 35% of fructose infusion is converted rapidly into pyruvate and then into lactate by the liver.

Ethyl alcohol (ethanol) infusion inhibits hepatic neouglucogenesis. In the presence of hepatic disease or when administered with fructose, sorbitol or biguanide, then lactic acidosis may result from ethanol.

Treatment

Like the treatment of type A lactic acidosis, the treatment of type B lactic acidosis should also always be directed at the underlying causes and ensuring adequate oxygen delivery to the tissues. The treatment of type B lactic acidosis is very difficult than type A lactic acidosis. If possible, causes should be removed first then symptomatic treatment is started. Large amounts of alkali are necessary for treatment of this type B lactic acidosis, due to the continuing lactate production. Therefore, alkalinisation with $NaHCO_3$ is the main stay of therapy of this type of lactic acidosis. Isotonic $NaHCO_3$ (1·4%) should be used to bring the pH back to normal, but slowly over about 6 hours. If hyperkalaemia coexists, then this therapy will be beneficial for it, as the K^+ will enter the cells with the pH rises. If hyperglycaemia exists insulin may be required.

Attempts have also been made to remove the lactate by dialysis or by stimulating the pyruvate dehydrogenase, which will encourage the conversion of lactate to pyruvae and will remove the latter via the TCA cycle. Glucose and insulin seldom help in the treatment of type B lactic acidosis as glycolysis is stimulated and gluconeogenesis is inhibited.

CVP line and urinary catheter should always be inserted to monitor the progress of therapy, as circulatory overload with cardiac failure is a serious complication during the treatment of type B lactic acidosis. Haemodialysis may be required to treat cardiac failure. Repeated estimation of blood-gas is essential in any disturbance of acid-base balance and in these circumstances it is of great practical value for repeated measurement of lactate levels.

METABOLIC ALKALOSIS

Metabolic alkalosis is less common than metabolic acidosis. It occurs due to the excess production of base or excess loss of noncarbonic acid (H^+), preserving HCO_3^-. It is characterisied by increase in plasma bicarbonate, a fall in blood H^+ concentration and a small compensatory rise in PCO_2. In a healthy normal person when the plasma HCO_3^- rises above normal, then the urinary excretion of HCO_3^- increases rapidly. It is, therefore, very unusual to observe metabolic alkalosis in the presence of normal renal function. Uncompensated severe metabolic alkalosis has very high mortality rate. Typical findings of metabolic alkalosis are pH > 7.4, P_aCO_2 > 45 mm of Hg, H^+ concentration < 36 nmol/L, HCO_3^- concentration > 32 mmol/L.

In metabolic alkalosis log HCO_3^-/H_2CO_3 component of Henderson-Hasselbalch equation is increased due to the raised HCO_3^- concentration and thus pH rises. Compensation occurs by hypoventilation (respiratory acidosis). This conserves CO_2 and increases PCO_2, so that H_2CO_3 rises and thereby modifies the increases in pH by restoring the ratio of HCO_3^-/H_2CO_3 to normal.

$H_2CO_3 \leftrightarrows CO_2 + H_2O$ ..... Equation shifts to the left.

This compensation may be limited till hypoxaemia results from hypoventilation, particularly if the pateint is breathing room air. It appears that respiratory stimulation from hypoxaemia is stronger than the compensatory depression due to alkalosis and thus oxygenation is often maintained despite a metabolic alkalosis.

The formula for the expected raised $PaCO_2$ which occur during compensation in a metabolic alkalosis is: .6 × (measured HCO_3^- – 24) + 40. If the measured $PaCO_2$ is higher than expected, then one should think that this present metabolic alkalosis is mixed with respiratory acidosis. On the other hand, if the measured $PaCO_2$ is less than expected $PaCO_2$, then it can be thought that this metabolic alkalosis is partially compensated or mixed with respiratory alkalosis. The compensation of metabolic alkalosis by elevating $PaCO_2$ is more erractic than that of metabolic acidosis and $PaCO_2$ usually does not rise above the level of 55 mEq/L. This is because the hypoxaemia which is caused by hypoventilation will limit the compensatory rise of $PaCO_2$ that is described before.

The differential diagnosis of metabolic alkalosis is based on urinary Cl^-, i.e. urinary Cl^- < 2D mEq/L and urinary Cl^- > 20 mEq/L. This is because: due to compulsion of electroneutrality there are only two methods to add HCO_3^- to a compartment of ECF – either loss of Cl^- or retention of Na^+. In the ECF the only anion that is present in sufficient quantity is Cl^-. Cl^- is lost with H^+ or NH_4^+. So the loss of H^+ or

NH_4^+ is equivalent to gain of HCO_3^-. The net effect is loss of Cl^- and gain of HCO_3^- leading to metabolic alkalosis.

Classification of metabolic alkalosis according to urinary Cl^-.

A. Chloride responsive or urinary Cl^- $\leq$ 20 mEq/L.
   1. *Renal loss*: Diuretics, cystic fibrosis.
   2. *GI loss*: Suction, vomiting, chloride wasting diarrhoea
B. Chloride resistant or urinary Cl^- > 20 mEq/L
   1. Excess mineralocorticoids: Cushing and Conn syndrome
   2. Excess steroid administration.
   3. Bartter's syndrome.

Causes of Metabolic Alkalosis

1. Loss of H^+ ions

i. Renal— Primary and secondary hyperaldosteronism (discussed later).
ii. K^+ depletion— Acid (H^+) may be lost from the kidney by hypokalaemia with its paradoxical combination of acid urine and alkaline ECF.
iii. Conn's syndrome and Cushing's syndrome.
iv. Drugs—Diuretics (thiazide, frusemide) and corticosteroids
v. GI Tract—Vomiting, nasogastricsuction, pyloric stenosis, high intestinal obstruction etc.
vi. Chloride deficiency (Fact file- V).

2. Gain in alkali (HCO_3^-)

Metabolic alkalosis is also caused by administration of large amount of alkali by ingestion of oral antacids or infusion of $NaHCO_3$. There is also metabolic conversion of organic acid anion such as lactate and citrate to HCO_3^-, causing alkalosis. This situation is observed after a massive blood transfusion when the citrate is metabolised by liver over the next 48 hours to HCO_3^-, resulting in metabolic alkalosis.

There are important relationships between the handling of Na^+, K^+ and H^+ by kidney. Metabolic alkalosis is perpetuated when there is a reduction in ECF volume. The explanation is that in collecting duct final adjustment of urine composition is made by reabsorption of Na^+ in exchange of secretion of both K^+ and H^+ from tubular cells into the lumen. Thus, if the kidney avidly retains Na^+ (in hypovolaemic), it can not retain K^+ or H^+, leading to metabolic alkalosis (Table 8.13).

If, in addition to metabolic alkalosis, there is low intracellular K^+ concentration because of potassium depletion (hypokalaemia due to any cause), then there is obligatory more secretion of H^+ in place of K^+ and the resulting alkalosis will be even greater. When aldosterone and other mineralocorticoids (which increase the drive of tubular Na^+ reabsorption) present in excess such as in primary or secondary hyperaldosteronism, then they have the similar effect.

Chloride is also very important in this context, because normally at various sites in the nephron Na^+ can be reabsorbed along with either chloride or bicarbonate. To maintain neutrality with raised

FACT FILE - V

Metabolic alkalosis causes hypoventilation and elevates PCO_2 as a compensatory mechanism. But, this compensation is more erratic than for acidosis and generally PCO_2 does not exceed 55 mm of Hg. To maintain the electroneutrality in alkalosis due to addition of more HCO_3^-, there are two ways: either loss of an anion such as Cl^- or retention of cation such as Na^+. So the most useful biochemical parameter is to measure the level of urinary chloride which forms the basis of classification of metabolic alkalosis. The only anion that is present in sufficient quantity in extracellular fluid (ECF) to be lost is Cl^-. It is lost with H^+ or NH_4^+. The net effect is loss of HCl or NH_4Cl to gain HCO_3^-. The loss of HCl or NH_4Cl is equivalent to loss of Cl^- for $HCO3^-$. The two organs which are capable of inducing a loss of Cl^-, together with gain of HCO_3^- are stomach (vomitting, intestinal obstruction, etc) and the kidney (absorption of Na^+ as bicarbonate to maintain ECF volume).

Hypokalaemia is an almost constant feature of alkalaemic disorder (alkalosis produces hypokalaemia or hypokalaemia produces alkalosis), but is more prominent in those of metabolic origin. This is due to renal or extra renal losses of K^+ (diarrhorea, suction, vomitting etc) in varying degrees. This condition also commonly occurs after several days of IV therapy where K+ replacement is inadequate, diuretic therapy, diarrhoea, hyperaldosteronism and other common causes of hypokalaemia.

Normally 98% of total body K^+ remains as intracellular. K^+ depletion causes metabolic alkalosis by two mechanism: (a) during K^+ depletion, kidney vigorously attempts to conserve it, causing increased secretion of H^+ and concomittant increase in blood base. (b) K^+ is the major intracellular cation. Hypokalaemia induces intracellular K^+ to enter the extracellular space to maintain near normal serum level. This extracellular migration of K^+ forces the intracellular migration of H^+ and alkalosis. The net result is extracellular increase of $HCO3^-$. This explains how mineralocorticoids causes hypokalaemia and alkalosis.

This also explains how low serum K^+ level (hypokalaemia less than 3.5 mmol/L) reflects a severe depletion of intracellular K^+. In turn hypokalaemia have several adverse effects. It includes neuromuscular weakness, polyuria, sensitisation to digitalis induced arrhythmia and increased ammonia production which can highten the risk of hepatic encephalopathy. Alkalosis stimulates anaerobic glycolysis and increases the production of lactic acid and ketoacids. Alkalosis reduces the release of O_2 to the tissues by tightening the bond between O_2 and Hb. But chronic alkalosis negates this effect by increasing the concentration of 2-3-DPG level in RBC.

Table 8.13: Causes of metabolic alkalosis

Chloride responsive (urinary chloride < 20 mmol/L)
Renal
Diuretics, hypercapnia
GI
Vomiting, diarrhoea, nasogastric suction,
GI fistula, abuse of antacids, villous adenoma,
excessive administration of alkali ($NaHCO_3$), etc.
Chloride resistant (urinary chloride > 20 mmol/L)
Primary hyperaldosteronism
Secondary hyperaldosteronism
Severe hypokalaemia
Cushing's syndrome, Bartter's syndrome, etc.
Miscellaneous
Milk alkali syndrome, alkali therapy, massive blood transfusion, etc.

HCO_3^- absorption, the Cl^- is excreted through kidney. So, urinary Cl^- level is increased in hyperaldosteronism, Cushing's syndrome and in K^+ deficiencies, etc. But, urinary chloride is low when HCl is lost from stomach or intravenous $NaHCO_3$ and diuretics are administered. In such condition when chloride is deficient, there is preferential reabsorption of bicarbonate instead of Cl^- which will make an alkalosis more worse. This will also prevent the additional excretion of bicarbonate by the distal tubule which is usually necessary as a compensation to correct an established metabolic alkalosis.

The classic typical example of metabolic alkalosis is sustained vomiting due to any cause. In normal condition, when H^+ are secreted into the gastric lumen, then HCO_3^- (byproduct of H^+ formation) from parietal cells is absorbed in the blood. This subsequently is neutralised by reabsorption of the secreted H^+ from the small bowel. In sustained vomiting, the initial loss of H^+ from the body initiates the alkalosis. But the kidney is unable to restore the homeostasis by retaining H^+. Because there is also deficit of Na^+ and water due to constant vomiting, causing enhanced tubular Na^+ reabsorption in exchange of K^+ and H^+ (explained before). As K^+ is also lost in vomiting, there is an intracellular K^+ deficit. So in the absence of K^+, tubular H^+ secretion or lost in the lumen is magnified and alkalosis is sustained. Chloride is also lost in the vomit, so there is enhanced bicarbonate reabsorption by the renal tubule (Fig. 8.13).

Use of diuretics, particulary if it is aggressive leading to ECF volume depletion, may have similar effects. Due to inhibition of Na^+ absorption at proximal tubule by diuretics, more Na^+ is delivered to the collecting duct for reabsorption which causes more secretion of H^+. ECF volume depletion by diuretics also enhance the level of renin, angiotensin and aldosterone which increases the drive of Na^+ reabsorption at collecting tubule in exchange of H^+ and K^+ causing sustained alkalosis.

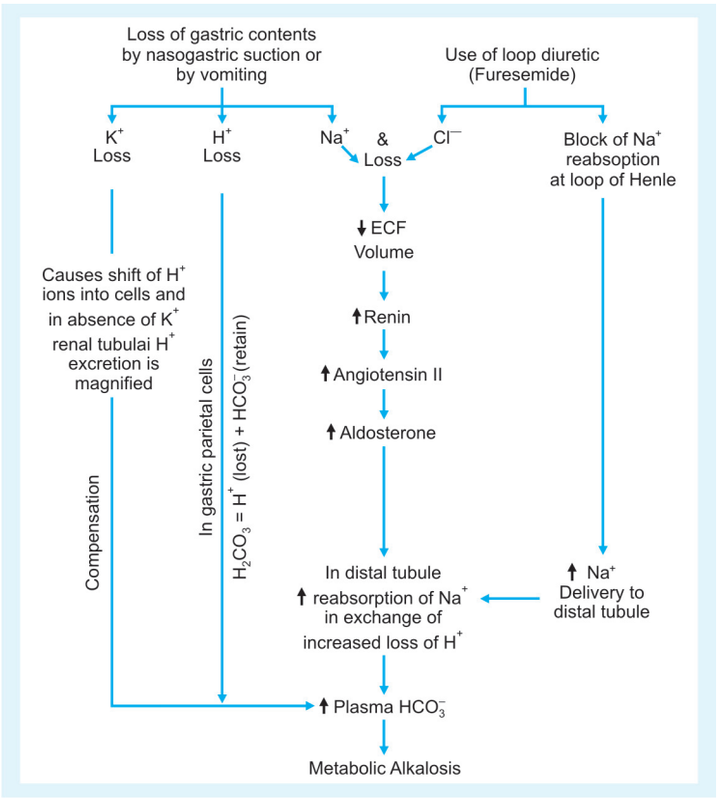


Fig. 8.13: Pathogenesis of metabolic alkalosis. This is due to the loss of gastric contents or use of loop diuretics

Kidney

In the proximal tubule there is obligatory Na^+ absorption, the extent of which is controlled by ECF volume. In the distal tubule Na^+ is reabsorbed in exchange for K^+ and H^+ under the influence of aldosterone. This is the cause of alkalosis in aldosteronism. Thus, hypokalaemia occurs with alkalosis due to the increased excretion of both K^+ and H^+ for increased reabsorption of Na^+. In renal cause of retention of HCO_3^-, causing alkalosis, correction of pH alone without treatment of the underlying disease will result in recurrence and persistence of the metabolic alkalosis.

Clinical Effects of Metabolic Alkalosis

The clinical effect of metabolic alkalosis are tetany, hypocapnic vasoconstriction, left hand shift of O_2 dissociation curve, mental changes, and hypokalaemia.

Treatment of Metabolic Alkalosis

Severe metabolic alkalosis may be a life threatening condition, especially if it is accompanied by hypokalaemia. But, it is uncommon. Treatment of this form of alkalosis includes the following:

i. Restoration of ECF volume: This may involve transfusion of NaCl, plasma or blood. It is important to say that to give chloride, NaCl is the simplest form, if Na load is not contraindicated.
ii. Restoration of plasma K^+ concentration: It is possible by using KCl or K^+ conserving diuretics, such as triamterene or amiloride, if not contraindicated.
iii. Inhibitiion of aldosterone (where appropriate): This is done by using spironolactone.

iv. Inhibition of carbonic anhydrase: This is performed by acetazolamide which will produce retention of H^+ ions.
v. Direct acidification: sometimes HCl, NH_4Cl, lysine or arginine may be used for the correction of metabolic alkalosis. These may all be given intravenously and will result in the release of free H^+ ions. HCl should only be administered through a central venous line at a rate of 0.2 m.mol of H^+/Kg/hour. The maximum dose of H^+ which is about 300 to 500 mmol/day should not be exceeded.

One sixth molar NH_4Cl has also been used as a source of acid, because two molecules of NH_4Cl condense to form one molecule of urea and two molecules of HCl. But it is contraindicated in hypokalemic patient as further K^+ loss is induced.

vi. Loss of H^+ by vomiting or gastric suction causing alkalosis: This can be controlled easily by ranitidine which reduces the H^+ concentration of gastric secretion.

MORE ABOUT ANION GAP

For electrical neutrality to exist, the number of anions (negatively charged ions such as Cl^-, HCO_3^- etc) must be equal to the number of cations (positively charged ions such as Na^+, Mg^+, etc.). When these two numbers are not equal, the difference between them is called the anion gap. The anion gap may be calculated in several ways and the normal range will therefore vary between different laboratories. One method of calculation which can be done on a routine electrolyte estimation is $(Na^+ + K^+) - (Cl^- + HCO_3^-)$. This gives a value between 11 to 19 m.mol/L. It represents approximately the sum of some anions such as protein, phosphate, lactate and 3-hydroxybutyrate, etc. which are usually not measured. Some laboratories also exclude K^+ from the calculations of anion gap which gives a lower normal range.

Causes of high anion gap

i. Uraemic acidosis.
ii. Keto acidosis.
iii. Salicylate poisoning.
iv. Lactic acidosis.
v. Methanol, ethylene glycol and paraldehyde toxicity.

All of these above mentioned factors causes acidosis with high anion gap. But there are many other causes of acidosis in which the anion gap is not abnormal. Because in such cases chloride replaces bicarbonate, for example, diarrhoea.

vi. Dehydration.

Causes of low anion gap

i. Dilutional states
ii. Hypoalbuminaemia − albumin, at normal blood pH, has marked negative charge and therefore accounts for most of the anion gap.
iii. Hypernatraemia, hypermagnesaemia, hypercalcaemia
iv. Paraproteinaemia— Here the increased viscosity of blood interferes with blood sampling. Paraprotein: immunoglobin produced by neoplastic plasma cells proliferating abnormally, e.g. myeloma protein.

Minor variations in the anion gap should be interpreted with care, since it is calculated from four variables. However, it is of value in detecting an abnormality before more specific investigation can be undertaken.

EFFECTS OF ACID-BASE DISTURBANCES

Continuously, acid-base disturbances due to metabolic ($\uparrow\downarrow H^+$ and $\uparrow\downarrow HCO_3^-$) or respiratory ($\uparrow\downarrow PCO_2$) causes are going on in our body. So, homeostatic mechanisms are also acting dynamically to meet with these disturbances and to bring back the plasma pH to normal. But, acute or prolonged disturbances can outpace these homeostatic mechanisms and result in a variety of clinical responses. Among these the most frequently found acid base disturbances is acidosis. Alkalosis occurs less frequently, but is more harmful than acidosis. Acid-base disturbances cause multiple changes in different organs, with myriad of interrelations and interactions. So, it is sometimes very difficult to understand the cause or effects of acid-base disturbances on different systems.

Effects on CVS

There are different separate responses of CVS due to separate changes for PCO_2 and pH. Again, it is very difficult to separate the responses of CVS due to changes in CO_2 tension alone from the changes for sympathoadrenal stimulation which occurs during hypercapnia. So, it is very difficult to elucidate the actual effect of acid-base alteration on the CVS system. In general, if PCO_2 is maintained constant then an increase or decrease in pH causes depression of myocardial contractility with fall in stroke volume and cardiac output, associated with a decrease in peripheral vascular resistance. In addition, the responsiveness of heart to the catecholamine is also diminished in metabolic acidosis. On the other hand, hypercapnia produces increased stroke volume and cardiac output by increasing sympathetic activity. The effect of hypercapnia on the peripheral vascular tissue depends on the degree of sympathetic innervation of it. Richly innervated organ (kidney) respond to hypercapnia by vasoconstriction, whereas poorly innervated organs (cerebral cortex) respond by vasodilation. On the other hand, during hypocapnia there is generalised vasoconstriction independent of sympathetic innervation (Table 8.14).

The effects of acid-base disturbance on heart rate (HR) should be discussed in steps: (i) effect of changes of pH directly on HR, and (ii) effect of catecholamine and ACh due to changes in pH on HR. In an isolated heart preparation (denervated or blocked) acidaemia causes

Table 8.14: Clinical effects of acidosis and alkalosis

	Direct effect	*Indirect effect*	*Net clinical effect*
Decreased pH (acidosis)			
Heart rate	↓	↑↑	↑↑
Cardiac contractility	↓	↑	0
Arterial resistance	↓↓	↑	↓
Venous resistance	↑	↑	↑↑
Pulmonary resistance	↑	↑	↑↑
Cerebral blood flow	↑	↑	↑↑
Airway resistance	↓	↑↑	↑
Renal circulation	↑	↓↓	↓
Serum K^+	↑	0	↑
Ionised Ca^{2+}	↑	0	↑
Increased pH (alkalosis)			
Heart rate	0	0	0
Cardiac contractility	0	0	0
Arterial resistance	↑	0	↑
Venous resistance	0	0	0
Pulmonary resistance	0	↓	↓
Cerebral blood flow	↓	0	↓
Airway resistance	↑↑	↓	↑
Renal circulation	0	0	0
Serum K^+	↓	0	↓
Ionised Ca^{2+}	↓	0	↓

↓ = Decreased, ↑ = Increased, 0 = No effect

bradycardia. But, in normal heart with intact nerve supply the effect is different. When pH decreases from 7.4 to 7.1, the HR increases indirectly as a result of the effect of epinephrine which is released from the adrenal medulla in response to acidaemia. In severe acidosis, when pH further decreases below 7.1 then the effect is bradycardia. This bradycardia is due to the increased vagal tone and accumulation of ACh (acetylcholine) as a result of decreased metabolism of it in the acidic environment. So, clinically in normal healthy patient, acidosis (respiratory or metabolic) will cause initially tachycardia which is followed later by bradycardia, as the depressant effect of parasympathetic system overworks on the initial stimulating effect of sympathetic system.

Myocardium is also sensitive to the changes in PCO_2 and pH both. So, atrial and ventricular arrhythmias are common in acid-base disturbances. But, it is not clear whether the arrhythmia is directly due to the changes in pH or due to the changes in extracellular K^+, secondary to pH changes. Arrhythmia may also be due to pH related changes in Ca^{2+}, Mg^{2+} and catecholamine levels. A change of 0·1 unit of pH is related to change in K^+ level of 0.5 to 1.5 mmol/L in opposite direction. In acidosis, high intracellular H^+ concentration causes hyperkalaemia, but causes reduction of intracellular K^+ concentration. This alters the resting membrane potential of myocardium and causes arrhythmia. Decreased pH lowers the threshold value for ventricular fibrillation and increased pH elevates it. Therefore, acid-base disturbances are frequently accompanies by ventricular arrhythmia. Decreased pH also causes an increase in ventricular ectopic by elevating the level of circulating catecholamines. Among all the volatile anaesthetics halothane sensitises the myocardium maximally to the catecholamines. But in healthy patient, this is of little clinical significance.

Acidosis itself causes depression of myocardial contractility. This direct effect of depression of myocardial contractility is due to the impairment of Ca^{2+} entry into the cells or decreased release of Ca^{2+} from the intracellular storage site such as sarcoplasmic reticulum (SR). On the other hand, acidosis increases the level of circulating catecholamines. This increased level of catecholamines stimulate the myocardial contraction and overcome the direct depressant effect of acidosis. Therefore, the net result of acidosis is increased myocardial contraction. But, this occurs till the fall of pH upto 7, beyond which the direct depressive effect of acidosis predominates over the sympathetic stimulating effects. Thus mild acidosis, i.e. fall of pH upto the level of 7 will increase catecholamine level which will elevate the cardiac output as a result of (i) increased in heart rate, (ii) myocardial contractility, (iii) venous tone (pre load), and (iv) simultaneous decrease in SVR (after load). But, when the pH goes further down below 7, then the cardiac depressant effects of acidosis are greater than the stimulant effects of catecholamine on myocardium and cardiac output will fall. This also explains why a patient taking Ca^{2+} channel blocker will demonstrate decrease in contractility at a relatively slight change in pH.

Alkalosis does not induce the increased catecholamine secretion, but increases the responsiveness of myocardium to the circulating catecholamines. Thus, it produces an elevation of myocardial contractility and O_2 consumption. On the other hand, alkalosis or hypocapnia constricts coronary vessels and elevates coronary vascular resistance, thereby providing less O_2 to the myocardium. On the other hand, hypocapnia or alkalosis shifts O_2 dissociation curve to the left, providing less O_2 extraction by the myocardium or

less tissue unloading. So, the net effect of alkalosis on myocardium is increased myocardial contractility, less O_2 supply to the heart and small myocardial O_2 reserve. In severe alkalosis, unbound plasma Ca^{2+} level decreases which possibly further reduces the myocardial contractility.

The effect of acid-base disturbances on peripheral vasculature is also very complicated. In general, the direct effect of acidosis on systemic arterial bed (not the pulmonary) is vasodialtation. But, this is not true in metabolic acidosis which causes vasoconstriction. In respiratory acidosis there is elevation of CO_2 level in blood which crosses the cell membrane of vasculature smooth muscle more readily than H^+. Intracellularly this CO_2 is converted to carbonic acid and the resultant decrease in intracellular pH is responsible for the decrease in vascular smooth muscle tone. In metabolic acidosis reduction of intracellular pH is not so great as respiratory acidosis, because H^+ has the limited intracellular diffusibility compared with CO_2. On the other hand, due to release of more catecholamines vasoconstriction is the result of metabolic acidosis. This vasoconstriction induced by metabolic acidosis continues, until the pH falls to 7·2. Below that level vasodilation will again occur in response to metabolic acidosis. On the other hand, both metabolic and respiratory acidosis causes pulmonary vasoconstriction. But, when compared with hypoxic pulmonary vasoconstriction, vasoconstriction caused by acidosis or alkalosis is less. Acidosis or alkalosis also enhances the normal hypoxic pulmonary vasoconstriction response. Thus acidosis increases the pulmonary artery pressure and resistance. This is due to the constriction of pulmonary capillary sphincter and also due to the increase in venous return, secondary to acidosis induced peripheral vasoconstriction. Furthermore, catecholamine induced increase in cardiac output due to acidosis produces an increase in pulmonary blood flow and causes further increase in pulmonary artery pressure.

The individual vascular bed responses differently to acidosis. This is because of the varying contributions of direct and indirect effect of acidosis, type of acidosis, and the degree of sympathetic innervation. Metabolic acidosis will directly dilate the arterial bed of skin, skeletal muscles, kidney, splanchnic, uterine and coronary vasculature. Indirect effect of acidosis is mediated through the sympathetic system causing constriction. Thus, the net effect of acidosis on vascular bed is: (a) richly innervated organ such as kidney responses by vasoconstriction, (b) poorly innervated cerebral cortex responses by vasodilatation, (c) splanchnic beds response by vasoconstriction and (d) other vascular beds have variable changes.

Normally the coronary vascular constriction or dilatation, its resistance, and its blood flow mainly depends on the local myocardial O_2 demand which is controlled by heart rate, force of myocardial contraction and after-load, etc. These are again varied by acid-base changes. So, it is very difficult to define the coronary response to acid-base changes. But, the general rule is that acidosis causes dilatation and alkalosis causes constriction of the coronary vascular beds. Therefore, hyperventilation can increase the myocardial ischaemia and lactate levels by significantly reducing the coronary blood flow.

The venous side of vascular bed responses by constriction to both the metabolic and respiratory acidosis, acting both by directly and indirectly. Alkalosis also tends to produce vasoconstriction, except the pulmonary vasculature which dilates in alkalosis.

Effects on Respiratory System

Alteration of acid-base status also effect the respiration and O_2 delivery to tissues through the changes on minute ventilation and the O_2-dissociation curve. Acidosis increases minute ventilation and causes right wards shifting of O_2-dissociation curve (i.e better delivery of O_2 to the tissues). The increase in minute ventilation is accomplished by a substantial increase in tidal volume and little increase in respiratory rate (Kussmaul breathing). The rise of minute volume is about twice as great, if the fall in pH is due to the rise in PCO_2 (respiratory acidosis) than if the same fall in pH is due to the increase in metabolic acidosis (H^+). This is because CO_2 produced by respiratory acidosis diffuses more readily across the blood-brain barrier than H^+, produced from the metabolic acids.

Hypercapnia increases the ventilation by stimulating the central and peripheral chemoreceptor upto maximum PCO_2 of 80 to 90 mm of Hg (11 to 12 KP_a). But above that level of PCO_2 ventilation decreases. 80% of the changes in minute volume is caused by the effect of PCO_2 on the medullary chemoreceptors, while the lesser percentage of changes in minute ventilation is due to the stimulus, originating from the peripheral chemoreceptors. However, as the peripheral chemoreceptors are stimulated by changes in both the pH and PCO_2, but the medullary receptors are stimulated only by the passage of CO_2 across the blood-brain barrier and the subsequent increase in H^+ concentration in CSF. CO_2 stimulates the centrally mediated respiration by decreasing the pH of ECF of brain which perfuse the central chemoreceptor on the ventrolateral surface of the medulla. This takes place slowly over several minutes. But the increase of PCO_2 and reduction of pH produce a more rapid effect, within seconds, through the peripheral chemoreceptor of the aortic and carotid bodies. The respiratory stimulation by CO_2 among normal healthy individual varies widely (0.5 to 5 L/minute/mm Hg), but in the same individual the CO_2 response curve is similar at different times. The normal CO_2 response curve shows that respiratory acidosis will increae the minute ventilation by 2 to 3 L/minute for each 1 mm of Hg increase in PCO_2. The CO_2 response curve is shifted

to the left by acidosis and to the right by alkalosis (opposite to the O_2 dissociation curve). The volatile anaesthetic agents decrease the slope of CO_2-response curve in a dose dependent manner.

The acid-base disturbances also modify the airway resistance by direct (local) and indirect (through sympathetic − parasympathetic axis) way. Directly, the increased CO_2 level, by easily diffusing inside the cell, increases the intracellular H^+ and causes smooth muscle relaxation and reduction of airway resistance. Indirectly, the effects of hypercapnia causes bronchoconstriction by means of vagal stimulation. In normal healthy patient, the indirect constricting vagal effect predominates over direct local bronchodilating effects, causing net increase in air way resistance and work of breathing. Conversely, reduced PCO_2 level (in hypocapnia or respiratory alkalosis) produces a direct bronchoconstrictive effect, which is partially reduced by a centrally mediated bronchodilating effect. However, the direct bronchoconstrictive effect of hypocapnia is clinically predominant and useful in matching the ventilation with blood flow in both healthy and pathological lungs such as in pulmonary embolism.

Both the CO_2 level and pH of blood alter the position of O_2-dissociation curve. An increase in PCO_2 or decrease in pH (i.e acidosis) shift the O_2 dissociation curve to the right, causing an increased P_{50} level. P_{50} is the partial pressure of O_2 in blood when Hb is 50% saturated and the normal value of P_{50} is 27 mm of Hg. An increased P_{50} means high O_2 partial pressure with same 50% saturation of Hb, which helps in better or more delivery of O_2 to tissues at the same 50% saturation of Hb. On the other hand, hypocapnia and alkalaemia cause a shift to the left of O_2 dissociation curve and decrease in P_{50} level which means low O_2 partial pressure with same 50% saturation of Hb i.e. lesser delivery of O_2 to the tissues. During acidosis the P_{50} is increased by about 2 mm of Hg by a reduction of pH of 0.1units (10 nmol/L). Another cause of increased O_2 delivery to the tissues in acidosis is Bohr effect. The Bohr effect describes that the affinity of Hb for O_2 decreases as the level of H^+ in Hb increases. Thus, it increases the availability of O_2 to the tissues. Contrary, alkalosis or decrease in H^+ concentration in Hb increases the affinity of Hb for O_2. This causes less delivery of O_2 to the tissues and increases its absorption by Hb in the lung. In normal healthy patient, this Bohr effect has an overall important effect on absorption of O_2 by Hb at pulmonary level and delivery of O_2 by Hb at the tissue level. This is because O_2 affinity of Hb is greater in the normally somewhat alkalotic lung and lesser in the more acidotic tissue. In acidosis, the rightward shift of the O_2-Hb dissociation curve occurs immediately. But after 20 to 30 hours, the concentration of 2, 3 DPG (2,3 diphosphoglycerate) level falls and restores the O_2 affinity of Hb. Thus it shifts again the O_2-Hb dissociation curve back to the left. The 2, 3-DPG concentration decreases in acidosis because glycolysis in RBC is impaired in an acid environment and the glycolytic intermediates for the 2, 3-DPG production is depleted. Thus, the right shift of O_2 dissociation curve produced by a decrease in pH is partially antagonized by the decrease in 2, 3-DPG level induced by a decrease in intracellular pH.

Tissue oxygen delivery is the product of cardiac output and arterial oxygen content ($CO \times Hb \times SO_2$ and dissolved oxygen). A metabolic acidosis decreases delivery of O_2 to tissues by reducing CO which is partially compensated by the right shift of the O_2 dissociation curve. Whereas a metabolic alkalosis reduces O_2 delivery by both decreasing CO and shifting the O_2 dissociation curve to the left.

So, consequently correction of metabolic acidosis should always be the under correction and not the over correction.

Effects on Nervous System

Like other vascular beds, a rise in arterial PCO_2 also results in cerebral vasodilatation and increased cerebral blood flow. At P_aCO_2 of 80 mm of Hg, the cerebral blood flow becomes double. When P_aCO_2 is reduced to 20 mm of Hg, the cerebral blood flow will become half of the normal value due to the cerebral vasoconstriction. But below 20 mm of Hg of arterial CO_2 tension, the cerebral blood flow does not further reduce. This is due to accumulation of lactate by hypoxia which again stimulate the vasodilatation and limit further the reduction of blood flow.

As the H^+ can not cross the blood-brain barrier, so the neurological changes from acid-base imbalance are only due to the changes of PCO_2 which crosses the blood-brain barrier. The changes of CO_2 concentration on both the direction also causes changes in the pH of CSF on both the direction which impairs neuronal function and may lead to changes of mental status and coma. Increasing the pain threshold during hyperventilation are also probably the result of this. These clinical effects are more pronounced in respiratory acidosis or alkalosis than metabolic acidosis or alkalosis, because CO_2 originating from respiratory acidosis rather than H^+ originating from metabolic acids (H^+) is permeable to blood-brain barrier. Cerebral metabolism increases with acidosis and is maximum at pH of 7. But CO_2 has little direct effect on cerebral metabolism.

Respiratory acidosis causes hypothermia. It is due to the impairment of function of central thermoregulation centre and also due to the cutaneous vasodilatation, increasing heat loss.

Acidosis also causes an increase in the level of circulating catecholamines and stimulation of the sympathetic nervous system. Epinephrine is released from the adrenal glands and norepinephrine is released from the nerve terminals. In mild acidosis, this elevated catecholamine level tend to counteract the direct depressant effects of acidaemia on organ function. However, in severe acidosis the cellular response to catecholamine stimulation decreases and the direct depressant effect of acidosis on

cellular function becomes more apparent, despite the increased catecholamine levels.

Effects on Enzymic Activity

Each enzyme has its optimal pH level for its optimal activity. Again the cellular functional integrity depends upon the balance of activity of different intracellular enzymes. So if the pH varies beyond its normal limits, then enzymic chaos results and the cellular functions are deranged. This is because the activity of some enzymes are enhanced, while that of others are reduced.

Renal Effects

The response of renal vasculature to acidosis is vasoconstriction. As acidosis worsens, the renal vascular resistance also gradually increases and blood flow decreases. This renal vasoconstriction is the ultimate response after a balance between the direct, indirect and systemic effects of acidosis on renal vasculature. Metabolic acidosis causes increased renal vascular constriction than the respiratory acidosis for an equal change of pH. This is because increased PCO_2 in respiratory acidosis increases the availability of CO_2 to cross the cell membrane and relaxes the vascular smooth muscle cells, reducing the intracellular pH. Catecholamine mediated vasoconstriction of renal vasculature predominates over the vasodilating effect of acidosis (Fact file - VI)

Uteroplacental Effects

The acid-base disturbances affect the foetus in two ways − directly and indirectly. Directly the acid-base disturbance acts on the foetus through changes of PCO_2, as CO_2 is readily diffusible across the placenta. Passage of H^+ and HCO_3^- through the placenta is very slow and, therefore, metabolic acidosis or alkalosis will cause little change in foetal pH for several hours. The acid-base disturbances indirectly acts on the foetus through the changes in placental blood flow. The changes in foetal pH also produce the similar effects in foetal organ function as seen in adult. The direct effect of acidosis on the uteroplacental blood flow is vasodilatation. But, in severe acidosis, the overall effect on uterine blood flow is minimum. This is because the vasodilating effect of acidosis is opposed by the vasoconstricting effects of sympathetic stimulation by acidosis.

The direct effect of alkalosis on uteroplacental vasculature is vasoconstriction. Alkalosis also causes a leftward change in the maternal O_2-Hb dissociation curve which increases the affinity of maternal - Hb for O_2 and less delivery of it to the foetus. So, severe maternal alkalosis causes foetal hypoxaemia and foetal acidosis due to the combined effects of uteroplacental vasoconstriction and decreased O_2 delivery to the foetus.

Effects on Ca^{2+} and K^+

There are three forms of Ca^{2+} in plasma. Approximately, 50% of plasma Ca^{2+} remains in unionised form and bound to plasma protein which is available for diffusion into the tissues. Another 45% of the plasma calcium remains in ionised form and chemically active. Remaining 5% plasma Ca^{2+} present as nondiffusable form, but bound to other

FACT FILE - VI

Intracellular pH

Attempts have been made to measure the intracellular pH (pHi) by inserting microelectrodes with tips smaller than 1 micron in diameter into the cell. Rough estimations of intracellular pH also can be made after the administration of indicator drugs or by examining the rates of pH dependent intracellular enzymic reactions. But all these methods, currently available, are open to methodological criticism. In addition, it is unlikely that the cells of all parts of the organism or indeed all parts of the same cell, are at the same pH level.

Neverthless, many studies have shown that during normal healthy circumstances the intracellular pH is roughly related to the extracellular pH (pHe), but is always lower than it i.e. when pHe is 7.4, the pHi is usually less than 7.

During acid-base disturbances the pHi: pHe ratio may alter. CO_2 is freely permeable across the cell membranes, so that respiratory changes are reflected by similar changes in pHe and pHi ratio. But the highly ionized substances such as HCl and $NaHCO_3$ do not cross the cell membrane. So, changes in their extracellular concentration have a negligible effect on pHi and pHe ratio.

Changes in the intra: extracellular ratio of the electrolytes such as sodium and potassium also do alter the ratio of pHi: pHe. However, as the concentration of H^+ is one-thousand to one-hundred-thousandth of the concentration of K^+, so the changes are not the result of a one to one exchange across the cell membrane. Moreover the total replacement of intracellular H^+ by extracellular K^+ would produce no measurable change in K^+ concentration. Neverthless in potassium deficiency the intracellular cation deficit is partly compensated by the movement of H^+ resulting in extracellular alkalosis and intracellular acidosis.

Cerebrospinal Fluid pH

The pH of CSF is controlled within very narrow range than the rest of the ECF of body. Compared with the arterial blood the CSF pH is lower by 0.1 units and the PCO_2 is higher by 7 to 9 mm of Hg, but the bicarbonate concentration is similar. As the elevation of PCO_2 increases the cerebral perfusion thus it eliminates more CO_2. So, the blood-brain PCO_2 difference is decreased in hypercapnia and increased in hypocapnia.

The CSF acid-base status can be modified only by the changes in PCO_2 of CSF. So the changes in metabolic acid-base status are not mirrored in the pH of CSF, because the blood-brain barrier is relatively impermeable to H^+ and HCO_3^-, although CO_2 equilibration is rapid. Consequently, respiratory acid-base disturbances cause an plasma equivalent CSF change. So, during long-standing metabolic disturbances, lasting several hours and days, the pH of CSF remains almost unchanged, whilst the change of it in respiratory acidosis or alkalosis is corrected within hours. The compensation for respiratory change is accompanied by a change in HCO_3^- (not H^+) of CSF, so that the pH of CSF returns towards normal values. Although occasionally incomplete, such compensation for respiratory disturbances and the minimal response to non-respiratory changes, result in the relative constant pH of CSF. But till now, the parts played by the active and / or passive mechanism in the adjustment of HCO_3^- of CSF are so far uncertain. Similarly, the role of the brain cells in generating HCO_3^- is not known.

plasma components. In acidosis, H^+ ions compete for the negatively charged binding site of albumin where Ca^{2+} is attached. Thus, H^+ displaces the Ca^{2+} from its binding site and increases its ionised serum level. Reversly, alkalosis causes an increase in the available protein binding sites and reduction of ionised Ca^{2+} concentration with hypocalcaemia. This causes tetany or mild disturbances in cardiac contractility.

Serum K^+ and pH levels are usually inversely related. So, when pH falls plasma K^+ level rises and vice versa. In acidaemia, H^+ enters the cell along the concentration gradient and displaces the intracellular K^+ to maintain the intracellular electrical neutrality. K^+ comes out of the cell and causes hyperkalaemia. It is estimated that for each 0.1 unit change in plasma pH causes 0.6 mmol/L change in K^+ concentration in plasma. But this relation is not always linear.

PRACTICAL APPROACH

1. pH 7.39
   $PaCO_2$ 43 mm of Hg
   PaO_2 90 mm of Hg
   HCO_3^- 25 mEq/L
   This patient has normal acid-base balance or fully compensated any acid-base disorder. History and clinical examination will suggest.
2. pH 7.41
   PaO_2 64 mm of Hg
   $PaCO_2$ 40 mm of Hg
   HCO_3^- 23 mEq/L
   SaO_2 90%
   BE 0
   This patient has normal acid-base balance or near fully compensated any acid-base disorder with mild hypoxaemia.
3. pH 7.20
   $PaCO_2$ 80 mm of Hg
   PaO_2 82 mm of Hg
   HCO_3^- 26 mEq/L
   BE 0
   SaO_2 92%
   This patient is suffering from uncompensated severe respiratory acidosis with no hypoxia. Uncompensated because HCO_3^- within normal range.
4. pH 7.33
   $PaCO_2$ 66 mm of Hg
   PaO_2 75 mm of Hg
   HCO_3^- 34 mEq/L
   This patient has partially compensated respiratory acidosis with mild hypoxia.
5. pH 7.39
   $PaCO_2$ 55 mm of Hg
   PaO_2 60 mm of Hg
   HCO_3^- 38 mEq/L
   This patient has completely compensated respiratory acidosis with moderate hypoxia.
6. pH 7.50
   $PaCO_2$ 30 mm of Hg
   PaO_2 100 mm of Hg
   HCO_3^- 25 mEq/L
   This patient is suffering from uncompensated respiratory alkalosis. Respiratory alkalosis because $PaCO_2$ falls. Uncompensated because HCO_3^- does not rise. It is within normal range.
7. pH 7.42
   $PaCO_2$ 32 mm of Hg
   PaO_2 98 mm of Hg
   HCO_3^- 20 mEq/L
   The patient has compensated respiratory alkalosis. Respiratory alkalosis because $PaCO_2$ falls to 32 mm of Hg and compensated because HCO_3^- comes down.
8. pH 7.44
   $PaCO_2$ 25 mm of Hg
   PaO_2 99 mm of Hg
   HCO_3^- 20 mEq/L
   This patient has partially compensated respiratory alkalosis. If it is fully compensated, then HCO_3^- is expected to fall more.
9. pH 7.13
   $PaCO_2$ 42 mm of Hg
   PaO_2 140 mm of Hg
   HCO_3^- 14 mEq/L
   This is a case of uncompensated metabolic acidosis. Acidosis and uncompensated because the present pH value is far below the normal value. Metabolic acidosis because only the HCO_3^- falls far below the normal range. Uncompensated because $PaCO_2$ does not change. In compensated stage it will fall.
10. pH 7.26
    $PaCO_2$ 30 mm of Hg
    PaO_2 130 mm of Hg
    HCO_3^- 10 mEq/L
    This is a case of partially compensated metabolic acidosis with hyperoxaemia. Metabolic acidosis because the level of HCO_3^- fall with the fall of pH. In a case of fully compensated stage the formula for expected $PaCO_2$ is: $(1.5 \times HCO_3^-) + 8 \pm 2$. So, here if it was a fully compensated metabolic acidosis, the expected $PaCO_2$ is: $(1.5 \times 10) + 8 \pm 2 = 23$ m Eq/L. But here $PaCO_2$ falls up to 30 mm of Hg. So, it is partially compensated.
11. pH 7.55
    $PaCO_2$ 38 mm of Hg
    PaO_2 120 mm of Hg
    HCO_3^- 34 mEq/L
    This is a case of uncompensated metabolic alkalosis with hyperoxaemia. Metabolic alkalosis because pH is elevated and HCO_3^- is raised. Uncompensated because $PaCO_2$ is not raised. It is within normal range.
12. pH 7.55
    $PaCO_2$ 50 mm of Hg
    PaO_2 84 mm of Hg
    HCO_3^- 50 mEq/L
    This is a case of partially compensated metabolic alkalosis. Why it is metabolic alkalosis is easily understood. In a fully compensated case the formula for expected rise of $PaCO_2$ is: $6 \times (\text{measure } HCO_3^- - 24) + 40$. So, here if it is a fully compensated metabolic alkalosis, then the expected $PaCO_2$ should be: $.6 \times (50 - 24) + 40 = .6 \times 26 + 40 = 55.6$ mEq/L. But here $PaCO_2^-$ is elevated only up to 50 mm Hg. So, this metabolic alkalosis is partially compensated.

9 Water Balance

INTRODUCTION

Water is the most vital and abundant component of the body. It constitutes about 60 to 70% of our total body weight or lean body mass (LBM) (It is better to use the term LBM than total body weight.) within which the major cations like Na^+, K^+, Ca^{2+}, H^+, Mg^{2+} and anions like Cl^-, PO_4^-, HCO_3^- and proteins are dissolved. Without water there will be no form of life. It forms the intracellular medium within which the metabolic reactions of cell, responsible for life, takes place and also forms the extracellular medium through which the transport and exchange of different solutes between the intracellular and extracellular spaces take place. Water deprivation brings about death more earlier and easily than that of food. If water is given instead of food, then life may continue for several weeks by the loss of body fat and tissue proteins.

Total body water (TBW) in an average human being weighing about 70 Kg varies between 45 to 50 litres it is 60 – 70% of 70 kg. In female, it is 10% less than male. So, in female the TBW constitutes about 50 to 60% of lean body mass (LBM). Therefore, TBW in female weighting about 70 Kg is 40 to 45 litres. But the above values vary mostly with the relative degree of obesity of an individual, because body water content is inversely related to the adiposity of organism. Hence, as female has more body fat, it contains less TBW in relations to LBM than male and in a lean person the value of TBW is higher thant that of an obese person. Therefore, in general woman contains more fat and less water than man.

The total water of a body is considered to be distributed within two main components: the intracellular (IC) and the extracellular (EC). The water of intracellular component constitutes about 55% of TBW or 40% of total (or lean) body weight (LBM). The remaining 45% of the TBW constitutes the extracellular fluid component or 20% of total body weight or lean body mass (LBM). Of this 20% extracellular body water, 15% remains in the interstitial compartment and 5% remains in the intravascular compartment. The cell membrane actually provides the boundary between these two IC and EC components (Table 9.1).

The IC fluid component represents the sum of fluid contents of all the cells in a body. It is neither a continuous nor a homogenous phase. The cell membrane plays an important role, controlling the IC and EC fluid volume and their composition. This is done in the following way. A membrane bound ATPase dependent Na^+-K^+ pump exchanges K^+ inside the cell and Na^+ outside of the cell in 2:3 ratio. This is due to the relative impermeability of cell membrane to Na^+ in relation to K^+. Therefore, Na^+ is concentrated in the EC fluid and is the most important determinant factor for extracellular osmotic pressure and osmolality. Whereas K^+ is concentrated in the IC fluid and acts as the most important determinant factor for IC osmotic pressure and osmolality. This IC and EC osmotic pressure and osmolality determines the IC and EC fluid volume. Protein (anion) is a nondiffusible solute and impermeable to cell membrane. This results in high IC protein concentration and is also responsible for intracellular (IC) osmotic pressure and osmolality. The unequal exchange of 2 ion of K^+ going into the cell against 3 ion of Na^+ going out of the cell by the Na^+-K^+-ATPase pump, situated on the cell membrane, maintains this relative IC hyperosmolar condition and is critical for functions of the cells. Therefore, interference of this Na^+-K^+-ATP pump due

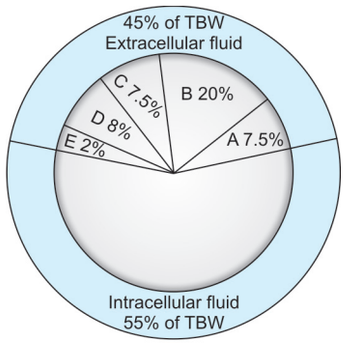
Table 9.1: Percentage of body fluid compartment of a 70 Kg adult male

Compartment	*Fluid as percent of total body wt (%)*	*Fluid as percent of total body water (%)*	*Total fluid volume (L)*
Intracellular	40	55	28 L
Extracellular	20	45	14 L
(i) Interstitial including connective tissue, bone, lymph, cartilage, transcellular etc.	15	37	10.5 L
(ii) Intravascular	5	8	3.5 L
Total	**60%**		

to any cause such as ischaemia, hypoxia, poison, etc; leads to progressive swelling of cells and ultimately its death.

Like intracellular (IC) fluid component, the extracellular (EC) fluid component is also not a continuous or homogenous phase. Rather, it is a heterogenous collection of fluids. It is postulated that 55% of TBW is present in the IC component and the rest 45% of TBW is in the EC component. The EC fluid component is again divided into the following subcompartments : interstitial fluid and lymph (20%), intravascular fluid (8%), fluid in dense connective tissue and cartilage (7.5%), inaccessible bone water (7.5%), transcellular water (2%). The transcellular fluid is the part of EC fluid component which is separated from other extracellular fluid by an epithelial membrane. Thus, the transcellular fluid includes : CSF, joint or synvial fluid, intraocular fluid, fluid in pleural or pericardial or peritoneal cavity, fluid in the duct of digestive gland, intraluminal fluid of GI system, etc. The EC fluid provides medium for different electrolytes, nutrients, waste products, enzymes, hormones, gases, etc, to move from one place of its origin to another. Therefore, maintenance of EC fluid volume is also very critical. The Na^+ is quantitatively the most important EC fluid cation and is the major determinant factor for the EC fluid volume and pressure which is parallel to the intravascular fluid volume and pressure. The changes in total body Na^+ content is, therefore, related to the EC and intravascular fluid volume and pressure. The total body Na^+ content further depends on its intake through oral or intravenous route and excretion through renal, and extrarenal route (Fig. 9.1).

Normally, very little amount of interstitial fluid remains in free form, because it is usually present in chemical association with an extracellular substance, called proteoglycans forming a gel. This interstitial or tissue fluid is formed from the plasma by the process of diffusion



A = Dense connective tissue and cartilage
B = Interstitial fluid and lymph
C = Bone water
D = Intravascular compartment
E = Transcellular water
TBW = Total body water

Fig. 9.1: Schematic representation of distribution of body water in different compartment (in % of TBW)

or filtration through capillaries. This fluid occupies the intercellular space and forms the connecting link for the transport of nutition, gases and metabolic end products between the blood capillaries, tissue cells and lymph. It constitutes the internal enviornment of body which surrounds the cells. Interstitial fluid is also derived from the cells due to intracellular activities. The amount of interstitial fluid formed from blood depends upon : (i) the capillary permeability, (ii) the differences of hydrostatic pressure between capillary and the interstitial fluid, (iii) the difference of collidal osmotic pressure of blood and interstitial fluid. It is obvious that anything that increases the capillary permeability will also increase the amount of interstitial fluid that is formed. Regarding the blood presure and osmotic pressure, it is known that at the arterial end of capillary, the average blood pressure (hydrostatic pressure) is about 32 mm of Hg and at the venous end it is about 10 mm of Hg. On the other hand, the colloidal osmotic pressure of blood at both the ends of capillary is same and is about 25 mm of Hg. Therefore, at the arterial end the net filtration pressure is 32 − 25 = +7 mm of Hg which is directed towards the interstitial fluid. On the otherhand, at the venous end, due to fall in blood or hydrostatic pressure the net filtration pressure is negative which is 10 − 25 = − 15 mm of Hg and in the opposite direction i.e. from interstitial fluid to the capillary. Thus, at the arterial end of capillary water, electrolytes, nutrients, gases and the other solutes pass from the intravascular to interstitial compartment and at the venous end they pass in opposite direction and maintain the homeostasis of water in interstitial compartment. Moreover, the magnitude of these forces differs at the various tissue beds. Arterial capillary pressure is determined by the precapillary sphincter tone. When the tone of sphincter increases, there is less flow of blood through the capillaries and the capillary pressure is reduced. Thus, some capillaries which require high pressure (e.g. glomeruli) maintain low precapillary sphincter tone, while high sphincter tone is maintained for low pressure capillaries of muscles (Table 9.2).

The amount of interstitial fluid formed from the tissue cells, depends upon the degree of metabolic activity of the cells. It should be noted that the tissue cells produce water as an end product of the carbohydrate, fat and protein metabolism.

Table 9.2: Composition of fluid in different compartment of body

Intracellular (mEq/L)				↔	*Interstitial (mEq/L)*				↔	*Intravascular (mEq/L)*			
Na^+	10	Cl^-	4		Na^+	140	$Cl-$	110		Na^+	140	$Cl-$	100
K^+	140	PO_4^{2-}	100		K^+	4	HCO_3^-	30		K^+	4	HCO_3^-	26
Ca^{2+}	1	SO_4^{2-}	2		Ca^{2+}	3	PO_4^{2-}	2		Ca^{2+}	3	PO_4^{2-}	2
Mg^{2+}	40	HCO_3^-	10		Mg^{2+}	3	SO_4^{2-}	1		Mg^{2+}	3	SO_4^{2-}	1
		Protein (or 16 gm/dl)	50				Protein	6				Protein (or 7 gm/dl)	24

This metabolic water is added to the already existing interstitial fluid. More the degree of activity, more will be the metabolic water formed and consequently the amount of interstitial fluid will increase. Two important exceptions of the usual haemodynamic events of the capillary pressure are : (i) the capillaries of lungs where hydrostatic blood pressure is about 0.6 mm of Hg and (ii) the capillaries of kidney where glomerular hydrostatic pressure is about 60 to 80 mm of Hg. If hydrostatic blood pressure is increased within capillaries, then it will interfere the return of water to the venous end of capillaries and if it is excess than the amount which is drained by lymphatics then it will result in excess accumulation of interstitial fluid, causing oedema.

It is believed that the composition of interstitial fluid is same as that of the lymph, except that its protein content is negligible. So, its colloidal osmotic pressure is very low. The composition and volume of interstitial fluid is regulated by the constant interchange of it between the blood and lymph. The specific gravity of interstitial fluid varies between 1.015 to 1.023. It may contain few erythrocytes. But regarding the white cells, the interstitial fluid contains a good number of lymphocytes and a small number of granulocytes. Blood proteins and nutrient contents of it are very low. It does not contain platelets, but may also clot very slowly. It contains higher concentration of waste products, but glucose, salt and water contents of it are more or less same as that of plasma (Fact file- I).

The interstitial fluid constitutes the internal media or enviornment in which the tissue cells are bathed. The cells draw in O_2 and nutrition from this fluid and excrete their metabolites into it. Hence, interstitial fluid may be regraded as the medium which supplies all the immediate requirement of the cell. Interstitial fluid also acts as a great reservoir of water, salts, nutrition, etc. This function is very important. Because in any condition, when the blood volume is increased or diminished, then the new physical forces are set up by which the blood volume is kept constant with the help of this tissue reserve. For example, during haemorrhage the capillary pressure becomes very low and goes below the colloidal osmotic pressure of the capillary which remains same. Due to this relative higher colloidal osmotic pressure in the capillaries water is drawn in from the tissue or interstitial space, so that blood volume is restored. When water is drawn away from blood, such as due to diuresis, excessive sweating, diarrhoea etc, blood volume and blood pressure will be lowered. But the plasma proteins will be more concentrated. This will increase the colloidal osmotic pressure of blood. This increased osmotic pressure of plasma and reduced blood pressure will increase the rate of absorption of water from the tissue fluid and thus the blood volume will be kept constant. On the other hand, when blood volume increases as for instances by IV infusion of large quantities of isoosmotic saline, then the fluid will pass out into the tissue spaces due to two causes: (i) saline will dilute the colloids and reduce the capillary colloidal osmotic pressure and at the same time, (ii) by increasing the volume of blood will raise the blood pressure, and will cause more filtration. Both these factors will cause more fluid to run out into the tissue spaces, until blood volume comes back to the original level.

FACT FILE - I

The capillary endothelium acts as freely permeable membrane to water, anions, cations and many diffusible substances such as urea, glucose, amino acids, etc, except protein. As a result the solute concentration between the plasma and interstitial fluid is same. Each contains sodium and chloride as the principle cations and anions, respectively. As protein is a non diffusible anions, it remains in plasma at a higher concentration. The concentration of Cl– is slightly higher in interstitial fluid. This is due to maintain electrical neutrality which is called Donnan equilibrium.

The intravascular fluid compartment is restricted to the vascular space, enclosed by endothelium and the fluid in it is called plasma. Most electrolytes, glucose, amino acids, enzymes, hormones, water, etc, can freely pass between the plasma and the interstitial space, resulting in nearly identical composition of interstitial fluid and palsma. But protein can not pass freely between the plasma and interstitial space. This is due to tight intercellular junction between the adjacent endothelial cells. As a result plasma protein mainly albumin remain in high concentration in the intravascular compartment and act as only osmotically active solute.

Different Nomenclatures and Definitions

To understand the water and electrolyte balance properly, it is mandatory to know the concentration of electrolytes and other solutes in the solution accurately. Usually, the concentration or quantity of solutes in a solution is expressed as percentage, gram moles, equivalent, etc; per litre. Furthermore, to complicate the things the concentration of solution can be expressed as quantity of a solute per volume of solution or per weight of solvent. At present the concentration of solution is expressed by the system of international unit (SI). These systems of international units are : molarity, molality, osmolality, osmolarity, etc.

According to Avogadro's principle the number of molecules represented in one mole of substance is 6.023×10^{23}. A mole or gram molecular weight (i.e. molecular weight in gram) is the amount of substance equal to its molecular weight expressed in grams. When the amount equal to the molecular weight in grams of a solute is dissolved in 1 L of solvent, then it is called the one molar (M) solution. For example, when 98.016 gm of H_2SO_4 (molecular weight of H_2SO_4 is 98.016) is dissolved in 1 L of water, then it produces one molar solutions. When molecular weight in gram

of a solute is dissolved in 1 Kg of solvent then it is called one molal (m) solution. Therefore, the number of moles of a solute per litre of solution is called molarity. On the otherhand, the number of moles of a solute per kilogam of solution is called molality.

Osmosis refers to the movement of solvent (e.g. water) across a semipermeable membrane into the region where there is higher concentration of non diffusible solute. This non diffusible solute is known as the osmotically active particles. The term osmosis and osmoles is only applicable to non diffusible solutes. The amount of this non diffusible (or non dissociable or osmotically active particles) solutes present in solution is expressed as osmoles, like moles. One osmole of non dissociable solute is equal to the 1 mole or molecular weight in gram of dissociable solute. The number of osmoles of nondissociable solute per litre of solution is called osmolarity. On the otherhand, the number of osmoles of non dissociable solute per Kg of solvent is known as osmolarity (Fact file- II).

The relation between the osmole and mole is that when each mole of dissociable solute ionizes then it results in n × osmole, where n represents the number of different types of ions produced by dissociate solutes. For example, when one mole of highly dissociable solutes such as NaCl is dissolved in water it produces 1 osmole of Na^+ and 1 osmole of Cl^- or 2 osmole of ions. Therefore, one osmole (osm) of dissociable solutes (such as NaCl) is equal to the one mole of that substance, divided by the number of freely moving particles or ions that each molecule of that substance librates in solution. Therefore, 1 mole of NaCl = 2 osmol of NaCl. Hence 1 osmol of NaCl = ½ mole of NaCl. In another exampl, one mole of Na_2SO_4 would dissociate into Na^+, Na^+ and SO_4^{2-}, supplying 3 osmol. So, 1 osmol of Na_2SO_4 is 1/3 mole of it. Therefore, osmolality is the number of particles (different ions) per litre of water and osmolarity is the number of particles per Kg of water.

The molecular weight of glucose is 180. Therefore, one mole or one gram molecular weight (gm mole) of glucose is 180 gm. Hence, if 180 gm of glucose is dissolved in 1 litre of water, then this solution will represent molar concentration of 1 mol/L and as the glucose is non dissociable and non diffusible solute (or osmotically active particles), so the solution will also represent osmolar concentration of 1 osmol/L. On the otherhand, NaCl is a dissociable solute. It ionizes in solution and each ion represents an osmotically active particles. Molecular weight of NaCl is 23 + 35.5 = 58.5. Therefore, if 58.5 gm of NaCl is dissolved in 1 litre of water then the molarity of this solution is 1 mol/L and osmolarity is 2 osmol/L.

In body fluids, the concentration of different solutes are much lower. So, they are expressed as millimole per litre (m.mol/L) which is equal to the one thousandth of one mole per litre. Thus, 1 mol of NaCl is 58.5 gm and 1 m.mol = 58.5 mg.

In vivo or in the body the dissociation of dissociable solutes remains incomplete. So, a solution of NaCl containing 1 m.mol/L of solute contributes osmolarity slightly less than the theoretical 2 m.osmol/L.

Equivalent is also commonly used as measuring unit for solutes that ionizes in solution and produces ions. Actually it is the measuring units of ions in a solution produced from dissociable solutes. The number of equivalent of each ion is the number of moles of these ions divided by its valency or charge. Thus, 1 mole (M) solution of NaCl yields 1 equivalent of Na^+ and 1 equivalent of Cl^- per litre of solution. Hence, one equivalent of Na^+ = 23 and one equivalent of Cl^- = 35. Similarly, one molar solution of $CaCl_2$ yields 2 equivalent of Ca and 2 equivalent of Cl^-, but 1 equivalent of Ca^{2+} is 40 ÷ 2 = 20. Gram equivalent is the molecular weight in gram divided by the number of valency of ion present or equivalent which is expressed in gram. One milli equivalent (mEq) is one thousandth of one equivalent.

The concentration of solution is also measured by percentage. This percentage can be expressed as percent by weight or present by volume. Weight in grams of a solute per 100 gms of solution is known as percent by weight and the same amount of solute in gram dissolved in 100 ml of solution is known as percent by volume.

Electrolytes and Colloides

The electrolytes are the compounds which can be dissociated into anions and cations, when it is in molten state or in solution. The example of electrolytes are: salts, acids, bases, etc. On the otherhand, the non electrolytes are the compounds which can not be dissociated in its solution of water, after the passage of currents.

When sugar, urea, NaCl, etc, are dissolved in water, they result in a clear solution. This is called true or crystalloids solution. On the otherhand, when the protein, starch, glycogen, etc, are dissolved in water they result in thick, opalescent solution. This is called colloidal solution. But, the actual difference between a crystalloid and colloid solution depends on the size of the molecules of solute in the solvent. If the size of the molecules of a solute is greater than 200 mμ, they remain as suspension. While, if the size of the molecules of a solute is less

FACT FILE - II

Tonicity is a physiological term, whereas osmolality is a chemical term and may be confused with the previous one. But, it should not be done. The critical difference between these two terms is that all solutes contributes to the osmolality, but only solutes which do not cross the cell membrane is responsible for tonicity. Because, the term tonicity is used to describe the osmotic pressure created by nondiffusible solid of a solution in relation to that of plasma. The substances such as urea, glucose, ethanol, methanol, etc, can diffuse across the cell membrane freely. Therefore, they do not alter the distribution of water between the IC and EC fluid compartments and can not contribute to tonicity. But, they contribute to osmolality. Whereas, the substances such as mannitol and sorbitol can not cross the cell membrane and is only restricted to the EC fluid compartment. Therefore, they contribute both to the osmolality and tonicity.

than 1 mμ they remain as true clear solutions. Therefore, the size of the molecules in a colloid solutions varies between 1 to 200 mμ. To understand the difference between a crystallod and a colloid one should have a clear idea regarding the forces that help the solute particles to stay in solution which are roughly as follows :

i. Inherent movement of the solute particles i.e. diffusibility of solute.
ii. Inherent movement of the solvent molecules which continuously dash against the solute particles and thus help to keep them in solution.
iii. Electric charge – positive or negative - carried by the solute particles which by constant attraction or repulsion also help to form uniform solution.
iv. Hydration or carrying water molecules with the solute molecules.

If the solute particles are very small (below 1 μm), then all these above mentioned forces will act to their maximum. Thus, it will result in a permanent true clear solution. Now, if the solute particles be gradually made larger and larger, their own movement or diffusibility will gradually be reduced and ultimately will be almost nil. Then, the other forces such as the dashing forces of the solvent molecules, electric charges, etc, will further try to keep the large solute particles somehow in solution and will be able to do so upto a certain extent. This is called colloid solution. If then the solute particles be made still larger (over 200 μm), then all the forces will completely fail and the solute particles will not go into solution at all. Then they remain in suspension or as insoluble state. Hence, if the relation between solute and solvent be studied as a series of phenomenon, it will be found that at one extreme end there is complete solubility or true crystalloid solution and at the other extreme end there is complete insolubility. While in the intermediate stages there will be a phenomenon of semi solubility. This is called the colloidal solution (Fact file- III).

FACT FILE - III

The difference between the IC and EC fluid compartment is that in IC fluid the principal cation is K+ and the principal anion is phosphate (PO42–). Further, there is high protein content inside the cell due to impermeability of it to the cell membrane. But the cell membrane is permeable to different ions, glucose, urea, water, etc. Therefore, there is continuous movement of water across the cell membrane and equalizes the osmotic pressure between the IC and EC fluid compartment. However, at equilibrium the osmolality between the IC and EC fluid compartment is not equal. This is also due to the active movement of water and diffusable particles across the cell membrane and produces any induced osmolal gradient. This is the fundamental principle which help to understand the physiology of fluid and electrolytes.

Thus, other factors remaining constant the real difference between a true crystalloid solution and colloid solution lies in the size of the solute particles and not upon their chemical nature. Hence, a colloid may be defined as a substance which by the reason of the size of its molecules is slowly diffusible rather than soluble in water and is incapable of passing through an semipermeable membrane. In this substance the solute particles are proportionally larger than the solvant molecules.

Method of Exchange of Substances Between Different Fluid Compartments

The exchange of different substances and water between the different fluid compartment in the body mainly occur by three processes. These are: filtration, diffusion and osmosis.

Filtration

It is the process by which undissolved particles are separated from a liquid through a membrane as a result of a mechanical force which is called the filtering force. It is done through a porous substance. This filtering force is either gravity or hydrostatic pressure which may be positive or negative. The important examples of filtration are: (i) absorption from the small intestine, (ii) passage of water, salts, food stuffs, etc. from the blood stream to the interstitial fluid, (iii) filtration in glomeruli.

Diffusion

Molecules of a substance are continuously in motion. This motion is least in the solids, intermediate in the liquids and maximum in the gases. When the two such substances are kept in contact or is separated by a membrane, the molecules of the two substances will pass into each other, until an uniform admixture is obtained. This spontaneous admixture of the molecules of the two substances due to their inherent molecular movement is called the diffusion. Anything that alters the molecular movement of the substances also alter the rate of diffusion, proportionally. The rate of diffusion of a substance across a membrane depends on: (i) the concentration of substances on the two sides of membrane, (ii) for charged substances the electrical potential across the membrane, (iii) permeability of these substances through the membrane, (iv) pressure difference between the two sides of the membrane, because pressure imparts the greater kinetic energy. In human some clinical examples of diffusion are: (i) absorption from intestine, (ii) exchange between plasma and red cells, (iii) exchange at the capillary bed such as nutrients, O_2, CO_2, metabolic waste products etc, (iv) exchange at the lung capillaries of O_2 and CO_2, etc.

Diffusion of substances through the cell membrane between the intracellular and interstital fluid take place by the following mechanism: (i) through different protein channels in the cell membrane, (ii) directly by diffusion through the cell membrane, (iii) by carrier protein situated on the cell membrane such as glucose, amino acids, etc. Water, O_2, CO_2 and many other different lipid soluble molecules diffuse through the cell membrane directly. Different ions such as Na^+, K^+, Cl^-, etc, diffuse the cell membrane poorly, because of the unfavourable voltage

potential across the membrane which is created by the Na^+-K^+ pump. Therefore, these ions can only diffuse by the help of specific protein channels.

The capillary endothelial cell wall is only 0.4 to 0.6 µm thick, consisting of a single endothelial cell layer situated on the basement membrane. The gap or cleft between the two adjacent endothelial cells is only 5 to 6 nm. Water, O_2, CO_2 and other many lipid soluble substances can diffuse directly through the endothelial cell membrane from both the sides which is governed by the hydrostatic and colloidal osmotic pressure of tissue and capillary. Only glucose, Na^+, K^+ and other water soluble substances with low molecular weight cross the intercellular clefts.

Osmosis

When the solute dissolved in water at two different concentrations are separated by a semipermeable membrane, then the diffusion of water, (but not the solute) from lower to higher concentration through this semipermeable membrane is called osmosis, provided the solute itself is not permeable to the membrane. The water moves on both direction, but from lower solute concentration to higher solute concentration is more. Then, a time will come when the movement of water molecules from both the side is same, so that no further alteration of volume of solution on any side of the membrane will take place. At this stage, the hydrostatic pressure of solution at the concentrated side neutralizes the attractive force of this higher concentrated solution for water molecules. This attractive force is called the osmotic pressure. This is the force under which a solvent moves from lower solute concentration to higher solute concentration, when a selectively permeable membrane separates these two solutions of different concentration. The osmotic pressure does not depend on the size of the molecules of solute, but upon the total number of discrete particles of solute per unit volume of solution. If the solute is ionisable, the osmotic pressure will be proportionaly more. If more hydrostatic pressure is applied on the side of the solution of higher concentration, then water will pass from higher concentrated solution to the lower concentrated solution, opposite to osmosis. This is called ultrafiltration.

If the two solutions are separated by a semipermeable membrane and have the same osmotic pressure, then they are called isotonic. But if one have the less osmotic pressure than another, then it is called the hypotonic and if one have higher osmotic pressure than another, then it is called the hypertonic. For example, 0.9 percent NaCl solution is isotonic with blood or plasma and commonly known as normal saline. A5 percent solution of glucose has also similar osmotic pressure like plasma and is isotonic. Therefore, these two solutions such as 0.9% NaCl and 5% dextrose is isotonic, but they are not isosmotic. Because, they have not similar number of solute particles per unit volume of solutions. Clinical examples of osmosis are: absorption from the intestine, exchange in the capillary bed, regulation of urine formation, reabsorption of CSF, etc.

Water Metabolism and Its Balance

Life first evolved in an aquatic medium. So, there will be nothing to be astonished that water is the most essential component of life. Of the three factors such as water, salt and food, water is the most important for survival of life. So, deprivation of water will kill a subject much earlier than deprivation of salt and food. It must be remembered that the water content of the body is derived from two sources: (i) from the food and drink, and (ii) from the cells as the end product of metabolism. The former is called as the exogenous water and the latter is called as the endogenous water. The body water remains in two states: (a) Free states i.e. not combined with anything. Most of the body water remains in this from. Various substances can remain dissolved in this form of water and be removed by ultrafiltration. (b) Bound water. This is very small in quantity and remains combined with colloids and other substances.

The endogenous water comes from the cells as an end product of metabolism. Almost the whole amount of H^+ ion coming from solid food is converted into water, but only about 5 gm of hydrogen is excreted in the form of ammonia, urea etc. Different food stuffs yield different amount of water. Its approximate figures are given below:

100 gm of fat gives 100 gm of water
100 gm of starch gives 50 gm of water
100 gm of protein gives 40 gm of water
100 gm of alcohol gives 120 gm of water

Water is continuously being lost and supplied to the body. But, still the total water content of the body is kept more or less constant, by maintaing a balance between the supply and loss. This indicates that there must be an efficient machinery for maintaing the water balance.

Water requirement and loss

The total water requirement of an adult under ordinary conditions is about 2500 to 3000 ml. This is about 1 ml per calorie of energy intake. Half of this quantity i.e. 1500 ml or ½ ml of water per calorie intake should be taken as free drinks.

Supply of water		
1. Drink		1400 ml
2. Solid food (all solid foods contain some water as free form)		800 ml
3. Metabolism		400 ml
	Total	2600 ml
Loss of water		
1. Kidney		1500 ml
2. Skin (visible and unvisible perspiration)		600 ml
3. Lungs		400 ml
4. Faeces		100 ml
	Total	2600 ml

The above figures are average and the approximate gain or loss by any one of these routes may rise or fall under various conditions. The loss of water through skin varies according to the temperature and the humidity of atmosphere and also upon

the amount of muscular exercise done. In hot climates and with exercise this excretion of water through skin may vary from 3 to 10 litres per day. Higher atmospheric humidity reduces the water loss through the skin. Water excretion by lungs also increases in hot dry weather. In diarrhoea, dysentry, cholera, etc, more water is lost through the faeces. While in condition of diuresis more water is passed out by the kidneys. The water secreted in the digestive juices is not lost. Because it is completely reabsorbed and about 5 to 7 litres of water circulate in this way per day. The loss of water through saliva and lacrymal secretions is negligible under normal conditions (Fig. 9.2).

Positive and negative water balance

Physiologically water balance is said to be positive in growing infants, children, convalescents, athlets, pregnant women, etc, who are storing water and building their body tissues. During positive water balance each gram of protein is laid down with about 3 gm of water. Whereas fat and glycogen are deposited with less amount of water. When diet is changed from higher fat to higher carbohydrate, then more water retention takes place and the balance becomes more positive.

Water balance is negative under the follwoing conditions: (i) when the subject is thirsty, (ii) when a preexisting oedema is clearing up due to diuresis, (iii) when diet is changed from high protein to carbohydrate and fat. In any condition of increased water loss, the relative proportion of Na^+ and K^+ content of the fluid which is going to lost will indicate whether the water is coming chiefly from the extracellular or the intracellular sources. The fluid with high Na^+ content will indicate extracellular source, whereas the fluid with high K^+ content will indicate intracellular source, provided intake of these two electrolytes remains constant.

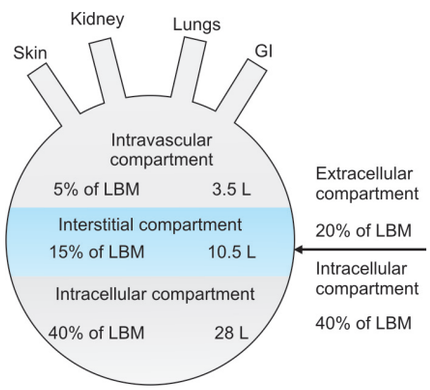


Fig. 9.2: Distribution of total body water (TBW) in the different compartment of body. (LBM = Lean body mass)

Regulation of Water Balance

Inspite of large amount of water is constantly appearing in and disappearing from the body, a fairly accurate balance is maintained between its gain and loss which indicates that there must be a strong regulating machinery. The mechanism which regulates this water balance in our body is very intricate and is not yet fully known. However, the following factors are closely involved in it. These factors are: endocrine, renal, respirations and thirst.

Endocrine

A number of endocrines take part in water regulation. These are posterior pituitary, hypothalamus and adrenal cortex.

Posterior pituitary and hypothalamus

From the posterior pituitary gland antidiuretic hormones (ADH) or vasopressin is secreted which has got immence influence upon the water balance. It increases the reabsorption of water from the distal renal tubules and thus reduces the urine volume. It is very interesting to note that the secretion of this hormone is controlled by the water content of the body. Excess of water depresses, while dehydration stimulates the secretion of this hormone. This is constituted through hypothalamus. The hypothalamus controls the secretion of ADH from posterior pituitary through the supra-optico-hypophyseal tract. Excess of water dilutes blood and reduces the osmolality of ECF as a result of which the hypothalamus is depressed (the specialised neuron in the supraoptic and paraventricular nuclei of the hypothalamus are very sensitive to the osmolality of ECF) leading to less secretion of ADH from the posterior pituitary and consequently diuresis is produced with the maintenance of blood volume and osmolality of tissue fluid. When body water is reduced, osmolality of ECF increases and subsequently hypothalamus is stimulated. Thus, more ADH is secreted and consequently urine volume is reduced with maintenance of blood volume and osmolality of tissue fluid. Hypothalamus also controls the formation of urine by regulating the renal circulation and general blood pressure through sympathetic nervous system.

Adrenal cortex

Adrenal cortex secretes aldosterone which plays an important part in the maintenance of water balance of body. The secretion of aldosterone is controlled by the angiotension II and also by the high serum K^+ and low serum Na^+ level. The aldosterone regulates the water balance through release of ADH from posterior pituitary, mediated through serum K^+ and Na^+ level, causing retention of water and thus increase the blood volume. In adrenal cortical insufficiency there is decreased reabsorption of Na^+ and as a result more Na^+ is lost through the urine. This causes increased reabsorption of K^+. Along with the decreased reabsorption of Na^+ the reabsorption of Cl^- is also depressed. Therefore, there is consequential changes in the composition of body fluids. The intracellular crystalloid osmotic pressure exceeds that of the extracellular crystaloid osmotic pressure and water flows from the extracellular fluid to the intracellular fluid. Plasma volume decreases and there is haemoconcentration.

Renal

In physiological condition when water content of the body rises such as by excess

water intake or by the infusion of saline, etc, then kidneys excrete more water. This effect is due to: (i) Incresed blood volume and consequently the rise of blood pressure and thereby increased filtration pressure. (ii) Dilution of plasma protein reducing colloidal osmotic pressure and consequently increasing the available filtration pressure. (iii) Increasing the number of active glomeruli which was dormant till now. (iv) Depressing the degree of water reabsorption by the renal tubules through direct inhibition of hypothalamus and pituitary ADH mechanism. (v) Increase of central blood volume enhances the urine output through the inhibition of secretion of ADH. It is also suggested that inhibition of ADH secretion takes place reflexly through the stimulation of stretch receptors present in the left atrial wall. (vi) Less secretion of renin, angiotensin II, aldosterone and decreased absorption of water. Among these, the forth and sixth factors are most important in regulating the water excretion by the kidneys under physiological conditions.

Lungs and skin

These channels also take considerable part in regulation of water balance by excreting the variable amounts of water.

Thirst

When more fluid is lost such as in diarrhoea, vomiting, diuresis, sweating, haemorrhage, etc, then the subject feels thirsty and drinks water. So, thirst may be defined specifically as the 'hunger for water'. In this way the amount of lost water is replenished. In hybernating animals metabolism is so slow that the water produced by the oxidation of food stuffs within the cell is enough to equalise the water loss. Hence, under such condition no thirst is felt. During thirst drinking is stimulated by two types of stimulli acting on the hypothalamus: (i) rise in ECF osmolarity even with or without any change in blood volume, and (ii) a fall in blood volume even with or without any change in ECF osmolarity (Fig. 9.3).

Osmoreceptors in the lateral preoptic area of the hypothalamus are very sensitive to the changes in blood volume or extracellular osmolarity. Activation of these receptors by decrease in blood volume or increase in ECF osmolarity induces thirst and causes individual to take water. This is the major defense mechanism of body against hypovolaemia and hyperosmolarity. Because it is the only mechanism that increases water intake voluntarily. On the otherhand, ADH and aldosterone is the protective mechanism and acts only when the excess water has been accumulated or lost. Contrary, when an appropriate amount of water has been drunk the sensation vanishes because of the acitivity of oral and gastric receptors. Unfortunately, the thirst mechanism is only operative in conscious patient who is capable of drinking.

Plasma Osmolality

There is a great confusions regarding the use of apparent inter changable terms such as the osmolarity (measured in osmol/L) and osmolality (measured in osmol/Kg). The term osmolality is defined as the number of osmoles per unit of total weight of solvent in Kg. Whereas, the term osmolarity is defined as the number of osmoles per unit of total volume of solutions in litre. Therefore, unlike osmolarity, osmolality is not affected by the presence of various solutes in solution (as it refers only one solute). In plasma the osmolality and osmolarity is same and varies between 280 to 300 m.osmol/Kg and 280 to 300 m.osmol/L respectively. This numerical equivalent is explained by the almost negligible amount of solute, contained in biological fluid and by the fact that most osmotically active particles which are dissolved in water has density of one. Therefore, in plasma m.osmol/L is equal to m.osmol/Kg, but still the more accurate term to use in clinical practice is osmolality.

The osmolality of plasma and ECF is equals (as they remain in equilibrium) and is equivalent to the sum of the concentration of all dissolved solutes, but Na^+ (cation) and its anion such as Cl^- and HCO_3^- constitutes the major (90%) osmotically active particles in plasma. Plasma glucose and urea make a smaller contribution. Therefore, plasma osmolality (Posm) is estimated from the follwoing formula:

Posm = Na^+ conc. + plasma glucose conc. + plasma urea conc.

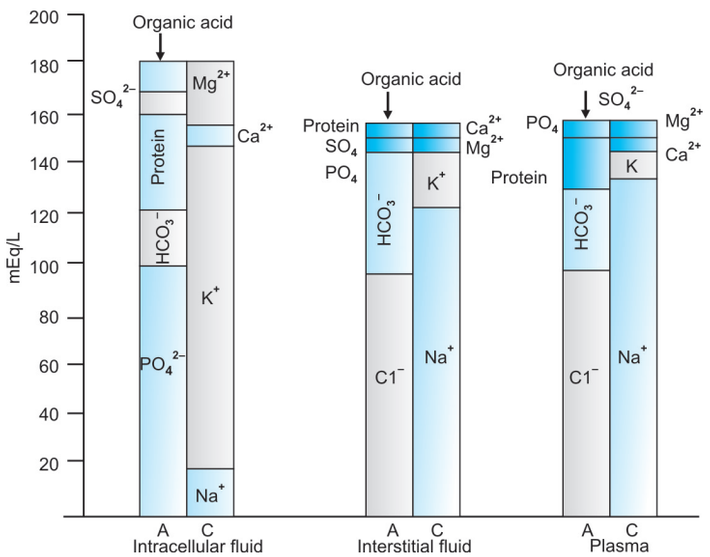


Fig. 9.3: This figure shows the distribution of electrolytes in intracellular fluid, interstitial fluid and plasma. A = Anion, C = Cation

= 1.86 (Na^+) + Glucose /18 + BUN/2.8
(all unit in m.osmol/Kg)
=290 m.osmol/Kg
[NB: NaCl does not dissociate completely *in vivo* and thus contributes 1.86 m.osmol/L. 180 gm of glucose contributes 1 mosm of particles. When glucose concentration is expressed in mg/dl, it is divided by 18 to convert it to m.osm/Kg of H_2O. Urea does not dissociate. The molecular weight of urea is not 28 but it contains 2 atoms of nitrogen per molecule and the concentration of nitrogen is not measured as urea concentration but as blood urea nitogen concentration. Thus, the molecular weight of 2 nitrogen molecules (14 each) rather than the molecular weight of urea is used in calculation. As urea does not dissociate therefore, 28 mg of urea nitrogen contributes 1 m.osm. Blood urea nitrogen (BUN) concentration is usually expressed as mg/dl. Thus, urea nitrogen concentration is divided by 2 to 8 to calculate the m.osm/Kg].

Osmolal gap

The difference between the measured and theoretically calculated value of osmolality of plasma is known as the osmolal gap. The normal value of plasma osmolality gap is 280 to 300 m.osm/L. This gap increases when there is presence of high concentration of osmotically active abnormal particles in plasma which are not usually come during the measurement of normal osmolality. These abnormal osmotically active particles are: mannitol, keton bodies, glycine (used during transurethral resectomy), ethanol etc. The osmolal gap may also be present and become high during hyper protenaemia and hyper lipidaemia. This is because during both these conditions there is increase of plasma volume without increase of Na^+ concentration. Osmolal gap may also increase during the renal failure, because of retention of many small solutes which are not meauserd during the measurement of osmolality.

Calculation of Water Requirement

Assessment

Before calculation of water requirement, it needs the assessment of loss. The loss of water is called dehydration. It is assessed clinically by history, clinical examination and laboratory investigation.

From history we can know how long the patient is suffering from the loss of fluid and its severity, as for example the frequency and the volume of vomitting, diarrhoea, bleeding, etc. The specific clinical features of dehydration are : dryness of mouth, thirst, hypotension, loss of skin turgor, tachycardia, ↓jugular venous pressure, ↓urine output, ↓CVP, etc. With normal renal function the loss of water is associated with less urine output than 0·5 ml/Kg/hour. Therefore, by clinical examination the patient can be assessed for severity of dehydration. Clinically the severity of dehydration is classified as mild, moderate and severe. Mild dehydration is described as loss of 3L of water (4% of total body weight) which is manifested as sunken eyes, dry mucous membrane and loss of skin turgor. Moderate dehydration is described as loss of 4 to 6 L of water (5 to 8% of total body weight) which is manifested as hypotension, oliguria and tachycardia in addition to the manifestation of mild dehydration. Severe dehydration is described as loss of > 7 L of water (8 to 10% of total body weight) which is manifested as severe oliguria and compromised cardiovascular function.

The laboratory investigation to assess the severity of dehydration are : the degree of haemoconcentration, ↑albumin concentration in blood in absence of anaemia and hypoprotinaemia, ↑BUN concentration, ↑urine osmolality (> 650 m.osm/Kg).

Calculation

Regardless of the disease process, there is both sensible and insensible loss of water and electrolytes from the body. In normal healthy individual the sensible water loss occurs through urine, sweat and faeces, but the insensible loss of water occurs through skin and lungs. The insensible water loss per day accounts for about 25 to 30% of total water loss of a day. The major route of sensible water loss is kidney. Kidney also excretes the solute overload which is taken with food and is produced by metabolism through urine, mixing with water. The final solute concentration in the urine varies from 1200 to 50 m.osm/L of H_2O.

Protein is catabolized to urea, PO_4^{2-} and SO_4^{2-}. One gram of protein contains 150 mg of nitrogen and this 150 mg of nitrogen is converted to 5 m.mole of blood urea nitrogen BUN). Thus, 5 m.osm of solute is yielded from each gram of protein. On the otherhand, the normal daily protein requirement is 1 to 2 gm/Kg/day. Therefore, the protein used per day produces 5 to 10 m.osm of solute/Kg/day as BUN. The second major solute load comes from electrolyte balance. The daily Na^+ requirement is 1 m.mol/Kg/day and the daily K^+ requirement is also 1 m.mol/Kg/day. Hence, the daily total Na^+ and K^+ requirement is 2 m.mol/Kg/day. This same amount is also excreted perday with the equal amount of added anions to maintain homeostasis. Therefore, the total load of excreted electrolytes is 4 m.mol/Kg/day (the additional solute of 2 m.mol/Kg/day is due to other electrolytes such as Cl^-, HCO_3^-, Mg^{2+}, SO_4^{2-}, etc). In addition, a small amount of osmoles are produced by metabolism of lipids which release phosphates and uric acid. Hence, the total solute load which is to be excreted is 10 to 15 m.osm/Kg/day. But it may be higher in catabolic patients who receive large amount of electrolytes and lower in starving patient. To excrete this normal solute load in a normal individual, the usual urinary output is 0.5 ml/Kg/hour with normal urine osmolality. In extreme cases, it may vary in any direction such as very low urinary volume (500 ml/day which is called obligatory urine output) with very high osmolality or very high urinary volume with very low osmolality (Fig. 9.4).

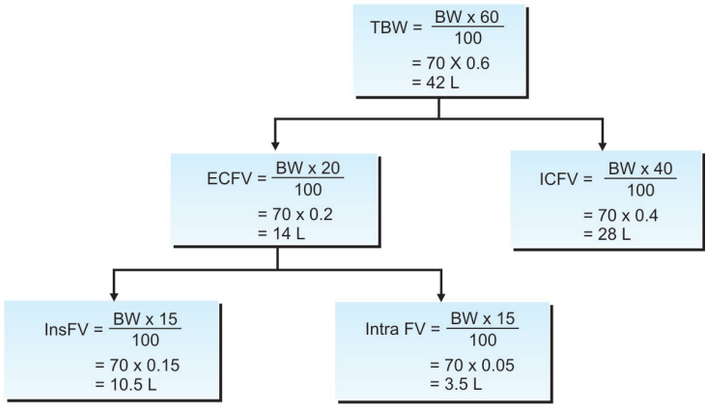


Fig. 9.4: Distribution of total body water (TBW) in litre of a 70 Kg body weight (BW) adult male

In the previous part of this chapter, we have already discussed that a normothermic 70 Kg patient with normal metabolic rate may loss about 2600 ml of water per day. So naturally this patient will need the same amount of water to maintain this water balance. Allowing 400 ml of water to gain from cellular metabolism, now this healthy patient needs 2600−400 = 2200 ml of water/day from external source. Hence, the thumb rule for daily water requirement of a 70 Kg individual is 30 to 35 ml/Kg/day. With this water, the normal Na^+ requirement is 1 m.mol/kg/day or 60 to 80 m.mol/day and like Na^+, the K^+ requirement is also 1 m.mol/Kg/day or 60 to 80 m.mol/day. Thus, a 70 kg healthy individual requires the daily provision of 2200 to 2600 ml of water with approximate 70 m.mol of Na^+ and K^+each. This can be provided by 1500 to 2000 ml of 5% dextrose and 500 ml of 0.9% NaCl, with 1 gm of KCl (15 m.mol) is each 500 ml of fluid.

Perioperative Fluid Therapy

For operative procedures, the patients are kept fasting for prolonged periods before operation, during which time the patient has both sensible and insensible loss of water. Again during surgical procedures, they also loss blood, ECF into the third space, and also water through the kidney as urine. They also loss water from skin, gut and lungs during the whole perioperative period. So, every patient needs the amount of water which is required for the normal maintenance plus the extra loss. For the loss of small amount of blood (< 20% of total blood volume) the patient does not need any blood transfusion. In such circumstances, only crystalloids electrolyte solution such as compound sodium lactate is sufficient. But, unfortunately, the crystalloid solutions quickly leave the intravascular compartment and is distributed in ECF compartment. Therefore, the blood volume is maintained only by infusion of crystalloid if atleast 3 times of the volume of blood loss is infused. Alternatively, the colloid solution which remain in intravascular compartment for longer period may be infused in a volume equal to that of the estimated loss.

During surgery, at the site of operation due to tissue injury there is sequestration of fluid from the intravascular compartment to the interstitial compartment. But this fluid does not take part in the normal metabolic process and is frequently referred to as the 'third space loss'. This loss of fluid volume in third space is proportional to the severity of tissue injury. This plasma like third space fluid is not contained in any anatomically separate space and can not be measured easily. It is reabsorbed 48 to 72 hours after surgery.

In minor surgery any IV fluid in the dose of 1 to 1.5 ml/Kg/hour is sufficient to meet the requirement for the normal maintenance. But, for any major abdominal surgery a volume of 5 to 6 ml/Kg/hour of fluid during operation, in addition to 1.5 ml/Kg/hour as normal maintenance requirement and transfusion of blood for any excessive blood loss is the rule. For any major surgery the volume of IV fluid and the volume of blood needed to be tansfused should be guided by the CVP, urine output, plasma osmolality, cardiac output, preload, intra arterial blood pressure, serum electrolyte concentration, etc. In the postoperative period, after replacing the total loss, the fluid should be administered only in the maintenance dose. Additional fluid in the form of compound sodium lactate or 0.9% NaCl is needed in the following condition such as loss of gastrointestinal fluid through nasogastric tube or fistula, loss of serum or blood through the drains or continued third space loss for first 24 to 48 hours after very major surgery. Usually, K^+ is not administered for the first 24 hours after surgery. This is because there is large release of endogenous K^+ from catabolism and tissue trauma which impose restriction of its use.

During the postoperative period there is increased release of ADH, cortisol, aldosterone, etc, due to the stress. These cause renal retention of Na^+ and water and excretion of K^+. But, still the restriction of water and Na^+ during the immediate postoperative period is inappropriate. This is becuae there is increased loss of water and Na^+ by evaporation and into the third space during the immediate postoperative period. Patients with renal failure also require fluid replacement for abnormal losses, but the total volume needed should be determined by the urine output and serum electrolyte concentration. Fluid and electrolyte requirement in infants and small children differ from those in the adults.

10 Electrolyte Balance

SODIUM BALANCE

Introduction

Although Na^+ is abundantly present in drinking water, milk and all the ordinary diet, but it is most commonly taken as eating salt. The normal daily requirement of Na^+ in an adult person is 1 to 1·5 mEq/Kg/day (or 5 to 10 gm/day). But usually the average intake of sodium is much higher than its daily requirement and is about 8 to 10 gm/day. So, naturally Na^+ deficiency is very rare. Daily Na^+ excretion is generally same as daily intake. To maintain a normal balance, usually, it is lost through sweat and faeces, but the final adjustment is made by kidney through urine. Urinary Na^+ excretion may be as little as 2 mEq/day during salt restriction and may go upto 700 mEq/day after salt loading. In case of Na^+ the mEq and m.mol are numerically same as the valency of Na^+ is one and m.mol is obtained by dividing the mEq by valency (Fact file-I). It is discussed in more details in chapter—water balance.

The Na^+ in plasma provides 90% of the total base of the body. It works in the body in two forms: sodium ion and sodium compound. All the functions of Na^+ ion are usually accomplished by maintaining the normal resting membrane potential. Therefore, the function of Na^+ ions in body are:

i. It initiates and maintains the contraction of heart.
ii. It is essential for the normal functions of cells.
iii. It is essential for the contraction of voluntary and involuntary muscles.
iv. It excites nerves as opposed to Ca^{2+} ions, which reduces the excitation of nerves.

On the other hand, sodium compounds are present in our body as bicarbonate, phosphate, chlorides, proteinates, etc. The functions of sodium compounds in our body are:

i. Maintains blood reaction: This is done in many ways. For instance (a) sodium bicarbonate is the chief buffer of blood and other body fluids. (b) The acid and alkaline sodium phosphates (NaH_2PO_4 is acid and Na_2HPO_4 is alkali) also constitute an important buffer system. (c) Sodium which remains combined with plasma proteins (sodium proteinates) can also act as a buffer. (d) Sodium of NaCl can also fix acids with the help of phenomenon known as chloride shift.
ii. Controls reaction of urine: Kidneys regulate the urine reaction by altering the proportion of acid and alkaline sodium phosphate in the urine.
iii. Reaction of pancreatic juices and bile: This is due to the presence of sodium carbonate.
iv. Maintain osmotic pressure: NaCl is the chief regulator of the osmotic pressure of body fluids.
v. Helps in the formation of HCl in gastric juices: NaCl takes part in the series of reactions and as a result of which HCl is manufactured by the stomach.
vi. Maintains water balance:

The Na^+ balance in our body is intimately related to the ECF volume and water balance. This is because it is widely distributed primarily in the extracellular fluid space, including the interstitial and intravascular space (whereas intracellular space is primarily dominated by K^+) and crosses the capillary bed readily. On the otherhand the distribution of the Na^+ between the intracellular and extracellular fluid space is restricted and determined by Na^+-K^+-ATPase pump, situated on the cell membrane. There are two types of disorder of Na^+ balance: hypernatraemia and hyponatraemia.

FACT FILE - I

1 gm of NaCl gives 17 mEq of Na^+ ions, whereas 1 gm of sodium itself gives 43 mEq of Na^+ ions. In the body the net Na^+ balance is equal to total Na^+ intake which is average 150 to 200 mEq/day minus both extrarenal and renal Na^+ loss. The kidneys play an very important role in Na^+ balance, because it has enormous variable capability to excrete Na^+ which varies between 1 mEq/L to more than 100 mEq/L.

Hypernatraemia

It is defined as plasma Na^+ concentration above 150 m.mol/L. It is nearly always the result of either loss of water in excess of Na^+ where Na^+ may be lost or not (hypotonic fluid loss or only water loss) or retention of large quantities of Na^+ itself with retention of water or not. In the first condition the hypernatraemia is a relative one because the total Na^+ content in body remains same as only the water is lost and is associated with reduced ECF volume and hyperosmolality. Contrary, in the second condition there is true hypernatraemia because the total Na^+ content in the body is increased even if the water content is increasd or not and is associated with

increased ECF volume and also hyperosmolality. So, the clinical assessment of volume status and osmolality of blood is important in the diagnosis and management of hypernatraemia. Therefore, hypernatraemia is classified into three forms: (A) hypernatraemia with increased body Na^+ content, (B) hypernatraemia with normal body Na^+ content, (C) hypernatraemia with low body Na^+ content. Now, though there is different types of hypernatraemia, the common abnormality of all these hypernatraemic states is hyperosmolality of ECF which causes drawing of excess fluid from the intracellular compartment and intracellular dehydration (Fact file- II)

A. Hypernatraemia with increased total body Na^+ content

Usually this is an iatrogenic condition in origin and is mainly due to the excessive exogenous salt gain. It commonly results from the administration of hypertonic saline or administration of excessive amount of sodium bicarbonate during cardiopulmonary resuscitation. It is also caused when the isotonic fluids are given to patients who have only insensible loss of hypotonic fluid, containing less Na^+. Patients suffering from primary hyperaldosteronism and Cushing's syndrome may also have this condition. Management of this condition is comprised of induction of diuresis by loop diuretic, which excretes Na^+ provided the kidney function is normal. Urine or water output is balanced in part by 5% dextrose which does not contain any Na^+. If the patient suffers from renal dysfunction, then dialysis or haemofiltration is the way of management of this type of hypernatraemia.

FACT FILE - II

Total body Na^+ content is directly proportional to the extracellular fluid (ECF) volume. Therefore, changes in total body Na^+ content results in variation of ECF volume. A positive Na^+ balance increases the ECF volume. Contrary a negative Na^+ balance reduces the ECF volume. On the otherhand, Na^+ is the predominant extracellular cation. So, Na^+ in the ECF reflects the total body Na^+ content. Na^+ in the ECF compartment remains in equilibrium between the interstitial and intravascular fluid compartment. Hence, plasma Na^+ content more or less indicates total body Na^+ content and the water balance.

B. Hypernatraemia with normal total body Na^+ content

This condition occurs when there is only loss of water, containing no or minimal amount of Na^+. Therefore, the total body Na^+ content remains normal or slightly decreased, but in relation to water its concentration is always higher. So, there is hypervolaemia (drawing of fluid from cells), hyperosmolality and hypernatraemia. Without loss of Na^+ the excessive loses of pure water via skin and respiratory tract is very rare. But some examples of this condition are fever, hyperventilation, thyrotoxicosis, etc. However, the most common cause of this condition is diabetes insipidus. In diabetes insipidus, there is either decrease in ADH secretion from the posterior pituitary gland or failure of the renal tubules to respond to the normally circulating ADH. Hence the first condition is called the central diabetes insipidus and the later is called the nephrogenic diabetes insipidus (Table 10.1).

In central diabetes insipidus the lesion or pathology is usually found in and around the hypothalamus or pituitary gland. So, it is commonly seen following pituitary tumour, neurosurgical procedures of brain, head trauma, etc. It is also developed following the brain death. The central diabetes insipidus is diagnosed by history of polyuria (> 8 L/day), polydypsia (even in the absence of hyperglycemia) and low urinary osmolality than plasma. In unconscious patient absence of thirst associated with diabetes insipidus can easily produce marked water loss and hypovolaemia. The diagnosis of central diabetes insipidus can be confirmed by increase in urinary osmolality by administration of ADH (or vasopressin) from exogenous source. There are two preparations of vasopressin such as in aqueous solution and in oil. However, the aquous preparation of ADH is the treatment of choice. It is used in the dose of 5U at the interval of every 4 hours through subcutaneous route. Oil preparation of vasopressin is also used in the dose of 0·3 ml/day only through IM route. It is long acting and therefore frequently causes water intoxication. There is another synthetic analogue of vasopressin, called desmopressin (DDAVP) with 12 to 24 hours duration of action. It is available as an intranasal preparation and can be used both for the ambulatory or preoperative patient in dose of 5 to 10 mg per day or twice daily.

Nephrogenic diabetes insipidus is commonly due to (i) chronic renal disease, (ii) secondary to side effects of certain drugs such as lithium, mannitol, amphotericin B, etc, (iii) certain electrolyte disturbances such as hypercalcaemia and hypokalaemia, (iv) certain other diseases such as sickle cell disease, hyperproteinaemia,

Table 10.1: Causes of hypernatraemia

A.	**Hypernatraemia with increased body Na^+ content**
	Excessive Na salt ingestion
	Infusion of hypertonic saline
	Administration of excess $NaHCO_3$
	Administration of excess of steroid
B.	**Hypernatraemia with normal body Na^+ content**
i.	Extrarenal loss of only water without Na^+
	Fever
	Hyperventilation
	Thyrotoxicosis
ii.	Renal loss of water without Na^+
	Central diabetes insipidus
	Nephrogenic diabetes insipidus
	Chronic renal failure
C.	**Hypernatraemia with decreased body Na^+ content**
	Renal hypotonic fluid loss
i.	Osmotic diuresis (mannitol, urea, glucose)
ii.	Extrarenal hypotonic fluid loss
	Vomitting
	Diarrhoea
	Excessive sweating

etc, (v) sometimes congenital. In these condition there is normal plasma level of ADH (vasopressin), but the kidneys fail to respond to normally circulating ADH and unable to concentrate the urine, resulting in excretion of huge amount of hypoosmolal urine. The diagnosis can be confirmed by the failure of kidney to produce a hyperosmolal urine, still following the administration of exogenous vasopressin. The treatment of this condition is intake of adequate fluid which will try to keep the water balance of our body normal and specific management of underlying aetiology. Administration of loop diuretics in nephrogenic diabetes insipidus paradoxically reduces the urine output as it reduces the water load to the collecting tubules where ADH acts. Proteins and sodium restriction can similarly decrease the urine output.

C. Hypernatraemia with low total body Na^+ content

In this condition, the patient losses both Na^+ and water, but the Na^+ loss is less than the loss of water (loss of hypotonic fluid). Therefore, there is low body Na^+ content (due to Na^+ loss) but still hypernatraemia (due to more loss of water than Na^+). The loss of hypotonic fluid may be due to renal or extrarenal cause. The example of renal loss of hypotonic urine causing hypernatraemia and low body Na^+ content is osmotic diuresis by mannitol, glucose, etc, where water is lost more than Na^+. On the otherhand, the example of extrarenal loss of hypotonic fluid causing this condition are vomitting, diarrhoea, exercise, excessive sweating, etc, where there is more water than Na^+ loss.

Clinical Manifestation of Hypernatraemia

The clinical manifestation of hypernatraemia is mainly due to the hyperosmolality of ECF which causes shifting of water from the intracellular compartment and cellular dehydration. The major consequences of hypernatraemia and hyper osmolality of ECF involve the CNS and the severity depends on the rapidity with which the hyperosmolality develops. The cellular dehydration causes reduction of cell volume and water content of the brain which produces restlessness, hyperreflexia, seizures, coma and ultimately death. The reduction of cell volume and water content of brain causes rapid decrease of brain volume and increased permeability of vascular structure which may produce rupture of cerebral veins resulting in focal intracerebral and / or subarachnoid haemorrhage. Hence, patient may present with pyrexia, nausea, vomitting, convulsion, coma or virtually any type of neurological syndrome. Chronic form of hypernatraemia is better tolerated than its acute form. Serious neurological damage and convulsions are more common in children and particularly when the plasma Na^+ concentration exceeds 158 m.mol/L.

Treatment of Hypernatraemia

The majority of hypernatraemic patients are hypovolaemic because though water in ECF compartment is increased, but the total water content of body is decreased due to intracellular dehydration. Therefore, the aim of management of hypernatraemia is the restoration of volume of ICF compartment and osmolality of ECF compartment and correction of underlying problem. The water deficit can be corrected by the following way:

Water deficit = Normal TBW − Present TBW

If a 60 Kg man is found to have a plasma Na^+ concentration of 160 m.mol/L then the present TBW can be calculated from the following equation, such as:

Nomal TBW × 140 = Present TBW × 160

[Normal plasma Na^+ concentration = 140 m.mol/L]

∴ Present TBW =

[Normal TBW × 140] ÷ 160

= [60 × 0·6 × 140] ÷ 160

[0·6 = 60% of body weight is water]

= 31.5 L

∴ Water deficit =

Normal TBW − Present TBW

= [60 × 0.6] − 31.5 L

= 36 − 31.5 L

= 4.5 L

This hypernatraemia and hypovolaemia should be corrected slowly over 48 to 72 hours. Because rapid correction of hypernatraemia and hypovolaemia may cause cerebral oedema, convulsions, permanent neurological damage and even death. During this management serial measurement of Na^+ concentration is performed and plasma Na^+ concentration should not be reduced faster than 0·4 to 0·6 m.mol/hour. Regarding the type of fluid, hyper natraemic patients with decreased total body Na^+ should be given isotonic saline to restore the both plasma volume and body Na^+. Because this isotonic saline is taken as relative hypotonic in patients with severe hypernatraemia and the Na^+ in normal saline helps to restore the depletion of total body Na^+. Once volume and Na^+ depeltion has been corrected, further correction of any water deficit can be accompanied with isotonic 5% dextrose.

Until the aetiology of hypernatraemia and fluid deficit is corrected properly all elective surgeries should be cancelled in patients suffering from severe hyper natraemia (> 150 m.mol/L).

Hyponatraemia

It is a very common hospital finding and is defined as plasma Na^+ concentration of less than 135 m.mol/L. It may occur relatively as a result of water retention (dilutional) or as a result of true Na^+ loss (depletion) or both. Therefore, hyponatraemia is associated with normal, decreased or increased ECF volume. But in all these forms there is hypo osmolality of the ECF compartment. Due to this reduced osmolality, water moves from the ECF compartment to the IC fluid compartment and swelling of cells (mainly brain) with water intoxication occurs.

Na^+ ion is present only in the water portion of plasma which constitutes about 93%

of whole plasma. But, in the laboratory, it is measured against the whole (100%) plasma and is expressed as m.mol per litre of whole plasma. In hyperlipidaemia and hyperprotenaemia this water portion of plasma is decreased, but the whole plasma volume remains same. Hence, in such condition the measurement of concentration of Na^+ against whole plasma is decreased (as water content decreases), but its concentration against only water portion of plasma (which is not constituted by lipids, proteins, etc) is normal. Therefore, the measurement of Na^+ against whole plasma in these conditions show false hyponatraemia. Hence, this type of hyponatraemia is called pseudohyponatraemia. However, the routine measurement of plasma osmolality with Na^+ level in hyponatraemic patients rapidly excludes this pseudo form. This pseudo form of hyponatraemia will not confuse us, if plasma Na^+ concentration is measured by ion specific electordes. Because this method directly assess the aquous phase of Na^+ and produce exact result.

Like hypernatraemia, hyponatraemia is also classified according to the presence of relative water retention (dilutional) without loss of Na^+ or true Na^+ loss (depletion) into three forms:

a. hyponatraemia with decreased total body Na^+ content,
b. hyponatraemia with normal total body Na^+ content,
c. hyponatraemia with increased total body Na^+ content.

A. Hyponatraemia with decreased total body Na^+ content

This is caused by progressive loss of both Na^+ and water, but the Na^+ loss exceeds the water loss. Hence, there is hypo natraemia and decreased total body Na^+ content. (If water loss exceeds the Na^+ loss, then this causes hypernatraemia with decreased total body Na^+ content). Assessment of volume status reveals hypovolaemia. This Na^+ and water loss may be renal or extrarenal. The examples of renal loss are: administration of diuretics, Addison's disease, renal tubular acidosis, salt losing nephropathies etc. In such renal causes of hyponatraemia usually the urinary Na^+ concentration exceeds 20 m.mol/L. The examples of extrarenal Na^+ and water loss are from GI tract such as diarrhoea, vomiting, etc; or in the third space such as during peritonitis, surgery, etc. In such extrarenal cause of hypo natraemia the urinary Na^+ loss is less than 10 m.mol/L, except vomiting. In vomiting there is metabolic alkalosis which obligates the concomitant excessive excretion of Na^+ and HCO_3^- through kidney to maintain electrical neutrality in the urine.

B. Hyponatraemia with normal total body Na^+ content

In this condition there is no Na^+ loss, but hyponatraemia is due to only water overload. This situation is caused by: glucocorticoid insufficiency, hypothyroidism, drug therapy by cyclophosphamide and SIADH (syndrome of inappropriate ADH secretion). Hyponatraemia associated with glucocorticoid insufficiency is due to excessive secretion of ADH along with hypersecretion of corticotrophin releasing factor in the absence of adequate glucocorticoides. In this condition there is modest excess of TBW and modest increase of ECF volume with normal total body Na^+ content showing hyponatraemia. It also may be due to iatrogenic origin. This iatrogenic cause is due to the excessive administration of IV fluids with low Na^+ content in the patient with loss of isotonic fluid (Table 10.2).

C. Hyponatraemia with increased total body Na^+ content

In this condition there is an increase in both the TBW and total body Na^+ content, but overload of water exceeds that of Na^+. Hence, hyponatraemia occurs. The examples of this situation are: congestive heart failure, renal failure, nephrotic syndrome, cirrhosis of liver, etc. In these circumstances hyponatraemia results from the progressive impairment of excretion of both Na^+ and free water by kidney, but the accumulation of water exceeds the accumulation of Na^+. The pathophysiology of this condition parallels the severity of underlying disease process (Fig. 10.1).

Clinical Manifestation of Hyponatraemia

The clinical manifestation of hyponatraemia is primarily due to the increase

Table 10.2: Causes of hyponatraemia

A.	Hyponatraemia with decreased total body Na^+ content (hypovolaemia)
i.	Renal loss (urine Na^+ > 20 m.mol/L)
	Diuretics
	Osmotic diuretics (mannitol, glucose)
	Mineralocorticoid deficiency
	Renal tubular acidosis
	Salt losing nephropathy
ii.	Extrarenal loss (urine Na^+ < 10 m.mol/L)
	Diarrhoea
	Vomitting
	Third space loss
B.	**Hyponatraemia with normal total body Na^+ content (normovolaemia or hypervolaemia)**
i.	Low plasmaosmolality
	Syndrome of inappropriate ADH
	Glucocorticoid insufficiency
	Hypothyroidism
	Drug therapy
ii.	Normal plasma osmolality
	Pseudohyponatraemia—hyperlipidaemia, hyperproteinaemia and hyperglycaemia
C.	**Hyponatraemia with increased total body Na^+ content (hypervolaemia)**
	Congestive heart failure
	Renal failure
	Nephrotic syndrome
	Cirrhosis of liver

Group A is a depletional syndrome. So saline is required. Group B and C (except pseudohyponatraemia) is dilutional syndrome. So fluid restriction is required.

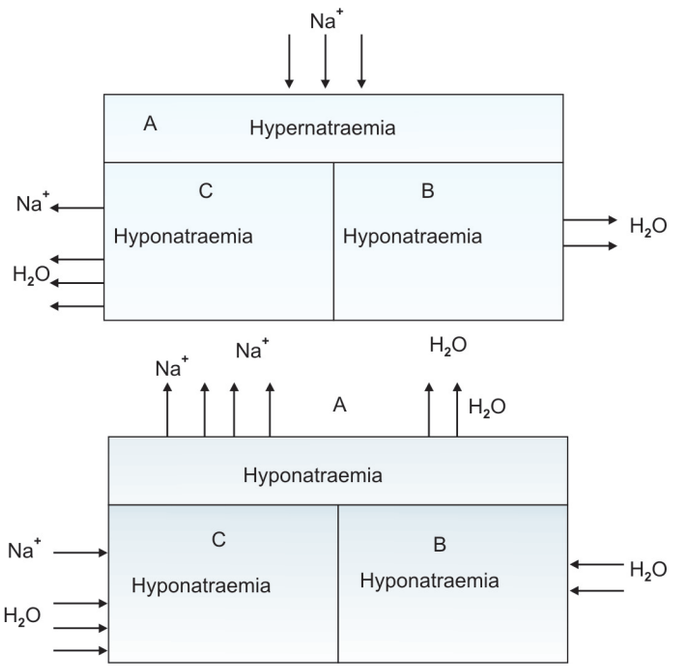


Fig. 10.1: Pathophysiology of hyponatraemia

in intracellular fluid volume and affects mainly the brain cells. So, there is subsequent cerebral oedema and increase in ICP causing nausea, vomitting, delirium, convulsions, coma and even death. But the symptoms vary with the magnitude of reduction of plasma Na^+ level and the rapidity with which the plasma Na^+ level falls. Patients with mild hyponatraemia (Na^+ level between 125 to 135 m.mol/L) are usually asymptomatic or associated with mild symptoms such as anorexia, nausea, vomiting, weakness, etc. Moderate hyponatraemia (Na^+ level between 120 to 125 m.mol/L) is associated with symptoms such as lethargy, confusion, etc. While the severe hyponatraemia (Na^+ level < 120 m.mol/L) is associated with convulsions, coma or death. Chronic hyponatraemia is less symptomatic than acute hyponatraemia. This is because in previous condition there is enough time for compensation by losing intracellular solutes along with extracellular loss of Na^+ which help to restore the cell volume to normal. In chronic hyponatraemia, the neurological manifestation are not due to the changes of cell volume, but rather due to the changes in cell membrane potential by low extracellular Na^+.

Treatment of Hyponatraemia

Like hypernatraemia the management of hyponatraemia also includes the correction of plasma Na^+ level and the underlying disease process. Acute sympomatic hypo natraemia is a medical emergency condition. So, it needs prompt intervention by using isotoic saline, but the rapidity with which hyponatraemia is corrected is a matter of controversy. This is because very rapid correction of hyponatraemia is associated with serious permanent neurological sequelae. But the general agreement is that correction period should not be less than 12 hours, and after which the plasma Na^+ level should not be less than 125 m.mol/L. The rapidity with which the hyponatraemia can be corrected slowly or very slowly depends on the severity of symptoms. However, the following tailored correction rate is followed: for mild hyponatraemia < 0.5 m.mol/L/hour, for moderate hyponatraemia < 1 m.mol/L/hour, and for severe hyponatraemia < 1.5 m.mol/L/hour.

In hyponatraemia the amount of Na^+ which is needed (Na^+ deficit) to make the desired plasma level can be calculated as follows :

Na^+ required or deficit = TBW × (desired or required Na^+ conc. − measured Na^+ conc). Here, TBW is total body water and not the total body weight.

If the weight of a patient is 70 Kg and the present plasma Na^+ concentration is 120 m.mol/L.

Then the required total Na^+ in m.mol/L = $70 \times 0.6 \times (130 - 120) = 420$

[0·6 indicates TBW and is approximately 60% of body wight, 130 m.mol/L is the desired level of plasma Na^+ level to be raised]

Normal saline contains Na^+ = 154 m.mol/L.

Hence, the patient should receive $420 \div 154 = 2.72$ L of normal saline.

Isotonic saline is generally the treatment of choice for hyponatraemia with decreased total body Na^+ content. On the otherhand, hyponatraemic patients with normal or increased total body Na^+ content should be treated with more water restriction. More specific treatment also can be instituted for hyponatraemia. For example, hormone replacement for thyroid or adrenal hypofunction which can be started to correct hyponatraemia. For heart failure patient, the aim of management is to increase the cardiac output.

Problems during anaesthesia of a patient suffering from altered Na^+ balance results from the changed patho physiology due to hyper or hyponatraemia and as well as from the underlying disorders. Hyper or hyponatraemia present either as hypo or hypervolaemia. Therefore, both these manifestation should be corrected before elective surgery. Hypovolaemic patients are sensitive to hypotension. Therefore, vasodilating and negative inotropic agents such as volatile anaesthetics, histamine releasing agents, barbiturates, etc; should be used cautiously. Due to the reduction of the volume of distribution of drugs in

hypovolaemia the doses of all the therapeutic agents also should be reduced. Regional anaesthesia is also very sensitive to develop hypotension due to hypovolaemia. If there is hypervolaemia, it should also be corrected by diuretics before surgery. Any abnormalities of cardiac, renal and hepatic function also needs proper evaluation and correction before anaesthesia and surgery.

POTASSIUM BALANCE

Introduction

K^+ is the major intracellular cation. The intracellular concentration of it is 140 to 150 m.mol/L and this intracellular K^+ constitutes about 98% of total body K^+ content. Only 2% of total body K^+ content remains in the extracellular space or fluid. This extracellular K^+ concentration is 4 m.mol/L. The regulation of intracellular K^+ concentration is poorly understood. The extracellular K^+ concentration generally reflects the plasma concentration and the balance betwen the K^+ intake and excretion of it. Under some pathological conditions, the redistribution of K^+ between the ECF and ICF compartment can result in marked changes in the extraellular K^+ concentration without the change in total body K^+ content or change in intake and excretion. This extracellular concentration of K^+ is regulated precisely, because many of the cell functions are very sensitive to this change in ECF potassium concentration. For example, slight changes of plasma K^+ concentration has an important impact on neuromuscular transmission and cell membrane potential, most significantly on myocardial cell. An increase in plasma K^+ concentration (which is in equilibrium with ECF K^+ concentration of only 3 to 4 m.mol/L) from its original value can cause cardiac arrhythmia or even cardiac arrest.

The daily intake of K^+ usually ranges between 50 to 200 m.mol/day (average 80 m.mol/day) but in a single meal this K^+ intake may rise as high as 500 m.mol. Therefore, the failure to rapidly rid of the ECF from this high ingested K^+ load could cause life threatening hyperkalaemia. Similarly, a small loss of K^+ from the ECF could may cause severe hypokalaemia in the absence of rapid and appropriate compensatory response.

Normally, the daily intake of K^+ is equivalent to the daily excretion of it. Renal excretion of K^+ can vary from as little as 5 m.mol/L to over 100 m.mol/L, according to the intake and output in the absence of any renal pathology. This maintenance of K^+ balance depends primarily on excretion by the kidney. Kidney excretes 90 to 95% of the ingested K^+, whereas the remaining 5 to 10% K^+ is lost through the faeces and sweat. Thus, kidney is the principal organ to control the body K^+ rapidly and precisely in wide variations of intake and abnormal loss. In the kidney about 90 to 100% of filtered K^+ is reabsorbed actively by the proximal tubules and the thick ascending limb of the loop of Henle. Therefore, nil to 10% of filtered K^+ escapes this reabsorption and which is excreted through urine. Normally, the K^+ which is excreted in the urine is the result of distal tubular secretion. This K^+ secretion in the distal tubules is coupled to aldosterone mediated reabsorption of Na^+. Therefore, if the GFR is normal, then this amount is adequate to maintain K^+ balance by excreting it through urine. For this reason, hyperkalaemia is very uncommon in the presence of normal renal function. However, if the GFR is reduced then excessive active secretion of K^+ by the distal nephron is necessary to avoid the progressive accumulation of K^+ in the the blood and eventual hyperkalaemia.

The control of K^+ distribution between the ECF and the ICF compartment also plays an important role in K^+ homeostasis. This is because 98% of the total body K^+ remains in the cell and they can serve as a soaking site for the excess of K^+ from the ECF compartment during hyperkalaemia or as a source of K^+ during hypokalaemia. Thus, the redistribution of K^+ between the ICF and the ECF compartment provides a first line of defence against the changes in K^+ concentration in ECF compartment. The K^+ of ECF compartment is pumped into the cell in exchange of Na^+ by the ubiquitous Na^+-K^+ ATPase pump, situated on the cell membrane in a ratio of $3Na^+$ to $2K^+$ ions. This creates a–ve intracellular voltage and is responsible for resting membrane potential. The intracellular K^+ concentration remains constant at around 140 m.mol per litre though a Na^+-K^+ ATPase pump acts continuously. This is because of some passive leakage of K^+ from cells through some separate K^+ selective ion channels, other than Na^+-K^+ ATPase pump. This Na^+-K^+ ATPase pump is stimulated by insulin and β-adrenergic agonist and this effect is exploited to treat hyperkalaemia. It is inhibited by acidosis. Therefore, hyperkalaemia is commonly associated with acidosis, diabetes and use of β-blocker. The plasma K^+, therefore, is a very sensitive factors, influencing the shift of K^+ between the ECF and ICF compartment of muscle cells which are the principal storing site of K^+.

Urinary Excretion of Potassium

Generally, the extracellular concentration of K^+ parallels with the excretion of it through urine. It is excreted mainly by the secretion of tubular cells in the distal nephron and the whole things are mediated by the aldosterone hormone. Extracellular concentration of K^+ is the major determinant factors of aldosterone secretion from the adrenal gland. Hyperkalaemia stimulates the secretion of aldosteone, whereas hypokalaemia suppresses it. The other major stimulus to aldosteroen secretion is angiotensin II. Thus, any factors that inhibit the renin-angiotensin system will inhibit the secretion of aldosterone and blunt the renal response to rise in plasma K^+. These include ACE inhibitors, NSAID (by blocking prostaglandin mediated renin

release) and β-antagonists (by inhibiting the release of renin mediated by the renal nerves). Drugs which block the action of aldosterone such as spironolactone, amiloride, etc, also cause hyperkalaemia, particularly if the GFR is low.

Intercompartmental Shifts of Potassium

It is already discusssed that like urinary excretion the intercompartmental shifting of K^+ between the ECF and ICF is also very important to maintain the homeostasis of it or the concentration of it in ECF which is most important for life. This intercompartmental shift of K^+ is mediated by changes in: extracellular pH, levels of circulating catecholamines, levels of circulating insulin, hypothermia and plasma osmolality. Except these, exercise also transiently increases the plasma K^+ level due to the release of it from muscle cells. This increase of plasma K^+ concentration is parallel to the duration and intensity of muscular activity.

The changes in extracellular pH directly affects the extracellular K^+ concentration. This is because the intracellular fluid buffers upto 50% of an acid load or H^+ and the remaining are excreted through kidney. During acidosis extracellular H^+ enters the cell and displaces the intracellular K^+. Thus K^+ comes out of the cell to maintain the intracellular electrical balance and increases the plasma K^+ level. During alkalosis the reverse occurs and plasma K^+ concentration decreases. A thumb rule of maintaing the relationship between the plasma K^+ concentration and blood pH is that plasma K^+ concentration changes nearly 0.5 to 0.7 m.mol/L for every 0.1 U change of arterial pH in any direction.

The increased level of catecholamines by sympathetic stimulation also decreases the plasma K^+ level by enhancing the intracellular uptake of it. This is mediated by the Na^+-K^+ATPase pump which is contolled by β-adrenergic receptors. Catecholamines through β-receptors stimulate this pump which pushes two K^+ ions inside the cell inexchange of drawing three Na^+ ions out of the cell. Therefore β-adrenergic stimulant decreases the level of plasma K^+ concentration. Contrary, β-blockers increases the concentration of plasma K^+. On the otherhand, α-adrenergic activity impair the intracellular movement of K^+ and increases the concentration of plasma K^+.

Changes in the circulating levels of insulin also alter the plasma K^+ concentration. It also acts the same way through Na^+-K^+ATPase pump, like catecholamines and increases the uptake of K^+ in the liver and skeletal muscle cells. Thus, administration of insulin decreases the plasma K^+ level and helps to treat hyperkalaemia.

Hypothermia decreases the plasma K^+ level by increasing the cellular uptake of it. Contrary, the increased temperature of body reverses this shifting and increases the plasma K^+ level. Changes of plasma osmolality also changes the plasma K^+ level. Increased plasma osmolality due to hypernatraemia, hyperglycaemia or administration of mannitol, etc, increases the plasma K^+ concentration. The explanation of it is like that increased plasma osmolality causes the shifting of water from ICF to ECF compartment. This causes cellular dehydration and increased intracellular K^+ concentration which results in movement of K^+ from inside to outside of the cell and increased plasma K^+ level.

There are two types of disturbances of K^+ balance in our body. These are hypokalaemia and hyperkalaemia.

Hypokalaemia

It is defined as plasma concentration of less than 3.5 m.mol/L. It occurs as a result of : (i) inadequaqte intake or (ii) excessive loss or (iii) both. Excessive loss may be of two types — loss through urine, stool, sweat or shift from ECF to ICF compartment. In this circumstances of shifting from ECF to ICF compartment, the total K^+ content in the body remains same.

When the K^+ intake is very low, then the reabsorption of it in the nephron is enhanced. This causes gradual fall of urinary excretion of K^+ to about 5 m.mol/day which is obligatory. But this continuous minimum loss of K^+ through urine and further daily continuous loss of K^+ which is near about 5 to 10 m.mol/day through stool and sweat can result in gradual depletion of body K^+, provided this minimum amount is not replaced daily by intake. On the otherhand, if K^+ reabsorption in renal tubules is impaired, then urinary loss will be greater and there will be quick manifestation of hypokalaemia, provided intake of K^+ is still inadequate. As kidneys have enormous ability to reabsorb the filtered K^+ and decrease the urinary K^+ excretion to only 5 m.mol/day, therefore marked reduction in K^+ intake are required to produce hypokalaemia. In hypokalaemia the plasma K^+ level correlates very poorly with the total body K^+ deficit. A decrease in plasma K^+ from 4 to 3 m.mol/L usually represents 100 to 200 m.mol of deficit. Whereas a plasma K^+ level below 3 m.mol/L can represent a deficit between 200 to 400 m.mol (Table 10.3).

Hypokalaemia also occurs, even though, intake is adequate. This is due to the presence of excessive loss. This excessive loss of K^+ is either through renal route or through gastrointestinal tract. Excretion of K^+ through the urine rises, whenever there is increased delivery of Na^+ to distal tubule. This increased delivery of Na^+ to distal tubule causes increased reabsorption of it in exchange of increased K^+ secretion which is lost through the urine. This mechanism of excessive renal K^+ loss is found in uncontrolled diabetes, and use of loop diuretics such as frusemide, thiazides etc. Excretion of K^+ through the urine is also increased, whenever there is high concentration of aldosterone which promotes the excessive reabsorption of Na^+ in the distal tubule in exchange of excessive loss of K^+. The causes of this high concentration of aldosterone is: Conn's syndrome,

Table 10.3: Causes of hypokalaemia

A.	**Reduced intake**
	Inadequate dietary intake
	K^+ free IV fluid
B.	**Increased loss through urine**
	Conn's syndrome (pri. hyperaldosteronism)
	Secondary hyperaldosteronism such as heart failure, ECF depletion, renal artery stenosis, cirrhosis, nephrotic syndrome etc.
	Cushing's syndrome
	Renal tubular acidosis, hypomagnesaemia
	Renin excess
	Diuretics
	Batter's syndrome
	Uncontrolled diabetes
	Amphotericin's B, Carbenicillin
	Liddle's syndrome
C.	**Increased loss through GI tract**
	Vomitting, Diarrhoea, malabsorbtion sysdrome
	Aspiration of upper GI contents
	Drainage through fistula
	Villous adenoma of colone
D.	**Intercompartmental shift**
	Metabolic alkalosis
	Insulin, β-blocker
	Hypothermia

secondary hyperaldosteronism, Cushing's syndrome, etc. Most often the secondary hyperaldosteronism results from enhanced secretion of renin in response to inadequate renal perfusion (e.g. heart failure, hypoalbuminaemia, renal artery stenosis, Cirrhosis, nephrotic syndrome etc). Enhanced secretion of renin increases the secretion of aldosterone through angiotensin I and angiotensin II pathway. In patients with ECF depletion there are high plasma levels of renin, angiotensin I, II and aldosterone. The GFR is maintained by angiotensin II mediated efferent arteriolar constriction. So the distal Na^+ delivery is relatively preserved but the aldosterone drives the urinary losses of K^+. The other causes of renal loss of K^+ are: renal tubular acidosis, hypomagnesaemia, ketoacidosis, some drug therapies such as carbenicillin, amphotericin B etc, and salt wasting nephropathies. The causes of increased loss of K^+ through GI route are: vomitting, diarrhoea, malabsorption syndrome, abuse of laxative, nasogastric suction, losses of secretin through fistula, villous adenoma, etc. Dialysis by low K^+ containing fluids also causes hypokalaemia. Continuous increased sweat formation sometimes cause hypokalaemia, provided when it is associated with low K^+ intake. Uraemic patient have normal or high plasma K^+ concentration, though it has total body K^+ deficit. This is due to the acidosis which causes shifting of K^+ from ICF to ECF compartment. Any factor which moves K^+ into the cells will cause the increased intracellular K^+ concentration, including that in the cells of the distal tubule. This also enhances the secretion of K^+ and hence its urinary losses. This mechanism operates in alkalosis from any cause. Therefore, alkalosis and hypokalaemia are commonly associated with each other.

Except alkalosis, hypokalaemia due to intracellular movement of K^+ also occurs during insulin therapy, β-adrenergic agonists and hypothermia. Hypokalaemia also occurs following transfusion of frozen red cells. Because these cells lose K^+ during the preservation process and take up K^+ from plasma following reinfusion.

Clinical Manifestations and Diagnosis

Hypokalaemia can produce widespread dysfunction of organs by increasing the threshold for initiation of action potential. Most patients remain asymptomatic until plasma K^+ concentration falls below 3 m.mol/L. At first the diagnosis of hypokalaemia may be suggested by tiredness and muscular weakness. Other neuromuscular effects of hypokalaemia include muscle cramping, tetany and rarely rhabdomyolysis. In extreme cases the patient may be unable to walk or climb stairs. Reduced intestinal motility or paralytic ileus may occur in hypokalaemia. Cardiovascular effects in hypokalaemia are most prominent and include ventricular arrhythmia, decreased cardiac contractility, low BP, potentiation of the adverse effects of digitalis, etc. Typical ECG changes occur during hypokalaemia and these are: (i) sinus rhythm with normal QRS complex, (ii) increased P-wave amplitude, (iii) prolongation of the P-R interval, (iv) depression of ST segment, (v) T-wave flattening and inversion, (vi) increasingly prominent U-wave.

Hypokalaemia induced by diuretics is often associated with metabolic alkalosis. This is because kidneys absorb more Na^+ to compensate for intravascular volume depletion due to diuretics in exchange of K^+. In presence of hypokalaemia as there is less availability of K^+, so Na^+ will absorb in exchange of H^+ causing alkalosis. Also bicarbonate is absorbed to compensate the diuretic induced hypochloraemia. Therefore, the end result of diuretics is hypokalaemia and hypochloraemia assoicated with metabolic alkalosis. Long standing hypokalaemia damages renal tubular structure and results in failure of the antidiuretic response to ADH. Therefore, gradually patients with hypokalaemia may present with nocturia or polyuria and polydipsia (Fig. 10.2).

In most cases of K^+ depletion, the plasma K^+ concentration is low. But, in some cases the factors that move K^+ out of the cell, may help to maintain a normal plasma K^+ level in spite of the low body K^+ content as for example diabetic ketoacidosis. On the otherhand, patients with metabolic alkalosis or who have been taking excessive insulin or β-adrenoreceptor agonists may have a low plasma K^+ level, despite a normal total body K^+ content. This is because of movement of K^+ into the cells. Therefore, in mentioning the cause of hypokalaemia, the measurement of urinary K^+ excretion may be helpful. A value of urinary K^+ concentration less than

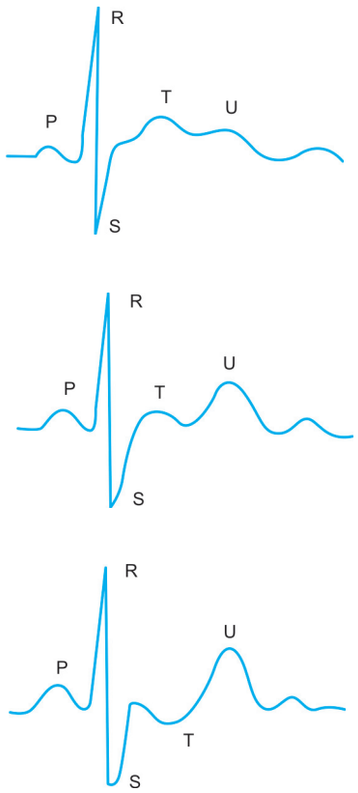


Fig. 10.2: The effects of hypokalaemia on ECG. It is characterised by: gradual increase in amplitude of P-wave, progressive increase of P-R interval, depression of ST segment, progressive flattening of T-wave and increasingly prominent U-wave

20 m.mol/day makes abnormal renal K^+ loss unlikely. While a urinary K^+ excretion more than 50 m.mol/day in the presence of hypokalaemia suggest a renal cause.

Management

Giving K^+ salt orally or through IV route treats hypokalaemia. But the mode of treatment of hypokalaemia (either oral or through IV route) depends on the severity of organ dysfunction and the degree of hypokalaemia. IV replacement of K^+ should usually be reserved for patient with serious cardiac dysfunction or severe muscle weakness. Otherwise, oral replacement of K^+ is the choice of management. During IV replacement of K^+ continuous ECG monitoring and periodic assessment of muscle strength is mandatory. The goal of IV K^+ therapy is to manage the emergency and not necessarily to correct the entire K^+ deficit. For IV K^+ replacement KCl is usually used. Any other associated salt and water deficit with hypokalaemia should be replaced first. This is because any IV administration of K^+ is avoided, until adequate urine output is established. Dextrose containing solutions should generally be avoided for IV replacement of K^+. Because the resulting hyperglycaemia and secondarily increased secretion of insulin may actually lower the plasma K^+ level, even further. During IV replacement the dose of K^+ should not exceed 10 to 20 m.mol/hour or 240 m.mol/day.

The oral route for K^+ replacement is most commonly practised and safer. It is used for non emergency circumstances. Oral KCl (1 gm = 13·4 m.mol of K^+) is a satisfactory preparation, unless metabolic acidosis is present. Otherwise, in acidosis $KHCO_3$ is used. This oral KCl preparation may cause GI irritation, oesophageal and small bowel erosion, strictures, etc. In alkalosis KCl is preferred, because it also corrects the chloride deficit. The dose of oral preparation of KCl is 80 to 100 m.mol/day. A diet rich in K^+ such as bananas, citrous fruit, milk, chocolate, etc, are also helpful in hypokalaemia. If hypokalaemia is found to be difficult to correct in patient who have had diuretics, then it should be thought that there may be an associated Mg^{2+} deficiency. Therefore, correction of this Mg^{2+} deficiency is necessary before hypokalaemia is treated to normal. Oral replacement of K^+ deficit usually requires several days.

Anaesthetic Consideration

Hypokalaemia is a very common perioperative finding. It is found that patients with plasma K^+ concentration of less than 3 m.mol/L are at increased risk of cardiac arrhythmia. So, these patients should be taken as serious and all the precautionary measures like continuous ECG, IV replacement of K^+, acid-base balance, use of nerve stimulator, etc, should be taken. But the patients who have plasma K^+ concentration between 3 to 3.5 m.mol/L produce problem to take the decision, especially in such circumstances if elective surgery should be done or not. This is because in such circumstances the incidence of intraoperative cardiac arrhythmias do not increase in asymptomatic patient with chronic K^+ level between 3 to 3.5 m.mol/L. Further it is not suggested to infuse K^+ preoperatively, depending sloely on the plasma K^+ level in the absence of any symptoms. Therefore, the decision regarding the performing an elective surgery in hypokalaemia with plasma K^+ level between 3 to 3.5 m.mol/L should depend on the presence or absence of any symptoms or organ dysfunctions such as cardiac arrhythmia, etc, and the rapidity and the magnitude of change of plasma K^+ level from the previous one. In general, chronic mild hypokalaemia where plasma K^+ level runs between 3 to 3.5 m.mol/L and there is no cardiac arrhythmia or other organ dysfunction does not appear to increase the anaesthetic risk appreciably. But this will not be applicable to patient who is taking digitalis, though his plasma K^+ level is near about 4 m.mol/L. So, it is reasonable to repeat the measurement of plasma K^+ level and to obtain an ECG for detection of cardiac arrhythmia before any induction of anaesthesia in patients who are considered at the increased risk from the effects of hypokalaemia (Fig. 10.3).

No specific anaesthetic drugs or technique appear to be superior for use in hypokalaemic patient. But, it is important to monitor the ECG continuously, during the perioperative period for evidence of any adverse effect of hypokalaemia. Any new evidence of hypokalaemia on the ECG requires prompt treatment with IV administration of K^+ in the dose of 0.5 to 1 m.mol repeatedly, until the ECG reverts to normal. As the K^+ depleted heart is vulnerable to the arrhythmogenic effect

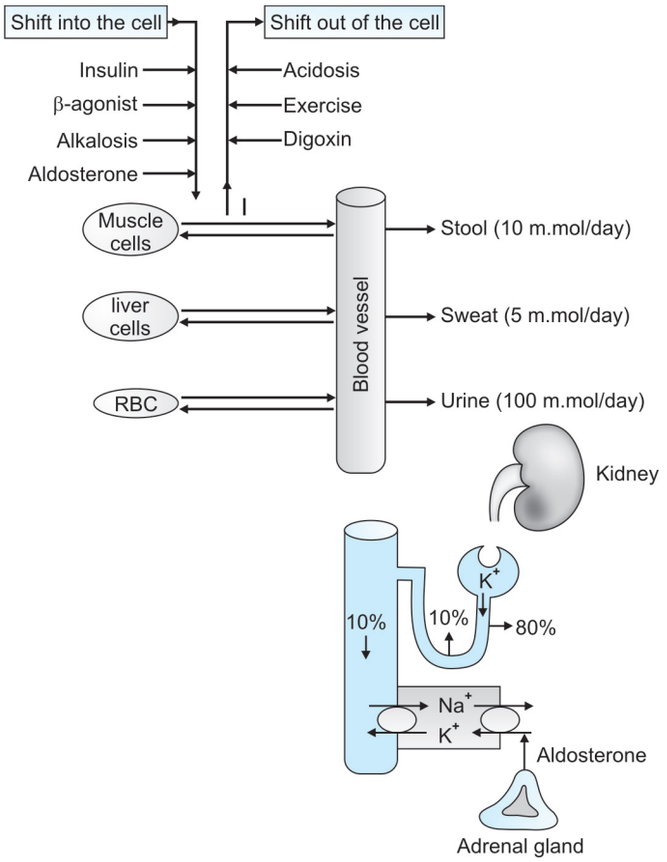


Fig. 10.3: The total body K^+ metabolism by the mechanism of secretion of K^+ in distal renal tubule, intercompartmental shifting and excretion through stool, urine and sweat

of catecholamines, digitalis and calcium, so their perioperative use should be very carefuly restricted. During surgery, IV fluid should be selected to avoid glucose load. This is because hyperglycaemia may contribute to more hypokalaemia, the cause of which is explained before. Continuous capnography and measurement of arterial blood gas and pH are helpful for confirming the proper management of ventilation. Because hyperventilation can produce further alkalosis and hypokalaemia. Hypokalaemic patients have increased sensitivity to neuromuscular blocking agents. So, a prudent approach is to reduce the dose of muscle relaxant to 30 to 50% and use of nerve stimulator to follow the degree of muscular paralysis and the adequacy of reversal. Chronic hypokalaemia is associated with decreased myocardial contractility and hypotension. Therefore, patient with chronic hypokalaemia might be unusally sensitive to the cardiac depressant effect of volatile anaesthetic agent. There is also evidence that epinephrine used with local anaesthetic agents to perform axillary block in hypokalaemic patient is associated with arrhythmia shown by ECG. So, it is prudent to avoid the use of epinephrine with local anaesthetic agent in patient suffering from hypokalaemia.

Hyperkalaemia

Hyperkalaemia is defined as plasma K^+ concentration greater than 5·5 m.mol/L, where the usual normal plasma value of it varies between 3·5 to 5·5 m.mol/L. It is a less common disturbance of K^+ balance than hypokalaemia, becaue the kidneys have enormous capacity to excrete K^+ which may go upto 400 to 600 m.mol/day (average 500 m.mol/day). Usually the hyperkalaemia can result from: (i) decreased renal excretion of K^+, (ii) shifting of K^+ from intracellular to extracellular compartment, without any change in total body K^+ content (iii) increased intake of K^+ and (iv) combination of these factors.

Increased intake of K^+

Increased intake of only K^+ is a rare sole cause of hyperkalaemia. This is because there is enormous capabilities of adaptation for excretion of K^+ by kidneys which ensures rapid elimination of it, in response to increased dietary load or consumption. However, iatrogenic hyperkalaemia may result from over zealous parenteral K^+ replacement or usual amount of replacement of K^+ in patients with renal insufficiency or patients taking insulin or β-blockers. Other source of iatrogenic hyperkalaemia are: transfusion of stored blood, chronic consumption of potassium preparation of any drug (such as potassium penicillin), taking K^+ salt as substitute of Na^+ salt where much Na^+ intake is prohibited, etc. The K^+ concentration in one unit of stored blood can increase from 25 to 35 m.mol/L after 24 days of storage. Therefore, where there is risk of hyperkalaemia large transfusion of old whole blood should be avoided. On the otherhand, this hyperkalaemia can be minimised by transfusing only the packed red cells (Table 10.4).

Decreased renal excretion of K^+

Chronic hyperkalaemia is also virtually associated with decreased excretion of K^+ by kidney due to: (i) decreased GFR, (ii) decreased aldosterone acitivity or reduced K^+ secretion from the distal nephron. The reduced GFR is due to the reduced circulation or hypovolaemia which causes acute oliguric renal failure. This acute renal failure causes hyperkalaemia due to decreased excretion of K^+. On the otherhand, reduced

Table 10.4: Causes of hyperkalaemia

A.	**Increased intake**
	High K^+ intake through food
	Chronic ingestion of drugs containing K^+ compound
	Excessive IV therapy with K^+
	Na+ salt subsitute by K^+ salt
B.	**Impaired renal excretion**
	i. Reduced GFR
	Renal failure, reduced renal blood flow (shock)
	Urinary tract obstruction
	ii. Impaired tubular secretion of K^+
	Hypoaldosteronism
	Addison's disease, 21-hydroxylase deficiency
	ACE inhibitior, NSAID
	β-blockers, K^+-sparing agents
	SLE, Sickle-cell disease
C.	**Intercompartmental shift of K^+**
	Acidosis, diabetes, β-blockers
	Tissue hypoxia, succinylcholine
	Strenous exercise
	Water depletion (ECF hypertonicity)
	Rhabdomyolysis
D.	**Enhanced Cl^- reabsorption**
	Cyclosporine
	Gordon's syndrome
E.	**Psudohyperkalaemia**
	Incorrect blood sampling
	Tissue damage during venepuncture
	Red cell haemolysis
	Marked leukocytosis and / or thrombocytosis

circulation or shock is also associated with acidosis and increased catabolism which again causes hyperkalaemia. Therefore, this hyperkalaemia further aggravates the hyperkalaemia which is already produced by oliguric renal failure.

Hyperkalaemia due to decreased excretion of K^+ from renal tubule may be due to decreased aldosterone activity. At the distal nephron aldosterone causes reabsorption of Na^+, inexchange of K^+ which is excreted through urine. In the absence of aldosterone Na^+ is not absorbed, so K^+ is not secreted and causes hyperkalaemia. Hypoaldosteronism may be due to primary defect in the synthesis of aldosterone hormone or a defect in the renin - angiotensin - aldosterone system. The defect of aldosterone synthesis again may be due to primary adrenal insufficiency (Addison's disease) or congenital 21 hydroxylase adrenal enzyme deficiency, which is needed to synthesize the mineralocorticoids. These patients show impaired ability to increase the secretion of aldosterone in response to hyperkalaemia as a positive feed back compensatory mechanism. They are usually asymptomatic but create problem when they are given with K^+ sparing diuretics or intake of K^+ increases.

Factors which also interfer the action of renin angiotensin aldosterone system may cause the hyperkalaemia. This is even more apparent when this renin angiotensin aldosterone interference is accompanied by impairment of renal function and reduced excretion or secretion of K^+ due to this renal dysfunction. ACE-inhibitors interfer the secretion of angiotensin II mediated release of aldosterone and thus also cause hyperkalaemia. NSAID inhibit the secretion of renin by inhibiting the synthesis of prostaglandin and thus causes hyperkalaemia. Heparin, including the low molecular weight compound also inhibits the production of aldosterone by the cells of zona glomerulosa and can lead to sever hyperkalaemia in a subset of patients with underlying renal disease, diabetes mellitus and those receiving K^+ sparing diuretics.

Decreased secretion of K^+ by the distal and collecting tubules may be the principal cause of hyperkalaemia. It results from either impaired Na^+ reabsorption or increased Cl^- reabsorption. So, they also often have varying degree of Na^+ wasting or loss and hyperchloremic metabolic acidosis. This may be intrinsic or acquired defect. Such defect may even occur in the presence of normal renal function. It is characterised by unresponsiveness or resistance to aldosterone therapy. So, it may be called as pseudoaldosteronism. The other acquired causes of decreased secretion of K^+ in distal tubule are SLE, diabetic neuropathy, sickle cell anaemia, etc. The decreased secretion of K^+ is also caused by K^+ sparing diuretics which antagonize the action of aldosterone activity and produce the effect of pseudoaldosteronism.

Shifting of K^+ from ICF to ECF

The hyperkalaemia may also occur due to the movement of K^+ out of the cells. This is commonly due to the administration of succinylcholine, intravascular haemolysis, break down of cells due to any cause, acidosis, excessive exercise, massive tissue trauma, rhabdomyolysis, etc. The average increase of plasma K^+ concentration after administration of succinylcholine is 0.4 to 0.6 m.mol/L. But it may be exaggerated following severe trauma, massive burn, or following lower motor neuron disease. Insulin deficiency and hypertonicity (e.g hyperglycaemia) promote K^+ shift from the intracellular compartment to the extracellular compartment. The severity of exercise induced hyperkalaemia is related to the degree of exertion. It is due to the increased release of K^+ from muscles and is rapidly reversible which is often associated with rebound hypokalaemia. Treatment with β-blockers rarely cause hyperkalaemia, but may contribute to the elevation in plasma K^+ concentration, seen with other conditions. Hyperkalaemia may also occur with severe digitalis toxicity due to the inhibition of Na^+-K^+ ATPase pump. Uraemia may also impair the activity of Na^+-K^+ ATPase pump and produce hyperkalaemia. Arginine hydrochloride is used to treat metabolic alkalosis. But it may cause hyperkalaemia because the arginine cations enter the cells and potassium anions move out of the cell to maintain the electrical neutrality.

Pseudohyperkalaemia is a condition where there is artificial or spurious elevation of plasma K^+ concentration during its measurement in laboratory. This is due to the release of K^+ out of the red cells,

because of haemolysis in a blood specimen immediately following venipuncture. The other contributing factors for pseudohyperkalaemia may also include prolonged use of tourniquet causing haemolysis, repeated fist clenching, release of K^+ from lysis of white cells and lysis of platelets in marked leucocytosis and thrombocytosis, etc. (Figs 10.4A to C).

Clinical Manifestation

The most important and common effects of hyperkalaemia are found on cardiac and skeletal muscles. Hyperkalaemia reduces the threshold for initiation of action potential and thus causes sustained spontaneous depolarization of muscle cells like succinylcholine. This is the mechanism of manifestation of hyperkalaemia. Cardiac manifestation of it are likely to occur when plasma K^+ concentration crosses over 7 m.mol/L. In general the plasma K^+ values over 6 m.mol/L should be treated. The earliest ECG changes during cardiac manifestations of hyperkalaemia includes increased T-wave amplitude (peaked T-wave). More severe degree of hyperkalaemia may also result in prolonged PR interval, prolonged QRS duration, delay in AV conduction and loss of P-wave. Then, with gradual increase in plasma K^+ concentration there is loss of R-wave amplitude with progressive widening of QRS complex which merges with the T-wave and produces a sine wave pattern in ECG. More severe hyperkalaemia produces VF and asystole.

Since, the resting membrane potential of cell is related to the ratio of intracellular and extracellular K^+ concentration, so the hyperkalaemia partially depolarizes the cell membrane. This partial, prolonged and sustained depolarization impairs the membrane excitability which is manifested as muscular weakness. This may progress to flaccid paralysis (like succinylcholine) and hypoventilation if the respiratory muscles are involved. Hyperkalaemia also inhibits the reabsorption of NH_4^+ in the thick ascending limb of the loop of Henle and renal aminogenesis. Therefore, the net renal acid excretion is impaired which resluts in metabolic acidosis. This may further exaccerbate the hyperkalaemia due to the movement of K^+ out of the cells.

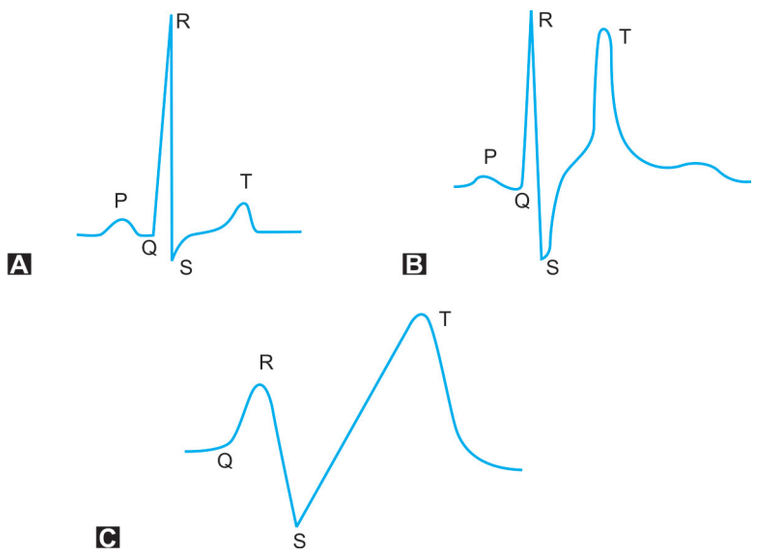


Fig. 10.4A to C: The effects of hyperkalaemia on ECG. It is characterised by : loss of P wave, decrease in amplitude of R-wave, ST-segment depression, widening of QRS complex, shortened QT interval and peaked T-waves. Thus the graph of ECG resembles a 'sine wave'.
A = Normal ECG, B = Transition, C = Sine wave

Treatment

Chronic hyperkalaemia is commonly due to the impaired K^+ excretion by kidney, except some rare causes. If the aetiology is not readily apparent and the patient is asymptomatic, then the pseudohyperkalaemia should be thought first and excluded. The severe chronic renal insufficiency due to oliguric acute renal failure, caused by hypovolaemia also should be ruled out. The history will also guide regarding the excessive K^+ intake or any drug that impairs the handing of K^+ causing hyperkalaemia. The estimation of effective circulating volume, extracellular fluid component or urine output are also essential part of the physical examination which help to find out the exact aetiology of hyperkalaemia. The severity of hyperkalaemia is determined by the symptoms, plasma K^+ concentration and ECG abnormalities.

The appropriate renal response to hyperkalaemia is to excrete at least 200 m.mol/day of K^+. In most cases, the reduced renal K^+ loss is due to the impaired K^+ secretion. This impaired K^+ secretion again may be due to either hypoaldosteronism (less synthesis) or resistance to its renal effect. This can be determined by evaluating the K^+ loosing response of aldosteron after administration of exogenous mineralocorticoids. Primary adrenal insufficiency should be differentiated from secondary hypoaldosteronism (hyporeninemic hypoaldosteronism) by examining the renin aldosterone axis. Therefore, the plasma renin and aldosterone levels should be measured.

The approach to therapy for hyperkalaemia depends on its degree which is determined by the plasma K^+ concentration, associated muscular weakness and changes on the ECG. Potentially the fatal effect of hyperkalaemia rarely occurs unless the plasma K^+ concentration goes above 7 m.mol/L which is associated with profound weakness, QRS widening, absence of P-waves or vantricular arrhythmia with cardiac arrest. Hence, to avoid this lethal outcome, plasma K^+

concentration exceeding 6 m.mol/L should always be treated immediately. The treatment of hyperkalaemia is aimed at reversing the cardiac manifestation, removing the muscle weakness and restoring the plasma K^+ concentration to normal. The treatment modalities should depend on the severity of manifestations and the cause of hyperkalaemia.

Severe hyperkalaemia requires emergency treatment directed at minimizing the membrane depolarization, shifting K^+ into the cells and promoting the K^+ loss. In addition the exogenous K^+ intake and antikaliuretic drugs should be discontinued. In emergency, calcium gluconate is the drug of choice and reduces the membrane excitability. The usual dose of calcium gluconate is 5 to 10 ml of 10% solution which is administered over 2 to 3 minutes. Its effects are very rapid (within minutes) and antagonizes the cardiac effects of hyperkalaemia. But, unfortunately, the results is very short lived (30 to 60 minutes) and the dose should be repeated. If the initial dose of calcium gluconate can not produce any change in ECG, then the 2nd dose also can be repeated after 5 to 10 minutes. Instead of calcium gluconate, calcium chloride also can be used in the dose of 3 to 5 ml of 10% solution.

Insulin causes K^+ to shift into the cells by mechanism described before and is so used to treat hyperkalaemia. It is used with glucose, because glucose also stimulate the secretion of endogenous insulin and prevents hypoglycaemia if occurs. Only glucose also can be used to treat hyperkalaemia by stimulating the pancreatic β cells to release insulin. But this action is very delayed. The recommended dose of exogenous insulin is 10 to 20 units of regular veriety with 25 to 50 gm of glucose. If effective the plasma K^+ concentration will fall by 1 to 1·5 m.mol/L in 20 to 30 minutes and the effect will last for several hours. Hyperglycaemic patients should not be given glucose. They will only receive insulin. Acidosis causes shifting of K^+ out of the cells and hyperkalaemia. Therefore, alkali therapy with intravenous $NaHCO_3$ shifts K^+ into the cells and reduce hyperkalaemia. This is administered as an isotonic solution in the dose of 130 m.mol/L and will decrease the plasma K^+ conc within 20 minutes. Ideally alkali should be reserved for severe hyperkalaemia which is associated with metabolic acidosis. β-adrenergic agonist also promote the cellular uptake of K^+. Thus, it may be useful in acute hyperkalaemia associated with massive transfusions. When it is administered pareterally or in nebulized form, the onset of action is 30 minutes and lowers the plasma K^+ concentration by 0·5 to 1·5 m.mol/L. This effect lasts for 2 to 4 hours.

If the renal function is adequate, then the loop and thiazide diuretics (often in combination) may enhance K^+ excretion. So, they may be used as an adjunct to the management of hyperkalaemia. Sodium polystyrene sulfonate is a cation exchange resin. It also pormotes the excretion of K^+ in exchange of Na^+ in the GI tract. It is used through oral or rectal route and each gram binds with 1 m.mol of K^+ and release 2 to 3 m.mol of Na^+. When given by mouth the usual dose of sodium polystyrene is 25 to 50 gm which is mixed with 100 ml of 20% sorbitol to prevent constipation. This will lower the plasma K^+ concentration by 0·5 to 1 m.mol/L within 1 to 2 hour of its administration and the action lasts for 4 to 6 hours. Another way of treating hyperkalaemia is dialysis. It is effective in severe and refractory hyperkalemia. Among the dialysis, haemodialysis is more safer and effective than peritoneal dialysis. The rate of decreases of plasma K^+ level by haemodialysis is 50 m.mol/h, whereas the rate of removal of plasma K^+ level by peritoneal dialysis is only 15 to 20 m.mol/hour.

Anaesthetic Consideration

It is the general agreement that plasma K^+ concentration should be kept below 5·5 m.mol/L before any elective anaesthesia and surgery. If this is not possible elective anaesthesia and surgery should be postponed in patients with hyperkalaemia. In emergency circumstances anaesthetic technique should be adjusted simultaneously at both direction such as by preventing any further increase and lowering the plasma K^+ concentration by previously mentioned different techniques. Ventilation always should be controlled and monitored by capnography to prevent the accumulation of CO_2 causing respiratory acidosis which could result in transfer of K^+ from intracellular to extracellular sites. It is found that 10 mm decrease in P_aCO_2 causes decrease in plasma K^+ concentration by about 0·5 to 1 m.mol/L. Metabolic acidosis due to arterial hypoxaemia should also be considered which prevents hypokalaemia. The use of succinylcholine is contraindicated in the presence of hyperkalaemia, because there is no reliable method to prevent succinylcholine induced K^+ release.

Care should be given regarding the periopertive intravenous fluid, because most of the solutions contain K^+, as for example lactated Ringer's solution contain K^+ in the concentration of 4 m.mol/L. Hyperkalaemia accentuates the effect of muscle relaxants and decreases its intraoperative requirements. So, the practical approach in such circumstances is to titrate the dose of neuromuscular blocking agent by the use of nerve stimulator. Unlike the plasma Na^+ concentration, hyperkalaemia is not associated with alterations in the dose requirement of volatile anaesthetics.

Intraoperatively all the patients should be monitored carefully and continuously by ECG. Drugs such as Ca^{2+}, glucose and insulin should be kept ready for any acute hyperkalaemia.

CALCIUM BALANCE

Introduction

Calcium (Ca^{2+}) is the principal component of human skeleton and is the 4th most common inorganic element in the body. The total calcium content of a normal

adult human body is about 20 to 25 gm/Kg of lean body mass (LBM). The bone and teeth constitutes about the 98% of the total body calcium. The remaining 2% of it is distributed in different tissues of body such as muscle, plasma, lymph, liver, etc. In plasma the Ca^{2+} level (ionized plus nonionized) varies between 9 to 11 mg/100 ml of blood. This level is maintained fairly constant and is very critical. Calcium (Ca^{2+}) in the plasma is remained in the following form: diffusible and nondiffusible. Diffusible calcium again remains in two forms— ionized and non ionized. The examples of ionized Ca^{2+} in plasma are : $CaCl_2$, Ca-gluconate, etc and the examples of non ionized Ca^{2+} in plasma are Ca-citrate, Ca-bicarbonate, Ca-phosphate, etc. The nondiffusible Ca^{2+} remains in plasma in combination with plasma protein, specially albumin (Fact file- III).

Among the total plasma Ca^{2+}, 50% remains as free ionized form and the remaining 40% stays as protein bound. Then, another 10% remains as complex with anion such as citrate and amino acids. Within these, it is the free ionized Ca^{2+} which is the most physiologically important. Normally, the concentration of free ionized Ca^{2+} in plasma is 4·5 to 5·5 mg/dl or 2·38 to 2·66 mEq or 1·19 to 1·33 m.mol/L. (Here mEq and and m.mol are not numerically same as the valency of Ca^{2+} is two and m.mol is obtained by dividing the mEq by valency). Lowering of this free ionized Ca^{2+} concentration due to any cause produces tetany. However, the reduction of the total calcium content in the body or the non diffusible portion in the plasma due to diminished plasma protein does not cause tetany. It proves changes in plasma protein (mainly albumin) concentration affect the total Ca^{2+} content of the body, but not the ionized Ca^{2+} concentration. The general rule is that for each increase or decreae of 1 gm/dl of albumin, the total plasma Ca^{2+} level increases or decreases approximately 0·8 to 1 mg/dl, respectively. The free ionized plasma Ca^{2+} level also changes directly with the changes of blood pH. This is due to the changes of degree of protein binding capacity of Ca^{2+} (Fig. 10.5).

FACT FILE - III

Molecular weight of calcium is 40. Body content of it is regulated by PTH-related protein, vit D and calcitomin. The intracellular Ca^{2+} concentration is very low which is 100 n.mol/L. This is due to active pumping out of Ca^{2+} from the cell and active pumping in into the sarcoplasmic reticulum. The extracellular concentration of Ca^{2+} is 1 m.mol/L.

Alkalosis decreases the concentration of ionized Ca^{2+} and acidosis increases it. The thumb rule is that the concentration of ionized Ca^{2+} increases approximately 0·16 mg/dl for each decrease in 0·1 unit of plasma pH and vice versa. The plasma phosphate concentration also varies inversely with the plasma Ca^{2+} level. An increase in the phosphate ions cause a corresponding decrease in Ca^{2+} ion and vice versa. However, the product of calcium and inorganic phosphate of blood (10 mg Ca^{2+} × 5 mg PO_4^{2-}) is kept constant and is about 50. This inverse relation of pH and phosphate concentration of plasma with Ca^{2+} in blood may be due to the increased excretion or deposition of Ca^{2+} in the bones.

Ca^{2+} has enormous importance for the function of body. It is involved in nearly all the essential biological functions. These are: contraction of heart muscle, coagulation of blood, maintenance of normal neuromuscular excitability, release of different neurotransmitter and hormones, activation of different enzymes, control of permeability of capillary endothelium, formation of bones and teeth, etc. Although 2% of body weight is constituted by calcium and 98% of this total body calcium is in the bone and teeth, still the maintenance of remaining small extracellular or plasma Ca^{2+} concentration is crucial for homeostasis. In adult the Ca^{2+} intake and loss are same. This is called the calcium balance. When Ca^{2+} is retained in the body, then the balance is called positive. It is found during growth, pregnancy, etc or during recovery after calcium starvation. On the otherhand, when the loss of Ca^{2+} is more than the intake, then the balance is called negative. It is found during the hyperactive condition of thyroid and parathyroid, in calcium deficiency and in certain other diseases such as rickets, osteomalacia, etc.

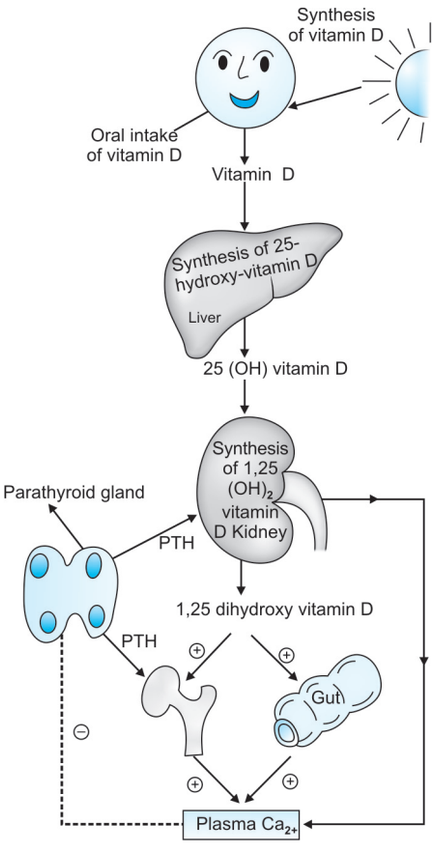


Fig. 10.5: The homeostasis of Ca^{2+} which is maintained by interaction between PTH and vitamin D. Only ionized free Ca^{2+} controls the secretion of PTH. Normally 50% of total plasma Ca^{2+} exists in serum as free ionized form. Remaining 40% of Ca^{2+} exists as protein bound, mainly with albumin. Next remaining 10% of Ca^{2+} exists as complexed form with organic compound such as citrate, phosphate, etc.

The average intake of Ca^{2+} in adults is about 700 mg/day. It is absorbed mainly through the upper part of small intestine under the influence of vit D and parathyroid hormone (PTH). Its absorption varies greatly according to the different types of food. On high protein diet only 20% of dietary Ca^{2+} is absorbed, while on low protein diet it is

only 5%. Upto 80% of the daily Ca^{2+} intake is normally lost through faeces. Soluble inorganic forms of Ca^{2+} is much better absorbed. It is probable that the organic Ca^{2+} in food is converted to inorganic form, before it can be absorbed. Insoluble Ca^{2+} compounds are never absorbed. Thus, the presence of phytic acid in cereals produces formation of calcium phytate which is insoluble and does not absorbed. Oxalates may have the similar effect. Calcium phosphates are also not absorbed.

Ca^{2+} is also excreted through urine which is about 150 to 200 mg/day, but it may varies from as low as 50 mg/day to 300 mg/day. About 98% filtered Ca^{2+} is reabsorbed through the proximal renal tubules and the ascending limb of the loop of Henle. This is parallel to the reabsorption of Na^{+}. But the difference is that the distal renal tubular reabsorption of Ca^{2+} is controlled by parathyroid hormone (PTH). This is unlike the Na^{+} whose reabsorption is controlled by aldosterone at the distal site. The PTH is secreted by the chief cells of parathyroid gland. It also increases the absorption of Ca^{2+} from the gut and mobilises Ca^{2+} from bone into the plasma. The increased secretion of PTH also enhances the reabsorption of Ca^{2+} in the distal nephron and decreases its excretion and vice versa.

Control of Calcium Metabolism

The plasma Ca^{2+} level is normally maintained by equal amount of input and output. The input of Ca^{2+} is related to: absorption from GI tract, reabsorption from bone, and reabsorption by kidney. In contrast the output of Ca^{2+} is related to: depostion in bone, urinary excretion, secretion into the GI tract, and sweat formation. All these input and output and the subsequent plasma Ca^{2+} level is closely regulated by three hormones: PTH, vit D, and calcitonin which act primarily on bone, distal renal tubules and the small bowel.

Among these factors, PTH is the most important agent for regulation of plasma Ca^{2+} concentration. Normally, it increases the plasma Ca^{2+} level by: mobolizing Ca^{2+} from bone, increasing renal reabsorption of Ca^{2+} and excretion of PO_4^{2-} at distal tubule and increasing indirectly the intestinal absorption of Ca^{2+} via acceleration of 1,25- dihydroxy cholecalciferol (DHCC) synthesis in kidney. The secretion of PTH from parathyroid gland is regulated by the plasma Ca^{2+} level (Fact file- IV). Increase in plasma Ca^{2+} concentration decreases the secretion of PTH and vice versa.

Vitamin D also helps in Ca^{2+} homeostasis in body. It exists in several form, but the most active biological form of it is 1,25-DHCC. It is formed from the cholecalciferol, first in the liver by conversion to 25-cholecalciferol and then in the kidney by conversion to 1,25-DHCC. The last conversion of vit D is catalyzed by PTH. Like PTH, the active biological form of vit D also helps in intestinal absorption of Ca^{2+}, renal reabsorption of Ca^{2+} and potentiation of the action of PTH on bone.

Calcitonin is another polypeptide hormone whose action is opposite to PTH. It also helps in Ca^{2+} homeostasis in the body. It is secreted from the para follicular cells of the thyroid gland. It inhibits the mobilisation of Ca^{2+} from bone and increases the excretion of Ca^{2+} through urine by inhibiting its reabsorption at distal renal tubules. Thus, the calcitonin tries to decreases the plasma Ca^{2+} level in oppose to the action of PTH. Hence, hypercalcaemia stimulates its secretion and hypocalcaemia inhibits its secretion from parafollicular cells of thyroid glands.

There are two types of disturbances of Ca^{2+} balance: hypercalcaemia and hypocalcaemia.

FACT FILE - IV

Parathyroid hormone (PTH) has direct effect on bone and renal tubules. It promotes reabsorption of Ca^{2+} from bone and renal tubules. It has also indirect effect which is mediated by increasing the conversion of 25-hydroxycholecalciferal to the more potent hormone 1,25-dihydroxycholecalciferol (DHCC). This results in increased Ca^{2+} absorption from food in gut and increased mobilisation of Ca^{2+} from bone. In regulating Ca^{2+} homeostasis, PTH plays an important role. This is because dietary Ca^{2+} and vit D are rarely deficient. 98% of total body calcium is in bone. This remains in dynamic equilibrium between extracellular fluid and store, by the process of deposition and reabsorption.

Hypercalcaemia

Hypercalcaemia is one of the most common biochemical abnormalities. It is detected most frequently during routine biochemical analysis in asymptomatic patients. It may present with chronic symptoms or occasionally patients present as acute emergencies with severe hypercalcaemia and dehydration. It occurs as a result of variety of disorders which are associated with increased or decreased secretion of PTH. In primary hyperparathyroidism the primary or intital defect lies in the parathyroid gland which causes independent increaed secretion of PTH and hypercalcaemia. In hypercalcaemia due to other cause (described in table) there is decreased secretion of PTH. This decreased secretion of PTH (effect not the cause) is due to the reflex suppression of its secretion by hypercalcaemia due to other causes. In chronic hypocalcaemia due to other causes there is reflex compensatory increase in hypersecretion of PTH. This secondary hyperparathyroidism can however sometimes result in gradual autonomous secretion of PTH and subsequent hypercalcaemia. This is called tertiary hyperparathyroidism.

Hypercalcaemia is also associated with malignancy. In malignancy this hypercalcaemia is due to abnormal secretion of some humoral mediators (such as PTH like substances, prostaglandins, cytokines etc) from tumour cells which release Ca^{2+} from bones or due to direct bony metastases. In Paget's disease and chronic immobilization, hypercalcaemia is due to increased turnover of Ca^{2+} from bone. Hypercalcaemia in the milk alkali syndrome, granulomatous disease (e.g. sarcoidosis), hypervitaminosis of vitamin D,

etc. is due to the increased GI absorption of Ca^{2+}. Still in many circumstances, the mechanism responsible for hypercalcaemia is poorly understood.

Clinical Manifestations

The most of the patients of hypercalcaemia are asymptomatic. About 50% of patients with primary hyperparathyroidism and hypercalcaemia may go unregonised until patient presents with some renal calculi. 10% of first stone formers and 20% of recurrent stone formers have primary hyperparathyroidism. Patients of hypercalcaemia due to malignancy can have a rapid onset of symptoms or may have clinical features according to the site of malignancy which help to localise their pathology. Hypertension is common in hypercalcaemia. Other symptoms and signs of hypercalcaemia include polyuria, polydypsia, renal colic, anorexia, nausea, lethargy, dyspepsia, etc. Peptic ulcer, pancreatitis and renal failure may also complicate the hypercalcaemia. The ECG signs of hypercalcaemia include shortened ST segment, shortened QT interval, premature ventricular contraction due to depressed cardiac conductions, etc. (Table 10.5).

Table 10.5: Causes of hypercalcaemia

A.	**With elevated PTH levels**
	• Primary hyperparathyroidism
	• Tertiary hyperparathyroidism
	• Lithium induced hyperparathyroidism
B.	**With low PTH levels**
	• Milk-alkali syndrome
	• Malignancy
	• Multiple myeloma
	• Paget's disease of bone
	• Vitamin D hypervitaminosis
	• Granulomatous disorder (tuberculosis, sarcoidosis)
	• Thiazide diuretics

Diagnosis and Treatment of Hypercalcaemia

The most important step in the management of hypercalcaemia is the measurement of PTH level by specific radioimmunoassay. If the PTH and urinary calcium level is elevated, then diagnosis about hyperparathyroidism is confirmed. On the other hand, if PTH level is low, urinary Ca^{2+} is high and no other apparent cause of hypercalcaemia is found, then malignancy with or without bony metastases is very likely. Low plasma phosphate and increased alkaline phosphate level support the diagnosis of primary hyperparathyroidism or malignancy. Hypercalcaemia may cause nephrocalcinosis and impairment of renal tubular function, causing hyperuricaemia and hyperchloraemia. Unless the source of hypercalcaemia is obvious, all the patients should be screened for malignancy with X-ray, MRI or isotope bone scan. The patient should also be screened for myeloma by ESR, serum protein electrophoresis, level of immunoglobulins, and urinary Bens Jones protein.

Symptomatic hypercalcaemia is usually associated with dehydration. So, it requires rapid treatment by rehydration which is accomplished by administration of IV saline (to replace as much as 4 to 6 L deficit of water or to keep urinary output at 20 to 30 ml/h). This rehydration should be followed by brisk diuresis to accelerate the excretion of Ca^{2+}. Regarding diuresis the clinician should be cautious that premature diuresis or excessive diuresis after rehydration may increase the plasma Ca^{2+} level by additional fluid depletion. During rehydration the patient may need monitoring with CVP in old age or who is suffering from renal impairment. After rehydration and diuresis the plasma Ca^{2+} level may come down, but still remains above the normal level, though the potential risk for cardiovascular and neurological complications of hypercalcaemia are removed.

Patients who are not responding to proper rehydration and mild diuresis or have severe hypercalcaemia (total Ca^{2+} >15 mg/dl) may require additional therapy by bisphosphonates, glucocorticoids or calcitonin. Among the bisphosphonates, pamidronate is used in the dose of 90 mg IV slowly over 4 hours. It is the agent of choice in hypercalcaemia, because of its prolonged duration of action. Pamidronate causes a fall in plasma level of Ca^{2+} which is maximum at 2 to 3 days and lasts for few weeks. Unless the cause of hypercalcaemia is removed such as by the surgical removal of parathyroid gland, the patient should be followed up with an oral bisphosphonate after an emergency IV therapy. Calcitonin for the treatment of hypercalcaemia is used in the dose of 2 to 5 U/Kg through subcutaneous route. Haemodialysis for the treatment of hypercalcaemia may be necessary in the presence of cardiac or renal failure. Glucocorticoids is helpful in the setting of vit D induced hypercalcaemia such as granulomatous disease states.

Hypercalcaemia in patients with primary hyperparathyroidism responds less well to pamidronate and glucocorticoids than the hypercalcaemia due to malignancy. Urgent removal of parathyroid gland in primary hyperparathyroidism (such as adenoma, hyperplastic gland) is occasionally required, but strenous attempts should be made to replace the fluid deficits and lower the plasma Ca^{2+} level before administering anaesthesia in such patient. Post operative hypocalcaemia is not uncommon after the removal of parathyroid gland during the first two weeks after surgery. But the residual suppressed parathyroid tissue gradually recovers and plasma Ca^{2+} level comes to normal.

Anaesthetic Consideration

Before and during the operation of a hypercalcaemic patient every attempt should be made to normalise the ionised plasma Ca^{2+} level, if it is already high and to avoid the circumstances which will raise it. So, perioperative acidosis should be checked by any cost. Therefore, ventilation must be controlled and monitored by capnography during GA. Adequate hydration should

be continued pre and intraoperatively with great care to avoid hypervolaemia. So, IV fluid therapy in hypercalcaemic patient should be monitored by CVP or pulmonary artery pressure, especially in patients with decreased cardiac reserve. The periodic measurement of K^+ and Mg^{2+} level in plasma also should be done during rehydration and diuretic therapy for detection of any iatrogenic hypokalaemia and hypomagnesemia in hypercalcaemic patients. At last patient should be monitored periodically by checking the plasma ionized Ca^{2+} level through out the whole perioperative period.

Table 10.6: Causes of hypocalcaemia

	Ionized Ca^{2+} concentration	*Total Ca^{2+} concentration*	*Plasma PTH concentration*	*Plasma phosphate concentration*
Hypoparathyroid	↓	↓	↓	↑
Pseudohypoparathyroid	↓	↓	↑	↑
Alkalosis	↓	N	N	N
Renal failure	↓	↓	↑	↑
Vitamin D deficiency	↓	↓	↑	↑
Hyperphophatemia	↓	↓	↑	↑
Precipitation of Ca^{2+}	↓	↓	↑	↑
Pancreatitis				
Fatembolism				
Chelation of Ca^{2+}	↓	↓	↑	↑

↑ = Increased, N = Normal, ↓ = Decreased

Hypocalcaemia

The incidence of hypocalcaemia is less common than that of hypercalcaemia. It should be diagnosed only on the basis of plasma ionized free Ca^{2+} concentration, but not on the basis of total plasma Ca^{2+} concentration or total body Ca^{2+} content. Because the most common cause of hypocalcaemia is low plasma albumin with normal free ionized Ca^{2+} concentration. Contrary, ionized free Ca^{2+} level may be low in the face of normal plasma Ca^{2+} concentration during alkalosis as a result of hyperventilation. Therefore, when the direct measurement of plasma free ionized Ca^{2+} level is not available then the total plasma Ca^{2+} concentration should be corrected for increase or decreae of plasma albumin level. Hence, as almost all the laboratories routinely report the total serum Ca^{2+} concentration, but it is the ionized concentration which is biologically important and should be measured (Table 10.6).

Symptomatic hypocalcaemia is most commonly due to decreased plasma Ca^{2+} concentration resulting from hypoparathyroidism. On the otherhand, this hypoparathyroidism may be due to surgical, idiopathic or pseudo causes. Surgical hypoparathyroidism commonly occurs during thyroid surgery, but this complication is only permanent in 1% of thyroidectomy. Transient hypocalcaemia develops in 10% of patients after 12 to 36 hours, following subtotal thyroidectomy for Grave's disease. Idiopathic hypoparathyroidism is sometimes occurred with autoimmune disease of the adrenal gland, thyroid gland or ovary at any age. Pseudo hypoparathyroidism is usually an autosomal dominant syndrome where there is development of tissue resistance to PTH. Hypoparathyroidism may be associated with hypomagnasemia, because deficiency of magnesium is postulated to impair the secretion of PTH and antagonize its effects on bone. In chronic renal failure, hyperphosphotemia may also be the common cause of hypocalcaemia. Hypocalcaemia may also occur as the result of vitamin D deficiency which again may result from malabsorption, reduced intake or abnormal metabolism of vitamin D.

Acute severe ionized hypocalcaemia may also occur when the large amount of Ca^{2+} chelating agents such as citrate are administered during blood and plasma transfusion. The degree of hypocalcaemia during transfusion of blood depends on the rate of administration and the ability of bone to provide additional Ca^{2+} and the liver which metabolises the citrate. Similarly, transient hypocalcaemia may also result following the rapid infusion of large amount of albumin. Another cause of hypocalcaemia is pancreatitis. It is due to precipitation of Ca^{2+} with fats, following the release of lipolytic enzymes and fat necrosis.

Other less common cause of hypocalcaemia include: hypersecretion of calcitonin (e.g. calcitonin secreting medullary carcinoma of thyroid) and use of large dose of heparin, protamine, glucagon, etc.

Clinical Manifestations

The fall of ionized Ca^{2+} concentration increases the relative proportion of neuroexcitatory ions such as Na^+, K^+, PO_4^{2-}, etc, and produces hyper excitability of peripheral nerves. This is called tetany. It is the clinical manifestation of hypocalcaemia and occurs when the ionized free Ca^{2+} concentration goes below 0·8 m.mol/L (3·2 mg/dl) in the absence of alkalosis or total plasma calcium level is < 2m.mol/L (or < 4 mEq/L). Alkalosis may be produced by excess intake of alkali, profuse vomiting or increased breathing. It causes tetany without reducing the total plasma Ca^{2+}. This is because alkalosis alters the ionic balance and decreases the amount of ionic free Ca^{2+} without affecting the total Ca^{2+}concentration. Also alkalosis increases the proportion of the neuroexcitatory ions and makes the peripheral nerve fibres and central nervous system more excitable. Children are more sensitive to tetany than adult. Magnesium depletion should also be considered as a possible

contributing factor for hypocalcaemia and tetany.

Tetany is commonly manifested in children as a triad of carpopedal spasm, laryngeal stridor and convulsion, though one or more of these signs may be found independent of others. In carpopedal spasm the hand adopts a characteristic figure which include flexed (Fig. 10.6) metacarpophalengeal joint, extended interphalangeal joint of fingers and thumb, and apposition of thumb with fingers. Stridor is caused by the closer of glottis. Furthermore, the adult patients complain of feeling of tingling sensation in the hands and feet, and around the mouth. The latent tetany also may be present when the signs of overt tetany are lacking. It is best recognised by eliciting the carpopedal spasm by inflating the sphygmomanometer cuff on the upper arm above the systolic BP. A less specific sign of hypocalcaemia is Chvostek's sign where tapping on the facial nerve near the styloid process causes twiching of the facial muscles.

Other clinical manifestations of hypocalcaemia include paresthesia, confusion, lethargy, cardiac irritability leading to arrhythmia, decreased cardiac contractility causing hypotension, etc. ECG findings are not chracteristic of hypocalcaemia.

Treatment

Symptomatic hypocalcaemic or tetany is a medical emergency condition. So, it should be treated immediately. Instant IV injection of 10 to 20 ml of 10% Ca-gluconate will gradually raise the serum free Ca^{2+} concentration and control the situation. Instead of a Ca-gluconate, 3 to 5 ml of 10% $CaCl_2$ also can be used. However, during IV administration of calcium, it should be remembered that 1 gm of Ca-gluconate contains 90 mg (or 45 mEq or 225 m.mol) of calcium and 1 gm of $CaCl_2$ contains 272 mg (136 mEq or 68 m.mol) of calcium. Also, it should be kept in mind that 1000 mg of Ca-gluconate and 400 mg of $CaCl_2$ provides the same 100 mg of elemental calcium and when any commercial preparation of Ca^{2+} is given as equal amount of elemental calcium, the influence of different preparation on ionized Ca^{2+} is equivalent. During the management of hypocalcaemia, serial measurement of ionized free Ca^{2+} level in plasma is mandatory. The Ca^{2+}, Mg^{2+}, PO_4^{2-} and K^+ are predominantly intracellular ions. So, their abnormalities frequently coexist with hypocalcaemia. Therefore, their plasma concentration should be checked periodically, particularly PO_4^{2-} and Mg^{2+} and should be treated. After the initial bolus dose, repeated bolus doses or continuous infusion of Ca^{2+} in the dose of 0·5 to 2 mg/Kg/hour may be necessary to obtain a prolonged effect of calcium therapy.

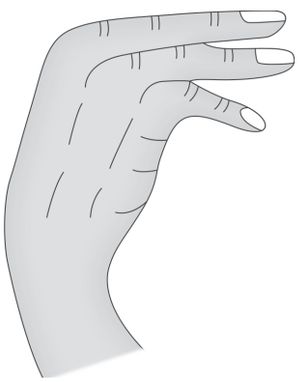


Fig.10.6: Carpopedal spasm or Trousseau's sign

An intramuscular injection of 10 ml Ca-gluconate may also be given to obtain a more prolonged effect. To control tetany alkalosis should also be reversed acutely. This can be accomplished by encouraging the rebreathing of expired air in a paper bag or administering 5% CO_2 in O_2.

Anaesthetic Consideration

During anaesthesia of a hypocalcaemic patient in the perioperative period, one should always try to recognize and treat the adverse effects of hypocalcaemia. An anaesthesiologist will also give his full effort preventing the further decrease of plasma Ca^{2+} level in the face of hypocalcaemia, once it is checked. Therefore, alkalosis should be prevented by avoiding hyperventilation and monitoring it by capnometre. During treatment of metabolic acidosis by $NaHCO_3$, hence, one should be careful about the overdrive alkalosis and will repeatedly check the ionized plasma free Ca^{2+} level in patient with the history of hypocalcaemia. There is chance of developing life threatening hypocalcaemia during GA, in patient with renal insufficiency, under going vascular surgery. In such circumstances a clinician should be very careful and will take proper measures.

Normally, administration of few units of whole blood, containing citrate as preservative, does not cause any probelm. This is because Ca^{2+} is rapidly mobilised from body stores which is kept as reserve and maintain the normal plasma Ca^{2+} level. But, during emergency, when the citrated blood is transfused very rapidly e.g. 500 ml in every 10 minutes, then there is chance of patient developing hypocalcaemia. This chance of hypocalcaemia is further aggravated in the presence of cirrhosis of liver, hypothermia and renal dysfunction where metabolism of citrate is impaired.

Continuous monitoring by ECG is useful during perioperative period to facilitate the diagnosis of hypocalcaemia. It produces cardiac depression and hypotension. Hence, anaesthetic agents which have negative inotorpic effects on heart such as barbiturates, volatile agents, etc; should be used carefully. Responses to neuromuscular blocking agents can be potentiated by hypocalcaemia. So, their use should be monitored by nerve stimulator. Lastly, during intraoperative interpretation of plasma free Ca^{2+} level, importance should be given to the transfusion of protein (albumin) and colloid during hypotension due to surgical trauma. This is because plasma albumin and colloid level change the free ionized Ca^{2+} level, though the total plasma Ca^{2+} level remains same.

11 Autonomic Nervous System and its Pharmacology

INTRODUCTION

All the functions of our body are controlled by nervous system. It is divided anatomically into peripheral nervous system (consists of peripheral nerves) and central nervous system (consists of the brain and the spinal cord) and physiologically into somatic nervous system and autonomic nervous systems (ANS). The somatic nervous system controls the function of our body's voluntary muscles and helps in carrying different somatic sensations from the skin, joint, muscles, and the other structures of body. On the other hand, the autonomic nervous system is a part of the nervous system which controls different activities of visceras, blood vessels, glands, and other parts of our body which are not under our direct control. Almost a century ago, in 1898 the autonomic nervous system was actually described first by Langley. It was called at that time as the visceral, vegetative or involuntary nervous system. Unlike the somatic nervous system, in periphery the ANS consists of nerves, ganglia and plexuses which innervate the heart lungs, blood vessels, glands, other viscera and smooth muscles in various tissues. Therefore, it is widely distributed throughout the body and regulates their function over all visceras except voluntary muscles and somatic sensation, without a person's conscious control. So, its actions are generally independent of a person's will and below the level of consciousness.

Like the somatic nervous system, ANS also has both the central and peripheral divisions and afferent and efferent paths. But, unlike the somatic nervous system, the control of ANS is mostly homolateral. On the other hand, like the somatic nervous system it has got both the spinal (Fig. 11.1) and cranial outflows. Higher centres like the hypothalamus, thalamus, corpus striatum and cerebrum control this autonomic nervous system. Certain other special higher centres, situated in the medulla, pons and midbrain are also included in this system and control it.

The activities of the somatic and autonomic nervous system always run in parallel. But, at many important levels of the central nervous system, there are free intercommunications between these two nervous systems. However, cerebrum controls both these systems. Although involuntary, yet the autonomic nervous system is not altogether beyond the voluntary control. For example, by meditation and yoga the HR, BP, visceral sensation, etc, which are controlled by the ANS can be modulated.

All the innervated structures of our body, except some parts of the skeletal muscles and cutaneous sensory structures, which are innervated by the somatic nerves are supplied by the ANS. The important difference between the autonomic and the somatic nervous system is that the most distal synaptic junction in the ANS which occur in the ganglia are situated entirely outside the cerebrospinal axis. This is unlike to the somatic nervous system where the most distal synaptic

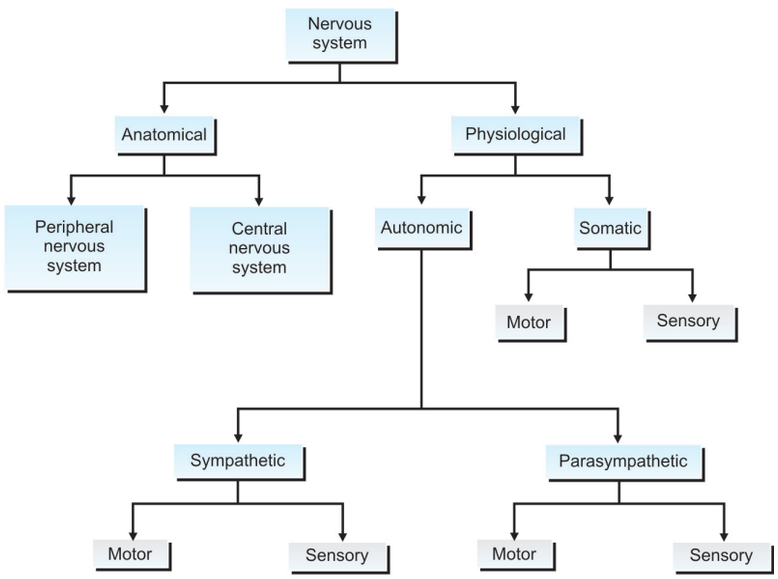


Fig. 11.1: Classification of the nervous system

connections lie with in the spinal cord, or anywhere within the cerebrospinal axis. These ganglia of ANS which are situated outside of cerebrospinal axis are small and complex in structures and contain axodendritic synapses between the preganglionic and postganglionic neurons. Whereas the somatic nervous system contains no peripheral ganglia and the most distal synapses between the pre- and post-ganglionic neurons are located entirely within the cerebrospinal axis.

The autonomic nerves which are situated outside (Table 11.1) the cerebrospinal axis form an extensive peripheral plexuses on organs, but such network is absent in somatic nervous system. All the nerves of somatic nervous system are myelinated and has no peripheral ganglion. So there is no question of preganglionic or postganglionic fibres in the somatic nervous system, as it comes directly from the anterior horn cells of spinal cord or from the nuclei of cranial nerves as postganglionic fibres. On the other hand, the preganglionic fibres of the ANS is myelinated, but the postganglionic fibres are non-myelinated.

A major goal during the administeration of anaesthesia on a patient is to maintain an optimum level of homeostasis or equilibrium between the two divisions of ANS i.e. sympathetic and parasympathetic nervous system during maximum surgical stress and strain. This is because modification and ablation of these stress and strain responses controlled by ANS may improve the perioperative outcome. So, an intelligent administration of anaesthetic care to a patient requires a full and comprehensive knowledge of ANS and its pharmacology. In addition, many diseased states such as diabetes may impair the functions of the ANS to a significant extent and may thereby alter the expected responses of a patient to surgery and anaesthesia.

Like the somatic nervous system, the ANS is also divided into two parts the centres of ANS and the peripheral autonomic nerves (Fig. 11.2).

Centres of ANS

Extensive ramifications of ANS exists in the brain above the level of spinal cord. But, there is no exclusive localised central controlling area for ANS (i.e. the centre of ANS) in the brain. Considerable intermixing and integration of the somatic and the autonomic nervous systems occur there. So, somatic responses are always accompanied by autonomic visceral responses and vice versa. The probable theory is that the highest centre in the brain, regulating ANS is situated in the hypothalamus. Within it the posterior and lateral nuclei are primarily sympathetic, while the anterior and medial nuclei are primarily parasympathetic. Many higher centres of ANS are also located in the pons, midbrain and medulla which are related to the cranial nerves. Therefore, the centres of ANS in the brain and spinal cord consist of the following:

i. Area of ANS controlling the visceral function is located in the cerebral hemisphere. These constitute the limbic system.
ii. Autonomic centres in the brain-stem and medulla are located in the reticular formation and is related to the cranial nerves outflow.
iii. Autonomic centres in the spinal cord are located in the intermedio-lateral column of gray matter of it. In it the intermedio-lateral group of neurons are present in the segments of spinal cord extending from T_1 to L_2 (lateral horn cells) and from S_2 to S_4 vertebral level, constituting the spinal sympathetic and parasympathetic outflow respectively.

The hypothalamus and the nucleus tractus solitarius are generally regarded as the principle loci for integration of all the functions of ANS which include the regulations of body temperature, water balance, metabolism of protein, cardohydrate and fat, regulation of blood pressure, emotions, sleep, respiration, control of sexual responses, etc. During the function of ANS signals are received from different parts of the body through the ascending spinobulbal pathways and also from the limbic system, neostriatum, cerebral cortex and other higher brain centres. Then it reaches to the hypothalamus and nucleus tractus solitarius. Subsequently stimulation of the nucleus tractus solitarius and the hypothalamus activates the descending bulbospinal pathways, and stimulates the hormonal output (which are known as the neurotransmitters of the sympathetic and the parasympathetic system) to mediate the autonomic responses.

Table 11.1: Some differences between autonomic and somatic nervous system

	Autonomic	*Somatic*
Organ innervated	All the visceral organs, blood vessels, glands, etc. except skin and skeletal muscles	Skeletal muscles and skin
Nerve fibres	Preganglionic-myelinated Postganglionic - nonmyelinated	Myelinated (no pre- or postganglionic fibres)
Distal most synapse	Outside CNS (in ganglia)	Within CNS
Efferent transmitter	Acetylcholine and noradrenaline	Acetylcholine
Peripheral plexus	Present	Absent
Effect of nerve section on organ supplied	Activity maintained and no atrophy of organs	Paralysis and atrophy of skeletal muscle and loss of sensation of skin

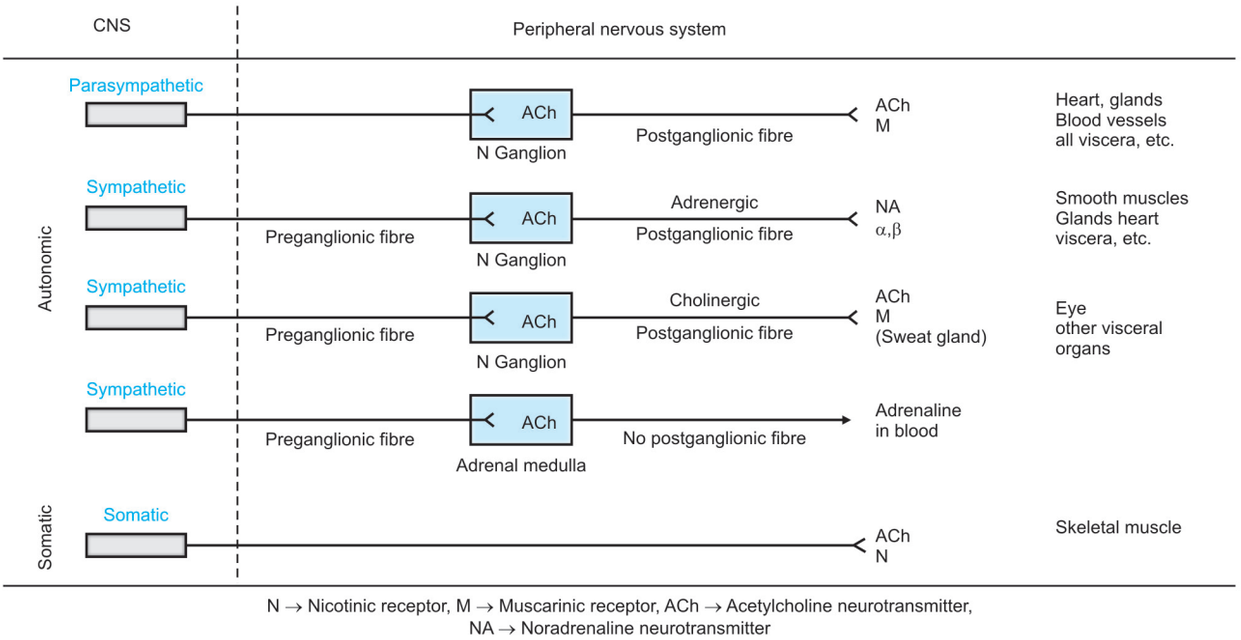


Fig. 11.2: The general outlay of different part of autonomic and somatic nervous system

PERIPHERAL PARTS OF THE ANS

Like the somatic nerves, the peripheral autonomic nerves also has the afferent and efferent fibres.

Autonomic Afferents

Except some local axonal reflexes, most of the visceral autonomic reflexes are mediated through the afferent fibres, the centre of autonomic nerves in cerebrospinal axis (brain and spinal cord) and the effarent fibres. The afferent fibres running from the visceral structures to the spinal cord form the first link of autonomic reflex arc. These autonomic afferent fibres are non-myelinated and are carried to the cerebrospinal axis by the autonomic visceral nerves, such as: vagus, pelvic, splanchnic or other autonomic nerves through which also efferent autonomic fibres come out. For example, most of the fibres (4/5) of vagus nerve are afferent or sensory and rest (1/4) of it are efferent or motor. Many autonomic afferent fibres such as from the blood vessels, skeletal muscles, and certain other integumental structures are also carried through their respective somatic spinal nerves instead of any separate autonomic visceral nerves.

As most of the autonomic visceral nerves carry the non-myelinated autonomic afferent fibres, the cell bodies of these afferent fibres are located in the dorsal or posterior root ganglia of the spinal nerves in vertebral canal, at the spinal level and the sensory autonomic ganglia of cranial nerves, e.g. nodose ganglion of vagus within skull at the cranial level. They transmit different afferent impulses from visceral such as pain, pressure, stretching, etc. which are responsible for the cardiovascular, respiratory and other visceral reflexes. For sympathetic reflexes the dendrites of the neurons of dorsal root ganglion collect impulses from the periphery, and then run through the visceral nerve, sympathetic chain, ganglia (without making any synapse) white ramus and spinal nerve to end in the cell body of dorsal root ganglia. After that the axons of the cell body of dorsal ganglion transmit impulses to the lateral horn cells or the dorsal horn cells of spinal cord.

The neurotransmitter responsible for transmission of these affarent autonomic sensory impulses are not properly known. However, the substances P (neuroactive peptide) is present in abundance in the afferent autonomic sensory fibres of dorsal root ganglia and the dorsal horn cells of spinal cord like the somatic sensory fibre. So, this peptide is considered as the leading candidate among the transmitters that passes the visceral nociceptive stimuli from the periphery to the spinal cord or brain through ANS. Other neuroactive peptides which are also responsible for transmission of autonomic sensory impulses are somatostatin, vasoactive intestinal polypeptide (VIP), and cholecystokinin. Enkephalins, present in the interneuron of dorsal horn cells of the spinal cord (within the area termed the sustantia gelatinosa) also have the visceral antinociceptive effects. It inhibits the release of substance P and diminishes the activity of cells that project from the spinal cord to the higher centres of ANS in CNS. The excitatory amino acids, such as: glutamate and aspartate (which act through the NMDA receptor) also play a major role in the transmission of sensory

responses (both autonomic and somatic) in the spinal cord.

Autonomic Efferents

The efferent or motor pathway of ANS is also functionally divided into the sympathetic and parasympathetic systems. Most of the viscera receives both the sympathetic and parasympathetic innervation and functionally they are antagonistic to each other. However, the level of activity of an innervated internal organ at a given moment is the algebraic sum of the sympathetic and parasympathetic activity during that period. Despite the conventional concept of antagonism between these two divisions of ANS, their activities on specific structure may also be either discrete and independent, or integrated and interdependent. For example, the effects of sympathetic and parasympathetic stimulation on the heart and the iris show a pattern of functional antagonism in controlling the HR and the pupillary aperture. But, their actions on the male sexual organs are complementary to each other and are integrated to promote the whole sexual function. On the otherhand, most of the blood vessels, spleen, sweat glands and hair follicles receive only the sympathetic innervation, while the ciliary muscles, gastric and pancreatic glands, receive only the parasympathetic innervation.

The neurotransmitter for all the efferent preganglionic autonomic fibres (both sympathetic and parasympathetic), all the postganglionic efferent parasympathetic fibres and only few postganglionic efferent sympathetic fibres is ACh (acetylcholine). So, they are called cholinergic fibres. Whereas the neurotransmitter for majority of the efferent postganglionic sympathetic fibres is norepinephrine (NE). So, they are called the adrenergic fibres.

SYMPATHETIC NERVOUS SYSTEM

The activation of sympathetic nervous system elicits reaction what is traditionally called the 'fight or flight' response. It includes: the redistribution of blood flow from the nonvital structure such as skin, different splanchnic regions and skeletal muscles to the vital organs, increased cardiac function, sweating, salivation, pupillary dilatation, etc. Under normal circumstances, the sympathetic system is continuously active and the degree of its activity varies from moment to moment and from organ to organ. The adjustments of body to a constantly changing enviornment are usually accomplished by the sympathetic part of the ANS. Under the circumstances of stress, the lack of sympathetic function becomes evident by the fall of HR, BP, body temperature, etc, and cannot be regulated. Other examples of lack of the effect of sympathetic nervous system are that the concentration of glucose in the blood doesnot rise when it is needed and compensatory responses to haemorrhage, hypoxia, excitement, exercise, etc. are lacking.

The outflow or efferent of sympathetic nervous system takes place only from the thoracolumbar region of spinal cord. It extends from the first thoracic to the 2nd or 3rd lumbar segment of spinal cord. The cell bodies of this spinal component of central part of sympathetic nervous system lie in the lateral horns of the grey matter of the spinal cord (the intermediolateral columns).

The nerve fibres arising from these cell bodies of the lateral horns of the spinal cord extend peripherally to three types of ganglion.

i. paravertebral ganglia, grouped as paired sympathetic chain,
ii. collateral or prevertebral unpaired ganglia,
iii. terminal ganglia near the target organs. (Table 11.2).

The effarent sympathetic nerve fibres first pass out as axons of the lateral horn cells of the spinal cord, and then run through the anterior root of spinal nerves. These preganglionic effarent sympathetic fibres are thinly medulated and β type. So, they are looked white. Then, they leave the spinal nerve in the form of a branch, called the white ramus communicans and enter the ganglion of sympathetic chain. Now, they may end in the corresponding ganglion to create postganglionic fibre or may simply run through the sympathetic chain to other ganglia situated above or below in the same sympathetic chain and there they create the postganglionic fibres. The efferent postganglionic sympathetic fibres which arise from the ganglion of sympathetic chain are non-medulated. Hence, they are looked grey. They run back from the ganglion to join again with the spinal nerve in the form of another branch, called the grey ramous communicans and

Table 11.2: Some differences between the parasympathetic and sympathetic nervous system

	Parasympathetic	*Sympathetic*
Origin	Cranio-sacral outflow (III, VII, IX, X cranial nerves and S_2-S_4 spinal segment)	Dorso or thoraco-lumbar outflow (T_1 to L_2 / L_3 spinal segment).
Ganglia	Situated on or close to the organ supplied.	Situated away from the organs supplied
Pre: Post ganglionic fibre ratio	1:2 to 1:3 (except in enteric plexus)	1:10 to 1:100
Postganglionic fibre	Short	Long
Neurotransmitter at target level	Acetylcholine (ACh)	Noradrenaline (most), ACh (sweat gland, pilomotor, adrenal medula).
Stability of neurotransmitter	ACh - rapidly destroyed and have very local action	NA is stable, diffuses and have actions over wider area.
Important function	Conservation of energy (anabolic)	In stress and emergency (catabolic).

then are ultimately distributed along all the spinal nerves throughout the whole body such as to the pilomotor, pseudomotor (sweat gland), blood vessels, skin and to the other organs of extremities which are not controlled by the somatic nervous system. It is to be noted that all the spinal nerves, extending from the first cervical to the coccygeal vertebral segment, possess gray rami communicans which carry the postganglionic sympathetic fibres and arises from all the ganglia of sympathetic chain and supply the whole body except visceras. But only the thoracic and upper 2 or 3 lumbar spinal nerves have the white rami communicans, which carry the preganglionic fibres to the sympathetic chain arising from 1st thoracic to 2nd or 3rd lumbar spinal segments.

Some preganglionic sympathetic fibres arise directly from the paravertebral ganglia of the sympathetic chain without making any synapses there and run to the prevertebral or collateral ganglion. From there collateral ganglia post-ganglionic sympathetic fibres arise and innervate the visceral structures of the thorax, abdomen, and pelvis. The prevertebral or collateral ganglion supplying the thoracic, abdominal and pelvic viscera contain cell bodies from where the postganglionic fibres arise. They receive preganglionic fibres from the T_5 - T_{12} thoracic segments of the spinal cord directly through the sympathetic chain without making synapses there. Many of the upper thoracic sympathetic fibres arising from the paravertebral ganglia of sympathetic chain form terminal plexuses, such as: the cardiac, oesophageal and pulmonary plexuses and supply these organs. The sympathetic distribution to the head and neck is through the cervical sympathetic chain and its three ganglia. All the postganglionic sympathetic fibres from this cervical chain arise from the cell bodies located in these three cervical ganglia. But, all the preganglionic sympathetic fibres supplying head and neck arise from the lateral horn cells of the upper thoracic segments of the spinal cord, as there are no sympathetic fibres that leave the CNS above the first thoracic level.

Sympathetic Ganglia

There are three types of sympathetic ganglia. These are:

i. Paravertebral ganglia forming the sympathetic chain,
ii. Unpaired prevertebral or collateral ganglia,
iii. Terminal ganglia.

Paravertebral Ganglia

They are about 22 pairs in numbers, (3 cervical, 11 thoracic, 4 lumbar, 4 sacral, and 1 coccygeal) lying on both the sides of the vertebral bodies and are connected with one another by the nerve fibres in the form of a chain which is called the paravertebral sympathetic chain. It extends from the base of the skull to the front of the coccyx. These ganglia are also connected to the spinal nerves by white and grey rami communicans. The white rami are only restricted to the segments of the thoracolumbar outflow, because they carry only the preganglionic myelinated sympathetic fibres that exit from the spinal cord through the anterior spinal roots, arising from the lateral horn cells. The grey rami arises from all the ganglia and carry the postganglionic fibres back to the corresponding spinal nerves for distribution to the sweat glands, pilomotor muscles, blood vessels, joints, skeletal muscles of the trunk and limbs and the skin of whole body. Therefore, as a rule, there should be one ganglion for each spinal or vertebral segment of spinal cord. But, they show a tendency to coalesce at the cervical, sacral and coccygeal region. For instance, the eight cervical ganglia in the neck is fused to form three ganglia, such as: the superior, middle and inferior cervical ganglia. In the thoracic region there are twelve ganglia on each side. The first thoracic ganglion in man sometimes fuses with the inferior cervical ganglion, forming the stellate ganglion. In the lumbar region there are usually four and in the sacral region there are about 4 to 5 ganglia. In the coccygeal region the terminal portions of the two sympathetic chains fuse together and form a single ganglion in front of the coccyx which is called the coccygeal ganglion.

Unpaired Prevertebral or Collateral Ganglia

They lie in the thorax, abdomen and pelvis in close relation to the aorta and its big branches, and supply postganglionic sympathetic fibres to the visceras. These are the coeliac, superior mesenteric, aorticorenal and inferior mesenteric ganglion. The preganglionic sympathetic fibres to the coeliac ganglion are supplied by the lateral horn cells of T_5 - T_{12} spinal segments. The coeliac ganglion innervate the liver, spleen, kidney, pancreas, small bowel and the proximal colon. The preganglionic sympathetic (Fig. 11.3) fibres after arising from the T_5 to T_{12} spinal segments bypass the chain of the paravertebral sympathetic ganglion, without making synapses there and form the greater splanchnic nerve (containing only the preganglionic fibres). It ends in coeliac ganglion and make synapses there. Then, the postganglionic fibres from the coeliac ganglion innervate all the above mentioned visceras forming plexuses over them. Some preganglionic fibres of the splanchnic nerves do not synapse in the coeliac ganglion and innervate the adrenal medulla directly.

The preganglionic fibres arising from the lateral horn cells of the T_{10} to T_{11} segment of the spinal cord may bypass the chain of the paravertebral sympathetic ganglion and form the lesser splanchnic nerve. It ends in the aorticorenal ganglion which is considered as the the lower detached part of the coeliac ganglion. The least splanchnic nerve arises from the lateral horn cells of the 12th thoracic segment of the spinal cord and join the renal plexus. Then it ends in a small ganglia from where the postganglionic sympathetic fibres arise and supply the kidney and the ureter.

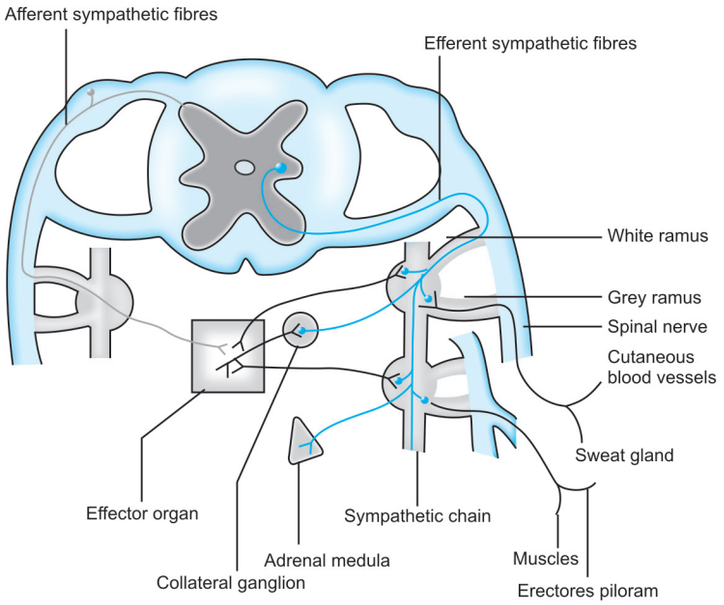


Fig. 11.3: The principles of peripheral distribution of motor and sensory components of sympathetic nervous system. Blue lines are preganglionic sympathetic fibres. Red lines are postganglionic sympathetic fibres. Green lines are sensory sympathetic fibres

The superior mesenteric ganglion innervates the distal colon, and the inferior mesenteric ganglia innervates the rectum, bladder and genitalia.

Terminal Ganglia

They are situated in close relation to the organs which are supplied by them. They are few in number and include ganglia connected with the urinary bladder, rectum and some ganglia in the region of the neck. The adrenal medulla and other chromaffin tissues are homologous to the sympathetic ganglias. This is because all of them are derived embryologically from the neural crest cells. But the adrenal medulla differs from sympathetic ganglia in that the principal catecholamine that is released from adrenal medulla is epinephrine (adrenaline). Whereas, norepinephrine or noradrenaline is the prinicipal catecholamine of other sympathetic ganglion and is also released from the postganglionic sympathetic nerve endings.

The characteristics of sympathetic outflow or efferents are:

i As the sympathetic ganglions are close to the CNS, so the preganglionic fibres are short and postganglionic fibres are long.

ii. The sympathetic efferent distribution is diffuse in character and the response is not confined to the organs supplied by the segments from which they originate. Thus, this allows a more dramatic and widespread response with diffuse discharge from the sympathetic system.

iii. Sympathetic fibres pass through multiple ganglia before it finally synapses with a postganglionic neuron or fibre.

iv. Sympathetic system has an system of amplification. This is because a preganglionic terminal fibre synapses more than twenty postganglionic cells in one ganglion, and thus a large number of postganglionic neurons arise from a single preganglionic neuron. In addition, synaptic innervation overlaps with each other, so that one ganglion cell may be supplied by several preganglionic fibres.

In contrast, the parasympathetic system has its ganglia very near to or within the organs which are innervated by them. Thus, the parasympathetic distribution is much more localised, limited and circumscribed in its influences. In most organs, the relationship or ratio between the number of preganglionic and postganglionic parasympathetic fibres is 1:2 (i.e. there is localized and least amplification) with exception that the ratio of preganglionic vagal fibres to the postganglionic cells in the Auerbach's plexus has been estimated to be about 1:8000.

The cell bodies of the somatic motor neurons lie in the ventral horn of the grey matter of spinal cord. The axon from this somatic motor neuron passes through the ventral root of the spinal nerve. It then passes through the somatic spinal nerves and reaches the muscles where it divides into many terminal branches and each of which innervates a single muscle fibre. Thus, more than 100 muscle fibres of a muscle may be supplied by one motor neuron to form a motor unit. At each neuromuscular junction the axonal terminals of each nerve fibre loses its myelin sheath and forms a terminal arborization that lies opposite to a specialized surface area on the muscle cell membrane, called the 'motor end plate'. Mitochondria and synaptic vesicles containing neurotransmitters are concentrated at the nerve terminal near the end plate. Through trophic influences of the nerve, the nuclei of a skeletal muscle cell, lying in close proximity to a synapse, acquire the capacity to activate the specific genes which synthesise the synapse-localised specific proteins or receptor proteins. Thus, nicotinic receptors are synthesised at the motor end plate.

PARASYMPATHETIC NERVOUS SYSTEM

Elimination of the parasympathetic nervous system is not incompatible with life. This is because it discharges only localised and discrete functions which are not essential for life. Like the sympathetic system, this system is not concerned with the stress and emergency conditions. It mainly governs those activities of our body which are more associated with the digestive and

genitourinary functions. The function of parasympathetic nervous system is concerned primarily with the conservation of energy and maintenance of organ functions, during the periods of minimal activity. This system reduces the HR and BP, stimulates the G1 movement and secretion, helps in the absorption of nutrients, protects retina from excessive light, and empties the urinary bladder, and rectum, etc. Still, however many parasympathetic responses are protective in nature.

Parasympathetic outflow or efferent (motor) takes place through the cranial (midbrain and medulla) and the sacral nerves only. The cell bodies for the cranial outflow of the parasympathetic nervous system lie in the nuclei of cranial nerves, such as: III (midbrain), VII, IX and X (medulla) cranial nerves. Whereas the cell bodies for sacral outflow of parasympathetic system lie in the lateral horn cells of sacral segment of the spinal cord. Like sympathetic system the presence of peripheral ganglion is also a characteristic feature of the parasympathetic system. But unlike the sympathetic system, the ganglia of parasympathetic system lie in or near the viscera, except the meckel's ganglion which are situated at a distance from the supplying viscera. and the otic ganglion. Hence, the parasympathetic nervous system exerts a more localised action than the sympathetic nervous system.

Parasympathetic Outflow or Efferent

1. Cranial outflow

The cranial outflow of parasympathetic nervous system takes place through four cranial nerves — oculomotor III, facial VII, glossopharyngeal IX and vagus X nerves.

(i) Oculomotor nerve or cranial nerve III

The parasympathetic fibres of oculomotor nerve arise from the cranial part of oculomotor nucleus (Edinger-Westful nucleus). They come out of the cranium through the oculomotor nerve and relay in the ciliary ganglion, from where the postganglionic parasympathetic fibres arise and pass through the short ciliary nerve to supply the ciliary muscles and sphincter pupillae.

(ii) Facial nerve or cranial nerve VII

The parasympathetic portions of facial nerve arise from the dorsal nucleus (superior salivary or lacrimatory nucleus) and pass out in the following two ways:

a. One group of fibres passes through the greater superficial petrosal nerve to the sphenopalatine ganglion (Meckel's ganglion), from where the postganglionic parasympathetic fibres arise and supply the lacrimal glands, plain muscles, blood vessels and glands of the palate and nasopharynx.
b. Another group of fibres passes through the chorda tympani nerve to join the lingual nerve. Then, at the floor of the mouth the fibres separate from the lingual nerve to end in the ganglia, such as; sublingual and submaxillary ganglion, close to the sublingual and submaxillary glands. Postganglionic parasympathetic fibres arise from these ganglia and supply the secretory and vasodilator fibres to these glands. (Afferent taste fibres from the ant 2/3rd of tongue also ends in this dorsal nucleus forming a reflex arc for salivation. Hence, its name is superior salivary nucleus).

(iii) Glossopharyngeal nerve or cranial nerve IX

Preganglionic parasympathetic portion of this nerve arises from the dorsal nucleus (inferior salivery nucleus). Then, it passes along the tympanic nerve and the lesser superficial petrosal nerve to the otic ganglion. Here, the postganglionic parasympathetic fibres arise which pass along the auriculotemporal nerve and supply the secretory and vasodilator fibres to the parotid gland. (Taste fibres from the posterior 1/3 of tongue end in this nucleus and form a reflex arc for salivation. Hence, the name of this nucleus is inferior salivary nucleus).

(iv) Vagus nerve or cranial nerve X

The vagus is the most important parasympathetic nerve. It is widely distributed and carries the parasympathetic fibres practically to every corner of the body. The preganglionic fibres in vagus arise from the dorsal nucleus situated in the medulla and run through this nerve. Then the fibres supplying the individual organs pass out of the vagus trunk separately to end in the ganglia in or near that viscera, from where the post ganglionic parasympathetic fibres arise and supply that viscera, as mentioned below. The vagus nerve in addition, also carries a far greater number of parasympathetic afferent fibres (but apparently no pain fibres) from the viscera to the medulla. The cell bodies of these fibres lie in the nodose ganglion.

a. **Heart:** Preganglionic efferent parasympathetic fibres of the vagus reach the heart near the SA and the AV node. Postganglionic parasympathetic fibres arise from the ganglionic cells near the SA and AV nodes, and supply inhibitory fibres to the junctional tissues, cardiac muscles and the dilator fibres of the coronary vessels.
b. **Lungs:** Vagus supplies the constrictor fibres to the bronchial muscles.
c. **GI tract:** Vagus supplies the GI tract from the oesophagus to the caecum. Preganglionic parasympathetic vagal fibres reach the tract at the Auerbach and Meissner's plexuses. Postganglionic parasympathetic fibres arise from the Auerbach's plexus and Meissner's plexus. Fibres from the former plexus supply the muscle coats to stimulate the intestinal movements and to inhibit the sphincters. Fibres from the latter plexus supply the vasodilator and secretomotor fibres to the glands and mucosa.
d. Pancreas: Parasympathetic vagus fibres supply the secretory fibres to the pancreatic alveoli, as well as to the Islets of Langerhans.

e. **Gallbladder:** Action of the vagus on the gall bladder is reverse of the sympathetic fibres.
f. **Liver and kidney:** Parasympathetic vagus has no appreciable effect.

2. Sacral Outflow

The sacral outflow of the parasympathetic nervous system consists of axons that arise from the lateral horn cells of the 2nd, 3rd and 4th sacral segments of the spinal cord. After that, it proceeds as preganglionic fibres through the corresponding anterior roots and the trunk of spinal nerves. Then, they come out of the spinal nerves and unite to form a single nerve, on each side, called the nervi erigentes (preganglionic). After that they relay in the hypogastric ganglia (parasympathetic terminal ganglia) from where the postganglionic parasympathetic fibres arise to supply the urinary bladder, prostate and the whole of the large intestine, except caecum.

Actions of the nerves of the sacral outflow are:

i. Movement of GI tract is stimulated and sphincters are inhibited (reverse of sympathetic).
ii. Also supplies dilator fibres to the blood vessels of external genitalia. This vasodilation is an important factor for causing erection of penis (hence the name nervi erigentes).

3. Spinal Parasympathetic

Posterior spinal nerve roots contain certain parasympathetic fibres, which on stimulation produce vasodilatation. These fibres are said to be parasympathetic due to their action. But, unlike that of the other vasodilator parasympathetic fibres, their actions are not abolished by atropine. These fibres are known as antodormic vasodilator fibres, as their impulses pass out against the general afferent impulses of the posterior nerve roots, and extend up to the posterior root ganglion. Local stimulation by irritants, applied to the skin, produces vasodilatation through these fibres. This is known (Fig 11.4) as the axon reflex. The vasodilatation is produced due to the liberation of ACh at the nerve endings.

CONCLUSION

Though the actions of the sympathetic and the parasympathetic nervous system are antagonistic in nature, but it is not always true. Because, it depends upon: (i) the efficacy of the neurotransmitters, released by either of the system, (ii) the area of innervation and (iii) the relative density of supply of these two nervous systems on a particular area. For example, the sympathetic stimulation markedly enhances the peripheral vascular resistance, but it is not altered appreciably by the activity of the parasympathetic system. The explanation is like that generally most of the vessels involved in the control of blood pressure are innervated only by the sympathetic nerve fibres and these fibres are continuously active. Whereas the parasympathetic nerve fibres which serve the blood vessels are normally restricted to small areas of the body and vasodilatation in these areas does not contribute appreciably to the fall of systemic blood pressure. So, to decrease the blood pressure, it is more significant to paralyse the continuous sympathetic activity, rather than to stimulate the parasympathetic activity (Table 11.3).

The motor or efferent fibres of autonomic nervous system is again traditionally classified into cholinergic and adrenergic nervous systems on the basis of chemical neurotransmitters through which they work. The postganglionic efferent autonomic nerves containing the ACh as their neurotransmitter at their effective site is called the cholinergic nerves and the nerves containing norepinephrine (NE) and epinephrine (EPI) as their neuro transmitter at their effective site is called the adrenergic nerves.

The cholinergic receptors are protein in nature and are situated on the cell membrane. They react with ACh or any other cholinomimetic (like ACh) drugs to cause

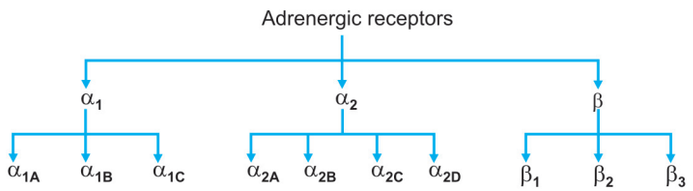


Fig.11.4: Adrenergic receptors

Table 11.3: Cholinergic and adrenergic nerves

The cholinergic nerves include:

1. All the motor nerves that innervate the skeletal muscles.
2. All the postganglionic parasympathetic neurons. So parasympathetic system is also called the cholinergic system.
3. All the preganglionic parasympathetic and sympathetic neurons.
4. Some postganglionic sympathetic neurons supplying the sweat glands and certain blood vessels.
5. Preganglionic sympathetic neurons that arise from the greater splanchnic nerve and innervate directly the adrenal medulla.
6. Some central cholinergic neurons.

The adrenergic nerves include:

1. Postganglionic sympathetic neurons.
2. Some interneurons.
3. Certain central neurons.

the cell to respond. Two types of cholinergic receptors are recognised—muscarinic and nicotinic. The muscarinic receptors are the G-protein coupled receptor in nature (discussed below) and the nicotinic receptors are the ligand or cation channel molecules with gates. (Ligand is an organic molecule that donates the necessary electrons to form the coordinate covalent bonds with metalllic ions. Also, the ligand is an ion or molecule that reacts with another molecule to form a complex).

The cholinergic agonists are agents or drugs that act on the cholinergic receptors like ACh. These drugs are also called the cholinomimetic drugs. The cholinergic antagonists are the agents or drugs that bind with the cholinergic receptors and block the access of ACh or other cholinergic agonist to the ACh-receptors and prevents their actions. These drugs are also called the anticholinergic or cholinergic blocking or cholinolytic drugs.

The adrenergic receptors are also protein in nature and situated on the cell membrane. They react with adrenergic agonists and cause the cell to respond. Adrenergic receptors have been classified into α and β receptors, which are further subclassified into α_1, α_2 and β_1, β_2 receptors. Among all these the α_2 receptors are primarily located on the presynaptic membrane and are inhibitory in nature. The α_1 and β_2 receptors are primarily located on the surface of smooth muscle cells of different organs. The β_1 receptor is primarily located on the cardiac tissue. Drugs mimicking the action of NE are called the sympathomimetic drugs and drugs inhibiting the effects of NE are called the sympatholytic drugs.

Due to the advent of molecular biology, α_1 receptor is again subclassified into α_1A , α_1B , α_1C and α_2 receptor is again subdivided into α_2A , α_2B , α_2C, α_2D and β receptor is subdivided into β_1 , β_2 , β_3 receptor. But, such subclassification is only for scientific analysis and research. The adrenergic drugs currently available for clinical use are still classified as the traditional pattern – α_1 , α_2 and β_1, β_2 agonist or antagoist.

RECEPTORS (FIG. 11.5)

The receptors are macromolecules and protein in nature. However, chemically they may be the nucleic acid in nature. Large number of receptor proteins have been identified, cloned, studied and their primary sequence of amino acids (AA) have also been worked out. Each receptor has two parts—intramembranous and extramembranous and is made up of several non-identical units. Each unit again has polar and no-polar portions. The non-polar portion of the amino acid (AA) sequence of the receptor protein is buried in the cell membrane and the polar portion tends to come out in the aqueous medium on both sides of the cell membrane. The small molecules of agonist or antagonistic agent bind to the outer polar site of the receptor molecule and are capable of tripping the balance of the electrical charges by altering their distribution.

Thus, this tripping of balance of the electrical charge brings out the conformational changes at the inner polar site of receptor, and initiates the binding of the G proteins with the receptor at innerside of the cell membrane. This is the mechanism of action of the G protein coupled receptor such as all the adrenergic receptors and cholinergic muscarinic receptors. On the otherhand, binding of agonist and antagonist or ligand at the outer polar site of some receptors bring about changes in its quarternary structure and the relative aligment of their subunits which results in opening of a centrally located cation channel. This is the mechanism of action of some receptors with intrinsic cation channel such as cholinergic nicotinic receptor. Thus, the receptors subserve two essential functions. These are:

i. Recognition and binding of some specific molecules which are called the ligand or agonist-antagonistic agent at outside on the specific binding domain of the receptor and its activation (receptor).

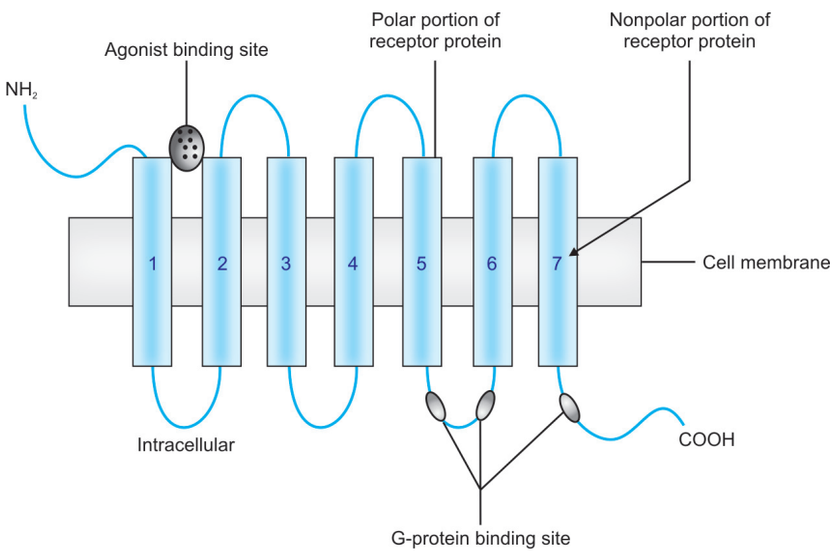


Fig. 11.5: Type of receptor which is coupled with G-protein. Each receptor consists of 7 cylinders, each of which represent a membrane spanning helical segment of amino acids. The cylinders are connected by 3 loops on each side of the membrane. The amino terminus of the receptor lies on the extracellular surface. The carboxy terminus lies on the cytoplasmic side. The approximate location of the agonist and the G-protein binding sites on the receptor are shown in the diagram

Table 11.4: A number of G-proteins have been described. They are distinguished by their α-subunits. The important G-proteins and the effector's chemical through which they act are tabled above. The other G-proteins which are not tabled above are Gn, Gk, G_{13}, Gt, etc.

G-protein	*Effector system or second messanger*
Gs	Adenylyl cyclase ↑, Ca^{2+} channel ↑
Gi	Adenylyl cyclase ↓ , K^+ channel ↑
Go	Ca^{2+} channel ↓
Gq	Phospholipase C ↑

ii. Transduction of the outside signal into the response of cell through a highly complex multi-step process (Table 11.4).

According to the type of receptor activation and its transduction into functional responses within the cell, the responses can be grouped into 5 major categories. These are agonistic, partial agonistic, antagonistic, partial inverse agonistic and inverse agonistic. Receptors falling in one category of function have also been found to possess considerable structural homology and may be considered to belong to one family. According to the mechanism of action, the receptors are broadly classified into two families: the receptors coupled with or acting through the G-protein and the receptors coupled with or acting through the ion channel.

Receptors Coupled with or Act through G-proteins (Table 11.5)

These form a large family of receptors which are situated on the cell membrane. It includes adrenergic receptors (α_1 α_2 β_1 β_2), cholinergic muscarinic receptors (M_1 M_2 M_3), dopamine receptors (D_1 D_2), adenosine rceptors (A_1 A_2), GABA - B receptors, opioid - α , κ , δ receptors and others. They act through one or more GTP-activated proteins for response of the cell. So, they are called the G-protein coupled receptors. All such receptors which act through the G-protein have a common pattern of structural organization. These receptor molecules have 2 to 7 membrane spanning helical structures which are made up of a specific sequence of amino acids and connected with each other by 3 extracellular and 3 intracellular loops. The final amino terminal ($-NH_2$) of the amino acid chain lies on the extracellular surface and the final carboxy terminus (−COOH) of the amino acid chain lies on the cytoplasmic site. The agonist binding site of the receptor is located somewhere between the helics on the external surface. Whereas, the G-protein binding site of receptor is located at the cytosolic segments of the receptor (Fig. 11.6).

Table 11.5: Receptors coupled with or Act through G-proteins

Receptor	*G protein*
β - adrenergic	Gs, Gi , Go , Gn , Gq
Muscarinic	Gi , Gs, Gk
α_2 - adrenergic	Gi , Gs , Gn , Go
GABA - B	Gi , Go , Gk
Dopamine D_2	Gi , Go , G_{13}
5 - HT	Gi , Gq , Gs , Gk , Gt

The G-protein which bind with the intracellular portion of receptor is composed of α, β and γ subunits. A number of G-proteins, distinguished by their α-subunits, also have been described. These are: Gs, Gi, Ge, Gq, etc. Different receptors act through different G-proteins and different G-proteins again next act through different effectors substances or pathways. These effector substances or pathways are called the second messengers (first messengers are agonist and antagonists or ligands) and they produce according to their nature either stimulatory or inhibitory responses in the cell. The effector pathways or second messengers through which the G-proteins act are: adenyl cyclase (AC), phospholipase -C (PLC) and channel regulation protein. This channel regulation protein should not be confused with the ACh receptors (or nicotinic receptor) and Na^+ channel protein, which are actually the receptor with intrinsic ion channel (discussed later) and present at the motor end plates or other sites.

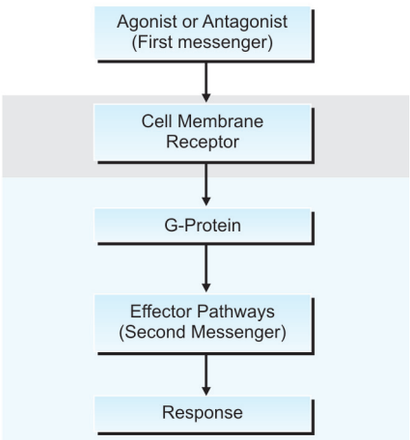


Fig 11.6: Inside the cell

Effector substances (Second messenger)

(i) Adenyl Cyclase (AC)

When an agonist binds with a receptor at the outside of the cell membrane, then the receptor makes a coupling with the G-protein at the inside of the cell membrane, and activates it. Subsequently activated G-protein causes activation of AC (effector pathway)→ it results in intracellular accumulation of cAMP → causes phosphorylation or activation of protein kinase (PK_A) → causes alteration of functions of many enzymes, ion channels, carrier proteins, etc. This is manifested as many cellular functions such as increased contractility, impulse generation, relaxation of smooth muscles, glycogenolysis, lipolysis, hormone synthesis, etc. For example, when epinephrine acts on the β-receptor situated on the cardiac muscle cell membrane, then it activates the Gs protein within the cell which in turn stimulates the adenyl cyclase (AC), a type of effector pathway or second messenger. The reverse occurs when the AC is inhibited by the inhibitory Gi protein (Gi is inhibitory and Gs is stimulatory G-protein), which is activated by the receptor when an antagonist acts on the receptor and stimulates it. As for example, action of acetylcholine (ACh) on muscarinic M2 receptor (located in the myocardial cell membrane) activates an inhibitory G-protein (Gi) inside the cell. Subsequently, the activated inhibitory

G-protein (Gi) opposes the activation of adenyl cyclase (AC) and inhibits the accumulation of cAMP. Thus ACh produces inhibitory responses in the cell. Receptors which act through the G-protein (Gs or Gi) and adenyl cyclase pathways are: adrenergic β (↑), adrenergic α_2 (↓), muscarinic M_2 (↓), dopamine D_1 (↑), dopamine D_2 (↑), adenosine A_2 (↑), adenosine A_1 (↑), etc. (Table 11.6).

(ii) Phospholipase - C (PLC)

Coupling of G-protein (Gs) with the receptor at inside of the cell membrane, after binding of the agonist with the receptor at outside of the cell membrane causes activation of an another effector pathway (second messanger) which is called the phospholipase - C (PLC). This causes hydrolysis of phosphatidyl inositol 4, 5 bisphosphate (P1P2, a membrane phospholipid) → causes generation of inosital triphosphate (IP3) and diacylglycerol (DAG) → results in mobilization of Ca^{2+} from the intracellular depots by IP3 and DAG → activates protein kinase C (PKC) → ↑ Ca^{2+} and activated PKC mediates all the cellular functions i.e. contraction, secretion, transmitter release, neuronal excitibilty etc. Like adenyl cyclase (AC), PLC can also be inhibited by the inhibitory G-protein (Gi) when the opposite responses would be expected. Receptors which act through the G-protein (Gs or Gı) and phospholipase C pathways are adrenergic α_1 and muscarinic M_1, M_3 receptors (Fig. 11.7).

(iii) Channel regulation protein

Coupling of receptors with G-proteins on the inner side of the cell membrane, due to the binding of agonists with receptors on the outside of the cell membrane causes opening or closing of other different ionic channels. These are protein in nature and are specific for Ca^{2+}, K^+, Na^+ ions. These are situated on the cell membrane and cause depolarization or hyperpolarization of the cell membrane. Gs-protein opens Na^+ and Ca^{2+} channels on the myocardial and skeletal muscle cell membrane. So, these are stimulatory in nature. On the otherhand, Gi and Go open the K^+ channels in the heart and smooth muscles and close the neuronal Ca^{2+} channels. Opening of K^+ channel causes hyperploarization of cell. So, these are inhibitory in nature. Closing of Ca^{2+} channel is also inhibitory in nature. Physiological responses like positive or negative inotropic effects, chronotropic effects, transmitter release, smooth muscle relaxation or contraction, etc., also occur through this mechanism (previously mentioned other mechanisms also take part). Examples of these categories of receptors are adrenergic β_1 (Ca^{2+}↑), dopamine D_2 (Ca^{2+}↓), Adrenergic α_2 (K^+↑).

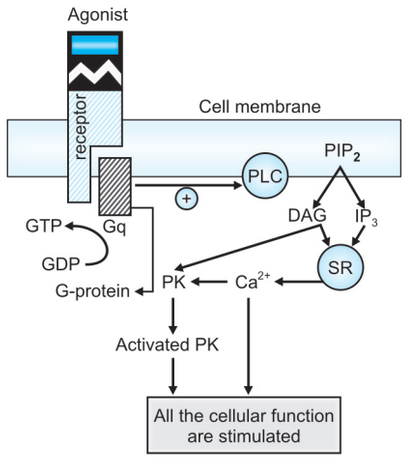


Fig. 11.7: Diagram shows the phospholipase C effector pathway for cellular response. SR → Sarcoplasmic reticulum

Table 11.6: Different receptors which act through different effector substances

Adenylyl cyclase ↑ → cAMP ↑		
Receptors :		
	Adrenergic - β	Adrenergic - α_2
	Dopamine - D_1	Dopamine - D_2
	Adenosine - A_2	Adenosine - A_1
	Histamine - H_2	Muscarinic - M_2
	Glucagon	5 - HT , GABA - B
	Prostacyclin - IP	Opioids - μ , δ
Prostaglandin EP_2		Prostaglandin EP_3 will in this position
Phaspholipase C : IP_3 - DAG → Ca^{2+} ↑		
Receptors:		
	Adrenergic - α_1	
	Histamine - H_1	
	Muscarinic - M_1 , M_3	
	5 HT_2	
	Bradykinin	
	Angiotensin	
	Leukotriene	
Channel regulation protein		
	Ca^{2+} ↑	Ca^{2+} ↓
Receptors		
	Adrenergic -β_1	Dopamine -D_2
		GABA - B
		Opioid -κ
		Adenosin - A_1

K^+ ↓
Adrenergic -α_2
Dopamine -D_2
GABA - B
Muscarinic - M_2
Adenosin - A_1

Receptors with Intrinsic Ion Channels

These receptors do not act through the G-protein present within the cell and the second messenger effector system such as AC, PLC, channel regulation protein, etc. But these receptor molecules, present in the cell membrane are composed of 5 subunits (2α + β + γ + δ) and enclose a cylindrical ion channel for the passage of

ions such as Na^+, K^+, Ca^{2+}, Cl^-, etc. All the subunits of this type of receptor generally have four membrane spanning domains and the amino acid (AA) chain traverses the full width of the membrane six times in each domain. The subunits of the receptor are arranged around the centre channel like a rosette and the α-subunit usually bears the agonist and antagonist binding sites.

Normally, these receptors with intrinsic ion channel at the centre remains closed. But when the agonist molecules bind to the α-subunit of the receptor, then all the other subunits move apart, opening the central pore of the channel and allow the passage of partially hydrated Na^+ ion and other cation. Anions are prevented from passing through the channel, because it is lined with positive charges. Receptors such as: nicotinic cholinergic (at motor end plate), GABA-A, glycine, NMDA, 5 HT3, etc. fall in this catagory. In these type of receptors agonists directly operate the ion channels through their binding site situated within the receptor, without the help of a second messenger or coupling with G-protein. The onset and offset of responses through this class of receptors is the fastest than the receptors which act through G protein.

ADRENERGIC RECEPTORS

The chemical structure, classification, subclassification and mechanism of action of different types of adrenergic receptors are already described previously with other receptors. The remaining aspect of individual adrenergic receptors are discussed here.

(i) α_1 Receptor

Location and responses of α_1 receptors are as follows:

i. Arteriole's smooth muscle : Coronary arteries → constriction, Skin and mucosa → constriction, skeletal muscles → constriction, cerebral vessels → constriction, pulmonary vessels → constriction, abdominal viscera → constriction, renal vessels → constriction.
ii. Veins**:** Constriction.
iii. Heart: No α receptors.
iv. Lung: Bronchial smooth muscles - no α receptor
Bronchial gland - decreased secretion
v. Eye: Radial muscle of iris - mydriasis
Lacrimal gland - ↑ secretion
vi. Stomach & intestine : Motility-decrease Sphincter - contraction
vii. Bladder: Detrusor- no α receptor
viii. Ureter: Motility increase
ix. Uterus: Pregnant - contraction
x. Smooth muscle of prostate and bladder neck: Contraction and obstruction.
xi. Male sex organ: Ejaculation
xii. Spleen capsule: Contraction
xiii. Skin-Pilomotor: Contraction
xiv. Sweat gland: Secretion (Table 11.7).

Agonists of α_1 receptor are methoxamine and phenylephrine and its antagonist is prazocin. Prazocin is a selective α_1 antagonist. So, its use in benign prostatic hypertrophy avoids postural hypotension and other deleterious effects that occur with other less specific α_1-antagonists.

(ii) α_2 receptor

The α_2 receptors are found in the CNS, peripheral nervous system and in the variety of other organs which include platelets, liver, pancreas, kidney and the eye etc. The predominant α_2 receptor which is found at the human spinal cord was identified as the α_{2A} subtype.

The α_2 receptors can be presynaptic or postsynaptic, but predominantly they are presynaptic. The presynaptic α_2 receptor may act either as a heteroreceptor or a autoreceptor (An autoreceptor is a presynaptic receptor that reacts with the neurotransmitter which is released from its own presynaptic nerve terminal, providing a feedback regulation. A heteroreceptor is a presynaptic receptor that responds to substances other than the neurotransmitter, released from that specific nerve terminal).

Among the many presynaptic receptors that have been identified, the α_2 receptor is of the greatest clinical importance. Presynaptic α_2 receptor regulates the release of NE and ATP through a negative feedback mechanism from its own presynaptic nerve terminal. Stimulation of α_2 receptor on the presynaptic membrane by the released NE from that nerve terminal inhibits the subsequent release of NE. Clonidine is a prototype of α_2 agonist. Then by stimulating the presynaptic α_2 receptor, it inhibits the release of NE and produces hypotensin. The action of clonidine in relief of pain by stimulation of α_2 receptor is discussed in elsewhere. Highly densed α_2 receptors are found in the cortex and medulla. Stimulation of these α_2 receptors at this level is responsible for the bradycardia and hyotensive action of α_2 agonist. Presynaptic α_2 receptors and cholinergic receptors inhibit the release of NE, whereas the presynpatic β-receptors stimulate the release of NE.

Table 11.7: Differences between α_1 and α_2 receptor

	α_1	α_2
Location	Post junctional	Prejunctional Postjunctional (at few sites)
Function	Vascular smooth muscle - contraction Gut smooth muscle relax Gland - secretion	↓Transmitter release ↓Synaptic outflow Vasoconstriction
Selective agonist	Methoxamine, phenylephrine	Clonidine Dexmedetomidine
Selective antagonist	Prazosin	Yohimbine
Nonselective antagonist	Phentolamine Phenoxybenzamine	Phentolamine Phenoxybenzamine

Location and responses of α_2 receptors at other sites are:

i. Coronary artery — Constriction
ii. Artery of skin and mucosa — Constriction
iii. Renal artery — Constriction
iv. Veins — Constriction
v. Intestine — Decreased motility and secretion

(iii) β receptors

Like the α-receptors, β-receptors are also the member of a superfamily of all the receptor which acts through coupling with G protein. They have seven helics of amino acids which are woven through the cell membrane. These transmembrane domains are labelled by numbers from M1 to M7. Antagonists have the specific binding sites on the receptor, whereas the agonists are more diffusely attached to the hydrophobic membrane spanning domains of it. The extracellular portion of the receptor ends as an amino group. A carboxyl group occupies the intracelular terminus and it is here where the phosphorylation or activation of receptors occurs. At these cytoplasmic domains, interaction of receptor with G-proteins occur. The β-receptors have the structural and functonal similarities with the cholinergic muscarinic and adrenergic α-receptors, but not with the cholinergic nicotinic receptors (Table 11.8).

β-receptors are subdivided into β_1, β_2, β_3 (as already discussed). All of them increase cAMP through activation of the G-protein and adenylate cyclase effector pathway. Traditionally, the β_1 receptors are thought to be concentrated more on the cardiac tissue and β_2 receptors on cardiac, vascular, bronchial and other smooth muscles. This model of distribution of β_1 and β_2 receptor is still useful for the pharmacological manipulation them by the specific drugs. But, the role of β_2 receptors is more important during heart failure than normal cardiac function. The β_2 receptor population in the ventricles and atria are 15% and 30% of the total β receptors, respectively. These β_2 receptors play an important role in compensation during cardiac failure and help to maintain the responses to catecholamine stimulation. β_1 receptors are down-regulated during chronic catecholamine stimulation and CHF. But the β_2 receptor population remains unaffected till the endstage of congestive cardiac failure. In additon to positive inotropic effects, β_2 receptors in human atria participate in the regulation of heart rate. Thus, β_2 agonism may have a significant effect on cardiac contractility and rate.

Location and responses of β_1 and β_2 receptors:

i. *Heart:* SA node (β_1, β_2) - ↑heart rate; Atria (β_1, β_2) -↑contractility, ↑conduction velocity; A.V node (β_1, β_2) - ↑automaticity, ↑conduction velocity. HIS-Purkinje system (β_1, β_2) - ↑automaticity, ↑conduction velocity; Vent-tricles (β_1, β_2) - ↑contractility, ↑conduction velocity, ↑automaticity, ↑ idioventricular pacemaker.
ii. *Arterioles:* Coronary (β_2) - dilatation; skeletal muscle (β_2) - dilatation; Pulmonary (β_2) - dilatation; Abdominal viscera (β_2) - dilatation; Renal (β_1, β_2) - dilatation.
iii. *Veins* (β_2): Dilatation
iv. *Lung, tracheal and bronchial smooth muscle* (β_2): Relaxation
v. *G I* (β_1, β_2): Decreased motility
vi. *Gall bladder* (β_2) : Relaxation
vii. *Detrusor* (β_2): Relaxation
viii. *Uterus* (β_2): Relaxation
ix. *Spleen capsule* (β_2): Relaxation
x. *Skeletal muscle* (β_2): Increased contractility, glucogenolysis.
xi. *Liver* (β_2): Glycogenolysis, gluconeogenesis
xii. *Islet* (β_2): ↑ Secretion
xiii. *Fat cells* (β_2): Inhibition of lipolysis

Table 11.8: Difference between adrenergic β_1 , β_2 , β_3 receptors

	β_1	β_2	β_3
Location	Heart, kidney	Heart, bronchi, blood vessels, uterus, intestine, eye, urinary tract, gall bladder etc.	Adipose tissue
Specific agonist	Dobutamine	Salbutamol, Terbutaline	Under research
Specific antagonist	Metoprolol, Atenolol	Butoxamine, α-methyl propranolol	Under research
NE	Strong action	No or very weak action	Strong action
EPI	Strong action	Strong action	Weak action

(iv) Dopamine Receptor (DA)

Dopamine is an intermediate product during biosynthesis of norepinephrine (NE) and epinephrine (EPI). It acts through five dopamine receptors. Among them DA_1 and DA_2 receptors are the most prominent. Dopamine also acts on α and β receptors.

DA_1 receptors are post-synaptic and are located at renal, mesenteric and vascular smooth muscles. It mediates the vasodilatation response. DA_2 receptors are presynaptic and inhibits the release of NE. DA_2 receptors are also located in the brain, which mediate nausea and vomiting. The antiemetic action of droperidal and metoclopramide acts through these DA_2 receptors.

SUMMARY

After the attachment of adrenergic agonists to the adrenergic receptors, the extracellular signal is transformed into an intracellular signal by coupling of a stimulated α_1, α_2, β_1, β_2 adrenergic receptor with the G-proteins. This signal transformation is known as the signal transduction. Each class of adrenergic receptor couples to a different type of G-protein which in turn is linked to different types of effector pathway or second messengers such as adenyl cyclase (AC), phospholipase C, etc. Thus, α_1 receptor is linked to Gq protein and in turn is linked to activation of

phospholipase C. Contrarily the α_2 receptor is linked to Gi protein and is responsible for the inhibition of adenyl cyclase. β-receptor is linked to Gs protein and in turn is linked to stimulation of adenyl cyclase. ACh receptor is linked to Gi protein and in turn is linked to inhibition of the effector system, named adenyl cyclase.

G-protein has three subunits − α, β and γ. The α-subunit is most variable and determines the type of activity (Table 11.9) of G-proteins. According to the variety of α-subunit, G-protein may be of stimulatory (Gs), inhibitory (Gi) or inactive (Go) and Gq. The α-subunit may split off from the mother molecule of G protein and behave independently, whereas β and γ subunit may remain together. In the resting state, G-protein is attached to guanosine diphosphate (GDP). When the G-protein is activated through the receptor, then it leads to displacement of GDP by GTP. GTP is attached with α-subunit of the activated G-protein. Then G-protein splits up simultaneously into two parts, consisting of α-GTP and the β–γ subunit. The released α-subunit of G-protein with the GTP then binds to the second messenger molecule, such as: the adenyl cyclase and activates it and then converts its attached GTP to GDP. Therefore, GDP returns to its resting state and is detached from the α-subunit of G protein. Then the α-subunit rejoins again with the β-γ subunit and reconstructs the G-protein, waiting at the inner surface of the cell membrane with the receptor for further activation (Fig. 11.8).

Both β_1 and β_2 receptor stimulation by an agonist activates the G-protein which in turn enhances or activates the AC. Activated AC increases the intracellular concentration of cAMP. Thus, increased intracellular cAMP concentration activates the protein kinase, which then further phosphorylates or activates many other other target proteins. Thus, target phosphorylation elicits a variety of cellular responses and complete the path between the receptor and the effector response.

Table 11.9: Responses of effector organs due to to adrenergic and cholinergic nerve impulses

Organ	*Receptor*	*Adrenergic response*	*Cholinergic response*
HEART			
SA node	β_1 , β_2	↑ Heart rate	↓ Heart rate
Atria	β_1 , β_2	↑ Contractility, ↑ conductivity	↓ Contractility / conductivity
AV node	β_1 , β_2	↑Automaticity, ↑ conductivity	↓Conduction - AV block
Purkinje system	β_1 , β_2	↑ Automaticity, ↑ conductivity	Little effect
Ventricle	β_1 , β_2	↑Contractility	Little effect
		↑ Conduction velocity	Little effect
		↑ Automaticity	Little effect
		↑ Idioventricular pacemaker	Little effect
ARTERIOLES			
Coronary	α_1, α_2	Constriction +	Dilatation
	β_2	Dilatation + +	–
Skin and mucosa	α_1, α_2	Constriction + + +	Dilatation
Skeletal muscle	α_1, α_2	Constriction + +	Dilatation
	β_2	Dilatation + +	–
Cerebral	α_1	Constriction +	Dilatation
Pulmonary	α_1	Constriction + +	Dilatation
	β_2	Dilatation +	–
Abdominal viscera	α_1	Constriction + + +	–
	β_2	Dilatation +	No effect
Renal	α_1, α_2	Constriction + + +	–
	β_1, β_2	Dilatation +	No effect
VEIN			
Systemic	α_1, α_2	Constriction + +	No effect
	β_2	Dilatation + +	–
LUNG			
Bronchial muscle	β_2	Relaxation +	Contraction + +
	α_1	↑ Secretion	Secretion + +
Bronchial gland	β_2	↓ Secretion	–
INTESTINE			
Motility / tone	α_1 , α_2 , β_2	Decrease +	Increase + + +
Sphincter	α_1	Contraction +	Relaxation +
Gland secretion	α_2	Decrease +	Increase + + +
Gall bladder and bile duct	β_2	Relaxation	Contraction +
EYE			
Iris (radial muscle)	α_1	contraction	No effect
Iris (sphincter muscle)	–	No effect	Myosis (contraction) + + +
Ciliary muscle	β_2	Relaxation	Contraction for near vision +
Lacrimal gland	α	Secretion +	Secretion + + +
URINARY BLADDER			
Detrusor	β_2	Relaxation	Contraction + + +
Trigone, sphincter	α_1	Contraction ++	Relaxation + +
URETER			
Motility, tone	α_1	Increase	No effect
Uterus	α_1	Contraction	Variable
	β_2	Relaxation	–
Sex organs (male)	α_1	Ejaculation	Erection + + +

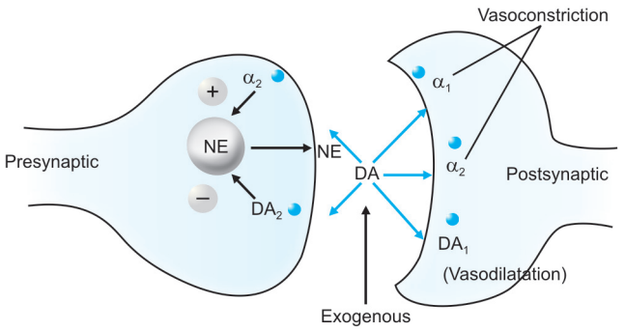


Fig. 11.8: Schematic representation of α_1, α_2 and DA_1 receptors on the postsynaptic membrane and α_2, DA_2 receptor on the presynaptic membrane. When dopamine is administered exogenously, then activation of DA_1 receptor on the postsynaptic membrane causes vasodilatation. While activation of DA2 receptor on the presynaptic membrane causes inhibition of NE release. Large doses of dopamine also activaes α_1 and α_2 receptor on postsynaptic membrane and cause vasoconstriction. It also activares the α_2 receptor on the presynaptic membrane and inhibit the release of NE. NE is released from the presynaptic sympathetic terminal and acts on α_1 and α_2 receptor on the postsynaptic membrane, causing vasoconstriction

G-protein and effectors system (i.e. adenyl cyclase, phospholipase-C, etc.).

The negative inotropic action of halothane and other volatile anaesthetic agents is mediated through the inhibitory G-protein (Gi) and ↓ cAMP concentration. Other possible mechanisms of negative inotropic effects of halothane are: attenuation of the release of neurotransmitter from the peripheral sympathetic neuron, blockage of calcium channel in the heart and thus alteration of the calcium fluxes from sarcoplasmic reticulum and reduction of the cardiac contraction. Hence, it proves that the negative inotropic effect of inhalational anaesthetics occurs at several sites.

Stimulation of α_1 receptor results in inhibition of the adenyl cyclase and this inhibition is mediated by the Gi protein (Fig. 11.9).

Actually, the α_1 receptor acts through the G-protein but activates phospholipase C in the inner surface of the cell membrane. Activated phospholipase C, then, increases the hydrolysis of phospho-inosotol diphosphate (P1P2) to triphosphate and diacylglycerol (DAG). These two compounds, then, mobilize the intracellular calcium stores from the sarcoplasmic reticulum and causes in marked increase in intracellular calcium ion concentration. This calcium then binds to calmodulin (calcium sensitive intracellular protein) which subsequently activates the myosin light chain kinase. This myosin light chain kinase then phosphorylates the myosin light chain and facilitates the interaction between the actin and myosin, resulting in muscular contraction. In other cells, calmodulin stimulates other kinases resulting in other cellular effects.

The myocardial cells respond according to the receptors and the agonist or antagonist(the first messenger) i.e NE, EPI, dopamine, ACh, etc which act on the receptor (Table 11.10). The two opposing effects, i.e. inhibition or stimulation depends on the type of the receptor,

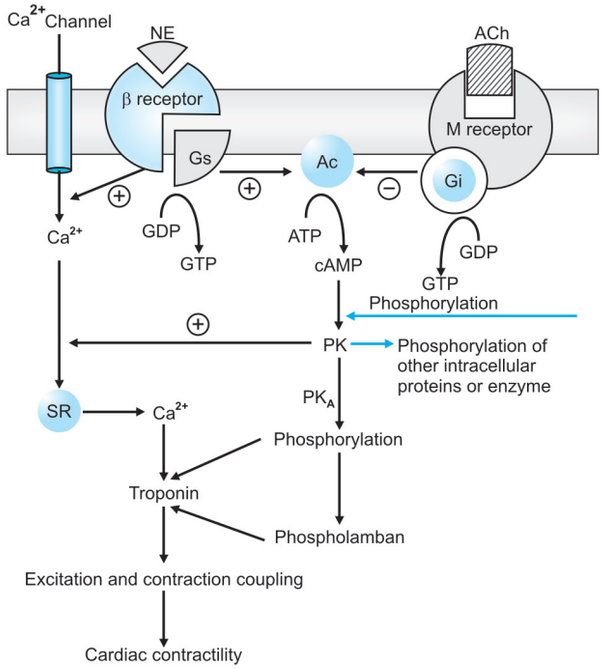


Fig. 11.9: NE binds to β-adrenergic receptors on the outer surface of the cell membrane and induces some conformational changes within the receptor. This permits attachment of the receptor with Gs protein (stimulatory G-protein) and activation of it. Now, the activated Gs protein binds with GTP and its active subunit is dissociated. Activated Gs now activates the enzyme AC (adenylyl cyclase), located on the cytoplasmic side of the membrane. Then, activated AC hydrolyses ATP to cAMP. Now, cAMP phosphorylates and activates the protein kinase (PK_A). The activated PK_A then phosphorylates many functional proteins including troponin and phospholamban. Phospholamban and troponin interact with Ca^{2+}, resulting in increased force of contraction. Intracellular Ca^{2+} is made available by direct entry from outside as well as from the intracellular stores. Direct entry of Ca^{2+} from outside is through Ca^{2+} channel situated on the cell membrane, which is again facilitated by Gs protein and phosphorylation of PK. Action of ACh on the muscarinic receptor (M) activates the inhibitory G-protein (Gi), which opposes the activation of AC by Gs protein

Table 11.10: The difference of adrenergic responses mediated through α and β receptor

	α-actions		*β-actions*
1.	Constriction of arterioles and veins→ rise in BP (α_1 and α_2 action, α_1 action predominates)	1.	Dilatation of arterioles and veins → fall of BP (β_2 action)
2.	Little action on heart	2.	Cardiac stimulation (β_1 and β_2, but β_1 action predominates → cause ↑heart rate, ↑force of contraction and ↑conduction velocity.
3.	On bronchous – no α action	3.	Bronchodilatation (β_2)
4.	Contraction of radial muscle of iris→ mydriasis (α_1 action)	4.	No effect on iris and ciliary muscle
5.	Decreased aqueous secretion	5.	Enhanced aqueous secretion
6.	Intestinal relaxation (α_1 , α_2) contraction of sphincters (α_1)	6.	Intestinal relaxation (β_2 action)
7.	Bladder trigone – contraction (α_1) and sphincter spasm	7.	Detrusor – relaxation (β_2)
8.	Uterous – contraction (α_1)	8.	Uterous – relaxation (β_2)
9.	Insulin secretion – inhibited (α_2)	9.	Insulin secretion - increased (mild) Glucagon secretion – increased (β_2)
10.	Liver – no action	10.	Liver → glycogenolysis (β_2) → hyperglycaemia Muscle → glycogenolysis (β_2) → hyperlactacidemia Fat → lipolysis (β_2) → increased FFA
11.	Male sex organs – ejaculation	11.	Sex organ → no action
12.	Smooth muscle of prostate and bladder neck → contraction with obstruction (α_1)	12.	No effect

UP AND DOWN REGULATION OF β-RECEPTORS

The number of postsynaptic β-adrenergic receptors are not fixed at the site of action. However, the number of receptors change continuously and significantly, matching with the amount of adrenergic agonists and antagonists which are releases in the synaptic cleft. It is found that 30 minutes after denervation or blockade by an antagonist, there is an increased number of receptors. This is called the 'up-regulation' and is the explanation for the sudden rebound phenomenon of tachycardia, ischaemia and increased incidence of MI, after sudden discontinuation of β-blocker, e.g. atenolol, propranolol, metoprolol, etc.

Reversely, if the receptors are continuously or tonically exposed to an agonist, then the responses wane rapidly, despite continuous exposure to adrenergic agonists. This is due to the reduction of number of receptors or the reduction of sensitivity of the receptors to agonists. This phenomenon is called the 'desensitization'. There are three underlying mechanism for desensitization: uncoupling (phosphorylation), sequestration and down regulation.

Uncoupling

It is found that when an agonist continuously binds with a receptor, then it promotes the phosphorylation of the receptor's serine residues near the intracellular carboxy terminus of it. This allows it to bind with a protein, called β-arrestine, which hinders its (receptor) interaction with the Gs protein or coupling, causing desensitization by blocking the signal transduction.

Sequestration

This is a well described, but poorly understood process. It does not apear to be related to the phosphorylation. It is reversible if the agonist stimulaton ceases, with the receptor being returned to the cell surface.

Down-Regulation

It is just opposite to the up regulation. Here, destruction of the receptor is increased or synthesis of the receptor is decreased due to continuous exposure of the receptor to an agonist. It is a slow process than uncoupling and sequestration, and refractoriness develops over weeks and months and receeds slowly. CHF is the most important example of down regulation.

Another example of up-and down-regulation of β-adrenergic receptors is the disease of thyroid gland. The activity of thyroid gland influences the receptor density, with hyperthyroidism decreasing the density and hypothyroidism increasing the density.

CHOLINERGIC RECEPTORS

The receptors on which ACh or agents whose actions are like ACh act are called the cholinergic receptors and these agents are called the cholinergic agonists. There are two types of cholinergic receptors—muscarinic and nicotinic.

ACh has no specificity for these two types of cholinergic receptors, but these two types of receptors structurally and functionally are of distinct classes and have significantly different responses to ACh. Lately, specific agonist to the individual cholinergic receptor has emerged with a definite structure—activity relationship. Chemically, all the cholinergic agonists are of quarternary ammonium compound and have an atom which is capable of forming a hydrogen bond with the

cholinergic receptor through an unshared pair of electrons. The distance between the two (i.e. the ammonium group and the atom) determines whether the agonism is muscarinic or nicotinic. When the distance is 4.4 Å then the agonist has muscarinic action and when the distance is 5.9 Å then the agonist has nicotinic action.

(i) Muscarinic Cholinergic Receptors

These receptors belong to the superfamily of G-protein coupled receptors. Therefore, it also consists of 7 helical membrane spanning hydrophobic amino acid segments, where aminoterminus ($-NH_2$) lies outside the cell and carboxy terminus (−COOH) lies inside the cell. They have a greater similarity or homology to the α and β-adrenergic receptors than to the nicotinic cholinergic receptors. These cholinergic receptors are selectively stimulated by a chemical substance named muscarine. So, they are called as the muscarinic receptors. It can be blocked by atropine. These muscarinic receptors are located in many visceral organs, such as: heart, blood vessels, eye, smooth muscles, glands, CNS, ganglion, etc.

These muscarinic receptors are also present on the presynaptic membrane of post ganglionic cholinergic nerve endings. Activation of these presynaptic muscarinic receptor inhibits the further release of ACh. This is also one of the mechanism of action of α_2-adrenergic agonist which acts on the prejunctional cholinergic receptors to decrease ACh release with some clinical relevance. Similar one also have been demonstrated on adrenergic terminals, activation of which inhibits the NA release. All the blood vessels have muscarinic receptors located on the endothelial cells, though most of them lack cholinergic innervation. Activation of these endothelial muscarinic receptors release EDRF (endothelium derived relaxing factor) which diffuses in the smooth muscle and cause relaxation with vascular dilatation.

Muscarinic receptors have been divided into 5 subtypes and named as M1 to M5 on the basis of their primary structural variability which includes a huge cytoplasmic loop situated between the fifth and sixth membrane spanning domains. Out of these, the first three receptors (M1, M2, M3) have been clearly functionally defined, while the responses indicated through M4 and M5 receptor subtypes are not well defined. Most organs have more than one subtype of receptor, but usually one subtype predominates in a given tissue. The M1 receptors are primarily a neuronal receptor, located on the ganglion cells and central neurons; specially in the cortex, hippocampus and corpus striatum (though all subtypes of muscarinic receptors are present in the CNS). It also plays a major role in mediating gastric secretion and relaxation of lower oesophageal sphincter on vagal stimulation. Cardiac muscarinic receptors are predomintly of M2 subtype, while smooth muscle and glandular ones are of M3 subtype. Therefore, M2 and M3 subtype receptors together mediate most of the well recognised muscarinic actions.

As described previously, the muscarinic receptors are the G-protein coupled receptors. The M1 and M3 (and probably M5) subtypes function through the Gq/11 type of G protein and activate the membrane bound phospholipase C (second messenger), generating inositol triphosphate (IP3) and diacylglycerol (DAG). Actually, stimulation of phospholipase C causes the immediate hydrolysis of phosphotidylinositol polyphosphates, which are the components of the plasma membrane, and form inositol triphosphates. This in turn releases the Ca^{2+} intracellularly from the ER, and causes the contraction of (Table 11.11) smooth muscle of GI tract and glandular secretion. The M2 (and probably M4) receptor subtype functions through the Gi and Go type of G protein. It inhibits the membrane bound AC (adenyl cyclase) which in turn opens the K^+ channels, causing hyperpolarization and suppression of the activity of voltage gated Ca^{2+} channels. Thus it causes reduced pacemker activity of SA node, slowing of the conduction and decreasing of the force of contraction of heart.

The responses of the muscarinic receptor to its agonists and antagonists are slower. They may be excitatory or inhibitory. However, they are not necessarily linked to the changes in ion permeability, like nicotinic receptor.

(ii) Nicotinic Cholinergic Receptors

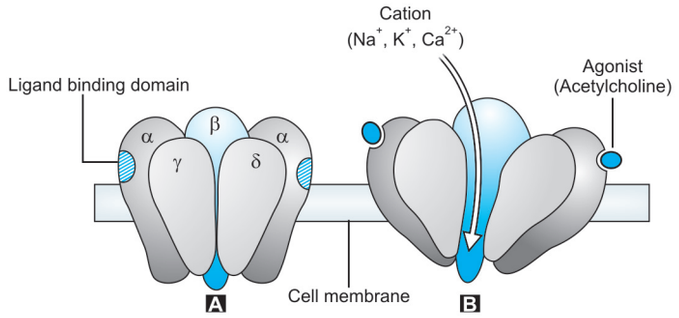
These receptors belong to the superfamily of ion gated channel (i.e. ion channel

Table 11.11: Site of cholinergic transmission and type of receptors involved

Site	***Type of receptor***	***Specific agonist***	***Specific antagonist***
All postganglionic parasympathetic nerve endings	Muscarinic	Muscarine	Atropine
Inside the ganglia (both sympathetic and parasympathetic)	Nicotinic (N_n)	Nicotine DMPP (selective)	Hexamethonium
Few postganglionic sympathetic (sweat gland, some blood vessels, nerve endings)	Muscarinic	Muscarine	Atropine
Adrenal medulla	Nicotinic (N_n)	Nicotine DMPP (selective)	Hexamethonium
Skeletal muscle : motor endplate	Nicotinic (N_n)	Nicotine PTMA (selective)	Curare
CNS (cortex, basal ganglia, spinal cord, other sites)	Both muscarinic and nicotinic	Muscarine Nicotine	Atropine Curare

DMPP = Dimethyl phenyl piperazinium, PTMA = Phenyl trimethyl ammonium ACH is agonist to both muscarinic and nicotinic receptors

through the receptor with gates) and are selectively activated by nicotin. So, they are called the nicotinic receptors. Nicotinic receptors are located only at the motor endplates in the neuromuscular junctions and in the peripheral autonomic ganglion. Those which are located in the motor endplates can be blocked selectively by tubocurarine, decamethonium (ten carbon atom structure) or other nondepolarizing muscle relaxant. But, those which are located at the autonomic ganglion can be blocked selectively by hexamethonium (six carbon atom structure), which has no effect at the motor endplates (Figs 11.10A and B).



Figs 11.10A and B: This is a schematic representation of a receptor with an intrinsic ion channel. An example of this type of receptor is the nicotinic receptor.
A. shows a closed nicotinic cholinergic receptor. This molecule is composed of 5 subunits such as: 2α , β, γ and δ subunits, enclosing a cylindrical ion channel.
B. shows, when two molecules of ACh bind to the two α-subunits of a nicotinic receptor, then, all the subunits of the receptor move apart.This opens the central pore of the receptor and allows the passage of cation. Anions are blocked from passing through the channel by the positive charges lining it. In other cases K^+, Ca^{2+} ions move through the channel, depending on its ion selectivity

The nicotinic receptors or ion gated channels are pentameric membrane proteins in structure, which form the passage for non-selective cations among these the most important cation is Na^+. There are two α-subunits and one each of β, ε and δ subunit in each nicotinic receptor. The α-subunit represents the binding site for both agonists (ACh, nicotin, etc.) and antagonists (curarins and decamethonium). At birth, γ subunit occupies the position of ε (epsilon) subunit, which is normally present in an adult receptor. But, within the first two weeks of life, this γ subunit is replaced by ε subunit. This change in subunit converts the receptor from one, with low conductance and a relatively long duration of opening of channel to a receptor with a high conductance but a brief duration of opening of channel.

Therefore, there are important structural and functional differences of nicotinic receptors during their developments in life. But, it is important to mention that the important drug binding subunit or α-subunit remains constantly present in the receptor throughout the life. Again, there are eight subtypes of the α-subunit which are named as α_2-α_9 and three subtypes of the β-subunit which are named as β_2-β_4. Although, not all the combinations of α and β subunits are functional, but the number of permutations and combinations of these subtypes of α and β subunit that yield (Fig. 11.11). many functional receptors is sufficiently large to produce a pharmacological variation and classifications of all these receptor subtypes. On the basis of location and selective action of agonist and antagonist, two subtypes of nicotinic receptor such as N_M and N_N (previously labelled as N_1 and N_2) are also recognised. N_m receptors are present at the skeletal muscle's endplates and mediate the skeletal muscle contraction. Whereas the N_N receptors are present at the autonomic ganglion (sympathetic and parasympathetic), adrenal medulla (embryologically derived from the same site as ganglionic cells), spinal cord and certain areas of the brain. The difference between the N_M and N_N receptor is that the pentamer of N_N receptor consists only of α and β subunits and constitutes the primary pathway for transmission in a ganglion.

These 5 subunits (2α, β, ε, δ) of a nicotinic receptor surround a channel through which the cations like Na^+ and Ca^{2+} may enter or K^+ may exit the cell. So, it is called the ion channel. For the channel to open, both the α-subunit should be occupied by agonists, such as ACh. Occupation of one α-subunit by ACh will not open the channel. Thus, if one α-subunit is occupied by ACh and the other is empty, then the channel remains closed with no flow of ions, no change in electrical potential and no muscular contraction. On the otherhand if one site is occupied by ACh and another site by an antagonist, such as: pancuronium, then the channel will also remain closed and no contraction of muscle. Similarly, if both sites are occupied by pancuronium the channel also remains closed. From this discussion it is clear that for the action of agonist (ACh) two molecules are needed which bind with the two α-subunit of nicotinic receptor. But for the action of antagonist (nondepolarising muscle relaxant) only one molecule is sufficient which bind with one α-subsunit of nicotinic receptor.

The response of nicotinic or ion-channel receptor to ACh is instantaneous, but usually lasts for few miliseconds only. This

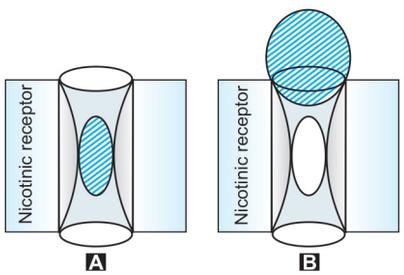


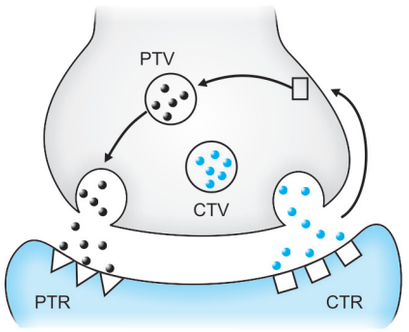
Fig. 11.11: A→Open channel block, B→Closed channel block

is because ACh is rapidly destroyed by true acetylcholinesterase present in the synaptic cleft. This ultrashort acting response of a nicotinic N_M receptor to ACh gives the motor endplate a greater flexibility to neural stimulation. This contributes profoundly not only to the viability of an organism or animal, but also to its ability to control its own body movements precisely.

In addition to the binding of α-subunit by ACh or its antagonist, there are another two types of channel block—open and closed. With open-channel block (first type), a drug enters the channel, after it is opened by ACh. But, the drug molecule cannot travel all the way through the channel. Entering the opened channel the drug molecule temporarily binds at some point within the wall of the channel. Thus, it blocks the ionic flow through the channel and prevents depolarization and muscular contraction. So, intensity of this type of neuromuscular block depends upon (Table 11.12) the degree of previous opening of the channel and the total activity of the system. Thus, this open type of channel block of nicotinic receptor is termed as 'use dependent'. This type of open channel block is driven by the difference of electrical potential across the membrane, and the charge which is inherent to the molecular structure of the drug, responsible for the block. So, the duration of this type of open channel block is partially dependent on the identity of the drug molecule. In closed-channel block (second type), the drug molecule stay at the mouth of the already closed channel and block it and thus prevents ion flow. Channel opening is not required and this type of block is, therefore, not use dependent. As this type of closed channel block is not due to drugs binding at the ACh binding site by competitive antagonism, so the classic agents that inhibit cholinesterase are ineffective to prevent this type of block and fell to initiate the contraction of muscle (Fig. 11.12).

In the motor endplate or on the postsynaptic membrane of the ganglia, the nicotinic receptors are present only opposite to the presynaptic area and are absent on the rest of the muscle cell membrane. The usual density of nicotinic receptors at a motor end plate is 10000/sq μm and is the centre of accomplishing successful neuromuscular transmission. A number of intracellular (utrophin, syntrophin) and extracellular (agrin, laminin, dystroglycan) proteins have been identified, those direct and help in the formation of the nicotinic receptors in the motor endplate and on the postsynaptic membrane in the ganglia within hours of the presynaptic terminals reaching the myocyte (muscle cell) or the postsynaptic neurons during the development of motor endplate or ganglion in intrauterine life. Only the postsynaptic areas of the cell membrane is depolarised by ACh and generates an action potential which next spreads along the whole cell membrane of myocyte from the synaptic point, resulting in the contraction of muscles or transmission of the impulses by the neurons through ganglion.

The action of ACh on the nicotinic receptor can be prolonged by its repeated doses, or by anticholinesterase, or by long acting cholinomimetic agents, such as succinylcholine. In such circumstances, the initial depolarisation and propagation of impulse along the cell membrane of a muscle fibre, which is seen as fasciculation, is quickly followed by a blockade of transmission and muscular relaxation. This clinical effect is due to the Na^+ channels which are present on the cell membrane of the myocyte just around the postsynaptic or motor endplate area. In normal circumstances, after the first impulse of



PTR : Primary transmitter receptor,
PTV : Primary transmitter vesicle,
CTR : Cotransmitter receptor,
CTV : Cotransmitter vesicle

Fig.11.12: This is a schematic diagram of transmission by cotransmitter. Cotransmitter is stored in the prejunctional nerve terminal like the primary transmitter, but in a separate vesicle. Sometimes, the cotransmitter is stored in the same vesicle with the primary transmitter. Nerve impulses coming to the nerve terminal release both the transmitters at the same time, but from the separate vescicles specific for each or from the same vesicle containing both. After release, acting on the cotransmitter receptor, the cotransmitter modifies the responsiveness or the effects of primary transmitter. Sometimes it even substitutes it. Cotransmitter may also act on the prejunctional receptors and modulate the release of the primary transmitter

Table 11.12: Differences of subtypes of nicotinic receptors

	NM nicotinic receptor	*NN nicotinic receptor*
Location and function	Neuromuscular junction → contraction of muscle	Autonomic ganglia → Transmission of impulse through ganglia. Adrenal medulla → Release of catecholamines, CNS → site specific excitation and inhibition
Nature	Has intrinsic ion channel, Pentamer of 2α , β , δ and ε or γ subunits	Has intrinsic ion channel Pentamer of only α and β subunits
Transducer mechanism	Passage of cation (Na^+ , K^+)	Passage of cation (Na^+, K^+, Ca^{2+})
Agonist	Nicotine	Nicotine
Antagonist	Tubocurarine and other muscle relaxants	Trimethaphan and hexamethonium.

depolarisation these Na^+ channel at the perisynaptic area gets time for rest During this rest period they become repolarized and become ready to transmit the next impulse for next muscular contraction. But, when ACh is used repeatedly or its concentration is increased at the motor endplate by anticholinesterases or when succinylcholine is used, whose action is much longer than ACh, then the perisynaptic Na^+ channels remain continuously in depolarised state and do not get time for recovery or repolarization before further transmission of impulse. Thus, it block the subsequent transmission of impulses which are continuously generated at the motor endplate by succinylcholine or anticholinesterase or repeated doses of ACh and produce molecular paralysis. This is discussed more elaborately in chapter 7.

TRANSMISSION OF IMPULSES

New Concept

For many years ACh, dopamine NE GABA, histamine, etc. were considered as the only neurotransmitters for transmission of impulses. But, recently many other compounds have also been identified as neurotransmitters. They are: purines (ATP, adenosine); peptides (vasoactive intestinal peptide or VIP, neuropeptide - Y or NPY; substance-P or SP, enkephalins, somatostatin etc.); 5-HT, calcitonin gene related peptide (CGRP) and many other small molecules such as NO, etc. Furthermore, a peculiar non-adrenergic and noncholinergic transmission has also been demonstrated in the autonomic innervation of gut, vas deferens, urinary tract, salivary glands and certain blood vessels where nerve stimulation is able to evoke responses, even in the presence of total adrenergic and cholinergic blockade (Fact file-I).

Before the recognition of the newer transmitters, 'one neurone - one transmitter' model was the accepted theory. But it has now become apparent that this classical model was an over-simplification. Many peripheral and central neurons have been shown now to release more than one active substance when stimulated, i.e. more than one neurotransmitter may be co-localised in the same nerve terminal and synaptic transmission may be mediated by the release of more than one neurotransmitter.

The most common combination of neurotransmitters in nerves are NE, ATP and NPY in the sympathetic nervous system and ACh, VIP in the parasympathetic nervous system and SP, CGRP, ATP in the sensorimotor nerves. These newer transmitters are called the co-transmitters and the transmission caused by them is called the co-transmission. The co-transmitter is stored in the same neuron, but in distinct synaptic vesicles and at distinct locations. On being released by the presynaptic nerve impulse, these cotransmitter may serve to regulate the presynaptic release of the primary neurotransmitter and / or postsynaptic sensitivity to it (neuromodulator role). The co-transmitter may also serve as an alternative transmitter in its own right.

FACT FILE - I

The diameter of each vesicle or quanta is 300 µm and each vesicle contains 10,000 molecules of ACh (the range of which varies from 1000 to over 50,000 per vesicles). The difference between the central cholinergic transmission and the cholinergic transmission in the neuromuscular junction is that very few vesicles are present in the presynaptic terminal in CNS and these vesicles look clear under the electron microscope.

Release of contents of one vesicle causes opening or stimulation of 2000 receptors situated on the postsynaptic membrane and produce a miniature potential of 0.5 mV. Upon activation of the receptor by ACh, its intrinsic channel opens for about 1 millisecond. During this brief period of interval, about 50,000 Na+ ions traverse the channel through this opened receptor. Thus, each channel that is opened results in depolarization of 0.00022 mV. When impulses arrive at the presynaptic nerve terminal, then 100 to 300 vesicles or quantas release their contents and bring about changes in the normal resting membrane potential of the post synaptic membrane above the threshold level. This is called the excitatory post synaptic potential (EPSP) which is about +50 to +100 mV.

In case of many, but not all there is evidence that NE and ATP act as co-transmitters. Being released by the same nerve, they act on α_1-adrenoreceptors and P_2-purinoreceptors respectively to produce vasoconstriction. The first component of contraction appear to be mediated by the voltage dependent P_2 calcium channels and ATP, while the sustained later part of the contraction is mediated by NE through the receptor, operated by α_1 calcium channels.

Neuromodulation also modify the process of neurotransmission. Such neuromodulators may be the circulating neurohormones, local agents or neurotransmitter substances, which are released from the same nerve or form other nerves nearby. Neuromodulation can occur either prejunctionally by decreasing or increasing the release of the amount of neurotransmitter from presynaptic membrane or post-junctionally by altering the effect of neurotransmitter on postsynaptic membrane. In all the known examples where both pre-and postjunctional neuromodulation occur, they act in concert, either to alternate or augment the effective transmission.

Examples

NPY neurotransmitter is localised with NE and ATP transmitters at nerve endings. After release, it acts as a neuromodulator – prejunctionally it inhibits the release of NE from the nerve terminal and postjunctionally it enhances the action of NE. In spleen, skeletal muscles, cerebral vessels, coronary vasculature etc, NPY has direct vasoconstrictive actions. In heart and brain, NPY is used by the local intrinsic neuron as the principal transmitter to cause vasoconstriction. Actually, the release of the type of neurotransmitter depends on the frequency of stimulation or nerve impulse.

ACh and VIP neurotransmitters coexist in the parasympathetic nerve endings of many organs. They are stored in separate vesicles and are released differently at different stimulation frequencies. They both

modulate transmission by acting on pre and post-junctional site.

Steps of Transmission

Before discussion of this part of the chapter, we will have to define two terms : conduction of impulse and transmission of impulse. The term 'conduction' is defined as the passage of an impulse along an axon to the synapse. And the term 'transmission' is defined as the passage of an impulse across a synaptic junction, between an axon and a muscle fibre or between two axons. Thus, the term transmission includes the release of transmitter and the action of transmitter on the postjunctional membrane.

Conduction of impulse to synapse

At the resting state of a cell, the transmembrane or resting membrane potential (RMP) varies between –70 mV to –90 mV. This is due to the high negativity inside of the cell and high positivity outside of the cell. It is established and maintained by the high intracellular concentration and high cell membrane permeability of K^+ ion, coupled with low permeability and active extrusion of Na^+ ion from inside of the cell in exchange of K^+ which enter the cell by the Na^+- K^+ ATPase pump. On arrival of an electrical impulse or stimulus the voltage sensitive Na^+-channel on the cell membrane is activated and the channel is opened. Thus, there is a sudden increase in conductance of Na^+ into the cell through the cell membrane and a positive overshoot of the transmembrane potential, resulting in depolarization to occur. Therefore, inside of the cell becomes 20 mV positive or + 20 mV and outside of the cell becomes negative which are opposite to the resting state of the cell. After this depolarization, rapid inactivation of the Na^+ channel and opening of the K^+ channel occurs. This permits K^+ ions to move out of the cell and thus repolarization occurs. This means inside of the cell again becomes −ve like the resting membrane potential (with the extrusions of K^+), which had become +ve due to the entry of Na^+ during depolarization. Then, after repolarization in the refractory period, ionic distribution which is now reversed by Na^+ remaining inside the cell and K^+ remaining outside of the cell is normalised by the activation of Na^+-K^+ ATPase pump, involving an adenosine triphosphatase (ATPase). This Na^+-K^+ ATPase pump is activated by Na^+ at the inner and by K^+ at the outer surface of the membrane. Now Na^+ goes out and K^+ comes into the cell. Thus the action potential (AP), which is generated by depolarization and repolarization sets up a local circuit of current and activates the ionic channels at the next excitable part of the axonal cell membrane or next node of Ranvier in a myelinated fibre and is propagated without any decrement. Although not important in axonal conduction, but Ca^{2+} channels in other tissues (e.g heart) also contribute to the action potential by prolonging the depolarization by its inward movement. This influx of Ca^{2+} also serves as a stimulus to initiate the other multiple intracellular events, such as: muscular contraction, secretion, etc.

Release of transmitter

Different neurotransmitters such as excitatory or inhibitory are stored at the presynaptic nerve endings in different synaptic vesicles. The non-peptide neurotransmitters (ACh, NE, etc) are largely synthesized at the terminal regions of the axons and is stored there in multiple synaptic vesicles. Peptide neurotransmitters (SP, ATP, NPY, etc) are found in large dense core vesicles which are transported down the axon from their site of synthesis in the cell body. After their formation, the vesicles are clustered at nerve terminals in some particular discrete areas underlying the presynaptic plasma membrane, termed the 'active zone'. These active zones often are aligned with the tips of the postsynaptic fold. After the impulse reaches the nerve endings, the vesicles move and fuse with the presynaptic axonal membrane. Then all the contents of the vesicles are extruded into the synaptic cleft. This fusion and fluidization of the vesicular and axonal cell membrane is promoted by the impulse itself and by the entry of Ca^{2+} ion into the nerve ending. A number of proteins like synaptotagmin, synaptobrevin, neurexin, syntaxin, etc, are also located on the vesicular and axonal membranes which participate in this fusion and fluidisation of the vesicular and axonal membrane, resulting in extrusion of tranmitters. This is called exocystosis.

This exocystosis or the release of neurotransmitters in the synaptic cleft is also modulated by the neurotransmitter itself or some cotransmitter, through the activation of some specific receptors located on the prejunctional membrane. For example, the release of NE is inhibited by NE itself and by some other cotransmitter such as dopamine, adenosine, etc, acting on the presynaptic α_2 receptors and dopamine receptor, respectively. While isoprenaline acting on the presynaptic β_2 receptor increases the NE release. Similarly α_2 and muscarinic receptor agonists acting on the presynaptic and other α_2 and muscarinic receptors inhibit the release of ACh at the autonomic neuroeffector site, but not in the ganglia and the skeletal muscles. Stimulation of the presynaptic nicotinic receptors also enhance the release of nerve transmitters in the motor neurons. Adenosine, dopamine, glutamate, GABA, PGS (prostaglandins), enkephalins, etc, have also been shown to influence the release of various neurotransmitters.

Action of transmitters on postjunctional membrane

The released neurotransmitter diffuses across the synaptic cleft and combines with the specific receptors on the postjunctional membrane. Depending on its nature, the neurotransmitters induce an excitatory postsynaptic potential (EPSP) or an inhibitory postsynaptic potential (IPSP).

a. EPSP

In this type of action potential (AP) there is an increase in the permeability of Na^+ ions and occasionally Ca^{2+} ions inside the

cell, causing depolarisation which is followed by efflux of K^+, causing repolarisation. This results in excitatory AP and propagation of impulse.

b. IPSP

In this type of action potential, there is no increase in the permeability of Na+, but there is only an increase in the permeability of smaller ions such as K^+ and Cl^-. So that K^+ moves out and Cl^- moves into the cell, resulting in hyperpolariston of the cell. The normal electrical potential difference across the cell membrane is called the polarized state of the cell where inside of the cell is negative and outside of the cell is positive. Hyperpolarisation means inside of the cell becomes more negative, which is normally present during the resting condition of a cell. This is called IPSP. The changes in some special channel permeability that cause this type of potential change i.e. hyperpolarisation are specifically regulated by some specialised postjunctional receptors and some specific neurotransmitters acting on it. The ligand-gated protein channels which belong to a large superfamily usually include the nicotonic receptor, glutamate receptor, certain serotonin ($5\text{-}HT_3$) receptor purine receptors, etc. They conduct primarily the Na^+ permeability and cause depolarisation. So, they are excitatory in nature. On the otherhand, the GABA and glycine receptors which conduct Cl^- permiability cause hyperpolarisation and are inhibitory in nature.

Without any impulse in the resting state, there is continuous and spontaneous slow release of some isolated quanta of transmitters at the synaptic cleft. This produces a minimal electrical response or action potential below the threshold level at the post-junctional membrane which is called the miniature endplate potential (MEPP). This is associated with the minimum maintenance of physiological responsiveness of the effector organ. Thus a slow level of continuous electrical activity within the motor unit of skeletal muscle is very important and is needed since the skeletal muscle lacks the inherent tone.

Post-junctional activity

MEPP cannot generate action potential above the threshold level like EPSP, which is needed to generate a propagated postjunctional AP resulting in nerve impulse (in neuron), contraction (in muscles), secretion (in glands) and other cellular activities. But multiple MEPP work together to form a clinically effective action potential resulting in EPSP. An IPSP stabilises the postjunctional membrane and resists the depolarising stimuli. Whether a propagated impulse or some other response will occur, it depends on the summation of all the excitatory and inhibitory potential.

Termination of action of neurotransmitter

Following the attachment with the receptor, the transmitter is either locally degraded (e.g ACh) or is taken back into the prejunctional neurone by active uptake (e.g NE) or diffuses away into the extracellular space and enters the circulation. The rate of termination of the transmitter's actions governs the rate at which responses can be transmitted across the junction. The termination of the action of only amino acid neurotransmitters result from their active transport into the neurons and the surrounding glia cells. Peptide neurotransmitters are hydrolysed by various peptidases and also dissipated by diffusion.

Neurotransmitters

Adrenergic Neurotransmitters

The adrenergic (more precisely called the noradrenergic) neurotransmitter is mainly related to the postganglionic sympathetic nerve endings. There are three structurally closely related endogenous adrenergic neurotransmitters. These are noradrenaline, adrenaline and dopamine.

i. Noradrenaline (NA) or norepinephrine (NE)

It naturally acts as neurotransmitter in certain areas of brain and at all the postganglionic sympathetic nerve endings except the sweat glands, hair follicles and some sympatheitc vasodilator fibres where the acetylcholine acts as a neurotransmitter.

ii. Adrenaline or Epinephrine (EPI)

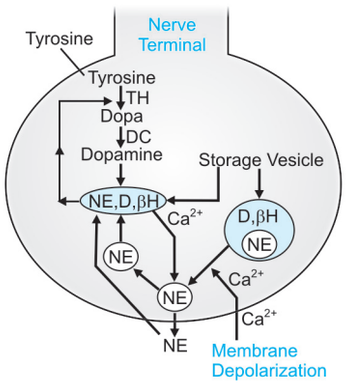
It is mainly secreted from the terminal end of presynaptic neuron in adrenal medulla. Because it acts as the sympathetic ganglia where only the preganglionic fibres end, but no postganglionic fibres exit from it. Adrenaline may have some role as neurotransmitter in some places of brain also.

iii. Dopamine (DA)

It is normally the major neurotransmitter in the basal ganglia, limbic system, CTZ, anterior pituitary of the CNS and in some places of peripheral nervous system.

Synthesis of adrenergic neurotransmitter or catecholamines (CA)

Primarily the adrenergic neurotransmitter such as dopamine, NE, and EPI are synthesised from tyrosine. It is actively transported to the postganglionic sympathetic nerve endings directly from the circulation. Tyrosine is first synthesised from phenylalanine in the liver with the help of an enzyme named phenylanine hydroxylase. It is also available directly from the diet. In phenylketoneuric patients, there is lack of phenylalanine hydroxylase enzyme. So, in these patients tyrosine is not synthesized in the liver. Tyrosine is available for these patients only from diet. The enzymes that participate in the formation of NE from tyrosine at the nerve ending are synthesized in the cell bodies (Fig. 11.13) of the neurons and are then transported along the axons to their nerve terminals. In the nerve endings, as a first step, tyrosine after entering from the circulation is converted to dihydroxy phenylalanine (DOPA) by the enzyme named tyroxine hydroxylase (TH).



TH : Tyrosine hydroxylase, DOPA : Dihydroxy phenylalanine,
DC : DOPadecarboxylase, DβH : Dopamine β-hydroxylase,
NE : Norepinephrine.

Fig. 11.13: The synthesis, release and reuptake of NE at sympathetic nerve terminal

This is a rate-controlling step for the biosynthesis of NE. Because tyrosine hydroxylase is activated following stimulation of the adrenergic nerves. This enzyme is activated by cyclic AMP-dependent or Ca^{2+}-Calmodulin dependent protein kinase C. Thus, this activation or phosphorylation of TH catalysed by protein kinase C may be associated with increased tyrosine hydroxylase activity. This is an important acute mechanism for increasing the catecholamine synthesis in response to increased nerve stimulation. On the otherhand high levels of NE inhibit TH and low levels stimulate this enzyme. During sympathetic stimulation, an increased supply of tyrosine will also increase the synthesis of NE. Chronic stress can also elevate the TH levels by stimulating the synthesis of new enzyme. When the TH level is reduced quantitatively, it may reduce NE synthesis significantly and may account for the changes in wakefulness of an individual. Inhibition of TH by α-methyl-P-tyrosine results in depletion of catecholamines. Thus, this also can be used in pheochromocytoma before surgery, and also in the inoperable cases (Fig. 11.14).

In the next step, DOPA is converted to dopamine by the enzyme, called the DOPA decarboxylase. In the course of synthesis of adrenergic neurotransmitter, the hydroxylation of tyrosine to DOPA and the decarboxylation of DOPA to dopamine, takes place in the cytoplasm of the nerve terminal. About half of the dopamine formed in the cytoplasm is then actively transported into the dopamine-β-hydroxylase (DβH) enzyme containing storage vesicle. In the storage vesicle the dopamine is converted to norepinephrine (NE) by the enzyme, named dopamine-β-hydroxylase (DβH). The remaining dopamine in the cytoplasm is metabolised to homovanillic acid (HVA).

In Parkinson's disease, the central dopaminergic functions are altered. So, administeration of DOPA can improve the dopaminergic function in the brain. This is because DOPA, but not the dopamine, crosses the blood brain-barrier. Dopamine can act as a neurotransmitter in some cells. But in most adrenergic neurons, dopamine

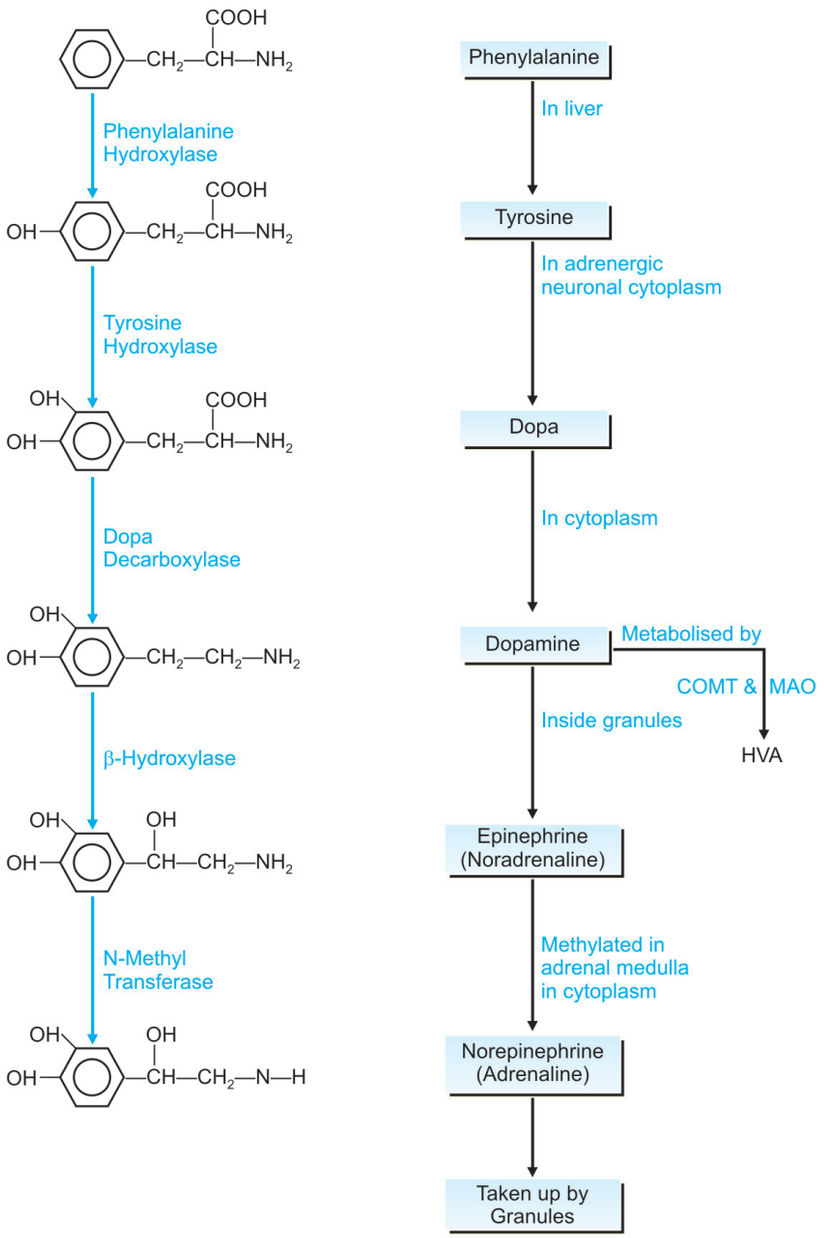


Fig 11.14: Biosynthesis of N_2

is catabolised quickly by the enzyme monoamine oxidase (MAO), found in the mitochondria.

The enzyme DOPA decarboxylase is nonspecific and can also act on some closely related substances. For example, this enzyme can form 5HT from hydroxytryptophan and α-methyl dopamine from α-methyl DOPA. The latter, i.e. α-methyl dopamine may function as a false neurotransmitter and is used in the treatment of hypertension.

In the adrenal medulla, in some discrete regions of the brain and in certain ganglia there is an additonal enzyme, named phenylethanolamine N-methyltransferase (PNMT). This enzyme methylates about 85% of the NE to EPI. Glucocorticoids from the adrenal cortex, passing through the adrenal medulla, can activate this system, so that the stress induced steroid release can cause the increased level of EPI production from adrenal medulla. In adrenal medulla, NE is stored as chromaffin granules in the vesicles. These vesicles also contain extremely high concentration of ascorbic acid, ATP and some other specific proteins, such as : chromograffins, the enzyme DBH and peptides including enkephalin and neuropeptide Y. In sympathetic nerve terminal under electron microscope two types of storage vesicles are found: (i) large dense core vesicles corresponding to chromaffin granules and (ii) small dense core vesicles containing NE, ATP and membrane bound dopamine-β-hydroxylase (DBH) enzyme.

Storage of catecholamines

After synthesis of NE or EPI it is stored in the synaptic vesicles as granules at the adrenergic nerve terminal. The vesicular membrane actively takes up the dopamine from the cytoplasm. Then the final step of synthesis and storage of NE takes place inside the vesicles. The vesicles also contain calcium, varieties of peptides or proteins, and ATP which looks under electron microscope as granules. The proteins of synaptic vesicles can be classified functionally into two classes. One class consists of transport proteins that provide the channels and pumps and are needed for uptake and storage of neurotransmitters. Another class consists of proteins that are involved in the direction of movement and the docking reactions of the synaptic vesicular membrane with the presynaptic membrane.

The NE is stored in the vesicle as a complex with ATP (in ratio of 4:1), and is absorbed on the surface of a protein, called the chromograffin granules. In the adrenal medulla, the NE thus formed within the vesicles and absorbed on the chromaffin granules again diffuses out into the cytoplasm of the cell where it is methylated and EPI is formed. EPI so formed, is again taken up by a separate set of vesicles.

Functionally there are two types of vesicles at the nerve terminal : recycling population of synaptic vesicles that are used normally, and a reserve population of synaptic vesicles that is mobilised only on extensive stimulation during emergency. Transmitters that are newly synthesised or newly taken up from synaptic cleft are preferentially incorporated into the recycling vesicles and are released during the normal stimulation of nerve. Sympathomimetic drugs that mimic adrenergic neurotransmitter are also taken up presynaptically and are stored in the recycling vesicles. Among the reserve population of vesicles, only 10% stays in the readily releasable condition. But, only 1% out of this 10% readily releasable reserve population is released during each depolarisation which implies a significant functional reserve.

Release of catecholamines

The release of contents of synaptic vesicles into the synaptic cleft is called exocytosis. When an AP reaches the nerve terminal, then the presynaptic plasma membrane depolarizes and the voltage gated calcium channels situated on it open at the active zone. As a result, the intracellular Ca^{2+} concentration increases and triggers the docking, fusion and fluidization of the vesicular and presynaptic membrane, causing pouring out of all the vesicular contents, such as NE, EPI, ATP, DBH, chromograffin granules, etc, in the synaptic cleft. In addition, the vesicles which contain peptides like enkephalin, neuropeptides-Y, etc., as cotransmitters are also simultaneously released. The release of this vesicular content is modulated by many presynaptic receptors, of which α_2-inhibitory control is dominant. Many chemical compounds, such as angiotensin II, prostacyclin, histamine, etc. may also potentiate the release of transmitters. While ACh (acetylcholine), prostaglandin E, etc. inhibit this release. Tyramine (a sympathomimetic amines) induces the release of NE. But, it is done by displacing the NE from the nerve ending binding sites and by exchange diffusion, utilizing amine carrier of uptake-I. This process is not called exocytosis and does not require Ca^{2+} (Fig. 11.15).

In adrenal medulla, the chromaffin cells synthesize and stores the NE or EPI and their preferential release depends on the nature of the stimulus. Nicotinic agonists or depolarizing agents cause the preferential release of NE, whereas histamine predominantly elicites the release of EPI. Protein kinase C plays an important role in regulating the secretion of catecholamines from NE containing chromaffin cells.

Uptake of catecholamines after its release

There are two very efficient mechanisms by which NE and other catecholamines is recaptured after its release from the nerve terminal. Released NE and other catecholamines is rapidly reuptaken by nerve terminals (uptake-1) or reuptaken by non neural tissues (uptake-2) (Fig. 11.16).

Uptake - 1

This is first and most important step for the inactivation of the released NE. The half-life of NE in its biophase (i.e. in the extracellular space in close proximity to the receptor after combination with it) is very short. The majority of the released NE is transported back into the nerve ending for

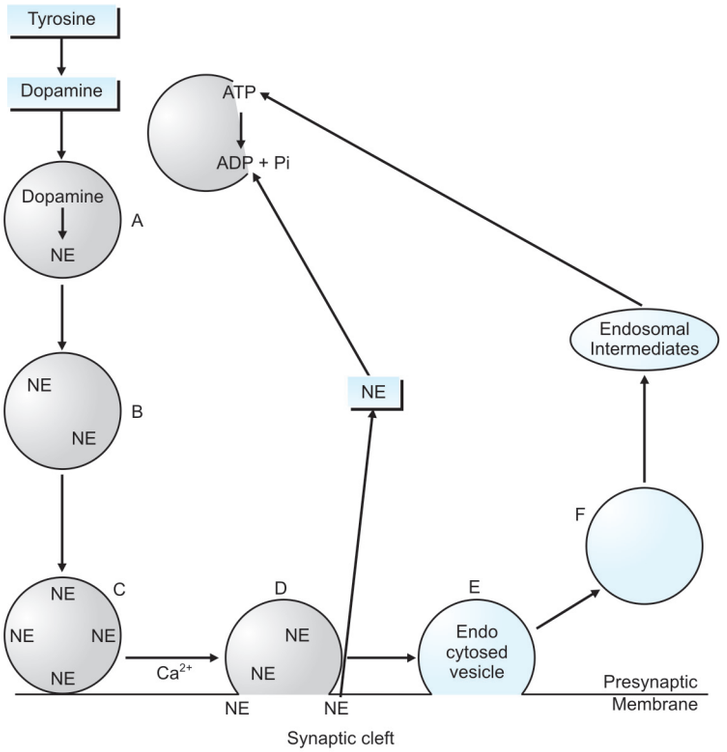


Fig. 11.15:
Stage A : Synthesis or active transport of NT (neurotransmitter) such as norepinephrine (NE) in synaptic vesicles.
Stage B : Movement of the vesicle with NT towards synaptic membrane.
Stage C : Docking of the vesicle at the active zone.
Stage D : Ca^{2+} influx after depolarization triggers exocytosis of vesicle and release of NT.
Stage E : Empty vesicle is endocytosed.
Stage F : Recycling, empty vesicle

the reuse by an active amine pump (transporter), which is present at the presynaptic neural membrane. This active amine pump is a large hetero-oligomeric molecular complex, containing eight or nine different subunits. This amine transport system across the axoplasmic membrane is Na^+ dependent and can be blocked selectively by a number of drugs, including cocaine and the tricyclic antidepressants, such as impramine. Thus, they cause an enhanced response to catecholamines, as the more NE is available to the receptors on the post synaptic membrane. Cocaine and tricyclic antidepressants also block the reuptake of NE in the vesicle from the axoplasm.

A number of other highly specific transport system have also been identified for the reuptake of dopamine, norepinephrine, serotonin and a variety of other amino acid neurotransmitters. These transport or reuptake system may be viewed as targets for many specific drugs, which are used in clinical practice, such as cocaine (block dopamine transport or reuptake), fluoxetin (block serotonin transport or reuptake), etc. Then, NE is driven from axoplasm into the vesicle by the electrochemical proton gradient across the membrane of the synaptic vesicle. After reuptake in the axoplasm of the nerve terminal, a small amount of NE which is not taken up by the vesicle is deaminated by MAO enzyme. There are several organ specific forms of this enzyme. After reuptake or new synthesis, some vesicular NE constantly leaks out into the axoplasm and is recaptured or metabolized by this mechanism. This reuptake of NE into the vesicle from axoplasm is inhibited by reserpine.

This reuptake of NE in the nerve terminal and then in the vesicle is not always specific for that neurotransmitter. So, some compounds that are similar to NE in structure may also enter the nerve terminal and vesicle, causing depletion of the actual neurotransmitter. These structurally similar compounds are called the false or pseudotransmitters and have great clinical importance in the management of hypertension.

The integrity of this uptake-1 system varies from tissue to tissue. As for example, reuptake of NE is lowest or minimum in the peripheral blood vessels (where the rate of new NE synthesis is highest). Conversely, the highest rate of reuptake of NE is found in cardiac tissues with less rate of synthesis of NE. Thus, those drugs that inhibit the biosynthesis of NE (e.g. α-methyl dopa) have more effects on blood vessels and blood pressure. While those that affect the reuptake of NE (e.g. cocaine, desipramine and its congeners, such as guanethidine and many H_1 antihistaminics) have more influences on the cardiac rate and rhythm.

When NE passes through the pulmonary circulation then 25% of the circulating NE is removed by the lung tissues, while EPI and dopamine passes unchanged. However, the functional significance of this removal of NE by the pulmonary vasculature is not known. This effect may also account for some of the differences which is clinically observed in the right sided versus left sided infusions of vasopressors. Pulmonary hypertension also accounts for diminition of NE uptake.

Uptake - 2

After release in the synaptic cleft, the inactivation of NE also occurs by its uptake through other tissue cells, enzymatic breakdown in synaptic deft and diffusion in the interstitial fluid followed by absorbtion by vasculature. This process of uptake 2 of catecholamine is ubiquitous and is present in glial, hepatic, myocardial and other tissues. This has no physiological

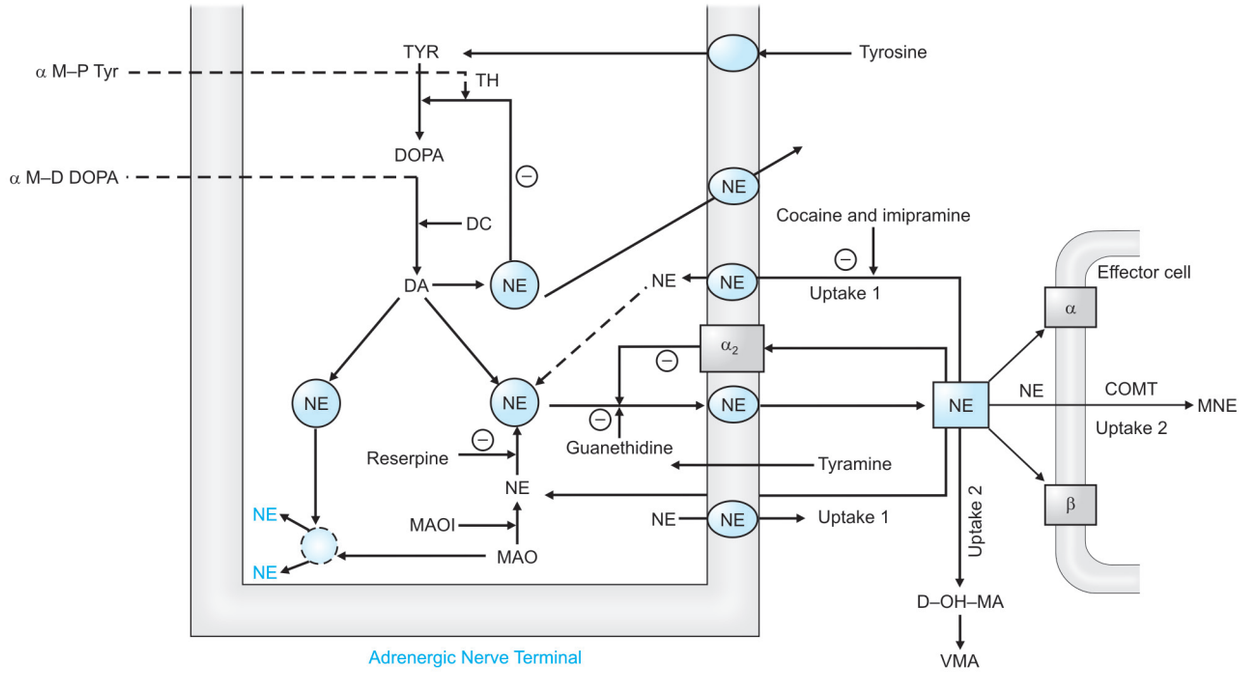


Fig. 11.16: Schematic representation of adrenergic neurotransmission and its modification by drugs. TYR→ Tyrosine, α M-P-Tyr→α methyl-P-tyrosine, α M-DOPA→ α methyl DOPA, D-OH-MA→ Dihydroxy mandelic acid, MNE→ Metanorepinephrine, VMA→ Vanillyl mandelic acid, DA→ Dopamine

or pharmacological importance. It is not inhibited by uptake-1 inhibitors (cocaine, imipramine, fluoxetine etc).

Metabolism of catecholamines

The pathways of metabolism of catecholamines are depicted in the diagram. During storage, release and reuptake of catecholamines at the nerve endings, a small amount always escapes and enters the circulation. In the circulation, NE is metabolised by the mono-amino-oxidase (MAO) and catecholamine-o-methyl-transferase (COMT) enzyme very rapdily. So, inhibition of MAO by MAOI greatly increases the sympathetic function. The metabolism of catecholamine also occurs in the liver and kidney. EPI liberated from adrenal medulla is also metabolised by the same pathway. The final product of both NE and EPI metabolism is 3 methoxy 4 hydroxy mandelic acid or vanilyl mandelic acid (VMA) which are excreted through the urine. The other major metabolites excreted through the urine are 3-methyoxy-4-hydroxy phenylglycol, along with some normetanephrine and metanephrine. These metabolites are mostly conjugated with glucoronic acid or sulphate before excretion through urine. Only 25 to 50 µg of NE and 2 to 5 µg of EPI are excreted in the free form in 24 hours urine. However, metabolism by MAO and COMT in the circulation doesnot play an important role in terminating the action of catecholamines liberated at the nerve terminal. Very quick reuptake of NE and EPI from the synaptic cleft and store in the vesicles, and little metabolism (Fig. 11.17) by the two catabolic enzymes account for the efficient clearance of catecholamines liberated at the nerve terminal. Due to this rapid clearance of catecholamines (NE and EPI) from the circulation by MAO and COMT the half-life of most of the biogenic amines or NE and EPI in plasma is very short which is less than 1 minute. So the very short half-life of these catecholamines necessitates their administeration by infusion. Another consequence of short half-life of these catecholamines is that their production in the body can not be measured by their plasma level, rather by the measurement of the metabolic products of these catecholamines. For example, the screening of NE producing pheochromocytoma is done by frequently measuring the plasma or urine level of VMA but not the plasma level of NE.

Cholinergic Neurotransmitters

Acetylcholine (ACh) is the cholinergic neurohumoral transmitter and occupy the major portion of the autonomic as well as the somatic synapses. The sites of synthesis of this cholinergic neurotransmitter and the description of its rceptors are discussed before. So here, we will discuss only the mechanism of synthesis, storage and inactivation of ACh.

Synthesis of acetylcholine (ACh)

Acetylcholine is synthesised intraneurally from choline (the source of which is described below) and acetyl CoA (formed

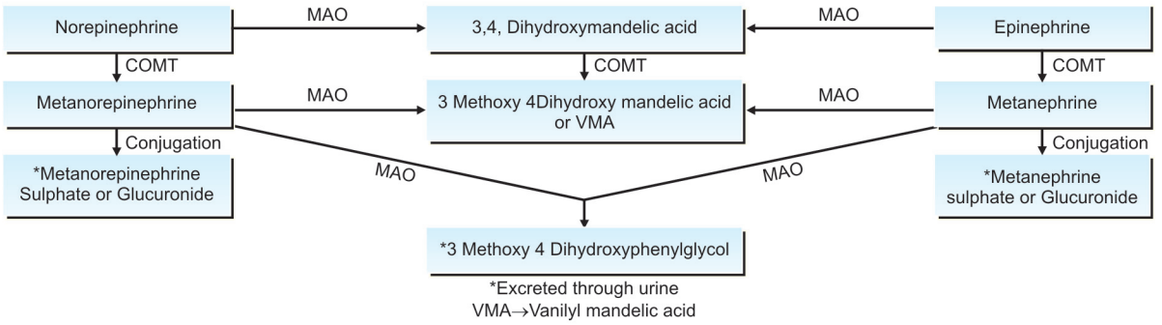


Fig 11.17 : Metabolism of catecholamines

during metabolism of glucose, fat and amino acid) by the enzyme, named choline acetyl transferase (ChAT) situated in the mitochondria. ChAT, like other protein constituents of the neuron, is synthesised within the perikaryon (cell body of the neuron) and then it is transported along the length of the axon to its terminal. Axon terminals also contain a large number of mitochondria, where acetyl CoA is synthesized from metabolism of glucose, fat and protein.

The sources of choline which is another component of ACh includes:

i. Dietary choline – a type of phospholipid.
ii. Hepatic synthesis of phosphatidylcholine from dietary precursors, such as: ethanolamines
iii Choline, released by hydrolysis from previously synthesised ACh.

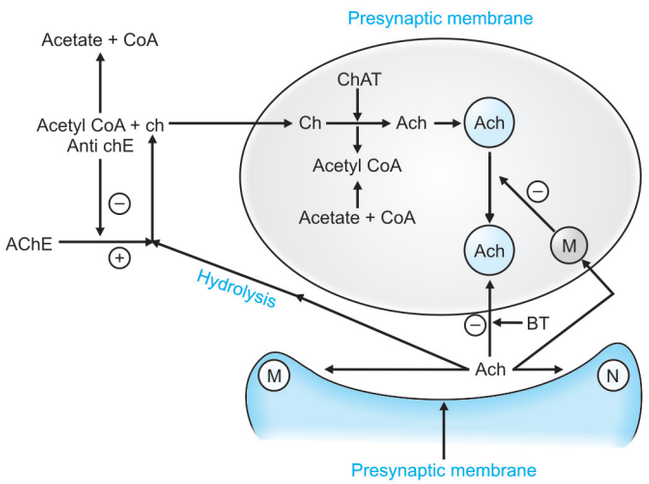
Among these three sources, the hepatic source for choline is the major and most important. After synthesis in the liver, the choline is transported as phospholipid to the nerve terminal through circulation and is actively taken up by the high affinity transport system situated on the neuroaxonal membrane. This hepatic synthesis appears to be largely responsible for determining the ACh levels at the nerve terminals. The level of circulating choline in blood also affects the amount of ACh released from nerve terminals, particularly when the rapid firing takes place at the cholinergic motor neurons. There is also some evidence that the availability of a precursor for the synthesis of ACh may limit the cholinergic activity.

It is found that despite the presence of high density of the choline acetyl transferase enzyme (ChAT) in the brain tissues, choline itself is not produced there, but is transported from the outsources. So, research is going on to develop the choline analogues to enhance the neural transmission in the brain and to treat the Alzheimer's disease.

Choline, after entering into the nerve cell, binds with the acetyl coenzyme A, present within the cell on the surface of the enzyme named choline acetyl transferase (ChAT). This enzyme facilitates the condensation of choline with the acetyl group of acetyl CoA. Thus, acetylcholine and CoA is produced. After synthesis, ACh is rapidly packed in the vesicles for immediate release during proper stimulation. ChAT enzyme also catalyzes the reaction in a reverse direction between the acetylcholine and CoA producing choline and acetyl CoA, but at a much slower rate than the forward direction (Fig. 11.18).

Storage and release of acetylcholine

After synthesis, ACh is rapidly packed in synaptic vesicles at the nerve terminals which are called the quanta. It has been calculated that a single motor nerve terminal contains near about 3,00,000 vesicles or quanta. In addition, an uncertain but possibly a significant amount of ACh is also present in the extravesicular cytoplasm. When the action potential reaches the nerve ending, then ACh is released from



ACh: Acetylcholine, Ch: Choline, ChAT: Choline acetyl transferase, AChE: Acetylcholine esterase, Anti-chE: Anticholine esterase, M: Muscarinic receptor, N: Nicotinic receptor, BT: Botulinus toxin, H: Chemicolinium.

Fig. 11.18: Cholinergic neuronal transmission

the vesicle in the synaptic cleft by the same mechanism as adrenergic neurotransmitters, but at the fixed presynaptic release sites (active zone) which are located opposite to the shoulders of the folding of postjunctional membrane. First quantas or vesicles containing ACh move toward these specific release sites or active zone of the presynaptic membrane which is influnced by the influx of Ca^{2+} like adrenergic transmission and fuse with the presynaptic membrane. Then, fluidization of the vesicular and synaptic membranes occur and throw out their contents in the synaptic cleft and on the post synaptic membrane receptors.

Inactivation of acetylcholine

After release in the synaptic cleft, ACh is rapidly broken down by hydrolysis into choline and acetate, but neither of these metabolites have significant pharmacological actions. This hydrolysis of ACh is catalysed by an enzyme called cholinesterase. There are two most important type of cholinesterases, present in the body. These are tissue cholinesterase or true cholinesterase and butyryl or pseudocholinesterase.

The tissue or true acetylcholinesterase is a postsynaptic membrane bound enzyme which is present at all the cholinergic synapses and destroys the ACh neurotransmitter, after it is released from the presynaptic membrane. It is called the 'true choline esterase' or 'tissue choline esterase', because it does not circulate in the plasma. It is also found in tissues that are not innervated by nerves e.g., erythrocytes. But, here its function is not exactly known.

Butyryl cholinesterase is also called the 'plasma choline esterase' or 'pseudo cholinesterase' and is found in plasma. It is synthesised in the liver and circulates in the blood. Its function in plasma in a normal healthy person is not known and the individuals who are genetically incapable of synthesising these enzymes are normal in all other regards. Only its importance lies in the destruction of some cholinergic drugs, e.g. succinylcholine which is used as a muscle relaxant during anaesthesia and is not destroyed by tissue cholinesterase or true choline esterase.

The molecule of true or pseudo cholinesterase has two areas: an anionic site which carries a strong negative charge and an esteric site which contain electrophilic amino acids. ACh molecule has a positive charge at the quarternary nitrogen atom. During hydrolysis, the positive charge of ACh is attracted by the negative charged site of the enzyme and is attached there. Then, an electrophilic attack on the molecule of ACh occurs and the acetate link is transferred from the choline to the amino acid site of the enzyme. After that the choline which is attached to the negatively charged anionic site of cholinesterase enzyme drifts away, leaving only the acetylated cholinesterase enzyme. The acetate link on the acetylated cholinesterase enzyme is subsequently attacked and broken down by a hydroxyl group forming water. After that the acetate also drifts away from the cholinesterase enzyme and the regenerated free enzyme becomes again ready to interact with another molecule of ACh.

Inhibition of the cholinesterase enzyme prevents the destruction of ACh in cholinergic synapses, and subsequently prolongs its action (muscarinic and nicotinic) in all the cholinergic systems.

Characteristics of cholinergic transmission at various sites

Characteristics of cholinergic transmission are not the same in different tissues. There are marked differences of cholinergic transmission at various sites. The examples are:

a. Skeletal muscle

Attachment of ACh with the nicotinic cholinergic receptor situated at the postjunctional endplate membrane causes marked increase in the permeability of Na^+ cations, through it due to opening of receptor channels. This results in localised depolarisation within the endplate (EPP) which triggers the muscle action potential and contraction.

b. Cholinergic autonomic nerve endings

Here, the ACh as first messenger acts through the muscarinic receptor and causes stimulation or inhibition of autonomic effector cells (smooth muscles and glands) by acting through the muscarinic receptor → G protein → effector system or second messenger complex, such as adenylcyclose and phospholipase-C. In contrast to skeletal muscles, all the cardiac and smooth muscles have their own intrinsic electrical activity. Here, the cholinergic transmission only modulates the cardiac and smooth muscle's intrinsic electrical activity, but does not initiate any new impulse or action potential. In intestinal smooth muscles the site of pacemaker activity continuously changes. But, in the heart spontaneous depolarisation normally arises from the SA node. Under pathological conditions, when SA node activity is depressed, then a new pacemaker activity can arise from any part of the conduction system as all of them have the intrinsic electrical activity. In basal conditions, individual muscle cells of the SA node show waves of depolarization. Cholinergic transmission causes inhibition of this spontaneous depolarization of the SA node by causing hyperpolarization of the cell membrane. These effects are, at least in part, due to the selective increase in the permeability of K^+.

c. Autonomic ganglia

The primary pathway of the cholinergic transmission in the autonomic ganglia is similar to that of neuromuscular junction of the skeletal muscles, i.e. through nicotinic receptors. Several secondary transmitters or modulators either enhance or diminish the sensitivity of postsynaptic membrane of the ganglionic cells to ACh. But, this sensitivity appears to be related to the membrane potential of the postsynaptic nerve's cell body or its dendritic branches.

d. Action of ACh on presynaptic sites

Action of ACh neurotransmitters on presynaptic cholinergic receptors appear to be present on sympathetic vasoconstrictor or adrenergic nerves. Activation of these presynaptic cholinergic receptors by ACh causes inhibition of further release of NE and produces vasodilatation. But, practically cholinergic innervation of the blood vessels is limited. So, clinical dilatation of blood vessels in response to the administration of ACh involves a separate mechanism which includes presynaptic inhibition of NE release. The vasodilator effect of ACh requires an intact layer of endothelium in the blood vessels. Activation of the presynaptic muscarinic ACh receptors results in the liberation of special vasodilator substances, called the endothelium derived relaxing factor (EDRF) or nitric oxide from the endothelium. It diffuses from the endothelium to the adjoining smooth muscle cells and causes relaxation with dilatation of blood vessels.

CATECHOLAMINES (CAS) (Fig. 11.19)

The parent structure of all the sympathomimetic agents is β-phenyl-ethyl amine which includes a benzene ring and an ethylamine side chain. When the 3rd and 4th position of this compound or benzene ring is substituted by a hydroxyl group (−OH), then this benzene ring is called the catechol ring and the β-phenyl-ethyl amine is called the dihydroxy phenylethylamine which is known as catecholamines. The catecholamines which are found naturally in the body are called endogenous catecholamines. They are NE, EPI and dopamine. Synthetic sympathomimetic agents, like isoproterenol, dobutamine, etc, also have the similar structure like endogenous catecholamines. So, they are called the non-endogenous catecholamines. There are other sympathomimetic agents whose structures are not like catecholamines. They are called non-catecholamine sympathomimetic agents. Some examples of this type of drugs are: metoproterenol, albuterol, terbutaline, methoxamine, phenylephrine, mephenteramine, metaraminol, etc.

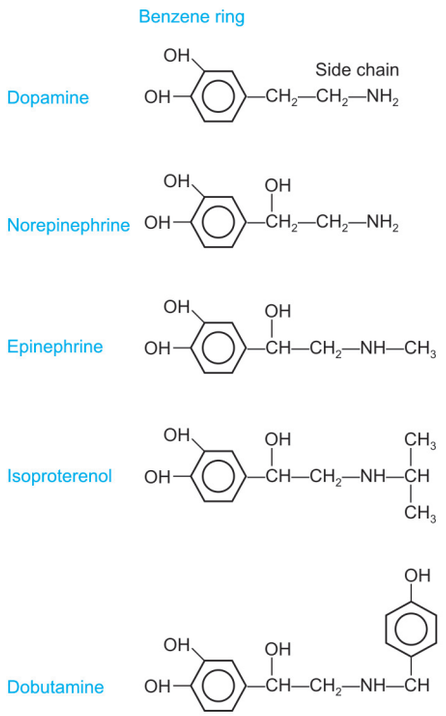


Fig. 11.19: Structures of some common catecholamines. The catechol nucleus is formed by a benzene ring with two adjacent hydroxyl groups

Due to the hydroxyl group, sympathomimetic agents of catecholamine group are quickly metabolised by COMT. But the absence of −OH group in non-catecholamine sympathetic agents increases their oral effectiveness and duration of action, as they are not metabolised by the COMT. They are primarily metabolised by MAO.

Non-catecholamine sympathetic agents that have a substituted α-carbon have a longer duration of action. This is because they are not metabolised by either COMT or MAO.

Endogenous Catecholamines

One Epinephrine (adrenaline)

The effects of an endogenous catecholamine such as epinephrine (EPI) on target organs are complex, as it is a potent stimulant of both α_1, α_2 and β_1, β_2 adrenergic receptors. Its particular and prominent actions are found on the heart than the vascular and other smooth muscles, although the occurrance of sweating, piloerection and mydriasis produced by EPI depend on the physiological state of the subject. The most potential therapeutic effects of EPI include its positive inotropic effects (β_1), positive chronotropic effects (β_1), enhanced conduction in the heart (β_1), smooth muscle relaxation in the vascular and bronchial tree (β_2) and peripheral vasoconstriction of the resistance vessels (α_1). Various effects of EPI at different sites are

a. Blood pressure

EPI is one of the most potent vasopressor agent. On rapid intravenous injection, BP rises rapidly which is proportional to the dose. The increase in systolic pressure is greater than the increase in diastolic pressure.

The mechanism of rise of BP due to epinephrine are:

i. Positive inotropic action — direct myocardial stimulation that increases the force of ventricular contraction.
ii. Positive chronotropic action— increase in heart rate.
iii. Constriction of vascular smooth muscles, particularly precapillary resistance vessels of the skin, muscle, mucosa, kidney, and veins.

Initially HR increases, but later it slows down markedly which is proportional to the height of the rise of blood pressure. This is due to the compensatory vagal discharge.

On small doses of 0·1 µg/Kg through IV route EPI reduces the blood pressure, and this is due to only β_2 receptor stimulant effect of EPI. But in higher doses there is a biphasic response (initially rises then falls). In higher doses this biphasic response is due to the greater sensitivity of epinephrine to β_2-receptors at high doses which

causes vasodilation than the α_1-receptor effect which cause vasoconstriction. The effects of EPI in doses as large as 0.5 to 1.5 mg through IV route (or 10 to 30 µg per minute) are: rise in systolic BP due to increased cardiac contractile force and a rise in the cardiac output. But, the diastolic BP decreases due to the decrease in peripheral resistance, owing to the dominant action on β_2-receptors, causing vasodilatation than α_1-receptors of resistance vessels, causing vasoconstriction. Heart rate, stroke volume, CO, left ventricular work load are all increased as a result of its direct cardiac stimulant effect and increased venous return to the heart. At higher doses, the effects of EPI on the peripheral resistance and diastolic pressure depends on the ratio between the α and β responses on the various vascular beds.

b. Vascular effects

The site of action of EPI on the vascular beds is at the smaller arterioles and precapillary sphincters, but various vascular beds react differently. EPI markedly decreases the cutaneous blood flow. However, in therapeutic doses, the blood flow to the skeletal muscle increases with EPI. This is due to its powerful and predominant vasodilating β_2-receptor action (β_1 is situated on the heart). But it is particularly counter balanced by the vasoconstrictory α-receptor action (both α_1 and α_2). In such situations, if a α-adrenergic antagonist is given, then the vasodilatation effect of β_2-receptor predominates and SVR decreases, resulting in acute fall of mean blood pressure. Reversely, EPI increases blood pressure considerably if the vasodilatation β_2-receptor action is blocked by some non-selective β-blocker.

c. Cerebral blood flow

The adrenergic receptors present on the cerebral vascular bed is predominantly α_1 (vasoconstrictor). So, the therapeutic doses of EPI causes cerebral vasoconstriction. This is due to the direct effect of EPI on cerebral vessels. But, clinically the main effect of EPI on cerebral circulation is conducted through the changes in systemic BP and not through these receptors. Again, the cerebral self or local autoregulatory mechanism tends to limit the increase in cerebral blood flow, caused by increase in BP (Table 11.13).

d. Renal effects

Kidney has both the α_1, α_2 and β_1, β_2 adrenergic receptors. Here, the vasoconstrictor effect of α-receptor predominates much more over the vasodilatatoin action of the β-receptor. So, the doses of EPI which cause little effect on mean arterial pressure, cause the tremendous decrease (40%) in the renal blood flow due to a consistent increase in renal vascular resistance by the predominant $\alpha_1$action. In spite of this, GFR is slightly altered and filtration fraction is consistently increased. Its cause is discussed in details in the renal chapter. Urine volume may be increased, decreased or unchanged. Due to the direct effect of EPI on β_1-receptor of juxtaglomerular apparatus, renin secretion is also increased.

e. Pulmonary effects

Pulmonary vasculature contains both the α_1 (vasoconstriction) and β_2 (slight vasodilatation) receptors. Due to the predominant α_1 action of EPI on pulmonary vasculature, arterial and venous pulmonary pressure is raised. Still, clinically the redistribution of blood from pulmonary circulation to systemic circulation does not occur. Rather, redistribution of blood from the systemic to the pulmonary circulation occurs and this is due to the strong vasoconstriction action of more powerful musculature of the systemic great veins. Therefore, the total effect is an increase in the pulmonary vascular pressure. Thus, by the same mechanism epinephrine in higher concentration may precipitate pulmonary

Table 11.13: Comparison of effects of NE and EPI (Intravenous infusion)

Response	*NE (norepinephrine)*	*EPI (epinephrine)*
Cardiac responses		
Heart rate	↓ (A)	↓
Stroke volume	↑ ↑	↑ ↑
Cardiac output	0, ↓	↑↑↑
Arrhythmias	↑↑↑	↑↑↑
Coronary blood flow	↑↑	↑↑
Blood pressure		
Systolic	↑↑↑	↑↑↑
Diastolic	↑↑	↑0↓
Mean	↑↑	↑
Pulmonary	↑↑	↑↑
Peripheral circulation		
Sytemic vascular resistance	↑↑	↓
Muscle blood flow	0,↓	↑↑↑
Cerebral blood flow	0,↓	↑
Renal blood flow	↓	↓
Cutaneous blood flow	↓	↓
Splanchnic blood flow	0,↑	↑↑↑
Metabolic responses		
Blood glucose	0,↑	↑↑↑
Blood lactic acid	0,↑	↑↑↑
Oxygen consumption	0,↑	↑↑↑

0 = No effect, ↓ = Decreased effect, ↑ = Increased effect, A = Increased after atropine.

oedema by elevating the pulmonary capillary filtration pressure.

f. Coronary circulation

Coronary vessels contain α_1, α_2 and β_2 receptors. Here, the vasodilatation action of β_2 receptors predominate over the vasoconstriction action of α receptors. So, coronary blood flow is increased by it or by cardiac sympathetic stimulation. Another mechanism of increased coronary blood flow by EPI is the elevated aortic blood pressure caused by it. Epinephrine increases the strength of myocardial contraction (β_1 action) and O_2 consumption which also dilates the coronary vessels by their local metabolic effects. This local metabolic dilatation effect of EPI on coronary arteries is mediated by adenosine, released from the cardiac myocytes due to hypoxia. Therefore, all these effects tend to overcome the direct coronary vasoconstriction effect of EPI that results from the activation of α receptor in coronary vessels.

g. Cardiac effects

Heart muscles contain predominantly β_1 receptors. But, β_2 and α receptors are also present in minimum concentration. Therefore, EPI is a powerful cardiac stimulant and acts mainly through the β_1 receptors. It increases the heart rate and often the sinus rhythm is altered. All the effects of EPI on cardiac tissue are largely secondary to this increase in heart rate. Because, when the HR is increased, the duration of action potential is consistently shortened and the refractory period is correspondingly decreased. The increased heart rate by epinephrine is due to the acceleration of the slow diastolic depolarisation phase or phase 4 of action potential and also due to the increased rate of the rise of transmembrane potential to the threshold level, at which point the action potential is triggered. The amplitude of AP and the maximal rate of the rise of depolarisation (phase 0) are also increased. Cardiac systole becomes shorter and powerful. CO increases. The work load of heart and O_2 consumption is also markedly increased by EPI. But, the cardiac efficiency which is determined by the work load relative to O_2 consumption decreases. EPI also increases the excitability and automaticity in the specialized tissues of heart. This is also due to the acceleration of the slow diastolic depolarisation phase of action potential. However, these changes in automaticity usually do not occur in the atrial and ventricular muscle fibres. These occur only in the cells of SA node.

Altered pacemaker activity due to increased automaticity by the exogenous EPI is rarely seen with conventional dose. But, ventricular extrasystole, tachycardia or even ventricular fibrillation may be precipitated by the release of small amount of endogenous epinephrine, when the heart has been sensitized by certain anaesthetic agents or in case of MI.

EPI shortens the refractory period of AV nodal tissue and decreases the grade of AV block, which usually occurs by the effect of many diseases, drugs and vagal stimulation.

Supraventricular arrhythmias may occur from the combination of action of epinephrine and cholinergic stimulation, if these two events occur at the same time due to any reason. Depression of sinus rate and AV conduction by vagal discharge probably plays a part in the EPI induced ventricular arrhythmias. So, various drugs (e.g. atropine) that block the vagal effect confer some protection against EPI induced ventricular arry thmias. The action of EPI in enhancing cardiac automaticity, and causing arrhythmias are effectively antagonised by β-adrenergic receptor antagonist.

h. Bronchial smooth muscle

Epinephrine has a powerful bronchodilating effect. This is particularly occurred when EPI is administered during the acute exacerbation phase of bronchial asthma due to allergic response to various drugs and autacoids. In such situations, EPI has a striking therapeutic effect as a physiological antagonistic agent to the substances that cause bronchoconstriction. The beneficial effect of EPI in asthma also arises from the inhibition of the antigen-induced release of inflammatory mediators from mast cells, and to a lesser extent from the diminution of the bronchial secretions and congestion within the mucosa. The inhibition of bronchial smooth muscle constriction by EPI which is induced by mast cell secretion (release of inflammatory mediators) is mediated through the stimulation of β_2-adrenergic receptors and the effects on bronchial mucosa (reduction of congestion) are mediated through the stimulation of α receptors.

i. Urinary bladder

The detrusor muscle of the bladder is relaxed as a result of the activation of β-receptors by EPI. This causes retention of urine. Again, α agonistic activity of epinephrine results in contraction of the trigonal and sphincteric smooth muscles, causing hesitancy and retention of urine. Activation of the smooth muscle contraction in prostate by EPI also promotes the urinary retention (α-receptor effect).

j. Effects on uterus

The response of EPI on uterine muscle varies with the species, phases of sexual cycles, state of gestation and doses of the drug given. During the last month of pregnancy and parturition, epinephrine inhibits the uterine tone and reduces the contraction which is mediated through its β_2-receptor agonistic action. So, β_2-selective agonists (ritodrine, terbutaline) have been commonly used to delay the premature labour by relaxing the uterine musculature.

k. GI

The effects of EPI on the smooth muscles of vascular system has more physiological

importance than their effect on the smooth muscles of GI tract. In general, GI smooth muscle is relaxed by EPI and this effect is due to the activation of both α and β adrenergic receptors. Tone, frequency and amplitude of intestinal contraction are all reduced. The stomach is usually relaxed, but the pyloric and ileocaecal junction are contracted. However, these effects of EPI on gastrointestinal system depend on the pre-existing tone of the muscles. If the tone is already high, then EPI causes relaxation of the smooth muscle and vice versa.

l. CNS effects

As epinephrine (EPI) is a polar compound, so it usually does not cross the blood brain barrier and enters the CNS. Thus, it is not a powerful CNS stimulant. Hence, restlessness, headache, tremor, apprehension, etc, produced by EPI are all due to the secondary effects of it on CVS, skeletal muscular system and its intermediary metabolites. It is not due to the direct effect of epinephrine on CNS. Though EPI does not enter the CNS, but some other sympathomimetic drugs can readily cross the blood brain-barrier and may produce the symptoms.

m. Metabolic effects

EPI increases the concentration of glucose and lactate in blood. It inhibits the secretion of insulin by its α_2-receptor action and stimulates the secretion of insulin by its β_2-receptor activation, both of which are contradictory. But, the predominant effect of epinephrine on insulin secretion is inhibition and rise of blood glucose concentration. Glucagon secretion is enhanced by the action of EPI on β-receptors, present on the α-cells of pancreatic islets. This also causes the increased concentration of glucose in blood. The effect of EPI to stimulate glycogenolysis in most of the tissues involves β-receptor stimulation.

EPI raises the concentration of free fatty acids in blood by stimulating the β-receptors in the adipocytes. This result is due to the activation of triglyceride lipase in the adipocytes which accelerates the breakdown of triglycerides to form the free fatty acids and glycerol. The plasma renin activity is also increased by epinephrine (β_1 effect). The serum K^+ concentration transiently rises (due to release from the liver), following the administeration of epinephrine. Later, a more prolonged decrease in K^+ concentration follows. Epinephrine administeration increases the basal metabolic rate by 20 to 30% So, in combination with the cutaneous vasoconstriction that the drug produces, pyrexia may result due to this increased metabolism.

n. Effects on secretary glands

In most of the secretary glands of GI tract, EPI inhibits the secretion. This is partly due to the reduced blood flow in gland, caused by vasoconstriction and partly due to the direct action of EPI on α and β receptors situated on the gland. On the lacrimal glands, it stimulates the lacrimation (α-receptor action) but causes scanty mucous secretion from the salivary glands. Sweating and pilomotor activity (α_1-receptor) is minimal after systemic administeration of epinephrine.

o. Effects on eye

Mydriasis occurs during the systemic administeration of EPI. It is due to the contraction of the radial muscles of iris (α_1 action). But, it does not occur when the EPI is instilled in the conjunctival sac, because it penetrates the cornea poorly. Epinephrine also lowers the intraocular pressure, especially in the wide-angle glucoma. However, the mechanism of this effect is not clear. But, both the reduced production of aquous humour due to vasoconstriction and the enhanced outflow due to mydriasis are the probable causes.

p. Skeletal muscle

Directly EPI does not excite the contraction of skeletal muscle. But, indirectly it facilitates the neuromuscular transmission. In ANS the stimulation of presynaptic α-receptor by epinephrine causes inhibition of the release of ACh. In contrast, stimulation of α-receptor by EPI at the somatic motor neurone causes a more rapid increase in transmitter release. The greater physiological and clinical importance of EPI on skeletal muscle is its selective β_2 agonistic activity which causes physiological tremor. This is due to the β receptor mediated enhancement of discharge from the muscle spindle.

Absorption, fate and excretion: EPI is not effective by oral administration. This is because it is rapidly metabolised in the GI mucosa during absorption by COMT and MAO enzymes which are present there and in the liver when circulates through the portal circulation. Because of its local vasoconstriction effect, the absorption of epinephrine from the subcutaneous tissues is also very slow. But after intramuscular injection absorption of EPI is more rapid. In emergencies, EPI is always used by IV route. When EPI is used by inhalation or through a nebulizer, then its action is largely restricted locally to the respiratory tract. However, arrhythmia may also occur, if a large amount of EPI is used through this route.

Epinephrine (EPI) is metabolised and inactivated by COMT and MAO enzyme which are present in all the body tissues, plasma and liver. The liver is rich in both the enzymes and is particularly important in this regard.

Administration and preparations: Epinephrine is unstable in alkaline solutions. So, it is always prepared in an acidic medium. It should always be protected from the air and light. Because, in air and light, the EPI is oxidised to adrenochrome which then turns from pink to brown due to the formation of its polymers.

EPI is used in different clinical conditions and through different routes, such as subcutaneous (most common), IV (during emergencies), inhalation and topical

(specific). So, a variety of formulation of EPI with different strength and concentration are available in market for use through different routes. The epinephrine injection which are available in different strengths are : 1:100 (10 mg/ml), 1:1000 (1 mg/ml), 1:10000 (0·1 mg/ml), 1:100000 (10 µg/ml) and 1:200000 (5 µg/ml). The patients vary tremedously in their response to catecholamines. Therefore, a patient's response should be carefully titrated with the dose of EPI when used through any route. During administration of EPI, appropriate measures should be taken to monitor the renal, cerebral and myocardial perfusion which is more important than a rigid adherence to the theoretical dosing scheme. An infusion rate of 1 to 2 µg/min of EPI predominantly activates the β_2 adrenergic receptors, causing vascular and smooth muscle relaxation. On the otherhand, a rate of 2 to 10 µg/min of EPI infusion activates both the $\beta_1$and β_2 receptors causing an increased heart rate, ↑conduction through the AV node and ↑contractility of the heart. Dose of EPI in excess of 10 µg/min by infusion causes marked α-stimulation with resultant generalised vasoconstriction and ↑BP.

EPI is a potent renal vasoconstrictor, acting directly through the stimulation of α-receptor and indirectly by the stimulation of the release of renin. So, to avoid the renal ischaemia dopamine in renal dose is frequently combined with the IV doses of epinephrine. The usual subcutaneous therapeutic dose of EPI in an adult is 0.3 to 0.5 mg. However, absorption of subcutaneous EPI is extremely slow. This is due to the intense local subcutaneous vasoconstriction. The effect of very large subcutaneous doses of epinephrine such as 0.5 to 1.5 mg, is roughly equivalent to an intravenous infusion in the dose of 10-30 µg/min which can result in life-threatening ventricular arrhythmias, hypertension and cerebral haemorrhage.

The normal dose of epinephrine by IV infusion during management of hypotension or shock is 0.01 to 0.1 µg/kg/min which is titrated according to the response. In emergency, the IV route for administration of EPI is preferred and the drug is used very slowly and very cautiously by diluting the solution. The IV dose is seldom exceeds 0.25 mg, except in cardiac arrest when the large doses can be used (3 to 5 mg or more) according to the response. In very emergency conditions such as asystole, VF, EMD and anaphylactic shock the recommended dose of epinephrine is 0.5 to 1 mg/70 Kg IV. The aim of this higher dose of EPI is to maintain the myocardial and cerebral perfusion by increasing the mean arterial pressure through intense peripheral vasoconstriction. However, more higher doses of EPI greater than 0.1 mg/Kg also have been studied during resuscitation of cardiac arrest, but does not appear to improve the rate of survival in adults. This higher dose of EPI is used only when the usual doses fail to respond. The endotracheal doses of EPI in emergency situations, when IV route is not available, should be at least double of the IV dose and is diluted in 10 ml of normal saline solution in adult patients. This is because epinephrine is well absorbed from the tracheal mucosa. 1% (1:100) formulation of EPI is only used for inhalation and should never be used for parenteral route. This is because inadvertent IV injection of 1:100 solution can be fatal. Inhaled EPI constricts oedematous mucosa and may be used in the treatment of severe croup and traumatic airway oedema. For inhalation, 1% solution of epinephrine is diluted with water or saline in 1:4 ratio and nebulized. This treatment can be repeated every 2 hours, with effects lasting for 30 to 60 minutes.

Adverse effects and contraindications: EPI causes more or less serious adverse effects. Less serious, but common adverse effects of epinephrine are transient restlessness, palpitation, anxiety, tremors, throbbing headache, etc. On the otherhand, more serious, but less frequent adverse effects are cerebral haemorrhage, angina, cardiac arrhythmias, etc, and all these are due to the large doses of EPI. The use of EPI is contraindicated in hypertensive, hyperthyroid and angina patients. It should be given cautiously during halothane anaesthesia and to patients who are receiving non-selective β-blockers. This is because its unopposed actions on the vascular α_1-adrenergic receptor may lead to severe hypertension. Halothane is known to sensitize the heart to catecholamines (CAS). So, the dose of epinephrine should be limited to 1 µg/Kg/30 min in the presence of halothane and to 3 µg/Kg/30 min in the presence of isoflurane and sevoflurane. CAS decreases the refractory period and thus renders the heart more susceptible to arrhythmias. Preexisting use of α_1- blockade can cause the paradoxical phenomenon of EPI reversal, because as the β_2-vasodilating effects are unmasked.

Therapeutic uses: EPI has limited therapeutic uses. But its major use is to provide a rapid relief during hypersensitivity reactions including anaphylaxis, arising from drugs and other allergens. Its cardiac effects may be of use in restoring the cardiac rhythm in patients with cardiac arrest. Other therapeutic uses of EPI are with local anaesthetics or as topical haemostatic agents, or for inhalation in the treatment of postintubation or infectious croup (Table 11.14).

When used with local anaesthetics or applied locally on the mucosal surface to stop bleeding, then the α receptor-mediated vasoconstrictive effect of EPI decreases bleeding in that area and slows the vascular uptake of local anaesthetic agents. Thus, it decreases the peak serum level of the local anaesthetic agent and prolonges its duration of action. Several studies have shown that elevation in the plasma levels of EPI after local application is relatively modest, but substantially less than the levels, seen during the physiological stress.

Table 11.14: A general protocol for management of suspected anaphylaxis

1. Suspected drugs likely to cause anaphylaxis should be stopped immediately.
2. 100% O_2 should be given with maintenance of airway.
3. Feet should be elevated with the patient lying flat.
4. Epinephrine should be used immediately. The recommended dose is 50 to 100 μg (0.05 to 0.1 ml of 1:1000 solution) IV over 1 minute, for hypotension with titration for further doses, as required.

   In patients with severe cardiovascular collapse, 0.5 to 1 mg (0.5 to 1 ml of 1:1000) may be required intravenously, in divided doses by titration. This should be given at a rate of 0·1 mg/min, stopping when a response has been obtained.

   Alternatively, epinephrine may be given IM in a dose of 0.5 to 1 mg (0.5 to 1 ml 1:1000) and may be repeated every 10 minutes according to the arterial pressure and pulse, until improvement occurs.
5. Intravascular volume expansion with crystalloid or colloid should be started immediately.
6. As a secondary measure, corticosteroids (100 to 300 mg hydrocortisone IV) and antihistamines (chlorpheniramine 10 to 20 mg by slow IV) are also given.
7. Catecholamine infusion is started:

   Epinephrine - 0.05 to 0.1 μg/Kg/min

   Norepinephrine - 0.05 to 0.1 μg/Kg/min
8. Sodium bicarbonate can be considered for acidosis (0.5 to 1 m.mol/Kg IV)
9. Bronchodilators may be required, if there is bronchospasm.

Management of patient with suspected anaphylaxis:

As soon as an anaphylaxis is suspected in a patient, it should be controlled by the following basic steps, which are given in table 11.14

2. Norepinephrine

Norepinephrine (NE) differs structurally from the epinephrine (EPI) by lacking the methyl substitution in amino group and is the major neurotransmitter among all the postganglionic adrenergic nerve endings. Normally, in adrenal medulla NE constitutes about 10 to 20% of the total catecholamine content. But, in pheochromocytoma, NE constitutes about 97% of the total catecholamine content in the adrenal medulla. This is due to the lack of enzyme, named N-methyl transferase.

Like EPI, the NE is also a direct adrenergic agonist, stimulating both the α and β receptors on the effector cells. But, the action of NE depends mainly on the ratio of its effectiveness on the α and β receptors. It is usually used for its potent α-agonism. NE is a potent agonist of α-receptors and has a relatively lesser action on β-receptors (than EPI). So, the peripheral or systemic vascular resistance is tremendously raised, due to the constriction of resistance vessels (α_1-action > β_2-action). This results in the elevation of systolic (β_1-action on heart, though less potent) and diastolic blood pressure (α_1-action on resistance vessel). Thus, pulse pressure is also increased. Cardiac output is unchanged or decreased (due to increase in systemic vascular resistance). Compensatory vagal reflex activity due to increased mean arterial pressure slows down the heart rate (↓HR). The increased systemic vascular resistance causes reduction of blood flow in the kidneys, mesenteric vessels, liver and other splanchnic areas. Coronary blood flow is increased due to the local coronary vasodilatation (here β-action predominantes over the α-action) and also due to the elevated aortic pressure. Patients with Prinzmetal's variant angina may be supersensitive to the α-adrenergic vasoconstrictor effects of NE. Unlike EPI, small doses of NE do not cause vasodilatation (in low doses, β-action of EPI predominates over α-action and the vessels dilate and cause reduction in BP) and does not reduce the blood pressure. The α-adrenergic blocking agents, therefore, abolish the pressor effects of the NE, but donot cause significant hypotension in low doses.

Other effects of NE, such as on bronchial muscles, mast cells, mucosa, eye, uterus, etc. are like EPI, but are not prominent in human beings. This is because, these are observed only when much larger doses of NE are given than EPI. So, NE is mainly considered as a pressor agent and is not considered as an effective 'hormone' like epinephrine.

Like epinephrine, NE is also not effective when given orally. It is also poorly absorbed through the subcutaneous route. It is rapidly metabolised in the body by COMT and MAO enzymes like EPI. Therefore, due to its short half-life of 2·5 minutes, a continuous infusion of NE is recommended. With less than 2 μg/min of infusion dose, the β stimulation effect of NE predominates. While with the usual infusion rate of more than 3 μg/min, peripheral vasoconstriction is elicitated from α stimulation of NE. Small amount of metabolites of NE are normally found in urine. But, in pheochromocytoma the concentration of metabolites of NE in urine is greatly increased.

The complications and contraindications of NE are similar to those of EPI. There is typical greater elevation of blood pressure by NE than EPI. The excessive doses can cause severe hypertension. So, careful monitoring of (Table 11.15) blood pressure is generally indicated during systemic administration of this agent. Blood pressure must be determined frequently during infusion and particularly during the adjustment of rate of infusion. Reduced blood flow to the organs such as the kidney and intestines impose a constant danger to these organs during the use of NE. So to ameliorate these renal effects, low dose of dopamine infusion also can be added to NE infusion. Pulmonary vascular resistance may be increased, so NE should be used with caution in patients with pulmonary hypertension. During IV infusion of NE, extravasation of drug can cause necrosis and sloughing of the tissues.

Like EPI, the NE has also limited therapeutic use. Like other sympathomimetic

Table 11.15: Dose dependent actions of adrenergic agents

Drug	*Receptor*	*Dose of infusion*
Norepinephrine	α_1 , β_1 , > β_2	4 to 10 μg/Kg/min (but much higher doses have been used in clinical practice)
Epinephrine	β_2 $\beta_1 + \beta_2$ α_1 Cardiac arrest	1 to 3 μg/Kg/min 2 to 10 μg/Kg/min > 10 μg/Kg/min 0.5 to 1 mg IV (bolus)
Dobutamine	$\beta_1 > \beta_2$, α_1	3 to 10 μg/Kg/min (but much higher doses have been used in clinical practice)
Dopamine	DA β α	1 to 3 μg/Kg/min 3 to 10 μg/Kg/min > 10 μg/Kg/min (or even higher doses)
Isoproterenol	$\beta_1 > \beta_2$	1 to 10 μg/min
Amrinone	Increase cAMP by PDE inhibition	0·75 mg/Kg/loading dose over 2 to 3 min, followed by 5 to 10 g/Kg/min infusion

amines, it is mainly used in shock to elevate the blood pressure. In the treatment of hypotension, the dose of NE is titrated to the desired pressure response.

Dose

2 to 4 μg/min by IV infusion.

3. Dopamine

It has been discussed in details in the chapter of heart failure.

ADRENERGIC AGONISTS

These include endogenous and exogenous catecholamines and non-catecholamine sympathetic amines. Among these endogenous catecholamines are discussed before. Here we will discuss only exogenous catecholamines and moncatecholamines which are adrenergic agoinst.

β-Adrenergic Agonists

The β-adrenergic agonists play a major role in the treatment of heart block and bronchoconstriction such as in patients with asthma or COPD. At first, for many years epinephrine was used as a bronchodilator. Later, ephedrine was introduced in 1924 as a bronchodilator. It has action on both α and β-receptors, but the action of ephedrine on β-receptors is more prominant than the α receptors. Then isoproterenol, a selective β-receptor agonist (both β_1 and β_2), without any α-adrenergic activity was developed in 1940. The recent development of β_2-selective adrenergic agonist with minimum β_1 cardiovascular effect and lack of α-adrenergic activity has changed the total scenario of management of asthma. But till now no selective β_1 agonist has been developed to control the cardiac problems. The drugs which are used as specific β_2 agonistic effect, but still in these group of drugs β_1 effect is greater than β_2 effect.

The specific β_1-adrenergic agonists are used to stimulate the rate and force of cardiac contraction. The chronotropic effect of specific β_1-adrenergic agonist is useful in the emergency treatment of arrhythmias, such as torsades-de-pointes, bradycardia, heart block etc. Whereas, the inotropic effect of specific β_1-adrenergic agonist is useful when it is desirable to augment the myocardial contractility.

(i) Isoproterenol

It is a potent nonselective β-adrenergic agonist with very low affinity or almost no action on α-receptors. It has powerful effects on both the β-receptors (β_1 and β_2), but its β_1-effect is significantly stronger than its β_2-adrenergic effects. The intravenous infusion of isoproterenol due to its prominent β_2-stimulating action relaxes the vascular smooth muscles (β_2-receptor dilates and α_1-receptor constricts the vascular smooth muscles), primarily of the skeletal muscles but also of the renal and mesenteric vascular beds, and lowers the SVR. So, diastolic pressure falls. But, systolic pressure is increased due to the positive inotropic and chronotropic effects of it (β_1 stimulating action). CO is increased due to the positive chronotropic and inotropic actions, coupled with decreased SVR. Large doses of isoproterenol may lead to palpitation, sinus tachycardia and more often serious arrhythmias. This is due to the strong β_1 effect of it. So, due to the development of other safe inotropes, its popularity has gradually declined, because of this side effects like tachycardia and serious arrhythmias. Isoproterenol helps in asthma, not only by bronchial smooth muscle relaxation (β_2-action), but also by inhibiting the antigen induced release of histamine and other mediators due to inflammation. But for many years in the treatment of bronchial asthma, isoproterenal has been replaced by other β_2-selective adrenergic agonists which cause lesser cardiac side effects.

During emergencies, isoproterenol is usually used parenterally by the IV route (infusion rates at 0.5 to 10 μg/min for adults) to increase the heart rate in patients suffering from severe bradycardia on heart block, particularly in anticipation with implantation of cardiac pacemaker or in patients with ventricular arrhythmia like torsades-de-pointes. In the past, it has been used in the treatment of bradycardia or heart block which is resistant to atropine. But, now it is no longer a part of the Advanced Life Support Protocol. It is readily absorbed when given by other parenteral routes, for example, as an aerosol, subcutaneous injection, etc. It is metabolised primarily in the liver and other tissues by COMT. Isoproterenol is a relatively poor substrate for MAO and is not taken up by the sympathetic nerve terminals to the same extent as NE and EPI. The duration of action of isoproterenol is, therefore, longer than that of EPI, but is still brief.

(ii) Dobutamine

It has been discussed in details in the heart failure chapter, along with dopamine.

β_2-Selective Adrenergic Agonist

As already discussed, nonselective β-adrenergic agonist, used in the treatment of asthma, also causes stimulation of β_1-adrenergic receptors in the heart. So, the drugs with preferential affinity for β_2-receptors than β_1-receptors have been developed. However, this selectivity is not absolute and at higher doses this preferentiality for β_2 than β_1 receptors becomes blurred. In addition, β_2-receptor stimulation in the SA node causes tachycardia.

The other aim to increase the usefulness of a selective β_2-receptor agonist in the treatment of asthma by modifying the structure of it is to lower the rates of metabolism of this drug and thus prolonging the therapeutic benefits and enhancing the oral bioavailability of it. This can be done by placing hydroxyl group at position 3 and 5 or substituting another moiety for the hydroxyl group at position 3 of phenyl ring of the β agonist. Thus this results in drugs, such as metaproterenol, terbutaline and albuterol (salbutamol) etc and these are not substrates for COMT. Thus, the addition of a bulky structure to the amino group of catecholamine increases the β_2 selectivity, decreases the affinity for α-receptor, and protects it against metabolism by COMT.

The another strategy for enhancing the preferential β_2 receptor activity of these drugs is to administer them by inhalation. This activates only the β_2 receptor in the airways and causes less systemic drug concentration. Thus, the less systemic drug concentration of the β_2 agonist prevents the activation of cardiac β_1 receptors and skeletal muscle β_2 receptor (stimulation of β_2 receptor of skeletal muscle causes tremor and limits the oral therapy). The β_2 adrenergic agonists given by aerosol have very rapid thrapeutic actions, generally within minutes (except salmeterol which has a delayed onset of action). Response to aerosol therapy depends on the technique of delivery of drugs to the distal airways which in turn depends on the size of the particles of the drug in aerosol, inspiratory flow rates, tidal volume, breath holding time and air way diameter. Only about 10% of the inhaled dose actually enters the lungs. Much of the remainder is swallowed and ultimately is absorbed through the stomach. Successful therapy by inhalation of β_2 adrenergic agonist requires each patient to be master regarding the inhalation technique of drug administeration. Whereas, particularly the children and elders fail to use the optimum technique. So, in these patients, spacer devices enhance the efficacy of inhalation therapy.

Other than the activation of pulmonary β_2 receptors and decrease of airway resistance, the selective β_2 adrenergic agonists have other major therapeutic effects in asthma, such as suppression of the release of leukotrienes and histamine from the mast cells in lung tissues, enhancement of mucociliary function, decreased microvascular permeability and inhibition of phospholipase A_2. It is becoming increasingly clear that airway inflammation is directly involved in airway hyper-responsiveness. So, the use of antiinflammatory drugs, such as inhaled steroids may also have primary importance.

The adverse effects of selective β_2 adrenergic agonists are due to the additional excessive side activation of β_1 adrenergic receptors. Hence, in patients at risk of underlying cardiovascular diseases this adverse effect can be reduced by administering the drug by inhalation, rather than orally or through other parenteral routes. Susceptibility to arrhythmia caused by these selective β_2 agonistic agents is due to the direct cardiac stimulation by β_1 or by β_2 induced hyperkalaemia. Skeletal muscle tremor (β_2 effect) is a relatively common adverse effect of β_2 selective adrenergic agonist. However, tolerance generally develops to this effect, but it is not clear whether this tolerance is due to the desensitization of β_2 receptors on skeletal muscles or adaptation in CNS. Tachycardia is another common adverse effects of β_2 adrenergic agonists and is primarily due to the β_1 receptor stimulation of the heart. It is still uncertain, to what extent the increase in heart rate is due to the activation of cardiac β_1 receptor or is due to the reflex effect that stems from the β_2 receptor mediated peripheral vasodilatation. However, during severe asthmatic attack, the HR may actually decrease during therapy with β_2 adrenergic agonist and it is due to the improvement of pulmonary function with consequent reduction of endogenous cardiac sympathetic stimulation. In patients with cardiac diseases, β_2 adrenergic agonists rarely cause significant arrhythmias or myocardial ischaemia. But, patients with underlying coronary artery disease or pre-existing arrhythmias are at greater risk. The risk of adverse cardiaovascular effects also increases in patients who are receiving other sympathomimetic drugs or MAO inhibitors.

Long term systemic administeration of β_2 adrenergic agonists, leads to down regulation of β_2 receptor and decreases its pharmacological responses. Chronic use of these drugs may also increase the airway hyperactivity. However, it appears that the tolerance to the pulmonary effect of these drugs is not a major clinical problem for majority of the asthmatic patients who do not exceed the recommended dosage of the β_2 adrenergic agonist and when given by inhalation.

When given parenterally, the selective β_2 adrenergic agonists may increase the concentration of plasma glucose, lactate and free fatty acids. Plasma K^+ concentration is increased and it may be especially important in patients with cardiac disease, particularly those taking cardiac glycosides and diuretics. Therefore, hyperglycemia may be worsened by these drugs and higher doses of insulin may be required. All these adverse effects of selective β_2 agonists are far less likely with the inhalation route, than with the oral or other parenteral routes.

Examples of some β_2 selective adrenergic agonists are metaproterenol (orciprenaline), albuterol (salbutamol), feneterol, formoterol, salmeterol, isoetharine, terbutaline, etc.

(i) Metoproterenol

Though metaproterenol is a selective β_2 adrenergic agonist, but less selective than terbutaline and albuterol (salbutamol). It is resistant to methylation by COMT. So, it is absorbed in the active form after oral administeration. Effects occur within minute of inhalation of metaproterenol and persists for several hours. However, after oral administration the onset of action is slower and its effects last for 3 to 4 hours.

(ii) Albuterol (Salbutamol)

It is also a selective β_2 adrenergic agonist and all the pharmacological actions of it are similar to terbutaline. It may be administered by inhalation or orally. When administered by inhalation, it produces significant bronchodilatation effect within 15 minutes and action lasts for 3 to 4 hours. The CVS effects of salbutamol is considerably weaker than those of isoproterenol, when the equivalent doses that produce comparable bronchodilatation are administered by inhalation.

(iii) Terbutaline

It is also a β_2 selective adrenergic agonist and is not a substrate for methylation by COMT. It can be administered orally or by inhalation or by parenteral (subcutaneous) routes. Effects are very rapid after inhalation or subcutaneous injection. After inhalation, the action of terbutaline persists for 3 to 6 hours. With oral administration, the onset of action is delayed by 1 to 2 hours.

α_1 Selective Adrenergic Agonists

The action of α_1 adrenergic receptors are predominant on vascular smooth muscles (though both α_1 and α_2 are present) and activation of both α_1 and α_2 receptors causes vasoconstriction, causing increased systemic vascular resistance (SVR) and increased BP. So, α_1 adrenergic agonists are useful in the treatment of hypotension and shock, and where peripheral vasoconstriction is needed, as in the treatment of hypotension in spnial anaesthesia. Phenylephrine and methoxamine are directly acting selective α_1 agonists. Whereas, mephenteramine and metaraminol are both the directly and indirectly acting selective α_1 adrenergic agonists. The indirect action means, a portion of the effect of the drug is mediated through the release of endogenous norepinephrine.

(i) Methoxamine

It is a selective, directly acting α_1 adrenergic agonist and increases the SVR and BP. It has no action on β adrenergic receptors and does not cause cardiac stimulation. The increase in BP is associated with reflex sinus bradycardia. This is because of the activation of vagal reflexes. Atropine can counteract this bradycardia. Methoxamine is administered through IV in the treatment of hypotension and shock.

(ii) Phenylephrine

It is also a directly acting selective α_1 adrenergic agonist. But, at very high concentrations, it may also activate the β receptors. The pharmacological actions of phenylephrine are similar to those of methoxamine and are used by intravenous infusion to raise BP. When given intravenously, phenylephrine has a rapid onset and relatively short duration of action (5 to 10 minutes). It may be given by bolus doses of 40 to 100 µg or by infusion at a starting rate of 10 to 20 µg/minute. Phenylephrine is also used as a mydriatic, nasal decongestant, and with local anaesthetics.

(iii) Mephentermine

It acts by both directly and indirectly stimulating the α_1 and β_1 receptors. Direct stimulation means, mephentermine produces both cardiac stimulation and vasoconstriction by directly activating α_1 (predominant) and β_1 (lesser extent) adrenergic receptors. Indirect stimulation means it acts by releasing endogenous norepinephrine (NE). It enhances the cardiac contraction and increases CO. Both the systolic (due to enhanced cardiac contraction and CO) and diastolic blood pressure (due to peripheral vascular constriction and increase in SVR) increases. The ultimate increase or decrease in CO depends on the increase in afterload and preload caused by mephentermine. If SVR increases tremendously, then CO may fall. In haemorrhagic shock naturally there is an increase in SVR and in the force of cardiac contraction due to the release of large amount of endogenous CAS. But still the CO falls and this is due to the severe reduction of preload (Table 11.16), reflecting severe hypotension. In spinal anaesthesia, there is reduction of SVR (afterload) which may increase the CO. On the otherhand, reduction of venous return (preload) may decrease the CO. But, the ultimate reflection of hypotension in spinal anaesthesia is due to ↓SVR, ↓preload and ↓CO. If the reduction of BP is not much below the level of 20% of MAP, then in such situations there is a definite increase in CO due to ↓SVR only (after load). But this small

Table 11.16: Adrenergic agonists and their receptors

Epinephrine (EPI)	α_1 , α_2 , β_1 , β_2 (no β_3 action or weak)
Norepinephrine (EPI)	α_1 , α_2 , β_1 , β_3 (no β_2 action or weak)
Isoprenaline	β_1 , β_2 , β_3 (no α action)
Dopamine	D , β_1 , α_1 (Dopamine receptor-D, predominates)
Dobutamine	α_1 , β_1 , β_2 (β_1 predominates)
Salbutamol	β_1 , β_2 (β_2 predominates)
Methoxamine	α_1 , β_1 (α_1 predominates)
Phenylephrine	α_1
Mephentermine	α_1 , β_1 (α_1 predominates)
Metaraminol	α_1 , β_1 (α predominates over β)

fall of BP is due to the slight reduction of preload, which is not upto that extent causing reduction of CO and severe hypotension. So, mephentermine is used to prevent hypotension which frequently accompanies spinal anaesthesia, in titrable doses to keep the BP at the preoperative level or within 20 to 25% of MAP.

The direct positive chronotropic effect of mephentermine on heart is generally counter balanced by the indirect vagal stimulation due to the rise in mean BP. So, the change in HR is variable, depending on the degree of vagal tone which again depends on BP. All the adverse effects of mephentermine are related to excessive rise of BP causing LVF, pulmonary oedema, etc, and arrhythmia (β_1 effect). Mephentermine is not a substrate for either MAO or COMT. So, it is orally active with longer duration of action (2 to 6 hours). It can cross the blood brain-barrier partially and so produce excitatory CNS effects at higher doses. During the treatment of hypotension the dose of mephentermine is usually titrated according to the fall of BP. It is presented as 15 mg in 1 ml amp or 3 mg/ml in 10 ml vial. Mephentermine is now used mainly to prevent and treat hypotension due to spinal anaesthesia.

(iv) Metaraminol

Metaraminol is a synthetic sympathomimetic amine. Like mephentermine, it is also a direct and indirect acting adrenergic agent that has agonistic effects on both α and β adrenoreceptors, although the α agonistic activity predominates. So, its main action is peripheral vasoconstriction.

Metaraminol causes a sustained increase in systolic and diastolic blood pressure, due to the increase in SVR and CO. But, the increase or decrease of CO depends on the elevation of SVR and preload. It also increases the pulmonary vascular resistance. Like mephentermine a reflex bradycardia also occurs with rise of BP. Like epinephrine the coronary blood flow is increased by metaraminol by an indirect mechanism.

It causes a slight decrease in respiratory rate and an increase in tidal volume. The cerebral blood flow is decreased by the administration of metaraminol. The renal blood flow is also decreased by it due to the renal vasoconstriction. The drug causes contraction of the pregnant uterus.

Metaraminol increases the glycogenolysis and inhibits the release of insulin, leading to hyperglycaemia. Lipolysis is similarly increased by it. The drug may also increase the O_2 consumption and body temperature.

Like mephentermine, metaraminol also causes CNS stimulation and produces headache, dizziness, tremor, nausea and vomiting. Rapid and large increae in blood pressure, resulting in LVF and cardiac arrest have also been reported after the administration of metaraminol.

Metaraminol is mainly used by intravenous infusion, diluted in saline or dextrose and the dose should be titrated according to the response. Bolus doses of 0.5 to 5 mg of metaraminol may be administered intravenously, but with extreme caution. Its onset of effect after IV administration occurs within 1 to 2 minutes, with maximum effect at 10 minutes and lasts for 20 to 60 minutes. The corresponding IM or SC dose of metaraminol for the prevention of hypotension is 2 to 10 mg.

Metaraminol is used as an adjunct for the treatment of: (i) hypotension occuring during general or spinal anaesthesia and (ii) for the management of hypotension, occurring during cardio-pulmonary bypass.

α_2- Selective Adrenergic Agonists

Many blood vessels contain α_2 receptors that promote vasoconstriction on stimulation. So, clonidine as a selective α_2 adrenergic agonist was initially developed as a vasoconstricting nasal decongestant. But, later it was found that clonidine, reduces the blood pressure by activating the presynaptic α_2 adrenergic receptors present in the CNS which controls the CVS. Such central presynaptic α_2 adrenergic receptor activation supressses the outflow of sympathetic nervous system activity from the brain. Therefore, there is a contradiction between the peripheral action of clonidine, causing hypertension and its central action, causing hypotension. But, the ultimate or resultant effect of clonidine depends on the predominancy of the site of action of the drug. As for example, when the clonidine is given intravenously, then there is acute rise in BP. This is due to the predominant activation of α_2 receptors in peripheral vascular smooth muscles. After IV administration, transient vasoconstriction and hypertension caused by clonidine is followed by hypotension which results from the decreased central outflow of impulse from central sympathetic nervous system. However, this hypertensive response of clonidine that follows parenteral administration is not seen when the drug is given orally.

(i) Clonidine

When clonidine was first synthesized in 1960, it was used to produce vasoconstriction (as a nasal decongestant) that was mediated through the stimulation of local peripheral α_2 adrenergic receptors on vascular system. But, later when clonidine was used, it was found that clonidine can cause hypotension, sedation, analgesia and bradycardia. Then, it was postulated that this action of clonidine is mediated through the central presynaptic α_2 adrenergic receptors.

The probable mechanisms of hypotension and analgesic effect of clonidine are:

i. Activation of the presynaptic α_2 receptors by clonidine in the lower brain stem region decreases the discharge from sympathetic preganglion fibres in the splanchnic nerve, as well as in the postganglionic fibres of the cardiac nerves.
ii. Clonidine also stimulates the parasympathetic outflow and this may contribute to the slowing of heart rate.
iii. Some of the antihypertensive effects of clonidine may also be mediated by activation of the presynaptic α_2 receptors

that suppress the release of norepinephrine from the preganglionic nerve endings.

iv. α_2 receptors are also located on the primary afferent terminals (peripheral and spinal) of the neurons of the superficial laminae of the spinal cord, and within several brain stem nuclei which are responsible for analgesia. This explains the analgesic effect of the α_2 receptor ago nist, clonidine.

v. Similar to a local anaesthetic agent, α_2 adrenergic agonists have also been found to produce the dose dependent blockade of conduction in nerve fibres, particularly of the C fibres than A-δ fibres. This can explain the local anaesthetic property of clonidine.

vi. Additionally, clonidine hyperpolarizes some neurons of the dorsal horn and renders them less resposive to afferent impulses. Thus, it can produce analgesia.

vii. Neuro-axial administeration of clonidine directly inhibits the sympathetic preganglionic neurons in the spinal cord. So, local anaesthetic agents when is combined with α_2 adrenergic agonists can increase the degree of sympatholysis, resulting in severe hypotension.

viii. Similar to opioids, clonidine also decreases the afferent noxious inputs through its interaction with the specific receptors in the spinal cord which are G-protein coupled. Like opioids, clonidine also reduces the substance P and the excitatory amino acids, which are released by peripheral nerves stimulation at noxious intensities.

Clonidine is well absorbed after oral administration. Bioavailability is 100% through the oral route. Peak effect of clonidine is observed within 1 to 3 hours after oral administeration and duration or half-life is 12 hours.

The major adverse effects of clonidine are dry mouth and sedation. Sexual dysfunction may occur. Marked bradycardia and hypotension is observed in some patients.

The major therapeutic use of clonidine is in the treatment of hypertension. Now, clonidine is useful in selected patients receiving anaesthesia, because it decreases the requirement of anaesthetics agents and increases the haemodynamic stability. Other potential benefits of clonidine in anaesthesia include preoperative sedation, anxiolysis, drying of secretions and analgesia.

(ii) Methyldopa

Methyldopa is also a selective α_2 adrenergic agonist and its antihypertensive action is exerted through its central action like clonidine which is by inhibiting the adrenergic neuronal outflow from the brain stem. Actually the methyldopa is a prodrug and an analog to DOPA. It is metabolized by decarboxylase in the adrenergic neuron to α-methyl-dopamine which is then converted to α-methyl norepinephrine. After that this α-methyl norepinephrine (which is called false neurotransmitter) is stored in the vesicles at the adrenergic nerve endings and acts as a false adrenergic neurotransmitter, replacing or substituting the true norepinephrine. Thus, when the adrenergic neuron discharges its neurotransmitter, then α-methyl norepinephrine is released instead of NE. As a vasoconstrictor (peripheral $\alpha_2$adrenergic agonistic action) α-methyl norepinephrine is as potent as NE (but NE has both α and β agonistic action). But, α-methyl norepinephrine acts in the brain to inhibit the adrenergic vasoconstrictive outflow and this central effect, which predominates than the peripheral effect, is principally responsible for its antihypertensive action.

Methyldopa reduces the peripheral vascular resistance (afterload) and preload. Thus, the increase or decrease of cardiac output depends on the intensity of reduction of afterload and preload. If afterload reduction is more than preload (younger patients with uncomplicated essential hypertension) CO increases. Alternatively, if preload reduction is more than afterload (as in older patients), then CO falls with a reduction in the stroke volume. Symptomatic orthostatic hypotension is less common with methyldopa than other antihypertensive agents which act on peripheral adrenergic receptors or autonomic ganglia. This is because methyldopa does not block baroreceptor mediated vasoconstriction. For this reason, it is well tolerated during surgical anaesthesia. Any severe hypotension produced by methyldopa can only be reversed by volume expansion, but not by a peripheral α-adrenergic agonist. This is because methyldopa does not block the peripheral α-receptors. In hypotension, like spinal anaesthesia where adrenergic neurons are blocked, peripheral α-adrenergic agonists are antidotes. But this is not possible in hypotension produced by methyldopa.

Renal blood flow and renal function is maintained during treatment with methyldopa. Plasma concentration of NE falls in association with the reduction of arterial pressure during treatment with methyldopa and this reflects the decrease in sympathetic tone, discharged from the CNS. In contrast, the reduction of BP by vasodilators is associated with the increased concentration of NE in plasma. Renin secretion is reduced, but this is not the major effect and is not responsible for the hypotensive effect of methyldopa.

In the brain, methyldopa acts on the α_2 adrenergic rceptors and inhibits the centres that are responsible for wakefulness and alertness. Thus, it produces sedation, drowsiness and depression. The medullary centres that control salivation are also inhibited by α_2-adrenergic receptors, and so methyldopa produces dryness of mouth. Other CNS effects of methyldopa include reduction in libido, parkinsonian signs, hyperprolactinemia and gynecomastia.

Methyldopa is absorbed actively through the GI tract by amino acid transport system, when administered orally. Its transport into the CNS is also an active process. So in spite of rapid absorption, the peak action of methyldopa is delayed by about 6 to 8 hours, even after an IV administration. This is due to the time taken by methyldopa to convert to its

active metabolites, α-methyl norepinephrine. The duration of action of a single dose of methyldopa usually lasts for about 24 hours.

Methyldopa is an active antihypertensive agent, but is not usually used as the first line of treatment. This is because of its frequent side effects, such as hepatotoxicity and haemolytic anaemia (Coomb's test becomes positive and that is due to the autoantibodies directed agonist - the Rh locus on erythrocytes). Therefore, methyldopa is reserved for patients in whom it may have a special value. For example, it is the preferred drug for treatment of hypertension during pregnancy which is based on its effectiveness and safety for both the mother and foetus.

Other Selective α_2 Adrenergic Agonist

(i) Apraclonidine

It reduces the formation of aqueous humour and is usually used topically to reduce the intraocular pressure.

(ii) Guanfacine

It is a more selective α_2 agonist than clonidine and has less side effects. Its mechanism of action is same as clonidine and is used in the treatment of hypertension.

(iii) Guanabenz

It is also selective α_2 adrenergic agonist. Its mechanism of action and therapeutic effects are similar to that of clonidine and guanfacine.

(iv) Tizanidine

It is also a selective α_2 adrenergic agonist, and is used as a muscle relaxant in the treatment of spasticity, associated with cerebral and spinal disorders.

(v) Brimonidine

Being a α_2 agonist, it is used topically to lower the intraocular pressure in patients with ocular hypertension or open angle glaucoma.

Miscellaneous Adrenergic Agonists

Ephidrine

It is both the α and β adrenergic receptor agonist (direct action) and also enhances the release of endogenous NE from the sympathetic neurons (indirect action). By its α action it increases the systemic vascular resistance (SVR) and BP, and by its β action it increases HR and CO. Ephedrine increases the coronary blood flow. It is a respiratory stimulant and also causes bronchodilatation. It is a potent CNS stimulant. Like amphetamine, it increases the cerebral blood flow. Mydriasis occurs after topical use. Ephedrine constricts renal blood vessels and may lead to a decrease in both the renal blood flow and GFR. It is not metabolised by MAO or COMT. So, it is also effective after oral administeration and this effect lasts for many hours. Ephedrine is excreted through the urine, largely as an unchanged form.

Previously, ephedrine was used in (i) Stokes, Adams attack, (ii) as a CNS stimulant in narcolepsy and depressive states, (iii) as bronchodilator in bronchial asthma, (iv) in urinary incontinence, etc. But now-a-days, ephedrine is replaced by more specific drugs for each disorder. Recently, ephedrine has only been used to treat hypotension occurring with spinal anaesthesia.

Untoward effects of ephedrine include the risk of hypertension, particularly after parenteral administeration or with higher than recommended oral dose. The parenteral dose of ephedrine is 3 to 30 mg which is titrated according to the response.

Other miscellaneous adrenergic agonists

Other miscellaneous adrenergic agonists are: amphetamine, methyl amphetamine and methyl phenidate.

Several sympathomimetic drugs, used primarily as a vasoconstrictor of nasal mucous membrane, when used topically are: propyl hexedrine, naphazoline HCl, tetra hydroxoline HCl, oxymetazoline HCl and xylometazoline HCl.

Phenylephrine, pseudoephedrine and phenylpropanolamine are the sympathomimetic drugs that have been used as oral preparation for the relief of nasal congestion.

USES OF SYMPATHOMIMETIC AGENTS IN HYPOTENSION AND SHOCK

Drugs with predominant α adrenergic activity can be used to raise BP in patients with decreased SVR, due to failure of sympathetic nervous system, such as: spinal anaesthesia, overdose of antihypertensive medications, etc. However, slight hypotension is not an indication for treatment by these agents, if there is adequate perfusion of vital organs, such as : brain, kidney, heart and lungs. But, in patients with spinal anaesthesia, where there is severe or total failure of the sympathetic nervous system, use of vasopressor drugs to increase SVR and to maintain perfusion in the vital organs is indicated. A number of sympathomimetic agents have been used for this purpose. But, the ideal agents would cause arterial constriction, with relatively little arteriolar constriction (the primary side for systemic vascular resistance), which would not increase the afterload and will not reduce CO, although will maintain the BP. However, no such ideal agent is currently available. Only midodrine shows promise in treating hypotension with this idea.

In other forms of shock, such as: haemorrhage, loss of fluid, etc, where the sympathetic nervous system does not fail, but the accompanying fall in BP generally leads to marked activation of the sympathetic nervous system. This in turn, causes increased peripheral vasoconstriction and ↑SVR and also an increase in the rate and force of cardiac contraction. In the initial stage of shock, this mechanism tries to maintain BP and cerebral blood flow, but blood flow to the kidneys, skin and other organs may be decreased, leading to impaired production of urine and metabolic

acidosis. But, later when the SVR tremendously increases and the preload severely falls, due to more haemorrhage and loss of fluid, then CO drastically reduces, causing more hypotension. Thus a vicious cycle is set up.

So, the initial therapy of shock involves basic life support and a specific therapy, such as: fluid or blood for hypovolaemic shock, antibiotics for septic shock, emergency cardiac catheterisation or surgical revascularisation or even angioplasty for cardiogenic shock. Mechanical left ventricular assisting devices, such as: the intra-aortic balloon pump (IABP) also may be important in maintaining CO and coronary perfusion in critically ill patients. In the setting of severely impaired CO, failing blood pressure leads to intense discharge of sympathetic outflow (provided the sympathetic system is not blocked) and vasoconstriction. This may further decrease CO, as the damaged heart pumps against a higher peripheral systemic resistance or the afterload. In such situations, medical intervention is designed to optimise the CO by manipulation of the cardiac filling pressure (preload), myocardial contractility (pump) and peripheral vascular systemic resistance (afterload).

Preload may be increased by administeration of IV fluid or reducing the dose of diuretics and nitrates (nitrates reduce the preload by dilating the venous side of the vascular system). If these measures do not lead to an adequate therapeutic response, it may be necessary to use vasoactive drugs in an effort to improve abnormalities of BP and flow. Many of these pharmacological approaches, while apparently clinically reasonable, are of uncertain efficacy. Adrenergic agonist may be used in an attempt to increase myocardial contractility or to modify the peripheral vascular resistance. In general terms, β adrenergic agonist increases the HR and the force of contraction, α adrenergic agonist increases the SVR and dopamine (in renal doses) promotes dilatation of renal and splanchnic vascular beds, in addition to activating β and α adrenergic receptors (in higher doses).

A number of sympathetic amines have been used to increase the force of cardiac contraction. But, some of these drugs have disadvantages. For example, isoproterenol is a powerful chronotropic agent and can greatly increase the myocardial O_2 demand. NE intensifies peripheral vasoconstriction and EPI increases the heart rate and may predispose the heart to dangerous arrhythmias. Dopamine is an inotropic agent that causes less increases in heart rate and promotes renal arterial dilatation. When dopamine is given in higher doses (>10 to 20 μg/Kg/min), it activates the α adrenergic receptors, causing peripheral and renal vasoconstriction. Dobutamine has complex pharmacological actions to increase the myocardial contractility with little increase in HR and peripheral resistance.

In most forms of shock, except few, where there is vasodilatation (e.g. spinal anaesthesia, septicaemia, anaphylaxis), there is intense reflex vasoconstriction. In such situations, the use of α adrenergic agonists may further compromise blood flow to the vital organs, such as: kidneys, brain, heart, guts, etc. as well as adversely increase the work of the heart. Indeed, in such situations, vasodilating drugs such as nitroprusside are more likely to improve blood flow in vital organs and decrease cardiac work by decreasing the afterload, if a minimally adequate blood pressure is maintained.

ADRENERGIC RECEPTOR ANTAGONISTS

α - Adrenergic Receptor Antagonist

Endogenous catecholamines (CAS), exogenous catecholamines and other non-catecholamine sympathomimetic or adrenergic agents mediate their actions through both the α and β or only through α and β receptor. Among these, the α_1 receptor mediated actions are confined only to the arterial and venous smooth muscle contraction.

Whereas the α_2 receptor mediated actions are:

i. Suppression of central sympathetic outflow.
ii. Increment of vagal tone.
iii. Facilitation of platelet aggregation.
iv. Inhibition of release of NE and ACh from presynaptic nerve endings.
v. Regulation of metabolic effects, including suppression of insulin secretion, inhibition of lipolysis, etc.
vi. Contraction of smooth muscles of some arteries and veins.

So, the α-adrenergic receptor antagonists have a wide range of pharmacological actions and every agent has different affinity for both the α_1 and α_2 receptors. For example, prazosin as a α receptor antagonist has greater affinity for α_1 than α_2 receptors. Whereas yohimbine is a selective α_2 antagonist and phentolamine has the same affinity for both receptors. α-receptor antagonists are also heterogenous in nature, because they vary widely in structure.

α_1 - Adrenergic receptor antagonist

Clinically, the most important effect of α_1 the receptor antagonist is observed in the cardiovascular system. Blockade of α_1 receptor causes vasodilatation and decrease in BP with decrease in SVR. This fall of blood pressure is more marked in upright than in supine position and in hypovolaemia. This fall in BP by α_1 receptor antagonist is usually counteracted by rise in HR and CO by reflex baroreceptor mechanism. There is also fluid retention during the use of α_1 adrenergic receptor antagonist.

The interaction between a α_1 receptor antagonist and a sympathomimetic amine (which sometimes occur in clinical practice) depends on the adrenergic agonist that is administered. For example: (i) Pressor response of phenylephrine can be completely suppressed by α_1 receptor

antagonist. (ii) Action of NE can be incompletely blocked by a α_1 receptor antagonist, because of residual stimulation of cardiac β_1 receptor by NE. (iii) Pressure response of EPI can be transformed to hypotension effects by the concomitant use of a α_1 receptor antagonist. This is because of the residual stimulation of β_2 receptors by EPI on the vasculature with resultant vasodilatation and hypotension.

α_1 receptor antagonist also inhibits the smooth muscle contraction of trigone, bladder sphincter and prostate, leading to decreased resistance to urinary outflow. Recent evidence suggests that there are two types of α_1 receptors such as α_{1A} and α_{1B}. Among these α_{1A} receptors are important in mediating catecholamines-induced prostatic smooth muscle contraction which can be inhibited by a specific α_{1A} receptor blocker, such as tamsulosin. Although, theoretically some α_1 receptors promote bronchial smooth muscle contraction, but the importance of α_1 receptor antagonist in asthma is minimal.

α_2 - Adrenergic receptor antagonist

α_2 receptors have an important role in the regulation of the activity of sympathetic nervous system, both peripherally and centrally. Activation of the presynaptic α_2 receptors inhibits the release of NE from the sympathetic nerve endings. Thus block of presynaptic α_2 receptors withdraw this inhibition and causes increased release of NE from the nerve endings, leading to activation of both α and β receptors in the heart and contraction of the peripheral vascular smooth muscles, with consequent rise in BP and SVR. Whereas the activation of presynaptic α_2 receptors in pontomedullary region of CNS inhibits sympathetic outflow and causes fall in BP. α_2 antagonist thus reverses this action and increases the sympathetic outflow and BP. Thus, on one side, the α_2 receptor antagonist increases the sympathetic outflow by acting peripherally on the receptors at presynaptic membrane and acting centrally at pontomedullary region. Thus, it increases the BP. On the otherside, α_2 antagonist directly blocks the peripheral vascular α_2 receptor which causes vasoconstriction and thus produces vasodilatation with decrease in BP.

Some α - Adrenergic Antagonists and their Therapeutic Uses

(i) Phenoxybenzamine

It irreversibly blocks both the α_1 and α_2 receptors (irreversible because furthur restoration of cellular responsiveness to α adrenergic agonists probably requires the synthesis of new receptors) and causes progressive lowering of BP and SVR. It is predominantly an arterial vasodilator. Thus, it increases the HR and CO (upto a certain level of fall of blood pressure) and this is due to reflex baroreceptor stimulation. During the use of phenoxybenzamine, pressor response of exogenously administered CAS is impaired and hypotensive response to EPI occurs. This is because of the unopposed β adrenergic receptor mediated vasodilatation by EPI. In normotensive subjects, BP in supine position is little affected by phenoxybenzamine. But, there is a marked fall in BP in standing position (orthostatic hypotension) and this is because of the antagonism of α receptor mediated compensatory vasoconstriction which is essential for maintaining BP in standing condition. In addition, the normal ability of a patient to respond to hypovolaemia and to anaesthesia induced vasodilatation is impaired by phenoxybenzamine, causing severe hypotension. The drug also increases the rate of peripheral turn over of NE. This is because the amount of NE that is released per nerve stimulation is increased by the blockade of presynaptic α_2 receptor. Phenoxy benzamine inhibits CAS induced cardiac arrhythmias. It also causes a shift of fluid from the interstitial to vascular compartment and it is due to vasodilatation of pre- and post-capillary resistance vessels.

The major clinical use of phenoxybenzamine is in the treatment of pheochromocytoma. A vast majority of pheochromocytomas are treated surgically. But this drug is used frequently to treat the patient where surgery is contraindicated or to prepare the patient for operation preoperatively. Initially phenoxybenzamine is started in the dose of 10 mg twice daily for 1 to 3 weeks before operation. Then, the dose is gradually increased till the desired lower level of BP is achieved. But the therapy by phenoxy benzamine may be limited by postural hypotension. The usual total daily dose of phenoxybenzamine in patient with pheochromocytoma is 40 to 120 mg which is given in two or three divided doses. The corresponding dose of phenoxy benzamine by intravenous infusion (diluted in dextrose or saline) over 1 hour is 10 to 40 mg. After the intravenous administration, the drug acts within 1 hour and has a duration of action for 3 to 4 days. Some anaesthesiologists donot routinely use phenoxybenzamine preoperatively for the preparation of patient before pheochromocytoma surgery. In patients with inoperable and malignant pheochromocytoma prolonged treatment with phenoxybenzamine may be necessary. Another approach for management of pheochromocytoma, particularly with a malignant disease, is administration of metyrosine. It is a competitive inhibitor of tyrosine hydroxylase which is the rate limiting enzyme in the synthesis of catecholamines. β adrenergic receptor antagonists or β blockers are also used to treat pheochromocytoma, but only after the administeration of an α receptor antagonist.

Phenoxybenzamine is the first α receptor antagonist which was also used previously for the treatment of benign hypertrophy of prostate (BHP). The mechanism of action of phenoxybenzamine in the treatment of BHP is the blockade of α receptors, situated on the smooth muscle of prostate and bladder base. Thus, it decreases the obstructive symptoms and decreases the need to urinate at night (α

receptor is responsible for the spasm of bladder trigone, bladder neck and prostate muscle, causing urinary obstruction). However, terazocine and other related drugs are safer and more preferred than phenoxybenzamine, as they are more specific α_1 adrenergic antagonists for this disorder.

The major side effects of phenoxybenzamine is postural hypotension which is accompanied by reflex tachycardia. Hypotension produced by α-antagonist may be severe, if there is hypovolaemia and there is history of concomitant use of vasodilator drugs.

(ii) Phentolamine and Tolazoline

Like phenoxybenzamine, phentolamine is also a competitive α adrenergic antagonist and have same affinity for both the α_1 and α_2 receptors. It also causes the blockade of 5 HT receptors and causes the release of histamine from mast cells. Tolazoline has similar function like phentolamine, but is less potent. Phentolamine and tolazoline both increase the G1 motility which can be antagonised by atropine.

Phentolamine can be used for a short-term basis to control hypertension in pheochromocytoma. Infusion of phentolamine may be used, but very cautiously. The adult IM dose of phentolamine for the control of paroxysmal hypertension is 5 to 10 mg. The drug may also be administered by IV infusion (diluted in dextrose or saline) at the rate of 0·1 to 0·2 mg/min.

(iii) Prazosin and related drugs

(a) Prazosin

It is also a potent selective α_1 adrenergic antagonist, with thousand fold greater affinity for α_1 receptor than α_2. But among the subtypes of α_1 receptors (α_{1A}, α_{1B}, α_{1D}) it has same affinity to all.

The pharmacological effects of prazosin are due to the result of blockade of α_1 receptors in arterioles and veins, leading to ↓ BP, ↓ SVR and ↓ preload. However, like other vasodilating drugs, it doesnot reflexly increase the HR at the clinical level. Again, it does not block the presynaptic α_2 receptor. Hence, it does not promote the release of NE from presynaptic sympathetic nerve endings in the heart. As the prasocin decreases preload more than afterload, so it does not increase CO (in contrast to vasodilators, such as hydralazine that have minimal dilatory effect on the veins). It also acts in the CNS and suppresses the central sympathetic outflow.

Prazosin is well absorbed when given orally with bioavailability of about 50 to 70%. Peak serum concentration through the oral route is generally reached within 1 to 3 hours after administeration.The plasma half-life of prazosin is 2 to 3 hours and the the duration of action is typically 7 to 10 hours. For the treatment of hypertension, prazosin is started initially in smaller doses such as 1 mg at bedtime, so that the patient is recumbent for at least several hours after its administration. Thus, it reduces the risk of syncopal reaction due to hypotension that may follow the first dose of prazosin. Then the dose is titrated upwards, depending on the blood pressure. The maximum effect of prazosin is generally observed with the total daily dose of 20 mg in patient with severe hypertension. For the treatment of benign prostatic hypertrophy (BPH), prazosin in the dose of 1 to 5 mg twice daily is usually used.

(b) Terazosin

It is structurally an analog of prazosin, but less potent than it. Like prazosin it is highly selective to α_1 receptors than α_2, with no discrimination among α_{1A}, α_{1B}, α_{1D} receptors regarding affinity. The oral bioavailability of terazosin is 90% and half life of elimination is approximately 12 hours with duration of action of 18 hours. The drug is taken as once daily dose to treat the hypertension and BPH. An initial first dose of 1 mg of terazosin is recommended. Then the doses are titrated upwards gradually, depending on the therapeutic responses. Terazosin in the dose of 10 mg/day may be required for maximal effect in BPH.

β-Adrenergic Receptor Antagonists

It has been discussed in the hypertension chapter.

CHOLINERGIC RECEPTOR (MUSCARINIC AND NICOTINIC) AGONIST AND ANTAGONIST

The cholinergic receptor agonists are the drugs or agents that act like ACh on both the cholinergic receptors, i.e. muscarinic and nicotinic. ACh is the endogenous cholinergic neurotransmitter which acts on both the muscarinic and nicotinic receptors. But there are other agents which also act selectively only on the muscarinic or the nicotinic receptors. So, they are called as the selective muscarinic or nicotinic receptor agonists, respectively.

Nonspecific Cholinergic Agonist

Acetylcholine (ACh)

It is an endogenous cholinergic neurotransmitter. It acts at all the cholinergic synapses in the central and peripheral nervous system of the body. Its actions are mediated through both the muscarinic and nicotinic receptors. Muscarinic receptors in the peripheral nervous system are primarily found on all the cells that are innervated by the preganglionic autonomic (sympathetic and parasympathetic) nerve fibre except the ganglionic cells, the postganglionic parasympathetic nerves and some postganglionic sympathetic fibres that supply the sweat gland, hair follicle and erector piloris. Muscarinic receptors are also present in the CNS and on certain other cells such as endothelial cells of blood vessels that receive little or no cholinergic innervation. Certain centres of the brain, such as hippocampus, cortex, thalamus, etc. also have a high density of muscarinic receptors. Nicotinic cholinergic receptors are only found at the

neuromuscular junctions, causing skeletal muscle contraction and at the peripheral autonomic ganglia (sympathetic and parasympathetic) including the adrenal medulla, because adrenal medulla itself is an autonomic ganglia.

As ACh acts on both the muscarinic and nicotinic receptors, so its pharmacological actions can also be divided into muscarinic and nicotinic actions.

(i) Muscarinic actions

It is due to the stimulatory action on muscarinic receptors. Muscarinic actions include actions on the heart, blood vessels, smooth muscles, glands, eye, viscera, mucous membrane, etc., where muscarinic receptors are abundantly present. Whereas, nicotinic actions include only actions on the skeletal muscles and autonomic ganglia where nicotinic receptors are only present.

(a) CVS

The main muscarinic effects of ACh on the CVS are vasodilatation, ↓ HR, ↓ conduction in heart, ↓ contractility of the cardiac muscle etc. ACh is not given systemically for any therapeutic indication. But, its importance lies within the mechanism of action of many cardiac glycosides, antiarrhythmic drugs, many other agents and following afferent stimulus from the viscera, during surgical intervention. IV small dose of ACh causes reduction of BP due to vasodilatation and there is reflex tachycardia due to reduction of BP. A relatively higher dose of ACh causes bradycardia and ↓ conduction in the cardiac tissues. However, IV large dose of ACh causes ↑ BP, specially after administration of atropine, which block the muscarinic receptors. This is caused by stimulation of the adrenal medulla and sympathetic ganglia by ACh which release CAS into circulation from adrenal medulla and at postganglionic sympathetic nerve endings (nicotinic actions).

ACh causes dilatation of both the pulmonary and coronary vasculature. This dilatation of coronary blood vessel is caused by the baroreceptor and chemoreceptor mediated reflex or by the release of NO. However, neither the parasympathetic vasodilator, nor the sympathetic vasoconstrictor fibre plays a major role in the regulation of coronary blood flow. It is effected by the local O_2 tension and local autoregulatory metabolic factors, such as: adenosine that determines the blood flow through coronary vessels. Though, most of the blood vessels do not receive cholinergic innervation, still the vasodilatation of it is mediated in response to ACh by the presence of muscarinic receptors on the endothelial cells, primarily of M_3 subtypes. When these receptors are stimulated by ACh, the endothelial cells release endothelium dependent releasing factor (EDRF) or nitric oxide, which diffuses to the adjacent smooth muscles and causes them to relax. Vasodilatation may also arise secondarily from the inhibition of release of NE from the adrenergic nerve ending by ACh.

Cholinergic parasympathetic fibres are extensively distributed in the SA node, AV node, atrial muscle, bundle of HIS, right and left bundle branch, and specialized conducting tissue of the heart, like purkinje fibres. The cholinergic innervation to ventricular myocardium is sparse. ACh acts on the cardiac tissues directly by stimulating the parasympathetic activity and indirectly by inhibiting the effects of adrenergic activity. The inhibition of adrenergic activity by ACh depends on the present level of sympathetic drive on the heart. Inhibition of this adrenergic drive by ACh, results partly from the inhibition of cyclic AMP formation and partly from the reduction in L-type Ca^{2+} channel activity. In SA node, the pacemaker activity of the SA nodal cells is caused by the presence of spontaneous diastolic depolarization phase or phase 4. At a critical level (i.e at the level of threshold potential), this spontaneous slow diastolic depolarization automatically initiates an action potential and a full cardiac cycle. ACh slows the heart rate by decreasing this rate of spontaneous diastolic depolarization and by increasing the repolarizing current (i.e., resting membrane potential become more negative) of SA nodal cells and thus delaying the attainment of threshold potential from RMP and delaying the cardiac cycle.

ACh also causes reduction of the force of contractility of cardiac muscles, slows conduction in conducting tissues and increases the refractory period. The decrement in AV nodal conduction is usually responsible for the complete heart block, that may be observed when large quantities of cholinergic agonists are administered systemically. With an increase in the vagal tone, (which acts through ACh neurotransmitter) such as: produced by digitalis glycosides, the increased refractory period of the AV node and the bundle of HIS can contribute to the reduction in frequency, with which the aberrant atrial impulses are transmitted to the ventricle and thus decreases ventricular rate during atrial flutter and fibrillation.

(b) Gastrointestinal, urinary tract and other smooth muscles

Smooth muscles of most of the organs are contracted by ACh as they are rich in muscarinic receptors. Thus, the tone and peristalsis of GI tract is increased and the sphincter relaxes, causing abdominal cramps and evacuation of bowel by ACh. Bronchial smooth muscles also contract by ACh, causing attack of bronchial asthma. Peristalsis of the ureter is increased. The detrusor muscles of urinary bladder contract, while the bladder trigone and sphincter relaxes by ACh, causing voiding of bladder.

(c) Glands

Secretion from all the cholinergically innervated glands is increased by ACh, causing salivation, sweating, lacrymation, etc. Tracheobronchial and gastric secretion is also increased by ACh. The secretion of pancreatic and intestinal glands also increases, but is not so marked. Secretion of milk and bile is not affected by ACh.

(d) Eye

Contraction of the constrictor muscle of iris by ACh causes miosis (constriction of the pupil). Contraction of ciliary muscles also cause loss of accommodation, increased outflow facility and reduction in intraocular tension.

(e) C N S

Naturally occurring cholinomimetic alkaloids such as pilocarpine, muscarine and aerocholin, etc. can cross the blood brain-barrier and evoke a characteristic cortical arousal and CNS stimulating response, which are similar to that produced by the injection of anticholinesterase agents. The arousal response of all of these three drugs can be reduced or blocked by atropine and related agents. But, choline esters e.g ACh, being a quarternary compound, does not cross the blood brain-barrier and does not produce any CNS symptoms.

(ii) Nicotinic actions

This is due to the stimulatory actions of nicotinic receptors. The nicotinic receptors are present in all the autonomic ganglia (both sympathetic and parasympathetic) and at the neuromuscular junctions of skeletal muscle.

i. **Autonomic ganglia:** Nicotinic receptors which are situated in both the sympathetic and parasympathetic (autonomic) ganglia can be stimulated by ACh, but only in higher doses. Higher dose of ACh, after IV atropine (to block the muscarinic action of ACh) causes ↑BP and tachycardia. This is called the nicotinic actions.
ii. **Skeletal muscle:** ACh causes contractions of skeletal muscles through the nicotinic receptor.

Nonspecific Cholinergic Antagonist

There is no such nonspecific single agent which blocks the action of ACh on both the muscarinic and nicotinic cholinergic receptor. All they are either muscarinic receptor or nicotinic receptor blocker. The specific muscarinic receptor antagonists and specific nicotinic receptor antagonists are discussed later.

Specific Muscarinic Receptor Agonists

The specific muscarinic receptor agonists can be divided into two groups:

i Some synthetic cholin esters → such as: methacholine, carbochol, bethanechol, etc.
ii. Naturally occurring cholinomimetic alkaloids → such as : pilocarpine, muscarine, arecoline etc.

Therapeutic uses of muscarinic agonist: Among the above mentioned muscarinic agonists, very few are used therapeutically. These are:

(i) Pilocarpine

Pilocarpine is obtained from the leaves of pilocarpus microphyllus and some other species of plants. It has prominent muscarinic actions and also stimulates the ganglia mainly through the ganglionic nicotinic receptors. It causes marked increase in sweating, salivation and other secretions as well. The cardiovascular effects of pilocarpine are complex. Small doses generally cause a fall in BP. But higher doses elicit a rise in BP and tachycardia, which is probably due to ganglionic stimulation (through the nicotinic receptos). Due to its high systemic toxicity, it is only used in ophthalmic medicine in the topical form. Applied to the eye, it penetrates the cornea and promptly causes miosis and ciliary muscle contraction. Thus, it reduces the intraocular pressure. So, the strength of 0.5 to 4% solution of pilocarpine is used in the treatment of glaucoma. It is usually better tolerated than anticholinesterase agents which by inhibiting the cholinesterase enzyme increases the level of ACh and produce the muscarinic actions. Pilocarpine is also used in the treatment of xerostomia following head and neck radiation and in Sjogren's syndrome by increasing the secretion from salivary and lacrimal glands.

(ii) Bethanechol

As bethanechol stimulates the smooth muscle contraction of the GI tract, so it is used in certain cases of postoperative abdominal distension, gastric atony or gastroparesis, in certain cases of congenital megacolon, adynamic ileus, etc. But, due to its many side effects prokinetic agents like metoclopramide (due to its combined cholinergic agonist and dopamine antagonist activity) and serotonin antagonist like ondansetron, have largely replaced bethanechol in the management of the previously mentioned disorders.

Bethanechol is also used in the treatment of urinary retention and inadequate emptying of the bladder, when organic obstruction is absent. The α adrenergic receptor antagonist are also useful in reducing the outlet resistance at the internal sphincter of urinary bladder.

Specific Muscarinic Receptor Antagonists (Anticholinergic Agents)

Specific muscarinic receptor antagonists only prevent the muscarinic action of ACh or other agonists by blocking their action only on the muscarinic receptors which are present at the neuroeffector sites of smooth muscles, cardiac muscles, glands, eye and CNS. These specific muscarinic receptor antagonists cannot block the action of ACh at the nicotinic receptor sites. In CNS the cholinergic transmission occurs both by the muscarinic and nicotinic receptors. These CNS muscarinic actions can also be blocked by specific muscarinic antagonists. Therefore, at high toxic doses muscarinic receptor antagonist causes CNS stimulation followed by depression. But, the anticholinergic agents that are quarternary compounds cannot penetrate the blood brain-barrier and have no effect on CNS.

Though the specific nicotinic receptor antagonists block the nicotinic actions of ACh which are mediated through the nicotinic receptors, but they are generally

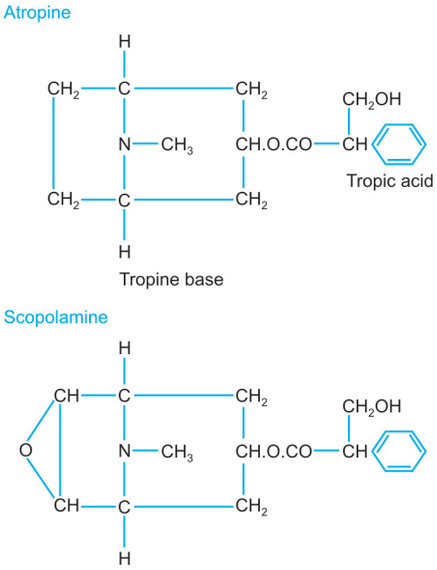


Fig. 11.20: Structure of anticholinergic agents

referred to as the ganglion blockers and neuromuscular blocking agents. However, they are usually not called as the anticholinergic agents. Anticholinergic agents are those which can block only the muscarinic receptors. All anticholinergic agents are competitive antagonists to ACh. (Fig 11.20).

Classification of anticholinergic agents

1. Natural alkaloids - Atropine, Hyoscine (scopolamine)
2. Semisynthetic derivatives - Homatropine, Ipratropium, atropine methonitrate
3. Synthetic derivatives -
   a. Specific antisecretory and antispasmodics
   b. Specific mydriatics - cyclopentolate, tropicamide
      i. Tertiary amines - Dicyclomine, pirenzepine, atropine (also available naturally)
      ii. Quaternary compound - glycopyrrolate, propanthelin, oxyphenonium, clidinium
   c. Specific antiparkinsonian - Benzhexol, procyclidine, benztropine.

In addition, many other drugs, such as: tricyclic antidepressants, phenothiazines, antihistaminics, etc. also possess significant antimuscarinic or anticholinergic actions.

Atropine

Naturally, atropine and its related alkaloids are obtained from many plants such as: Atropa Belladona (which means deadly nightshade), Atropa Acuminata, Hyascyamus Niger and Datura Stramonium (Datura) etc. The name Atropa Belladona represents a paradox. Because the term 'Atropos' comes from the oldest name of 'Three Fades', who cut the thread of life (i.e death) and the term 'Belladona' is derived from a type of practice of beauticians of the Venetian court who put the extract of these plants in their eyes to impart them a 'lustre'. For many centuries the belladona preparations were also known to ancient Hindus. In the Roman Empire and in the medieval ages, this deadly nightshade shrub (Atropa Belladona) was also frequently used to produce obscure or darkness and prolonged poisoning. During the ancient times in India the roots and leaves of some weeds, named Jimson weed which also contained atropine alkaloids, were burnt and this smoke was inhaled to treat asthma. British Colonist observed this and introduced the belladona alkaloids in western medicine as early as 1780 to treat asthma. From this idea ipratropium is used now as inhalation to treat the acute asthma. Then, Dr Mein in 1831 first isolated atropine in pure form and in 1867, Dr Bezold first showed that atropine blocked the cardiac effects of vagal stimulation.

Chemically, atropine is the ester of an organic aromatic 'tropic' acid and an organic aromatic 'tropine' base. Semisynthetic atropine ester, named homatropine is an ester of tropine base and mandelic acid. Its quarternary derivatives are obtained by adding a second methyl group to the nitrogen atom of this ester. The tropine base and tropic acid itself is devoid of any antimuscarinic activity. So, formation of an ester is essential for antimuscarinic activites. The presence of free OH group at the acyl portion of this ester is also important for antimuscarinic activity of atropine. When given parenterally, quarternary derivatives are more potent than their parent ester compounds on both the muscarinic receptors and the nicotinic receptors (ganglionic blocking activities). But, these quarternary derivatives lack the CNS activity, because they cannot cross the blood brain-barrier. Conversion of nitrogen from a tertiary group to a quarternary group also increases the blocking action at the nicotinic receptors.

Mechanism of action

Atropine blocks the muscarinic effect of ACh by competing with it at the binding site of muscarinic receptors. So, it is called the competitive antagonist. The binding site of atropine (competitive antagonist) and ACh on the receptor is situated in the cleft which is formed by the seven transmembrane helices of the muscarinic receptor. An aspartic acid which is present at the N-terminal portion of the third transmembrane helix of all the five muscarinic receptor subtypes is believed to form an ionic bond with the cationic quarternary nitrogen atom of ACh and the tertiary or quarternary nitrogen atom of the antagonist. However, atropine does not interfere with the synthesis or release of ACh at the cholinergic nerve endings. It has no intrinsic ACh like activity. So, atropine and its receptor combination does not produce any muscarinic response like ACh. As the antagonism between ACh and atropine is of the competitive type, so the direction of action depends on the relative concentration of the two at the muscarinic neuroeffector site, and the action can be reversed by increasing the concentration of atropine or ACh.

The dose of atropine required to produce the antimuscarinic or anticholinergic action by the blockade of muscarinic receptor varies from organ to organ. Salivary secretion is extremely sensitive

to the blockade by atropine, while the smooth muscle of GI tract, eye and the heart are less affected. In the CNS, cholinergic transmission at the subcortical and cortical level is predominantly muscarinic and can be blocked by atropine.

Pharmacological properties of atropine

(i) CNS

Atropine has almost no detectable effect on CNS in doses which are used clinically. In this dose it produces the peripheral effects only. At therapeutic doses (0.5 to 1 mg), atropine causes only mild stimulation of the medulla (including vagal, respiratory and vasomotor centres) and higher cerebral centres. But with higher toxic doses, atropine can produce sever cortical excitation, restlessness, disorientation, hallucination and delirium. With still higher doses, this stimulation of CNS is followed by depression, leading to circulatory collapse, respiratory failure and coma. Belladona alkaloids and other related muscarinic receptor antagonists are also used to suppress the tremor and rigidity of Parkinsonism by blocking the relative muscarinic cholinergic overactivity in the basal ganglia. Muscarinic receptor antagonists are also used to treat the extrapyramidal symptoms that commonly occur as side effects, after the antipsychotic drug therapy. Atropine also depresses the vestibular excitation which works through the muscarinic cholinergic pathway and thus exerts an antimotion sickness property.

(ii) CVS

The most prominent effect of atropine on CVS is tachycardia. It is due to the blocking of vagal action, mediated by the muscarinic M_2 receptors on the SA node. Sometimes, initial transient bradycardia often occurs before tachycardia. There are no accompanying changes in the blood pressure or CO by atropine. This is because the cholinergic impulses are not involved in the maintenance of vascular smooth muscle tone and BP.

The influence of atropine on the HR is most noticeable in healthy young adults in whom vagal tone is highest. Contrary in infancy and old age, even large doses of atropine may fail to produce tachycardia. This is because in this age group vagus has minimum action on the heart. Atropine often produces cardiac arrhythmias, but without any significant cardiovascular symptoms.

Many vagus nerve mediated reflexes, such as bradycardia or asystole, caused by oculo-cardiac reflex, anal stretching, peritoneal reflexes, etc, can be abolished by atropine. Atropine shortens the functional refractory period of the AV node and facilitates the AV conduction provided it is caused by the increased vagal tone. Thus, in some 1st and 2nd degree heart block caused by increased vagal tone atropine may lessen the degree of block. In some patients with complete heart block, the idioventricular rate may be increased by atropine. Occassionaly, in therapeutic doses atropine causes cutaneous vasodilatation and flushing. This may be a compensatory reaction, permitting loss of heat to balance the atropine induced rise in temperature due to inhibition of sweating.

(iii) Glands

Atropine markedly decreases the salivary, tracheo-bronchial, lacrymal and other secretions of body by blocking the muscarinic M_3 receptors which are responsible for these secretions. Atropine also inhibits the activity of the sweat glands innervated by the sympathetic cholinergic fibres because if acts as an anticholinergic agent. Thus, skin, mouth and eyes become dry; talking and swallowing may become difficult. Cephalic and fasting phase of gastric secretion is also markedly reduced, but the intestinal phase is partially inhibited by atropine. As both the HCO_3^- and H^+ secretion is blocked, so the pH of gastric secretion does not increase, i.e. does not becomes more alkaline. The secretion of mucin and proteolytic enzymes in stomach are more directly under the control of the vagus nerve than the acid secreting cells. So, atropine inhibits the secretion of mucin and the enzyme more than the acid in stomach. Intestinal and pancreatic secretions are not significantly reduced by atropine. Bile secretion is not under cholinergic control, so is not affected by atropine.

(iv) Smooth muscles

All the visceral smooth muscles that receive the parasympathetic or cholinergic motor innervation are relaxed and the sphincters are contracted by atropine. This is mediated by the muscarinic M_3 receptor blockade caused by atropine, because parasympathetic nerves enhance both the tone and motility of the GI tract and relaxes the sphincters acting through M_3 receptor. However, peristalsis of GI tract is only incompletely suppressed. This is because the intestine has a complex system of intramural local nerve plexuses that regulate the motility, and is not completely dependent on parasympathetic or cholinergic control. It is also regulated by some local reflexes, and other neurotransmitters (5 HT, enkephalin, etc) and hormones. Impulses from the CNS through vagus only modulate these intrinsic reflexes of intestine.

In a normal subject and in a patient with GI disease, atropine produces prolonged inhibitory effect on the motor activity of the stomach, duodenum, jejunum, ileum and colon. This inhibitory effect of atropine on the GI tract is characterised by a reduction in tone, amplitude and frequency of peristaltic contractions, resulting in relief from spasm and causing constipation. However, relatively large doses of atropine are needed to produce such inhibition.

In regulating the bronchomotor tone the parasympathetic neurons plays a major role. Vagal fibres make synapses and activate the nicotinic receptors of the parasympathetic ganglia, located in the wall of the airway. Short postganglionic parasympathetic fibres

come out from this ganglion and release ACh which acts on the M_3 muscarinic receptors in the airway smooth muscles. The submucosal glands are also innervated by these postganglionic parasympathetic neurons and have predominantly M_3 receptors. So, vagal stimulation causes airway smooth muscle contraction and increased tracheo-bronchial secretion. Thus, atropine causes bronchodilatation and reduces the airway resistance, especially in COPD and asthma patients by inhibiting this vagal cholinergic activity. Inflammatory mediators like histamine, prostaglandins, kinins, etc, also increase the vagal activity in addition to their direct actions on the bronchial muscles and glands, causing bronchoconstriction and increased airway resistance. Atropine also partially blocks their action by antagonizing the reflex vagal component and forms the basis of the use of anticholinergic agents, along with β-adrenergic agonists in the treatment of bronchial asthma. Thus, with the introduction of inhaled ipratropium (semisynthetic anticholinergic agent), anticholinergic therapy in COPD and asthma has been revived.

Atropine by its anticholinergic activity also decreases the normal tone and amplitude of contraction of the ureter and bladder. So, urinary retention may occur in older males, especially with prostatic hypertrophy during the use of anticholinergic agent.

Atropine also exerts mild antispasmodic action on the gall bladder and bile ducts. But, this effect is not usually sufficient to prevent the marked spasm and increased biliary duct pressure, induced by opioids. In such circumstances the nitrates are more effective than atropine.

(v) Eye

The muscarinic receptor antagonists or the anticholinergic agents block the responses of cholinergic neurotransmitter such as acetylcholine on the sphincter pupillae muscle of iris and the ciliary muscle of lens, which are responsible for constriction of the pupil and accommodation of vision. Thus, atropine dilates the pupil (mydriasis) and paralyses the accommodation reaction (cycloplegia). The wide dilatation of pupil causes photophobia. Due to blockade of the ciliary muscle the lens become fixed for far vision and the near objects become blurred. This is called the paralysis of accommodation or cycloplegia.

Thus, the topical instillation of atropine causes mydriasis, loss of light reflex, cycloplegia, photophobia and blurring of near vision, lasting for 7 to 10 days. The IOP (intraocular pressure) tends to rise, specially in narrow angle glaucoma by atropine. However, all these effects are caused by topical application of if and the conventional systemic dose of atropine produces minor ocular effects. Muscarinic receptor antagonists such as atropine, used as a mydriatic differs from the sympathomimetic agents, such as epinephrine. The latter causes only pupillary dilatation without loss of accommodation. Because sympathomimetic agents act only on the dilator muscle of pupillae and have no action on the accommodating ciliary muscle of lens.

Absorption rate and excretion

All the anticholinergic agents, such as the natural belladona alkaloids, the semisynthetic derivatives and the tertiary synthetic derivatives are well absorbed rapidly from the GI tract. But, the quarternary synthetic derivatives are poorly absorbed orally and their effects on the CNS are lacking. This is because these agents do not cross the blood brain-barrier. The half-life of atropine on parenteral administration is approximately 4 hours. Half of the dose of atropine is metabolised in the liver and the remainder is excreted unchanged through the urine.

Atropine Substitutes

Many semisynthetic and large number of synthetic derivatives of belladona alkaloids have been introduced in clinical practice, with the aim of producing more selective antimuscarinic actions. These synthetic derivatives are again classified as : quarternary compounds, tertiary compounds, mydriatics and antiparkinsonians.

Quarternary Anticholinergic Agents

The characteristics of quarternary anticholinergic compounds are:

i Poor oral absorption.

ii. Do not produce CNS and ocular effects after parenteral or oral administeration due to poor penetration in the brain and eye.

iii. Have higher nicotinic blocking property which may even occur at clinical doses, causing postural hypotension and impotence.

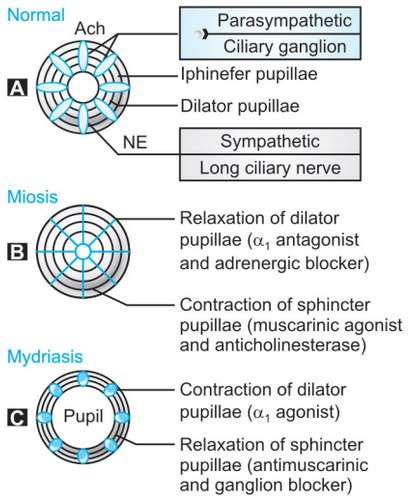
iv. At higher doses neuromuscular blockade may also occur due to the blocking of nicotinic receptor at motor endplate.

The following are the quarternary anticholinergic agents:

i. **Hyoscine butylbromide** − used as antispasmodic.

ii. **Atropine methonitrate** − used for abdominal colics and hyperacidity. As an aerosol, it is also used in bronchial asthma.

iii. **Ipratropium bromide** − It is used in the treatment of bronchial asthma by inhalation.Ipratropium bromide acts on the muscarinic receptors, located mainly on the large central airways (in contrast, sympathomimetics such as β_2 agonist act primarily on the peripheral bronchioles). The increased parasympathetic tone is the major reversible factor in (Fig. 11.21) chronic obstructive pulmonary disease (COPD). Therefore, it is more effective in COPD than in acute bronchial asthma. Another desirable feature of ipratropium is that in contrast to atropine, it does not depress the mucociliary clearance of bronchial epithelium. It has a gradual onset and late peak (60 to 90 minutes) bronchodilating action in comparison to inhaled sympathomimetics. So, it is more suitable for regular prophylactic use, rather than for rapid symptomatic relief during an acute attack.



Figs 11.21A to C: Autonomic control of pupil
A: Normal pupil, B: Miotic pupil, C: Mydriatic pupil

iv. **Tiotropium bromide** − It is a congener of Ipratropium with high bronchial selectivity in action.

v. **Propantheline** − used for the treatment of gastric ulcer by reducing the gastric secretion.

vi. **Oxyphenonium** − used for the treatment of peptic ulcer by reducing the gastric secretion.

vii. **Clidinium** − with diazepam it is used as antispasmodic in nervous dyspepsia, irritable colon, etc.

viii. **Pipenzolate** − used for infantile colics.

ix. **Isopropamide** − used in hyperacidity, nervous dyspepsia, irritable bowel syndrome, etc.

x. **Glycopyrrolate** − It is a potent and rapidly acting antimuscarinic agent, lacking central and ocular effects. Otherwise, all its clinical actions are like atropine. The dose of glycopyrrolate to control the muscarinic effects of neostigmine is 10 to 15 µg/Kg.

Tertiary Anticholinergic Agents

i. **Synthetic atropine** - already discussed

ii. **Dicyclomine** - Due to direct smooth muscle relaxation effect, it is used as an antispasmodic.

iii. **Pirenzepine** - It selectively blocks the M_1 muscarinic receptors and inhibits the gastric secretion, without producing typical atropine like side effects which are due to blockade of M_2 and M_3 receptor. The exact location of M_1 receptors through which pirenzepine exerts its antisecretory action is not definite. The more likely site of action of pirenzepine is the intramural plexuses and ganglionic cells, rather than the parietal cells.

Mydriatics

i. Homatropine - It is 10 times less potent than atropine and peak onset of action is 40 to 60 minutes. Mydriasis caused by homatrophine lasts for 1 to 3 days, while accommodation recovers in 1 to 2 days.

ii. Cyclopentolate - It is a potent and rapidly acting mydriatic agent. Mydriasis and cycloplegia occur in 30 to 60 minutes and lasts for a day.

iii. Tropicamide - It has the quickest (20 to 40 minutes) and briefest (3 to 6 hours) action.

Nicotinic Receptor Agonists and Antagonists

As described before, the nicotinic receptors are rosette-like pentameric structures enclosing a cation (Na^+) channel. Activation of this receptor causes opening of this channel and rapid flow of cations such as Na^+, resulting in depolarization and action potential of the membrane. These receptors are activated by nicotine (so it is such named) and blocked by tubocurarine or hexamethonium. Nicotinic receptors are classified into Nn and Nm (previously as N_1 and N_2) on the basis of their location and selective agonist and antagonist.

(i) N_M nicotinic receptor

They are located at the endplate of skeletal muscle and are activated by ACh, but selectively by phenyl trimethyl ammonium (PTMA). They are antagonised by tubocurarine and other non-depolarizing muscle relaxants. These receptors mediate skeletal muscle contractions.

(ii) N_N nicotinic receptor

They are present in the sympathetic and parasympathetic ganglionic cells, in adrenal medullary cells (as adrenal medulla is derived embryologically from same site as the ganglionic cells), in the spinal cord and in certain areas of brain. They are also stimulated by ACh but are selectively stimulated by dimethyl phenyl piperazinium (DMPP) and blocked by hexamethonium. They constitute the primary pathway of transmission in ganglia.

12 Preoperative Evaluation and Preparation

INTRODUCTION

The diversity and versatality of the subject of anaesthesia makes proper preoperative evaluation of each patient a major issue. This is because, a single anaesthetic procedure cannot meet all the various demands, of all the patients. The ultimate need of preoperative assessment, in patients about to undergo anaesthesia care, is to reduce morbidity and mortality, to improve the quality of anaesthesia, to optimise the patient's health and to return the patient to normal functioning, as early as possible. So, an anaesthesia programme should be made, keeping in mind the specific patients physiological status, psychological built-up, past and present medical conditions, previous surgical history, present complaints, drug allergy and intolerance, anaesthetic experiences of the past, and of course the planned surgical procedure. We should remember that improper and inadequate preoperative evaluation, is one of the major causes of all anaesthetic complications. So, every time surgery is planned in a patient, he should be evaluated thoroughly in the pre-anaesthetic clinic by an anaesthesiologist preferably, treated for any existing medical pathology and his health should be optimised, that is he should be made fit for anaesthesia.

PREOPERATIVE ASSESSMENT

Preoperative assessment is traditionally done by arranging a meeting between the patient and the anaesthesiologist. This facilitaties certain important purposes, and helps to make the patient comfortable, by rendering a healty patient – doctor relationship.

The Goals Achieved by Preoperative Assessment

1. It helps to know the medical history and the psychological make-up of the patient, to assess any known or unknown underlying pathology, to determine the required laboratory tests and specialized consultations, for optimising the patient's health. This decreases hospital stay and unnecessary delay in scheduling of surgery.
2. It helps the anaesthesiologist to select the proper anaesthesia care or programme for the operation planned, by understanding the patient's mental make-up and the medical history.
3. In this age of information technology, a preoperative meeting between the patient and the anaesthesiologist, helps inform and educate the patient about the anaesthesia services rendered, perioperative care and postoperative pain management. Patient education also helps reduce the patients anxiety, allay his fears and makes recovery faster and better.
4. It helps maintain a more optimal health of the patient by managing preexisting medical pathologies efficiently. Detection and treatment of conditions like respiratory tract infection, diabetes mellitus, congestive cardiac failure, etc. prior to delivery of anaesthesia, by proper and meticulous preoperative assessment, improves the quality of anaesthesia and optimises the health of the patient, thus reducing perioperative morbidity and mortality. The presence and severity of underlying medical problems may require consultation with specialists, for obtaining an optimal medical condition, before anaesthesia is actually delivered. The specialist's help can also be extended for better perioperative care.
5. It facilitates better perioperative care management and even helps make it less costly, by proper planning.
6. It helps obtain an informed consent from the patient, in the true sense, for all medicolegal purposes.

Routine Preoperative Anaesthetic Assessment

1. History

a. Name, age, sex, weight
b. Present complaints
c. Past medical history
d. Treatment history
   – Medicines being used currently.
   – Medicines that had been used in the past
   – Drug allergy and intolerance
e. Social history
   – History of addiction and habits, drugs, alcohol, tobacco, etc.
f. Non-specific factors
   – Obstetric history in females, pain history, etc.
g. Family history

– For malignant hyperpyrexia, porphyria, cholinesterase abnormality, etc.

h. History of previous surgery and anaesthesia

2. History to have an overall review of all systems

a. Respiratory system – History of smoking, bronchitis, common cold, asthma, chronic cough, etc.
b. Cardiovascular system – History of hypertension, palpitation, chest pain, syncope, dyspnoea, etc.
c. Gastrointestinal system
d. Genitourinary system
e. Musculoskeletal system
f. Neurology
g. Haematology
h. Endocrinology
i. Orthopaedics
j. Dermatology
k. Psychiatry

3. Physical examination of the patient

a. General condition – Pallor, cyanosis, jaundice, oedema, consciousness, aptitude, co-operativeness, activity level, etc.
b. Vital signs – Arterial blood pressure in both hands, examination of peripheral pulses, jugular and carotid pulsations, etc.
c. Airway – Neck mobility, jawbone size, tongue size etc., for intubation
d. Pulmonary evaluation – Auscultation for rhonchi, wheeze, crepts, or other sounds of lung pathology
e. Cardiovascular evaluation – Auscultation for murmurs, thrust, gallop and other adventitious sounds
f. Extremities – Oedema, clubbing, varicosity of veins, etc.
g. Neurological examination – Peripheral neuropathy, tremor, convulsion, seizure, etc.

4. Laboratory investigations

5. ASA Classification

History Taking

History taking is the most vital part of preoperative evaluation. It helps to establish all known past and present medical problems of the patients, plan the anaesthetic program, laboratory tests and post operative managenent efficiently. The medication history often reveals significant drug allergies, (rash, dyspnoea), drug interaction and drug intolerance (GIT problems). Even herbal medicines cause drug interactions, like garlic, often used to reduce blood pressure and cholesterol level, inhibits platelet aggregration and should be discontinued seven days prior to surgery. Ginseng, a root, is often used as an antistress factor is known to produce hypoglycemia and inhibition of coagulation cascade, and should be discontinued seven days prior to surgery. Meticulous history to review the various systems and their pathologies, if present, is one of the best tools for optimal assessment of a patient, along with optimal choice of laboratory investigations required and subsequently the perfect choice of anaesthesia care. Preoperative interview helps bring out important information and gives the anaesthesiologist enough time to motivate a patient for a healthy lifestyle, like maintaining blood pressure and blood sugar, reducing or even quitting smoking, if required, etc. This naturally improves the quality of the anaesthesia service and helps reduce morbidity and moratlity, due to anaesthesia (Table 12.1).

Table 12.1: The rule of three for history taking

1. The three aspects of acute history that effects preoperative evaluation of a patient waiting for anaesthesia are:
   - History of present health problems
   - Tolerance to exercise
   - How long ago the patient had visited his pirmary care physician
2. The three aspects of chronic history that effects preoperative evaluation of a patient waiting for anaesthesia are :
   - Medicines being used currently and allergy, if any, to any medicine
   - Family history
   - Social history
   - History of past illness
3. The three features of clinical examination are:
   - Vital signs of the patient
   - Pulmonary assessment
   - Cardiovascular evaluation

Laboratory investigation

Preoperative laboratory testing and its results had so far been the primary source of information of a patient's vital characteristics. But now, they are considerd ineffective as screening devices. The tests are considered useful only when the anaesthesiologist changes the anaesthesia plan according to the laboratory test results, for the benefit of the patient, and helps to optimise the health of the patients. But, it is not always true that the results of the laboratory tests are necessarily adjuvants to the patient's medical history and physical examination, for meticulous preoperative assessment.

Preoperative test with borderline or false-positive results can merely distract the anaesthesiologist's attention and cause no benefit at all. The anaesthesiologist may then pursue and treat this borderline or false-positive cases unnecessarily, causing unwanted delay in scheduling of surgery and also making the procedure expensive. Thus, unindicated routine laboratory testing can decrease the overall quality of anaesthesia care, by causing sheer confusion and is often harmful for the patients. So laboratory tests should only be implemented in patients, in whom it may decrease health hazards, mortality and morbidity due to anaesthesia. Extra-testing hardly provides medicolegal protection to the anaesthesiologist. When too many tests are ordered, the anaesthesiologist often tends to overlook the slightly positive or borderline cases, and that poses greater medicolegal risk to the doctor. Only those patients who actually suffer from a disease may benefit from the test specific for the disease (Table 12.2).

Table 12.2: Routine preoperative laboratory investigations

1.	Full blood count
	All male patients above 50 yrs of age
	All female patients
	All major surgical procedures
	Whenever pallor is detected clinically
2.	Routine urine examination (for sugar, blood, protein)
	All patients
3.	ECG (an ECG tracing is valid for a year, if there is no recent history of cardiac pathology)
	All patients above 50 years of age
	All patients with cardiac diseases, hypertension, chronic pulmonary diseases
4.	Blood glucose (FBS, PPBS)
	All patients with diabetes mellitus
	All patients with glycosuria
5.	Urea,creatinine electrolytes
	All patients more than 60 years of age
	All major surgical procedures
	All patients with diabetes mellitus
	All patients taking diuretic drugs
	All patients with renal diseases
6.	Blood coagulation tests
	All patients with bleeding tendencies
	All major surgeries
7.	Chest X-Ray
	All patients of acute cardiac diseases
	All patients of acute pulmonary diseases
	Chronic-on-acute cardiac or pulmonary diseases
	Malignant diseases
	Suspection of pulmonary tuberculosis
8.	Pregnancy test
	All female patients in the reproductive age

ASA classification

The ASA (American Association of Anaesthetists) in 2002, had set up a set of guidelines to be followed by anaesthesiologists during routine preoperative evaluation.

This helped the anaesthesiologists to do a meticulous and justified preoperative assessment, of a patient waiting for anaesthesia and surgery. It was not mandatory to follow these guidelines, but they were there to help the anaesthesiogists, whenever they were in a dilemna to take decisions.

The guidelines were :

1. In patients undergoing minimally invasive surgery, the anaesthesiologists opinion, based on the history and physical examination, should be considered more important than the results of the laboratory tests.
2. In patients undergoing surgery other than the minimally invasive ones, or if patient is not presently healthy, preoperative evaluation should always occur one day prior to the day of surgery.
3. Certain laboratory tests to be done as routine procedures in most invasive surgeries (Table 12.2).
4. Pregnancy test to be done in all female patients of the reproductive age group. (Table 12.3).

Table 12.3: ASA classification of patients waiting for surgery

Grade 1:	Normal, healthy patients, no pre-existing medical pathology, other than the disease for which surgery is planned.
Grade 2:	Patients with mild systemic disease, without any functional handicap.
Grade 3:	Patients with severe systemic disease, with functional handicap.
Grade 4:	Patients with severe life-threatening systemic disease.
Grade 5:	Moribund patients who would die without the surgery.
Grade 6:	Brain-dead patients who are being operated for removal of organs, for donor purposes.
Grade E:	Emergancy procedures - here the physical status is followed by E, e.g. -3E.

THE ANAESTHETIC PLAN

The choice of the final anaesthetic plan should be safe, comfortable for the patient, suit the competence and experience of the anasthesilogist, and of course depend on the type of surgery and the convenience of the surgeon. A detailed and meticulous preoperative evaluation enables the anaesthesiologist to draw an anaesthetic plan and discuss it in details with the patient. This helps assure quality anaesthesia service, reduce the patients anxiety and fear and reduce mortality and morbidity (Table 12.4).

Table 12.4: A routine anaesthetic plan

Fasting	
Premedication	
Plans of airway maintenance	
Anaesthesia planned:	
General anaesthesia:	Induction Muscle relaxation Maintenance Reversal
Regional anaesthesia:	Technique Drugs
Monitored anaesthesia care	
Oxygen supplementation	
Intraoperative management	
Monitoring of the patient	
Positioning of the patient depending on the surgery	
Fluid management	
Ventilation	
Special procedures, if required	
Postoperative management	
Fluid management	
Pain management	
Postoperative ventilation, if required	
Special care, if required	
Complication management	

PREANAESTHETIC PREPARATION

Routine preanaesthetic preparation is a must for every patient ready to undergo anaesthesia and surgery.

Fasting

It is an important event during the postoperative preparation of a patient, for surgery or anaesthesia. Aspiration of gastric contents into the lungs, is associated with high morbidity and mortality. Some very common causes for regurgitation of gastric contents and subsequent pulmonary aspiration are: pregnancy, obesity, full stomach, difficult airway, emergency surgery without proper preoperative medication, etc. Even 20 to 30 ml of gastric content

aspirated, can cause severe irreversible pulmonary damage. So, one of our main aims during preoperative preparation of a patient is to decrease the volume of gastric content, so that regurgitation is prevented (Table 12.5).

Gastric emptying time may be delayed due to metabolic disorders (diabetes mellitus or renal failure), head injury, pyloric stenosis, opiods, trauma, etc. Whereas, pregnancy and obesity increases the intra-abdominal pressure and causes passive regurgitation.

Antacids (not the particulate ones), like sodium citrate solution, given shortly before induction of anaesthesia, neutralises the acid in the stomach, but is not at all preferred by most anaesthesiologists as it increases the volume of gastric contents, causing further complications. Proton-pump inhibition and H_2 blockers decrease acid secretion in the stomach and are very effective. Gastric motility increasing agents, like metoclopramide, are very effective, especially in trauma patients being put up for emergency operation, more by the intravenous route than orally. Ranitidine may also be used routinely, especially in pregnant patients (Table 12.6).

Premedication

A preoperative interview between the doctor and the patient, thorough explanation of all planned and anticipated procedures and support-cum-compassion of the anaesthetic team, are not always enough to allay the fears and concern of the patient, and reduce all the unwanted stress factors. Certain drugs are often used to treat anxious patients preoperatively. Preoperative medication helps the anaesthesiologist to travel a comfortable road during the course of anaesthesia, and decreases morbidity and mortality to a great extent.

Special care should be taken to select the drugs for premedication of each patient individually, depending on the history and clinical examination of the patient, the surgery planned and the anaesthetic programme decided.

Table 12.5: Routine preanaesthetic preparation

1.	Patient education and psychological support, regarding all procedures planned.
2.	Sedation to be given the previous night, for a restful sleep.
3.	Fasting.
4.	Evacuation of the urinary bladder.
5.	Removal of false teeth and eyes, artificial limbs, contact lenses, jewelleries, nail varnish, etc.
6.	Loose OT dress to be worn.
7.	Identification tag to be put on the patient.
8.	Signature on the informed consent.
9.	Premedication.
10.	All resuscitative measures to be started, like intravenous line, noninvasive monitoring, etc.
11.	Documentation: Preoperative notes.

Metoclopramide

It is essentially a prokinetic drug, that is, it increases the gastroduodenal motility and hastens gastric emptying. Though it is structurally similar to procainamide, its pharmacological properties are absolutely different from procainamide. Metoclopramide is now widely used as an antiemetic.

It relaxes the pylorus and the first part of the duodenum, and thus hastens gastric emptying. It increases the lower oesophageal sphincter tone (LES), and prevents gastro-oesophageal reflux.It also increases intestinal peristalsis but has no action on gastric secretion.It has certain antidopaminergic actions, prolactin-secretion inducing action, and blocking of vomiting induced by narcotics. So, it is considered to be a relatively selective D_2 antagonist and its antiemetic action is due to D_2 antagonism in the CTZ. Peripherally, it has cholinomimetic actions, i.e, it increases acetylcholine release from the myenteric neurones.This inturn promotes gastroduodenal peristalsis, speeds up gastric emptying and increases the LES tone. Metoclopramide also blocks the $5HT_3$ receptors present in the CTZ and the vagal efferents in the GIT, but only in higher doses.

Metoclopramide is absorbed very rapidly when given orally, crosses the blood-brain barrier and the placental (Fact file- I) barrier, and is secreted in the breast milk.Its half life is 4-6 hours. It is partly conjugated in the liver and is excreted through the urine. It speeds up absorption of drugs like aspirin and diazepam, reduces the absorption of digoxin and decreases the effects of levadopa, by blocking the DA receptors in the basal ganglion.

Metoclopramide is well tolerated but certain extrapyramidal symptoms like dizziness, sedation, muscle dystonias and

Table 12.6: ASA guidelines for preoperative fasting in healthy patients presenting for elective surgeries

Clear liquid	Water, clear tea, fruit juice without pulp	2 hours
Breast milk		4 hours
Infant formula milk		4-6 hours
Animal milk	Cow, goat, buffalo	6 hours
Light meal	Toast	8 hours
Solid meal	Fish, chicken (high fat or protein content)	8 hours

FACT FILE- I

A good premedicant should:

- Help decrease the patients anxiety and stress.
- Decrease the secretion of the respiratory tract.
- Decrease salivary secretion.
- Decrease undesirable vagal reflexes.
- Reduce intraoperative awareness of the patient.
- Facilitate smooth recovery from anaesthesia.
- Reduce postoperative nausea and vomiting.
- Reduce postoperative restlessness of the patient.
- Reduce postoperative pain.
- Be safe for the patient.
- Protect the patient from the toxic effects of anaesthetics.
- Keep the patient optimised.

diarrhoea are not uncommom. Galactorrhoea, gynaecomastia and parkinsonism may occur, when the drug is used continuously for a long time.The dose is 10 mg orally, IM or IV.

It is an effective antiemetic agent for many types of vomiting like drug induced, postoperative, radiation sickness, chemotherapy-induced, migraine, etc.It is not very effective in motion sickness, and should be used very cautiously in pregnancy, as the safety factor is still not very well defined. It should also be used cautiously in lactating mothers, since it is secreted in the breast milk. It is the most effective gastrokinetic agent used to accelerate gastric emptying, especially when general anaesthesia has to be given in a patient posted for emergency surgery, when he has taken solid food less than 4 to 5 hours ago.

Ondansetron

This is a $5HT_3$ antagonist, first developed to control intense nausea and vomiting induced by chemotherapy or radiotherapy, in patients undergoing treatment for cancer. But, later it was found to be equally effective in controlling postoperative nausea and vomiting. Ondansetron blocks both the peripheral origin in the gut and the central pathway in the CTZ, of the emetogenic reflex. But neither does it reduce motion sickness induced nausea and vomiting, nor does it block the dopaminergic receptors. Unlike procainamide, it does not have any prokinetic action in the GIT. It blocks the $5HT_3$ receptors, thus inhibiting the action of 5HT in the GIT as well as in the CTZ. Thus, it is useful in combating the multifactorial origin of postoperative nausea and vomiting (Table 12.7).

Due to first pass metabolism, bioavailability of ondansetron after oral intake is about 60-70 %. CYP1A2, 2D6 and 3A can hydroxylate ondansetron. Drug interactions are rare. It is secreted through the urine and faeces as metabolites. The half life of ondansetron is 2-5 hours and duration of action is 4-10 hours. Side effects are rare. Dose to control postoperative nausea and vomiting is 4-8 mg IV and may be repeated after 4 hours.

[The other drugs have been discussed in the relevant chapters].

Informed Consent

All conscious, educated, competent patients have the right to either give or withhold consent for their treatment, or even a physical examination. A competent person is an adult, who is intelligent enough to understand his problems, remember the information given to him, and weigh out the risk – benefit ratio rationally, to make a decision regarding his treatment. No other peson can interfere with the decisions of such a competent person. To get the consent of the patient, all details of the anaesthetic procedures with its alternatives and complications should be discussed, so that the intelligent and competent person can understand and choose the best procedure for his treatment. A thorough discussion of the benefits versus the risks, often helps the patient choose the best option. All theoritical risks need not be detailed, instead the common and realistic ones should be explained. Life threatening complications,

Table 12.7: Some commonly used preoperative drugs

Drugs			*Route*	*Dose*
Drugs increasing gastric pH		Ranitidine	Oral	150 to 300 mg previous night and 2 hours before surgery
		Omeprazole	IM / IV	50 mg 2 hours before surgery
		Sodium citrate solution	Oral	40 mg previous night and 2 hours before surgery
			IV	40 mg slow IV over 40 minutes
			Oral	30 ml 10 minutes before surgery
Sedatives	BDZ	Temazepam	Oral	10 to 30 mg
		Lormetazepam	Oral	0.5 to 1.5 mg
		Lorazepam	Oral	1 to 2.5 mg
		Midazolam	Oral	0.2 to 0.5 mg
			IM	2 to 10 mg
	Non BDZ	Zopiclone	Oral	3.75 to 7.5 mg
Antiemetics		Metoclopramide	Oral/IM/IV	10 mg
		Ondansetron	IV	4 to 8 mg before surgery
Analgesics	Opioids	Morphine	IM/SC	10 to 15 mg
		Pethidine	IM	50 to 100 mg
	NSAID	Diclofenac	Oral/PR	50 to 100 mg
	Others	Paracetamol	Oral/PR	1 mg
Anticholinergics		Atropine	IM/IV	0.6 to 2 mg
		Glycopyrrolate	IM/IV	0.1 to 0.3 mg
Anxiolytics		Diazepam	Oral	5 to 10 mg

if likely, should always be innumerated. This often helps the patient and his guardian to accept the inevitable and prepares them mentally, allay their concern and anxiety to some extent.

Competent young adults over the age of 16 years can give their own consent, regarding their treatment. Competent children even below the age of 16 years, can give their own consent, especially if they can weigh out the risk – benefit ratio appreciably. If a competent child refuses treatment, the consent of the parents enables the doctor to proceed with all lifesaving procedures. The consent of the parents is enough to start treatment in patients below the age of 18 years, who are not competent. Verbal consent may be accepted in life-threatning and emergency conditions, but written ones are always preferred for medicolegal purposes. When the child or even the parent refuses treatment in an emergency and life-threatning condition, a court order may be sought to continue with the necessary treatment legally. Unconscious adults may be given essential treatment without consent, but it is always better to discuss the procedures with his guardian. Patients hospitalised with mental disorders may be treated without consent for his mental problems, but never for his associated physical ailments. But ECT always requires the consent of the patient or his guardian.

Restricted consent

Some competent patients may give consent for the treatment in general, but refuse cetain aspects of the treatment, e.g, blood transfusion. This is called restricted consent. The risks and the benefits of the procedures should be discussed in details with the patient, always in presence of a witness. All details of the patients restrictions and refusals should be noted in the consent form, duly signed by the patient and the witness. But in the end, the desire of a competent patient should be honoured.

Any procedure performed without a proper consent can lead to medicolegal assault of the anaesthesiologist. Treatment without consent is allowed only in dire emergencies or in life saving procedures.

Documentation

Maintenance of pre, intra and post operative anaesthesia record is of utmost importance in present day scenario.It helps to monitor the patient intraoperatively, deal with postoperative complications if any, and is the best document for all medicolegal purposes. Thus proper documentation ensures quality service.

Preanaesthetic record

A preanaesthetic record maintenance is absolutely mandatory nowadays. It should contain all the information about the preoperative evaluation of the patient by the anaesthesiologist and his team, including medical history, treatment history, laboratory test results, ASA classification of the patient and advice of the specialist, if required, for optimising the health of the patient. It should have the detailed anaesthetic plan, with all the alternatives clearly stated. All common and probable complications should be mentioned. It should also contain an informed anaesthesia consent, duly signed by the patient or his guardian.This record may be handwritten, narrative or printed forms may also be filled up with all the details.

Intraoperative record

This is a useful intraoperative monitor and assures quality anaesthesia service.It also helps to guide future anesthesia care. Hence this document should be accurate and precise.

It should include the following:

(i) Checking of the anaesthesia machine and other instruments, required to provide quality aneasthesia delivery and service, often referred to as the 'cockpit drill'.

(ii) Final evaluation of the patient before the induction of anaesthesia.

(iii) Checking for the duly signed anaesthesia consent, newer laboratory results, if any, and specialists advice for optimising the health of the patient, if required.

(iv) All information about the important and vital anaesthesia procedures like intubation, positioning of the patient, attachment of all invasive and noninvasive monitors, ryle's tube placement, etc.

(v) Details of intraoperative fluid management and blood product transfusion.

(vi) Details of all drugs administered with their dosage used and time of administeration.

(vii) Details of findings of all intraoperative monitoring and assistance.

(viii) All vital signs recorded every 5 minutes, if possible graphically.

(ix) Timing of all vital events lke intubation, excision, extubation, etc.

(x) Complications, if any, and how they were managed.

(xi) The patients condition during extubation and recovery from anaesthesia.

Postoperative record

The anaesthesiologist should always accompany the patient to the post anaesthesia care unit (PACU), and look after the patient till all the vital signs become normal and the patient is considered stable.He should give a detailed discharge note before the patient leaves the PACU, including the pain management procedures and the general condition of the patient during discharge from the PACU. Only then does the responsibility of the anaesthesiologist end.

CONCLUSION

The primary goal of an anaesthesiologist is to deliver quality anaesthesia service to the patient, decreasing morbidity and mortality in the process and most important, returning the patient to

his normal stable status as soon and as efficiently as possible. This whole procedure is a team work. A balanced harmony between the anaesthesiologist, surgeon, internist and specialist, ensures the best possible outcome. For the anaesthesiologist, the show is the longest, starting from meticulous preoperative evaluation and ending with the discharge of the patient from the post anaesthesia care unit (PACU), and hence the job is the toughest. Thus, preoperative evaluation and meticulous and thoughtful patient preparation, facilitates achieving the most sought after goals, improves quality care and reduces the cost of treatment. Perhaps the most productive and enjoyable part of clinical anaesthesia practice is interaction with the patient during preoperatiuve evaluation in the preanaesthetic clinic (PAC). Inefficient and inadequate preoperative assessment is nowadays the main reason for medicolegal assault against anaesthesiologists.

13 Local Anaesthetic Agents

HISTORY

The local anaesthetics (LA) are drugs or agents which temporarely prevent or cause the reversible loss of generation of impulses from any part of a neuron or temporarely stop the conduction of impulses through the nerve fibres when they come in contact with it, but without causing any structural damage. The term 'Local Anaesthesia' is restricted to the technique of infiltration of local tissue with a local anaesthetic agent, where only the nerve endings supplying that particular tissue is blocked. Whereas, the term 'Regional Anaesthesia' signifies the temporary block of conduction of impulses through a specific nerve or a group of nerves, supplying a particular region of the body like hands, legs, face, etc. Before the days of LA agents, in the sixteenth and seventeenth centuries, Ambrose Pare (French Surgeon) obtained the effect of local anaesthesia by producing direct mechanical compression on the nerve trunks. Then other European and American surgeons also followed this procedure of Ambrose during this time for local anaesthesia. For many centuries, the leaves of an indigenous shrub called Erythroxylum Coca was chewed by the people of Peru and Bolivia of South America as a CNS stimulant and appetizer. During this chewing they were used to feel numbness of their oral mucous membrane. But, at that period this associated numbness (the local anaesthetic effect) of their oral mucous membrane was not given much importance by them. They also never knew that these effects were primarily due to the local anaesthetic effect caused by principal alkaloid, named cocaine present in the leaves of these shrubs. However, it was first understood and this alkaloid was isolated by Neimann in 1860. Then, the physiological or local anaesthetic effects of cocaine were studied in details by Sigmund Frend in 1880. But he did not publish it. In 1884, when S. Frend was visiting his fiancé, his colleague Carl Koller took the opportunity and in his absence Carl Koller first declared and introduced the local anaesthetic properties of cocaine in an Opthalmological Congress. Thus he himself took all the credit of discovery of cocaine immediately. Then he performed an impressive series of experiments on himself and his colleagues, using the suspension of cocaine powder in distilled water. After that this news of Koller's work spread rapidly all over the world and subsequently cocaine solution was injected locally or applied topically by a wide variety of practitioners for local anaesthesia in both Europe and America. But the high systemic toxicity and addictive properties of cocaine had engineered the search for a better substitute of it. Thus, procaine came in 1905, which was synthesised first by Einhorn in 1904. It was less toxic than cocaine, but unfortunately it was quite unreliable and had a very short duration of action. Then, gradually many other non-promising LA drugs came and phased out. Such as, in 1930, dibucaine and tetracaine arrived which despite being much longer acting, still proved to be toxic in large volumes. Furthermore, these compounds, being esters like their predecessors were unstable at high temperature and thus could not be autoclaved. The another great disadvantage of these ester group of LA agents was that their metabolites had frequently caused allergic reaction which was sometimes very serious.

The next great milestone in local anaesthesia was the introduction of lignocaine in 1943. It was first synthesised by two scientists named Lofgren and Lundqvist in the laboratory of Astra. However, the beauty of lignocaine is that it was not an ester compound like their predecessors. Therefore, this drug was stable at high temperature and less toxic. It did not have such metabolites that could be implicated for allergic reactions. Hence, during that period it became the first prototype of a new class of local anaesthetic agents, called the amides. However, it is still now the most widely used local anaesthetic agent all over the world. Subsequently, the late 1950's saw the appearance of mepivacaine and prilocaine. In 1963, the introduction of bupivacaine in clinical practice was the begining of an era of long acting local anaesthetic agents in anaesthesia which are amides. But, the potential more cardiotoxicity of bupivacaine than lignocaine had provided the impetus for the development of ropivacaine which is the newest lesser cardiotoxic but long acting amide local anaesthetic agent. It became available by 1997 in most of the countries.

Other than LA agents, the local anaesthetic action can also be produced by

many other compounds such as some tertiary amines, certain alcohols and few other drugs such as propanol, antihistamines, quinidine, chlorpromazine etc. But, they are not used for this purpose because of their local irritation and other undesired prominent systemic effects. Local anaesthesia can also be produced by deep cooling, as for example by application of ice, CO_2 snow, ethylchloride spray, etc. on the surgical site.

CHEMISTRY (FIG. 13.1)

All the local anaesthetic agents bear the suffix – "caine". Structurally, they have two groups : a lipophilic aromatic group and a hydrophilic amine group. This amine group may be a secondary or a tertiary amine. An intermediate chain (alkyl or acyl) links these two groups through an ester or amide linkage. On the basis of this linkage local anaesthetics are classified into two broad groups.

When the linkage chain is an ester (−COO−), then they are called the ester local anaesthetics (esters of aromatic acids with amino alcohols). The examples of ester local anaesthetics are : cocaine, procaine, chloroprocaine, amethocaine, etc. Esters are unstable in solution and can not be autoclaved, because of their relatively unstable ester-linkage. They are also too short acting, because of their rapid metabolism (Fig. 13.2).

When the linkage chain is an amide (−NHCO−), then they are called the amide local anaesthetics. These amide local anaesthetics are again of two types : amides of aromatic acid with aliphatic diamines (aminoalkyl amides) and amides of amino acids with aromatic amines (aminoacyl amides). The examples of aminoalkyl amides are: cinchocaine and procainamide. The examples of aminoacyl amides are: lignocaine, prilocaine, mepivacaine, bupivacaine, etidocaine, ropivacaine, dibucaine, etc. Among all the amide local anaesthetics, only the hydrophilic amine group in prilocaine is a secondary amine. Otherwise all others have tertiary amines.

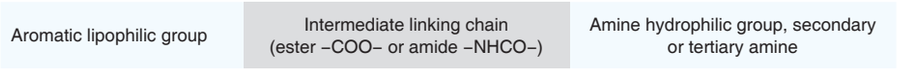


Fig. 13.1: Linkage of an anaesthetics

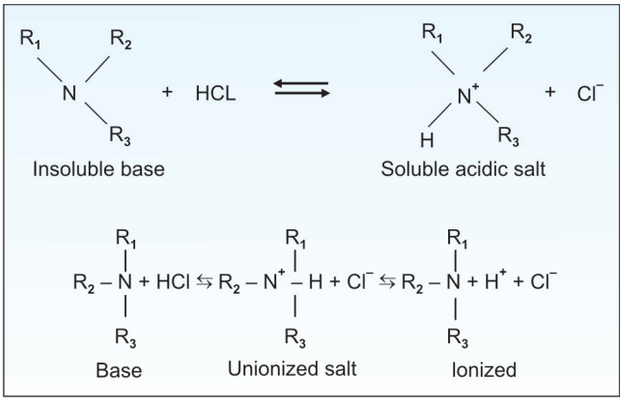


Fig. 13.2: Chemistry of an anaesthetics

The amine group in the structure of a amide local anaesthetic molecule confers it the property of an insoluble weak base (or proton acceptor). Thus it can combine with an acid to form a water soluble acid salt. This water soluble acid salt remains in more ionised form in commercially available water solution of it (as soluble in water) than its alkaline salt, which is not soluble in water and is usually stable.

All the local anaesthetic drugs, except ropivacaine are of racemic mixtures. However, only ropivacaine is unique, in that, it is available in a pure chiral form. This is important, because all the racemic mixtures have more toxicities and variable potencies, when compared to its chiral form. So, one of the major advantages of ropivacaine, in clinical use, is its less systemic toxicity than any other local anaesthetic agents, but with similar duration of action.

Features of Amide Local Anaesthetics in Comparison to Ester LA's

i. The amide groups of LA agents produce more intense and long lasting local anaesthesia than the ester group of local anaesthetic agents.
ii. The amide group of LA agents bind to α_1 acid glycoprotein and albumin in plasma.
iii. The amide group of LA agents are not hydrolyzed by plasma esterases like ester group of LA agents.
iv. The amide group of LA agent very rarely cause hypersensitivity reactions, than the ester group of LA and has no cross – sensitivity with ester group of LA.

Carbonated Local Anaesthetics

From the previous discussion, we already come to know that the original amide group of LA agents are insoluble weak base. So, the commercial preparations of these drugs are produced as soluble acidic (mainly hydrochloride by reacting with HCl) salts, with pH values ranging between 3 to 7. It is also clear from the previous discussion that in the solution of lower pH (i.e. in acidic situations), the drugs remain mainly in the ionised form, the ion of which can not penetrate or diffuse the nerve cell membrane easily. On the other hand, we also come to know that only the unionized form of molecule of LA agent penetrates or diffuse the nerve cell membrane easily and for its action from the inner side of the cell membrane of axon, it further undergoes intracellular

ionization. Thus, the unionised molecule of the LA agent helps in penetration through the nerve cell membrane, and for its action this unionised form of LA agent ionises first in the cell cytoplasm and then this ionised form acts at the inner side of the Na^+ channel which is situated on the cell membrane. The inner side of Na^+ channel which is situated on the cell membrane is the principal site of action of the LA agent. So, one would easily predict that due to more ionization of acid salt in the acidic solutions of LA agents it will have less penetrable form of LA molecule (i.e. unionised LA molecule). So, acidic hydrochloride preparation of LA agent will less penetrate the cell membrane and its intracellular concentration will be less. Hence, the acidic solution of LA agents would take a longer time for the onset of action, produce less intense block and have an increased incidence of missed block. Therefore, it can be predicted that alkalinization of the local anaesthetic solutions with $NaHCO_3$ (which is called carbonated local anaesthetic) prior to its injection will result in better action than its acidic solution, in respect of the onset, duration and density of action. This is because (Fig. 13.3) in alkaline carbonated form the LA agent remains more in the cell membrane-penetrable unionized form. But the main problem of this alkalisation of LA agent is that the formation of original molecule of LA agent by adding $NaHCO_3$ are weak base and are so insoluble in water solution of it.

A number of factors contribute to an enhanced effect of the carbonated LA agent, over its hydrochloride form. These are:

i. When the pH of the solution is more alkaline, then there is an increased concentration of uncharged or unionized base form of the LA agent which can easily penetrate the cell membrane.

ii. CO_2 diffuses rapidly to the interior of the cell membrane. Within the cell the CO_2 lowers the intracellular pH by forming H_2CO_3 and increases the ionization of the local anaesthetic agent. Intracellular ionisaton of the LA agent helps in two ways:

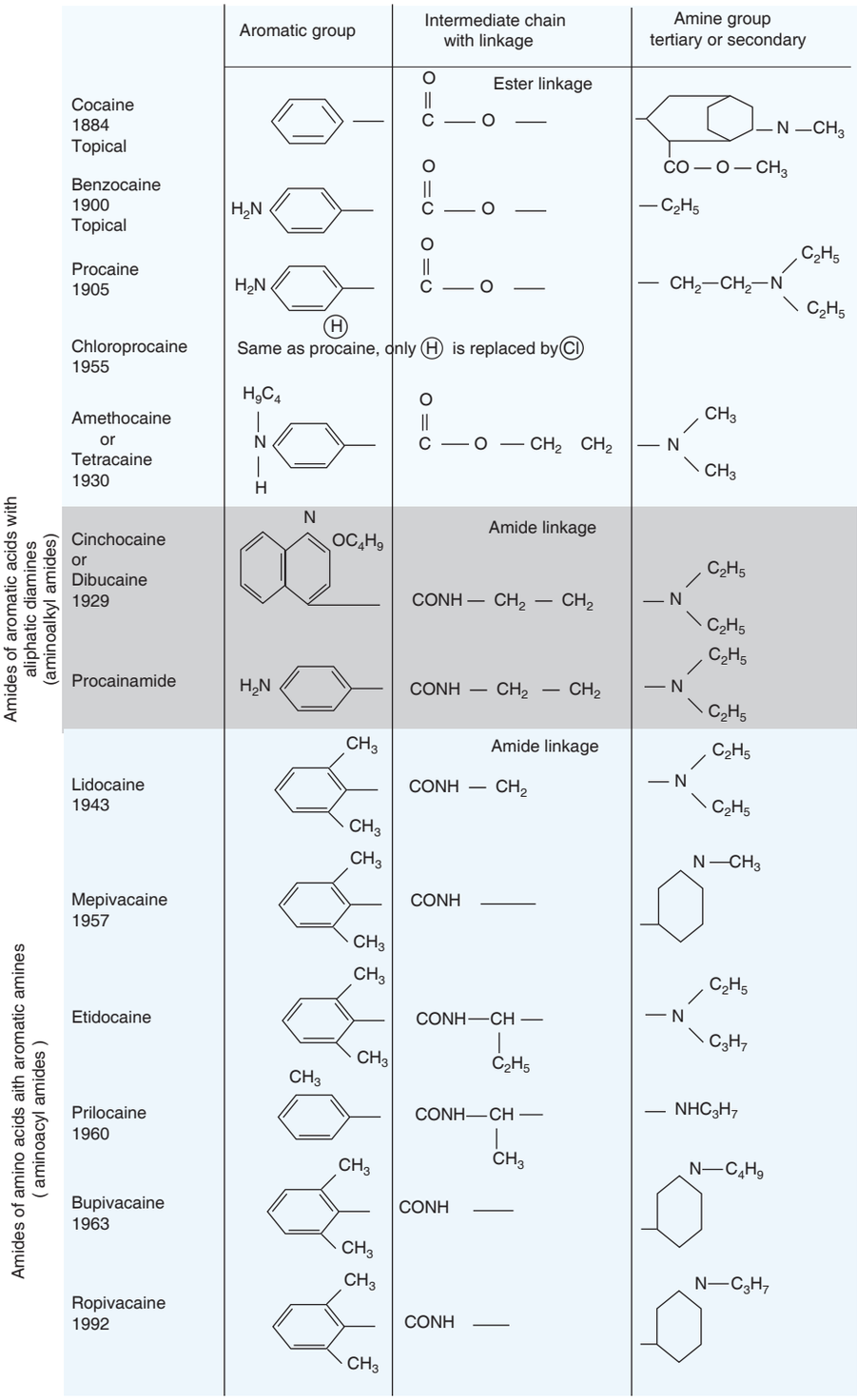


Fig. 13.3: Structures of various anaesthetics

a. release of more cations after intracellular ionization of LA agent enhances the nerve blocking activity and
b. reduction of the unionized base inside the cell increases the gradient of this form of the local anaesthetic agent and helps for further diffusion of this form into the cell.

Carbonated lignocaine is also superior to its hydrochloride form for epidural block in respect to the speed of onset, reduction in the incidence of missed segment and increased incidence of deep motor block.

Compounds with more lipophilic nature are obtained by increasing the size of the alkyl substitutes. These agents are more potent and produce long lasting effects than their less lipophilic congeners. For example, etidocaine has 3 more carbon atoms than lignocaine in the amine end of the molecule and is four times more potent and five times more long lasting.

CLASSIFICATION OF LA AGENTS

Local anaesthetic (LA) agents can be classified under different headings as follows :

A. Injectable

i. Low potency and short duration of action – cocaine, procaine and chloroprocaine.
ii. Intermediate potency and medium duration of action – lignocaine, prilocaine, mepivacaine.
iii. High potency and long duration of action – tetracaine, bupivacaine, ropivacaine, dibucaine, etidocaine.

B. Surface anaesthetic

i. Soluble – cocaine, lidocaine, tetracaine (amethocaine).
ii. Insoluble – Benzocaine, oxethazaine and butylamino benzoate (butamben).

C. Chemistry

i. Ester – cocaine, amethocaine (tetracaine), benzocaine, butamben, chloroprocaine, procaine.
ii. Amide – prilocaine, lidocaine, mepivacine, bupivacaine, etidocaine, ropivacaine.

As the amide group of local anaesthetic agents are structurally base, so it combines with acids to make a water soluble acidic salt which is stable and can be autoclaved. Otherwise, amide group of local anaesthetic agent itself being a base is not water soluble and is only soluble in relatively lipophilic organic solvents. So, for convenience most of the LA drugs are marketed as its soluble acidic hydrochloride salts. On the other hand, ester linked local anaesthetic agents are unstable in solution and can not be autoclaved. Ester linked local anaesthetic agents are degraded in plasma by hydrolysis, except cocaine and their metabolites are more prone to produce anaphylactoid reaction. Cocaine is metabolized predominantly by hepatic carbonyl esterase. P-aminobenzoic acid (PABA) is one of the important metabolites of all the ester type compounds that can induce anaphylactoid or allergic reactions. But amides are degraded by oxidative dealkylation in liver and hence anaphylactoid reactions are extremely rare (Fig. 13.4).

The lipophilic or lipid-soluble unionised form of amide LA agent (base or unprotonated) is the active form which can penetrate the nerve cell membrane. This unionised form of amide LA agent after entering the cell membrane is ionized and acts at the intracellular pole of Na channel to exert their LA action. In a marketed acidic solution of amide LA agent the unionized and ionised form of the LA compound remain in certain ratio. The equilibrium of ratio between the unionised and ionised portions of a particular local anaesthetic agent depends on the pKa value of that particular drug. The pKa value is the pH at which the unionised & ionised forms of the local anaesthetic agent remain in 50:50 proportion. Most of the local anaesthetics in clinical use are weak bases with pKa values varying between 7.5 and 9.5 (mainly around 8). The higher the pKa value of the drug, the stronger is its action as a base. Therefore, little of it will be available in the unionised (more will be ionised) form at normal body pH. As for example, pKa value of lignocaine is 7.86. So, at a tissue pH of 7.8, lignocaine will have unionized and ionized forms in the ratio 50:50. But at a pH of 7.4, only 25% of lignocaine will remain in the active unionised form and the rest 75% will remain in the nonactive ionized form. In an inflammed tissue, the pH is more acidic. So, the percentage of the active unionized form of LA agent will be lesser and the anaesthetic effect will be also low in the same concentration or dose for a given drug. The pKa value of procaine is 9. So, at pH 9 the unionised & ionised forms of the drug are at the proportion of 50:50. But at pH 7.4, only 25% of procaine remains in the unionised active and penetrable to cell form, and rest is in the ionized form. As, it is the unionized, lipid soluble moiety of a LA agent that can penetrate most rapidly the lipid rich barriers protecting the axon, so one would easily predict that procaine would penetrate the body tissues slowly at normal body pH. Thus the clinical utility of procaine is confined primarily to the circumstances in which the large lipid barriers are not encountered, such as during direct topical anaesthesia of the cornea or conjunctiva and spinal anaesthesia.

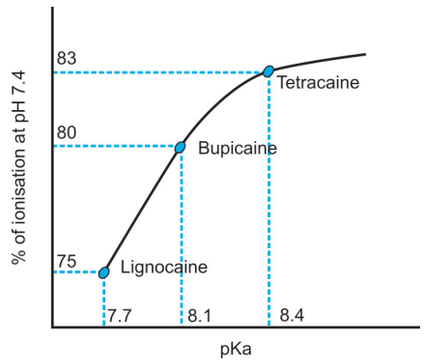


Fig. 13.4: This schematic diagram shows the percentage of charged ion of different local anaesthetic agents with different pKa value at pH 7.4

After injection in the tissue, the drug first moves from the site of injection to the area which is immediately outside the target nerve. This movement is through the subcutaneous or other tissues. The factors governing this first stage of journey of a local anaesthetic agent from the site of injection to the site of action at nerve fibre are: the concentration gradient, the mass or volume of the drug, the degree of ionisation and the solubility of the LA agent. Concentration gradient at the site of injection and the total mass depend on the volume and concentration of the drug injected. Greater concentration and bigger volume of injected drugs will cause a rapid increase in the therapeutic concentration of the drug at the nerve site. According to the theory of drug diffusion, larger size of the drug molecule has more difficulty in moving rapidly through the extracellular space. In fact, the speed of drug movement is more closely related to the square root of the size of the molecule. The molecular weight of all the local anaesthetic agents usually vary between 236 to 250 Da. Therefore, this factor plays a little role in the difference, regarding the speed of onset of the block among the LA drugs.

According to the previous discussion, it is found that at physiological pH most of the LA agents exist in a protonated or ionised form, while a much smaller portion exists as unprotonated or unionized form. Consequently, the sodium channel which is responsible for the cellular action potential is a protein in nature and is embedded in the lipid rich cell membrane. It is the inner intracellular pole of the Na^+ channel which is the site of action of the local anaesthetic agent. Unprotonated local anaesthetics are lipophilic in nature. Therefore, these molecules move easily and rapidly through the cell membrane (but not through the Na^+ channel) to arrive inside the cell. Subsequently, this unprotonated or unionised form then becomes protonated or ionized inside the cell and traverses through the water and electrolyte rich cytoplasm of the cell to attach to the inner side of the Na^+ channel. This protonated or ionised or cationic form of the local anaesthetic agent is responsible for most of the nerve blocking or Na^+ channel blocking effect, which acts from the interior of the cell membrane. Whereas, unprotonated, or unionized or the base form of local anaesthetic agent is responsible for penetration of the nerve fibre for its lipid solubility. Thus the unionised form is more important and active form than the ionised form.

Once attached to the intracellular part of the sodium channel, it appears that the local anaesthetic molecule can act on any one of the functional states of Na^+ channel. However, the local anaesthetic inhibits only the active sodium channels more strongly than the inactive sodium channels. Actually, the sodium channels pass through a cycle of different stages. This corresponds to the different functional states depending on the different phases of the action potential. The ability of a local anaesthetic molecule to bind with any given form of sodium channel is said to be the function of the position of that sodium channel in its cycle of action potential. It is also a dynamic process that channels are rapidly occupied and unoccupied by LA agents during a single action potential.

The pH of a tissue into which local anaesthetic is injected also directs the drug activity by altering the relative percentage of uncharged or unionised (unprotonated) and charged or ionized (protonated) molecule of the agent according to its pKa value. The uptake of drug by tissues largely results from the lipophilic absorption. So, as more of the drug will be lipophilic the more of the drug will be absorbed. Alkaline tissues alter the drug activity by matching the tissue pH with the drug pKa values and thereby favouring the unionised base for its absorption. The tissues also alter the effect of the drug by limiting the diffusion of the local anaesthetic agent from the site of injection. The tendency of the drug to be protonated (ionized) also depends on many other environmental factors, such as: temperature and medium surrounding the drug.

When pH of a local anaesthetic solution is lowered by addition of adrenaline, sodium metabisulphide (antioxidant), glucose, etc. then the tissue pH becomes more acidic (this is because buffering effect of local tissue is low) and availability of unionised form will be less. Thus, the power of penetration and intracellular concentration of LA agent decreases which in turn decreases the intracellular ionised form and hence the blocking action of the Na^+ channel from inside of the cell membrane. The mucous membrane also has minimal buffer reserve and so needs higher concentration of drugs for topical anaesthesia. The pH of all marketed plain solutions of LA agents varies from 4.4 (etidocaine) to 6.3 (lignocaine).

ANATOMY OF NEURON

The term 'Neuron' means nerve cell which consists of body and its processes such as dendrites and axon. They vary in shapes and sizes in different parts of the body. For example, its diameter varies from 5 µm (in cerebellum) to 120 µm (at the anterior horn cells of the spinal cord) and the length of axons also vary from a few micromillimeter to about 90 cm.

Within the cell body of neuron there is cytoplasm (axoplasm) and nucleus. The cytoplasm of the cell body is again differentiated into two parts such as under the cell membrane a superficial gel layer and a relatively fluid core. The outer gel layer of cytoplasm has a contractile property. This contractile property of the outer gel layer results in a continuous flow of axoplasm from the cell body to the periphery into the axon and dendrites. A large vesicular nucleus with a single prominent nucleolus is seen in every cell body of the neuron. In the cell body adjacent to the nucleus there is often seen a large granule, representing sex chromatin. In the cytoplasm of the cell

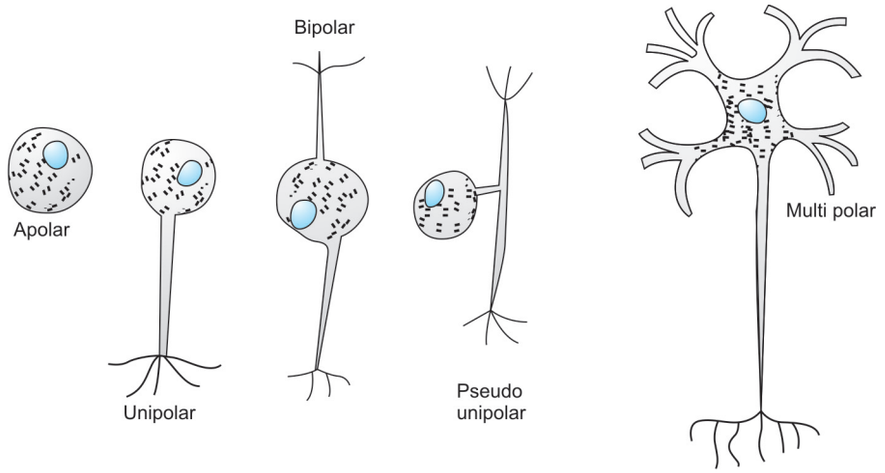


Fig. 13.5: Basic morphological features of different types of neurons

body near the nucleus there are also found many Nissel granules, numerous rod like mitochondrias, golgi apparatus and some fine long filaments called the neurofibrils. The neurofibrils and mitochondrias can enter into the axons from cell body, but the Nissel granules are not found in axon (Fig. 13.5).

Nissel granules are actually the endoplasmic reticulum and the granules covering them are called the RNP (Ribose Nucleo Protein). RNP are one of the most striking morphological features of the neuron and it indicates intense protein production with high activity. In dendrite the Nissel granules are rod shaped. In motor neurons they are coarse and flocculent, while in sensory neurons they are almost dust-like. Fatigue, poisons and sectioning of the axon cause Nissel granules to disintegrate into fine dust and eventually disappear.

Dendrites are the processes that carry impulses towards the nerve cell body from outside. They are generally shorter than the axon and contain many branches with Nissel granules. The number of dendrites of a cell body varies from nil to numerous. But as a rule they are multiple, relatively short, and follow a specific branching pattern (Fig. 13.6).

According to the number of processes, the neurons can be classified in the following:

i. Apolar neurons – They have no processes.
ii. Unipolar neurons – All developing neuroblasts pass through this stage when they have only one process, called the axon. In the adult humans such true unipolar neurons are not commonly seen. They are only found in the mesencephalic nucleus of the 5th cranial nerve.
iii. Bipolar neurons – Typically these neurons are spindle shaped, possessing a axon at one pole and a dendrite at the other. Neurons, developing from neuroblasts pass through this stage. In adults they are usually found in the retina, vestibular ganglion, spiral ganglion of cochlea and olfactory neuroepithelium.
iv. Pseudounipolar neurons – Such typical bipolar neurons are found in all the spinal ganglia and in the ganglia of the cranial nerves, other than the 8th. In this type of neuron, there is a single process with T-shaped divisions. One branch of the T is a dendrite coming from the periphery and the other is the axon, extending centrally.
v. Multipolar neurons – These neurons have most varied forms. They are Purkinje cells of the cerebellar cortex, pyramidal cells of the motor cortex, small neurons of the spinal nucleus of the trigeminal nerve, motor neurons of the ventral horn of the spinal cord, etc. Usually the shape of these neurons depends mainly on the number and position of the dendrites.

Axon is the process of a nerve cell body which carries impulses away from it. The term nerve fibre usually refers to the bundle of axons. The axon arises from that part of the nerve cell body, which is called the axon hillock. Axon contains no nissel granules. The number of axon of a cell body of a neuron is single but constant. If a neuron has only one process, then it will be the axon. The axis cylinder of an axon contains cytoplasm which is called axoplasma. It is a semifluid substance and is essential for nutrition and growth of the nerve fibre. The axon also contains many neurofibrils and mitochondria within its axoplasm and ends in numerous terminal buttons, called the telodendria (Figs 13.7A and B).

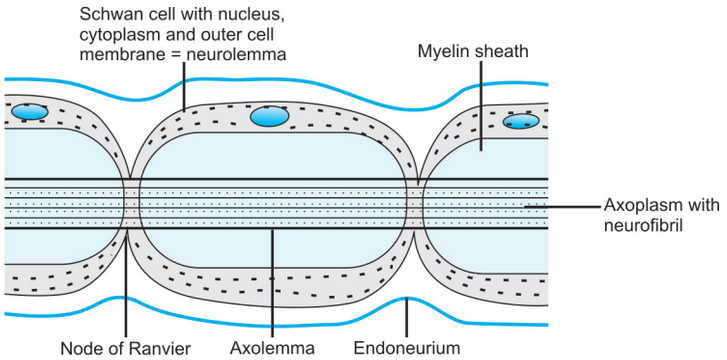
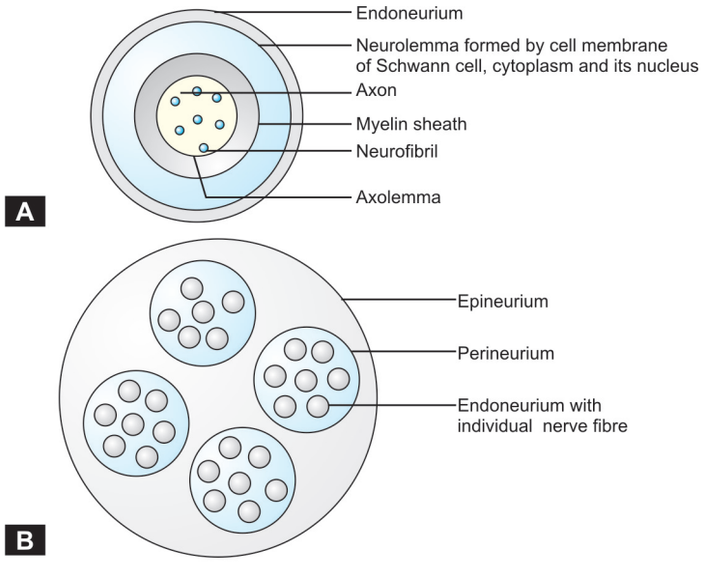


Fig. 13.6: Longitudinal section of a myelinated peripheral nerve



Figs 13.7A and B: Organisation of a trunk of peripheral nerve: (A) Cross section of a single nerve fibre, (B) Cross section of a nerve trunk

So long as the nerve fibre or axon remains within the grey matter of the central nervous system, it remains naked. Then as soon as it enters the white matter of the CNS, it gets the first covering, called the myelin sheath (white). After that when it comes out of the central nervous system, it receives a second covering called the neurilemma. When the nerve fibre terminates at the periphery on a target cell, then the neurilemma sheath is lost first, and next the myelin sheath. Lastly the axis cylinder of the axon ends as a naked process with out any coverings. Each motor nerve fibre at its termination breaks up into about 150 branches and each of these branches ends on a separate muscle cell or fibre. One motor nerve fibre or axon with all the muscle fibres that it supplies constitute one motor unit. Each motor unit is controlled by one motor nerve cell of the CNS. In the central nervous system the nerve fibres do not contain any neurilemma sheath. Myelination in CNS does not takes place by Schwann cells. It is occured by oligodendroglia cells which surround the axon in CNS and form the myelin sheath. Schwann cells take part in the formation of myelin sheath in the periphery. Like the peripheral nerves, the nerve fibres of the CNS also possesses the nodes of Ranvier, but these are not so obvious as in peripheral nerves.

Medullated (or Myelinated) Nerve Fibre and Myelinogenesis

In a myelinated nerve fibre, the central core is the axon. The outer cell membrane of the axon, which is called the axolema is here the actual impulse conducting membrane. The axon is filled with a viscus intracellular fluid, called the axoplasm. In a myelinated nerve fibre the axolema is surrounded by a sheath of lipid material, which is known as the myelin sheath. The myelin sheath is present in all the thick somatic nerve fibres, but not over the postganglionic autonomic nerve fibres. The somatic nerve fibres of 1μ diameter or less are not medullated. All the preganglionic autonomic fibres are also medullated. The myelin sheath is again lined by a delicate membrane which is known as the neurilemma sheath. However, this is nothing but the last turn of the Schwann cell and is formed during the formation of myelin sheath. In the last turn of the Schwann cell, there is a nucleus which is located near the most outer membrane of the Schwan cell. Thus the most outer Schwann cell membrane, nucleus and the irregular cytoplasmic strands inside the Schwann cell membrane constitute the Schwann cell sheath of neurilemma in all the matured nerve fibres.

In a medullated nerve, the myelinogenesis is caused by the depostion of myelin sheath around the axon by the Schwann cells. The axon is first enveloped completely by a Schwann cell. The Schwann cell then gives several turns around the axon by many concentric layers of cytoplasm and its cell membrane. Then the cytoplasm disappears from the concentric layers, leaving only the cell membrane of the Schwann cells, wrapping one on another. Thus, the compact myelin sheath consists only of several concentric layers of the Schwann cell membrane. Only the outer turn of the Schwann cell persists as the sheath of neurilemma with some cytoplasm, nucleus and the outer cell membranes. This myelin sheath acts as an insulator and prevents the flow of almost all the ions across the axolema. The myelin sheath is not continuous all over the whole axon, but is interrupted regularly at an interval by the nodes of Ranvier. In the nodes of Ranvier the myelin sheath is absent and the outer turn of the Schwann cell membrane (neurilemma) is dipped inwards over the axon. In comparison with the myelin sheath, the axolema and neurilemma in this region of the nodes of Ranvier are highly permeable to ions and takes part in the conduction of impulse alony the axon.

In case of unmyelinated nerve fibres, the axons are also buried within the Schwann cells. Here, the axons are enclosed by a Schwann cell, but it does not spin a myelin sheath around them. Non-myelinated nerves are abound in the CNS and in the dorsal nerve root. Myelination in CNS occurs by different process. Here the cell is oligodendroglia but not the Schwann cells which takes part in the process of myelination.

Thus, a medullated nerve fibre consists of the following structures from within outwards:

i. A central core of axon with semifluid axoplasm, which flows from the cell body of the neuron to the periphery. If the axon is sectioned, the axoplasm pours from the cut ends. The axoplasm contains numerous fibril like structure called neurofibril and mitochondria. The axolema (the cell membrane of the axon) separates the axoplasm from the surroundings structures.
ii. The axon is surrounded by a myelin sheath, which is interrupted regularly at the nodes of Ranvier.
iii. The neurilemma represents the outer most cell membrane of the Schwann cell and under it lies a thin layer of Schwann cell cytoplasm with its peripheral nucleus.
iv. At the most periphery outside the neurilemma sheath a single Schwann cell and a single axon is wrapped by a layer of permeable connective tissue, called the endoneurium. Several of these units are further bundled together within a sheath of squamous cells, known as the perineurium. This layer is more resistant than the endoneurium to the passages of chemical molecules. The perineural bundles can be seen with the naked eye. These multiple perineural bundles are packed by an another outermost connective tissue covering and constitutes a nerve. This outermost connective tissue covering of a nerve is called the epineurium. This layer protects the nerve from the external damage. It is more permeable than the perineurium and contains the nerve's blood vessels.

ACTION POTENTIAL AND TRANSMISSION OF IMPULSES

Action Potential

Action Potential (AP) is the sequence of changes of intracellular and extracellular electrical charges which accompanies the passage of an impulse along the cell membrane. This is the mechanism by which the nerve cells transmit the electrical signals. A typical cell membrane is a molecular lipid bilayer which is composed of phospholipids and cholesterol in the ratio of about 5:1. This lipid bilayer of cell membrane also contains many proteins which are absorbed on the surface or embedded in it. These proteins are known as the receptors or ion channels and are used for intracellular communication. The lipid bilayer character of (Fig. 13.8) the cell membrane is arranged in such a fashion that the long hydrophobic fatty acid tails of the phospholipid molecules that lie in the centre of the membrane and the polar hydrophilic head groups of the phospholipid molecules project in the cytoplasm or in the interstitial space.

In the resting state of the axon the outer surface of the cell membrane is positively charged and the inner surface of the cell membrane is negatively charged. So that, at rest, between the inside and outside of the cell membrane there is a difference of electrical potential which is about –70 mV. However normally this range varies between –60 to –90 mV. This difference in electrical potential at rest is known as the resting membrane potential (RMP) and this is necessary for the cell membrane to receive and transmit the impulses in the form of action potential. In order to maintain this resting electrical potential or polarized state, the nerve cell must resist their natural tendency to neutralize this difference in electrical potential by opposing the diffusion of ions across the cell membrane according to their concentration gradient. So, this diffusion is opposed and the polarized state or the concentration gradient of ions is maintained by an ATP energized Na^+ and K^+ membrane pumps which actively push Na^+ out of the cell and K^+ into the cell. For every $3Na^+$ is pushed out, $2K^+$ is pushed in.

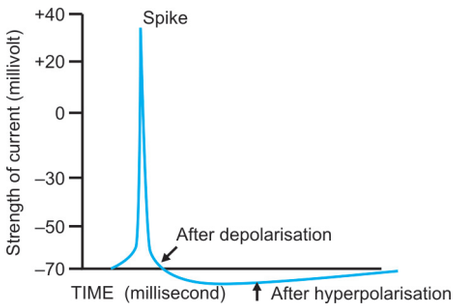


Fig. 13.8: Complete action potential. The first manifestation of action potential is depolarisation of membrane,i.e. influx of Na^+. After an initial –40 mv depolarisation, the rate of depolarisation increases. The point where this change of rate occurs is called the threshold or firing level. After the threlevel, the depolarisation level overshoots and crosses the iso-potential (or zero potential), to reach +40 mv. Then the membrane potential reverses and falls rapidly towards wards the resting level. This is called 'repolarisation'. When the repolarisation is 70% completed, the rate of change decreases,and the tracing approaches the resting level more slowly. The sharp rise and rapid fall of membrane potential is called the 'spike'. The slower fall at the end of repolarisation is called 'after-depolarisation'. After reaching the resting level, the membrane potential slightly moves in the hyperpolarising direction, to form a small but prolonged 'after-hyperpolarisation' state

In the resting state, the Na^+ concentration at outside of the cell membrane is higher than that of the inside of the cell membrane. Again, K^+ concentration at inside of the cell membrane is higher than that of the outside of the cell membrane. On the other hand, K^+ can penetrate through the cell membrane at the resting state, but not the Na^+. Positivity at outside of the cell membrane which is due to higher Na^+ concentration and other reasons also cause the K^+ to be pushed inside the nerve cell, producing higher K^+ concentration inside the cell. The axoplasm (cytoplasm of the axon) is also rich in proteins and organic acids, which are negatively charged and are too large to pass through the membrane (Fig. 13.9).

These are also responsible for the negativity of the inside of the cell in the resting state. Not all the ions are equally important for the maintenance of resting membrane potential. But each ion contributes to the aggregate potential

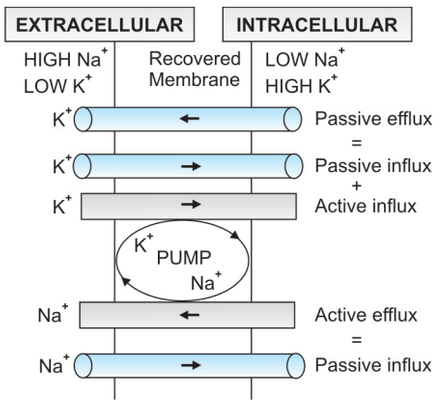


Fig. 13.9: Sodium pump is required to expell Na^+ from the interior of the nerve axon so that the internal Na^+ concentration is held to about 7% that of external fluid. At the same time pump drives K^+ uphill from a lower external concentration to about 28 times higher internal concentration

difference across the cell membrane which is based on the ratio of their concentration gradient between inside and outside of the cell and also based on the permeability of the cell membrane to that particular ion. The Na^+-K^+ pumps which are straddled in the cell membrane and require high energy phosphate (ATP) for their action are only responsible for maintaining Na^+ and K^+ gradient across the cell membrane at resting state. This gradient is again responsible for the influx of Na^+ into the cell and movement of K^+ out of the cell, during action potential. If this gradient is not maintained, then action potential is not possible.

In the resting state, the nerve fibre remains in a polarised state and the resting membrane potential lies around −70 mV. The inside of the nerve cell is negative and the outside of the nerve cell is positive. The permeability of Na^+ through the cell membrane is increased only when the stimulus reaches the cell membrane. It is the first event of the action potential. It has been postulated that in the resting state the calcium ions (Ca^{++}) remain bound to the protein surfaces of the membrane pores. It does not allow the Na^+ to permeate through these resting pores. During excitation this Ca^{++} is dislodged from its binding sites, and the permeability of Na^+ inside the cell is increased. With the entry of Na^+ inside the cell, the membrane potential gradually decreases. However, when the potential difference across the cell membrane comes to a critical or threshold level (approximately –40 mV for most cells), then there is a sudden and spontaneous increase in Na^+ permeability and Na^+ enters inside the cell membrane. Thus, the depolarisation starts with the onset of increase in Na^+ permeability of the cell membrane. This tremendous increase in Na^+ conductance during this period is known as activation of membrane. During depolarisation, this change in transmembrane potential is accompanied by a further increase in Na^+ permeability with the creation of a positive feedback loop by which the influx of Na^+ facilitates further Na^+ influx.

Thus, due to influx of Na^+ during depolarisation the reversal of potential across the cell membrane is occurred with the development of positivity inside of the cell membrane and negativity outside of the cell membrane. With the increase of positivity inside of the cell, further entry of Na^+ is prevented and calcium begins to bind with the proteins of the membrane pores. So, at the end of depolarisation, as soon as the transmembrane potential attains the voltage of approximately +50 mV, then Na^+ influx stops. In that situation, the cell attains an unstable condition because both the Na^+ and K^+ one inside of the cell with reverse potential (positivity inside the cell and negativity outside the cell). But this unstable condition cannot be allowed to continue indefinitely. So, at this point a less rapid, but more sustained change in the permeability of the cell membrane to K^+ occurs and this is beginning of repolarisation. With the beginning of repolarisation K^+ flows along its concentration gradient from inside to outside of the cell taking +ve charges with it. Thus the loss of +ve ions from inside of the cell causes a fall in the electrical potential of the axoplasm and reach the normal resting negative (– ve) value. But, indeed the change in K^+ permeability is sustained for a sufficient time and this is for the net potential difference across the cell membrane to reach −75 mV which is some what below the resting membrane potential (–70 mV). This hyperpolarisation, combined with the inactive sodium ion channel is responsible for the brief refractory period that each segment of a neuron requires following generation of an action potential.

In this hyperpolarization phase, though the resting membrane potential (i.e. negativity inside the cell and positivity outside the cell) is achieved, but the resting ionic status is not established (Na^+ inside and K^+ outside the cell). So, the resting ionic status is achieved now by the active Na^+-K^+ pump-mechanism and Na^+ begins to come out of the cell. Increased concentration of Na^+ outside the cell now causes the K^+ to diffuse back into the interior of the nerve cell.

Thus, the action potential cycle is completed with the establishment of a normal electrical potential status and normal ionic status. Now Na^+ and K^+ pumps maintain this concentration gradient of Na^+ and K^+ across the cell membrane.

Transmission of Impulses

The impulses are actually the propagated waves of depolarisation caused by the continuous coupling between the excited and the nonexcited regions of the cell membrane. It has already been discussed earlier that a resting nerve fibre remains in a polarised state with positive charges lined up along the outside of the cell membrane and negative charges along the inside of the cell membrane. Then as soon as the nerve fibre is excited at any point, then the polarity is changed at that point and for a brief period it is actually maintained at that point. However, this reversed polarity of cell membrane at that point of stimulation is due to the increased inward permeability of Na^+ through the membrane. Thus, a small area of depolarisation develops at

the point of excitation. Then a local circuit current flows between the depolarised area of membrane and the adjacent resting polarised area of the membrane. Thus an ionic current entering the axon through the excited depolarised region, flows down the axoplasm and exits through the surrounding resting membrane, causing depolarisation of the adjacent resting regions. Thus, positive current flows inward through the depolarised membrane and outward through the resting membrane and in this way a small circuit of current or a wave of depolarisation is completed which as a impulse travels in all directions along the entire length of the nerve fibre. Though, this local circuit current or the wave of depolarisation spreads away from the excited zone in both directions, but the regions behind the impulse having just been depolarised is absolutely refractory. So, the impulse propagation is unidirectional. After the wave of depolarisation, a repolarisation wave first occurs at the point of stimulus, a few ten-thousandths of a second later than the depolarisaton wave and spreads progressively along the membrane, following the similar directions as the depolarisation wave had spread previously. This type of conduction is observed in the non-medullated nerve fibres (Fig. 13.10).

However, in the myelinated nerve fibre conduction occurs in a similar pattern as described above. But the myelin sheath is an effective insulator. So, ions cannot pass through the myelin sheath. Therefore, the nodes of Ranvier only allows the ions to penetrate through it more easily. Nodes of Ranvier are 500 times more permeable than unmyelinated fibres. For this reason, the impulse or the wave of depolarisation is transmitted from one node of Ranvier to another, rather than continuously along the entire length of the medullated nerve fibre. Thus, the depolarisation in a myelinated axon jumps from one node of Ranvier to the next. So, this jumping or leaping of depolarisation from one node to another is known as the saltatory (saltare = to dance) conduction of impulse.

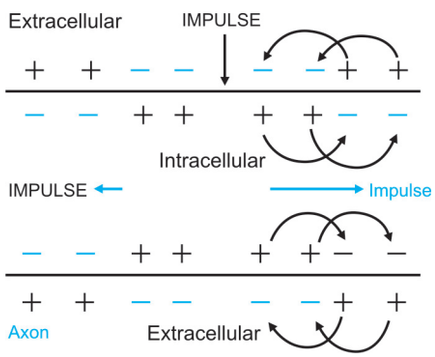


Fig. 13.10: This is a diagrammatic representation of current flowing along the cell membrane of an axon (axolemma), in an unmyelinated nerve fibre

MECHANISM OF ACTION OF LOCAL ANAESTHETICS

The local anaesthetic (LA) agents block the generation or conduction of nerve impulses by decreasing or stopping the entry of Na^+ ions through its channel inside the cell, during the depolarisation phase of AP. As the concentration of the LA agent is increased, then the rate of the rise of depolarisation potential to the threshold level and subsequently the initiation of AP is inhibited, causing slowing or total block of generation and conduction of nerve impulses (Fig. 13.11).

The LA agent acts through binding a site which is situated at the intracellular portion of the voltage sensitive Na^+ channel and raises the threshold value of the channel opening. This binding site of LA agent at the intracellular portion of the Na^+ channel is called the LA receptor. This Na^+ channel is nothing but a special protein through which Na^+ enters the cell, and also called the ion channel. Thus the Na^+ channel fails to open after binding with the LA agent and the Na^+ permeability fails to increase in response to an oncoming impulse or stimulation. The Na^+ channel is situated in the cell membrane with a small portion protruding inside and outside of it. It has an activation gate (A) near its

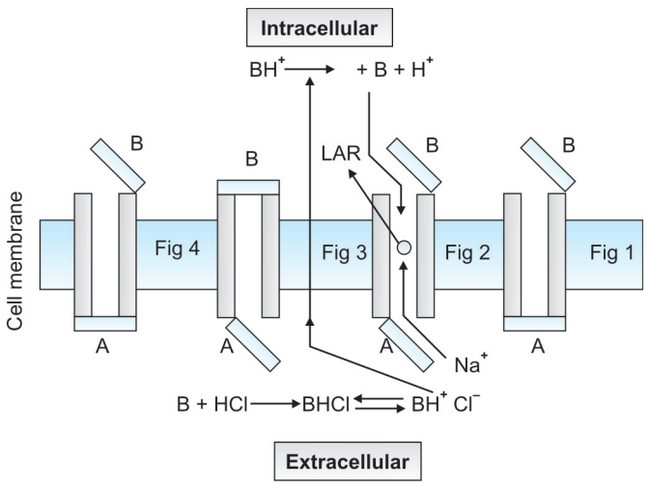


Fig. 13.11: This is a schematic diagram of axonal Na^+ channel in different phases of action. The picture also shows the site and mechanism of action of local anaesthetics. The Na^+ channel has an activation gate (A), near its extracellular mouth and an inactivation gate (B), at the intracellular mouth. In the resting state the activation gate (A) remains closed, while the inactivation gate (B) is open (Fig. 13.1). When the resting membrane potential (RMP, reaches the threshold level and depolarisation shoots up, then the activation gate opens and allows the Na^+ to flow in the cell along the concentration gradient (Fig. 13.2). Within a few milliseconds the inactivation gate closes and the flow of Na^+ stops (Fig. 13.3). After that the Na^+ channel recovers to the resting stage (Fig. 13.4) by opening of the inactivation gate and closing of the activation gate.
B = Insoluble local anaesthetic base, BHCl = Soluble hydrochloride of local anaesthetic (LA) unionized, BH^+ = Ionised form of LA, LAR = Local anaesthetic receptor

extracellular mouth and an inactivation gate (B) at the intracellular mouth. In the resting (Fig. 13.12) state, the activation gate (A) is closed and inactivation gate (B) remains open. During the depolarisation of AP when the threshold level of membrane potential has been reached, then the activation gate opens and allows the Na^+ ions to flow inside the cell, along the concentration gradient. At the resting state, the membrane is normally permeable to K^+ through the K^+ channel, but not permeable to Na^+ through the Na^+ channel. But, during the depolarisation phase of AP the nerve membrane transiently switches its permeability from K^+ selectivity to Na^+ selectivity. After the opening of activation gate within a few milliseconds, the inactivation gate (B) closes and ion flow ceases. But in this phase activation gate is still open. After that the channel recovers to the resting state in a time dependent manner with the closed activation gate (A) and opened inactivation gate (B) (Fig. 13.13).

At a physiological pH, the LA molecule is partly ionised and partly unionised. However the equilibrium between the unionised or unprotonated base form (BH) and the ionized or protonated or cationic form (B) of a LA agent depends on the pKa of it, the pH of the solution, and also the pH of the local tissue. The LA agent traverses the nerve cell membrane in its lipophilic unionised form (BH).

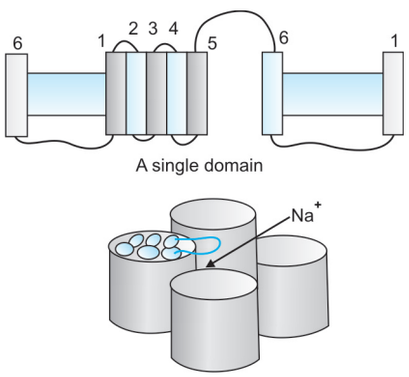


Fig. 13.12: Four domains forming the Na^+ channel

Then it reionises in the axoplasm and its ionised form approaches the LA receptor situates at the intracellular mouth of Na^+ channel. At the receptor the LA agent binds with the Na^+ channel and prevents its opening. It is the cationic or ionised form (B) of the LA agent which primarily binds to the receptor and is responsible for its action. The activated receptor has higher affinity or is more accessible to the LA agent, compared to the resting state of it. Binding of the LA agent to its receptor site stabilizes the Na^+ channel in the inactive state and thus reduces the probability of opening the channel and prevents the influx of Na^+ inside the cell. Thus it prevents the depolarisation part of action potential to initiate and block the conduction of impulses through a nerve fibre. Moreover, the exposure of LA receptor to higher concentration of Ca^{2+} reduces the inactivation of Na^+ channels and lessens the degree of block. Here, the generation of blockade of any conduction of impulses by the LA agent is not due to the hyperpolarisation of cell membrane. Infact, resting membrane potential is also unaltered, because the K^+ channels are not affected. These are blocked only by higher concentrations of the LA agent (Fact file- I).

The cationic form of LA agent is able to approach to its receptor site, only when the channel is opened and binds more avidly.

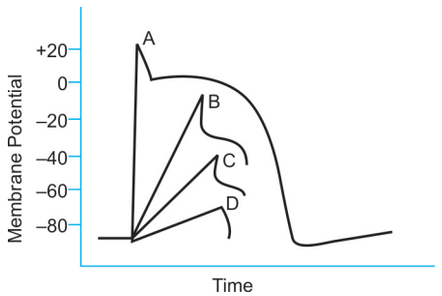


Fig. 13.13: This is the schematic diagram of action potential of different nerves, untreated or treated by LA agents. A=Action potential of a nerve untreated by a local anaesthetic, B,C,D=Show the effects of LA agents on the generation of action potential of a nerve fibre by progressively increasing the concentration

FACT FILE- I

The molecular weight of the neuronal Na^+ channel has been found to be of 300 KDa. Chemically, it is a glycoprotein and is composed of one large (α) and two small (β_1, β_2) subunits. The α-subunit encloses the Na^+ selective pore within its 4 homologous domains (I to IV) where each domain has 6 membranes spanning helical segments (S_1 to S_6) connected alternately by intracellular and extracellular loops. The wall of the pore is formed by the S_5 and S_6 segment of all the four domain, while the short nonhelical loops connecting S_5 - S_6 segments on the extracellular surface fold into the pore and serve as the activation gate. Voltage sensors located in the S_4 segment move vertically on depolarisation and open the activation gate by allosteric conformational change. A few milliseconds later, the short intracellular loop connecting the domains III and IV folds into the inner mouth of the pore, activating the channel. The LA receptor is located in the S_6 segment of domain IV.

Thus, a resting nerve is rather resistant to blockade and blockade develops rapidly when the nerve is stimulated repeatedly. The degree of blockade is also frequently dependent on higher frequency of stimulation. The onset of blockade is primarily related to the pKa value of the LA agents. Those with lower pKa values (7.6 to 7.8), such as lidocaine, mepivacaine, etc., are fast acting, because 30 to 40% of these LA agents remain in the unionized base form at pH 7.4 and it is this form of LA agent which only penetrates the axon membrane. Procaine, tetracaine, bupivacaine have higher pKa value (8.1 to 8.9). Thus only 15% or less of them remain in the unionized form at pH 7.4. So, they are slow acting. However, the chloroprocaine is an exception of it having rapid onset, despite high pKa value.

CLASSIFICATION OF NERVE FIBRES

Nerve fibres have been classified into different types under different headings :

i. Histologically – myelinated and non myelinated.
ii. Functionally – motor (efferent) and sensory (afferent).

iii. Chemically – adrenergic (mainly sympathetic) and cholinergic (mainly parasympathetic).
iv. According to the diameter of fibre and the conduction velocity of impulses.

Classification of Nerve Fibres According to their Diameter and Conduction Velocity

The physiological properties of nerve fibres vary with their diameter and conduction velocity of impulses. Thicker will be the fibre, higher will be the impulse velocity and peak potential, but lower will be the refractory period and the stimulus threshold. Erlanger and Gasser have classified the nerve fibres according to their diameters and conduction velocity into A, B and C. The A fibres are myelinated, somatic, afferent and efferent axons. B fibres are the preganglionic, myelinated, efferent, sympathetic axons. C fibres are the sympathetic and somatic, unmyelinated axons. Again the C fibres are of two types – the s C group and d r C group. The s C group of fibres are efferent, postganglionic sympathetic axons and the d r C group of fibres are the small afferent axons, found in the peripheral nerves and dorsal roots. In a peripheral somatic nerves, both A and C fibres are present.

If a peripheral nerve is stimulated at one end and the impulse is recorded through the oscilloscope at the other end, then a compound action potential formed in this nerve is found to be composed of four different deflections – α, β, γ and δ. These different deflections are due to the corresponding stimulation of different nerve fibres with different conduction velocities within this nerve. The α-deflection is due to the stimulation of nerve fibres, having comparatively larger diameter with higher conduction (Table 13.1) velocity. δ-deflection is due to the stimulation of nerve fibres having lowest diameter and slowest conduction velocity. The B fibres are histologically indistinguishable from small A fibres, but distinguishable principally from A fibres by the absence of negative action potential. The C fibres in a somatic nerve are stimulated only when the threshold stimulus is higher than the stimulus which is used in case of A fibres. Functionally, the C nerve fibres are distinguishable from the A fibres by slow conduction velocity, long spike duration and a high threshold value. The classification of nerve fibres according to their conduction velocity and diameter is already tabulated.

For the clinical blockade of a myelinated nerve fibre a segment or a length of atleast 6 mm (or preferably 10 mm), representing two to three nodes of Ranvier must be exposed to the local anaesthetic agent. Because it will deter the impulses from skipping over the blocked segment by a process which is known as the saltatory conduction. The motor nerves have greater internode distances, than the sensory nerves. This may account for the differential blocked, favouring the affection of more sensory than motor fibres in certain circumstances. Where the length of a nerve fibre available for exposure to local anaesthetic agent is short, then the decision to use a higher concentration of LA agent may be necessary in order to achieve desired effects. Whereas, if longer sections of a nerve is available for action then the contact with LA agent with less concentrations of drug would suffice. However, a certain minimum concentration of the local anaesthetic agent is necessary to block a nerve fibre of a given type. Hence, the clinical emphasis should always be on using the least effective concentration in the smallest volume that produces the desired degree of blockade. Motor and proprioceptive nerve fibres require higher minimum concentration of the LA agent for effective block, than the other modalities such as pain and temperature. Hence, if the achievement of motor akinesia is used as the yard stick for block effectiveness, then pain will never be experienced if there is full motor block. In such situation,

Table 13.1: Classification of nerve fibres

Types of fibre	*Diameter of fibre in μm*	*Velocity of conduction in m/sec*	*Location*	*Sensory function*	*Motor function*
(Myelinated)					
A - α	12 - 20	70 - 120	Afferent and efferent from joints and muscles	Proprioception	Somatic motor
A - β	5 - 12	30 - 70	Afferent and efferent from joints and muscles	Touch, Pressure	Somatic motor
A - γ	3 - 6	15 - 30	Efferent to muscle spindle	No sensory	Motor to muscle spindle
A - δ	2 - 5	12 - 30	Afferent sensory nerves	Pain, temperature and touch	No motor
(Myelinated) B	< 3	3 - 15	Preganglionic sympathetic fibres	–	Various autonomic functions
(Non myelinated) C-dorsal root (d, r, C)	0.4 - 1.2	0.5 - 2	Postganglionic sympathetic fibres	Pain, touch and temperature reflex response	No motors
C - sympathetic (s, C)	0.3 - 1.3	0.7 - 2.3	Afferent sensory nerves	–	Various autonomic functions

touch and tissue movement appreciation (proprioceptive mediation) may be occasionally experienced as pain or discomfort in nervous patients.

POTENCY, DURATION OF ACTION AND SENSITIVITY OF DIFFERENT NERVE FIBRES TO LOCAL ANAESTHETICS

Certain physicochemical conditions control the important biological properties of the local anaesthetic agents. Among these, the protein binding, dissociation ratio and lipid solubility are the most important ones. The affinity for protein (protein binding) is the predominant property that governs the duration of action of LA agents. The agents with high protein affinity occupy the active binding sites of the receptor for a longer period of time and therefore have a prolonged duration of action (e.g. bupivacaine and etidocaine). Drugs with somewhat lesser affinity for protein receptor have an intermediate period of action (e.g. lignocaine and mepivacaine). Whereas, procaine which is poorly protein bound is a short acting LA agent.

The dissociation ratio between the unionised and the ionised form of a LA agent is largely responsible for the speed of onset and the tissue penetration ability of the drugs. Those, being presented in more highly ionized form have inferior properties in this regard.

High potency of a LA agent is associated with high lipid solubility of it. This property also facilitates the solution of a LA agent to enter into the cell through the cell membrane and to reach the nerve fibre (site of action) from the site of injection. So, lipid solubility or hydrophobicity is the prime determining factor for intrinsic anaesthetic potency of LA drugs. After entering the cell, the ionised form of the LA drug is again attached to the hydrophobic LA receptor site of the Na^+ channel which is also related to the potency. But, clinically the correlation between the lipid solubility and potency of the drug is not precise. There is a difference between the in vitro and in vivo results. This difference in result between the in vitro and in vivo studies is related to a number of factors, such as volume of drug, concentration of drug, local vasodilatation or constriction, and tissue redistribution properties etc.

Usually the injected volume and the concentration of LA drug is important in the process of the spread of agent and achieving the adequate concentration of it around the nerves. Concentration of drug around the nerve fibre is also of prime importance in the development of diffusion gradient for nerve penetration. So, though high potency and long duration of action depends primarily on the lipid solubility of the drug, but the action of less lipophilic drugs can be prolonged by increasing the concentration and the volume of it at the injection site or near the nerve fibres. Vasoconstrictive effects of the LA drug also tends to prolong its action by reducing the rate of removal of it from the site of action by vascular absorption. Vasodilator property of the drug has opposite effects. Lignocaine causes greater degree of vasodilatation than prilocaine, causing more rapid vascular uptake and shorter duration of action. So, fewer molecules are available for nerve blockade and has a reduced potency, though lipid solubility of lignocaine is greater than prilocaine. High lipid solubility of etidocaine results in greater uptake of agent by adipose tissue in the epidural space, leaving fewer molecules available for nerve blockade, as compared to bupivacaine.

All the types of nerve fibres are affected by local anaesthetics, but fine and slower conducting nerve fibres are more readily blocked than the thicker and fast conducting fibres. This is because the sensitivity of block is determined by the diameter of the fibre. So, the fine fibres are blocked more easily than the thick fibres. But, these rules do not always hold good. For example, the myelinated preganglionic B fibres are more sensitive than the non-myelinated preganglionic C fibres, though the former is thicker than the latter. The preganglionic myelinated B fibres are most sensitive to all. So, vasodilatation and consequent hypotension is the first effect of spinal anaesthesia than the sensory blockade. Though the thick A fibres are certainly more resistant to local anaesthetic agents, but the fibres within them also differ in the critical length that must be exposed to the LA agent for effective block. Fine fibres have shorter critical length and so is more sensitive to the LA agents. Frequency dependent block also makes the fine sensory fibres more vulnerable to LA agents. This is because they generate high frequency, long lasting action potetial than motor fibres. The fibres subserving pain and temperature (A-δ) are more sensitive than C pain fibres. So, sometimes pathological pain, e.g. impending uterine rupture which is conducted by C fibres may break through an epidural block, which is relieving the physiological pain of labour. This is called the epidural sieve. Sensory A fibres are more sensitive than motor A fibres.

Thus the order of sensitivity of nerve fibres to local anaesthetic agents (starting from most sensitive to less sensitive) are: Pregrianglionic – Pain – Temperature – Touch – Proprioception (pressure) – Motor.

PHARMACOLOGICAL EFFECTS

The pharmacological effects of LA agents are described under three headings : local, regional and systemic.

Local Effects

The block of conduction of impulses through nerve and the relaxation vascular smooth muscle are the two most important local direct effects of local anaesthetic agents.

Regional Effects

Loss of pain, temperature, touch and pressure sensation are the regional effects of local

anaesthetic agents. Loss of motor power and vasomotor tone are also the regional effects of local anaesthetic agents.

Systemic Effects

The LA agent, injected locally is ultimately absorbed by the blood and produces systemic effects. However, this systemic effect depends on the plasma level of this drug. The production of nerve block by systemic administration of a LA agent requires very high doses, rather than local infiltration and is so systemically highly toxic. Hence, it is not used for conduction block of nerves by systemic administration. For example, lethal doses of lignocaine is necessary to block the sensory nerve endings when used systemically. Another example is that the analgesic properties of procaine infusion are due to its action on the CNS, rather than peripheral nerve blocking effect.

The chief systemic toxicities of LA agent are mainly divided into CVS and CNS effects, and this is principally due to its membrane stabilizing property. Therefore, the toxic effects when they occur affect mainly the organs which have excitable membranes such as the brain and myocardium. The incidence of systemic toxicity with local anaesthetic agent when used locally is also related to the total dose of drug given, vascularity of the site of injection, type of drugs used, speed of injection and whether the adrenergic agents have been used as an additive with the LA agent to delay the systemic absorbtion or not. However, in clinical practice the systemic toxicity is most likely to be encountered following the unintentional intravascular injection.

Action on CVS

Infiltration of the LA agent in conventional doses have no significant effect on the CVS. Infiltration in higher doses or inadvertent IV injection of the LA agent cause all the problems. They depress automaticity of SA node and suppress cardiac rhythms. They prolong the action potential of myocardium, increase effective refractory period, slow down conduction through AV node, bundle of His and Purkinje fibres and depress the myocardial force of contraction. All the LA agents reduce cardiac sensitivity to adrenaline.

The local anaesthetic agent such as procaine and procainamide have quinidine like effects. However, procaine is not used as an antiarrhythmic agent for its short duration of action, but procainamide is a classical anti-arrhythmic drug. The electro-physiological properties of the heart muscles are markedly altered by the high plasma concentration of LA agent, and then can itself induce cardiac arrhythmias. Lignocaine is not so cardiotoxic and used clinically as an antiarrhythmic agent. Bupivacaine is more cardiotoxic and may cause ventricular tachycardia, fibrillation or even cardic arrest. Cardiac toxicity of bupivacaine usually does not occur in subconvulsive doses or in the absence of severe electrolyte disturbances or respiratory and metabolic acidosis. Large doses of LA agent may also produce circulatory collapse, as a result of the medullary depression.

Action on Vascular Smooth Muscles

LA agent acts on the smooth muscles of blood vessels through different levels: local, regional and systemic. But the ultimate effect is both complicated and confusing. At the local level procaine is a vasodilator and cocaine is a vasoconstrictor. Mepivacaine is a vasoconstrictor at clinical concentration than prilocaine, lignocaine, bupivacaine in that order. Lignocaine exists in two isomers and the vasoconstrictive effect appears to be vested only on one of the isomers. In case of mepivacaine both the isomers have vasoconstrictive property.

However, at the regional level all the LA agents cause vasodilatation in the area, supplied by the blocked sympathetic fibres. At the systemic level the effects of LA agents on vascular smooth muscle are produced by reflex mechanism or through CNS involvement.

Action on CNS

Cocaine is primarily a CNS stimulant, producing euphoria, excitement, restlessness, tremor, twitching or convulsions. This is due to the inhibition of the inhibitory neurons of central nervous system, as the inhibitory neurons are more susceptible than the excitatory neurons. So, after inhibition of the inhibitory neurons, the excitatory neurons of CNS take an upper hand and produce convulsions. In the 2nd phase with increasing dose of cocaine, when the excitatory neurons are also blocked after the inhibitory neurons, then the total depressive effects of the LA agents become prominent. This is manifested by unconsciousness, respiratory depression, cardiac depression, coma and death. Cardiac depression of LA agents may be the result of medullary depression, other than direct action on myocardium and is compounded by convulsion with associated hypoxia.

Procaine and other LA agents are much less potent. At the safe clinical doses, they produce little or no CNS effect. But, at higher doses or after accidental IV injection it produces CNS stimulation, followed by depression like cocaine.

Lignocaine, on the contrary as CNS effect, causes sedation and higher doses produce excitation, followed by depression. The sedative effect of lignocaine which is observed after epidural administration is well recognized. Hypoxia and acid base disturbances lower the threshold, both to the CNS and to the cardiac toxicity of the LA agent.

Action on Autonomic Nervous System

Cocaine potentiates the action of autonomic sympathetic nervous system by inhibiting the catecholamine uptake at the synaptic level and then produces excitement, tachycardia, hypertension, etc. However, other local anaesthetic agents

block both the cholinergic and adrenergic receptors (but not found in clinical doses).

Hypersensitivity

The true hypersensitivity reaction to modern amide groups of LA agents is very rare. But it is reported and is more common in atopic individuals than the normal population. On the other hand, this term is frequently misused to describe the other adverse reactions of LA agents which is due to the accidental intravenous injection or frank over doses of it. Other modalities of reactions of LA agents which may be mistaken as allergic reactions is vasovagal attacks, which is often found during injection (may be due to fear) in a person with strong vagal activity. Hypersensitivity of LA agent is manifested as local oedema, urticaria, angioneurotic oedema, etc. Anaphylactic reaction is less common than the atopic reaction.

Hypersensitivity reactions to ester group of LA agents is not rare, and is more common than the amide group of LA agents. This is because the para-aminobenzoic acid (PABA) produced by the enzymatic cleavage of it in plasma is the principal metabolic product of the ester linked LA agents and this product is thought to trigger off the allergic reactions in centrain individuals. Amide linked local anaesthetic agents, on the other hand, are broken down in the liver but not in the plasma like the ester type of LA agent, producing PABA. However, as the methyl para-aminobenzoic acid (methylparaben) which is used as a preservative in multidose vials of drug of certain amide linked preparations is related to PABA and may produce hypersensitivity reaction. So, it is better to use preservative free vials, where the history of the problem of allergic reaction exists. There is also a history of cross-sensitivity between the ester group of LA drugs and p-aminobenzoic acid used in sunscreen, cosmetics, different food preservatives, etc. This is because all the benzoic acid esters are highly antigenic.

Absorption

All the local anaesthetic agents are totally absorbed in the systemic circulation after their parentral use through local tissue infiltration. But the systemic absorption of all the local anaesthetic agents after their infiltration in the tissues depends on several factors.

(i) Lipid solubility of the agent

It determines the proportion of the aqueous part of LA agent which is available for rapid removal by blood and the proportion of the lipid soluble part which is taken up by the tissues and thereafter slowly released into the systemic circulation.

(ii) Vascularity of the tissue

The vascularity of local tissues where LA agents are infiltrated also dictates the absorption of the LA agents in the circulation. The more vascular is tissue, the more is the absorption of the drug in the circulation and its systemic effects. This is also altered by the LA agent itself by its vasodilator or vasoconstrictor properties and by the adrenaline added into the LA solution. Absorption of the LA agent through the trachea and inflamed urethra is also as good as IV injection.

(iii) Absorption through various tissues and the GI tract

It is only good for LA agent like procainamide and so it is useful as oral antidysrrhythmic agent. But for lignocaine, after oral administration 70% is metabolized during its single passage through the liver. So, this route is ineffective for lignocaine. A comparison of the blood concentration of LA agents after their absortion following various routes of administeration, reveals that the plasma level of anaesthetic drug is highest after the intercostal blocks, followed by caudal epidural, lumbar epidural, brachial plexus and subcutaneous tissue infiltration in a decreasing order. Thus, use of a fixed dose of LA agent may be toxic in one area, but not in others. For example, 400 mg of lignocaine in intercostal block may easily cause the peak plasma level of 7 µg/ml, which is sufficiently high for CNS toxicity. Whereas, the same dose in brachial plexus block causes peak plasma level of only 3 µg/ml, which is rarely associated with CNS toxicity. Large volumes of diluted solutions of the LA agent cause higher blood level than the same dose in mg in smaller volume. This is because large volume causes larger spread with large surface area for absorption. With same anaesthetic profile lignocaine absorb more quickly than prilocaine, and bupivacaine than etidocaine.

Distribution

After infiltration of a LA agent in the tissues, it is gradually absorbed in the blood. In the blood, LA agent is bound to the plasma protein such as α1-acid glycoprotein but a quantititively more important contribution is also made by the palsma albumin and a small proportion remains free which enters the red cells. Then the LA is very rapidly removed from the blood by the other tissues and it is so rapid that even before proper mixing of the drug in circulation, the removal of LA agents by the other tissues is complete. So, full equilibrium with tissues takes many hours to develop. LA agents readily crosses the blood brain barrier and the placenta. It is distributed throughout all the body tissues, but the relative concentration in different tissues varies. A highly perfused organ shows higher concentration and less perfused organ shows less concentration. The LA agent is rapidly extracted by the lung tissue, so that the whole blood concentration of LA decreases markedly as these agents pass through the pulmonary vasculature. The lung tissue has a lower pH than the plasma and thus favours the transformation of the local anaesthetic into its ionised form.

The highest percentage of the injected dose of LA agent is found in the skeletal muscles. At the tissue level, local anaesthetic agents are also metabolized by

tissue enzymes. This is important for the esters than the amide local anaesthetics, but this has minimal clinical significance. The kinetics of this total process vary from drug to drug. But more prominently, this kinetics vary greatly with the anatomical site of the injection. The relative speed of absorption of LA agent from the site of injection are determined by the vascularity of site, and by the amount of local fat that bind the LA agent and makes its absorption into the blood stream slow. Nevertheless, different drugs given at the same site will also result in different plasma concentrations. Degree of ionization and solubility of an individual drug play some role in this process. Other important factors that play a role in this process are : the total dose of drug in mg, the speed of injection, the presence and absence of additives such as bicarbonate or adrenaline, the presence or absence of concomitant end organ diseases and the effect of surgical lesion on homeostasis. It is very interesting to know that plasma level of local anaesthetic agent does not correlate well with age, body habitus or gender.

Metabolism

LA agents are metabolized in the liver to form more water soluble compounds and so are rapidly excreted through the kidney than other agents. Amide local anaesthetics are mainly metabolised in the liver, whereas the most ester group of LA agents are hydrolysed in the plasma. In liver, the several pathways of metabolism that are mainly involved are: N-dealkylation, hydroxylation, and hydrolysis. Now, most of the local anaesthetics agents are tertiary amines. So N-dealkylation of the tertiary amine (e.g. lignocaine) produces a more water soluble secondary amine and renders it more susceptible to amide hydrolysis, like secondary amine such as prilocaine.

Hydroxylation of the aromatic nucleus of tertiary amine is also believed to occur in the case of lignocaine, mepivacaine, bupivacaine, etc. However, hydroxylation of these agents produce a compound which can be conjugated and so become solely water soluble. Thus, as much as 70% of all the amide LA agents may be broken down during their single passage through the liver. This high first-pass clearance of lignocaine in liver yields mainly the N-dealkylated product such as mono ethylglycine xylidine, which is itself moderately toxic and effective anti dysrrhythmic agent. However, the high clearance rate of lignocaine is markedly reduced in the presence of low cardiac output state. There is a strong relation between the class of local anaesthetic drug and the rate of hepatic metabolism. In addition, a small fraction of the injected dose of the LA agent is excreted unchanged directly through the kidney.

Procainamide (amino alkylamides → diamines) is metabolised more slowly than lignocaine (amino acylamide → tertiary amines) and a larger proportion of it is excreted unchanged through the kidney. Some degradation of amide type of local anaesthetic agent also occurs in tissues other than the liver. Less than 5% unchanged drug is excreted via kidney through the urine. Procaine and amethocaine are hydrolysed by pseudocholinesterase in plasma and compete with suxamethonium. Cocaine is not broken down by cholinesterase.

The water soluble metabolites of LA agents are rapidly excreted through the urine. But the lipid soluble local anaesthetic base, once filtered in the glomerulus are reabsorbed by the renal tube. In an acidic urine, it becomes highly ionized, then tubular reabsorption is inhibited and renal clearence increases.

Toxicity of Local Anaesthetics

The toxicity of LA agent mainly affects the CNS and CVS. The subconvulsive doses does not cause the circulatory depression, but may depress the CNS. However, like other drugs, the toxicity of LA agents is not the mere extension of their therapeutic action but has a distinct mechanism. It depends on the speed of vascular absorption, and trouble starts when the absorption and elimination of the drug does not balance. The occurrence of toxicity of LA agent is not related to the concentration of the solution injected, but rather to the total dose of drug. Similarly the site of injection and its vascularity also affect the speed of absorption of LA agent, as well as its toxicity. The relative overdose for a given plasma concentration in case of very young or old patients is not due to their raised sensitivity. So, widespread field block and excessive surface application should be avoided in such group of patients. The cause of toxicity of LA agents in correctly administered dose is due to gradual accumulation in body due to the continuous or repeated administration of gradual accumulation in body due to the short acting drugs. So, long duration of bupivacaine and rapid elimination of etidocaine has clear advantage for continuous infusion.

CNS Toxicity

Subjective signs

These are: light headedness, dizziness, visual and auditory disturbances such as difficulty in focusing and tinnitus, disorientation and drowsiness.

Objective signs

These are: shivering, twitching, tremor, convulsion, respiratory depression, respiratory arrest, coma and death.

There is an inverse relationship between the intrinsic anaesthetic potency of a LA agent and the doses required to induce CNS toxicity.

An increase in $PaCO_2$ decreases the convulsive threshold level of local anaesthetic agent by approximately 50%. The explanation is like that an elevation of $PaCO_2$ increases the cerebral blood flow a and so more anaesthetic agent is delivered to the brain rapidly. In addition, the diffusion of CO_2 in the neural cell decreases the intracellular pH and thus facilitates the conversion of unionised form of the drug to ionised form within the cell, which only bind with the hydrophobic receptor site of

the intracellular part of Na^+ channel. Thus the cationic or ionized form does not cross the nerve cell membrane, so that ion trapping occurs and increases CNS toxicity.

On the other hand, hypercapnia or acidosis decreases the plasma protein binding capacity of LA agents, and so increases the proportion of free drug available for diffusion into the brain. Seizure and CNS depression again produce hypoventilation and respiratory acidosis, which further exacerbates the CNS toxicity establishing a vicious cycle. So, in local anaesthetic toxicity prompt assisted ventilation correcting acidosis is essential.

Cardiovascular toxicity

The direct cardiac effects of LA agents are:

i. The LA agents decrease the rate of depolarisation in the fast conducting tissues such as Purkinje fibres and ventricular muscles. This reduction in the rate of depolarisation is believed to be due to decrease in the availability of fast Na^+ channel in cardiac cell membrane and myocardial depression.
ii. The duration of action potential and effective refractory (Fact file-II) period is decreased, leading to ventricular tachycardia, fibrillation, ectopics, etc.
iii. The ratio of effective refractory period and duration of action potential is increased.
iv. Bupivacaine depresses the rapid phase of depolarisation to a greater extent than lignocaine.
v. The rate of recovery from the use dependent block is slower in bupivacaine than lignocaine. This slow rate of recovery results in incomplete restoration of some Na^+ channel and less availability of it between two subsequent action potential. In contrast, recovery from lignocaine is complete. The effect of this differential recovery explains the antiarrhythmic properties of lignocaine and arrhythmogenic property of bupivacaine.
vi. The LA agents prolong the conduction time and thus increase the PR interval and the duration of QRS complex.
vii. The Extremely high concentration of local anaesthetic agents depress the spontaneous pacemaker activity in the SA node, causing sinus bradycardia and sinus arrest.
viii. All the LA agents have dose dependent negative inotropic action on cardiac muscles. This negative inotropic effect on myocardium is due to the inhibition of release of Ca^{2+} from the sarcoplasmic reticulum and also inhibition of Na^+ currents.

FACT FILE- II

The cardiac toxicity of the more potent LA agents such as bupivacaine appears to differ from that of lignocaine in the following ways:

i. The CC/CNS ratio, i.e., the ratio of the dose that is required to produce cardiac collapse (or toxicity), and the CNS toxicity is lower for bupivacaine than lignocaine.
ii. Ventricular fibrillation or any other ventricular arryth-mia usually occurs following IV administration of the bupivacaine, but not lignocaine.
iii. Cardiac resuscitation is more resistant following bupivacaine induced cardiac collapse than that of lignocaine.
iv. Pregnant patients are more sensitive to cardiac toxicity of bupivacaine than lignocaine.
v. Cardiac toxicity of bupivacaine is markedly potentiated by acidosis and hypoxia.

Local tissue toxicity

The volume and concentration of LA agent used clinically rarely produce localized nerve damage. But the evidence of local neurotoxicity, caused by LA agents is occasionally seen and depends on the type of agent used (the ester linked may be more neurotoxic than the amide linked anaesthetics), its concentration, the site of injection, osmolarity and pH of the solution, and the presence of other certain additives with it such as vasoconstrictors, antioxidants, preservatives, etc. Electron microscopy studies indicate that the perineuronium, Schwann cells and axons themselves may be damaged due to the neurotoxicity of LA agents. The advanced age and diseased states of the nervous tissue also enhance the susceptibility of LA agents to the neurotoxicity. The neurotoxicity in clinical practice is most commonly seen with spinal anaesthesia. Adrenaline has also been investigated as a possible contributor to the local anaesthetic neurotoxicity. The suspected mechanism is decreased intraneural blood supply due to vasoconstriction by adrenaline. Admixture of LA agent with antioxidant, such as sodium bisulphite, in the presence of a low pH has also been shown to be neurotoxic. So, for a safer and more effective alternative to these commercial solutions, adrenaline may be added to local anaesthetics freshly before use. There are many reports of inadvertent needle penetration of the globe of eyeball during peribulbar or retrobulbar block which is followed by injection of local anaesthetic agent in clinical concentration intraocularly. But, the retina which is a specialized nerve tissue did not undergo toxic changes in these circumstances. Concentration of lignocaine required to produce irreversible conduction blockade and permanent damage of nerve fibre in experimental conditions overlap the concentration which is used clinically, such as 2% lignocaine. But, practically this does not happen. This is because LA agents are not applied clinically directly to the nerve fibre in such concentrations.

So, although the LA is injected clinically at a much higher concentration than their physiological effective range, but they are usually diluted in the tissues during the process of transport from the site of injection to the site of action and hence no harm is produced. If this dilution does not occur then a permanent neural deficit do result. Thus, application of 5% lignocaine in hyperbaric solution, through a narrow intrathecal catheter is associated with high incidence of cauda-equina syndrome. However, anaesthetists should keep in mind that the concentrations of marketed LA solutions are neurotoxic and their dilution in tissue is essential for safe use.

Continuous spinal anaesthesia, using a micro catheter is associated with a high incidence of neurotoxicity, such as

radicular irritation, cauda equina syndrome, etc. Studies suggest that microcatheter facilitates a localized deposition of high concentration of drug which are inadequately dispersed or diluted in the CSF, leading to direct contact of a high concentration of drug around the sacral roots and consequent neurotoxicity.

THE ADJUVANT DRUGS TO AUGMENT THE CLINICAL EFFECTS OF LOCAL ANAESTHETICS

The most commonly used adjuvant drugs with LA agents to increase their efficacy and duration of action are adrenaline, noradrenaline, felypressin, hyaluronidase and sodium bicarbonate.

ADRENALINE

By its α-stimulant action, adrenaline constricts the vessels at the site of injection of LA agents and thus reduces its absorption through the blood. So, the local anaesthetic action is prolonged, the depth of block is increased and the toxicity of drug is reduced. As a whole, the quality and reliability of the block are improved. Adrenaline added to the local anaesthetic solution also provides a marker for inadvertent intravascular injection of it. Other vasoconstrictors, such as norepinephrine, phenylephrine, etc., also have been used with LA agents, but they are not superior than adrenaline in this purpose. The α-adrenergic receptors in spinal cord are also known to activate the endogenous analgesic mechanism and thus adrenaline also increases the depth of analgesic action of LA agents in the central neuraxial block. Therefore, where prolonged block is necessary, the addition of adrenaline with local anaesthetic agents reduces the number of repeated doses of it, and thus delays the onset of chronic toxicity and tachyphylaxis of the LA agents. Particularly, it is very valuable in highly vascular areas, e.g intercostals space, pelvic floor etc., than the less vascular areas e.g. epidural space. So, the aim of use of adrenaline differs from time to time. Sometimes it is to reduce the toxicity and sometimes it is to prolong the effect of LA agent. However, the presence of adrenaline in the LA solution makes the injection more painful. It also increases the chances of subsequent local tissue oedema and necrosis, as well as delays the wound healing by reducing the oxygen supply and enhancing the O_2 consumption in the injected area. Sometimes, the LA agent with adrenaline may raise BP and promote arrhythmia in susceptible individuals. The effect of adrenaline on long acting drugs, such as bupivacaine and etidocaine are less marked. In dentistry, always some form of vasoconstrictor is essential with most LA agents to diminish the bleeding during extraction of teeth. The inclusion of adrenaline in LA solution necessitates addition of antioxidants such as sodium metabisulphite or ascorbic acid. This is because adrenaline is stable in acidic solution only and this is provided by Na metabisulphite or ascorbic acid. But these agents reduce more the pH of LA solution, even less than 4 and increases the toxicity. In Britain, bupivacaine with adrenaline contains fewer additives and the pH is around 4.5 (Fact file- III).

Dose

Adrenaline should not be used in concentration more than 5 µg/ml (1:200000) which causes optimal degree of vasoconstriction. But, in dentistry as the total volume of drug used is small, so a higher concentration of adrenaline, such as 12.5 µg/ml (1:80000) is used. When injected IV accidentally, adrenaline is more dangerous than the local anaesthetic itself. If the total volume of local anaesthetic agent containing 100 to 150 µg of adrenaline is inadvertently injected intravenously, then it produces severe systemic effects such as tachycardia, arrhythmia, ventricular fibrillation, sweating, etc. for a brief duration. But, in a correctly placed block adrenaline is absorbed slowly from the tissue and no systemic effect occurs. Adrenaline is contraindicated in patient (i) taking certain antihypertensive drugs, (ii) taking tricyclic antidepressants, (iii) with thyrotoxicosis, (iv) for digital block, (v) for penile block, etc. Its use may be dangerous in epidural analgesia or anaesthesia for anterior spinal artery syndrome.

FACT FILE- III

Advantages and disadvantages of addition of vasoconstrictors in local anaesthetics may be tabulated as follows:

1. Prolongs the duration of action by decreasing the rate of removal from the site of injection in the circulation.
2. Reduces the systemic toxicity.
3. Increases the dose of the drug.
4. Increases the chances of local tissue oedema and tissue necrosis.
5. Delays wound healing by decreasing the oxygen supply, while increasing its consumption in the affected area.
6. Makes the injection more painful.
7. Increases the blood pressure and chances of arrythmias in susceptible persons.

NORADRENALINE

It is also an α stimulant, but less potent than adrenaline. So, in dentistry for the purpose of vasoconstriction and to reduce bleeding noradrenaline in a high dose such as 20 to 40 µg/ml (1:50000 to 1:25000) may be necessary. But this high doses of noradrenaline produces severe hypertension.

FELYPRESSIN

It is a synthetic polypeptide, related to vasopressin. As a vasoconstrictor it is also suitable agent like adrenaline, but less toxic. For example, it produces no changes in CVS in conditions where adrenaline in the dose of 12.5 is likely to produce tachycardia. With prilocaine it is more effective in prolonging the action of LA agents with less toxicity than adrenaline.

HYALURONIDASE

The enzyme hyaluronidase is frequently added to local anaesthetic agents for

regional opthalmic anaesthesia to promote the spread of drug (LA agents) through the intraorbital tissues. It breaks down collagen bonds and thus allows the anaesthetic solution to spread across the fine septal barriers of connective tissue. This action is accomplished by the reversible hydrolysis of hyaluronic acid which is the cement substance of intercellular connective tissues. However, to maintain the full activity of the product, refrigeration is important. Prolonged exposure of hyaluronidase to room temperature (> 48 hours) results in deterioration of enzyme potency. Autoclaving of solutions also results in destruction of the enzyme strength.

Hyaluronidase is added to the local anaesthetic solution in a concentration of 7.5 to 15 turbidity units/ml. Higher concentrations of it have no added advantage. Prior to its introduction, the volume of local anaesthetic agent injected into the orbital cavity for opthalmic regional anaesthesia was limited. This is due to the raised intraorbital and subsequently intraocular pressure as the LA solution does not spread quickly. Then the greatly improved standards of effective local anaesthesia for opthalmic surgery (especially cataract extraction), without compromising the intraocular pressure was made possible by adding hyaluronidase with the large volumes of LA injection. However, hyaluronidase reduces the duration of anaesthesia. This is because it increases the spread of LA agent and absorption and subsequently increases its absorption through the blood vessels. But, adrenaline reverses that tendency. It has allergic potential and is more myotoxic than enzyme free solutions. However, the use of hyaluronidase enzyme is not a substitute for less precise anatomical knowledge and poor technique for high quality opthalmic regional anaesthesia as it only facilitates the spread of LA injection along the path of least resistance of tissue. So, the LA solution should be placed accurately within the appropriate compartment. Hyaluronidase does not enhance brachial plexus block, nor does it influence the plasma levels of local anaesthetics agents.

Sodium Bi-carbonate

The tissue penetration and onset of action is enhanced by adjusting the pH of local anaesthetic solution towards the unionised base by the addition of small amounts of sodium bicarbonate. For each agent there is a pH at which the amount of unionised molecules (which only penetrate the cell membrane) of LA agent in solution becomes saturated. Increase in pH beyond that point results in the precipitation of the free base after which no further clinical benefit is achieved. Infact, a nuisance factor, such as blockage of needles by free base precipitate creates problems. There are also many literatures which are equivocal about the effectiveness of pH adjustment of LA agents by just mere adding $NaHCO_3$ in LA solution in various clinical circumstances. So many anaesthetists fail to see any benefit in their practice, after pH adjustment of local anaesthetics with sodium bicarbonate. However, alkalinised solutions should be used within 6 hours of their preparation. There is definite lesser pain during injection, when bicarbonate is used with LA agents.

GENERAL CONSIDERATION

Onset of Action

The speed of onset of block by a local anaesthetic agent is the specific property of that individual agent. But it also depends on the concentration of that particular agent. For example, (i) 0.25% bupivacaine has slow onset of action. But increasing the concentration to 0.75% hastens the onset of action. Beyond that concentration limit, the onset of action does not improve further (ii) Chloroprocaine's (pKa 9) onset of action is slow. This is due to the less availability of unionised molecule in normal tissue pH. But its low systemic toxicity allows its use in higher concentration (3%), and thus obviously improves the onset of action. So, in clinical use, 3% chloroprocaine has faster onset of action than 2% lignocaine.

Duration of Action

As we know that the duration of action of LA agents depend on the peripheral vascular effects of that agent, but most LA agents have biphasic effects on the vascular smooth muscles. At a low concentration these agents tend to cause vasoconstriction and at clinical concentrations they cause vasodilatation. Lignocaine is a potent vasodilator than mepivacaine and prilocaine, and has a shorter duration of action than these two. Pial vessels are dilated by bupivacaine, but constricted by ropivacaine.

Differential Sensory and Motor Block

Differential block means sensory block without affecting the motor nerves. This is ensured only with lower concentration of local anaesthetic agents. Bupivacaine and etidocaine profoundly have this property. Bupivacaine in a concentration of 0.125% produces adequate antinoception by affecting only the sensory fibres and without profound inhibition of motor activity. So, bupivacaine is widely used epidurally for obstetric analgesia and for post operative pain management without muscle weakness.

There are two probable explanations for this differential block:

i. The length of nerve fibre which is exposed to LA drug in epidural space can explain clinically the differential block. Because if the drug-exposed region of a nerve fibre is longer, then it yields a block by lower concentration of LA drug which is found in case of sensory nerve fibre. However, this does not explain the functional differential loss from peripheral nerve block.
ii. Selective ability to inhibit Na^+ channels over K^+ channels by lower

concentration of LA agent, which itself can produce a differential block. Because these channels are present in very different proportions in different types of nerves.

Site of Injection

The most rapid onset but shortest duration of action occurs following intrathecal or subcutaneous administration of the LA agent. Longest latency of onset and prolonged duration of action are observed following brachial plexus block. For example, bupivacaine in intrathecal route has onset of action within 5 minutes and duration of action is 3 to 4 hours. But, in brachial plexus block the onset of action of bupivacaine is 20 to 30 minutes and duration of action is ±10 hours.

Explanation

Lack of connective tissue sheath around the spinal nerve and deposition of drug in the immediate vicinity of the cord and the nerve are responsible for this rapid onset of action. But relatively small amount of drug used for intrathecal block is responsible for short duration of action. On the other hand, in brachial plexus block LA agent has to diffuse through various tissue barriers, before reaching the nerve which causes delayed onset of action. This also needs a large volume of drug and this larger dose is responsible for prolonged action.

pH Adjustment of Local Anaesthetic Solution

Addition of $NaHCO_3$ to the LA solution causes rapid onset of action. This is because increase of pH increases the amount of drug in unchanged base form and enhances its diffusion across the cell membrane, resulting in a more rapid onset of action. It happens with bupivacaine also. But till now, there is a controversy about the efficacy of technique of carbonation (just merely adding $NAHCO_3$ in acidic LA solution. I do not believe in this process because if causes precipitation) and pH adjustment of LA agent.

Mixture of Local Anaesthetics

The use of mixture of LA agents has become popular in recent years. The basis of this mixture is to compensate the delayed onset of action of one LA agent by early onset of action of another and also to compensate the shorter duration of action of one LA agent by longer duration of action of another. But recently, confusing results have come to the forefront. For example – a mixure of 3% chloroprocaine and 0.5% bupivacaine was used to produce short latency and prolonged duration in brachial plexus block. But, subsequent studies indicate that duration of epidural anaesthesia produced by this mixture is significantly shorter than bupivacaine alone. However, the clinicians should be cautioned not to use the maximum doses of two LA agents in the mixture, with the mistaken belief that toxicities of these agents are independent.

Pregnancy

Except mechanical factors (dilatation of epidural veins causing decreased epidural space and subsequent greater spread of local anaesthetic agent in pregnancy) increased sensitivity of local anaesthetic agent during pregnancy due to alteration in the hormonal level causes greater intensity of epidural anaesthesia. However, greater spread of epidural anaesthesia (the cause of which is explained above) only occurs during 1st trimester of pregnancy.

Pharmacokinetic Alterations of LA Agent by Patient's Age

Patient's age influences the pharmacological character of LA agent. For example half life of lignocaine, following IV administration is twice in old age than in young adults. Newborn infants have immature hepatic enzyme system and so they experience a prolonged elimination half life of lignocaine and bupivacaine. On this basis, a maximum infusion rate of 0·4 mg/kg/hr for bupivacaine in adults during epidural anaesthesia has been proposed. Whereas during continuous epidural anaesthesia by bupivacaine the rates of infusion for neonates and young infants should not exceed 0.2 mg/kg/hr. Similarly lignocaine infusion in neonates shouldnot exceed 0.8 mg/kg/hr.

Methaemoglobinaemia

Large doses of prilocaine is associated with methaemoglobinaemia. In general, 600 mg of prilocaine is required for development of clinically significant levels of methaemoglobinaemia. This is because metabolism of prilocaine in liver results in formation of O-toludin which is responsible for oxidation of Hb to methaemoglobin. This methaemoglobinaemia is spontaneously reversible or may be treated by IV methylene blue. The effect of methaemoglobin is that the patient appears to be cyanotic, but has normal oxygen saturation level. The effect of methaemoglobin on oxygen carrying capacity is not so important in a healthy adult, but can be significant in infants. So, prilocaine is generally avoided in infants.

SUMMARY

The local anaesthetic agents act by causing selective reversible restriction of permeability of sodium ions with free movement of potassium. Usually the sodium ion is restricted to the extracellular space except when the sodium ion channels are open, allowing diffusion through it. Potassium ion is freely diffusable across the membrane. But it selectively accumulates inside the nerve cell to preserve the electrical neutrality by balancing the cations. In an unexcited state, the electrical potential inside the cell is negative in reference to the outside of the cell. During conduction of impulse (action potential) ion gradients are altered along the nerve cell membrane by opening of the sodium ion channels.

Thus, sodium enters into the cell and increases the intracellular Na^+ concentration. This is called depolarisation of the cell. The Na^+ channels are lipoprotein in nature and are embedded in the cell membrane of nerve fibre along the entire width. The gate that opens and closes these channels is present on the axoplasmic side. The channel is most susceptible to LA agent in an open active state and remains inactive in this open state, preventing further depolarisation.

The changes in configuration of Na^+ channel is voltage dependent.But the LA molecule prevents this voltage shift which activates the Na^+ channel. So, LA molecule stabilizes the Na^+ channel in nonconducting configuration.

The LA molecule also has a minor effect on both potassium and the Ca^{2+} channels, which modulate the action of Na^+ channels. However, the K^+ and Ca^{2+} channel blockade by clinically available LA agents is so low that they do not contribute significantly to the conduction blockade.

The LA molecule in the nonionic form crosses the lipophilic hydrocarbon part of the nerve cell membrane to reach the axoplasmic end of Na^+ channel. In axoplasm the LA molecule becomes active in its ionic state and attach to the hydrophilic LA receptors of the Na^+ channel. This dual requirement of a LA molecule determines the chemical characteristic of local anaesthetic agent. One LA molecule blocks only one Na^+ channel.

When the cell membrane is rapidly depolarised from the resting –70 mv to +20 mV, then there is a rapid increase in the sodium channel permeability. The greater the magnitude of depolarisation, the greater is the permeability. Beyond +20 mV there is no greater increase in sodium conductance. This is because there is a definite number of Na^+ channels in the membrane. Also like the neuromuscular junction the conduction of nerves also have considerable reserve capacity. This is explained by the fact that even when 80 to 90% of the sodium channels are blocked, conductance of nerve impulses continue, although at a slower rate.

Local anaesthetic molecules have an aromatic ring (lipophilic) connected to a tertiary amine (hydrophilic) by a short alkyl chain and a hydrophilic bond (amide or ester). So, LA agents are amines and are called as amino-amides or amino esters. All the LA molecules are amphipathic,i.e., possessing both lipophilic and hydrophilic action at opposite sides of the molecule. They are weak bases and are able to accept proton or H^+ to change into a cationic form at pH below their pKa value. This can be calculated from the following formula:

$$pKa = pH + Log (cation / free\ base)$$

The lipophilic side of the LA molecule provides most of the lipophilic properties of the molecule. Its size restricts the movement of the amine (hydrophilic) group to an axis perpendicular to the aromatic ring. This linear relationship between the amine and aromatic group seems necessary to block the hydrophilic binding site of the receptor by the hydrophilic amine group. This also explains the movement of the amine group towards the receptor, while the aromatic lipophilic group is still embedded in the lipophilic nerve cell membrane.

The intermediate chain of LA molecule allows the reversible action of clinically useful LA agent. Since, without the intermediate chain and amide-ester bond, metabolism would be very difficult and toxicity would be unacceptable. Potency of LA increases as lipid coefficient of these lipophilic bonds increase.

Amines (hydrophilic group) are situated at the side of the molecule. It accepts proton and in cationic state is mostly involved in blockade of Na^+ channel. It is probable that the ionic movement of the hydrophilic group away from the lipophilic side of the molecule orients the amine group into a configuration that fits into the sodium channel receptor.

The lipophilic portion of the LA agent is involved in the molecular passage through the lipid membrane. So this facilitates the penetration of perineurium and as well as the nerve cell membrane. The bigger the lipophilic portion, greater the potency of the LA agent. The equilibrium of dissociation between the ionic and the nonionic forms of the LA molecule occurs inside the nerve cell. The hydrophilic group in the ionic form is the part of the molecule which is involved in entering the Na^+ channel to interrupt the Na^+ conduction. A specific distance is required between these two different groups and this is served by the intermediate chain. If the length is too short or too long, then there is minimal or no local anaesthetic activity.

Between the LA molecule and the receptor at the Na^+ channel a semispecific binding of reversible nature occurs. The speed of entry and exit of the LA molecules in these Na^+ channels is agent specific. The short and intermediate acting LA agents are short-in and short-out of Na^+ channels in character (e.g. lignocaine, procaine, mepivacaine). So, they are of early onset and shorter duration of action. The long acting agents (e.g. bupivacaine) are slow-in and slow-out of the Na^+ channels in character. So, they have a delayed onset and a longer duration of action. The bond between the receptor and the molecule of LA agent is weak in case of closed channels, but strongest and most rapid in open sodium channels.

When the lipophilic butyl group is added to the aromatic ring of procaine, then tetracaine is created which is 40 times more potent than procaine. Thus, 40 times increase in potency confirms that the lipophilic property of the LA molecule is the principle determinant of potency. If the same butyl group is added with a hydrophilic tertiary amine group, then the resultant molecule has a potency lower than procaine. It may be due to that, the hydrophilic region (receptor) near the Na^+ channel orients the hydrophilic amine

group of the LA molecule in that channel. So, the addition of the lipophilic butyl group with the hydrophilic amine group of the LA molecule prevents its orientation in the Na^+ channel and reduces the potency.

Protein binding capacity of LA agent determines the duration of action. Agents with greater protein binding capacity have a greater attraction for receptors and remain binding with the Na^+ channel for a longer period of time, causing longer duration of action, e.g. bupivacaine, etidocaine etc. Agents with poor protein binding capacity such as procaine, chloroprocaine, etc. are readily washed out from the channel causing shorter duration of action.

Regarding the alkalinisation by adding sodium bicarbonate to the LA solution, wherever it is possible without precipitation (because addition of sodium bicarbonate to lignocaine hydrochloride causes precipitation of lignocaine bicarbonate), decreases the latency to onset (has been reported in numerous series). For example, in mepivacaine where the pKa value is 7.6 and pH of commercial preparation is 5.5, then alkalinization is possible without precipitation. This alkalinisation increases the concentration of the unionised which is from less than 0.1% to about 40%. However, in more lipophilic agents like bupivacaine precipitation limits the amount of alkalisation and results are more equivocal.

Regarding toxicity, of LA agents the main determinants of toxicity include the total concentration versus free concentration which is again determined by the protein binding capacity and ionisation. Subarachnoid injection of a LA agent for spinal anaesthesia is associated with its lowest blood level.

Regarding relation between the lipid solubility and toxicity, the CNS toxicity of the LA agent in clinical setting is directly related to the lipid solubility. Penetration of the lipid membrane is a limiting step of CNS toxicity of the LA agent. So, more lipid soluble means more CNS toxic. While highly lipid soluble agents are more potent local anaesthetic agents, but their therapeutic and toxic ratio is narrow and degree of safety is less. Toxic form of a LA agent is the unionic unbound fraction in the blood which is available for penetration of the blood brain barrier. The early signs of CNS toxicity are reported in patients, when the unbound fraction begins to cause ionic changes within the CNS. Intra arterial injection of a small amount of LA agent cause vary rapid onset of massive CNS reaction, because the agent is delivered directly in high concentration to the CNS.

Regarding tissue toxicity, all the LA molecules are directly cytotoxic to nerve cells at some concentration. The balance between the ideal concentration to facilitate conduction block and cause nerve damage determines its therapeutic safety index. In addition to the cytotoxicity of anaesthetic agents itself, various buffers and preservatives added to the LA agents have been found in some cases to be cytotoxic.

Regarding allergy, true allergy to local anaesthetics is rare. The most common allergies are due to the ester agents and their metabolites like para-aminobenzoic acid (PABA). This may be due to ubiquitous presence of this aromatic PABA molecule in food preservatives, pharmaceuticals, cosmetics and in sunscreen lotions. Thus, previous exposure to PABA through these chemical agents may prime the immune system in some individuals for an immunologically mediated response to the metabolites of ester group of local anaesthetic agent.

Regarding the cardiac toxicity the specific CVS depression with highly lipid soluble agents such as bupivacaine and etidocaine is not only associated with their increased lipid solubility, but the specific binding of these agents to the cardiac conduction system also magnifies their cardiac toxicity. Bupivacaine has a quinidine like blocking action on the conduction system of heart. This increases activity in re-entrant pathways and predisposes the heart to the development of ventricular arrhythmia.

INDIVIDUAL DRUGS

Procaine and Procainamide

Procaine is a local anaesthetic agent with poor penetrative power and a short duration of action. This is due to its vasodilator activity and high pK value. This high pK value renders procaine highly ionised at a physiological pH of 7.4. So, after injection it is rapidly absorbed into the circulation and has less penetrative power in the tissues and nerve. Hence it is inactive as a surface anaesthetic. It is less potent than lignocaine and its duration of action is half than that of lignocaine. But, it can be greatly extended by the addition of adrenaline.

It is hydrolised in the plasma by pseudocholinesterase and in the liver to PABA (para-aminobenzoic acid) and di-ethyl aminoethanol.

There are several drug reactions with procaine or procainamide. These are :

i. PABA which is one of the metabolites of this group of LA agents is a potent inhibitor of the bacteriostatic action of the sulphonides.
ii. PABA itself acts as an allergen.
iii. PABA prolongs the effect of suxamethonium by competing for the same enzyme, i.e. pseudocholinesterase which is responsible for termination of action of them by hydrolysis.
iv. Anticholinesterase agents potentiate the toxicity of procaine and procainamide. So, it should not be used in patients suffering from myasthenia gravis.

Procaine and procainamide has antiarrhythmic effects like quinidine. But procaine is replaced by procainamide which too has antiarrhythmic properties and is not broken down by pseudocholinesterase, like procaine. At present, procaine has no indication for use LA or antiarrhythmic agent. It has been replaced by many newer and better drugs.

Lignocaine

It was first synthesised in 1943 by Lofgren in Sweden at the AB Astra laboratory, but was first introduced in clinical practice in 1948. It is of moderate potency and intermediate duration of action which varies with the site of injection, concentration and volume of drug, presence or absence of adrenaline, etc. It causes local vasodilatation which again causes quick absorption of it through the circulation and reduces the duration of action. Repeated injection of lignocaine causes tachyphylaxis. Now, it is one of the most widely used local anaesthetic agent in the world. It works rapidly and reliably to give both motor and sensory blockade. It can be used virtually by any route and is a standard antiarrhythmic agent when given IV without any preservative

Lignocaine is commonly marketed as its hydrochloride salt. But carbonate of lignocaine has remarkable penetration power, rapid onset of action and high incidence of deep motor and sensory blockade. Absorption of lignocaine through mucosal surface is very rapid and gives rise to high blood level. Absorption of it from the inflamed urethra is also as good as IV injection. Iantophoretic system (a needle free drug delivery system) for delivery of lignocaine and epinephrine is also available. But this system is generally used for superficial dermal procedures and provides anaesthesia up to the depth of 10 mm.

As lignocaine stabilises the membrane of damaged and excitable cells, so it is used for the treatment of ventricular ectopic foci. In therapeutic antiarrhythmic doses, it causes no change in the heart rate, does not depress the conduction in Purkinje tissue, does not widen the QRS complex and has no apparent myocardial depression. Instead, improvement in cardiac output and BP is observed when lignocaine is used in the treatment of dysrhythmias. But, it is less useful in supraventricular dysrhythmias. Great value of lignocaine is observed in the acute treatment of ventricular dysrrhythmias after MI and cardiac surgery and this is due to the lack of myocardial depressant effect of it.

Doses

Lignocaine in the concentration of 0.5 to 1% is used for local infiltration anaesthesia. The Maximum dose of lignocaine for infiltration is 4.5 mg/kg without adrenaline, and when adrenaline is used this amount can be increased by one–third. When extensive block with high volume of drug is required, then 0.25% lignocaine with adrenaline should be used. For intravenous regional anaesthesia 40 ml of 0.5% lignocaine without adrenaline is used. 1% lignocaine is sufficient for local nerve block. A concentration of 2% lignocaine with adrenaline (1:80,000 or 12.5 µg/ml) is used in dentistry. 1 to 2% lignocaine with or without adrenaline (1:200,000 or 5 µg/ml) is used in epidural anaesthesia. For surface application 4% lignocaine is used as a liquid or 10% as a spray or 5% as a gel.

For cardiac dysrhythmias, mainly ventricular, lignocaine is used in the dose of 1 mg/kg IV as bolus, then 4 mg/kg for the next 20 minutes which is gradually slowed down to 1 mg/minute as tissues begin to take up lignocaine less rapidly. Such infusion continued for days may give rise to systemic toxicity.

Safe upper limit of the dose of lignocaine for infiltration anaesthesia is of much dispute. Most commonly accepted view is 200 mg plain and 500 mg with adrenaline. But, here there is no mention of body weight and site of injection. Another recommended maximum safe dose of lignocaine is 6 mg/kg, but is possibly lesser for plain solution in vascular areas, while greater with adrenaline in less vascular areas. Toxic symptoms of lignocaine may occur at a plasma level of 3 to 5 µg/ml. Yet such a level is not uncommonly produced after a single shot epidural block using 20 ml of 2% lignocaine without adrenaline.

Lignocaine is metabolised in the liver to mono ethylglycine xylidide and glycine xylidide. The later can be metabolised further to monoethylglycine and xylidide. Both the monoethylglycine xylidide and glycine xylidide retain the local anaesthetic property.

Mepivacaine HCl

Regarding clinical activity and toxicity, mepivacaine is similar to lignocaine. But, it has a lesser inherent vasodilator property. So, duration of action of mepivacaine is 50% longer than lignocaine. The addition of adrenaline also prolongs its action by about 75%. Topically, unlike lignocaine, mepivacaine is not effective.

Bupivacaine

It was first introduced in clinical practice in 1963. Its structure is similar to that of lignocaine, except that the amine containing group is a butyl piperidine. It is 3 to 4 times more potent than lignocaine and longer lasting. Its long duration (Table 13.2) of action and tendency to provide more sensory than motor blockade has made it a popular drug for providing prolonged analgesia during labour or the postoperative pain. Analgesia for post-operative pain usually lasts for 4 hours or more when it is used through epidural route. While caudal administration of bupivacaine usually produces perineal analgesia for 8 hours or more.

When bupivacaine is given by repeated injections, then tachyphylaxis is much less common than that of lignocaine. Thus, safe and effective analgesia can usually be provided indefinitely (for several days) by taking the advantage of catheter and continuous infusions through if by epidural route.

Bupivacaine is more cardiotoxic than equi-effective doses of lignocaine. It causes severe ventricular arrhythmias and myocardial depression, than lignocaine if there is sudden inadvertent IV injection. Lignocaine and bupivacaine both rapidly block cardiac Na^+ channels during systole. But, bupivacaine dissociates from these Na^+ channels much more slowly than

Table 13.2: Physicochemical properties of local anaesthetics

	Procaine	*Lignocaine*	*Mepivacaine*	*Bupivacaine*	*Etidocaine*
Year of introduction	1905	1943	1957	1963	1972
Site of metabolism	Plasma (Ester hydrolysis)	Liver (Amide hydrolysis)	Liver	Liver	Liver
Onset of action	Slow	Fast	Fast	Intermediate	Fast
Duration	Short	Intermediate	Intermediate	Long	Prolonged
Equieffective anaesthetic concen	2% (Slow potency)	1% (Intermediate potency)	1% (Intermediate potency)	0.25% (High potency)	0.5% (High potency)
Protein binding (Duration of action)	6% (short)	65% (Intermediate)	75% (Intermediate)	95% (Long)	95% (Long)
Dissociation constant (pKa)	8.9	7.7	7.6	8.1	7.7
Onset time	Slow onset	Fast onset	Fast onset	Intermediate onset	Fast onset
Tissue penetration	Poor	Good	Good	Intermediate	Good
% base at pH of 7.4	2%	35%	35%	20%	35%
Lipid/water	0.6	2.9	0.8	27.5	14.1
Partition coefficient (Anaesthesia potency)	Low potency	Intermediate potency	Intermediate potency	High potency	High potency
Maximum single dose (plain solution)	800 mg	250 mg	300 mg	150 mg	300 mg
Maximum single dose (with adrenaline)	1000 mg	500 mg	500 mg	250 mg	400 mg

lignocaine during diastole. So, significant number of Na^+ channels remain blocked at the end of diastole with bupivacaine. Thus, this block caused by bupivacaine is cumulative and is responsible for more cardiac toxicity than lignocaine. A part of cardiac toxicity produced by bupivacaine is also mediated through centrally, as it is observed that small quantities of bupivacaine injected in the medulla produce malignant ventricular arrhythmias.

Different doses of bupivacaine in spinal and epidural anaesthesia is discussed in their specific chapters. Bupivacaine crosses the placenta, but very little in amount. So, it has a unique value in obstetrics. It is used extensively for lumbar epidural blockade in the concentration of 0.125 to 0.5%. Bupivacaine in a concentration of 0.125%, usually produces only sensory blockade, without affecting the motor function. So, for painless labour or walking epidural, where motor function is preserved but only analgesia is provided, then 0.125 to 0.25% of bupivacaine is the choice. When the concentration of bupivacaine is gradually increased from 0.125 to 0.25%, then there is gradually lesser chance of failure of sensory blockade, but more chance of motor blockade and vice versa. For a single dose epidural, the maximum safe dose of bupivacaine is 2 mg/kg. To provide prolonged or continuous analgesia, 30 mg bupivacaine at 2 hours interval is sufficient and this dose can be repeated for indefinite period. Maximum safe dose of bupivacaine is 2 to 3 mg/kg without adrenaline for infiltration. When adrenaline is added this amount can be increased by one-third.

Etidocaine HCl

Etidocaine is an engineered modification of lignocaine molecule with high potency and prolonged duration of action. It is mainly used in the Scandinavian countries and USA. Unlike bupivacaine, it has a rapid onset of action. So, because of its fast onset and prolonged action, compared to bupivacaine, etidocaine is in vogue in opthalmological practice. It is used clinically in 0.5%, 1% and 1.5% concentrations for any type of regional and infiltration block. This drug can also be used topically, but is rarely used by this route. It is less potent than bupivacaine in producing sensory block, but is more potent for motor block. So, it is usually recommended where prolonged epidural with high degree of motor blockade is necessary. For this purpose 20 ml of 1% etidocaine with adrenaline (1: 200,000 or 5 µg/ml) is used and the motor blockade lasts for 3 to 5 hours, though the sensory blockade is not always adequate. Hence, for obstetric pain relief etidocaine is less reliable than bupivacaine. This is because no concentration of etidocaine can produce effective sensory blockade without affecting motor block.

Prilocaine

It emerged first in 1960 from the AB Astra laboratory, though it had already been synthesised previously by Lofgren. Chemically it is an amino-amide compound and its pharmacological profile is similar to that of lignocaine. But its penetrative power is very good. It can be used for all types of local blockade in the same concentration like lignocaine. When used in epidural anaesthesia it produces higher incidence of motor blockade and a longer duration of action than lignocaine. However it has lesser vasodilator action

than lignocaine and thus used without any vasoconstrictor. For its increased volume of distribution (high therapeutic index) it is less CNS toxic and so also very suitable for IV regional anaesthesia. Administration of prilocaine gives rise to much lower plasma concentration than an equal dose of lignocaine. This is because of its more rapid metabolism and greater tissue uptake, due to less protein binding. It is only about 2/3 as toxic as lignocaine after a single dose. It is considerably less cumulative.

Prilocaine is unique among all the local anaesthetics for its propensity to cause methaemoglobinaemia. It is due to the metabolism of its aromatic ring to O-toludine in liver which induces methaemoglobinaemia. The development of methaemoglobinaemia after local administration of prilocaine is dependent on the total dose administered which is usually above 8 mg/kg of body weight. In a healthy person it is not a problem and can be treated by methylene blue in the dose of 1 to 2 mg/kg of body weight by infusion. However, methaemoglobinaemia following prilocaine has restricted its use in obstetric anaesthesia. The maximum concentration of methaemoglobin normally occurs between 4 to 6 hours after administration of prilocaine. Then it decreases gradually to the normal value in 24 hours. Though the occurance of methaemoglobinaemia contraindicates the use of prilocaine in many circumstances, but a transient rise in its level occurs in most of the people after its use and is harmless.

Ropivacaine

It is a derivative of bupivacaine and consists of a single enantiomer such as the S-stereoisomer. Whereas, bupivacaine consists of both isomers and lignocaine has no stereosymmetry. Ropivacaine is intrinsically less cardiotoxic. It is cleared more quickly from circulation, if the drug is injected IV erroneously and cardiac resuscitation is easy. An important mechanism for the cardiotoxic action of any local anaesthetic is the very slow reversal of Na^+ channel from the blockade. This is the hallmark of bupivacaine, and such slow Na^+ channel reversal with bupivacaine is associated with the persistent slowing of conduction re-entry circuits, ventricular tachycardia and ventricular fibrillation. The difference between the ropivacaine and bupivacaine is that the negative inotropic potency of ropivacaine is less than that of bupivacaine and the therapeutic index of ropivacaine is greater than that of bupivacaine. Again, ropivacaine is slightly less potent and has a shorter duration of action than bupivacaine and the convulsant dose of ropivacaine is larger than bupivacaine. Cardiotoxic effect of ropivacaine in pregnancy is not greater than in the non-pregnant state which is most advantageous for it. All this makes ropivacaine a significantly safer drug for local and regional anaesthesia in obstetrics. Interestingly, it seems to be even more motor sparing than bupivacaine.

Eutectic Mixture of Prilocaine (2.5%) and Lignocaine (2.5%)

The depth of local anaesthetic action of the mixture of prilocaine and lignocaine in the ratio of 1:1 by weight is in between the topical and infiltration anaesthesia. The efficacy of this combination lies in the fact that the mixture of prilocaine and lignocaine has a melting point less than that of either compound taken alone, i.e. below the room temperature and can exist at room temperature as an oil rather than as crystal, which can penetrate the intact skin. The maximum depth of penetration of this mixture in the skin is 5 mm. Onset of action of this local anaesthetic mixture is 1 hour. It is effective for surgical procedures involving the skin and superficial structures. The components of this local anaesthetic mixture is also absorbed into the systemic circulation. This eutectic mixture of LA agent should not be used on the mucous membrane or abraded skin, as rapid absorption of their component may result in systemic toxicity.

LOCAL ANAESTHETICS LARGELY RESTRICTED TO OPHTHALMOLOGICAL USE

Topical Anaesthetics in Ophthalmology

Topical anaesthesia is very essential in ophthalmological practice. It is used for the measurement of intraocular pressure, removal of sutures and foreign bodies, and for other superficial surgeries of the conjunctiva and cornea. Topical anaesthesia is also invaluable in preparing the conjunctiva for subsequent painless transconjunctival injections. Also, like the early part of this century, many cataract surgeries by phaco emulsification technique are now done under topical anaesthesia. The onset of action of all the commonly used local anaesthetic agents as topical drop is 15 to 20 seconds and last for 15 to 20 minutes. Initial stinging sensation of the conjunctiva is the chief side effect of topical anaesthesia especially in paediatric practice. A most useful means of avoiding this stinging sensation is to use 5% proparacaine drops, diluted by a sterile balanced salt solution, prior to the instillation of full strength LA agent. Physiological corneal protective mechanism will be in abeyance in topical anaesthesia (Table 13.3).

So, any rubbing of the eye must be prohibited. Prolonged use of any topical anaesthetic agent may result in corneal toxicity. Healing is delayed and cell division with migration is inhibited by topical anaesthesia. Alteration of lacrimation and tear film instability may also occur. Certain preservatives such as benzalkonium and chlorobutanol which are present in topical anaesthetic agents may be implicated for this effect. Idiosyncratic reactions to any topical anaesthetic agent may also occur. The rate of drug absorption in topical anaesthesia is intermediate between IV and subcutaneous injection and can not be influenced by the addition of adrenaline. Therefore, topically administered LA agents are also capable of attaining clinically significant serum concentrations. Digital occlusion of the lacrimal

Table 13.3: Local anaesthetics commonly used for topical ophthalmic anaesthesia (except cocaine)

Drug	*Concentration (%)*	*Maximum dose*	*Duration (minute)*	*Corneal toxicity*
Cocaine	1 - 4	1 mg/kg (20 drops 4%)	30	+++
Lignocaine	2 - 4	4 mg/kg, (up to 60 drops, 4%)	20	nil to least
Amethocaine (Tetracaine)	0.5	5 mg total (15 drops)	20	++
Proparacaine	0.5	10 mg total (30 drops)	20	+ –
Benoxinate	0.4	4 mg total (upto 15 drops)	20	least

puncta is a useful method of preventing the drugs from entering the nasolacrimal duct and thus gaining access to further mucosal surfaces from which additional absorption can occur. In topical anaesthesia it is also important not to exceed the safe clinical dose. As serious and even fatal reactions do occur with overdosing.

Local Anaesthetics Used Primarily at Mucous Membrane and Skin

Some local anaesthetics are too irritating or too ineffective to be applied on the eye. But they are useful as a topical anaesthetic agent on skin and mucous membrane. Their preparations are effective for the symptomatic relief of anal and genital pruritus, many acute and chronic dermatoses, etc. They are sometimes combined with glucocorticoids or antihistamines. Local anaesthetics used for these purposes are dibucaine, dyclonine hydrochloride and pramoxine hydrochloride.

14 Intravenous Anaesthetics

INTRODUCTION AND HISTORY

At the beginning of 17th century, some far-sighted pioneers conceived the idea of anaesthesia through the intravenous route. But, they lacked the appropriate technology and the suitable agents for intravenous administration. So, the time delay between the pioneer's thought and the advent of appropriate technology for administration of intravenous anaesthesia was about two centuries. After that there was further delay of about five to six decades because the suitable drugs were not invented to make the intravenous anaesthesia popular. Thus, the arrival of hexobarbitone, in 1932, marked the birth of a new age of anaesthesia in which intravenous induction and its supplementation became the norm. However, during this period it results in more comfort to the patient, but not necessarily more safety.

If we go back in the past, we will see that in 1665, for intravenous anaesthesia Johann Sigismund (a German physician) first injected rude opium intravenously to produce unconciousness. Then, Francis Rynd of Dublin, in 1845, used trocar and canuula for IV administration of morphine for the treatment of trigeminal neuralgia. After that, in 1872, Pierre, a professor of physiology of Bordeann, used chloral hydrate intravenously in a patient suffering from tetanus. But, Alexander Wood of Edinburgh was the true founder of intravenous anaesthesia by first using the Ferguson syringe ('syringe' came from Greek word 'syrinx' which means a tube or pipe).

During that period intravenous ether also had been tried on animals by Nilai Ivanovitch of Russia in 1847 for intravenous anaesthesia. This was a year after Morton's use of ether by inhalation. A 2·5 to 5% solution of ether in normal saline or in 5% glucose was used by him. He also used chloroform intravenously on animals in this way.

After that barbituric acid was first synthesised by Adolf Baeyer of Munich in 1864. But its sedative and hypnotic effects were not realised at that time. Then, in Munich, diethyl barbituric acid was also synthetised by Fischer and Von in 1903. At that time, this was known as Veronal. Then phenobarbitone was discovered in 1912 at else where in the world and only oral preparation of it was used. But sommifaine was the first barbiturate to be given intravenously. It was a combination of diethyl and diallyl barbituric acids and was used in France by Bardet in 1924.

During this period, Noel and Souttar also tried paraldehyde intravenously for sedation. Intravenous morphine and hyoscine were also employed by them for 'twilight sleep' in 1916. In 1923, Bumm introduced Pernocton. While 2 years later Zerfas, in USA used sodium amytal intravenously. This was soon followed by intravenous preparation of pentobarbitone or nebutal. Magill was the first person who demonstrate their clinical effects through intravenous route in Britain. Then Johu Silas Lundy of the Mayo Clinic attemped to popularise nembutal in USA in 1931. Inbetween this time Martin Kirschner tried bromethol intravenously in 1929 with moderate success.

Then, the invention of hexobarbiturate was the great breakthrough in the history of intravenous anaesthesia. It was the first drug to make intravenous anaesthesia popular and was first used in 1932 by Helmut. He was a professor of pharmacology at Dusseldorf (German) and director of pharmacology at Beyer. The historical significance of this event also was that it was the first happy partnership between an academic house and a big business house for any invention in medical science. Later, this partnership became a model which had been copied many times for the benefit of mankind. Thus, Helmut was the true father of intravenous anasthesia, though hexobarbitone was first synthetised in 1931 by Kropp and Taub in Elberfeld. It was first used in Great Britain in 1933 by Ronald Jarman.

BARBITURATES

History

Barbituric acid was first synthesised in 1864 by Baeyer which has no hypnotic property. Then, Fisher and Von first synthesised diethylbarbituric acid in 1903 which had hypnotic property. After that in between 1903 to 1932 many barbiturates with hypnotic property came, but they were slow in onset and had a long duration of action. So, they could not be used for IV anaesthesia. Thus, upto 1932 no intravenous drug was getting a strong foothold in anaesthesia. Finally in 1932, synthesis of methylated oxybarbiturate (hexobarbiturate) set the

stage. It had very good hypnotic property with very rapid onset and short duration of action. But, it had much excitatory side effects. Then, in 1934 actual breakthrough was done by the discovery of thiopentone. However, during the first report the proper pharmacokinetic and pharmacodynamic property of this drug was not known. At that time it was thought (wrongly) that the short duration of action of thiopentone is due to its rapid metabolism in the body. Thus, at that time hexobarbitone and thiopentone was used intravenously for induction and maintenance of anaesthesia like ether and chloroform by inhalation. So, overdose of the drug was frequently used due to short action (which was though at that time due to quick metabolism from body) causing many deaths resulting from hypotension. Hence, during that period IV anaesthesia was described as 'an ideal method of euthanasia'. One such example of many deaths by thiopentone is during the treatment of multiple casualties of war by thiopentone at Pearl Harbour. So, at that time it was also thought that though thiopentone has rapid onset and short duration of action, but it was toxic. But, later it was proved that the dose and the method of administration of drug rather than the drug's inherent toxicity caused the adverse outcome. Then Brodie first demonstrated that the effect of thiopentone were quickly terminated not by the rapid metabolism in body, but by the redistribution of the drug from their sites of action to other body tissues. However, in 1960, Price explained that during prolonged and large dose administration of thiopentone as the peripheral distribution site of it approached to saturation and equilibrium, then redistribution from the effector site to the other tissues was less effective and blood concentration rose quickly which ultimately caused CVS collapse and death (Fig. 14.1).

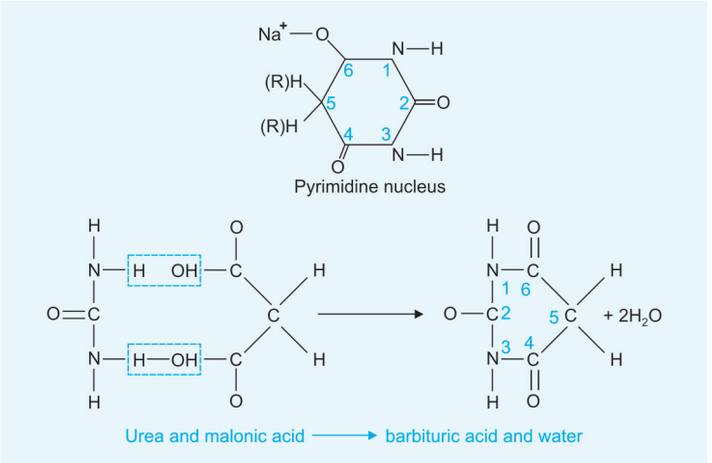


Fig. 14.1: Synthesis of urea and malonic acid

Chemistry

The barbiturates are the salt (usually Na^+) of barbituric acid. It is synthesised from urea and malonic acid. So, it is also called the malonyl urea. Barbituric acid actually has a pyrimidine nucleus. It is termed in North America by using the ending as 'al' (thiopental) and in Britain by using the ending as 'one' (thiopentone). It is available either in Keto or enol form and is acidic in nature due to the presence of H^+ at position 1. However, the Na^+ salt (at position 3) of barbituric acid is water soluble yielding highly alkaline solution. The presence of carboxyl group in the structure of barbituric acid at position 2 is responsible for the acidic character of barbiturates. This is because of the keto-enol tautomerisation, which is also favoured by its location between the two electronegative amido nitrogens. The enol form of barbiturates is favoured in alkaline solution and salts result. Barbiturates in which the oxygen atom at C_2 is replaced by a sulphur atom are called the thiobarbiturates. These are more lipid soluble than the corresponding oxybarbiturates.

Depending on the H, O, S, CH_3 in 1 and 2 position; barbiturates fall into four distinct groups as follows:

Oxybarbiturates (1 = H, 2 = O),
Methylated oxybarbiturates (1= CH_3, 2 = O),
Thiobarbituraes (1 = H, 2 = S),
Methylated thiobarbiturates (1= CH_3, 2 = S) (Fig. 14.2)

The sodium salt of thiopentone (thiobarbiturates) is a pale yellow hygroscopic powder with bitter taste. It is readily soluble in water and alkaline in property. The commercial preparation of thiobarbiturates contain 6 parts of anhydrous Na^+ carbonate.

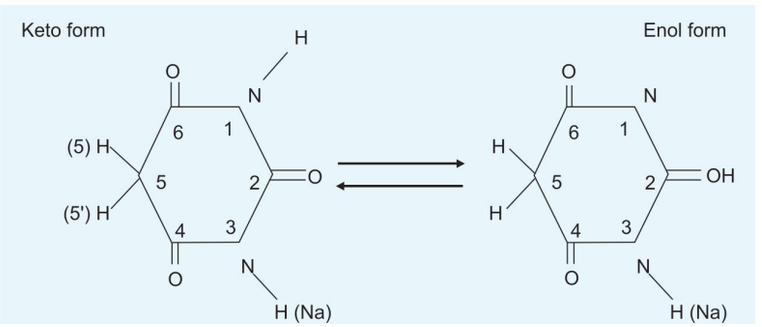


Fig. 14.2: Although, it is more correct to regard the barbituric acid as a pyrimidine derivative, but it is usually depicted in either the keto or enol form. The acidity of barbiturates is due to the hydrogen ion which migrates from the nitrogen of the position 1. In the keto and enol form of the barbituric acid the sites of substitution which are hypnotically active are identified as 1, 2 and 5. In aquous solution it dissociates into hydrogen ion and barbiturate ion. The Na-salts (in the position 3) are water soluble and can be administered parenterally

This prevents the formation of insoluble free barbituric acid from thiopentone by the reaction with atmospheric CO_2 and subsequent precipitation. The aqueous solution of thiobarbiturates is strongly alkaline and the pH of 2·5% thiopentone is about 10.5. The solution of thiobarbiturate (thiopentone) in water may remain stable at room temperature for upto 2 weeks after preparation but should not be used if they become cloudy (Table 14.1).

Structure – Activity – Relationship

The barbituric acid itself originally lacks the central-depressant activity.

i. The hypnotic activity is introduced into the barbituric acid if a side chain consisting of alkyl or aryl group (atleast if one of them is branched) is added at position 5 or 5′ in its structure.
ii. The sleep can not be produced very rapidly (in one arm-brain circulation time) after the IV injection of an effective dose of any oxybarbiturate. So, these have very limited use in clinical anaesthesia and are mainly employed as oral hypnotics and sedatives.
iii. Replacing the O of oxybarbiturates with S at position 2 produces thiobarbiturates which are more lipid soluble, and has more rapid onset and shorter duration of action. Example − Thiobarbiturates (thiopentone and thiamylal) have faster onset and shorter duration of action than oxybarbiturates (pentobarbital and secobarbital).
iv. The increased length of side chain in position 5 increases both the potency and the duration of action of barbiturates. Example, secobarbital and thiamylal is more potent than pentobarbital and thiopentone.
v. Methylation and sulphuration of barbituric acid increases the lipid solubility and the rate of penetration of barbiturates in CNS.
vi. Addition of methyl group at position 1 of oxy barbiturates (oxymethyl barbiturate) not only produce the rapid onset and short duration of action, but also increases the excitatory side effects.
vii. Methylated thiobarbiturates combine the rapidity of the onset of action and the convulsive activity of such severity as to preclude their use in clinical anaesthesia.
viii. Only thiobarbiturates and methylated oxybarbiturates are used in anaesthesia practice.
ix. The sterioisomerism has an important effect on the structure activity relationship of barbiturate. The L-isomer of pento, seco, thio and thiamylal are twice as potent as the D-isomers of it. These barbiturates are markated as racemic mixture. Methohexital has 4-stereoisomer.

Barbiturates are weak acid and in stomach (where pH is 1 or 2) they are practically unionised. Hence in aquous solution they can not be absorbed. So, their rate of absorption through gastric mucosa is related to their lipid solubility which property helps the molecules to pass through the lipid cell membrane gastric mucosal cells. Thus, methylated and thiobarbiturates are very rapidly absorbed by mouth and cause brief period of intense hypnosis when used orally as they are highly lipid soluble.

The approximate potency of the available barbiturate compounds relative to thiopentone is: thiamylal 1.1, thialbarbitone 0.5, thiobutobarbitone 0.7, methohexitone 2.5-3, enibomal 1, hexobarbitone 0.5.

Table 14.1: Classification of barbiturates

Ultra short acting	*Short acting*	*Long acting*
Methohexitone	Secobarbitone	Mephobarbitone
Hexobarbitone	Butobarbitone	Phenobarbitone
Thiopentone	Pentobarbitone	

Mechanism of Action

The barbiturates act throughout the whole CNS. In non anaesthetic doses it preferentially supresses the polysynaptic responses. Facilitation is diminished. Inhibition is enhanced. The site of inhibition of barbiturates in CNS is either the post synaptic area as for example the cortical and cerebellar pyramidal cells, cuneate nucleus, substantia nigra and thalamic relay neurons or the presynaptic area as for example the spinal cord. The enhancement of inhibition of conduction of impulses by barbiturates occurs primarily at the synapses where the neurotransmission is mediated by the inhibitory GABA neurotransmitter, acting through $GABA_A$ receptors (Fig. 14.3).

Barbiturates act mainly through the $GABA_A$ receptor complex at clinical concentration and correlate well with the anaesthetic potency of this agent. GABA is the principal inhibitory neuro transmitter in CNS which also acts through $GABA_A$ receptor. $GABA_A$ receptor has 5 glycoprotein subunit which assemble to form a internal chloride ion channel and have GABA, benzodiazepine and barbiturate binding sites. Activation of this $GABA_A$ receptor by binding with barbiturates at its own site increases the chloride ion conduction through the ion channel and causes hyperpolarisation of the cell membrane of neurone. Thereby it reduces the excitability of the post synptic neuron ($GABA_A$ receptors are referred to as the ligand-gated chloride ion channel) (Fig. 14.4).

Barbiturates enhance or mimic the action of inhibitory neurotransmitter such as GABA. By attaching to their binding site on the $GABA_A$ receptor, barbiturates decreases the rate of dissociation of GABA from their binding site on the receptor and increases the duration of GABA-activated chloride ion channel opening. Thus barbiturates enhance the action of inhibitor neurotransmitter named GABA. However at higher concentration but still in clinical range, barbiturates directly activate

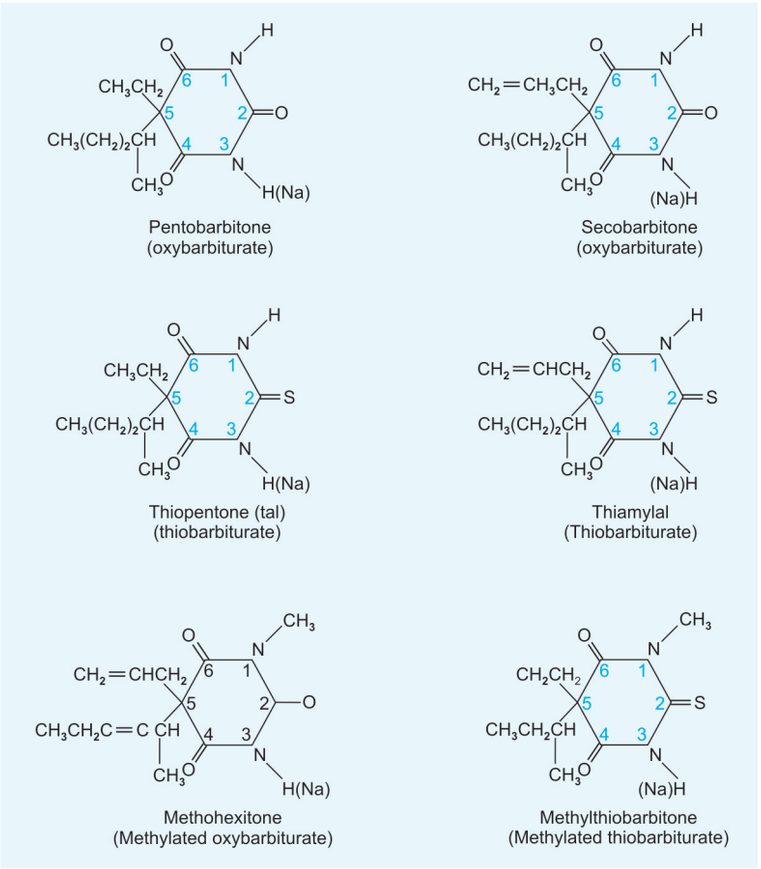


Fig. 14.3: Structure of various barbituric agents

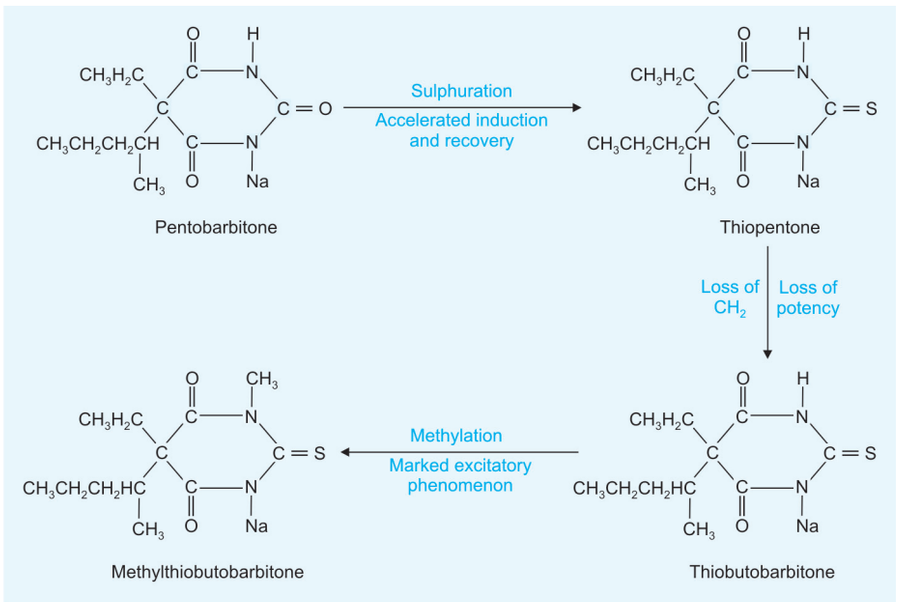


Fig 14.4: Mechanism of action of barbiturate

the chloride an channel after attaching to the barbiturate binding site on the receptor, even in the absence of GABA. This is known as the GABA-mimetic effect of barbiturates. Enhancement of action of GABA by barbiturates is responsible for its sedative and hypnotic effect. But, GABA-mimetic effect of barbiturates at higher concentration is responsible for the barbiturates anaesthesia. The mechanism of the underlying actions of barbiturates on $GABA_A$ receptor appears to be distinct from the action of either GABA or BDZ (benzodiazepine) on the same receptor.

These differences include the following:

i. Although barbiturates enhance the binding of GABA neurotransmitter to $GABA_A$ receptor, they also promote (rather than displace) the binding of BDZ.
ii. Barbiturates potentiate the GABA-induced chloride currents by prolonging the suppression of burst periods, rather than increasing the frequency of suppression of bursts as BDZ do.
iii. Only α and β subunits of $GABA_A$ receptors are required for barbiturates action, but not γ.
iv. Barbiturate's action on the receptor is not affected by the deletion of tyrosine and threonine residue in the β subunits that govern the sensitivity of $GABA_A$ receptor to activation by its agonist GABA (Fig. 14.5).

Except GABA receptor mechanism, there are other proposed mechanism through which barbiturates also act. These are:

i. Barbiturates also act on the glutamate receptors and reduce the glutamate induced depolarisation. Only the AMPA subtypes of glutamate receptor are blocked by barbiturates.
ii. At a higher concentration that produce anaesthesia, barbiturates also supress the high frequency repetitive firing of neuron as the result of direct inhibition of the function of voltage dependent Na^+ channel.

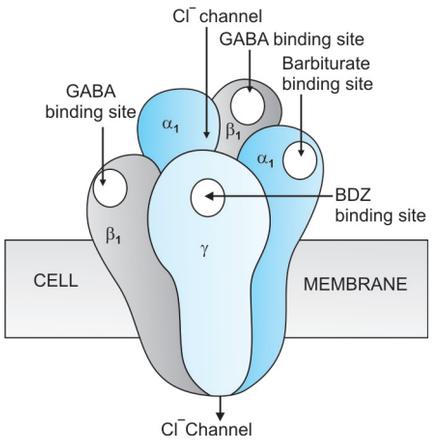


Fig. 14.5: This picture shows the GABA-BDZ-barbiturate receptor complex ($GABA_A$ receptor) with a chloride channel inside it. It is a pentameric protein composed of two α, two β and one γ subunits. There are total two sites for GABA binding on the two β subunits. There is a single binding site each for BDZ and barbiturate on the γ and α subunit, respectively. There is similarity between the $GABA_A$ receptor and the nicotinic acetylcholine receptor

iii. Still at higher concentrations, barbiturates also supress the voltage dependent K^+ channel and its conductances.

In summary, barbiturates activate the inhibitory $GABA_A$ receptors, inhibit the excitatory AMPA receptors and also inhibit the voltage dependent Na^+ and K^+ channel, like local anaesthetic agent. Barbiturates or thiopentone may act in a manner analogus to that of local anaesthetic agents by entering the cell membrane in the unionised form. Then, subsequently it acts from inside of the cell membrane by becoming ionised within the cell cytoplasm and exerting a membrane stabilizing effect by decreasing the Na^+ and K^+ conductance, decreasing the amplitude of the action potential and slowing the rate of conduction of impulse in excitable tissues. In high concentration, barbiturates also depress the enzyme involved in the glucose oxidation which inhibit the formation of ATP and thus depress the Ca^{2+} dependent action potential.

Pharmacokinetics of Thiopentone

Following IV injection of thiopentone, the blood concentration of it rises rapidly. The concentration of thiopentone in highly perfused organ, but with less tissue volume such as brain, heart, kidney, etc, also rises equally rapidly in parallel to its rise in concentration in blood and equilibrate quickly, resulting in induction of anaesthesia.

Thus, the rapid onset of action of thiopentone is due to:

i. the high blood flow to the brain,
ii. the high lipophilicity of the drug,
iii. its low degree of ionisation in blood.

The thiopentone remains as 60% non-ionised diffusible form in blood at pH 7.4. This helps it to diffuse in the brain in increased amount and only this non-ionised fraction of thiopentone crosses the blood-brain barrier. Hyperventilation increases the pH of blood and hence increases the non bound or nonionised fraction of thiopentone. Thus it increases the anaesthetic effect of it. So, thiopentone concentration in CSF reaches a level almost as high as that of the unbound portion of drug in the plasma and is responsible for induction of anaesthsia very rapidly. After that the amount of drug which is present in the blood after the first distribution to brain is distributed rapidly to the next highly perfused but large tissue volume organ such as liver, muscle, spleen, etc. Thus, within few minutes after injection, the blood (central pool) has given up about 90% of the injected dose of thiopentone to the tissues. First the drug is given up by blood to the brain and the patient becomes unconcious. Later the drug is given up by blood to other highly perfused tissues. As a result thiopentone concentration in blood falls rapidly. At that moment, as the concentration of drug in brain tissue is still high than that of the blood, so it diffuses back again in the blood from the tissue of brain and is redistributed to other tissues such as the muscles and fat. Thus, the decrease in brain concentration of thiopentone terminates its effect of induction of anaesthesia and helps in the arousal of patient from sleep. With thiopentone this whole event results in the awakening of patient within 5 to 15 minutes, after a single bolus injection of the usual anaesthetic dose (Fig. 14.6).

Equilibrium with the muscle is not attained untill a quarter of an hour after an IV injection has passed and thereafter, its concentration declines at a higher rate parallel to that of plasma. Despite its higher affinity for thiopentone, adipose tissue which is responsible for final redistribution of drug takes up the drug very slowly because of its poor perfusion. With fat/blood partition coefficent of 11:1, thiopentone will move from blood to fat as long as the conc. in the later is less than 11 times than that of the blood. The maximum deposition of thiopentone in fat occurs after approximately 2.5 hours of IV administration of it. The irreversible removal of thiopentone from the body i.e. elimination clearance by metabolism contributes little to the termination of the anaesthetic effect of the induction dose of it. Thus, in summary it can be concluded that the relatively brief duration of anaesthesia following a bolus induction dose of thiopentone is due to its redistribution from brain to muscle and later to fat tissues, but not due to metabolism in body.

In compartmental pharmacokinetic model, the central volume of distribution (V_C) of thiopentone exceeds the intramuscular space. This indicates that the brain like the intramuscular compartment is also a part of V_C and also explains the rapid onset of action of thiopentone.

When thiopentone is administered in large doses, i.e. by repeated multiple doses

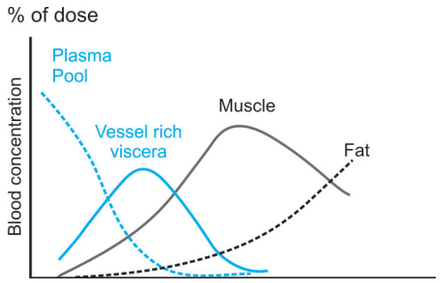


Fig. 14.6: Distribution of thiopentone in different tissues and organs at vious times after its IV injection

or by continuous infusion, then the capacity of lean tissue (muscle) to reduce the plasma concentration of drug by absorption or redistribution in it decreases progressively as the concentration of drug in tissue slowly approaches an equilibrium with the blood concentration. Then after the completion of distribution and redistribution and reaching on equilibrium the termination of the action of drug gradually depends on the slower process of reuptake into adipose tissues from muscle and metabolism in liver, resulting in prolonged drug effect. When thiopentone was administered for 3 to 5 days for cerebral resuscitation, then the redistribution sites (muslce, fat etc) reach equilibrium with the blood concentration and the enzymes responsible for metabolism in liver also soon approach saturation. Then, the recovery depends entirely on the nonlinear drug metabolism process and excretion through kidney and bile which took nearly 5 days. The first pass pulmonary uptake of thiopentone is only 14%.

In hypovolemic (haemorrhagic) shock patient, the anaesthetic dose reqiurement of thiopentone is very less. This is because the fraction of the administered dose removed from the brain tissue by distribution and redistribution to other tissues is very less. This is due to the decreased blood flow to other tissues which is again due to peripheral vasoconstriction for hypotension. In such situation, induction dose of thiopentone should be based on the lean body weight, rather than the total body mass. The usual dose of thiopentone which is based on the total body mass show an increased response in aged, obese and female patients. This is because the lean body mass which represents the principal site for distribution and redistribution represents smaller proportion of total body mass in these patients.

Acute tolerance was seen in thiopentone, i.e. the plasma thiopentone concentration at which the patient awakes is proportional to the initial dose used. The higher the induction dose of thiopentone is used, the lesser sensitive a patient will be to the subsequent doses. On the other hand, when a large amount of thiopentone is given, then the subsequent incremental dose necessary to maintain sleep become gradually less. This is because tissue equilibrium gradually occurs when small doses are required at long intervals. These not only replace the drug which has been detoxicated by metabolism but compensate for the increasing tolerance to metabolism.

The thiopentone is 60 to 80% protein bound in the plasma, predominantly to albumin. However, 40% of the injected dose is sequestreted in red blood cells.

Detoxification and Biotransformation of Thiopentone

10 to 15% of the inducing dose of injected thiopentone is broken down in liver per hour. 30% of the drug may remain in the body for 24 hours, after IV administration of the inducing dose. Liver has important role in the metabolism and also recovery from the excess doses of thiopentone which is rapidly removed from the brain by redistribution. Metabolism (oxidation and reduction) of thiopentone is occured by the cytochrome P_{450} system, situated in the endoplasmic reticulum (ER) of liver cells. Liver is the largest reservoir of ER and removes 50% of thiopentone from hepatic blood. Thus, it also plays a definite role for the short duration of action of the drugs after distribution and with redistribution in different tissues.

The pathways involved in the metabolism of barbiturates in liver are threefold:

(a) Side chain oxidation at C_5 position

Oxidation of radicals at the C_5 position of molecule is the most important step of biotransformation of thiopentone and is responsible for the termination of its biological activity. This oxidation of thiopentone results in the formation of alcohols, ketones, phenols or carboxylic acid which may appear in the urine as such or as conjugates of glucuronic acid.

(b) Oxidative replacement of sulphur at C_2 position

It forms a small quantity of drug's oxyequivalent such as pentobarbitone.

(c) Ring cleavage to form urea and three carbon fragment

Uptake and reuptake of thiopentone by muscle is mainly responsible for the early fall of arterial concentration with a modest (but imprecisely defined) contribution from metabolism in liver and uptake and reuptake by fat. Excretion of thiopentone occurs predominantly in the urine as inactive metabolites. The elimination half-life of thiopentone is 4 to 22 hours and can not be removed by dialysis.

Dosage and Duration of Action of Thiopentone

When thiopentone is injected intravenously, the maximum effect of it is found within about 1 minute. The duration of effect of a single induction dose of thiopentone in 4 to 5 mg/Kg is about 5 to 8 minutes. The induction dose of thiopentone for a healthy adult is 2.5 to 4.5 mg/Kg, for children is 5 to 6 mg/Kg and for infant is 7 to 8 mg/kg. The premedicated geriatric patient may require 30% reduction in dose, as compared with the younger patient. Concomitantly, when the midazolam, opiates, inhalational anaesthetics, ketamine, etc, are given with thiopentone, then it shifts the dose response curve of thiopentone to the left, in proportion to the dose of midazolam, opiates, inhalational agents, etc, which are administered. In hypothermia and circulatory failure state, the circulation time is decreased and the induction time is prolonged. Therefore, much lower doses of barbiturate is needed in such conditions. An acutely inebriated patient by alcohol requires less thiopentone to induce anaesthesia. While chronic alcoholic patients requires a higher dose of thiopentone than normal. This is due to the induction of enzyme, responsible for metabolism of thiopentone in liver. Clinically, there is no difference between

thiopentone and thiamylal in relation to dose, duration of action, potency, incidence of laryngospasm, respiratory depression and cardiotoxicity during induction. On the contrary, the induction dose of methoxital is 1 to 2 mg/Kg of BW. This is because methohexital is 2·5 times more potent than thiopentone.

Recovery

Recovery from anaesthesia produced by thiopentone depends on the total dose of the drug and the other agents which are concomitantly used with it during induction or during premedication to facilitate the induction. If a patient is anaesthetized for 30 minutes by induction dose of thiopentone, i.e. 4 mg/Kg and is maintained by 67% N_2O, 100 µg fentanyl and then a single 100 mg incremental dose of thiopentone, then the patient open his eyes at 3 to 4 minutes interval after N_2O is discontinued. Psychomotor functions will recover completely after 15 to 75 minutes and the psycophysiologic functions will recover completely after 8 hours. However, the abnormal sleep pattern in EEG is found for 12 hours. All these datas recommend not to drive vehicles for 24 hours after thiopentone induced GA.

Complication During Injection of Thiopentone

Pain

The incidence of pain is 1 to 2% when thiopentone is injected into a small vein on the back of the hand or wrist. But there is no incidence of pain when thiopentone is injected into the large veins. If extravasation of thiopentone occurs, then reactions ranging from slight pain, oedema, erythema and soreness to extensive local tissue necrosis can occur depending on the concentration and the total amount of drug injected. Venous sequelae such as thrombosis and phlebitis may not be seen, until few days postoperatively and its incidence is 3 to 4% in patient receiving thiopentone.

Intraarterial injection

If inadvertendly thiopentone in concentration more than 2.5% is injected intra arterially, then intense arterial spasm results, causing immediate excruciating pain spreading distally from the injection site to the hand or fingers. This intense arterial spasm may also cause oedema, hyperesthesia, anaesthesia, motor weakness and even gangrene or loss of tissue. But, sevearity of all these complications depend on the concentraion, dose, total volume and the rate of injection of thiopentone in the artery.

The pathology of these complications following intra-arterial injection of thiopentone is chemical endarteritis induced by high concentration (>2.5%) of it, leading to damage of endothelial, subendothelial and even muscle layer of artery and intra-arterial thrombosis causing gangrene or necrosis. Usually pulse is not felt, but the presence of pulse does not rule out the development of thrombosis. The aim of management of this dangerous complication following intra-arterial injection of thiopentone is to relieve the arterial spasm and to prevent the formation of thrombus, leading to resumption of circulation of blood. These can be achieved by (a) intra-arterial injection of papaverine (40 to 80 mg in normal saline) or 5 to 10 ml of 1% lignocaine which dilute thiopentone and relieve spasm, (b) blocking the sympathetic supply to the upper extirmity by stellate ganglion or brachial plexus block, (c) using heparin intravenously to prevent thrombosis, and (d) by using analgesic and alpha adrenergic antagonists. But, prevention is better than cure. So, as a prophylactic measure to avoid this complication, thiopentone should always be used maximally at a concentration of 2.5%.

Pharmacodynamics of Thiopentone

Effect on CNS

The thiopentone reversibly depresses the activity of all the excitable tissues such as brain, heart, etc. So, it produces a smooth, and rapid induction of anaesthesia. CNS is highly sensitive to thiopentone, but its direct effects on peripheral excitable tissues are weak. The antianxiety property of barbiturates are not equivalent to those exerted by the BDZ, especially with respect to the degree of sedation that is produced by BDZ with equivalent doses. Thus, thiopentone has small therapeutic window. Due to this small therapeutic window of thiopentone, it is not possible to achieve a desired effect regarding sedation like BDZ without evidence of much general depression of the CNS, like general anaesthesia. Thiopentone produces a dose related depression of EEG. By the effect of thiopentone, the wake α-pattern of EEG is replaced by higher amplitude and slower frequency delta and theta waves which gradually progress to burst supression and finally a flat EEG. This flat EEG can be maintained by continuous infusion of thiopentone in the dose of 4 mg/Kg/hour after a loading dose. As there is depression of central neuronal electrical activity so, cerebral O_2 demand which is necessary for and parallel to cerebral electrical activity is also reduced. But, this does not indicate the reduction of cerebral O_2 demand necessary for other cellular metabolic activity which only can be reduced by hypothermia. Along with this there is also parallel reduction of cerebral blood flow and reduction of ICP (provided there is no CO_2 retention following administration of thiopentone). But, the cerebral perfusion pressure is uncompromised, because ICP decreases more than the mean arterial pressure. So, thiopentone is the best drug for neurosurgical anaesthesia.

As there is no analgesic property, so pain perception and its reaction are relatively unimpaired by thiopentone, until the final and very deep stage of anaesthesia is reached. Contrary in small doses the barbiturates increase the reaction to painful stimuli. So, thiopentone has the hyperalgesic effect by subanaesthetic dose. This hyperalgesia or antanalgesia effect of subanaesthetic dose of thiopentone may

result only from the depression effect of barbiturate on some inhibitory system of the brain, (inhibition on inhibition causes excitation). But in full anaesthetic concentration, it inhibits both the inhibitory and excitatory part of the nervous system both at the spinal and cerebral level and thus produce the total depression of CNS instead of excitation.

Effect on CVS

In sedative or hypnotic doses barbiturates do not produce significant or overt cardiovascular depression, except for a slight decrease in BP and HR which occur normally during natural sleep. But, thiopentone is a direct myocardial depressant and depresses the myocardial contractility. However this is less than that of equivalent concentration of any volatile anaesthetic agent. The fall in pH of blood increases this cardiovascular toxicity of barbiturates. However, the mechanism of this myocardial depressant effect of thiopentone is unknown. It is not due to the alteration of Ca^{2+} uptake by cardiac sarcoplasmic reticulum like the halogenated inhalational anaesthetic agents. But the probable explanation is that in addition to depressing Na^{+} channels, they also reduce the function of at least two types of K^{+} channels. However, the direct depression of cardiac contractility occurs only when the large doses of thiopentone which is several times greater than those required to cause general anaesthesia are administered.

Thiopentone produces venodilatation and thus also reduces the preload and cardiac output. Therefore, HR increases via baroreflex mechanism due to the decrease of BP, but cannot compensate this reduced CO. The SVR remains unchanged by thiopentone. But inhigher doses there is also reduction of SVR and much reduction of BP. This is due to the decreased sympathetic tone and dilatation of peripheral resistance vessels. In a normal person, the slow pulse rates are usually quickened (due to fall of BP) and the fast pulse rates are slowed (if it is due to tension and anxiety but not due to shock) by thiopentone during the induction of anaesthesia. The cardiovascular depression is also obtained by partial inhibition of sympathetic transmission by higher doses of thiopentone. This is most evident in patients with congestive heart failure or hypovolemic shock, whose sympathetic reflexes already are operating maximally and in whom the barbiturates can cause an exaggerated fall in blood pressure.

In higher doses the thiopentone itself decreases the sympathetic outflow from CNS, resulting in decreased catecholamines level in blood. But it does not sensitize the heart to catecholamines. So, there is no arrhythmia by thiopentone during induction of anaesthesia, if hypoxia and hypercarbia are avoided.

The thiopentone induced tachycardia caused by hypotension increases myocardial O_2 demand. But, this is meeted by the proportional decrease in coronary vascular resistance and increase in myocardial blood flow (if aortic pressure is maintained) by thiopentone. So, thiopentone should be used cautiously in increased HR, low BP and ↓preload (e.g hypovolaemia, CHF, 1HD, heart block). The hypotensive effect of thiopentone is also exaggerated in patient who receives β-blocker. This is due to the blunted baroreflex, preventing tachycardia.

The IV bolus injection of thiopentone leads to high plasma concentration of drug, suddenly coming into contact with the heart, vasomotor centre and respiratory centre. So, in hypotensive patient with decreased CV reserve, thiopentone may lead to further decrease in venous return (preload), which in turn causes further fall in CO and decreased coronary blood flow. Thus, a vicious cycle can easily be established and may have disastrous effects. So, the IV bolus thiopentone anaesthesia is relatively contraindicated in cardiac patient where rapid hypotensive action is harmful. In contrast, inhalation induction technique has more gradual depressant effect and can be rapidly reversed.

Effect on respiratory system (RS)

Thiopentone reduces both the rate and depth of respiration until apnoea occurs. This depends on the dose and the speed of injection. The stimulatory respiratory response to both the hypercarbia and hypoxia by reflex mechanism mediated by chemoreceptor are depressed by thiopentone. The neurogenic stimulatory drive for respiration is diminished by hypnotic doses of thiopentone, but usually not more than during natural sleep. This neurogenic respiratory drive can essentially be eliminated completely by a dose which is three times greater than that normally used to induce sleep. However, such doses does not supresses the hypoxia drive, but eliminate the chemoreceptor drive by hypercarbia for respiration. At still higher doses powerful hypoxic drive also fails.

Coughing, sneezing, hiccough and laryngospasm may also occur when barbiturates are employed as IV anaesthetic agents. Among these laryngospasm is one of the chief complications of barbiturates anaesthesia. This laryngospasm that sometimes occur is due to the direct effect of thiopentone only on inhibitory system of brain leaving behind the excitatory part in low doses (inhibition on inhibition– described before). The laryngospasm may also be due to insertion of artificial airways, LMA, or ET-tube in a lightly anaesthetised patient. Laryngeal reflexes are less depressed after thiopentone than the equivalent dose of propofol. There is also low incidence of hypersalivation and rarely bronchospasm due to thiopentone. Still thiopentone is safe for asthmatic patient, though do not cause bronchodilation.

Effect on GI tract, kidney and liver

Hypoproteinaemia in patient with liver and renal disease leads to the circulation of greater amount of unbound portion of thiopentone than in normal persons. This causes exaggerated response of thiopentone even with the same dose. In hepatic failure patient the duration of action of

thiopentone is more prolonged in contrast to renal failure patient, where recovery is more rapid. Thiopentone also causes decreased urine output due to decrease in renal blood flow and GFR. This is because thiopentone causes renal vasoconstriction due to sympathetic stimulation from hypotension. So, correction of hypotension by administration of adequate IV fluid, prevents the renal effect of thiopentone from becoming a clinical problem. But, controversy exists, whether there is an increase in secretion of ADH from pituitary in response to thiopentone which may be responsible for decreased urine output.

There is also clinically insignificant increase in blood glucose levels and impairment of GTT after thiopentone anaesthesia.

The incidence of nausea and vomiting after thiopentone anaesthesia is less than that of inhalational anaesthesia. But, the incidence of nausea and vomiting is even lesser after midazolam and propofol than thiopentone.

Peripheral nervous structures

Barbiturates selectively depress the transmission of impulses through autonomic ganglia and reduce the excitation of nicotinic receptor at the motor end plate which is responsible for muscular action. So, at the skeletal neuromuscular junction the blocking effects of nondepolarising muscle relaxants are enhanced during barbiturates anaesthesia. These depressing actions of thiopentone at neuromuscular junction probably result from the inhibition of passage of current through the nicotinic cholinergic receptor.

Miscellaneous actions

Heat loss due to thiopentone induced muscular and cutaneous vasodilatation leads to post-operative shivering. It reduces the plasma cortisol level, but do not supresses the adrenocortical stimulation, during stress and strain of surgery. Thiopentone causes the dose related release of histamine, but it is rarely of clinical significance. After an injection of thiopentone, there may be an anaphylactoid reactions (urticarial rash, hives, oedema, bronchospasm and shock), but the incidence of it is very infrequent. Treatment of this thiopentone induced anaphylactoid reaction include epinephrine, IV fluid, steroid and aminophylline.

Sometimes, thiopentone causes mild muscular excitatory movements, i.e. hypertonicity, tremor, twitching and respiratory excitatory effect including cough and hiccup. This is probably due to the inadequate induction doses of thiopentonewhich evoke excitatory response, because inhibitory areas of brain are the first to be depressed. Atropine and opioids given as premedication prior to thiopentone help to reduce this muscular activity, but phenothiasines and scopolamine, used as premedication, exaggerate it.

Thiopentone does not have the curariform action and does not block the motor impulses directly. Muscular relaxation by thiopentone can be provided through the central nervous system depression. Thiopentone reduces the degree of hyperkalaemia, caused by suxamethonium. The drug causes some depression of intestinal activity and constriction of splanchnic vasculature by sympathetic stimulation due to hypotension.

Obstetric effects

The thiopentone does not depress the uterine tone or contraction. In CS when thiopentone is used in the doses of 6 mg/Kg, then the foetus is not usually depressed during delivery. This is due to the placental factors and redistribution of thiopentone in mother and foetus. The maximum concentration of thiopentone in foetal blood occurs at about 3 minutes after injection, at which time there is an equilibrium between the maternal and foetal blood concentraion. This also explain why umbilical cord blood concentration of thiopentone is half than that of the maternal blood during delivery. If delivery is done within 10 minutes of induction by thiopentone or ketamine, the baby is safe. But, neuro behavioural test of newborn shows better result afer ketamine induction than thiopentone.

Continuous infusions of thiopentone

The continuous infusion of thiopentone for maintenance of hypnosis is not generally used in anaesthesia practice. This is because of the prolonged recovery after completion of infusion of thiopentone. However this can be explained by the context sensitive half time graph (time taken by the drug to decrease to 50% of its plasma concentration) of thiopentone, in relation to other intravenous hypnotic agents used for anaesthesia. This CSHT graph is nothing but the representation of pharmacokinetic property of a particular agent which is discussed before. The successful continuous infusion by thiopentone can be achieved by maintaining blood concentration at the level of 10 to 20 µg/ml during induction, and 5 to 10 µg/ml during maintenance which is obtained by IV administration of 2 to 3 mg/Kg/hour of thiopentone.

Action as anticonvulsants

Barbiturates (thiopentone) and benzodiazepines (diazepam, midazolam, etc) can abruptly stop the seizures in convulsive patient. But, benzodiazepines have largely replaced thiopentone in acute treatment of seizures. This is because, though barbiturates have anti convalsant properties but it (except phenobarbital) possesses a high degree of selectivity and low therapeutic index. Thus, it is not possible by barbiturates to achieve the desired anticonvulsion effect without the evidence of general depression of CNS, like anaesthesia.

Mechnnism of actions of barbiturates as anticonvulsant:

i. Both the barbiturates and the benzodiazepines facilitate the action of inhibitory neurotransmitter named GABA and prolong the hyperpolarisation of post synaptic membrane. Thus, it inhibits the conduction of impulses and stop the convulsions.

ii. Barbiturates alters the postsynaptic membrane conductance of chloride ion and thus antagonise the glutaminergic and cholinergic excitation.
iii. They presynaptically block the Ca^{2+} entry into the nerve terminals and thus diminishes the transmitter release.
iv. They increase the threshold of convulsion in brain by inhibiting the kindling process more effectively.

Action as brain protection

Thiopentone protects the brain by following mechanisms:

i. It decreases the cerebral metabolism (which is only responsible for electrical activity) till the EEG becomes flat, after which no further suppression of metabolism (responsible for other cellular activities other than electrical) occur even with increased dose.
ii. Thiopentone enhances the reversed steal phenomenon in which vasoconstriction in healthy area of brain shunts the blood to the diseased areas. Thus the non healthy tissue of brain becomes less ischaemic.
iii. Thiopentone reduces both the ICP and blood pressure supplying the brain. But, the reduction of ICP is greater than blood pressure. Thus, it maintains the cerebral perfusion pressure. So, arterial hypnotension should be avoided to maintain the adequate cerebral perfusion pressure.
iv. It causes stabilization of the liposomal membrane and free radical scavenging of cell.
v. It attenuates the cerebral oedema, resulting from cranial surgery, head injury or cerebral ischaema. They may decrease the size of infarction and increase the survival rate.

Contraindications of The Use of Thiopentone

There are some occasions where it is necessary to use thiopentone with particular care or some times to avoid it completely. These occasions are:

i. Outpatients who have to leave the hospital alone. After regain of consciousness from thiopentone anaesthesia, there is a stage of euphoria when the patient is not fit to take care or to perform responsible actions by himself. So, driving a car is forbidden for 24 hours following thiopentone anaesthesia.
ii. Children are unsuitable for thiopentone as the sole anaesthetic agent, because they need relatively larger doses to produce a satisfactory depression of all the reflex activity.
iii. When the adequacy of the airway is in doubt, then thiopentone should be used cautiously.
iv. Thiopentone should not be used in patients with the history of hypersensitivity to barbiturates and asthama. Allergic reactions to thiopentone occur especially in persons who tend to have asthma, urticaria, angioedema or similar conditions. Hypersensitivity reactions in this category include localised swellings, particularly of the eyelids, cheeks or lips and erythematous dermatitis.
v. During anaesthesia on patient suffering from cardiac and peripheral circulatory failure the benefit of smooth and pleasent induction by thiopentone should be balanced against the deleterious effect of vasomotor and respiratory depression caused by it. In cardiac disease with fixed and low CO, such as in AS the vasodilation and consequent hypotension caused by thiopentone may lead to cardiac arrests. In shock patient where BP is maintained by sympathetically stimulated vasoconstriction, then vasodilation and depression of sympathetic system by barbiturates can produce fatal effect. However, such conditions are not necessarily absolute contraindication to the use of thiopentone, but should be used very cautiously by experienced person.
vi. Severe uraemia, where small dose of barbiturates produce prolonged effect are the relative contraindication for the use of thiopentone.
vii. Porphyria − In latent stage of this disease any barbiturate may cause an acute exaccerbation of symptoms with porphyrinuria, respiratory paralysis and frequently death. This is because barbiturates enhance porphyrin synthesis. So, the use of thiopentone in a patient with a history of prophyria is absolutely contraindicated.
viii. Untreated adrenocortical insufficiency − This is due to inability of such patient to respond to any form of stress, though thiopentone does not depress the release of adrenocortical steroids itself.
ix. Abnormal severe respiratory depression may follow after the use of thiopentone in dystrophia myotonica.
x. Untreated myxoedematous patient are sensitive to any IV anaesthetic agents. But thiopentone is the most sensitive amongst them.

Porphyrias

The porphyrins are chemical compounds which are formed by the binding of four pyrol rings. The examples of porphyrins are haem and its precursor compounds such as protoporphyrin, protporphyrinogen, coproporphyrinogen, uroporphyrinogen etc. During biosynthesis of heame, multiple steps are involved which are governed by particular enzymes. Deficiency of these enzymes results in increased concentration of that particular precursor of haem (or porphyrins) in blood and urine. This condition is called the porphyrias. Porphyria is classified according to the site of the defected enzyme such as hepatic porphyrias, erythrocyte porphyria, etc.

The acute attack of porphyria is precipitated by various triggering factors which include general anaesthetic agents such as barbiturates, sulphonamides, etc. Acute attack is characterised by abdominal (intermittent) pain, neurological symptoms, psychiatric sympotoms, etc. The diagnosis can be confirmed by examining the urine during

acute attack. The finding of raised aminolaevulinic acid (ALA) and porphobilinogen (PBG) in urine establishes the diagnosis. But, the urine should be protected from light during its collection. However, the concentration of ALA and PBG in urine will be normal in between the attacks.

BENZODIAZEPINE

History

Since antiquity to the begining of 19th century alcoholic beverages and some potions (containing laudanum and various herbals) had been used to induce sleep. Then, in the middle of nineteenth century the first pharmacological agent to be introduced as a sedative and soon, thereafter, as a hypnotic was bromide. After that, as sedative and hypnotic came chloral hydrate (1869) and paraldehyde (1882) which are rarely used now. Then, Fischer and Von Mering introduced barbiturates in the form of barbitone in 1903 and phenobarbitone in 1912. Thus, barbiturates reigned supreme till 1960. Then BDZ had started eroding their position after first discovery of chlordiazepoxide as benzodiazepine in 1957 and have now totally replaced them as sedative and hypnotics in anaesthesia practice.

Then the discovery of partial separation of sedative, hypnotic and anaesthetic properties from anticonvulsant properties which was a characteristic of phenobarbital (have only anticonvulsant properties) had led to the search for agents which have more selective effects on CNS. As a result, phenytoin with relatively nonsedative and high anticonvulsant property was developed in 1930 and then chlorpromazine in 1950 without any anticonvulsant but only with the taming properties was developed.

Introduction of barbiturates in the clinical practice strats the era of intravenous anaesthesia after an initial set back. But, the barbiturates have only hypnotic property. So the search for an ideal intravenous anaesthetic drug which should have hypnotic, amenestic and analgesic property was started. On that searching many drugs were steadily introduced in the clinical anaesthetic practice with varying degree of acceptance. Thus, with increasing number of better drugs and discoveries of superior methods of drugs delivery system, the use of intravenous anaesthesia continues to grow. But, as not a single drug has all the ideal property of anaesthesia, so the future of IV anaesthetic management involves the simultaneous use of several drugs with their specific properties. In 1988, a survey of mortality among 1,00,000 anaesthesia reveals that the practice of combined anaesthetic drug in small doses with their specific property may be safer than the use of only one or two drugs in high doses to extract the all properties which are exerted by many drugs in small doses. This is because a single drug in high doses has many side effects and increases mortality.

In 1955, as the first generation of benzodiazepine chlordiazepoxide was synthesised and in1957 it's hypnotic and sedative effects was first discovered. Then, in 1960 it was released as first orally used benzodiazepine. But, as chlordiazepoxide has no parenteral form, so it was not used for intravenous anaesthesia. After that, as benzodiazepine the diazepam was synthesized in 1959 and was used in anaesthesia through IV route. Then, gradually oxazepam, a metabolite of diazepam was synthesized in 1961 and lorazepam, a substitution of oxazepam was synthesised in 1971. Next major achievement was synthesis of water soluble benzodiazepine, midazolam in 1976. Its water solubility is pH dependent and formulated in a buffered acidic medium (pH 3·5). But it is most lipid soluble *in vivo* than diazepam and lorazepam. After that in 1977 benzodiazepine receptor was described. However, this is better termed as BDZ, GABA and barbiturate receptor complex which is discussed in later paragraph.

Chemistry

The term benzodiazepine is referred to the structure of a molecule that is composed of a benzene ring (A) fused to a seven membered 1-4-diazepine ring (B). However, since all the important benzodiazepines compounds contain a 5-aryl susbstituent ring, so the term has come to mean the 5-aryl-1,4-benzodiazepine. Then, various modifications in the structure of this ring systems have produced different compounds with similar activities. But, the substitutions at various position on these rings affect the potency and mechanism of biotransformation of these compounds. A special benzodiazepine ring, named the imidazole ring of midazolam contributes to its water solubility at low pH. The insolubility of diazepam and lorazepam in water requires propylene glycol for their parenteral preparations which has been associated with venous irritation and pain during injection (Fig. 14.7).

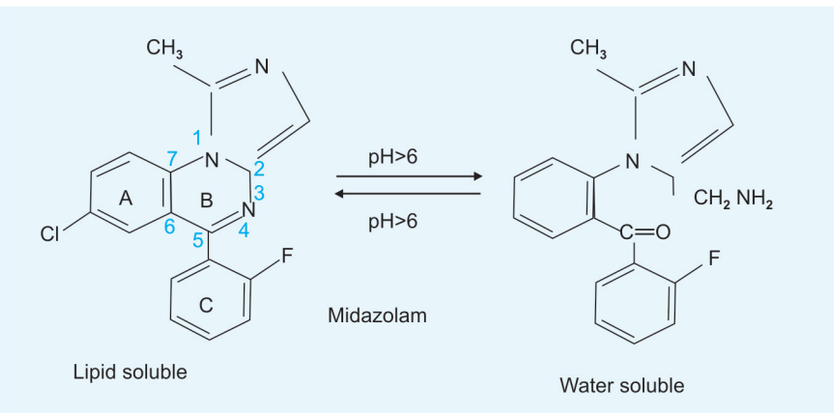


Fig. 14.7: Solubility of midazolam in lipid and water

BDZ – GABA – Barbiturate Receptor Complex or $GABA_A$ Receptor

Benzodiazepines (BDZs) act by occupying the BDZ receptors. Barbiturates and an another inhibitory neurotransmitter, named GABA also act by occupying the respective barbiturate and GABA receptors. But, actually they are not any separate receptor structure. They are truely the binding site of the benzodiazepine, barbiturate and GABA compound on a single large receptor complex, situated on the postsynaptic membrane which is called the BDZ-GABA-barbiturate receptor complex or $GABA_A$ receptor. This large $GABA_A$ receptor complex exerts the action of barbiturates, benzodiazepines and GABA after their binding with this receptor complex at their each specific site and ultimately by promoting and modulating the action of GABA. These large receptor complexes are found in higher concentration at cerebral cortex, cerebellum, olfactory bulb, hippocampus and substantia nigra. In lesser density this large receptor complexes are also found at spinal cord, brain stem and corpus striatum. The barbiturates and benzodiazepines both act through this receptor. But in contrast to the barbiturates, the benzodiazepines selectively inhibit the activity of this receptor in the limbic system, particularly the hippocampus.

GABA receptors are membrane-bound protein structure that can be divided into two major subtypes – $GABA_A$ and $GABA_B$. The $GABA_A$ receptor is composed of 5 subunits that coassemble to form an integral chloride channel. These receptors are responsible for most of the inhibitory neurotransmission in CNS. The BDZ does not act on the $GABA_B$ receptor, but acts only on $GABA_A$ receptor. Unlike the barbiturates, the BDZ do not directly activate the $GABA_A$ receptor, but require inhibitory neurotransmitter GABA to express their own effects, i.e. BDZ only modulates or promotes the effects of inhibitory neurotransmitter GABA. The BDZ modulates the GABA binding site and GABA alters the BDZ binding site in an allosteric fashion (Fig. 14.8).

Each $GABA_A$ receptor complex is believed to consist of a pentamer of homologus subunits. Mainly these subunits are α, β, γ and they coassemble to form a receptor. But, there are other subunits such as δ, ε, π and θ. Again 16 several isoforms of each subunit have also been cloned. These subunits and their isoform composition of the receptor complex may differ at different sites. The multiplicity of these subunits and their isoform generates heterogenesity in $GABA_A$ receptor and is responsible for their pharmacological diversity. The macromolecular complex of this $GABA_A$ receptor and the chloride channels within it also may be the site of action of many general anaesthetics, ethanol and inhaled drugs. The subunits of the $GABA_A$ receptor complex contain various ligand-binding site such as BDZ, GABA and barbiturate. The BDZ binding site is located on the γ subunit and GABA binding site is located on the β subunit of $GABA_A$ receptor complex. With the activation of GABA-BDZ and barbiturate receptor complex, the opening of chloride channel is triggered and hyperpolarization of post synaptic membrane occur. This leads to the resistant of neuronal excitation which is responsible for inhibition of transmission.

The pharmacological spectrum of intrinsic activity of BDZ includes 5 different types – agonist, partial agonist, antagonist, partial inverse agonist and inverse agonist. Antagonist blocks the action of agonist. Whereas the inverse agonist express no action from itself, but causes all the opposite action of agonist. For example an agonist such as midazolam have full positive intrinsic action of benzodiazepine and produce hypnosis, sedation, amnesia etc. Because it alters the configuration the $GABA_A$ receptor complex after binding with the BDZ binding site of this receptor complex which is called as the BDZ receptor. Thus, the binding affinity of GABA neurotransmitter

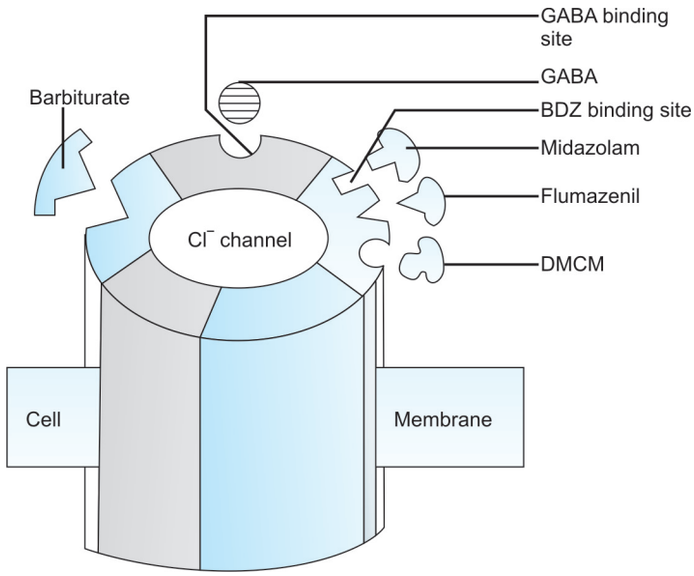


Fig. 14.8: A GABA - BDZ barbiturate receptor complex ($GABA_A$ receptor) with chloride channel. A part of it i.e. the BDZ - binding site (or BDZ-receptor) modulates the action of $GABA_A$ receptor in either direction. The agonist like midazolam facilitates the opening of GABA mediated Cl^- channel in the $GABA_A$ receptor complex and produces all the actions of benzodiazepine. Whereas the inverse agonist like DMCM hinder GABA mediated Cl^- channel opening producing the opposite action of midazolam. Whereas BDZ antagonist flumazenil blocks the action of both midazolam and DMCM. Barbiturate receptor is located in the other part of $GABA_A$ receptor. It also facilitates the action of GABA and is capable of opening the chloride channel directly

to the GABA binding site of GABAA receptor complex is increased and the chloride channel is fully opened. Whereas the antagonists (e.g. flumazenil) occupy the BDZ receptors, i.e. the BDZ binding site of $GABA_A$ receptor complex and have very little intrinsic action expressed by itself after binding with the receptor. Contrary, it blocks all the action of both agonist and inverse agonist by preventing the binding of them with the BDZ receptor (BDZ binding site of GABA receptor complex). Therefore there is no action of BDZ agonist and inverse agonist. In the absence of agonist and inverse agonist, antagonist does not itself cause any $GABA_A$-receptor function. So, they are also called the neutral in function. The inverse agonist has opposite intrinsic activity i.e. produce opposite effect of agonist in the absence of it. It reduces or inhibit the GABA synaptic transmission and since GABA is inhibitory, so the result of inhibition of GABA (inhibition on inhibition) causes CNS stimulation. The potency of these agonist, antagonist and inverse agonist is dictated by its affinity for the BDZ receptor and the duration of effect of these compound is dictated by the rate of clearance of these drugs from receptor. (Table 14.2).

It is still not known how the different effect of benzodiazepine (hypnosis, sedation, anxiolytic, amnesia, anticonvulsant and sleep) are mediated by the same receptor. For this there are two probable theories: (i) different receptor subtypes mediate different action and (ii) different action is due to different blood level of the drug. As for example, the anxiolytic effect of BDZ occurs at 20% GABA receptor occupancy, the sedation is observed with 30 to 50% receptor occupancy and the unconciousness at 60% receptor occupancy.

Table 14.2: The relationship between the different effects of midazolam and its receptor occupancy

Effect	*Receptor occupancy (%)*
Anticonvulsant	20 - 25
Anxiolysis	20 - 30
Slight sedation	30 - 50
Amnesia	
Reduced attention	
Intense sedation	60 - 90
Unconsciousness	
Muscle relaxation	
Anaesthesia	> 95

Different compounds of BDZs differ in their potency and efficiency. This is due to the different chemical structure of each drug which again dictates its particular physicochemical, pharmacokinetics and receptor binding characteristics. For example the order of receptor affinity (thus potency) of three BZD agonist from higher to lower is lorazepam > midazolam > diazepam. So the midazolam is 3 to 4 times and lorazepam is 5 times more potent than diazepam.

Chronic administration of BDZ produces tolerance and causes increased dose requirement. This is due to the down regulation of GABA-BDZ-barbiturate receptor or $GABA_A$ receptor complex. After the cessation of chronic use of BDZ, there is again upregulation of the receptor complex i.e. increased susceptibility to BDZ.

Pharmacokinetic of BDZ

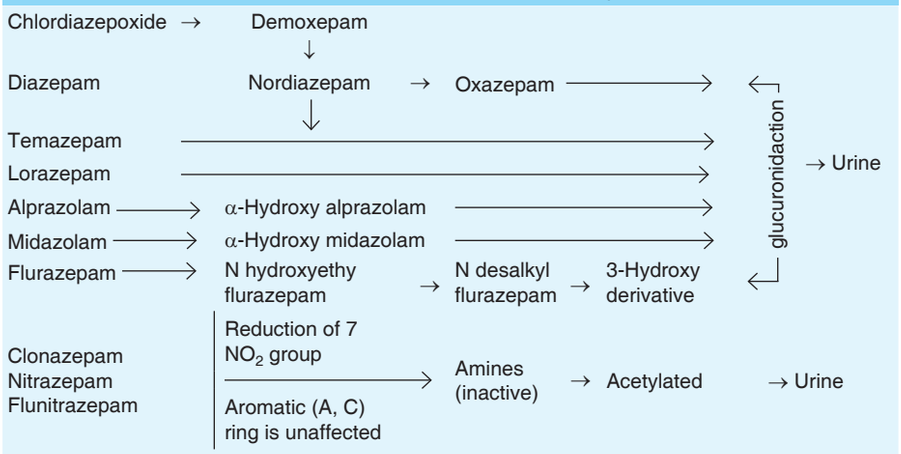
BDZ compounds used in anaesthesia are classified as: (i) long acting with half-life more than 24 hours (lorazepam), (ii) intermediate acting with half-life 6 to 24 hours (diazepam) and (iii) short acting with half-life less than 6 hours (midazolam) according to their plasma clearance. The clearance rate of lorazepam is 0.2 to 0.5 ml/Kg/min, the diazepam is 0.8 to 1.8 ml/Kg/min and midazolam is 6 to 11 ml/Kg/min. So, these drugs have different plasma disappearance curve after their bolus IV administration.

The onset of action of different BDZs depends on their lipid solubility and the duration of action depends on the rate of distribution and redistribution of these BDZ in different compartment of body like thiopentone and metabolism. For example, onset of action of midazolam and diazepam after IV administration is 30 to 60 sec. It is due to their high lipid solubility. But, the onset of action of lorazepam is 60 to 120 sec which is due to its less lipid solubility. The more rapid redistribution from CNS to other body tissues of midazolam and diazepam due to their higher lipid solubility compared to lorazepam also accounts for their shorter duration of action than lorazepam. Thus, the order of three agents according to their early onset and short duration of action is: midazolam < diazepam < lorazepam. Although midazolam is more water soluble and less lipid soluble at low pH, but its imidazole ring closes at physiological pH and causes an increase in its lipid solubility (Table 14.3).

Again, after the prolonged infusion of BDZ when the redistribution site of benzodiazepine becomes saturated and is in equlibrium with the primary site of action, then the blood levels of midazolam will decrease more rapidly than others BZD. It is due to its greater hepatic metabolic clearance rate than others. So, patient will awake faster after midazolam infusion than others. The more lipid soluble member of BZD enters the brain rapidly and have two phases of plasma concentration decay curve like thiopentone. The first decay curve is due to the redistribution and the later decay curve is due to the elimination by metabolism or directly through urine. A relatively shorter duration of action is seen with single dose of any BZD compound that is rapidly redistributed, even though it may have a long elimination half-life ($t_{½}$). So, using the elimination $t_{½}$ alone to predict duration of action may be misleading. However, the plasma $t_{½}$ determine the duration of action of drugs whose elimination is by far the dominant feature or when the drug is given repeatedly or by infusion.

BZDs are metabolised in liver by dealkylation and hydroxylation to many metabolites, some of which are also active. This explains why the effect or the

Table 14.3: Metabolism of benzodiazepine



Red colour = Long acting drugs, Green colour = Intermediate acting drugs, Black colour = Short acting drugs

biological half-life of some drugs may be much longer than the actual plasma t½ of the administered compound. Some BZDs (e.g. diazepam) undergo enterohepatic circulation and is also responsible for their long duration of action. Benzodiazepines are commonly administered orally or intravenously for premedication, sedation, or induction of GA. Midazolam, diazepam and lorazepam are well absorbed from gastrointestinal tract and the peak plasma level is usually achieved within 30 minutes, 1 hour and 2 hours respectively. Midazolam also can be used through intranasal (0.2 to 0.3 mg/Kg), buccal (0.07 mg/Kg) and sublingual (0.1 mg/Kg) route to provide effective preoperative sedation. The intramuscular injection of diazepam is very painful and the action is unreliable due to very erratic absorption of its oily preparation from muscle. In contrast, the midazolam and lorazepam are well absorbed after intramuscular injection with peak levels achieved within 30 and 90 minutes, respectively. However, the induction of general anaesthesia by BDZ only requires IV administration of them.

Metabolism

BDZs and their metabolites which are sometimes more potent than their parent compound bind to plasma protein. This extent of binding of these metabolites with plasma protein correlates strongly well with their lipid solubility and duration of action which ranges from 70% for alprazolam to nearly 99% for diazepam. The concentration of BDZs in CSF is equal to the concentration of free drug in plasma.

The plasma concentration of most of the BDZs exhibits two compartmental model, but three compartmental model appears to be more appropriate for the compounds with highest lipid solubility like midazolam. There is rapid uptake of BDZ by brain after IV administration like barbiturate. This rapid uptake by brain is followed by a phase of redistribution to the less well perfused tissue i.e. muscle. Muscle uptake is followed by again redistribution to fat.

As the metabolites of some BDZs are more active and biotransformed more slowly than their parent compounds, so the duration of action of many BDZs bear little relationship to the actual half-life of elimination of the drug that has been administered. All the BDZs crosses the placental barrier and secreted into breast milk.

BDZs are metabolised extensively in the liver by the enzymes of cytochrome P_{450} family. Some BDZs, such as oxazepam and lorazepam is not metabolised by these enzymes, but is conjugated directly in to the liver. Midazolam is rapidly metabolised by hydroxylation of its methyl group to α-hydroxy midazolam which has appreciable biological activity (elimination half-life 1 hour) and then is conjugated with glucoronic acid in liver.

Diazepam in the first phase is metabolised by the cytochrome P_{450} system in liver to N-desmethyl diazepam (nordiazepam) which is a long acting active metabolites. In the 2nd phase, this nordiazepam is again metabolised to oxazepam which is then conjugated with glucoronic acid and excreted through bile. The half-life of diazepam in plasma is between 1 to 2 days, while that of N-desmethyl diazepam (nordiazepam) is about 60 hours. Half-life of lorazepam in plasma is about 14 hours.

Pharmacodynamics of BDZ

Effects on CNS

The most prominent effects of BDZs on CNS are sedation, hypnosis, decreased anxiety, anterograde amnesia and anticonvulsion activities. The muscle relaxant effect of BDZ is independent to their sedative actions and is due to their action on the spinal cord and brain stem. It affects the activity of neural axis at all the levels, but some structures are affected much greater extent than the others. They are not capable of producing the same degree of neuronal depression at all the centres, as the barbiturates and volatile anaesthetics do.

All the BDZs have very similar pharmacological profiles, but neverthless they differ in selectivity to their different effects. So, the clinical usefulness of individual BDZ varies considerably. BDZs alone do not cause a true general anaesthesia, since awareness usually persist and relaxation which is sufficient to allow surgery can not be achieved by them. During induction of anaesthesia by BDZ with inducing doses, patients are clinically asleep, but EEG changes are not typical to sleep. In a dose related manner the BDZs gradually reduce the cerebral metabolic rate with reduction

of O_2 consumption ($CMRO_2$) and cerebral blood flow (CBF). They increase the seizure threshold and thus inhibit seizure. They have also cerebral protection effect against hypoxia. In this respect midazolam is superior to other BDZs, but is inferior to thiopentone.

BDZs also have the antiemetic effect and lorazepam has the highest result. As they produce anxiolysis, amnesia, sedation and hypnosis gradually, so they should be titrated for this effects and the end point of this titration is sedation or hypnosis. The onset of action is most rapid in midazolam, than diazepam and the last is lorazepam. But recovery with midazolam is faster than diazepam after bolus administration. With all the three BDZs (midazolam, diazepam and lorazepam) there is amnesia, but different level of sedation. Patient is concious and coherent, but amnestic for events and instruction (conscious sedation). With the intravenous preparation the memory loss by BDZs can occur independent of the loss of consciousness. When taken by mouth, it is not possible to demonstrate the amnestic action of BDZs in the absence of drowsiness and the usual small tranquillizing doses (diazepam 5 mg, lorazepam 1 mg) produce no amnesia. There is synergestic action between the midazolam and the regional anaesthesia in respect to ventilation. They do not cause hyperalgesia like the barbiturates.

Anticonvulsant properties

All the benzodiazepines have anticonvulsant properties. Among them midazolam, diazepam, and lorazepam have well defined roles in the management of status epilepticus. This action is due to their ability to enhance the GABA-mediated synaptic inhibition through BDZ-binding site (or benzodiazepine receptor) which is an integral part of the $GABA_A$ receptor.

Effects on CVS

The benzodiazepines display the minimal cardiovascular depressant effects, even at induction doses. The peak hemodynamic effects of BDZs occur within first 10 minutes after their intravenous administration. They all decrease the BP and increase the HR. With midazolam, these effects appear to be secondary to the decrease in peripheral vascular resistance (SVR), but with diazepam these are secondary to the decrease in left ventricular work load and cardiac output. Diazepam increases the coronary blood flow, possibly by increasing the interstitial concentration of adenosine. Accumulation of cardio depressant metabolite may also explain the negative inotropic effects of all the BDZ group of drugs. The predominant hemodynamic changes produced by BDZs are:

i. Reduction of MAP (in midazolam 12 to 26%) due to the decrease in SVR. In this respect midazolam has the highest effect than other BDZs, and is similar to thiopentone. The reduction of SVR for diazepam is upto 0 to 8% and for midazolam it is upto 0 to 18%. Still, they are safe and effective for induction with severe AS (arotic stenosis).
ii. PAP (pulmonary artery pressure) and PVR remains unchanged or slightly reduced. In midazolam both are unchanged, but in diazepam the effect varies between unchanged to minimum reduction.
iii. Right atrial pressure remains unchanged.
iv. Variable response to cardiac index (C1) unchanged in diazepam, 0 to 25% reduction in midazolam.
v. In patient with elevated left ventricular filling pressure, diazepam and midazolam produce NTG like effect by lowering the filling pressure and increaseing the CO.

The mechanism by which BDZs maintain a stable haemodynamic condition is due to the preservation of homeostatic reflex by them. Midazolam or any BDZ can block the stress response due to intubation or surgery. However, addition of N_2O with BDZs has slight synergistic effect to block this response. But addition of opiods with BDZ has supra additive synergistic effect and causes a greater decrease of BP and stress response than when used alone during intubation. However, the mechanism of this synergistic effect is not known, but probably is due to the reduction of sympathetic tone.

BDZs cause coronary vasodialtation which is seen after administration of therapeutic doses.

Effect on respiratory system

The hypnotic doses of BDZs produce minimal effect on respiration in normal subjects, but special care should be taken for children, aged, and alcoholics. It depresses the ventilatory response to hypoxia and CO_2. This depression is usually insignificant, unless the drugs are administered intravenously in large doses or in association with other respiratory depressants. Although the incidence of apnoea may be less common after BZD induction than after barbiturate induction, still sometimes even a small IV doses of diazepam and midazolam have resulted in respiratory arrest. Respiratory arrest or apnoea is more likely to occur during the concomitant presence of opioids. The steep dose response curve of midazolam shows slightly prolonged onset (compared with thiopentone) and high potency of it, necessitating careful titration to avoid over dose and apnoea. So, ventilation must be monitored in all the patients receiving IV benzodiazepines and resuscitation equipment must be immediately available.

The hypnotic doses of BDZs may also worsen the sleep related breathing disorder by adversely affecting the control of upper airway muscles and by decreasing the ventilatory response to CO_2. The latter effect may be sufficient to cause the hypoventilation and hypoxemia in some patients, especially with severe COPD. In some patients with obstructive sleep apnoea (OSA) syndrome, the hypnotic doses of BDZs may decrease the upper airway muscular tone and exaggerate the incidence of apnoeic episodes. Thus, many physicians consider OSA as contraindication for the use of

sedative and hypnotic agents like benzodiazepines. So, during administration of benzodiazepines caution should be exercised in patient who snore regularly. This is because partial airway obstruction may be converted to OSA under the influence of these drugs.

The central respiratory depression produced after administration of BDZs is greater in midazolam than diazepam. The slope of ventilatory response curve to CO_2 for BDZ is flat than normal, and is not shifted to the right like opiods. The peak onset of ventilatory depression effect with midazolam is 3 minutes and remain for about 60 to120 minutes. The faster the drug is given, the quicker the peak depression occur. The combination of opioids with BDZs produce a supra additive respiratory depression effect. Apnoea is common to midazolam than other BDZs and its incidence is similar to thiopentone.

Effects on GI tract

BDZs markedly decrease the nocturnal gastric secretions in human beings.

Induction and Maintenance Dose of BDZs

Among the BDZs, midazolam is the choice for induction of anaesthesia, because for its rapid onset, rapid recovery and lack of venous complications. Induction is complete when there is unresponsiveness to command and loss of eye lash reflex. On the otherhand, the induction with midazolam occurs less rapidly than thiopentone, but amnesia caused by it is more reliable. But the dose, speed of injection, premedication, age, ASA status and many other factors influence the induction time by BDZs. For example, midazolam in the dose of 0·2 mg/Kg induces anaesthesia within 28 sec, if given IV. Whereas diazepam in the dose of 0·5 mg/Kg takes 39 seconds for induction of anaesthesia, if it is given through the same route and in the same speed (Table 14.4).

Table 14.4: Uses and doses of commonly used benzodiazepines (BZD)

Agent	*Use*	*Route*	*Dose (mg/Kg)*
Diazepam	Premedication	Oral	0.2-0.4
	Sedation	IV	0.04-0.3
	Induction	IV	0.3-0.5
Midazolam	Premedication	Oral	0.5
		IM	0.07-0.2
	Sedation	IM	0.07-0.1
	Induction	IV	0.1-0.4
Lorazepam	Premedication	Oral	0.05
	Sedation	IM	0.025-0.05
		IV	0.025-0.05

Due to increased susceptibility to BDZ receptor, the elders need lower doses. In premedicated patient, induction dose of midazolam is reduced to 0.1 to 0.2 mg/Kg. Emergence (defined as oriented to time and pace) in healthy young patient after 10 mg midazolam is 15 minutes. In comparison between midazolam and thiopentone for hypnotic component in balanced anaesthesia, midazolam is superior for this use. This is because of the better amnesia and lesser hemodynamic changes produced by it. Midazolam reduces the opioid requirement than thiopentone. Amnestic period after an induction dose of midazolam is 1to 2 hours. Bolus loading dose of midazolam is 0.05 to 0.15 mg/Kg which maintains plasma level of 50 µg/ml. This is sufficient to keep the patient asleep and amnestic, but arousable at the end of infusion.

INDIVIDUAL BENZODIAZEPINE (BZD) (Fig. 14.9)

Diazepam

Chemically, diazepam is a benzodiazepine derivative. The main actions of it are:

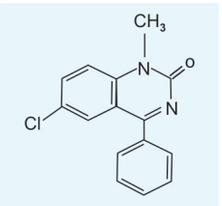


Fig 14.9: Diazepam

hypnosis, sedation, anxiolysis, anterograde amnesia, anticonvulsant and muscular relaxation. Like other BDZs, diazepam is also thought to act via the specific BDZ-receptors, found at synapses throughout the central nervous system, but concentrated especially in the cortex and midbrain. However, the individual receptor cannot directly act. They are closely linked with large complex $GABA_A$ receptos and appear to facilitate the activity of the inhibitory GABA neurotransmitter. The activated $GABA_A$ receptors by diazepam open chloride ion channels which then either hyperpolarize or short circuit the postsynaptic membrane. Thus hyperpolarization of the postsynaptic membrane reduces the action potential and inhibits the transmission of impulses.

The main action of diazepam on cardiovascular system is transient decrease of blood pressure and a slight decrease of cardiac output, but only following its IV administration. The coronary arterial blood flow is increased by diazepam. But this is secondary to the coronary arterial vasodilatation caused by accumulation of adenosine. A decrease in myocardial O_2 consumption has also been reported by it. Large doses of diazepam causes respiratory depression causing decreased tidal volume, respiratory rate, and minute volume. It may also cause apnoea necessitating IPPV. The hypoxic ventilatory drive is depressed to a greater extent than the hypercarbic drive. It is anxiolytic and so decreases the aggression, although sometimes paradoxical excitement may occur. Sedation, hypnosis and anterograde amnesia also occur after the administration of diazepam. The drug also has the anticonvulsant and slight analgesic property and depresses the spinal reflexes.

The toxicity or the side effects of diazepam are nothing but the excessive depression of CNS, including drowsiness, ataxia and headache. Tolerance and dependence to diazepam may occur with prolonged use of it, like other BDZs. So,

acute withdrawl of diazepam in these circumstances may produce insomnia, anxiety, confusion, psychosis or perceptual disturbances. Rashes, GI upset and urinary retention also have been reported as the side effects of it. The commercially available lipid preparation of IV diazepam is highly irritant to vein. So, it produces intense pain during intravenous injection. But its water preparation is not so irritant to do so. However, this preparation is not available commercially.

Diazepam is rapidly absorbed after oral administration. The bioavailability of it by oral route is 90 to 100%. On the otherhand, absorption of diazepam after IM administration of its lipid preparation is slow and erratic. This drug is 99% protein bound in the plasma. Diazepam is converted in the liver to its active metabolites. The major active metabolites of it is desmethyldiazepam (nordiazepam). The other active metabolites of it are oxazepam and temazepam which are further metabolised by glucuronidation. Due to this active metabolites, diazepam is a long acting agent.

Desmethyldiazepam has a half-life of >100 hours. The metabolites of diazepam are excreted through the urine. Diazepam decreases the MAC value of volatile anaesthetic agents and potentiates the action of nondepolarizing muscle relaxants. It is absorbed on the plastic and can not be removed by dialysis. The diazepam is used in anaesthesia for premedication in the dose of 0.2 to 0.5 mg/Kg orally, for sedation in the dose of 0.04 to 0.2 mg/Kg IV and for induction of anaesthesia in the dose of 0.3 to 0.6 mg/Kg IV.

Midazolam

Chemically, it is a water soluble imidazobenzodiazepine compound. Its main actions and mode of action is same as that of diazepam. Midazolam decreases the systolic blood pressure by 5%, diastolic blood pressure by 10% and SVR by 20 to 30%. The heart rate increased by midazolam is 20%. Midazolam in combination with fentanyl obtunds the pressure response during intubation to a greater extend than the thiopentone in combination with fentanyl. It decreases the tidal volume, but this is offset by an increase in the respiratory rate. The minute volume is thus little changed. However, this does not occur with increased dose of midazolam. With increased dose of midazolam, there is reduction of both the tidal volume and respiratory rate with reduction of minute volume. Apnoea occurs in 10 to 70% of patients when midazolam is used as an induction agent with the appropriate dose. The drug impairs the ventilatory response both to the hypercapnia and hypoxia (Fig. 14.10).

The anticonvulsant properties of midazolam in man is like that of other benzodiazepines. The cerebral O_2 consumption and cerebral blood flow are decreased in a dose related manner by midazolam, but a normal relationship is maintained between the two. When administered intrathecally or epiduraly, the drug has antinociceptive effects. A midazolam fentanyl induction sequence is associated with a lower incidence of post-operative vomiting than with a thiopentone-fentanyl sequence. This drug decreases the adrenergic response, but not the cortisol and renin response to stress during intubation and surgery. It causes significant inhibition of phagocytosis and bacteriocidal activity of leucocyte.

The oral dose of midazolam is 0.5 mg/Kg. The intramuscular dose of it is 0.07 to 0.15 mg/Kg. The intravenous dose of midazolam for sedation is 0.07 to 0.1mg/Kg which is titrated according to the response. The endpoint of sedation is drowsiness and slurring of speech, but response to command, however, is maintained. The dose of midazolam for induction of anaesthesia through IV route is 0.1 to 0.4 mg/Kg. The drug may also be administered intrathecally in an adult in the dose of 0.3 to 2 mg or epidurally in a dose of 0.1 to 0.2 mg/Kg. The bioavailability of midazolam when adminstered by the oral route is only 45% and by the intramuscular route is 80 to 100%. It is 96% protein bound in the plasma.

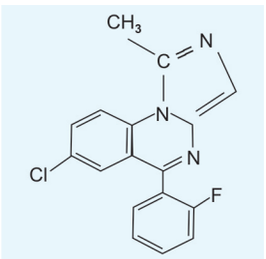


Fig 14.10: Midazolam

The midazolam is virtually completely metabolised in liver to its hydroxylated derivatives which are then conjugated to glucoronide and excreted through the bile and urine. Metabolites of midazolam also bind to the CNS benzodiazepine receptors and are pharmacologically active. Excretion of midazolam also occurs through the urine, predominantly as the hydroxylated derivatives which are formed in the liver. In the absence of renal function it can excrete solely through the bile. So, renal impairment has little effect on the excretion of midazolam. It produce little discomfort at the site of injection. Withdrawl phenomenon may also occur in children after prolonged infusion.

The short duration of action of midazolam is due to its high lipophilicity, rapid redistribution (but less than thiopentone and propofol), high metabolic clearance and rapid rate of eliminatoin. However, this may not be the true after prolonged infusion in intensive care unit. The use of midazolam in premedication decreases the MAC value of volatile anaesthetic agents by approximately 15%. The clinical effects of this drug can be reversed by physostigmine, flumazenil and glycopyrronium.

Lorazepam

Chemically, lorazepam is a lipid soluble hydroxy benzodiazepine compound. Mode of action of it is same as that of diazepam and midazolam. But the only difference is that the prolonged action of lorazepam makes it unsuitable for outpatients. It appears to have no direct cardiac effects. Mild respiratory

depression occurs following the administration of this drug which is of clinical significance only in patients with lung disease, elderly, children and neonates, etc. Like other BDZs, it also produces sedation, anterograde amnesia and anticonvulsant effects. But, the slow rate of onset of action of lorazepam would make it unsuitable, even through intravenous route for the control of status epilepticus, though it could be given as an anticonvulsant. However, clonazepam, another benzodiazepine is recommended as a more specific therapy for the control or prevention of convulsions. This drug has no effect on basal gastric acid secretion. When lorazepam is used as premedication, the circulatory cortisol and glucose levels fall. This is probably secondary to its anxiolytic effect. The prolonged action of lorazepam makes it most dependable agent for minimizing the emergence sequelae which is found, after the use of ketamine in adults. This can be achieved by the IV injection of lorazepam near the end of operation, but not by its premedicant use. So, to be effective lorazepam has to be given in the doses of 2.5 mg IV, but this may delay the complete recovery from anaesthesia (Fig. 14.11).

In adult the oral or sublingual dose of lorazepam is 1 to 4 mg/day in divided doses. For premedication in anaesthesia the lorazepam is used orally in a dose of 0.05 mg/kg. The intravenous or intramuscular dose of it for sedation is (Table 14.5) 0.025 to 0.05 mg/Kg. Intramuscular injection of lorazepam is painful. The bioavailability of this drug is 90% when administered by the oral or IM route. It is 80 to 90% protein bound in the plasma. Lorazepam is less extensively distributed in tissues than diazepam. Thus it has a longer duration of action than diazepam, despite the shorter elimination half-life of it. It is conjugated directly in the liver to glucuronide to form an inactive water soluble metabolite. 80% of an orally administered dose of lorazepam appears in the urine as the glucuronide. The elimination half-life of it is 8 to 25 hours. This is unaffected by renal disease.

The side effects of lorazepam are like that of other BDZs which are drowsiness, sedation, confusion, impaired coordination, etc, in a dose dependent manner. Paradoxial stimulation of CNS has also been reported after lorazepam and occurs more frequently when hyoscine is administered concurrently with it. The tolerance and dependence in lorazepam may occur with prolonged use of it and acute withdrawal in these circumstances may produce insomnia, anxiety, confusion, psychosis and perceptual disturbances.

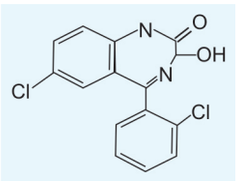


Fig. 14.11: Lorazepam

PHENCYCLIDINE – KETAMINE

Phencyclidine was the first agent among this group of drug. It was first synthesized by Maddox and was introduced in clinical practice by Johnstone in1959. During that period it was a very useful intravenous anaesthetic agent, but had high adverse psychological effect. So, it was withdrawn from the market gradually. Then came the cyclohexamine which was a congener of phencyclidine. It had the same anaesthetic property like phencyclidine, but had less analgesic property and more adverse psyclogical effects. So, it was also abandoned.

Then, ketamine as a derivative of phencyclidine was first synthesisd in 1962 by Stevens and was first used in human being in 1965. However it was released for clinical use in 1970 and is still now the most promising agent among the 200 phencylidine derivatives.

Chemistry

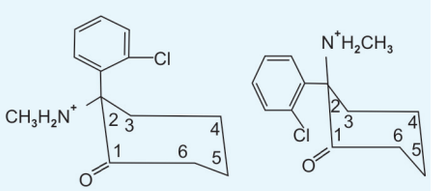
Chemically, ketamine is an aryl-cyclohexylamine compound and is a congener of phencyclidine. It is a partially water soluble white crystaline salt, with pKa value of 7.5. It is highly lipid soluble which is 5 to 10 times greater than that of thiopentone. Ketamine is available commercially as hydrochloride salt (pH 3.5 to 5.5) in concentration of 10 and 50 mg/ml in NaCl solution with benzethenium chloride as preservative. It has two optical isomers and the commercial preparation is a racemic mixture of both the isomer [S (+) and R (−)] in equal amounts, despite the (S) isomer being more potent and having less side effects than the (R) isomer (Fig. 14.12).

Pharmacokinetics

The onset and duration of action of an induction dose of ketamine is also

Table 14.5: Difference in duration of action of diazepam (10 mg) and lorazepam (2 mg)

	Diazepam	*Lorazepam*
Intravenous		
Peak effect	2 - 5 minutes	30 - 40 minute
Duration of sedation	20 - 50 minutes	3 - 6 hours
Amnesia	3 - 30 minutes	½ - 4 hours
Oral		
Onset of action	20 - 40 minutes	40 - 50 minutes
Route differences	Oral more rapid than intramuscular	Intramuscular more rapid than oral



S(+) = Ketamine hydrochloride

R(–) = Ketamine hydrochloride

Fig 14.12: Two stereoisomers of ketamine

determined by the same distribution and redistribution mechanism which is found in other parenteral anaesthetics agents such as thiopentone, propofol, benzodiasepines, etc. Ketamine's pharmacokinetic action have been examined in details after a bolus administration of an anaesthetising (2 to 2.5 mg/Kg), subanaesthetizing (0.25 mg/Kg) and a continuous infusion dose. However regardless of the dose, the ketamine's plasma disappearance can be described by a two compartmental model. The high lipid solubility of ketamine is reflected by its relatively large volume of distribution. The clearance rate of ketamine is also relatively high which accounts for its relatively short elimination half-life of 2 to 3 hours. Ketamine's large volume of distribution and rapid clearance make it suitable for continuous infusion without the drastic lengthening of duration of action, as seen with thiopentone. The protein binding capacity is much lower with ketamine than other parenteral anaesthetic agents. Thus, bolus administration of ketamine results in quick entry of it in CNS and very fast onset of action.

Metabolism

Ketamine is principally metabolised by hepatic microsomal enzyme and the principal metabolic pathway is N-demethylation which form norketamine (metabolite-I). Norketamine is then hydroxylated to hydroxynorketamine (metabolite - II) which is then next conjugated to water soluble glucoronide derivative and excreted through urine and bile. Norketamine is the active metabolites of ketamine and has 20 to 30% activity of its parent compound.

Pharmacodynamics

Effects on CNS

The primary site of action of ketamine is the thalamo-neocortical projection in brain. It depresses the cortex (association area) and thalamus, but simultaneously stimulate the limbic system and hippocampus. Thus, it creates the functional disorganisation between the midbrain, thalamus and cortex.

For ketamine's anaesthetic effect Na^+ channel blockade is not the mechanism of action.But its interaction with the NMDA (N-methyl-O-aspartate) receptor in brain mediate the general anaesthetic and analgesic effect of it. The interaction of ketamine with opioid receptor in brain and spinal cord also account for its analgesic effect. The S (+) enantiomer of ketamine has also been shown to have some opioid μ-receptor activity, accounting for part of its analgesic effect. The inhibition of wide dynamic range (WDR) of neuronal activity in the dorsal horn cells of spinal cord also account for the ketamine's analgesic activity at spinal level.

Cerebral metabolic rate, cerebral O_2 demand, CBF and ICP, etc. are all increased in ketamine anaesthesia. There is also generalised increase in sympathetic nervous system activity due to ketamine and all the above mentioned CNS effect of ketamine is due to this. But thiopentone and BDZ prevent all these responses.

Ketamine produces both dose-related unconsciousness and strong analgesia. During unconsciousness patient remains in cataleptic state, i.e. he is in sleep, but his eyes are opened. So, this anaesthetic state of ketamine is termed as the 'dissociative anaesthesia'. Although ketamine does not produce the classic anaesthetic state, still patients are remained in amnestic and unresponsiveness state to the painful stimuli. Corneal, cough and swallow reflexes are present, but they are not protective. There is amnesia during ketamine anaesthesia but it is less than BDZ. The low molecular weight, pK value near physiological pH and high lipid solubility of ketamine, allow it to cross the blood brain barrier very rapidly. So, the onset of action of ketamine is very rapid which is within 30 sec after IV administration. Lacrimation, salivation, ↑muscletone, purpousless movement of body, dilated pupil, nystagmus, etc. are all very common to ketamine anaesthesia.

The duration of action of 2 mg/Kg IV bolus dose of ketamine is 15 minutes and then full recovery to orientation about the place and time occur within 30 minutes. The plasma level of ketamine of 0.6 to 2 μg/ml is considered as the minimal concentration for GA. The short duration and early termination of effect of ketamine is thought to be due to the redistribution of it from brain (well perfused) to other body tissues (less perfused) like thiopentone and BDZ.

Analgesia due to ketamine occurs considerably at lower blood concentration than GA. This analgesic effect of ketamine also occurs at subanaesthetic dose of 0.25 to 0.5 mg/Kg IV. This analgesia due to ketamine even occurs at plasma level of as low as 0·1 μg/ml.

There are various undesirable psychological reactions during awakening from ketamine anaesthesia which are termed as the emergence reaction or emergence delirium. This emergence delirium of ketamine characterised by hallucination, vivid dreams, or illusions, etc, may sometimes result in serious patient dissatisfaction and can complicate the postoperative management. The incidence of this emergence reaction after ketamine anaesthesia ranges from 5% to 100% and abate within 1st postoperative hour. Though the exact mechanism of this emergence reaction is not known, but it is postulated that the psychic reactions that occur secondary to ketamine anaesthesia during recovery is due to the induced depression of auditory and visual relay nuclei, leading to misperception and /or misinterpretation of auditory and visual stimuli. Many factors affect this emergence reaction of ketamine such as age (less incidence in paediatric group), sex (women are more susceptible than man), dose (larger dose and rapid administration predisposes to higher incidence) and psychological susceptibility of person, etc. BDZs and among them the lorazepam is still the best drug to attenuate this ketamine induced emergence reaction.

The S-enantiomer of ketamine enables quicker recovery than the racemic mixture of

it. This is because lower doses of S-enantiomer is necessary to produce the equianaesthetic effect of the racemic mixture and has 10% faster hepatic clearance rate.

Effects on CVS

Due to increased sympathetic tone during ketamine anaesthesia there is increase in BP, HR, CO, myocardial O_2 consumption and demand. But, this increased myocardial O_2 consumption and demand is fulfilled by ↑CO and ↓ coronary vascular resistance in the normal heart by ketamine, so that the coronary blood flow is appropriate for the increased myocardial O_2 demand and consumption. This hemodynamic change is not related to the dose of ketamine i.e. a very small dose of ketamine also produces the same effect like higher doses. On the other hand, the ketamine induced hemodynamic changes are same in healthy patient and in those with variety of acquired and congenital heart disease (CHD). In patient with CHD, there are no significant changes in direction through shunt after induction with ketamine. Ketamine seems to cause more pronounced increase in PVR than SVR (PVR–pulmonary vascular resistance. SVR – systemic vascular resistance).

Ketamine enhances the sympathetic response by its centrally mediated action. But, the exact mechanism by which ketamine enhances the sympathetic tone is not known. But the probable explanation is that ketamine attenuates the pressure controlling baroreceptor function by effecting the NMDA receptor of the nucleus tractus solitarius of vagus. Directly ketamine is depressent to heart muscle but the centrally mediated sympathetic response of it override this direct response on myocardium. So, the ketamine anaesthesia experiences all the CVS effects which are described above. The sympathetic cardiovascular effects of ketamine are also mediated by the inhibition of both the central and peripheral catecholamine reuptake.

The raised sympathetic response during ketamine anaesthesia can be attenuated in clinical practice by:

i. the use of adrenergic antagonist (both α and β),
ii. the use of vasodilator,
iii. the prior administration of BDZ or thiopentone,
iv. very slow and continuous infusion of ketamine,
v. the use of inhalation anaesthetics.

Effect on RS

The central respiratory drive is minimally affected by ketamine with unaltered response to O_2 and CO_2. But there is transient decrease in minute ventilation due to respiratory depression after a blous dose of it. Seldom, very unusual high dose of ketamine produce apnoea. Usually, O_2 and CO_2 level in blood is maintained at normal level by the conventional dose, if no other sedative is used with ketamine.

By its sympathomimetic action ketamine produces bronchodilatation. In patient with reactive airway disease and bronchospasm, pulmonary compliance is also improved by ketamine. So it is a useful drug to treat the status asthmaticus which is unresponsive to conventional therapy.

Increased salivation caused by ketamine may produce upper airway obstruction and laryngospasm. Although laryngeal, pharyngeal and swallow reflexes are preserved in ketamine anaesthesia, but they are not co-ordinated and not protective. So, there is evidence that silent aspiration can occur during ketamine anaesthesia.

Uses

The poor risk patients with severe cardiovascular and respiratory disorders (except ischaemic heart disease and hypertension) are best suitable for ketamine induction and maintenance of anaesthesia. Hemodynamically compromised patient with hypovolaemia and cardiomyopathy are also the better subject for ketamine anaesthesia, but not the patient suffering from coronary artery disease. Profound analgesia, allowing the use of high inspired O_2 concentration without N_2O and added inhalational anaesthetics and bronchodilatation make the ketamine an excellent agent for induction in asthma patient. However, for extensive trauma or severe septic shock patient, we have to keep in our mind that ketamine has intrinsic myocardial depressant effect and it may be manifested if the sympathetic store is completely depleted in these group of patients before ketamine induction. The cardiac problems which can better be managed by ketamine than thiopentone are temponade, restrictive pericardities, congenital heart disease and especially those in whom the propensity for Right to Left shunt exist. Ketamine is also a very useful drug for patient with the history of potential malignant hyperthermia. It is not arrhythmogenic.

When ketamine is combined with BDZ and fentanyl or sufentanil in continuous infusion, then they attenuate the unwanted tachycardia as well as hypertension caused by ketamine alone and produce very satisfactory condition in cardiac anaesthesia for vulvular disease and IHD. This combination is also associated with minimum hemodynamic changes, perfound analgesia, dependable amnesia, and uneventful convalescence.

Ketamine also can be used for postoperative analgesia in subanaesthetic dose (≤ 1 mg /Kg), when one wishes to avoid narcotics, because of their respiratory depression and when there is also reason to avoid nonsteroidal agents such as ketorolac.

Ketamine is mainly used for short paediatric outdoor procedure, such as cardiac catheterisation, radiation therapy, radiological diagonostic procedure, dressing changes, etc. But, caution is advised during the use of ketamine in patient with elevated PVR. When used as supplementation for regional anaesthesia, ketamine (0.5 mg/Kg IV) combined with diazepam (0.15 mg/Kg IV) is better accepted by patient and not associated with greater side effects as compared with the unsedated patient (Table 14.6).

Table 14.6: Uses and doses of ketamine

Induction of GA	
0.5 - 2 mg/Kg IV	
4 - 6 mg/Kg IM	
3 - 10 mg/Kg oral	
Maintenance of GA	
0.5 - 1 mg/Kg IV (bolus)	With $N_2O + O_2$
10 - 50 µg/Kg/min IV	With $N_2O + O_2$
30-90 µg/Kg/min IV without N_2O	
Sedation and analgesia	
0.2 - 0.8 mg/Kg IV over 3 - 4 minutes	
2 - 4 mg/Kg IM	
10 - 20 µg/Kg/min IV (maintenance)	

Lower doses are used if other drugs such as opioids, BDZ or thiopentone are also given with ketamine.

Doses and Route of Administration

Ketamine can be administered through IV, IM, oral or rectal route. Dose of it depends on the route of adminstration and the desired therapeutic effect. The oral dose of ketamine is 5 to 10 mg/Kg, and the onset of action is 20 to 40 minutes. However the corresponding intravenous dose of it is 1.5 to 2 mg/Kg, administered over a period of 60 seconds. The onset of action of ketamine through IV route occurs within 30 to 60 seconds and the duration of action is 5 to 10 minutes. Through IM route the onset of action of ketamine is about 5 minutes and peak effect is at about 20 minutes. Ketamine may be infused intravenously at the rate of 50 µg/Kg/minute. The drug is also effective when administered extradurally (in an adult the dose is 10 mg) or intrathecally.

Side Effects and Contraindication

The side effects of ketamine are its contraindication for use. These are:

i Intracranial leison, increased ICP, cerebral ischaemia.
ii. IHD due to increased myocardial O_2 consumption and demand.
iii. Open globe injury.
iv. Vascular aneurysm.
v. Psychiatric disease such as schizophrenia.
vi. Eclampsia.
vii. Hypertension.

PROPOFOL

History

In 1970, the extensive search for derivatives of phenol as a substituent of it suddenly resulted in the development of 2, 6, di-isopropyl phenol (commonly named as propofol) which has strong hypnotic properties. Then, the first clinical trial of 2, 6, di-isopropyl phenol as hypnotic in 1977 confirmed the potentiality of it as an anaesthetic inducing agent. Initially, it was prepared in cremophor EL due to its insolubility in water. But, due to the increased incidence of anaphylactoid reaction because of the cremophor EL, the drug was reformulated as an emulsion in soyabean oil and egg white.

Chemistry

Chemically, propofol is a 2, 6-diisopropyl phenol. As it is an alkyl phenol derivative, so it is insoluble in water and remains as liquid oil at room temperature. It is highly lipid soluble. Therefore, the present emulsion formulation of propofol consists of 1% propofol, 10% soyabean oil, 2.25% glycerol and 1.2% purified egg phosphatide, without any preservative. But, disodium EDTA or sodium metabisulfite is added as preservative to inhibit the bacterial growth in USA. Without EDTA or metabisulfite the emulsion preparation of propofol should be used shortly after removal from the sterile packaging. Otherwise, significant bacterial contamination can cause serious infection as there is no preservative. This emulsion preparation of propofol is milky white in appearance and slightly viscous. It is stable at room temperature and is not light sensitive. This emulsion preparation is compatible with 5% dextrose solution.The pH of propofol is 7 and is commercially available as 1% solution (Fig. 14.13).

Pharmacokinetics

Propofol is only available as IV preparation for the induction and/or maintenance of GA. It is also used for conscious

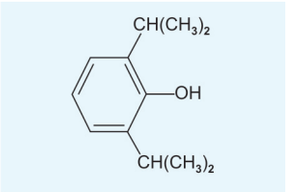


Fig. 14.13: Propofol: It is an alkyl phenol derivative

sedation to deep sedation by continuous IV infusion. The high lipid solubility of it results in an onset of action that is almost as rapid as that of thiopentone. Duration of action after a single equivalent bolus dose of propofol is also similar or even shorter than those of thiopentone. This is due to the rapid decline of plasma concentration of propofol after an IV bolus dose which can be fitted to a typical three compartment model of thiopentone and explain its rapid distribution, redistribution and clearance rate (elimination).

The initial volume of distribution of propofol is 20 to 40 litres and the initial distribution half-life of it is 2 to 8 minutes. Following an IV bolus dose of propofol, the plasma level initially declines rapidly due to redistribution from highly perfused but lower capacity tissue such as brain, heart, etc, to high capacity but lower perfusion sites such as muscle, liver, spleen etc. This initial clearance of propofol from the central compartment by redistribution is rapid (3 to 4 litre/Kg/minute) and is responsible for quick awakening and less hangover from single bolus dose of it. Thus this makes it a better agent for outpatient anaesthesia than the thiopentone and methohexitone (Fig. 14.14).

Propofol's pharmacokinetics may be altered by a variety of factors such as age, gender, weight, other medications, preexisting diseases, etc. A lower induction dose is recommended in elderly patients. This is because of their smaller initial volume of distribution. Women may require a higher dose of propofol than men and appear to awaken faster due to higher volume of distribution. Recovery after multiple doses or infusion of propofol is

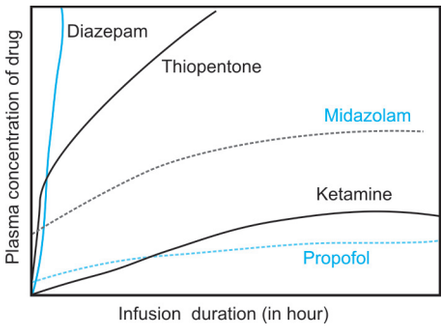


Fig. 14.14: The context sensitive half time or CSHT is the time for the plasma level of the drug to drop 50% after cessation of infusion. This figure shows context sensitive half-time (CSHT) for diazepam, thiopentone, midazolam, ketamine and propofol. The duration of infusion is plotted on the horizontal axis and the drop of plasma level is plotted along the vertical axis. The figure shows that the rapidity with which the drug level in plasma drops is directly related to the properties of that drug and the time of infusion. The longer the drug is infused, the longer is the half-time. It is also noted that the propofol and ketamine have significantly shorter context sensitive half-time (CSHT) than diazepam and thiopentone. So, this makes them suitable for prolonged infusion. The position of midazolam lies between diazepam, thiopentone and ketamine, propofol

much faster than thiopentone. This can be explained by its very high metabolic clearance rate in liver which is about 1.5 to 2.5 litre/minute and 10 times higher than that of thiopentone. This high metabolic clearance rate of propofol exceeds the hepatic blood flow. This also implies the existence of some extrahepatic metabolic clearance site of propofol which is still unknown. But, the lung does not take part as extrahepatic metabolic site of propofol. In liver, propofol is metabolised by conjugation to water soluble glucuronide and sulphates, which are excreted through bile and kidney. Metabolites of propofol are not active one. Although metabolites of propofol are primarily excreted through the urine, but the chronic renal failure does not affect the clearance of the parent drug. The pharmacokinetic of propofol do not appear to be affected by moderate cirrhosis. Use of propofol infusion for long term sedation in children who are critically ill has been associated with cases of lipedemia, metabolic acidosis and death.

Pharmacodynamics

Effect on CNS

The primary action of propofol are hypnosis and sedation, but the exact mechanism of these actions are not known. Probably it acts by enhancing the function of GABA activated chloride channel like benzodiazepine and thiopentone (Table 14.7).

But unlike thiopentone, propofol is not antianlgesic. The onset of hypnosis following IV administration of propofol in the doses of 2.5 mg/Kg is 30 sec (though it depends on the speed of injection) and duration of action (though dose dependent) is 10 to 15 minutes. The onset and duration of action of propofol also depends on the type and dose of premedication. Propofol can also be used in subanaesthetic or subhypnotic dose. Subhypnotic dose of propofol will only produce conscious sedation and amnesia, but no hypnosis or anaesthesia. The infusion of propofol in the dose of 2 mg/Kg/hr is necessary to provide amnesia in unstimulated patients. But, during surgery, higher infusion rate is necessary to prevent the awareness, if propofol is used alone.

The effect of propofol on epileptogenic activity is in controversy. Because the results from studies on the anticonvulsant effects of it are mixed. The propofol induced convulsion is very rare. The EEG amplitude increases when the propofol blood concentration varies between 3 to 8 µg/ml. But when the propofol concentration in blood rises above 8 µg/ml, then the amplitude of EEG decreases rather than increases and there is burst supression. The induction of GA by propofol is occasionally accompanied by excitatory phenomenon such as muscle twitching, spontaneous movement, opisthotonus or hiccup, etc. This is possibly due to the subcortical inhibitory glycine antagonism by propofol. Although these reactions may occasionally mimic tonic-clonic seizure, but actually propofol appears to have predominantly anticonvulsant properties. So, propofol can be successfully used to terminate the status epilepticus and may be safely administered in epileptic patients.

Propofol decreases ICP (30 to 50%) in both normal and in patient with already raised ICP. However, this decrease in ICP is also associated with decrease in cerebral perfusion pressure, both in normal and elevated ICP patient and therefore may not be beneficial. This is due to the much reduction of systemic blood pressure in comparison to the reduction of ICP. So, steps should be taken to support the mean arterial pressure and to elevate the cerebral perfusion pressure (>50 mm of Hg). Propofol also provides cerebral protective effects following ischaemic injury like thiopentone. It also acutely reduces IOP (Intra Ocular Pressure) by 30 to 40% and a small second dose is more effective in preventing the rise of IOP secondary to succinylcholine or ET tube intubation.

The propofol blood concentration (Cp_{50}) needed for loss of response to verbal

Table 14.7: Uses and doses of commonly used drugs for sedation and induction of anaesthesia

Thiopentone (2.5%)	Sedation	IV	0.5 - 1.5 mg/Kg
	Induction	IV	4 - 5 mg/Kg
Propofol (1%)	Sedation (infusion)	IV	25 - 100 µg/Kg/min
	Induction	IV	1 - 2 mg/Kg
	Maintenance	IV	50 - 200 µg/Kg/min
Ketamine	Induction	IV	1 - 2 mg/Kg
Methohexital (1%)	Sedation	IV	0.2 - 0.4 mg/Kg
	Induction	IV	1 - 2 mg/Kg
		Rectal (10%)	25 mg

command is 3.5 µg/ml and to skin incision is 16 µg/ml (propofol alone without narcotics, inhalational agents etc). This propofol Cp_{50} value for skin incision comes down to 2.5 µg/ml, when it is combined with BDZ (as premedication) and 66% N_2O. This value again comes down to 1.7 µg/ml, if narcotic is used in place of BDZ. Awakening from induction usually occurs when the blood concentration of propofol comes down to or below 1.6 µg/ml and orientation comes back when the plasma concentration comes down to 1.2 µg/ml.

Effects on CVS

Prpopofol produces a dose dependent decrease in blood pressure which is significantly greater than that produced by thiopentone. Prpopofol has both the vasodilation (venous and arterial) and myocardial depression effects. This appears to be due to the reduction in sympathetic tone and also due to the direct negative effect on the intracellular Ca^{2+} mobilisation in smooth muscle. Thus, there is decrease in the vascular smooth muscle tone and reduction in preload and afterload. As a result, there is decrease in systolic blood pressure, diastolic blood pressure, and systemic vascular resistance (due to vasodialtion). However, the changes in cardiac output, stroke volume, cardiac index produced by propofol depend on the changes in preload, afterload and SVR. Pulmonary artery pressure and pulmonary wedge pressure are also reduced by propofol.

The HR dose not change significantly with the reduction of BP after an induction dose of propofol. This suggest that propofol either reset or inhibits the baroreflex and thus reduces the tachycardia response to hypotension. Changes in HR and CO are usually transient and insignificant in healthy patients. But, it may be severe enough and lead to asystole, particularly in patients who are at the extreme of age, on negative chronotropic medications, undergoing surgical procedures, associated with ocular cardiac reflex, etc.

When patient is allowed to breath air or air plus O_2 and hypnosis is maintained only by propofol infusion in the dose 50 to100 µg/Kg/min, then SVR, BP, CO, CI are reduced. But, when the same patient is intubated and hypnosis is maintained by N_2O and propofol infusion of same dose, then SVR and BP does not reduce, but CO and CI falls. This is due to the presence of N_2O or surgical stimulus. So, intraoperative BP can not be reduced in intubated hypertensive patient by propofol only.

Infusion of propofol results in significant reduction in both myocardial blood flow and myocardial O_2 consumption. But the global O_2 supply/demand ratio is preserved.

Though the reduction of BP (due to vasodilation) and myocardial depression effect of propofol is blood concentration dependent, but the decrease in BP from propofol during infusion is much less than that seen following an induction bolus dose.

Effects on respiratory system

Propofol's effects on respiratory system is similar to that of barbiturates. So, like barbiturates it depresses the respiration and may produce apnoea. The onset, duration and incidence of apnoea due to propofol depends on the dose, speed of injection and the concomitant use of premedication. The incidence of propofol induced apnoea is greater than any other IV inducing agents and is preceded by marked reduction in tidal volume (40% decrease) and respiratory rate (20% decrease). So, there is unpredictable change in minute ventilation (decreased or increased).

During infusion of propofol the respiratory rate gradually decreases. Then, when the respiratory rate is fixed at lower level and still if concentration of infusion is gradually increased, then there is gradual decrease in tidal volume, but no change in respiratory rate. This is followed by apnoea. Propofol infusion inhibits hypoxic ventilatory drive. Ventilatory response to CO_2 is also decreased. Propofol induces bronchodilatation in patient with chronic obstructive pulmonary disease, although it can cause histamine release. So induction with propofol is sometimes accompanied by a lower incidence of wheezing in asthamatic and nonasthamatic patients, compared to barbiturates and is not contraindicated in asthmatic patients. The propofol induced depression of upper airway reflexes exceeds than that of thiopentone and can prove helpful during intubation or LMA placement in the absence of muscular paralysis by muscle relaxant.

Miscellaneous effects

Like thiopentone, propofol does not potentiate the neuromuscular blockade, produced by muscle relaxant. Propofol does not tigger the malignant hyperpyrexia and so is the anaesthetic of choice in such condition. It does not affect the corticosteroid synthesis or alter the normal response to ACTH stimulation. The incidence of anaphylactoid reaction, following propofol has been reported at about the same low frequency as does the thiopentone. But high percentage of patient who develops anaphylactoid reaction to propofol have the previous history of allergic response. So, the propofol should be used cautiously to the patient who will give the history of multiple drug allergies. It has significant antiemetic property and is a good choice for sedation or anaesthesia in patient who have high risk for nausea and vomiting. Sometimes, postoperative nausea can be treated sucessfully by IV bolus dose of 10 mg propofol. Although, propofol does cross the placental barrier, still it is considered safe for the use in pregnant patient and transiently depresses the activity of newborn as thiopentone (Table 14.8).

Doses

Premedication of patient with opiate and /or BDZ markedly reduces the induction and maintenance dose of propofol. Age also reduces the dose of propofol with or

Table 14.8: Uses and doses of propofol

Induction of general anaesthesia:
1 - 2.5 mg/Kg IV, reduced in patients over 60 years of age
Maintenance of general anaesthesia:
50 - 150 µg/Kg/min IV, reduced if combined with N2O, BDZ or an opiate
Sedation:
20 - 50 µg/Kg/min IV

without premedication. It can also be used successfully for patient controlled sedation (PCS) like patient controlled analgesia (PCA). But in this respect it is better than midazolam and it is due to its rapid onset and offset action. Propofol by its continuous infusion provides a readily titratable level of sedation and rapid recovery once infusion is terminated, irrespective of the duration of infusion.

DROPERIDOL

History

In 1950, Laborit and Hugnenard thought of a new anaesthetic technique which will produce a state of 'artificial hibernation or neurolept'. This new anaesthetic technique was without the need of muscular paralysis and was devoid of CVS and respiratory depression effect. Their concept regarding this technique was to block centrally the autonomic, endocrine and other centres which normally are activated in response to stress during surgery. This central block can be performed selectively by drugs which will produce artificial hibernation, in contrast to the entire depression of CNS which causes general anaesthesia. The first drug which was evolved for this purpose and was used in this concept was 'lytic cocktail'. It was a mixture of meperidine (analgesic), chlorpromazine or promethazine (tranquiliser) and atropine (antisialagogue). It can produce conscious sedation, but not the full GA.

Then, Janssen first synthesised haloperidol (which was the 1st member of butyrophenones group of drugs and the primary neuroleptic component of neuroleptic anaesthesia – NLAN) and phenoperidine (which is the meperidine derivatives). After that in 1959, DeCastro and Mundeleer combined these and used them as a forerunner of NLAN. Then, Janssen synthesised droperidol (a derivative of haloperidol) and fentanyl (phenoperidine congener). So, DeCastro and Mundeleer again used their combination and reported these to be superior than previous combination. Now, droperidol and fentanyl are the currently used combination for neuroleptic anaesthesia (NLAN).

The term 'neuroleptic' is synonymus with the term 'antipsychotic'. Initially this 'neuroleptic' term was used to denote the effect of chlorpromazine and reserpine which reduce the intiative and interest of patient for the external enviornment and as well as decrease the manifestation of emotions. This term 'neuroleptic' is still used now as a synonym for antipsychotic effect. But the more general term 'antipsychotic' is preferred now a days than neuroleptic. Despite their sedation effects, neuroleptic drugs generally are not used to treat anxiety disorders. This is largely because of their autonomic and neurological side effects, which paradoxically include severe anxiety and restlessness.

Mechanism of Action

Like all the antipsychotic drugs, droperidol acts by its potent dopamine D_2 receptor blocking action. Blockade of the dopaminergic projection to the temporal, prefrontal (constituting the limbic system) and mesocortical areas is probably responsible for the antipsychotic action of droperidol. Because dopamine overactivity at limbic system is responsible for the psychiatric condition. Dopaminergic blockade in the basal ganglia also appears to cause the extrapyramidal symptoms of droperidol while that in CTZ is responsible for the antiemetic action of it.

Droperidol like other antipsychiatric drugs also have the α-adrenergic blocking action, weak H_1-antihistamine action and anti-5-HT action.

Pharmacokinetics

The clearance rate of droperidol is 14 ml/kg/min and elimination half-life is 103 to 134 minutes, which indicates its short duration of action. The time course of disappearance of fentanyl and droperidol from plasma is same.

Pharmacodynamics

Effects on CNS

The effects of droperidol on CNS differ in normal and psychotic individuals. In normal individuals it produces indifferences to the surroundings, paucity of thought, psychomotor slowing, emotional quietening, reduction in initiative and tendency to go to sleep from which the subject is easily arousable. The spontaneous movements are minimized, but the slurring of speech, ataxia or motor in coordination does not occur. These have been referred to as the 'neuroleptic syndrome'. Now, there is tendency to use the term 'neuroleptic' to emphasize the more neurological aspects of this syndrome. The neuroleptic agents also have the characteristic neurological effcts including bradykinesia, mild rigidity, tremor and restlessness that resemble Parkinson's disease and is quite different from the sedative action of barbiturates and other similar drugs. These effects are appreciated as unpleasant by most of the normal individuals.

On the otherhand, in psychotic individuals it reduces the irrational behaviour, agitation, aggresiveness and controls the psychotic symptomatology. The disturbed thought and behaviour are gradually normalised and anxiety is relieved. Hyperactivity, hallucinations and delusions are supressed.

It potentiates the action of hypnotics, opioids etc. Performances and intelligence of an individual are relatively unaffected, but vigilance is impaired by droperidol. The medullary respiratory centre and other vital

centres are not affected. It has profound antiemetic action, exerted through CTZ.

Effects on CVS

Droperidol has vasodilating properties and decrease BP. This is due to the α-adrenergic blocking action of it. Directly, it has no action on myocardial contraction. But, it possesses some antiarrhythmic properties like quindine.

Effects on RS

Droperidol has very little effect on RS. So, no significant effect on respiratory rate and tidal volume is found.

Use

Droperidol is used as a component of NLAN. It is also used as antiemetic in the dose of 10 to 20 µg/Kg through IM or IV route. It reduces the incidence of nausea and vomiting upto 50% (Table 14.9).

Droperidol and Fentanyl Combination

In clinical practice of neuroleptic anaesthesia (NLAN), the droperidol and fentanyl combination is used in the ratio of 50:1 (droperidol 2.5 mg/ml and fentanyl 50 µg/ml). In this combination the droperidol produces the hypnotic, sedative and antiemetic effect, while the fentanyl produces the analgesic effect. The action of these two components in their combination are simply additive, but not synergistic. Consciousness returns after NLAN very promptly within 3 to 5 minutes.

Table 14.9: Uses and doses of combination of droperidol and fentanyl in the ratio of 50:1 (droperidol 2.5 mg/ml and fentanyl 50 µg/ml)

Induction of general anaesthesia:
0.1 to 0.15 ml/Kg with N_2O and O_2
Maintenance of general anaesthesia:
Fentanyl 0.02 - 0.05 µg/Kg/min
Sedation and analgesia:
0.5 - 1 ml IV repeated according to the desired effect
1 - 2 ml IM

Due to the presence of fentanyl, this combination produce respiratory depression. This respiratory depression can be antagonised by the administration of a narcotic antagonist. This combination also produce ↓ BP (droperidol effect) and ↓ HR (fentanyl effect – fentanyl induced increased vagal tone). However, there is no reduction in CO, if adequate blood volume is maintained. The combination of droperidol and fentanyl, used as NLAN (neurolept anaesthesia) is very helpful for short outdoor surgeries, diagnostic procedures, sedation during local anaesthesia or conduction anaesthesia. This combination can also be used as inducing agent in GA, performed by N_2O and muscle relaxant in the dose of 0.1 to 0.15 ml/Kg. The components of NLAN can be given separately or as a mixture. When given separately, then droperidol should be given first in the dose of 5 to 10 mg (5 to 15 µg/Kg). This is followed by incremental doses of fentanyl which varies between 50 to 100 µg. These drugs should be used with caution for the possibility of vasodilatation and hypotension. So a test dose of 1 to 2 ml is always recommended before the bolus induction dose. It is also recommended to give 200 to 300 ml of balanced salt solution and correct hypotension prior to induction. The customery dose of this combination for sedation is about 2 to 4 ml in divided doses, titrated to the desired level of sedation. It is very helpful for surgery which are associated with high incidence of post operative nausea and vomiting.

NLAN have several adverse effects such as:

i. *Muscle rigidity:* This is due to the fentanyl which can be treated by muscle relaxant.
ii. *Respiratory depression:* This is due to fentanyl which can be treated by opioids antagonist. But this may reverse the analgesic effect of opiate and precipitate hypertension.
iii. *Hypotension:* This is due to droperidol which can be treated by IV fluid and or α-adrenergic agonist.
iv. *Prolonged somnolence:* This is due to droperidol which is dose related and is reversed by physostigmine (2 mg). Physostigmine is not the specific antagonist of droperidol. Physostigmine clearance is rapid than droperidol, so resedation can occur.
v. *Extrapyramidal symptom:* It is manifested by dyskinesia of face and neck with speech and swallowing difficulties. It is due to droperidol which can be treated by diphenhydramine or benztropine.
vi. Psychological reactions sometimes occur, when used as premedicant and manifested as patient refuses to have surgery.
vii. *Hallucination,* e.g. weightlessness, loss of body image. (viii). Rare complication such as malignant–neuroleptic syndrome.

FLUMAZENIL (Fig. 14.15)

Flumazenil (imidazobenzodiazepine) was first synthesised in 1979 as BDZ – receptor antagonist or blocker. The benzodiazepine agonists have both the affinity for binding with the receptor and ability to produce maximal intrinsic activity such as hypnosis, sedation and amnesia. On the otherhand the antagonists have the same affinity to receptor for binding, but have no ability to produce any intrinsic activity. They just only block the physiological effects of agonist, inverse agonist and other molecules by preventing them to bind with the BDZ receptor. Inverse agonists have also affinity to receptor and have intrinsic activity which are opposite to the physiological effect of agonist. Partial agonists have affinity to receptor and produce submaximal intrinsic activity in the same direction as agonist.

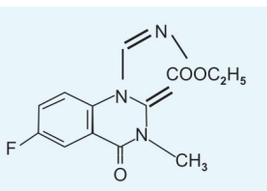


Fig 14.15: Flumazenil

Partial inverse agonists have affinity to receptor and produce submaximal intrinsic activity in the opposite direction to agonist. As flumazenil is the BDZ-receptor antagonist, its structure is similar to that of classical BDZ, except a phenyl group which is replaced by carbonyl group and blocks all the activities of BZDs and its inverse agonists. It was released for clinical use in 1991 (Fig. 14.16).

Flumazenil is a BDZ analogue and forms a complex with BDZ receptor with high affinity, great specificity and block all the effects of benzodiazepine agonist and inverse agonist with the minimal or none intrinsic activity. So, both the electrophysiological and behavioral effects of BDZ (agonist) and DMCM (inverse agonists) are blocked. Hence, it blocks both the depressant effect of BDZ and as well as the stimulant effect of DMCM. The DMCM has stimulant effect, because it is inverse agonist of BDZ receptor. So it produces all the oposite effects of BDZ. It replaces the BDZ agonists at the receptor level in a competitive (competitive antagonist) and concentration dependent manner. Flumazenil like other competitive antagonist does not displace the agonist from the receptor which is already attached. But, rather it occupies the receptor when an agonist dissociates from it and prevents the agonist from further attachment with the receptor. The half-life of a bond between a receptor and antagonist is few seconds and new bonds are then immediately formed. So, it is a dynamic situation where agonist and antagonist continuously compete with each other to occupy the receptor. The proportion of the receptor occupancy by agonist and antagonist obeys the law of mass action, and depends on the affinitly and concentration of the agonists and antagonists. As flumazenil (antagonist) is cleared from the plasma relatively rapidly, so, though it has high affinity to the receptor, the chance of the receptor reoccupied by agonist will increase and the potential for resedation will exist. Low dose of flumazenil in presence of high doses of agonist will only attenuate the deep CNS depression of agonist (unconsciousness and respiratory depression), but without attenuating other agonistic effects which occur at lesser receptor occupancy (drowsiness, amnesia). On the contrary, only the high doses of flumazenil in the presence of low doses of agonist will completely reverse all the effects of BDZ and can precipitate withdrawl symptoms in dependent patient.

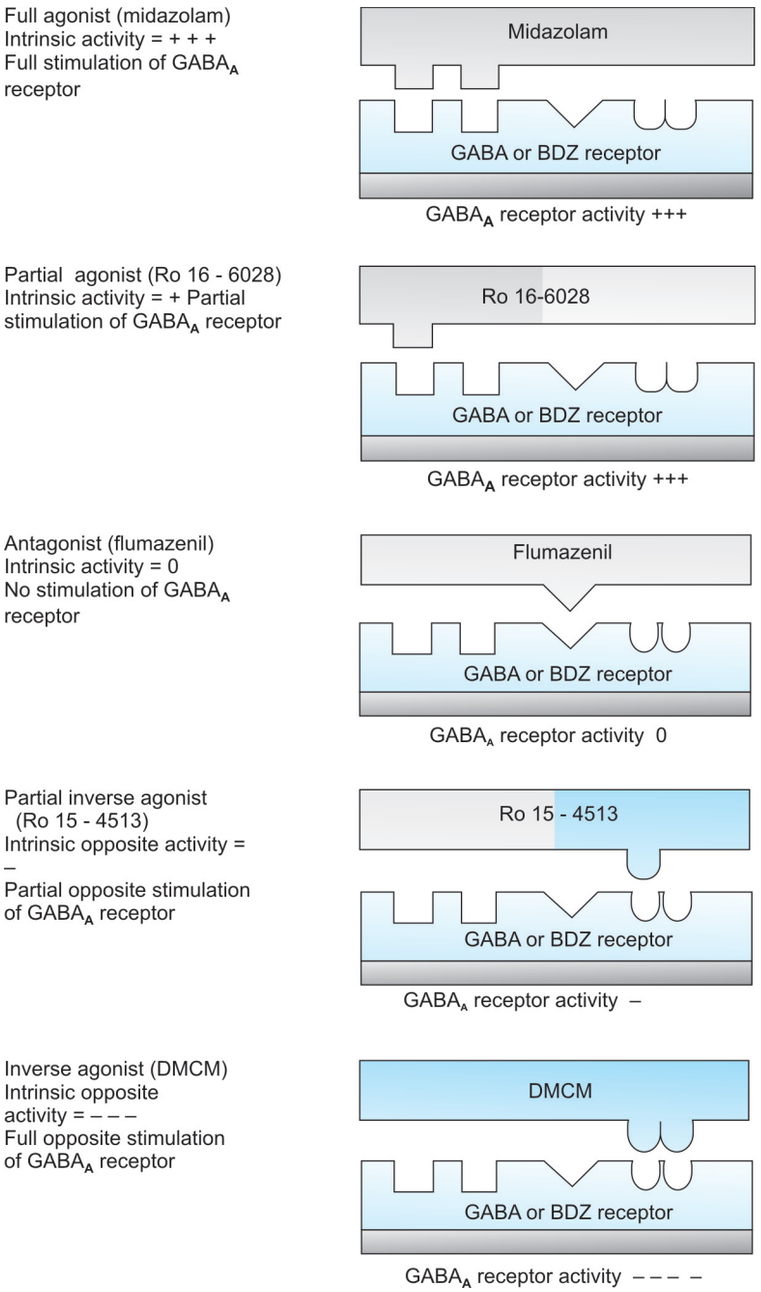


Fig. 14.16: GABA$_A$ receptor activity

Pharmacokinetics

In comparison with BDZ receptor agonists, flumazenil has highest clearance and shortest elimination half-life. The plasma half-life of flumazenil is only 1 hour. This shorter

half-life of it causes the potential risk of resedation due to the still presence of agonist in plasma. So, to avoid this draw back and to maintain a constant therapeutic blood level of antagonist, repeated administration or continuous infusion of flumazenil is required in the rate of 30 to 60 mg/min or 0.5 to 1 µg/Kg/min. Although, it is rapidly absorbed after oral administration, but less than 25% of the drug reaches the systemic circulation as a result of extensive first pass hepatic metabolism or clearance (Fig. 14.17).

Pharmacology

When flumazenil is given alone in the absence of any BDZ, then its intrinsic effects on BDZ receptor are difficult to observe or nil. As previously described, the flumazenil acts by replacing the BDZs from its receptor, so its onset and duration of action are governed by the law of mass action. Onset of action of flumazenil is very rapid and the peak effect reaches within 1 to 3 minutes. It rapidly reverses the unconsciousness, respiratory depression, sedation, amnesia and psycomotor dysfunction produced by the benzodiazepines according to the dose. It has no effect on EEG, cerebral metabolism and has no anticonvulsant properties. But, it reverses the anticonvulsant properties of BDZ. Higher dose of flumazenil is required to reverse the effects of lorazepam than diazepam and this is because of the greater potency of former. The duration of action of flumazenil is determined by its dose, the dose of agonist and the type of agonist. Usually the duration of action of flumazenil is 45 to 90 minutes, after a dose of 3 mg IV. Flumazenil will not reverse the opioid induced respiratory depression. It is completely devoids of cardio vascular effects.

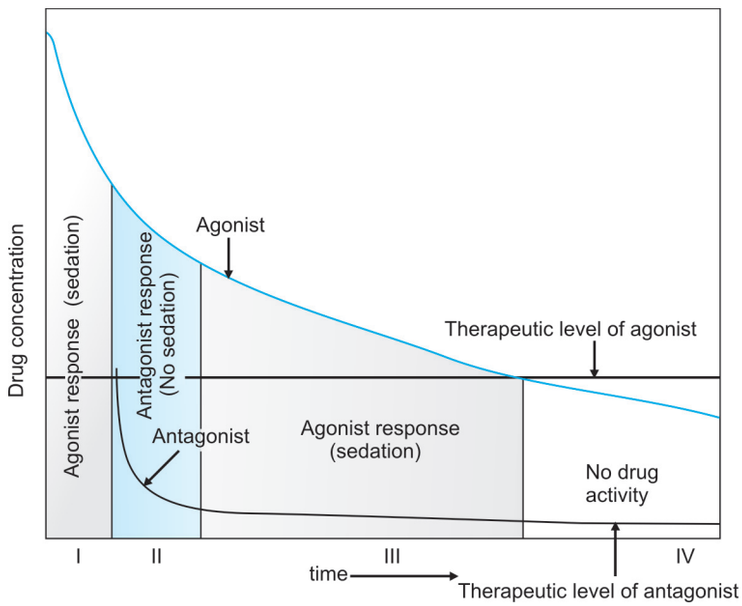


Fig. 14.17: The interaction of duration of action between the short acting antagonist and long acting agonist, causing resedation. The above red curve shows the gradual disappearance of agonist from the blood. The below green curve shows the disappearance of antagonist from blood. This agonist - antagonist interaction is represented by four condition:

I = Full agonistic response or sedation. In this phase antagonist is not administered.

II = Full antagonistic response or awake from sedation. In this phase antagonist is administered and the plasma level of both the agonist and antagonist is above their respective therapeutic level. Patient awake from sedation because antagonist completely block the action of agonist.

III Re-agonist response = resedation. This is because the plasma level of antagonist goes below its therapeutic level, but the plasma level of agonist still remains above its therapeutic level.

IV = No drug effect, with disappearance of both the action of agonist and antagonist. This is because plasma level of both the drugs goes below their respective therapeutic level

Metabolism

Like BDZs, flumazenil is also rapidly taken by the liver from plasma and is metabolised to N-desmethyl flumazenil, N-desmethyl-flumazenil acid and flumazenil acid which are later conjugated to glucoronids and excreted through bile and urine.

Use and Dose

Flumazenil is successfully used to reverse the effect of sedation, respiratory depression and amnesia produced by BDZs during the practice of anaesthesia. The dose of flumazenil varies with the particular BDZ being reversed. The duration of reversal is dependant on both the kinetics of agonist (benzodiazepine) and antagonist (flumazenil). To prevent resedation caused by longer acting BDZs, flumazenil may be administered by continuous infusion. The useful dose of flumazenil is 0.1 to 0.2 mg which is repeated upto total 1 to 3 mg over 1 to 3 minutes. This dose is usually sufficient to abolish the effects of therapeutic doses of benzodiazepines. However, the administration of series of small doses of flumazenil is preferred to a single bolus injection of it.

For diagnostic purpose, the flumazenil may be given in incremental doses of 0.2 to 0.5 mg IV upto 3 mg over 2-10 minutes. If there is no change in sedation, it is unlikely that CNS depression is based solely on BDZ overdose.

Flumazenil is not effective in the treatment of drug overdose by either barbiturates or tricyclic antidepressants. To the contrary, under such circumstances the administration of flumazenil may be associated with the seizures. The risk of seizures is especially high in patients, poisoned with tricyclic antidepressants.

OPIOIDS

History

Opium has been known to mankind for many centuries. It was first mentioned in Eber's papyrus (1500 BC) and in the writing of Theophrastus (300 BC) and Galen

(2nd century AD). On the otherhand, crude opium was available in Asia from two millennium ago before the discovery of modern anaesthesia. It was used throughout the middle ages in Europe as the preparation, named 'laudanum'. Crude opium is a dark brown and resinous material which is obtained from poppy (papaver somniferum) capsule. It contains two types of alkaloids: (i) alkaloid of phenanthrene derivatives–morphine (10%), codeine (5%), thebaine (0.2%), and (ii) alkaloid of benzoisoquinoline derivatives – papaverine (1%), noscapine (6%). Papaverine is devoid of opiate activity, but causes smooth muscle relaxation. Papaveretum is a preparation of crude opium containing the water soluble alkaloids of opium with 50% anhydrous morphine and the remaining 50% is a mixture of papaverine, codeine and thebaine.

Opium eating was a social custom in china. Before 1840, oral opium was the mainstay of analgesia. The first step of success in the introduction of opioids in anaesthesia was the isolation of morphine from opium by Seturner in 1803. It was named 'morphine' after the name of a Greek god of dreams named 'Morpheus'. It was first given hypodermically, using a vaccination lancet in 1836. Then, introduction of syringe and hollow needle in clinical practice by wood in 1853 finally permitted the opioids to be administered in a more precisely measured doses.

Morphin was frequently injected at that time intramuscularly as premedication or as a supplement during the ether and chloroform anaesthesia or as post-operative analgesia. Then in late nineteenth century, high dose of morphine (3 mg/Kg) with scopolamine was used as a complete anaesthetic agent. After that though this technique initially gain popularity, but rapidly fell into disfavour for its high perioperative morbidity and mortality. So, for the next 30 to 40 years anaesthesiologist never used opioid. Later, introduction of thiopentone as IV anaesthetic agent and introduction of concept of balanced anaesthesia led the renewed enthusiasm for the intraoperative use of opioids.

Diamorphine (heroine) was the first synthetic opioid which was synthesised in laboratory, in 1875, and marked the first chemical manipulation of natural opioids for the production of analgesia. Then, papaveretum was prepared, in 1909, as a pharmaceutically standardised preparation of crude opium. It was one of the first opiates to become available as solutions in ampoules.

The next important step in the history of opioid was the development of a completely synthetic opioid, named pethidine in 1939 (meperidine) in Germany. Later, during the World War II methadone was also developed in Germany and was originally named as 'dolfine' in the honour of Adolf Hitler. Then, fentanyl and alfentanyl was produced in 1962. Sufentanil followed soon after this.

Opioid receptors which are peptide in nature were also first discovered in 1979. The term opioid or opiate (which came from the term opium) is used to describe the drugs or chemical compounds that specifically bind to any of the several subtypes of opioid receptor and share the same pharmacological properties of the naturally occurring endogenous opioids. But the term 'narcotic' include the non-opioid compounds also.

Terminology

The word 'opium' is derived from the term 'opos'. This is a Greek word which means juice. So, the opium means drugs which are obtained from the juice of poppy capsule. The term 'opioid' refers broadly to all the compounds which are related to opium. So the 'Opiates' are drugs that derived from opium. The term 'narcotic' is derived from Greek word for sturpor. At one time the term 'narcotic' was referred to any drug that induced sleep and then it became associated with opioids. But now it is often used in legal context to refer the varieties of substances which have abuse or addictive potential (Table 14.10).

Classification

Opioids are usually classified into two groups according to their availability and mode of action.

A. According to their availability

1. *Naturally occurring*

Morphine, Codeine, Papaverine, Thebaine.

2. Semisynthetic

Codeine, heroin, dihydromorphone, thebaine derivative (etorphine, buprenorphine) The semisynthetic products of opioids are obtained from morphine by the following several changes:

i. Esterification of one hydroxyl group of morphine results in codeine (methyl morphine).
ii. Esterification of both the hydroxyl group of morphine results in heroin, (it is diacetylmorphine, made from morphine by acetylation at 3 and 6 position).
iii. Reduction of double bond in the benzene ring of morphine results in hydromorphone.
iv. Thebaine differs from morphine in that both the hydroxyl group of it are methylated and the ring has two double bond. It is an inactive opium derivatives. It is precursor of several clinically used compound such as oxymorphone, oxycodone, naloxone. Etorphine which is a thebaine derivatives, is thousand times more potent than morphine and is used for immobilization and anaesthesia in wild life management (Fig 14.18).

3. Synthetic

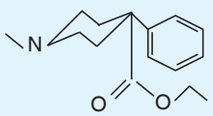
i. Morphinan series: Levorphanol, butorphanol.
ii. Diphenylpropylamine series: Methadone.
iii. Benzomorphinan series: Pentazocine.
iv. Phenylpiperidine series: Meperidine, fentanyl, sufentanil, alfentanil.
v. Many of these synthetic opioids are used experimentally for analgesia and

Table 14.10: Classification of opioid compounds

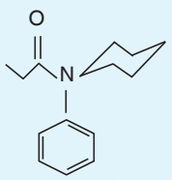
Natural occurring
Codeine
Morphine
Thebaine
Papaverine
Semi synthetic
Heroin
Codeine*
Thebaine derivatives (e.g. etorphine, buprenorphine)
Di-hydromorphone / Morphine
Synthetic
Morphinan series (e.g. levorphanol, butorphanol)
Phenylpiperidine series (e.g. meperidine, fentanyl, sufentanil, alfentanil, remifentanil)
Benzomorphan series (e.g. pentazocine)
Diphenylpropylamine series (e.g. methadone)
Morphinan series (e.g. levorphanol, butorphanol)
Phenylpiperidine series (e.g. meperidine, fentanyl, sufentanil, alfentanil, remifentanil)
Benzomorphan series (e.g. pentazocine)
Diphenylpropylamine series (e.g. methadone)

* Codeine is obtained both by naturally and by synthesis

Phenylpiperidine skeleton



Meperidine



Fentanyl

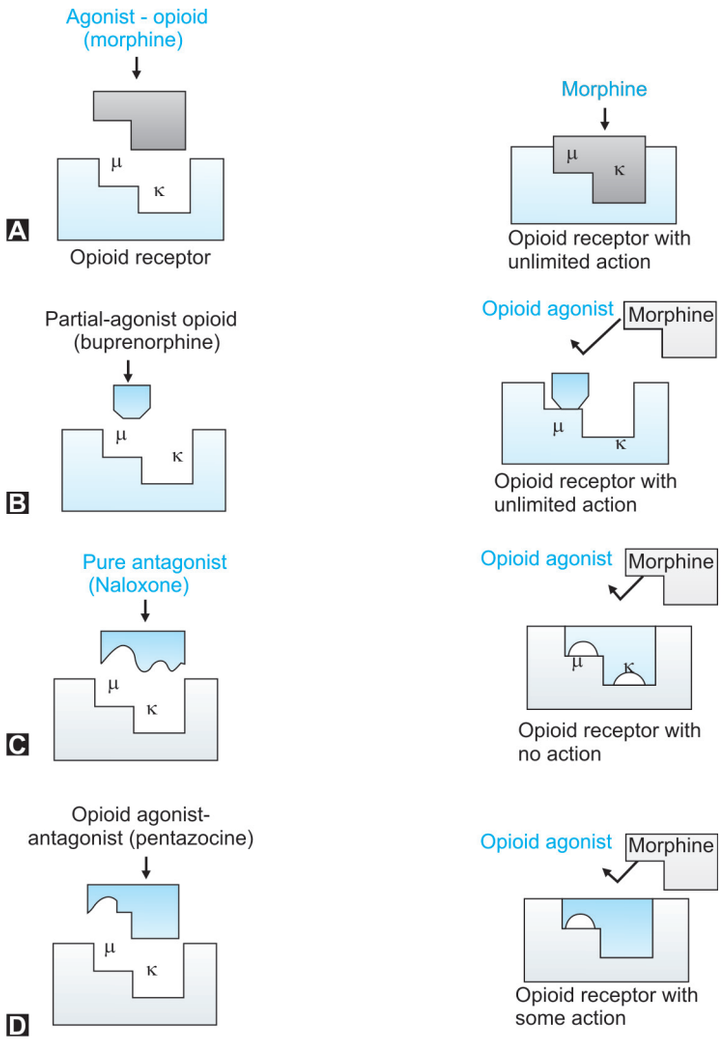


Fig. 14.18A to D: Opioid receptor interactions with agonist, partial agonist, mixed agonist and antagonist and antagoinst at two receptor sites - μ (mu) and κ (kappa).

A. Shows that an pure opioid agonist stimulates both the μ and κ receptor and analgesic action is unlimited.

B. Shows that a partial opioid agonist only combine with the μ-receptor with limited analgesic activity. κ-site remains unoccupied. It also prevents morphine to act.

C. Shows that an opioid antagonist occupies both the μ and κ receptor and prevents the agonist to attach with the receptor. But it has no intrinsic activity.

D. Shows the action of agonist - antagonist opioid which has mixed effect on μ and κ receptor. Analgesia is κ receptor related, while blockade occurs at the μ receptors

anaesthesia. But, only the morphinan, benzomorphinan and phenylpiperidine series are used clinically and play an important role in anaesthesia.

B. According to their mode of action on opioid receptor

i. *Agonist:* Produce full physiological effect in a dose dependent manner, acts on all types of opioid receptors and not blocks (antagonist) any, e.g. morphine, pethidine (meperidine), fentanyl and its congeners.

ii. *Partial or weak agonist:* They does not act on all the types of opioid receptors and thus cannot produce the full spectrum or magnitude of effects, regardless of the dose e.g. buprenorphine, butorphanol.

iii. *Mixed agonist and antagonist:* They acts as an agonist at one type of opioid receptor and as an antagonist (block) at another type of receptor, e.g. pentazocine, nalbuphine.

iv. *Antagonist:* They acts competitively to displace the agonist from the receptor by attaching with it. While it attaches with receptor, elicites no or little effect on its own at clinical dose (intrinsic effect) e.g. nalxone, naltrexone.

Table 14.11: Location of μ and δ receptors

μ receptor	*δ receptor*	*μ and δ*
Cortex (laminae I, IV)	Cortex (laminae II, III, V)	Cortex (lamina IV)
Thalamus	Amygdala	Nucleus ambiguous
Hypothalamus	Olfactory tubercle	Nucleus tractus solitarius
Corpus striatum	Corpus striatum	Vagal fibres
Periaqueductal gray mater	Nucleus accubens	Trigeminal nucleus
Hippocampus	Pontine nuclei	Substantia gelatinosa of spinal cord
Colliculus (Sup and inf)		
Interpeduncular nucleus		
Midbrain		

Opioid Receptor

In 1973, opioid receptors were first conceptualised from the hypothesis that all the opioids act on some macromolecules of the cell membrane which is protein in nature and modulates the pain, mood, hedonic (pleasure related) behaviour, motor behaviour, emeris, pituitary hormone release, GIT motility, etc. But, later this hypothesis was confirmed and these macromolecules were described as opium receptor.

Morphine and other opioids exerts their action by interacting with these opioid receptors. Radio-ligand binding studies have divided these opioid receptor into three types; μ (mu), κ (kappa) and δ (delta) and each has a specific pharmacological profile. However, they also have a distinct pattern of anatomical distribution in brain, spinal cord and peripheral tissues. Three subtypes of each receptor have also been proposed, but have not yet been cloned (Table 14.11).

μ (morphine or mu) receptor

This receptor is named after the drug morphine which is used in the study of this receptor. These μ-opioid receptor manifests high affinity for morphine, pethidine, fentanyl and its congeners. On the other hand, other opioid peptides such as β-endorphin, enkephalins and dynorphins also bind to the μ receptor but with lower affinity. These μ receptors are located both in the brain and spinal cord with highest concentration at the periaqueductal gray region, thalamus, nucleus tractus solitarious, nucleus ambiguous and substantia gelatinosa. Stimulation of these μ-receptors cause analgesia, respiratory depression, euphoria, miosis, reduced G1 motility, physical dependence, etc. The two subtypes of μ receptor have been described. These are μ_1 and μ_2 . Among these the μ_1 has more affinity for morphine. It mediates supraspinal analgesia and is selectively blocked by naloxonazine. Whereas the μ_2 receptor has lower affinity for morphine. It mediates spinal analgesia, respiratory depression and constipation.

κ (Ketocyclazocine or kappa) receptor

This receptor is named for its high affinity for keto cyclazocine drug which is used for the study of this receptor. Activation of κ-receptor causes mild to moderate analgesia, ceiling respiratory depression, dysphoria, hallucination, miosis, sedation, physical dependence, etc. Two subtypes of κ receptor, such as κ_1 and κ_3 are functionally important. Analgesia caused by κ agonists is primarily spinal and acts though κ_1 receptor. However, κ_3 receptors mediate supraspinal analgesia and is of lower ceiling character (Table 14.12).

δ (Delta) receptor

This receptor has high affinity for enkephalins and is present both in the spinal cord (dorsal horn) and brain (limbic area). Activation of this receptor causes analgesia, respiratory depression, affective

Table 14.12: Nature of interactions of opioid ligands on the three major types of opioid receptors

Opioids	*μ (mu)*	*κ (kappa)*	*δ (delta)*
Morphine	Ago (St)		Ago (W)
Meperidine	Ago (St)	Ago (W)	Ago (W)
Pentazocine	P. ago, Anta (w)	Ago (W)	P. ago
Buprenorphine	P. ago	Ago (M)	P. ago
Butorphanol	P. ago	Anta (M)	Ago (?)
Nalorphine	Anta (St)	Ago (St)	(?)
Nalbuphine	Anta (M)	Ago (M)	Ago (?)
Naloxone	Anta (St)	Ago (M)	Anta (W)
Naltrexone	Anta (St)	Anta (M)	Anta (W)
Enkephalin	Ago (M)	Anta (St)	Ago (St)
β-endorphin	Ago (St)	–	Ago (St)
Levorphanol	Ago (St)	–	–
Fentanyl	Ago (St)	–	–
Sufentanyl	Ago (St)	–	Ago (W)

P. ago = Partial agonist, Anta = Antagonist, St = Strong action, M = Moderate action, W = Weak action. Ago = Agonist.

behaviour, reduced GI motility etc. The δ mediated analgesia is mainly spinal (as δ receptors are present mainly in dorsal horn of spinal cord), but the affective component of supraspinal analgesia appears to involve the δ receptor present in the limbic areas. They are also responsible for dependence. The proconvulsant action is more prominent in δ receptor agonists. Myenteric plexus neurones express high density of δ-receptor which mediate reduced GI motility.

Table 14.13: Action of different types of opioid receptors

μ *(mu receptor)*	κ *(kappa receptor)*	δ *(Delta receptor)*
Analgesia	Analgesia	Analgesia
μ1-supraspinal	κ3-supraspinal	
μ2-spinal	κ1-spinal	
Respiratory depression (μ2)	Respiratory depression	Respiratory depression
Euphoria	Dysphoria, hallucination	Affective behaviour
Miosis	Miosis	
Reduced GI motolity		Reduced GI motolity
Sedation	Sedation	
Physical dependence	Physical dependence	

σ (Sigma) receptor

Now, it is no longer considered an opioid receptor, becuase it is neither activated by morphine, nor blocked by naloxone. However, certain opioids like pentazocine, butorphanol, etc, binds to σ-receptor. Certain effects such as dysphoria, psychotomimetic action, tachycardia, mydriasis, etc, caused by pentazocine like drugs are believed to be mediated by σ-receptor and are not reversed by naloxone (Table 14.13).

Cellular Mechanism of the Action of Receptor

All the three types of opioid receptors (μ, κ, δ) have been cloned and their functions are studied extensively. All these receptors are belongs to the G-protein coupled receptor family. This group of receptors constitutes about 80% of all the known G-protein coupled receptor family in the body which also includes muscarinic, adrenergic, GABA and somatostatin receptors. Amino acid sequence of these opioid receptors is very similar to somatostatin than other receptors. Opioid receptors have three parts – extracellular, transmembrane and intracellular. The amino acid sequence of these three opioid receptors (μ, κ, δ) are 60% identical and greater similarities among them exist in the transmembrane and intracellular part of it. However, the specific amino acid sequence in the extra cellular part of these opioid receptors are the key factor in determining the ligand-specific action.

The opioids modulate the synaptic transmission through opioid receptors by both the presynaptic (indirect) and postsynaptic (direct) facilitatory and inhibitory actions. Inhibitory action is mediated by Gi/Go protein and excitatory effect is mediated by Gs protein. G-protein coupled receptors are situated mostly on the prejunctional neurons. They generally exercise inhibitory modulation by decreasing the release of junctional transmitter. Various monoadrenergic (NA, DA, 5HT), GABA, and glutamate (NMDA) pathways are also intricately involved in opioid actions (Table 14.14).

Opioid receptor-activated G-protein effector system can be divided into two categories – short term effectors acting through K^+ and Ca^{2+} channels and longer term effectors acting through cAMP and adenylcyclase system. All opioid receptors inhibit the opening of Ca^{2+} channel and both the μ and δ receptors also activate the K^+ channel. Thus, the decrease in intracellular Ca^{2+} influx can inhibit the neurotransmitter mobilization with release of it and become a component of the mechanism of opioid induced analgesia. The K^+ channel effect results in hyperpolarization of neuronal membrane and decreases synaptic

Table 14.14: Receptor subtypes and action of various opioids

		Action	
	Receptor subtype	*Agonist*	*Antagonist*
Analgesia			
supraspinal	μ , κ , δ	Analgesic	No effect
spinal	μ , κ , δ	Analgesic	No effect
Respiratory function	μ	Decrease	No effect
GI tract	μ , κ	Decrease motility	No effect
Psychotomimesis	κ	Increase	No effect
Sedation	μ , κ	Increase	No effect
Diuresis	κ	Increase	
Hormone regulation			
Prolactin	μ	Increase	Decrease
Growth Hormone	μ and/or δ	Increase	Decrease
Neurotransmitter release			
Acetylcholine	μ	Inhibit	
Dopamine	μ δ	Inhibit	

transmission. The changes in cAMP may underline the opioid induced modulation of the release of neurotransmitter such as substance P.

Mechanism of Analgesia

The opioids when used systemically act through many higher CNS centres such as amygdala, mesencephalic reticular formation, periaqueductal gray matter (PAG), the rostal ventral medulla, etc. But the role of these higher brain centre, containing opioid receptor in opioid analgesia is still in controversy. Action of opioids at PAG result in impulse that modulate the degree of inhibition, coming from different neuronal pools and contribute in reducing the transmission of nociceptive information from peripheral nerves to the spinal cord. The rostral ventromedial region of medulla also modulates the nociceptive tansmission in the dorsal horn of the spinal cord. Opioid action at PAG controle this region of medulla by direct neural connection. Thus, opioids by systemic administraton activates the total analgesic system in CNS (Fig. 14.19).

Spinal opioid giving through the spinal or epidural route produces analgesia by direct action on the spinal cord only at the level of administration. Subtantia gelatinosa of spinal cord possess dense collection of opiate receptors (μ, κ, δ) and direct application of opioid to these receptors of spinal cord creates intense analgesia by their action at the presynaptic level by reducing the release of substance P. Opioid in the spinal cord also acts on the opioid receptors of dorsal horn cells and inhibits the sharp pain stimulation conducted by the A-δ fibres. At the dorsal horn cells opioids also block the excitatory postsynaptic potential summation and thus inhibit the dull persistent pain sensation, transmitted via the C fibres. This summation is much easier to block before the pain occurs than to treat. This concept explains why preemptive analgesia is more effctive than analgesia after stimulation. Opioids also modulate the pain sensation by preventing the excitatory threshold reduction at the dorsal horn cells.

By some peripheral mechanisms acting outside the CNS, opioids also produce analgesia. In the periphery opioid receptors are located at the nerve terminals of presynaptic affarent neurons and the immune cells, infiltrating the inflamed tissue and produce endogenous opioids for the peripheral receptors. Opioid act on these receptors at the periphery and produce analgesia.

Opioids agonist also produce local anaesthetic like effect on the surface of the excitable cell membrane and reduce pain. Serotonergic pathways may also take part in the opioid mediated analgesia. Some opioids also act through $GABA_A$ receptors like benzodiazepine and barbiturates.

The concentration of opioid receptors and the proportion of its subtypes can change with age and this explains the variation of pain sensitivity with age. Certain opioids can have a duration of action that extends beyond its plasma half-life and it is because of the high affinity of this drug to μ receptor. For example, buprenorphine has very high affinity for μ receptor and very slower dissociation rate from it explains the cause for difficulty in reversing its respiratory depression effects with naloxone.

Other parts of CNS which also contain opioid receptors are basalganglia, limbic area, etc, and they are responsible for the action of endogenous opiates. Cardiosvascular system also contains opioid receptors which are responsible for the receptor mediated opioid's actions in myocrdial ischaemia, shock and other cardiovascular events.

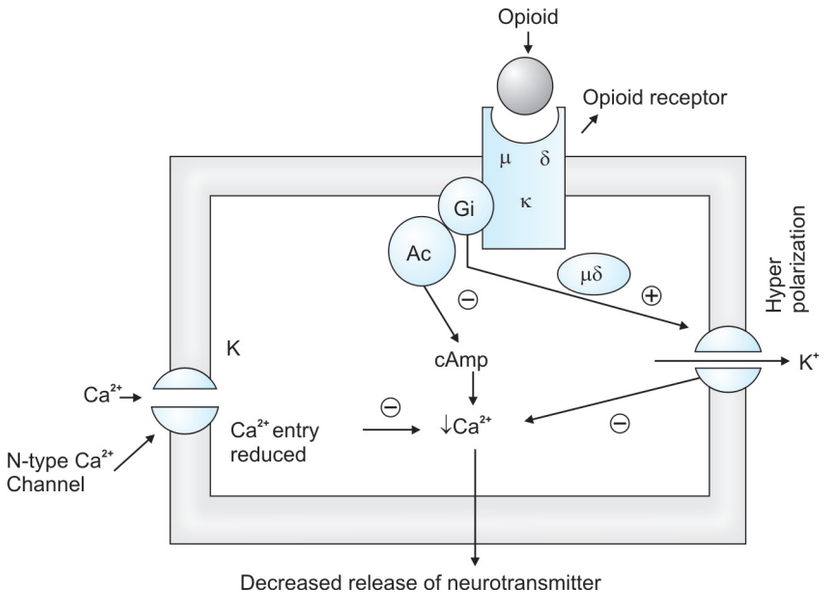


Fig. 14.19: All these 3 types of opioid receptors (μ ,κ § exercise inhibition and decrease the release of junctional neurotransmitter. Various monoaminergic pathways such as NA, DA, 5-HT, GABA, and glutamate (NMDA) pathways are intrically involved in opioid actions. Opioid receptor activation reduces intracellular cAMP formation. It also opens K^+ channel mainly through μ and δ receptors. It also suppresses the voltage gated N type Ca^{2+} channel mainly through κ receptors.These actions result in hyperpolarization and reduced availability of intracellular Ca^{2+}. Thus it causes the decrease in release of neurotransmitter from CNS and myenteric neurons and block pain pathway

Endogenous Opioids

In 1970, a number of peptids were isolated from brain, spinal cord, plasma, GIT, placenta, etc, which also have affinity for opioid receptors (μ, κ and δ) and have morphine like action. So, it was hypothesised that these peptides constitute an

endogenous opiate system which normally modulates the pain perception, mood, hedonic (pleasure related) behaviour, motor behaviour, emeris, pituitary hormone release, GIT motility, diuresis, modulation of respiratory responses to stimuli and drugs, reduction of stress, etc. These endogenous opioid peptides are active in very small amount and there actions can also be blocked by naloxone. Endogenous opioid peptides are classified into 3 different families and each is derived from a distinct large precursor polypeptide. These three families are endorphin family, encephalin family and dynorphin family.

Endorphins (Endorphin family)

There are many endorphins in this family. But, the β-endorphin (β-END) is the most important among all the endorphins in this family. It has 31-amino acids and pro-opio-melanocortin is its precursor. This precursor is cleaved to form ACTH and β-lipotropin (β-LPH). The β-LPH is again cleaved to form β-END. The highest concentration of β-END occur in the pituitary gland, and in the medial, basal, and arcuate regions of the hypothalamus. The presence of β-END in spinal cord is debetable. Outside the CNS, the β-END exists in GIT, placenta, and plasma.

Enkephalins (Enkephalin family)

The most important enkephalins are methionine-enkephalin (met-ENK) and leucine-enkephalin (leu-ENK). They are pentapeptides. Pro-enkephalin is the precursor of met-ENK. The prodynorphin is the precursor of leu-ENK and dynorphin. The enkephalins are widely distributed in many areas of CNS such as amygdala, globuspallidus, striatum, hypothalamus, thalamus, brain stem, dorsal horns, etc, that receive affarent nociceptive information. Enkephalins have also been isolated in the peripheral nervous system such as peripheral ganglia, ANS, adrenal medulla, GIT and as well as plasma. Enkephalins may also elicit analgesia through the modulation of release of substance P from the dorsal horn cells.

Dynorphins (Dorphin family)

The prodynorphins is the precursor of dynorphins and are found in the hypothalamo neurohypophyseal axis. Dynorphin functions primarily as neuromodulators in the CNS by interracting with μ, δ and κ receptor. Dynorphin also appears to be distributed in other areas of CNS which are relevant to nociception such as the periaqueductal grey region, limbic system, thalamus, dorsal horn of spinal cord, etc. Dynorphin is thought to play a more important role for nociception at the spinal cord level (by activation of κ-receptor) than in the brain. It may also control centrally the function of CVS.

A functional interaction occurs between the nociception and the endogenous opioids. The preliminary processing of the afferent nociceptive information first occurs at the dorsal horn cells of spinal cord. Both the dynorphins and enkephalins are active in these areas. The 2nd processing station for nociception reside in the mid-brain, brainstem and thalamus. High concentration of dynorphins, enkephalins and β-endorphin can be found in these areas. Higher brain centre such as limbic system, amygdala, cortex where final processing occur and involved in the affective dimensions of pain contain significant population of neurons where dynorphin, enkepahlin and β-endorphins are found.

Neurophysiological Actions of Opioids

Analgesia

The dull and viseral pain is better relieved than the somatic pain by opioids. The nociceptive pain arising from the periheral receptor is better relieved than the neuretic pain arising from the neural structure due to its damage. Other associated reactions to intense pain such as apprehension, fear, autonomic effects, etc, are also reduced by opioids. Suppression of pain perception by opioids is also selective without effecting other sensation and without producing generalised CNS depression (in contrast to General anaesthetic agents). Perception of pain and reaction to it are both altered, so that pain becomes no longer an unpleasant or distressing element. So, patient tolerates pain better under opioids.

Opioids also act on the substantia gelatinosa of dorsal horn cells and inhibit the release of excitatory neurotransmitter from the primary affarent fibres carrying pain impulse. This action of opioids appears to be exerted through the interneurons which are involved in the gating process of pain impulses. The release of substance P from the primary affarent fibres in the spinal cord and its post synaptic action on the dorsal horn neurons is also inhibited by opioids. The action of opioids at supraspinal sites such as medulla, midbrain, limbic and cortical areas may also alter the processing and interpretation of pain impulses as well as send the inhibitory impulses through descending pathways to the spinal cord. Several aminergic and other neuronal systems also appear to be involved in the action of opioids. Simultaneous action at spinal and supraspinal sites greatly amplifies the analgesic action of opioids.

Sedation

Sedation or hypnosis produced by opioids is different from other sedatives or hypnotics such as benzodiazepine, barbiturates, etc. Drowsiness and indifference to the surroundings as well as to his own body is occurred by opioids without any motor incoordination, ataxia or apparent excitement (contrast to alcohol). Opioids have weaker amnestic effect compared with propofol, barbiturates, midazolam or other benzodiazepines.

Mood and Subjective effects

Opioids relieve anxiety and produce calmness. It causes loss of apprehension, and

lack of initiative. Limbs feel heavy. It causes transient flushing and hot sensation due to the release of histamine. There is mental clouding and inability to concentrate. Patients who are suffering from pain, anxiety and those who are addicted perceive it as a great pleasure. It produces euphoria or dysphoria.

CTZ

Nausea and vomiting can result from opioids. It especially occurs if stomach is full and patient stands or moves about. The mechanism of action of nausea and vomiting produced by opioids is due to sensitisation of CTZ centre by vestibular and other impulses.

Edinger-Westphal Nucleus

Opioids stimulate the EW nucleus or release the cortical inhibition on it and thus produce miosis. No miosis is found by topical application of opioids on conjunctiva.

Other Cortical Areas and Hippocampal Cells

Excitation of CNS by opioids is seen in some individuals. This is due to the stimulation of some cortical areas and hippocampal cells by it. So, opioids have no anticonvulsant action, rather precipitate it. Muscular rigidity is another feature of opioids. The proconvulsant action of opioids also has been ascribed due to the inhibition of release of GABA inhibitory neurotransmitter from the hippocampal interneurones.

EEG Changes

The neurophysiological changes produced by large doses of opioids and inhaled anaesthetics are different. In contrast to gradual burst suppression and ultimate a flat EEG which is found as the effect of inhalational anaesthetics, a ceiling effect is reached by opioids. Once ceiling effect has been reached then subsequent increased dose of opioid does not affect the EEG. Low dose of opioids produce minimal changes in EEG. Higher doses result in high voltage (δ-delta) waves, suggesting a state of consistent with anaesthesia. Transient, isolated (not generalised) sharp waves activity is also seen after large dose of opioids.

Neuro protection effect

Role of opioids in neuroprotection is controversial.

Cerebral blood flow

Opioids decrease (10 to 25%) the cerebral metabolic rate and the intracranial pressure by causing cerebral vasoconstriction.

Neuroexcitatory phenomenon

Opioids cause neuroexcitatory phenomenon ranging from delirium to grandmal seizure like activity. Opioids also cuase other types of neuroexcitation ranging from nystagmus to only flexion or extension of single extremity to repetitive clonic – tonic activity. Initially, on IV injection opioids frequently stimulate coughing, which is of brief duration. This is followed by supression of cough. Meperidine is notorious for its CNS excitability. However, the mechanism of neuroexcitability caused by meperidine is unique which is described below. It is related to its N-demethylation metabolite, named normeperidine, which is twice as likely to cause CNS excitation and convulsion as meperidine and have half the analgesic potency. The CNS adverse effects associated with mepiridine include disorientation, hallucination, tremors, twitching, myoclonus, psychosis and seizures. Treatment of CNS excitability produced by meperidine is supportive and includes cessation of administration of meperidine, substitution with another opioids for analgesia and administration of BDZ for signs and symptoms of CNS irritability. For the treatment of CNS excitability caused by opioids naloxone should be avoided because it can further precipitate seizure by unmasking the excitatory effects when depressant effects are antagonised. Normeperidine has a long elimination half-life (15 to 40 hours) and is excreted via kidney after its hydrolysis to normeperidinic acid which is inactive.

The probable mechanisms for neuroexcitatory phenomenon of opioids are:

i. The opioids cause increase in the glutmate activated current.
ii. The changes in central catecholamine concentration through dopaminergic pathways.
iii. Increase in the release of excitatory neurotransmitter such as met – and leu-enkephalin, which posses epileptogenic properties.
iv. Disinhibition of the pyramidal cells of hippocampus.
v. More recent work suggests that certain excitatory actions of opioids may be related to their coupling to mitogen activated protein kinase cascades (Table 14.15)

If opioids are anaesthetics?

It is a debatable question for many years and still is not resolved. High incidence of awareness during large doses of only opioid anaesthesia highlighted this potential problem. Unconciousness, defined by unresponsiveness to verbal command can be produced with opioids, but is very unpredictable and inconsistant. On the other hand, all the opioids cause reduction

Table 14.15: Factors responsible for intra-operative awareness

1.	No premedication.
2.	Obstetric anaesthesia.
3.	Improper anaesthetic plan.
4.	Escessive use of muscle relaxant.
5.	Inadequate use of analgesic.
6.	Morbidly obese patient.
7.	ASA grade III and IV where less anaesthetic drugs are used.
8.	Prolonged time for intubation.
9.	Cardiac surgery.
10.	Laryngoscopy, bronchoscopy etc.

of MAC value of inhaled anaesthetics. Thus, potency ratio of fentanyl/sufentanyl/alfentanyl/remifentanyl which is based on MAC reduction is approximately 1:12:1/16:1.2. Opioid's analgesic effects reach a ceiling that is subanaesthetic. The exact mechanism of opioids for amnesia and anaesthesia is in doubt. The ability of opioids to produce full analgesia in subanaesthetic concentration and loss of conciousness in higher concentration may be mediated by different mechanism. A dual mechanism for anaesthetic effect of opioids has been proposed in addition to the receptor mediated effects which is responsible for analgesic effects of opioids (Fig. 14.20).

Awareness is defined as the 'spontaneous recall of events occurring during general anaesthesia and surgery'. The conscious recollection of this memory is called the explicit memory. When the patient can not recollect its memory in conscious state this awareness is called the implicit memory. Usually auditory function is left largely intact by opioid and is responsible for awareness during anaesthesia. The overall incidence of intraoperative awareness is 1%. There are also other factors which are responsible for intraoperative awareness. Clinically, intraoperative awreness is monitored by motor and autonomic function. Motor functions during anaesthesia such as eyelid motion, coughing, movements of limbs, facial grimacing, etc are signs of inadequate amnesia. Whereas autonomic functions during anaesthesia such as hypertension, tachycardia, mydriasis, tearing, sweating, salivation, etc, indicate light level of anaesthesia. The monitoring of muscular activity as an indicator of awareness is useful, because muscle movements usually occur before awareness occur. CNS activity also can be meausred by auditory evoked response and EEG. Raw EEG has limited value for awareness monitoring. Bispectral analysis (it is a power spectrum analysis which is a mathemetical technique of EEG transformation) obtain an index number after using processed EEG and correlate well with sedation or anaesthesia by hypnotic or anaesthetic drug, but not by opioids. Opioids does not alter BIS except in high doses.

Muscle rigidity

Opioids often increase muscle tone and produce muscular rigidity. Sometimes this may progress to severe stiffness. The incidence of it may vary from 0 to 100%. In conscious state this rigidity is often manifested as hoarseness of voice. Clinically, the significant opioid induced muscular rigidity begins usually after the patient loses consciousness. Rigidity of the abdominal and/or thoracic muscle (wooden chest syndrome) impair both spontaneous and controlled ventillation in a non-paralysed patient. Rigidity of muscles casuses: ↓ pulmonary compliance, ↓ FRC, ↓ ventilation, hypercarbia, hypoxaemia, etc. It also causes ↑ CVP, ↑ PAP and ↑ PVR etc. Rigidity also causes ↑ ICP and ↑ O_2 consumption. The rigidity and abnormal muscle movement may also occasionally occur during emergence from opioid anaesthesia. This abnormal muscle movement ranges from only flexion or extension of single extremity to multiple tonic-clonic movements.

The precise mechanism for this opioid induced abnormal muscle movement is not known. However, the probable hypothesis are: (i) the alteration of dopamine concentration within the striatum of brain by opioids and (ii) the stimulation of GABA nergic interneurones.

Pruritus

The exact mechanism of opioid induced pruritus is not known. But definitely it is not due to the release of histamine or allergic manifestation by opioids which was previously thought. Because naloxone reverses this pruritus and confirmed the opioid receptor-mediated central mechanism of it. Face, particularly the nose is the commonest site for opioid induced pruritus. Nasal scratching may stimulate ventilation and counter the opioid induced respiratory depression. This may be the mechanism why the nose is the commonest site of pruritus induced by opioids. Pruritus on the nose by spinal opioid may also be due to the opioid triggered neural transmission at a distant site.

Thermoregulation and Shivering

Shivering is a common phenomenon in patients recovering from anaesthesia. Its physiological role is to produce heat. But, its occurence in relation to anaesthesia is inconsistent and is incompletely understood. Neverthless, the post-operative shivering can cuase several undesirable physiological consequences. These are increase in O_2 consumption, incerease in CO_2 production,

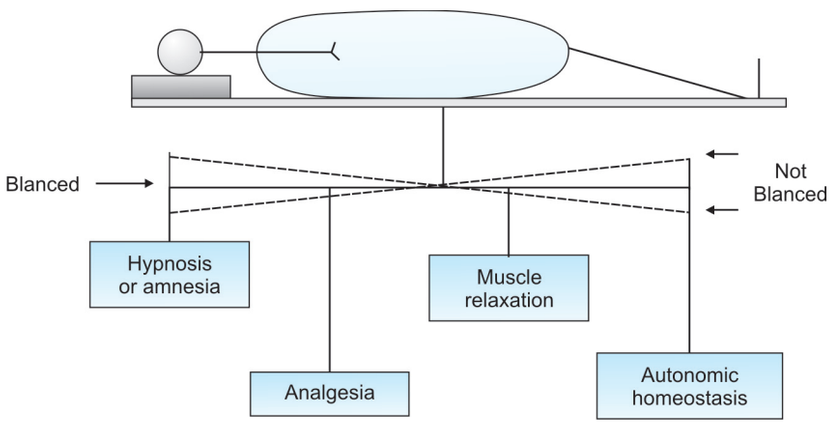


Fig. 14.20: Four components of balanced anaesthesia

↑ minute ventilation, ↑ cardiac output, ↓ mixed venous O_2 saturation and difficulty to measure the O_2 saturation of Hb by pulse oximetry. Opioid ligands and its receptors have a functional role in thermoregulation. For example, μ-receptor stimulation produces hyperthermia. Whereas κ-receptor agonists result in hypothermia. Opioids like inhaled anaesthetics also reduces thermoregulatory threshold and cause shivering.

Meperidine is unique among all the opioids in its ability to effectively terminate or at least attenuate the shivering in approximately 70 to 80 % of patients. Shivering related to blood transfusion can also be controlled with meperidine. Usually 25 to 50 mg slow IV administration of meperidine is effective. However, in the presence of opioid antagonist larger doses of meperidine may be necessary. IV fentanyl, sufentanil and morphine are not as effective as meperidine to reduce the shivering. The cause of this underlying difference and the mechanism for the ability of opioids to attenuate shivering is unclear. Meperidine administered spinally or epidurally is also effective in treating shivering that occurs during epidural anaesthesia.

Respiratory System

All the opioids stimulating μ-receptors cause dose dependent depression of respiration. This is because high concentration of opioid receptors are found in supraspinal respiratory centres such as nucleus solitarius, nucleus retroambigualis and nucleus ambigus. Opioids also depress the respiratory rate through pontine and medullary respiratory centre, because endogenous opioid receptors are also present in high concentration in brain stem nuclei regulating respiration. Opioid induced effects on respiratory rate and pattern include: delays in expiration, long respiratory pause, irregular and/or periodic breathing, apnoea, decreased tidal volume. Prolonged expiratory pause induced by opioid causes greater reduction in respiratory rate than in tidal volume (Fig. 14.21).

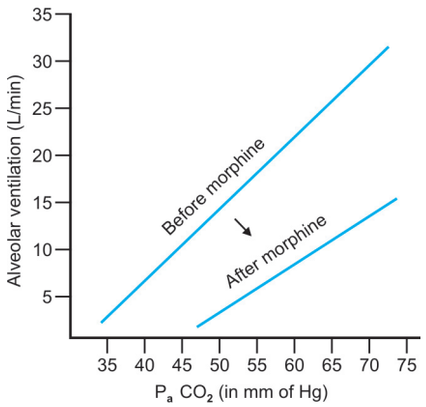


Fig. 14.21: The displacement or shifting of CO_2 curve downward and to the right after use of morphine

The stimulating effect of CO_2 on ventilation is significantly reduced by opioids. Resting PCO_2 in plasma increases and the ventilatory response to CO_2 challenge is blunted, resulting in shift of the CO_2 response curve down ward and to the right. These effects are mediated through the respiratory centres in the brain stem. The apneic threshold, i.e. highest P_aCO_2 at which a patient remains still apneic is elevated. Opioids also decrease the carotid body chemoreceptor and hypoxic ventilatory drive. High doses of opioid can eliminate the spontaneous respiration without producing unconsciousness. So, the patient will still follow the verbal command and often breath when directed to do so. Gender differences may exist in these effects with women demonstrating more respiratory depression.

Opioids decrease the pain and anxiety induced hyperventilation and thus prevent respiratory alkalosis, though large doses of opioids decrease pulmonary compliance and impair ventilation due to its muscular rigidity and respiratory depression effect. On the other hand, the opioid analgesic therapy improves breathing by alleviating the pain and decreasing the voluntary muscle tone related to pain which results in improved dynamic of total respiratory compliance.

Opioids, especially dextromethorphan have centrally mediated antitussive action, but are not necessarily linked to respiratory depression. Again cough may be precipitated after IV bolus opioids. It is due to the stimulation of irritant receptors in tracheal smooth muscle. However this cough is not vagally mediated, because atropine pretreatment does not affect it. Pretreatment with inhaled β-adrenergic agonist significantly reduces this incidence of cough associated with IV opioids injection.

Opioids blunt the somatic and autonomic responses during tracheal intubation by depressing the upper airway and tracheal reflexes. Thus, it allow the patient to tolerate better the ET-tube without coughing and bucking. Hence, on emergence from GA where patient is anaesthetised only with potent inhalational agents and no opioid, routinely cough and buck prior to regaining consciousness. Whereas, when the patient is adequately treated with opioids can awake without such disturbances, even while they are still intubated.

Morphine and meperidine can cause histamine induced bronchospasm in susceptible patients. Although, the opioids can affect the contractile responses of airway smooth muscles, but the clinical significance and relevance of this opioid induced effects on airway resistance remains controversial. Because opioids can also help by avoiding the increases in bronchomotor tone in asthma. Opioids can decrease the airway smooth muscle tone and have long been used in the management of asthma. Fentanyl has antimuscarinic, antihistaminergic and antiserotoninergic actions. So, it may be more effective than morphine in patients with asthma or other bronchospastic diseases.

Certain IV anaesthetics, including opioids, minimally alter the pulmonary function of gas exchange. The minimal impact of opioids on hypoxic pulmonary vasoconstrictic (in contrast to the effect of the potent inhaled anaesthetics), the associated haemodynamic stability, and the stability of bronchomotor tone, all contribute to

the minimal interference with pulmonary gas exchange which is observed after use of opioids and many other IV anaesthetic agents.

Factors affecting the opioid induced respiratory depression

i. Dose: Opioids cause dose dependent respiratory depression and have no ceiling effect.
ii. Sleep: Sleeping patients are more sensitive to opioids and sleep apnoea is an additional risk factor.
iii. Old age: Respiration of aged patient are more sensitive to opioids for depression and its probable causes are decreased clearance, increased elimination half-life, increased brain sensitivity.
iv. Neonates: Neonates are more sensitive to morphine on the basis of weight than adult. Low lipid solubility of morphine limits its penetration to blood brain barriers. But in neonates and infants morphine easily penetrates the brain and this is due to immature blood brain barriers which make the neonats and infants more sensitive to morphine than adult. On the other hand, children are not more sensitive to more lipid soluble opioids (mepridine,fentanyl, sufentanyl) because penetration of these drugs into the brain is not affected by blood brain barrier maturity, but depends on their lipid solubility.
v. Other CNS depressant: Potent inhaled anaesthetics, alcohol, barbiturates, BDZ, etc, potentiate the respiratory depression action of opioids. Exceptions are droperidol, and clonidine.
vi. Pain: Pain counters the respiratory depressant effects of opioids.
vii. Hyperventilation with hypocarbia enhance the activity of opioids. On the other hand hypercarbia has the opposite effect. However, the possible of explanation of this response is increased unionised state of opioid with hypocarbia which facilities its brain penetration and vice versa.

Cardiovascular System

The opioids not only provide analgesia, but also promote stable haemodynamic conditions both in the presence and absence of noxious stimuli. Large doses of opioids, administered as sole primary anaesthetic agent, result in stable hemodynamic situation throughout the operative period. The close association between the distribution of opioid receptor, cardiovascular regulatory centre (N. solitarius, dorsal vagal nucleus, N. ambiguous, parabrachial nucleus) and autonomic regulatory centre in CNS explain the cause of this stable hemodynamic condition by opioids. Endogenous opioid peptides are also associated with the sympathetic and parasympathetic centres in brain which also control the cardiovascular function. Different opioid receptor, occupying the ventrolateral periaqueductal gray region which is the key central site for analgesia, also affects the haemodynamic control.

Activation of μ-opioid receptor suppresses the somato sympathetic reflexes which are transmitted by the unmyelinated C-afferent fibres at the level of spinal cord and modulate them at brain stem. These actions also contribute to the anaesthetic capabilities of opioids. Opioids thus modulate the stress responses by its action on the hypothalamo – pituitary – adrenal axis. Most opioids reduce the sympathetic tone and enhance the vagal tone. Ablation of sympathetic tone can occur by all the modern opioids.

The direct actions of opioids on myocardium are significantly less than other IV and inhalational anaesthetic agents. However the direct effects of different opioids on myocardial contractility is different and controversial. Meperidine has been reported to produce decrease, increase or mixed effects on the myocardial contractlity. On the other hand, morphine has positive inotropic effect. However, most hemodynamic variables including HR, BP, CO, SVR, PVR usually remain unchanged after fentanil, sufentanil and ramefentanil. Morphin reduces both the venous and arterial tone. These changes result in decrease in afterload, venous return and preload. Arterial dilatation is of shorter duration and is of less intensity than venodilatation. This vasodilatation is caused by the release of histamine and is responsible for hypotension. This hypotension again stimulate sympathetic system as a compensatory mechanism. The hypotension produced by opioids can be eliminated or minimised by: volume loading, H_1 and H_2 histamine anatagonists, Trendelenburg position and slow infusion of drugs.

Some reports show that the patients with good left ventricular function become hypertensive more frequently due to opioids than patient with poor left ventricular function during surgery. The explanation of this phenomenon is like that: the patients with good myocardial function could increase cardiac index in response to increase in SVR induced by surgical stimuli. Thus, the patients with limited myocardial reserve could not always maintain CO in the face of ↑SVR. So, their BP does not increase and at times decreases. This rise of BP after opioid, especially during intubation and surgical stimulation has been most often due to the light general anaesthesia which is resulted from the underestimation of opioid dose and faulty timing of drug administration. So opioids should be administered in a fashion which will permit establishment of peak effect before noxious stimuli.

The predominant and usual effect of opioids on the heart rate is to produce bradycardia, resulting from stimulation of central vagus nucleus. The opioid induced bradycardia can be prevented by vagal block with atropine. The blockade of sympathetic chronotropic actions by opioid may also play an important role in opioid induced bradycardia. Meperidine in contrast to other opioids rarely results in bradycardia, but it can cause tachycardia. Tachycardia after meperidine may be due to its structural similarity to atropine or normeperidine or due to its early toxic CNS manifestation.

Opioids depress the cardiac conduction and thus slows the AV nodal conduction, prolongs PR interval, increases AV nodal refractory period, prolongs duration of action potential of Purkinje fibres and prolongs the QT interval. This effect may be related to enhanced Ca^{2+} entry during the plateau phase of action potential or depression of the outward K^+ current during terminal repolarisation of action potential. Clinically the disturbances of cardiac conduction due to opioids are very rare. But they may be more likely to occur in the presence of Ca^{2+} entry or β-adrenergic blocker.

Compared with inhalation anaesthetic agents, the opioids cause better preservation of myocardial function. The hypotension produced by morphine is not due to the myocardial depression like inhalational agents. Opioid receptor stimulation results in reduction of infarction size. High doses of opioids maintain better myocardial perfusion and O_2 supply/demand ratio than inhalational agents.

Morphine and meperidine cause release of histamine which causes sympatho adrenal activation. This is documented by significant increase in plasma epinephrine and norepinephrine level in response to opioids. This hormonal alteration contribute to the cardiovascular changes seen after morphine and include an increase in cardiac index. Decrease in arterial blood pressure and SVR is also due to this histamine effect. Meperidine causes histamine release more frequently than most other opioids, including morphine, fentanyl, sufentanil and remifentanyl. Unlike morphine and mepridine, the fentanyl, sufentanil, remifentanil do not produce increase in plasma histamine and hypotension. Although, the μ-opioid agonist modulate the adrenal secretary response to pain, still the adrenal secretory response to haemorrhage is preserved.

Hormonal Response

Stress response is totally a physiological process that occurs when a patient enounters a significant insult from injury and/or surgery. The main part of this stress response is the neuroendocrine component which works through some centres, situated in the brain and release the corticotropin releasing hormone from para ventricular hypothalamic nucleus and locus caeruleus, responsible for nor epinephrine/autonomic nervous system. During stress or surgical insult hypothalamus secrets trophic hormones which stimulate pituitary to release ACTH, GH, renin, prolaction, ADH etc. Thus, the level of cortisol, catecholamines, glucagon, thyroxine is increased. However, the plasma level of anabolic hormones such as insulin and testosterone are decreased. This increased level of stress hormones during GA and surgery cause haemodynamic instability and periopetrative catabolic metabolism which contribute to operative mortality.

In general, the inhalational anaesthetic agents cannot supress this stress response, but only mask it. But, opioids can do it to certain degree. Only combinations of different anaesthetic agents and technique control the stress response best. Opioids are potent inhibitor of hypothalamus pituitary adrenal axis. It reduces the stress responses by blocking the nociception at different levels of neural axis.

Fentanyl and its congeners are more effective than morphine and meperidine in modifying these hormonal responses to surgery. Increased stress response is detrimental to very ill patient undergoing major procedure. Increased catecholamine increases cardiac risk and increased protein catabolism delay recovery. So, the reduction of stress response by opioids during surgery reduces the morbidity and mortality.

Renal Effects

Morphine and meperidine prevent the release of ADH which occurs in response to stress Thus, the absence of increase in plasma ADH, renin and aldosterone level indicate that opioids most likely preserve or minimally alter the renal function in human subject. Opioids reduce the tone of bladder's smooth muscle, but increase the tone of bladder sphincter, causing retention of urine. Opioids also cause the increased contraction of ureter smooth muscle.

Gastrointestinal Effects

The opioid receptors and the endogenous opioids are found through out the GI tract. So, the opioids produce the wide spread effects on GI tract by supraspinal (vagus nerve mediated), spinal and as well as by peripheral mechanism. Opioids increase the tone and decrease the motility of GI tract and are more likely to have full stomach, regardless of their 'NPM' status. Opioids lower the oesophageal sphincter activity causing relaxation but spasm of pyloric, ileocaecal and anal sphincter. It causes decrease in all GI secretion. Epidural and intrathecal opioids also reduces the GI tract motility. Naloxone reverses the opioid induced delays of gastric emptying.

Opioids induce the spasm of CBD and sphincter of oddi and thus reduce the caliber of CBD and increase the billiary duct pressure. The opioid induced reduction of caliber of CBD is greatest with morphine and is insignificant after fentanyl or sufentanil. This spasm of biliary system can completely be counteracted by naloxone, glucagon, nitrates, theophylline and partially by atropine. The meperidine has dual effect. In lower concentration, it produces the anti muscarinic effect and in higher concentration it produces the biliary spasm. Neither of these respone of meperidine is affected by naloxone.

The little but big problem during perioperative period is the post operative nausea and vomiting which is caused by opioids. Opioids stimulate the centre of CTZ situated in the postrema of medulla and at possibly through δ-receptor. This central action of opioid combined with their action on GI tract promotes nausea and vomiting. There is very little evidence to suggest that any one opioid is constantly

more emetogenic than other. Neverthless, in one particular patient, changing from one opioid to another influence the incidence of associated nausea and vomiting. Factors that increase the incidence of nausea and vomiting are age (paediatric group is more susceptible), sex (females are more prone), obesity, history of motion sickness, anxiety, certain surgical procedures (laparoscopy), opioid premedication, intensity of pain, gastric distension and N_2O. Propofol significantly reduces the incidence of nausea and vomiting.

Nausea and vomiting caused by opioids are of great concern to post-operative patients. So, attempts should always be taken to minimise their occurance. Some efficient antiemetic therapies commonly used in anaesthesia are:

i. Anticholinergic drug such as scopolamine can be given through IM or IV or transdermal patch to reduce the postoperative nausea and vomiting. Glycopyrrolate is ineffective in this respect as it cannot penetrate the blood brain barrier. Atropine is effective to some extent.
ii. Droperidol (0·005 to 0·07 mg/Kg IV) is very effective to reduce the post-operative nausea and vomiting caused by opioids. It acts by its anti dopaminergic action.
iii. Dopamine antagonist such as metoclopramide, is also effective. It acts centrally at CTZ and peripherally at GI tract.
iv. Serotonin antagonist such as ondansetron may be highly effective. But it is associated with low incidence of headache (3%), liver enzyme elevation and high cost benefit ratio.

Obstetric Effects

Morphine and meperidine (not fentanyl, sufentanil, alfentanil) adversely affect IVF (*in vitro* fertilisation) due to their teratogenic potentiality. So, they are not used for this purpose. Parenteral administration of opioids prior to delivery in obstetrics practise remains a commonly used method of analgesia despite the known adverse maternal, fetal and neonatal effects of it and it is due to the arguably superior alternatives other than epidural analgeria. Meperidine (50 mg IV) has been suggested to result in less neonatal depression than morphine. This is because of the immaturity of the foetal blood brain barrier which allows greater than normal brain penetration of the relatively less lipophobic morphine compared with meperidine. Soon after injection, morphine and mepridine rapidly cross the placenta barrier and cause significant blood level in newborn. The elimination half-life of meperidine in newborn can be as long as 23 hours.

Sufentanil is highly bound to plasma protein and thus impedes its placental transfer. Placenta takes up more sufentanil compared with the other opioids and acts as a drug depot. Thus, placental transfer is reduced in case of sufentanil and transfer to the foetus may be least when delivery occurs within 45 minutes of this drug administration.

Meperidine increases the uterine contraction and shorten the labour in a dose dependent fashion which is not reversed by naloxone.

Though, traditionally opioid is not used in GA for caessarean section, but recently patient with severe PIH and CVS problems are induced with newer congener of opioids to promote CVS stability. Maternal effects are deemed beneficial, because naloxone is used for reversal of neonatal respiratory depression. Opioids excrete through breast milk and depress the neonatal neurobehaviour. Newborn of addicted mother exihibits opioids withdrawal symptoms and require appropriate treatment.

Occular Effects

All the opioids prevent the increase in intraocular pressure, associated with succinylcholine and/or tracheal intubation.

Allergic Reaction

The true anaphylactoid reactions to opioids are rare. But most commonly local reaction occur and this may be due to preservatives or histamine release. Naloxone and antihistamins partially attenuate these histamine induced opioid reactions.

Pharmacokinetic

Opioids are weak base and when dissolved in sloution, then they dissociate into protonated or ionised fraction. The relative proportion of these protonated (on ionised) and free base (on nonionised fraction) depends on the pH solution and the pKa value of the agent. Free base or nonionised form is more lipid soluble than the ionised or protonated form. High lipid solubility increases the entry of opioid at the site of action i.e central nervous system and facilitates its rapid onset of action. On the other hand, opioid receptors recognise an opioid molecule in protonated form and the intensity of opioid effect is closely related to the concentration of the ionised portion of the drug in the cell. Thus, the speed of onset and intensity of action is a complex function of lipid solubility and the percentage of ionization which again depends on the tissue pH and pKa value of the drug like the local anaesthetic agent which is discussed in the respective Chapter No. 13.

Opioids are bound to plasma proteins (albumin and α_1-acid glycoprotein) to some extent. Opioid molecules that are bound to plasma protein cannot pass from blood to CNS or any other tissues. Only the unionised and unbound fraction (free base) passes from the blood to tissues where it is ionised and make the concentration gradient which promotes the further diffusion. Hence, the concentration gradient, lipid solubility and the palsma tissue partition coefficient determines the rate at which the opioid diffusion in tissue takes palce. Morphine has low diffusible fraction and is a slow onset opioid. This is because of its low lipid solubility. On the other hand, alfentanil has high diffusable fraction and is a rapid onset opioid. This is because of its high lipid solubility than morphine.

After IV injection, plasma concentration (central compartment) of opioids rise to a peak level within one circulation time like thiopentone and propofol. Thereafter, the plasma concentration of opioids falls very rapidly due to distribution and redistribution of it to the peripheral tissues and later slowly due to metabolism and excretion through the liver and kidney. This is also like barbiturates, propofol and benzodiazepine.

In general opioids are cleared from plasma by biotransformation (conjugation with glucuronic acid) in liver. Kidney also plays a role in conjugation of opioids. Blood and tissue esterase are also responsible for metabolism of remifentanil. Subtle difference of pharmacokinetic of different opioids are also due to its uptake by pulmonary tissue. This is because the rise-time to peak concentration in plasma of an opioids is influenced by the percentage of pulmonary uptake of it. 75% of fentanil is taken up by the lung due to its high lipophilicity and is subsequently released rapidly.

Morphine

The pharmacokinetic of morphine is notably different from its fentanyl congeners. Due to its low lipid solubility, there is little first pass uptake of morphine by the lung. The pKa value of morphine is 8 which is greater than the physiological pH of blood. So, after IV injection only 10 to 20% of morphine remains as unionised form. This property and low lipid solubility limits the ability of morphine to penetrate tissues, particularly the CNS and explain its slow onset of action. But in neonates and infants where the blood brain barrier is not properly build up, morphine has high penetration power in CNS (Table 14.16).

Morphine is principally metabolised in liver by glucuronide conjugation. Kidney is also an important site for extrahepatic metabolism (40%) of morphine. M_3G (morphine 3-glucuronide) is a major metabolite of morphine without any analgesic property. Another metabolite of morphine named M_6G (Morphine 6 glucuronide) accounts for 10% of the total metabolites of morphine. It is more potent analgesic than morphine itself which also acts through μ-receptor.

Bioavailability of orally administered morphine is significantly lower than the pareneral route and is only 20 to 30%. This is due to the hepatic first-pass effect. M_6G is the primary active component when morphine is administered orally due to high hepatic extraction.

Meperidine

Unlike morphine, after IV injection the first-pass uptake of meperidine by the lungs is approximatley 65%. Meperidine's physicochemical properties are not like morphine, but more similar to those of fentanyl congeners. Its pKa value is 8.5. So, it is less unionised (<10%) at physiological pH of blood. Meperidine is more lipid soluble than morphine, but it is more highly bound to plasma protein than morphine, i.e. 70% to α_1-glycoprotein. In contrast to morphine, meperidine binds to plasma albumin in minor extent.

The principal metabolites of meperidine are normeperidine, normepe – ridinic acid and meperidinic acid. All these are produced by N-demethylation and diesterification of meperidine in liver. Only less than 5% meperidine is excreted unchanged through kidney. Normepridine has analgesic and as well as neuroexcitatory property (twice as potent as parent compound in producing seizure). This epileptogenic property of meperidine make its therapeutic index low than that of morphine.

Normeperidine is excreted through kidney and have greater elimination half-life than meperidine. So, repeated administration of meperidine cause accumulation of this toxic metabolites in patient with renal failure and producs seizure.

Fentanyl

A three compartmental model is typically used to describe the pharmacokinetic property of fentanyl, instead of two compartmental model which is used for morphine and meperidine. Like meperidine, after IV injection the first-pass uptake of fentanyl by lungs is 75%. Its pKa value is 8·4. So, like meperidine at physiological pH of blood, unionised diffusible form of fentanyl is <10% and ionised form is >90%. So, diffusible fraction of fentanyl (unionised base) is less. But fentanyl's high lipid solubility increases its large volume of distribution in tissues than morphine and meperidine. Less unionised form explain less availability form of fentanyl for brain tissue and delayed onset of action (than alfentanil). On the other hand, high lipid solubility explain quick transfer of it to the CNS and rapid onset of action. So, the actual onset of action of fentanyl is the resultant effect of this two properties. High lipid solubility of fentanyl also explain more uptake of it by tissue and prolonged action. 80% of injected fentanyl is bound to plasma protein and 40% are taken up by RBC.

Fentanyl is metabolised mainly in the liver by N-dealkylation and hydroxylation. It has high hepatic clearance rate. Norfentanyl, the primary metabolite of

Table 14.16: Physical characteristics of opioids that determine the distribution

Agent	*Protein binding*	*Unionised (diffusible) fraction*	*Lipid solubility*
Morphine	+ +	+ +	+
Meperidine	+ + +	+	+ +
Fentanyl	+ + +	+	+ + + +
Alfentanil	+ + + +	+ + +	+ + +
Sufentanil	+ + +	+ + +	+ + +
Remifentanil	+ + +	+ + +	+ +

fentanyl is detectable in urine for upto 48 hours after single bolus IV administration. It is inactive and has no analgesic or toxic property.

Alfentanil

The unique physicochemical properties of alfentanil is its pKa value which is only 6.5. So, at physiological pH of blood it is mostly (90%) in unionised and diffusible form. But, alfentanil is highly protein bound and is of low lipid soluble. Thus, despite intense protein binding and lower lipid solubility diffusable fraction of alfentanil make its early penetration in CNS. This explains alfentanil's short latency to peak effect (early onset of action) after IV injection. Alfentanil's lower lipid solubility, compared with fentanyl, cause its less amount of uptake by the lipid rich brain tissue. This mechanism explains alfentanil's rapid offset of action.

The volume of distribution of alfentanil is 0.4 to 1 lit/Kg, whereas that of fentanyl is 3 to 6 lit/Kg. This is due to the low lipid solubility of alfentanil than fentanyl and causes less tissue accumulation of this drug. This mechanism is also largely responsible for the short elimination half-life of alfentanil in spite of its lower clearance rate than fentanyl (alfentanil's celarance rate is 4 to 9 ml/Kg and fentanyl's is 10 to 20 ml/min/Kg)

Noralfentanil is the major metabolic product of alfentanil. Other metabolites of alfentanyl metabolism are desmethylalfentanil, desmethyl noralfentanil and others. Any of the metabolites of alfentanil have little or no analgesic activity.

Sufentanil

It is often reported that sufentanil is 5 to 10 times more potent than fentanyl. The pKa value of it at physiological pH is same as that of morphine i.e. 8. Therefore only a small amount (20%) exists in the unionised form. After IV injection, first pass pulmonary extraction and retention of sufentanil in lungs are similar to those of fentanyl. However, this physiochemical property is of little clinical importance to sufentanil. This is because sufentanyl is twice as lipid soluble as fentanyl and is highly protein bound (93%) including α_1-acid glycoprotein. The major metabolic pathways of sufentanyl include N-dealkylation, oxidative N-dealkylation, oxidative O-demethylation and aromatic hydroxylation in liver. Major resultant metabolites of sufentanil include N-phenylpropanamide. Sufentanil is tightly bound to receptor. This property along with the high degree of plasma protein binding capacity and lower volume of distribution, are the probable explanation of sufentanil's shorter elimination half-life and shorter duration of effect as compared to fentanyl, despite the fact that it is highly lipophilic. Infact, after intraoperative infusion of sufentanil for less than 6 to 8 hours of duration, the effects of opioid would dissipate as least as rapidly as those produced by similar infusions of alfentanil.

Remifentanil (G187084B)

Remifentanil is the first ultrashort acting opioid for clinical use as a supplement to GA. The pharmacokinetic properties of remifentanil are best described by three compartmental model like fentanyl and its congeners such as alfentanil and sufentanil. Although, it is chemically related to the fentanyl congeners, but is structurally unique because of its ester linkage. Remifentanil's ester structure contributes its susceptibility to hydrolysis by plasma and tissue – nonspecific esterases, resulting in rapid metabolism of it. Like fentanyl it is not significantly metabolised or sequestreted in the lungs. Its metabolic clearance is several times greater than that of the hepatic blood flow. This explains its widespread extrahepatic metabolism, i.e. in plasma.

Remifentanil is a weak base with pKa value of 7. Its free base is formulated as a solution in glycine. As glycine has been shown to act as an inhibitory neurotransmitter and causes reversible motor weakness when injected intrathecally, so remifentanil is not approved for spinal or epidural use. Remifentanil is highly protein bound (70%), mainly α-acid glycoprotein. In blood, remifentanil is metabolised primarily by enzymes which are present in the erythrocytes. Therefore, it is not a substrate for pseudocholinesterase, and is not influenced by pseudocholinesterase deficiency. The primary metabolic path way of remifentanil is de-esterification to form a carboxylic acid, which have very low analgesic property and is inactive. This metabolite is excreted through urine, though its pharmacokinetic is not appreciably influenced by renal and hepatic failure.

Factors that alter the pharmacokinetics and pharmacodynamics of opioids

Factors that change the pharmacokinetics and pharmacodynamics of opioids are:

Age

Neonates exibit the reduced rate of elimination of opioid. This is due to the immature mechanism for metabolism of opioid resulting in extended elimination half-life of them. At the end of the 1st year this initial extended elimination of opioid quickly is normalised and at the end of 1st decade of life maximum opioid metabolic capacity is achieved (Fig. 14.22).

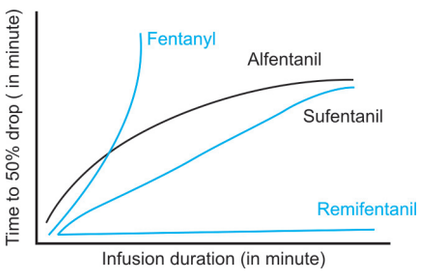


Fig. 14.22: The context sensitive half-time (CSHT) of different opioids. Among all the opioids the time necessary to achieve a 50% decrease in the plasma concentration (CSHT) of remifentanil is very short and is not influenced by the duration of the infusion

However, at the old age, the pharmacokinetic changes play a little role, rather the pharmacodynamic changes which are primarily responsible for the decreased dose requirement of opioid. The small pharmacokinetic change in old age that results in higher peak concentraion after a bolus dose of opioid is due to the low cardiac output and small central volume of distribution.

Weight

Pharmacokinetic parameters of opioids are more closely related to the lean body mass than the total body weight. This is because more than 90% of body's metabolic process is thought to occur in lean tissue. So, the dose regimens should be based on the lean body mass than the total body weight. But, estimation of lean body mass is a cumbersome calculation and total body weight closely relates to lean body mass. So, the dose regime based on total body weight is a clinically acceptable alternative.

Renal failure

Renal failure has major implication on the duration of action of morphine and meperidine. But, renal failure has less marked implication on the duration of action of fentanyl and its congeners.

Patient with renal failure develops very high level of M6G after morphine administration. M6G is μ-agonist with similar or greater potency than morphine. So, there is every chance of life threatening respiratory depression in renal failure patient after administration of morphine. Clinical paharmacology of meperidine is also significantly altered by renal failure. So, morphine and meperidine is not a good choice for renal failure patient. If they are used at all, then dose should be decreased and patient should be carefully monitored.

In contrast to morphine and meperidine, the clinical pahrmacology of fentanyl and its congeners is not grossly altered by renal failure. Decrease in plasma protein binding capacity increases the free fraction of fentanyl and its congeners and subsequently increases their action. Clearance of this fentanyl group of opioids is not affected by renal failure. Because although the metabolites of this group of opiod accumulate in renal failure, but they are inactive and non-toxic.

Pharmacokinetics and pharmacodynamics of remifentanil and sufentanil are unaltered by impaired renal function. But action of alfentanil is increased in renal failure.

Hepatic failure

Even though the liver is the primary responsible organ for metabolism of opioid, but the degree of liver failure that commonly observed in perioperative patient does not have major impact on pahrmacikinetic of most of the opioids, except liver transplantation. The possible explanation of this is the huge metabolic reserve of liver.

There are numerous ways by which liver disease can influence the pharmacokinetics of opioids. These are:

i. Reducing metabolic capacity (cyclochrome P-450 system and conjugation).
ii. Reducing hapatic blood flow.
iii. Reducing plasma protein binding capacity.
iv. Oedema and increasing the total body water – thus increasing the distribution characteristic of drug (volume of distribution).
v. Increasing metabolic capacity by enzymetic induction in early alcoholism.

Because of these numerous mechanism by which the liver disease may alter the pharmacokinetics of opioid, it can be difficult to predict exactly how an individual patient with liver disease will respond to opioid administration.

Pharmacokinetic of morphine is relatively unchanged by liver failure, because substantial amount of metabolism of morphine is done by kidney. On the other hand, the pharmacokinetic of meperidine is altered by liver failure. Like meperidine, alfentanil's pharmacokinetics is also altered by hepatic failure. Fentanyl's pharmacokinetic is not altered by hepatic failure. Remifentanil is perhaps the prototype example of an opioid whose pharmacokinetic is completely unchanged by liver disease.

Anaesthetic Technique

The routine anaesthetic induction is usually achieved by combining a loading dose of fentanyl (2 to 6 μg/Kg) with any sedative or hypnotic such as most commonly thiopentone or propofol and a muscle relaxant. The doses of sedative or hypnotic should be significantly reduced for induction of anaesthesia if opioids are used. Ketamine (0.5 to 2 mg/Kg) provide more haemodynamic stability compared with thiopentone or propofol after fentanyl or other opioids, especially in patient with cardiovascular diseases. Opioids can ameliorate or eliminate the cardiovascular responses to noxious stimuli, and thus control the changes in HR, BP, pulmonary capillary wedge pressure and other aspects of stress response that occur during laryngoscopy, intubation and surgery. Fentanyl and suffentanil should be administered 4 to 6 minutes, and alfentanil and remifentanil should be administered 1 to 2 minutes prior to any stress or stimulation. Once stress response is achieved and catecholamines are released, then opioids are less effective in maintaining haemodynamic stability. Response to laryngoscopy is better controlled with opioid than with esmolol.

After induction the anaesthesia is usually maintained by N_2O with O_2 and low concentration of potent inhalation anaesthetic, plus intermittent boluses (25 to 50 μg every 15 to 30 minutes) or continuous infusion (0·5 to 5 μg/hour/Kg) of fentanyl or other opioids. For short surgical procedures lower doses of fentanyl as bolus or infusion can be used. Premedication by BDZ may reduce the dose of this also supplementation. Propofol infusion may also be used during maintenance as a part of balanced anaesthesia.

Fentanyl plasma concentration of 1 to 2 ng/ml provide analgesia. But, levels of at least 2 to 3 ng/ml is usually required during surgery for adequate analgesia, if the N_2O as only inhaled agent is used. This plasma level can easily be achieved by initial bolus dose of fentanyl as 4 to 8 µg/Kg, followed by continuous infusion of 2 to 4 µg/Kg/Hour. This will often results in adequate plasma levels of 3 to 6 ng/ml.

Excessive doses of fentanyl or other congeners of it may result in postoperative respiratory depression. This is more likely, if fentanyl is given emperically without making titration with pain to some clinical endpoint. Somebody give additional fentanyl in the dose of 1 to 2 µg/Kg during closing of peritoneum to attenuate the hemodynamic response during extubation. But, it may lead to troublesome respiratory depression postoperatively. Another useful clinical approach to attenuate the haemodynamic responses during extubation is to wait for spontaneous ventilation to resume. Then, administer additional titrated dose to 25 to 50 µg of fentanyl to produce respiratory rate to 10 to 12 /min prior to tracheal extubation. Sufentanil, alfentanil, remifentanil are also can be used in place of fentanil.

Continuous Opioid Infusion

The continuous infusions of modern opioids is better alternatives to intermittent bolus technique. It maintains continuously a desired plasma level, a desired drug concentration at effected site and a steady state condition by replacing the drug in plasma that is removed by redistribution and metabolism.

The advantages of continuous infusion of newer opioids such as fentanyl and its congener over intermittent bolus doses are :

i better haemodynamic stability,
ii decreased total dose,
iii decreased side effects,
iv. more rapid recovery of consciousness,
v. less respiratory depression and less need for opioid antagonist,
vi. decreased discharge time.

The dose of continuous infusion of opioid is often reduced gradually to obtain a lower effective plasma concentration level and thus it avoides accumulation, when the redistribution of drug declines and the peripheral compartment comes to an equilibrium with the central compartment after being fully saturated. Computer assisted continuous infusion (computer controlled infusion pump – CCIP) deliver the drugs based on the pharmacokinetic data of a particular agent which feed in the computer. CCIP calculates the necessary infusion rate from the population based pharmacokinetic data of this particular drug to achieve the targated concentration and then CCIP gradually decreases the rate of infusion based on this particular drugs pharmacokinetics. Now CCIP is becoming increasingly popular.

High Dose Only Opioid Based Anaesthesia

The popularity of high dose only opioid based anaesthesia was first established by morphine and it has most commonly been employed in cardiac anaesthesia. But, this popularity of high dose only opioid anaesthesia had been gradually diminished due to several factors.

These include:

i. Lack of significant benefit from very large dose of opioid.
ii. Recent trend towards the 'first track' anaesthesia.
iii. Opioid as sole anaesthetic is not consistently reliable for seduction .
iv. The frequent need to intervene the hypotension caused by high dose opioid based anaesthesia with vasoactive agents.
v. Excessive post-operative respiratory depression.
vi. Intra operative haemodynamic instability, (only by high dose of morphine). So, morphine is not recommended for high dose opioid anaesthesia.

But, now newer opioids are administered in higher doses by continuous infusion with other anaesthetic agent and are still important and effective anaesthetics for patients undergoning cardiac and other extensive operations.

Fentanyl

Many different techniques are used for fentanyl with high doses. Initial bolus injection of fentanyl range from 5 to 75 µg/Kg. But there is little benefit of administering loading bolus doses of fentanyl more than 5 to 30 µg/Kg. These doses will establish plasma fentanyl concentration between 10 to 30 ng/ml, which is sufficient to provide stable hemodynamic condition during induction and intubation. Then continuous infusion in the dose of 0.1 to 1 µg/Kg/min is used for cardiac surgery.

This high dose fentanyl anaesthesia is very effctive and safe for paediatric cardiac surgery also. It reduces the incidence of intraoperative ventricular fibrillation in neonates undergoing cardiac surgery.

Alfentanil

Large doses of alfentanil (150 µg/Kg) may be used with or without thiopentone or propofol for induction of anaesthesia. But, only large doses of alfentanil is not suitable for induction. For cardiac surgery induction and maintenance of anaesthesia with alfentanil (25 to 75 µg/Kg loading dose plus 1 to 2 µg/Kg/min infusion) and propofol (0.25 to 1 mg/Kg bolus plus 80 to 100 µg/Kg/min) is relaible and stable.

Sufentanil

Sufentanil is superior to fentanyl for high dose opioid anaesthesia in cardiac surgery. The advantages are: more rapid induction, better attenuation of intubation reflexes, greater reduction of left ventricular stroke work, more stable haemodynamic condition intraoperatively and post-operatively, early recovery and extubation, and more decrease of BP than equivalent doses of fentanyl.

Dose: For induction sufentanil is used as bolus dose of 2 to 20 µg/Kg or infused over 2 to 10 minutes.

For significant cardiovascular disease etomidate is a better drug combination

with sufentanil. Alternative to etomidate, propofol can be used. Interestingly, sufentanil requirements become triple when midazolam is employed instead of propofol for induction. Etomidate (0.1 to 2 mg/Kg) plus sufentanil (0.5 to 1 µg/Kg) provide excellent haemodynamic stability during induction. Maintenance of anaesthesia by infusion of sufentanil (1 to 2 µg/Kg/H) in a balanced anaeshetic technique, achieves the advantages of an opioid-based anaesthesia and avoids prolonged opioid action post-operatively.

Remifentanil

In high dose opioid anaesthesia the datas regarding remifentanil are insufficient and nothing can be commented. Remifentanil has been employed in cardiac anaesthesia. The pharmacaokinetics of remifentanil were studied in patients undergoing CABG with CPB. The volume of distribution of remifentanil increases by 86% with institution of CPB. The elimination clearance also decreases by 7% for each degree of decrease of temperature below 37°C. So, infusion rate of remifentanil should be changed to maintain a constant plasma remifentanil level. It was shown that the induction with remifentanil (2 µg/Kg) together with propofol and maintenance with remifentanil at the dose of 0.25 to 0.5 µg/Kg/minute provided appropriate anaesthesia for minimally invasive CABG surgery.

Transdermal and Transmucosal Opioid Delivery

These two routes for opioid delivery system have enormous potentialities to improve the analgesic therapy by increasing the patient's compliance, reducing the pain associated with drug delivery, increasing the drug bioavailability, and increasing their analgesic efficacy.

Transdermal

The transdermal opioid delivery technique requires both the high water solubility (for passage through dermis) and high lipid solubility (for passage through corneum) property of the agent. Again the drug should also be of low molecular weight, highly potent (little amount causes clinical effect) and have no skin irritation effect.

At present, fentanyl (but no other opioid) is only available for transdermal delivery system. The advantages of it are no first-pass metabolism by the liver, improved patient's compliance, consistant analgesia, simple noninvasive type of delivery in nature and giving no pain during administration of drug.

After application of transdermal patch, plasma fentanyl level reach the plateau level very slowly extending between 8 to 16 hours and then also falls very slowly after removal of the patch as absorption of the drug which is deposited in the skin still continues. The half-life for decline of fentanyl level after removal of patch is 17 hours.

This transdermal route for administration of fentanyl is very effective for pain management in cancer patient. Faster acting route should be used initially during the acuteness of situation and then to switch over to the transdermal route. This transdermal drug delivery system can also be enhanced by iontophoresis (external electric current). So, patient receiving opioid by iontophoresis requires fewer additional opioid analgesic.

Transmucosal

This route for drug delivery can be achieved through oral, lingual, oropharyngeal, nasopharyngeal, sublingual, rectal or tracheobronchial mucosa (by inhalation). Among them the sublingual route is the most convenient for patients. But increased salivary secretion and subsequent swallowing of this saliva may convert this route to oral and prevent the increased systemic availability of drug due to hepatic fast pass metabolism. But this sublingual route eliminates hepatic first-pass metabolism increasing systemic availability and improves patient's compliance. As mucosa is rich in blood vessels and lymphatics, so absorption of drug will be faster and onset of action will be rapid if drug is administered through this route. This route of administration of drug is usually used for premedication, post operative pain management and treatment of chronic pain. Highly lipid soluble opioids such as buprenorphin, fentanyl and its congeners such as methadone are more effectively absorbed sublingually.

Sublingual buprenorphine

It is a potent, synthetic, mixed agonist and antagonist opioid with long half-life and readily absorbed by sublingual route. When the tablet of buprenorphin is swallowed, then it is almost completely metabolised by liver after absorption due to first pass metabolism. So, it is not used orally. But systemic bioavailability after sublingual route is 50% of that following IV administration. When sublingual buprenorpnin (0.3 mg) is given one hour prior to surgery then it provides a reliable preoperative sedation, intraoperative and post operative analgesia, similar to IM morphin. But as the onset of action is slow (3 hours), so the sublingual buprenorphin is not effective for immediate post-operative pain relief. The percentage of post-operative pain relief by sublingual buprenorphin is 80%, requiring supplementation for more higher success rate (if required).

Transmucosal morphine

Buccal morphine for analgesia is not promising (initial report was promising, but subsequent report disproved it). Low lipid solubility than other opioids make it a bad candidate for this route. In addition, bitter taste of morphine initiates salivation and subsequent swallowing which then become pray to first-pass liver metabolism. Bioavailability of sublingual morphine is 6 times lower than the equivalent dose by IM route.

Transmucosal fentanyl

The oral transmucosal preparation of fentanyl is made of fentanyl citrate which

is incorporated in a sweet lozenge. This is called oral transmucosal fentanyl citrate or OTFC. When consumed, it partly absorbed through oral mucosa and partly swallowed and absorbed through GI tract. But drug bioavailability is greater through oral transmucosal route than GI tract. The recommended dose of transmucosal fentanyl ranges from 5 to 15 μg/Kg depending on the desired degree of sedation and analgesia. Peak plasma concentration after OTFC administration occur at 15 to 30 min and then declines after 1 hour. The speed of onset of analgesia with OTFC is equal to that of IV morphine and elimination half-life is 7 hours which is similar to that of IV route also.

Unlike transdermal route, OTFC does not leave any depot in mucosa after it is removed. As some fraction of OTFC is swallowed and absorb through GI tract, so total systemic bioavailability is only 50% as buprenorphin, but much greater than sublingual morphine. Like systemic fentanyl, OTFC also causes nausea, vomiting and respiratory depression.

Other routes through which opioids can also be administered are intranasal, intratracheal inhalation and rectal.

INDIVIDUAL μ-RECEPTOR AGONIST

Morphine (Fig. 14.23)

Still now morphine is the gold standard μ-receptor agonist among all. So, against this gold standard agonist the potency of other newer opioid analgesic drugs are measured, though individual response may vary dramitically among μ-receptor agonists. As for example, some patients cannot tolerate morphin, but have no problem with equianlagesic dose of methadone. However, the actual underlying mechanism of it is still not known. Chemically, morphine is a phenanthrene alkaloid derivative. It is an agonist on μ, κ and δ receptors. But, its affinity for μ-receptors is much higher than that for the other two receptors. The effects of morphine, therefore, are primarily due to the result of μ-receptors activation. Like other opioids, morphine also appears to extent their effects by decreasing the intracellular Ca^{2+} concentration which in turn increases the K^+ conductance and causes hyperpolarisation of the excitable cell membrane. Thus, the decrease in membrane excitability may decrease both the pre and post synaptic responses (Table 14.17).

Due to difficulties, morphine is not synthesised still now in laboratory and is obtained from opium (extract of unripe seed capsule of poppy plant – papaver somniferum). The milky juice, opium, is dried and powdered to make opium powder which contain number of alkaloids and these alkaloids are divided into two distinct chemical classes, phenanthrenes and benzylisoquinolines. Morphine has minimal effects on the CVS. The predominant effect of morphine on CVS is orthostatic hypotension secondary to the decrease in systemic vascular resistance, at least part of which is mediated by histamin release. The drug may also cause bradycardia when administered in high doses. The principal effect of morphine on respiration is depression with decreased ventilatory reponses to hypoxia and hypercarbia. It also has the potent antitussive action. Bronchoconstriction may occur with the use of high doses of it.

Morphine is a potent analgesic agent and may also cause drowsiness, relief of anxiety and euphoria. Miosis is produced by this drug as a result of stimulation of the Edinger Westphal nucleus in brain. Seizures and muscular rigidity may occur with the use of high doses of morphine. It decreases the gastrointestinal motility and decreases the gastric, biliary and pancriatic secretion. It also increases the common bile duct pressure by causing the spasm of sphincter of oddi. The drug may also cause nausea, vomiting and constipation. The morphine increases the tone of ureters, detrusor muscle of bladder and sphincter. Thus, it may precipitate the urinary retention. Mild diaphoresis and pruritus may result from morphine due to histamine release. Morphine increases the secretion of ADH and may therefore lead to impaired water excretion and hyponatraemia. The drug may cause a transient decrease in adrenal steroid secretion (Table 14.18).

In general, morphine like other opioids are quickly absorbed through stomach and rectal mucosa. However, the more lipophilic newer opioids are absorbed by the nasal and buccal mucosa also. It adequately penetrates the tissue of spinal cord following epidural or intrathecal administration and produce profound analgesia which lasts for about 12 to 24 hours. As, the nature of morphine is more hydrophilic and absorption by the nerve tissue of spinal

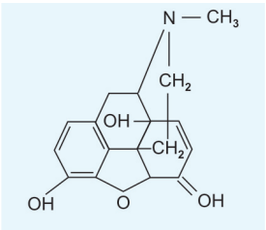


Fig 14.23: Morphine

Table 14.17: Derivative of phenanthrene and benzoisoquinoline

Phenanthrene derivatives	*Benzoisoquinoline derivatives*
Morphine (10%)	Papaverine (1%)
Codeine (0.5%)	Noscapine (6%)
Thebaine (0.2%)	
Thebaine, papaverine and noscapine are nonanalgesic.	

Table 14.18: Causes of morphine induced hypotension

i.	Release of histamine.
ii.	Bradycardia due to vagal stimulation.
iii.	Decrease in sympatheitc tone (centrally mediated).
iv.	Arterial and venous dilatation (direct and indirect).
v.	Large doses and rapid administration.
vi.	Sequestration of blood in splanchnic area.

cord is less than the other highly lipophilic agents (fentanyl, sufentanil, etc), so rostral spread of morphin after intrathical administration in CSF is more and this increases the incidence of respiratory depression. In contrast, the highly lipophilic agents such as fentanyl and its congeners produce very localised effects on spinal cord due to their quick absorption in the local nerve tissue and produce more segmental analgesia than morphine. Bioavailability of morphine by oral route is only 25% due to its first-pass metabolism in liver. The shape of the time–effect curve of morphine vary with the different route of administration. Compared with other more lipid soluble opioids such as codiene, heroin, methodone, fentanyl congeners, etc, the morphine crosses the blood-brain barrier at a considerably lower rate and equilibrates very slowly between the plasma and CSF.

About 1/3 of the absorbed morphine is protein bound, predominantly to albumin. It does not persist in tissues 24 hours or tissue concentration remains very low after the last dose.

The major pathways for morphin metabolism is conjugation with glucuronic acid in the liver. The major metabolites are morphine-6-glucuronide (M6G), morphine-3-glucuronide (M3G) and small amount of morphine 3, 6, diglucuronide. Both the M3G and M6G compounds are polar, and cross the blood brain barrier easily to produce significant clinical effects. M6G is responsible for most of the morphine's analgesic activity in patient receiving chronic oral morphine.

Very little morphine is excreted unchanged through urine. It is eliminated by glomerrular filtration primarily as M3G. However, 90% of total excretion takes place during the first day.

Morphine should be used with caution in the presence of hepatic failure. Because, the drug may precipitate hepatic encephalopathy. Similarly, the use of morphine in patients with hypopituitarism may precipitate coma. Like other opioids, it also decreases the apparent MAC value of coadministered volatile agents. Most of the actions of this drug are reversed by naloxane, although the analgesia afforded by the epidural administration of morphine is well preserved after the administration of naloxone. Morphine cannot be removed by haemodialysis or by peritoneal dialysis.

Meperidine

It is a synthetic phenylpiperidine derivative and predominantly μ and κ receptor agonist. It was first synthesised as an atropine substitute, in 1939, and has same actions like anticholinergics. So though chemically unrelated to morphine, still it has many similar actions like it and has been shown to interact with many opioid receptors. Its actions can also be blocked by naloxone. The mechannism of action of mepiridine is same as morphine. It decreases the intracellular Ca^{2+} concentration which in turn increases the K^+ conductance and causes the hyperpolarisation of the excitable cell membrane. Thus, the decrease in membrane excitability by meperidine results in decrease of both pre and post synaptic responses (Fig. 14.24).

Like morphine, meperidine also causes orthostatic hypotension. This is due to the combination of effect of histamine release and α-adrenergic blockade that it produces. The drug also has a mild quinidine like effect and anticholinergic properties (dry mouth, tachycardia, blurred vision etc). Meperidine is a potent respiratory depressant, having a greater effect on tidal volume than on the respiratory rate. It obtunds the ventilatory response to both hypoxia and hypercapnia. It has little antitussive action and chest wall rigidity may occur.

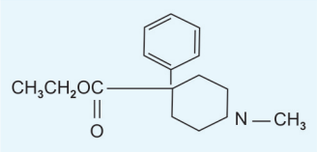


Fig. 14.24: Meperidine

Meperidine is 1/10 as potent as analgesic than morphine. It appears to cause more euphoria, but less nausea and vomiting than the equipotent dose of morphine. Miosis and corneal anaesthesia may follow the topical use of this drug. In common with other opioids, meperidine decreases the rate of gastric emptying. This drug appears to cause less marked increase in the bile duct pressure and less depression of the intestinal activity (and therefore constipation) than equipotent doses of morphine. This drug is less responsible for increase in the ureteric tone. It may increase the amplitude of contractions of the pregnant uterus.

The important differences between the meperidine and morphine are:

(i) Meperidine has dose to dose 1/10 analgesic potency of morphine.
(ii) After IM injection of mepridine, the onset of action is more rapid. But the duration of action is shorter (2 to 3 hours) than morphine.
(iii) It does not effectively supress the cough.
(iv) Spasmodic action on smooth muscles by mepridine is less marked. So miosis, constipation, urinary retentions etc. caused by meperidine are less prominent than morphine. Liability to induce biliary spasm by meperidine is low.
(v) As mepiridine is equally sedative and euphoriant like morphine, so it has similar abuse potential.
(vi) The degree of respiratory depression produced by meperidine at equianalgesic doses is equivalent to morphine.
(vii) It causes less histamine release. So, it is more safer in asthamatics than morphine.
(viii) It has also local anaesthetic actions. Corneal anaesthesia may seen after systemic administration.

It is absorbed by all routes, but absorption may be erratic after intramuscular injection. The adult oral dose of meperidine is 50 to 150 mg at 4 hours interval. The

corresponding dose of meperidine by the IM route is 25 to 150 mg and by intravenous route is 25 to 100 mg. Meperidine may also be administered via the epidural route and a dose of 25 mg is usually employed. The drug acts within 15 minutes when administered orally and within 10 minutes when administered intramuscularly. The duration of action is 2 to 4 hour. The bioavailability of meperidine when administered orally is only 40 to 70%. It is due to the significant fast pass metabolism of it by liver. The drug has a bioavailability of 100% when administered intramuscularly.

Meperidine is 50% protein bound in the plasma. The drug crosses the placenta and the mean cord blood concentration at delivery is 70 to 90% of the maternal blood concentration.

Meperidine is mainly metabolised in liver. It is hydrolysed to meperidinic acid which in turn is conjugated. Meperidine is also N-demethylated to normeperidine which may then be hydrolysed to normeperidinic acid and subsequently conjugated. This conjugated meperidinic and normeperidinic acid is excreted through bile and kidney. Normeperidine may accumulate in the presence of renal or hepatic failure. It has 50% analgesic potency of the parent compound and marked convulsant properties. Meperidine also appears to be effective in the treatment of post anaesthetic shivering.

Severe reactions may follow after the administration of meperidine to a patient, being treated with MAO inhibitors. The reactions are delirium, hyperthermia, hypo or hypertension, rigidity, convulsion, coma and death. This reaction is due to the blockade of neuronal reuptake of serotonin by meperidine and the resultant serotonergic over activity at the synaptic level. So, meperidine and its congener (diphenoxylate, loperamide), dextromethorphan and tamadol should not be used in patient taking MAOI. However, similar interaction wtih other currently used opioids have not been observed clinically.

Promethazine enhances the meperidine induced sedation. Amphetamine enhance the analgesic property of meperidine while counter acts its sedation effect.

Tramadol

Tramadol is a synthetic codeine analogue with dual mechanism of action. It is a weak μ-receptor agonist and to lesser extent δ and κ-receptor agonist. Part of its analgesic effect is produced by the inhibition of reuptake of norepinephrine and serotonin. So, inhibition of pain perception partly involves the activation of descending serotonergic and noradrenaergic pathways. Tramadol as analgesic is 1/5 to 1/10 as potent as morphine and can be given by various parentral routes. So, in the treatment of mild to moderate pain it is effective. But, for the treatment of severe chronic or acute pain tramadol is less effective. Tramadol has no clinically significant cardiovascular effects after IV administration. Respiratory rate, minute volume and P_aCO_2 remain essentially unchanged following IV administration of therapeurtic doses of this drug. It has no demonstrable effect on the bile duct and sphincter activity. The tramadol is 20% protein bound in the plasma and 80% of the administered dose of it crosses the placenta. The bioavailability of tramadol following oral administration is 70 to 100%.

The primary O-demethylated metabolite of tramadol is 2 to 4 times as potent as the parent drug and may account for part of its analgesic effect. The tramadol is supplied as racemic mixture. The (+) enantiomer binds to the μ-receptor and also inhibits the serotonin uptake. While the (–) enantiomer only inhibits the norepinephrine uptake and stimulates the adrenergic receptor.

The recommended dose of tramadol ranges from 50 to100 mg after every 4 to 6 hours interval, with maximum daily dose of 400 mg through all the routes of administration. The paediatric dose of tramadol is 1 to 2 mg/Kg at 4 to 6 hours interval. This compound undergoes hepatic metabolism and renal excretion with elimination half-life of 6 hours. It is less respiratory depressant compared with equianalgesic dose of morphine and the degree of constipation is less than that which is seen after the equivalent dose of codeine.

Its abuse potential is unclear. It can cause seizure by reducing the seizure threshold. Because of its inhibitory effect on serotonin uptake, tramadol should not be used in patient taking MAOI. The use of tramadol is not recommended in patients with end stage renal failure. The dosage interval of tramadol should be increased to 12 hours in patients with renal or hepatic failure. The drug is not licensed for intraoperative use as it may enhance intraoperative recall during N_2O anaesthesia. Tramadol appears to be effective in the treatment of postoperative shivering. It can be slowly removed by haemodialysis.

Fentanyl and its Congeners (Sufentanil, Alfentanil, Remifentanil)

Fentanyl

Fentanyl is a synthetic amine opioid and is structurally related to the phenyl piperidine nucleus. It is a pure μ-receptor agonist and 100 times more potent than morphine as an analgesic in an equivalent doses (Fig. 14.25).

The mechanism of action of fentanyl is same as that of morphine and meperidine. The adult dose of fentanyl for premedication by the intramuscular route is 50 to 100 μg. For the induction or supplementation of general anaesthesia an intravenous dose of 1 to 100 μg/kg may be used. Fentanyl may also be administered via the epidural

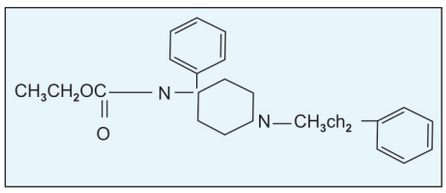


Fig 14.25: Fentanyl

or spinal route and a dose of 25 to 50 µg is usually employed. The drug acts within 2 to 5 minutes when administered intravenously. A small dose of fentanyl has a duration of action of 30 to 60 minutes. Whereas high doses (> 50 µg/Kg) may be effective for 4 to 6 hours.

It has rapid onset and rapid termination of action after a small bolus dose and has relative CV stability. Recovery from analgesic effect of fentanyl is very fast. However, with large dose or after prolonged infusion, the action is prolonged and recovery is delayed like long acting opioids. All the effects of fentanyl are like pure µ-receptor agonist such as morphine. Muscle rigidity such as chest wall rigidity (wooden chest phenomenon) is also common after IV bolus doses of fentanyl and its congeners. This muscle rigidity is centrally mediated and may be an effect of the drug on µ-receptors, located on GABA-nergic interneurones. Rigidity can be mitigated by slower administration (avoiding bolus) or by pretreatment with nonopioid anaesthetics such as IV inducing agents, e.g thiopentone, propofol, etc. or by muscle relaxants. High dose of fentanyl also can cause neuroexcitation.

The most significant cardiovascular effect of fentanyl is bradycardia which is of vagal in origin. Cardiac output, mean arterial pressure, systemic and pulmonary vascular resistance and pulmunary capillary wedge pressure are unaffected or decreased by the administration of fentanyl. It also obtunds the cardiovascular responses to laryngoscopy and intubation (Table 14.19).

Fentanyl is a potent respiratory depressant opioid causing decrease in both the respiratory rate and tidal volume. It also diminishes the ventilatory response to hypoxia or hypercarbia. The drug is also a potent antitussive agent. It causes minimal release of histamine. Bronchospasm is thus rarely precipitated by the drug.

Fentanyl though is 100 times more potent as an analgesic than morphine, but has little hypnotic or sedative activity. Miosis is produced as a result of stimulation of the Edinger Westphal nucleus. There have been several reports of seizure like motor activity, occuring in patients who receives fentanyl. However, no epileptic like spike wave patterns are demonstrable on EEG after the use of fentanyl.

Fentanyl decreases the gastrointestinal motility and decreases the gastric acid secretion. It also doubles the CBD pressure by causing spasm of the sphincter of Oddi. The drug increases the tone of ureters, detrusor muscle of bladder and vesicular sphincter. High doses of fentanyl will obtund the metabolic stress response to intubation and surgery. Unlike morphine, fentanyl does not increase the activity of ADH. Like other opioids fentanyl also decreases the apparent MAC value of co-administered volatile anaesthetic agents and increases the effect of nondepolarising muscle relaxants. The drug is pharmaceutically incompatible with thiopentone. So, they should not be mixed in the same syringe. It is unknown whether fentanyl is removed by hemodialysis or not.

As fentanyl is highly lipid soluble, so it rapidly crosses the blood-brain barrier and an equilibrium between the plasma and CSF concentration is rapidly approximated within 5 minutes. Then the concentration of fentanyl in plasma and CSF rapidly decline due to redistribution of it from low volume but highly perfused group of tissues (brain) to other high volume but less perfused group of tissues such as muscle and fat. The short duraion of action of a single dose of fentanyl is due to this quick distribution and redistribution to other tissues from brain tissues, rather than quick metabolism and elimination of it through liver and kidney. So this is like thiopentone, propofol and ketamine. When saturation and equilibrium of the high volume but less well perfused tisues occurs, then duration of fentanyl's effect prolongs and elimination half-life reaches to 3 to 4 hours.

Therefore, after higher doses or prolonged infusions fentanyl becomes a long

Table 14.19: Doses of commonly used opioids in different routes

Drugs	*Use*	*Route*	*Doses*
Morphine	Premedication	im	0.04 - 0.25 mg/Kg
	Intraoperative	iv	0.2 - 1mg/Kg
	Post-operative	im	0.04 - 0.25 mg/Kg
		iv	0.02 - 0.1 mg/Kg
Meperidine	Premedication	im	0.5 - 1.5 mg/Kg
	Intraoperative	iv	1 - 2 mg/Kg
	Post-operative	im	0.5 - 1.5 mg/Kg
		iv	0.2 - 0.5 mg/Kg
Fentanyl	Intraoperative	iv	1- 100 µg/Kg
	Post-operative	iv	0.5 - 2 µg/Kg
Sufentanil	Intraoperative	iv	0.2 - 30 µg/Kg
Alfentanil	Intraoperative	iv	5 - 100 µg/Kg
	Maintenance	iv	0.5 - 3 µg/Kg/min
Remifentanil	Intraoperative (loading dose)	iv	1 µg/Kg
	Maintenance	iv	0.5 - 10 µg/Kg/min

Opioids have large therapeutic window. This is indicated by wide range of doses of opioids. The doses of opioids also depends on other anaesthetics which are administered simultaneously. During IV infusion of it, tolerance develops rapidly, usually within 2 to 3 hours and infusion rates should be increased gradually. For obese patients, the doses of opioids should be calculated according to their lean body weight or ideal body weight but not on total body weight.

acting opioid. Fentanyl is absorbed orally, but bioavailability by this route is only 33%. The drug is 90% protein bound in the plasma. Fentanyl undergoes both the hepatic metabolism and renal excretion. It appears to be metabolised primarily by N-dealkylation to norfentanyl with subsequent hydroxylation of this. The parent compound is metabolised to hydroxypropionyl derivatives. The drug may also undergo hydroxylation and amide hydrolysis in liver. Some entero hepatic circulation of the drug may also occur. The 10% of an administered dose of fentanyl is excreted in the urine. The elimination half-life of fentanyl is 1.5 to 6 hours.

Sufentanil

All the pharmacokinetic and pharmacodynamic properties of sufentanil is similar to that of fentanyl, except it is 10 times more potent than fentanyl (i.e 1000 time more potent than morphine). The chemical structure of sufentanil is similar to that of fentanyl and is related to phenylpiperidine nucleus. The pharmacokinetic properties of sufentanil are also adequately described by a three compartmental model like fentanyl. After IV injection, the first-pass pulmonary extraction, retention and release of sufentanil are also similar to those of fentanyl (Fig. 14.26).

The intravenous dose of suphentanil is 0.5 to 50 µg/Kg. The dose via the epidural route is 10 to 100 µg. The optimal postoperative dose of sufentanil is 30 to 50 µg. When administered intravenously, the drug acts within 1 to 6 minutes and the duration of effect is 0·5 to 8 hours. Though the drug is normally administered intravenously, it is 20% absorbed when

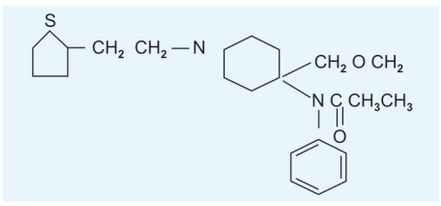


Fig. 14.26: Sufentanil

administered transdermally. Sufentanil is 92% protein bound in the plasma, predominantly to α-1 acid glycoprotein. It is twice as lipid soluble as fentanyl. The major metabolic pathway of sufentanil include N-dealkylation, oxidative O-demethylation and aromatic hydroxylation. Major metabolites of sufentanil include N-phenyl propanamide. The 60% of an administered dose of sufentanil appears in the urine and 10% in the bile. The elimination half-life of sufentanil is 119 to 175 minutes.

Like other opioids, sufentanil also decreases the MAC value of the co-administered volatile anaesthetic agents by 60 to 70%. The drug should be used with caution in the presence of renal or hepatic failure, although the kinetics appear to be unaltered.

Remifentanil (G 187084 B) and alfentanil

They are also synthetic pure µ opioid receptor agonist, related to phenylpiperdine nucleus. The pharmacological properties of these two opioids are same as fentanyl, except few differences. These compounds have very rapid onset and predictable termination of effects. The potency of remifentanil is equal to fentanyl but 20 to 30 times greater than that of alfentanil. Analgesic effect of both of these compounds occur within 1 to 1.5 minutes after IV administration. Alfentanil is metabolised in liver and elimination half-life is 1to 2 hours. Remifentanil is unique in that it is metabolised by plasma esterase. So, elemination of remifentanil from body is independent of the hepatic metabolism and renal excretion and the elimination half-life of it is only 8 to 20 minutes. Therefore, there is no prolongation of effect of remifentanil after repeated doses or prolonged infusion. After 3 to 5 hours of infusion of remifentanil, recovery of respiratory function can be seen within 3 to 5 minutes. While full recovery from all the effects of remifentanil occur within 15 minutes. The major metabolite of remifentanil i.e. remifentanil acid which is 2000 to 4000 times less potent than the parent compound and is excreted through kidney. Remifentanil is ideally suited for short surgical procedure where rapid recovery is the goal. It is also very useful in longer procedure where rapid emergence from anaesthesia is important such as neurosurgery.

However, due to short duration of action, remifentanil alone is a poor choice for post-operative analgesia. It is generaly given by continuous intravenous infusion, because its short duration of action make bolus administration impractical.

Alfentanil can be used intraspinally. But remifentanil is not being used intraspinally, because glycine used in the commercial preparation as preservative can cause temporary motor paralysis.

Individual Opioid with Both Agonistic and Antagonistic Activity

The opioids with both agonistic and antagonistic property are usually produced by alkylation of the piperidine nitrogen and addtion of a three carbon side chain such as propyl, allyl or methylallyl to the structure of morphine. Buprenorphin is a partial agonist at the µ-receptor but antagonist at the κ-receptor. The other compounds are µ-antagonists and full or partail agonists at the κ-receptors. Agonists and antagonistic opioids are less prone to abuse, because they cause less euphoria and are associated with less drug seeking behaviour and physical dependence.

Pentazocine

It is a benzomorphan derivative of morphine and have both agonistic action on κ-receptor and weak antagonistic action on µ-receptor. So, it is an agonistic and antagonistic opioid.

CNS effect of pentazocine is like morphine, including analgesia, sedation and respiratory depression. It is ½ to ¼ as potent as morphine. The analgesic action of pentazocine is due to its agonistic action

on κ-receptor. Higher doses of it (60 to 90 mg) elicit dysphoric and psychotomimetic effect. The possible mechanism for this side effect caused by pentazocine is the activation of supraspinal κ-receptor by it which can be reversed by naloxone. Ceiling to both the analgesia and respiratory depression effect occur after administration of 30 to 70 mg of pentazocine.

Pentazocine depresses the myocardial contractility, but causes ↑BP, ↑HR, ↑SVR, ↑pulmonary artery pressure, ↑left ventricular end diastolic pressure and ↑cardiac work load (left ventricular work index). It also increases the blood catecholamine level. All these changes show that pentazocine increases the myocardial O_2 demand and may precipitate the myocardial ischaemia. Pentazocine appears to cause less *nausea* and vomiting and less marked rise in biliary tract pressure than an equivalent dose of morphine. The drug decreases both the gastric and small intestinal motility.

Though pentazocine has weak antagonistic action on μ-receptor, but it does not antagonise the respiratory depression effect produced by morphine. But, when pentazocine is given in patient dependent on morphine or other μ-receptor agonist, then it may precipitate withdrawl or reduce its analgesic effect.

However, the potentiality for abuse of pentazocine is less than that of morphine, but prolonged use can lead to physical dependence on it. The drug is also well absorbed when administered orally. Orally the bioavailability of pentazocine is only 20%. It is due to the significant hepatic first-pass metabolism of it. The adult oral dose of pentazocine is 50 to 100 mg given at 3 to 4 hours interval. The corresponding parenteral dose of it is 30 to 60 mg at 3 to 4 hours interval. The drug is irritant when injected intramuscularly or subcutaneously. The pentazocine acts within 2 to 3 minutes when administered intravenously and within 20 minutes when administered intramuscularly. The duration of action of this dose of pentazocine is 3 to 4 hours. Metabolism of pentazocine occurs in the liver by oxidation and glucuronidation. However, 60% of the administered dose of it is excreted though the urine within 24 hours. Among this 2 to 10% remains unchanged. The elimination half-life of pentazocin is 2 hours and can be removed by hemodialysis (Table 14.20).

Buprenorphine

It is a semisynthetic, highly lipophilic opioid which is derived from thebaine. It is a partial μ-receptor agonist, but dissociates very slowly from the later leading to prolonged analgesia. Buprenorphin substitutes for morphin at the low level of dependence on later, but precipitate withdrawal in highly dependent subject. Thus it reflects its partial agonistic action at the μ-receptor. Being a partial agonist, buprenorphine like other agonist-antagonistic group may antagonise the effects of morphine and cause symptoms of abstinence in patient who is receiving pure μ-agonist (morphine like drug) for several weaks. Thus, it restricts its usefulness if other μ-agonists are used. Buprenorphine also appears to have a high affinity for κ-receptors which are antagonistic in nature.

The structure of buprenorphine is similar to morphine but is 33 times more potent than it. Its high lipophilicity and high receptor affinity causes its receptor's association and dissociation action very slow. So, it possesses much longer half-life which is near about 160 minutes (fentanyl half-life is 6 minutes). Hence, plasma level of buprenorphine does not correspond to the CNS effect. Buprenorphine's onset of action is slow. Its peak action may not occur untill 3 hours. Its duration of action is also prolonged (≤ 10 hours). Metabolism of it occurs in the liver with biliary excretion of most of its metabolites such as buprenorphine-3-glucuronide, nor-buprenorphine and buprenorphne which are less potent and have lower affinities for the μ-receptor. Thus, most of the drug is excreted through faeces.

Buprenorphine produces analgesia and other CNS effects like morphine. It has minimal cardiovascular effects. The heart rate may decrease by upto 25% and the systolic blood pressure may fall by 10%, following the administration of it. Buprenorphine produces respiratory depression and has antitussive effects, similar to that produced by morphine. The respiratory depressant effects of buprenorphin is not completely reversed by even larger doses of naloxone. This is probably because of more tight binding of buprenorphine with opioid receptors. Doxapram, however, will do so. Severe respiratory depression has occured when BDZ have been coadministered with buprenorphine. It may cause the release of tryptase and histamine from the lung parenchymal mast cells and may increase pulmonary vascular resistance. It also produces miosis and decrease cerebral glucose metabolism by upto 30%.

It is well absorbed by most of the routes. The recommended analgesic dose of buprenorphin is 0.3 to 0.4 mg by oral, IM, IV or sublingual route for premedication, as the analgesic component in balanced anaesthesia and for postoperative pain control. The drug is also effective when

Table 14.20: Haemodynamic effects of opioid agonist - antagonist compared with morphine

Drug	*Cardiac workload*	*Blood pressure*	*Heart rate*	*Pulmonary artery pressure*
Morphine	↓	↓	↓	↓
Pentazocine	↑	↑	↑	↑
Buprenorphine	↓	↓	↓	↓
Butorphanol	↑	↑	=	↑

administered by the epidural route and a dose of 0.3 mg has been recommended for this. The drug is well absorbed when administered orally, but undergoes a significant first-pass liver metabolism. Therefore, the sublingual route is preferred than oral when parenteral route is not used. The bioavailability of buprenorphine is 40 to 90% when administered intramuscularly and 44 to 94% when administered sublingually. It is not removed by haemodialysis. Opioid withdrawal symptoms develop slowly (5 to 10 days) after buprenorphine is discontinued following long term administration.

Butorphanol

Chemically it is a morphine congener with profile of action similar to that of pentazocine. Like pentazocine it is agonist at κ-receptor which is responsible for its analgesic effect, but more potent than pentazocine (2 mg butorphanol = 30 mg pentazocine). Its activity at μ-receptor is either antagonistic or partially agonistic. However, the antagonistic property of butorphanol at μ-receptor are weak and do not usually interfere with the use of other opioid agonist in anaesthesia. It is 5 to 8 times as potent as morphine.

In healthy subject, the butorphanol produce no or minimal CVS changes. But, in cardiac diseased patient the butorphanol causes changes similar to that produced by pentazocine. It causes ↑cardiac index, ↑left ventricular end-diastolic pressure, ↑pulmonary artery pressure. So, the butorphanol is not useful in patient with CCF or at increased risk for myocardial ischaemia or history of previous MI. The major side effects of butorphanol are drowsiness, weakness, sweating, nausea and CNS stimulation. While the incidence of psychotomimetic side effects (quantitatively) of butorphanol is lower than that of equianalgesic dose of pentazocine, but they are qualitatively similar.

Butorphanol is subject to less abuse and has less addictive potential. It is only available in parenteral form. The recommended dose of butorphanol is 1 to 4 mg IM or 0.5 to 2 mg IV.

Opioid Antagonists

The antagonists of opioid receptors (specific or non specific) are the important armours for scientific research of opioids and its receptors. In early 1950, nalorphine and levallorphan was evaluated as opioid antagonist for clinical use, though they have agonistic action. But later they were discarded due to the high incidence of side effects. Then, in 1960, naloxone was introduced and had established its efficacy as an antagonist for opioid induced respiratory depression.

Classification of agonist – antagonist opioids

i. Not used as analgesic
   Nalorphin, Levallorphan
ii. Used as analgesic
   Pentazocine, Nalbuphine
iii. Partial/weak agonists
   Buprenorphine, Butorphanol
iv. Pure antagonist
   Naloxone, Naltrexone

Naloxone (Fig. 14.27)

Slight minor changes in the structure of an opioid molecule can convert its agonistic action into an antagonistic action on opioid receptors. The most common example of such a substitution is N-methyl group which is a typical for μ-receptor agonist. So, such substitution transforms morphine to nalorphine; lavorphanol to levallorphan and oxymorphone to naloxone or naltrexone. Some of these substituted opioid congeners are completely competitive antagonist at μ-receptor, but agonist at κ-receptor. So, they can be used as agonist-antagonistic opioid. Hence, these nalorphine, levallorphan and nalbuphine, etc, can also be used as analgesics like pentazocine, butorphanol and buprenorphin, because though they are antagonistic at μ-receptor, but are agonistic at κ-receptor. However, some of the substituted opioid congeners have antagonistic action on all the opioid receptors without any agonistic action on any opioid receptor. These are naloxone, naltrexone, etc. Later specific opioid receptor antagonists were developed which are not congener of opioids for example, nalmefen which is pure μ-receptor antagonist. Norbinaltorphimine and naltrindole is specific κ and δ-receptor antagonist, respectively.

Thus, naloxone chemically is a substituted oxymorphone derivatives. Its mode of action is a competitive antagonist at μ, κ and δ receptors. Naloxone itself produce no effects. It means it has no intrinsic effects like morphin when it combines with opioid receptors independently or if opioids with μ-receptor agonistic action is not administered previously. If opioid is used previously, then naloxone rescue the respiratory depression effect of opioids and in addition, it can reduce or reverse the opioid induced analgesia, nausea, vomitting, pruritus, urinary retention, rigidity, biliary spasm, etc. Hence, these drugs may precipitate the acute withdrawl symptoms in opiate addicts. The mechanism of action is that it blocks all the opioid receptors and prevents the manifestation of actions of opioid agonist, those work through these receptors.

In shock and certain form of stress when the endogenous opioid system is activated, then the opioid antagonist naloxone also have visible consequences. It attenuates the hypotension associated with shock of diverse origin including that caused by anaphylaxis, endotoxin, hypovolaemia, etc. Naloxone also apparently acts to antagonise the actions of endogenous opioids that are mobilised by pain,

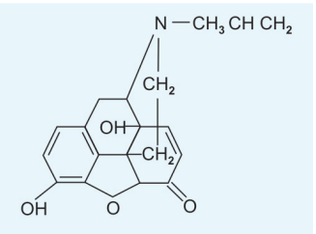


Fig 14.27: Naloxone

stress and that are involved in the regulation of blood pressure by CNS.

However, high dose of naloxone (12 mg) alone have intrinsic agonistic effect. But this is of little clinical significance. Dose of naloxone in excess of 0·3 mg/Kg show increased systolic blood pressure.

Endogenous opioid peptides usually participate in the regulation of pituitary secretion by exerting tonic inhibitory effects on the release of certain hypothalamic hormones. Thus, administration of naloxone by removing this inhibition increases the secretion of corticotrophine releasing factor and elevates the plasma concentration of ACTH. Thus, the elevated ACTH increase the plasma concentration of cortisol and catecholamines.

Naloxone can also be administered through IV, IM or subcutaneous route. But the drug should be administered intravenously in small incremental doses, until the desired end point of reversal of respiratory depression without reversal of analgesia is reached. This is because at different blood level naloxone anatgnise the different actions of morphine. Small dose (0·4 to 0·8 mg) of naloxone given 1M or IV does not reverse the μ-receptor mediated analgesic effects of opioids. But it reverses only the respiratory depression effect and so respiratory rate increases within 1 to 2 minutes. Higher dose of naloxone is needed to antagonise the respiratory depression effect of buprenorphine. Sedative effect of opioid is also reversed and blood pressure, if depressed, returns to normal. If IV access is not available, then naloxone in dose similar to that given by IV is effectively absorbed after intratracheal administration. Naloxone also reverses the psychotomimetic and dysphoric effects of agonist-antagonistic agents such as pentazocine. But for this much higher doses are required.

Opioids decrease the sympathetic outflow through their action on CNS (brain and spinal cord). α-adrenergic agonist (clonidine) and opioids perform this through their action on the preganlionic sympathetic neurons. Opioid antagonists block this action of opioids and increase sympathetic outflow. This explain clonidine's effectiveness in blocking haemodynamic stimulation following naloxone.

Side effects like increased HR, BP and more serious complication like pulmonary oedema may follow the administration of naloxone due to this sympathetic stimulation. So, opioid reversal by naloxone should be avoided in patient in whom the increased HR and BP could be detrimental. Patient with coronary artery disease could be adversely affected by naloxone, because of this sympathetic stimulation. Opioid reversal by naloxone may be hazardous in patient with pheochromocytoma.

The onset of action of naloxone after IV administration is 1 to 2 minutes and duration of effect is about 30 to 60 minutes. Although naloxone is rapidly absorbed through GI tract (91%), it is almost completely metabolised by liver before reaching the systemic circulation (only 2%) and so it must be administered parenterally. It is mainly metabolised by glucuronidation.

Recurrence of respiratory depression after administration of naloxone is due to its short half-life and as well as reuptake of opioid by μ-receptor from peripheral compartmental tissues. So, renarcotisation occurs more frequently after the use of naloxone during reversal of the longer acting opioids such as morphine.

Naloxone acts through μ, δ and κ-receptor, but has greatest affinity on μ-receptor, through which anti-respiratory depression and antianalgesic action is mediated. It is unlikely that analgesia is always spared. But, careful titration by naloxone often restore adequate spontaneous ventilation with out reversal of analgesia.

The other probable conditions where naloxone can be used are :

i. Hemorrhagic shock.
ii. Septic shock.
iii. Post anaesthetic apnoea in infants where opioid is not used.
iv. Primary apnoea and periodic breathing associated with hypoxia.
v. In the treatment of alcoholism (alcohol interacts with many neurotransmitters and endogenous opioid system in the brain. Mesolimbic dopamine system is mainly affected and the links between alcohol and opioid system play an important role in alcohol addiction).
vi. To reverse the effects of some non-opioid CNS depressants (BDZ and barbiturates → opioid – GABA receptor interactions).
vii. To ameliorate the neurological deficit in spinal cord and brain trauma.
viii. To reduce the obesity and clonidine overdose.
ix. To diagnose the suspected opioid overdose.

Naloxone may also partially antagonise the ketamine and N_2O induced analgesia.

Sometimes naloxone enhances the analgesia and morphine requirements is significantly less in patient receiving it. Proposed possible mechanism for this paradoxical effect of naloxone is the enhanced release of endogenous opioids by it and up regulation of opioid receptors.

Naltrexone

It is a μ , δ and κ-receptor antagonist. It differs from naloxone by:

i. Naltrexone is longer acting,
ii. Its half-life is 8 to 12 hours,
iii. It can be used by oral route.

Naltrexone is not subjected to much first-pass hepatic metabolism as naloxone. So, its duration of action approaches 24 hours after moderate oral dose.

Oral naltrexone in the dose of 5 to 10 mg reduces the severity and frequency of respiratory depression, pruritus, nausea and vomiting assocated with morphine without diminishing analgesia. Like naloxone, naltrexone also stimulate CVS.

It is mainly used for the treatment of opium addiction and alcoholisms due to its longer acting and effectiveness by oral route.

Nalmefene

Its structure is similar to naloxone and naltrexone, but has greater affinity to μ than δ and κ-receptor. It is long acting both after oral and parenteral administration. Bioavailability after oral administration is 50%. Plasma half-life varies from 3 to 8 hours. It produces little intrinsic effect when administered by itself without previous adminstration of opioids.

Interaction Between Inhaled Anaesthetic and Opioid

During N_2O administration cardiovascular function is usually preserved. But N_2O-opioid combination cause ↓CO, ↓HR, ↓BP and ↑SVR, ↑PVR, and ↑coronary vascular resistance, resulting in impaired coronary blood flow. Deterioration of cardiac function with N_2O-opioid combination is due to increase in after load (↑SVR and ↑PVR). This deterioration is not evident during routine monitoring of BP due to elevated SVR.

Analgesia produced by N_2O is mediated partly by opiodergic system and cause infra-additive interaction between N_2O and opioid. So the advent of short acting IV anaesthetics (e.g. propofol) and volatile anaesthetics with blood-gas partition coefficient equal to that of N_2O (e.g sevoflorane) has recently decreased the popularity of N_2O in balanced anaesthesia. Except halothane, combination of low concentration of other volatile anaesthetics and opioid is beneficial for compromised ventricular function. New volatile anaesthetics such as isoflurane, desflurance, sevoflurane cause only little myocardial depression.

Low concentration of isoflurane and high dose of sufentanil is very effective and safe to treat the intraoperative hypertension without producing myocardial depression and with out decreasing CO in coronary artery surgery. Halothane plus opioid anaesthesia to control hypertension produce ↓BP and ↓CO which exacerbate regional myocardial hypoperfusion and increase the lactate production. Some potent newer inhaled anaesthetics (isoflurane, desflurane) increase sympathetic nervous system activity, but this can be attenuated by opioid.

Interaction Between Sedative – Hypnotic and Opioid

BDZ is the ideal agent to combine with opioids. This combination acts as synergistic fashion (supra additive) and potentiate to reduce the dose of opioid. The BDZ and opioid combination preserve ventricular function but reduce B.P, SVR, CI, HR due to sympathetic depression and venodilatation. So, in patient with poor ventricular function this drug regime may be hazardous. Fluid loading can attenuate decrease in BP, ventricular filling and CO.

Barbiturates, droperiol, ketamine, etomidate and propofol are some of the other sedative-hypnotics which can be combined with opioid. Hypotension after barbiturate-opioid combination is due to venodilation causing decreased cardiac filling and myocardial depression due to decreased sympathetic nervous activity.

Propofol and opioid combination has the same effect like BDZ and opioid combination. Together they provide unconsciousness and block the responses to noxious stimuli, whereas neither drug alone reliably does the both. Propofol + fentanyl or sufentanil anaesthesia provide acceptable condition for coronary artery by pass surgery. Sometimes, mean arterial pressure can derease to a levels that may jeopardize coronary perfusion. MAP and HR can decrease upto 35% and 16% respectively.

Etomidate and ketamine can be combined with opioid without loss of cardiovascular stability in cardiac surgery. Etomidate and fentanyl combination cause less hypotension than propofol-fentanyl combination.

15 Inhalational Anaesthetic Agents

INTRODUCTION AND HISTORY

In the ancient times the main anchors of analgesia and anaesthesia during surgery, especially before 1800, were the oral opium, laudanum (an opium derivative), mandragora (a juice from 'mandrake' plant) and the liberal use of alcohol. Then, Anton Mesmer had given much importance to the psychological preparation of the patient and he introduced mesmerism in Europe, as a mode of anaesthesia in surgery. This was between 1750 and 1800. At that time, many literatures was also full of references of many wondrous sleeping potions, ranging from Snow White's apple to the mandrake plant used by Shakespeare's Cleopatra. But, the modern inhalational anaesthesia was dawned by the introduction of inhalational anaesthetic agents, such as N_2O in 1844, ether in 1846 and chloroform in 1847.

Around 1628, William Harvey had first discovered the circulation. He also first observed the difference in colour between the pulmonary venous and pulmonary arterial blood. But, he was unable to draw any firm conclusion, regarding the functions of lungs and the cause of difference in colour between the pulmonary venous and arterial blood. Then, in-between 1660 and 1670, Robert Boyle and Robert Hooke understood that some component of air is absorbed by the lungs and is responsible for that difference of colour between the blood of pulmonary vein and artery. After that, Harvey had discovered the different components circulating in blood and developed an intravenous technique for therapeutic purposes. At that time, the basic scientific work on respiration by Priestly, Lavoiser and Laplace had also led to the possibility of use of different breathing gases and vapours for therapeutic reasons (Fig. 15.1).

When Priestley was in Birmingham, he experimented with many gases for therapeutic purposes. During this period his friend, Pearson had recommended the inhalation of ether for the recovery of different lung diseases. Then in the period between 1780 and 1800, Thomas Beddoes, a physician and a chemist of Oxford and a friend of this group of scientists, founded a Pneumatic Institution in Bristol for the study of this pneumatic therapy for the treatment of different diseases of patients. Among the gases that Beddos had used for therapy of the patients were oxygen, CO_2, water gas (mixture of H_2, CO, CO_2) and hydrogen. But Chaussier had first used O_2 in medicine in 1780 for neonatal asphyxia. In 1798, Beddos and Humphry Davy met each other, while they were on a holiday in Cornwall. There, Beddos invited Davy to be the superintendent of this Pneumatic Institution in Bristol. Davy was only 19 years old then. Here, Davy undertook a series of experiments on the effects of breathing of N_2O. Once he had a severe inflammation of his gum with acute pain. During an experiment with this pain, he breathed three large doses of N_2O. The pain was diminished and then Davy had suggested the probable use of N_2O as analgesic with definite advantages during surgical operations. This was the first experiment and suggestion in 1800 by Davy that surgical analgesia might be achieved by inhalation of N_2O. So, inhalational anaesthesia can be dated back to that very suggestion with dawn of modern inhalational anaesthesia where many modern volatile anaesthetics were delivered with sophisticated electronic vapourisers. Davy also realized the pulmonary blood flow. He also suggested that cardiac output and pulmonary blood flow could be measured by estimating the rate at which N_2O is taken up by the lungs. During that period to assist the work of Davy, Sir James Watt also made a special N_2O container. But, after few years due to some unknown reason Davy or his contemporaries did not further pursue the idea of deliberately inhaling N_2O to produce surgical analgesia (Fig. 15.2).

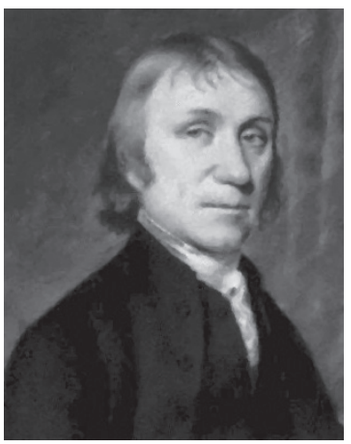


Fig. 15.1: Joseph Priestley

After that Davy's work was known to many and influenced Colton after 44 years. Surprisingly, at that time gases and

Fig. 15.2: Humphrey Davy

vapours were not only breathed in with the hope that they might cure various diseases, but were also inhaled for pure entertainment and amusement purposes. So, Davy also named N_2O as the 'laughing gas'. As this form of entertainment did not seem to cause any long-term harmful effects, so it was widespread in certain rich social circles in Europe. During that period similar use of ether vapour, named as 'ether frolics' was also wide-spread in America. We get the description of such entertainments using laughing gas and ether frolics in the works of great poets, like Samuel Taylor and Robert Southey.

In 1824, the first deliberate use of inhaled gas to produce anaesthesia was performed by Hickman on an animal for surgical operation. He used CO_2 for anaesthesia. But, his experiment and contribution in medical science was not recognized by the medical body at that time. Thus, it was he who introduced the concept of anaesthesia, using an inhaled substance. The first recorded general anaesthesia administered by inhalation of gases in humans was in 1842 by Long and Clarke, using ether. Then, on 16th October 1846, Morton first successfully demonstrated publicly ether anaesthesia at Massachusetts General Hospital. The

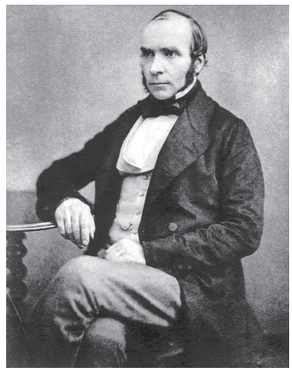


Fig. 15.3: John Snow

operation was the removal of a vascular tumour from just below the mandible and was held at place in what is now called the 'Ether Dome' at Massachuset's General Hospital. The patient who gave the informed consent for operation was a young man named Edward Gilbert Abbott, a printer and journalist and Mr Warren was the surgeon.

Then, in 1847, Pierre Flourens, a Paris physiologist suggested that ether gradually affected the higher cerebral centres, the cerebellum, the spinal cord and finally the medulla oblongata where the cardiovascular and respiratory centres are situated as anaesthesia is gradually deepened. Flourens had also previously demonstrated that the cardiovascular and respiratory centres were located in the medulla.

After that, John Snow, an eminent physician of London also became interested in ether, soon after its introduction. Even before Gudell, he described the five stages of ether anaesthesia in his publication in 1847. According to him the first three stages were of light anaesthesia. The fourth stage is comprised of what we call as the surgical anaesthesia (Fig. 15.3) and in fifth, respiration would become progressively shallow and eventually stopped. Snow quickly realised that the method of administration of ether was faulty. So, he developed many apparatuses for delivering ether to the patient with different known concentration in an attempt to increase the safety. At that time,

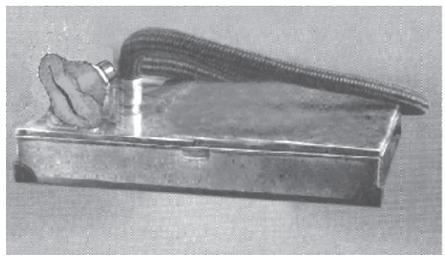


Fig. 15.4: Snow's inhaler

in 1847, two deaths associated with ether anaesthesia were reported. The first was a young woman at Grantham of Lincs and the second was a 52 year old man at Essex in Colchester Hospital. Snow's inventory work was stimulated further by these first report of deaths. Then, Snow investigated many other potential volatile agents for inhalational anaesthesia instead of ether such as benzene, bromoforms, ethyl bromide, ethyl nitrate and amylene in the last 10 years of his life from 1848 to 1858. During this time, in 1857, two patients had also died, while he was administering amylene to the patients. Then, he was the first to suggest that there was an inverse relationship between the lipid solubility and potency of the inhalational anaesthetic agents. During that period, around 1850, many different types of apparatus were also developed to improve the vaporisation of ether. It was also tried by preventing the cooling of liquid ether which occurs when it is evaporated. Many scientists also tried to prevent the dilution of ether vapour which occurred with air during administration of it (Fig. 15.4).

Chloroform was first identified in 1831. But, in 1847 the anaesthetic properties of chloroform in animals were first described by Pierre Flourens. It was first used on humans at St. Bartholomew's Hospital of London by Dr Lawrence under the name of 'chloric ether' in the spring of 1847. But, the use of chloroform in clinical practice was first made in vogue by Simpson. Then it was popularised by his two assistants who experimented with chloroform by inhaling it themselves in Simpson's

house. Simpson then read a report in Edinburgh Medical Society and described chloroform as a new anaesthetic agent which could be used as a substitute for sulphuric ether in surgery and midwifery. Gradually, after 1847, due to the works of Simpson and Snow chloroform became a favoured anaesthetic agent in Britain than ether. Simpson who had worked more on chloroform also had been impressed by ether, but was trying to overcome the disadvantages of ether associated with its administration. He had also been trying for inhalational anaesthesia with other organic volatile agents before chloroform. Then, he finally considered that chloroform had major advantages over ether (Fig. 15.5).

Snow, who had worked more on ether, later also abandoned ether and accepted chloroform as better agent. But, he recognised the dangers of chloroform, if the vapour was too strong. To overcome this danger, Snow invented an instrument by which a fixed percentage of chloroform could (Table 15.1) be delivered. Then within a few months, chloroform displaced ether and became the most popular anaesthetic agent in Britain. On 28th January of 1848, just little more than two months after the introduction of chloroform, first death due to chloroform was reported. The patient was a 15 years old boy named Hannah Greener of New Castle. The anaesthesia was given for a minor operation by Dr. Meggison. Then, Snow gave 5000 anaesthesia by chloroform with only one death. So, he recommended not to use chloroform

Fig. 15.5: Young Simpson

Table 15.1: The advantages of chloroform over ether (as thought by Simpson)

1. Less volume was needed and it was therefore cheaper.
2. It was more pleasant for the patient and induction was quicker.

in concentration more than 4% in an air-mixture. Then, due to toxicity chloroform gradually lost its favour in England (Table 15.2).

Ether did not regain much popularity in Britain until B Jeffries came from America and advocated ether as being much safer than chloroform, in 1872. Then, two years later in 1874 Clover introduced his gas-ether sequence. After that ether became accepted as safe agent for all-purpose anaesthesia.

The major war in which inhalational anaesthetics were used first was the Crimean War in the period of 1850. Even after the introduction of ether for anaesthesia in surgery by Morton, surgeries were still being rampantly performed without any form of anaesthesia in European teaching hospitals. At that time, different countries had also adopted one of these two anaesthetic agents − ether or chloroform and different methods of their administeration. Thus, chloroform was very popular and was used more frequently in Scotland, greater part of Europe and South America. While ether was favourite in England and North America. At that time, there was also much controversy regarding which was the more safer of the two (Table 15.3).

Then, a committee was set up in 1864 which drew attention to the dangers of chloroform. But, the committee also considered ether to be impractical, because it provided a lengthy induction and a prolonged excitatory phase. This commitee

Table 15.2: The toxicities for which chloroform lost it popularity

1. Gradual fall of BP with deepening of anaesthesia,
2. Sudden cardiac arrest during light anaesthesia, due to ventricular fibrillation or vagal inhibition.

also recommended the use of a mixture of ether and chloroform or the use of chloroform for induction and then switching over to ether for maintenance. Then, ACE mixture (alcohol, chloroform and ether in the ratio of 1:2:3) was introduced in anaesthesia practice and gained considerable acceptance. This also opened the door for other important new concepts and the committee suggested that different anaesthetic agents may be needed for different types and stages of an operation, because there was no single perfect universal agent.

Clover worked intensively both on chloroform and ether, in 1862. He invented a chloroform inhaler which enabled the anaesthetists for accurate measurement and administration of a desired percentage of a mixture of air and chloroform to reduce the risks. This took the form of a large bag which was slung over the back of an anaesthetist and contained a mixture of 45% of chloroform vapour with air. So, Clover was selected in the committee which investigated chloroform extensively and he realized its danger. So, he abandoned chloroform and set to work to make

Table 15.3: The advantages and disadvantages of ether vapour over chloroform

Advantages

1. A relative lack of toxicity, especially in light planes of anaesthesia,
2. Excellent muscle relaxation, without severe respiratory depression,
3. Lack of cardiac depression, even if overdose produced respiratory depression,
4. Relatively non-toxic products of metabolism (alcohol, acetaldehyde and acetic acid),
5. Little tendency to cause dysrhythmias.

Disadvantages

1. The risk of explosion and fire, although explosions have never been described during the administration of ether and air mixture, even when diathermy has been used.
2. Stimulation of the secretion of mucus.
3. Post-operative nausea and vomiting.
4. A slow induction and recovery due to its high solubility in blood.

the administration of ether simpler, easier and accurate. He later worked on inducing anaesthesia with nitrous oxide before adding ether. In 1877, Clover invented his portable regulating ether inhaler which made ether more popular at the expense of chloroform. Another Clover's achievements was his teaching that ether could safely be given over long periods with the desired and adequate depth of anaesthesia. By 1870 in this way ether had largely won the game. Then, the two agents N_2O and ether remained the mainstays of inhalational anaesthesia for the next 80 years (up to 1950) (Fig. 15.6).

After experiment with chloroform and ether, amylene was also used successfully for inhalational anaesthesia by Snow. But, it was quickly abandoned following two deaths. Then, came ethyl chloride for its rapid action and the relative freedom from side effects. But, ethyl chloride in its active pure chemical form was difficult to obtain as it was highly volatile. Again, at that time there was no such technically improved vapouriser for the use of ethyl chloride. So, ethyl chloride was introduced as local anaesthetic spray, especially for dentistry, rather than general inhalational anaesthesia. In 1894, this local use of ethyl chloride by dental surgeons resulted in accidental general anaesthesia. Thus, the apparent ease for use of ethyl chloride led some surgeons to adopt it for GA. The first death associated with the use of ethyl chloride was reported in 1899. Then gradually, the dangers of ethyl chloride soon became apparent, as general anaesthetic agent over the chloroform and ether. So, several anaesthetists used ethyl chloride just for induction of anaesthesia and then changed over to ether or chloroform for maintenance.

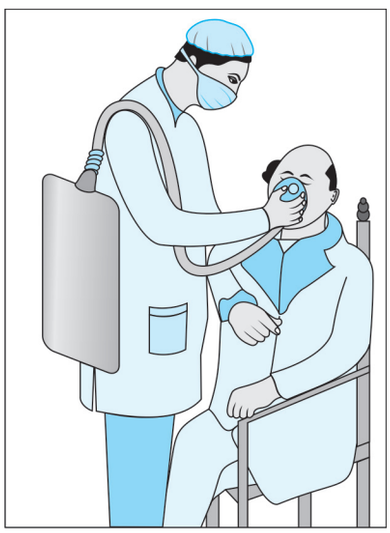


Fig. 15.6: Joseph Clover monitoring the patients pulse while giving anaesthesia by chloroform vapour from a bag

Towards the end of the nineteenth century after a rush of innovation, the development in anaesthesia became dramatic. At that time, antiseptic methods were also developed in the surgical fields which was parallel to the development of anaesthesia. The combination of this development of antisepsis in surgery and the development of anaesthsia gradually allowed the development of prolonged and delicate surgery that could not have been possible before the beginning of 20th century or the end of 19th century. But, during that period still it was very difficult to convince a surgeon that anaesthesia required its own specialist. It required someone who was perfectly skilled to select the anaesthetic agents and apparatus which are most suitable for that patient according to his physical conditions and the proposed operation. However, though late, still this realization came first from Britain, followed by America and much later from the different parts of the Europe. Then from 1800's to 1900's there were many significant changes in inhalational anaesthesia. But, it was more a period of consolidation.

At the end of the 19th century, two German pharmacologists, named Meyer and Overton suggested that the potency of inhalational anaesthetic agents increase with their lipid solubility. This hypothesis was based on the assumption that anaesthetic agents act on the brain which is rich in lipids. In 1922, the fifth edition of Hewitt's book was published which helped to uphold the standard of British anaesthesia. The influence of this book was wide spread. Hewitt emphasized in his book that N_2O anaesthesia was possible without hypoxia. He also suggested that chloroform was especially dangerous during induction. During that time, ether and chloroform were still the main anaesthetic agents, but ethyl chloride and N_2O were often used for induction. During this period Simpson's open-drop method for ether administration was most popular, though in 1917 the first Boyle's machine had already appeared. From this time onwards, the speed of progress in anaesthesia was very fast and was continued to do so. Before 1930's the anaesthetists administered the mixture of only volatile anaesthetic agents as balanced anaesthesia which produced unconsciousness, muscle relaxation and analgesia. This balanced method of anaesthesia by mixture of gases had reduced the amount of a particular toxic drugs and also reduced the hazards of anaesthesia.

However the actual concept of balanced anaesthesia had started in 1911 by George Crile. He taught that 'psychic stimuli' must be obliterated by light general anaesthesia with volatile anaesthetic agents while the noxious stimuli due to surgery must be blocked by local anaesthesia. In 1926, Lundy of the Mayo's Clinic had first introduced the term 'balanced anaesthesia' by combination of premedication, regional analgesia and general anaesthesia, using one or more volatile anaesthetic agents, so that pain relief was obtained by judicious mixing of agents and techniques. While anaesthesia was first divided into three basic components such as narcosis, analgesia and relaxation by Rees and Gray of Liverpool. Gray named these components of GA as the 'triad' of narcosis, reflex supression and relaxation (Table 15.4).

In the early part of 1930's, there were also certain important innovations in anaesthesia. During that period, blind nasotracheal intubation only under the

Table 15.4: Important innovations in anaesthesia in early 1930

1. The popularization of endotracheal intubation by Magill and Rowbotham.
2. The appearance of bromethol, divinyl ether, cyclopropane, trichloroethylene.
3. The induction of anaesthesia by intravenous barbiturates.

volatile anaesthetic agents was increasingly used. But there was difficulty in obtaining good relaxation of the jaw and larynx with ether only. So, controlled respiration with muscle relaxation was used with cyclopropane during that period. Thus, when Griffth at Montreal first used curare in 1942, to deal with hypoventilation and apnoea by controlled ventilation, then it was already well established and so IPPV became a routine procedure.

The two World Wars had greatly influenced and changed the scenario of both surgery and anaesthesia. The doctors had learnt a lot during their army tenure and had practised those anaesthetic procedures during their later civilian life. That led to the massive development in anaesthesia speciality. Then technical improvements in anaesthesia and academic recognition of it was followed gradually. In 1935, in London, the first examination for Diploma in Anaesthesia was held successfully.

In 1917, Haldane had first popularised the modern medical use of oxygen. In 1995 Helium was first isolated by a British chemist and Nobel prize winner, named Sir W. Ramsay. The respiratory stimulating effect of CO_2 was first shown by Herman and Escher in 1870. This was followed by recommended use of 5% CO_2 in anaesthesia by Haggard and Henderson in 1921. However, then many fatal accidents had occured with accidental overdosage of CO_2. So, Waters pointed out that the ill effects of inadequate ventilation were not due to hypoxia, but due to the excess of CO_2, in 1920's. When Waters started to use cyclopropane, he extensively developed a CO_2 absorption system, though CO_2 absorption during anaesthesia was pioneered by John Snow.

In the first half of the twentieth century, a number of other volatile anaesthetic agents also enjoyed immense popularity. These included ethylene, acetylene, premixed O_2 and N_2O (or entonox) trichloroethylene, cyclopropane, methyl-n-propyl ether, ethyl vinyl ether, etc. Ethylene was more potent than N_2O and had shorter induction period. Therefore, more oxygen could be used with it than N_2O which was the main disadvantage of the use of latter. But, the main disadvantage of ethylene was that this gas was highly inflammable. During that period it was used mainly in USA and 20 massive explosions were reported. So, ethylene was abandoned and paved the way for acetylene.

Characteristics of acetylene were similar to ethylene. There was rapid induction and recovery by acetylene, and also there was possibility of administering O_2 upto 50% with it. It was used mainly in Germany and USA. It was also highly inflammable and multiple explosions were reported.

Then, in 1945 premixed N_2O and O_2 (80:20) in a cylinder at a pressure of 700 lb/in^2 was used in USA. Later, it was found that at room temperature and at a pressure of 2000 lb/in^2 certain proportions of N_2O in O_2 remains as a gaseous phase due to the solvent action of O_2 at this pressure. This is called the Poynting effect. Tunstall had described this phenomenon making the point that upto 75% of N_2O remains in gaseous phase with O_2 under this condition. He also first reported the clinical use of mixture of 50% N_2O and 50% O_2 contained in one cylinder for the relief of pain during childbirth. Cooling of such a mixture produces liquid N_2O at the bottom of the cylinder. This remains liquid even when the cylinder is rewarmed. In these circumstances, if the cylinder is used, it will first deliver the gas mixture with high O_2 content and later with high N_2O content. So delivery of constant mixture of N_2O and O_2 from the cylinder can only be assured either by preventing cooling or by inverting the cylinder many times after rewarming if cooling occurs. Thus, entonox (50:50 mixture of N_2O and O_2) was prepared and sold commercially (Fig. 15.7).

The trichloroethylene had long been used in the industries both as a fat solvent and for dry cleaning. Its poisonous properties had also long been recognized and this poisonous property was used especially to produce numbness and anaesthesia along the distribution of fifth cranial nerve to relieve trigeminal neuralgia. But, its general anaesthetic properties was described in 1911 and 1933. Then, it was used to anaesthetize 300 patients in 1935. If trichloroethylene was used in

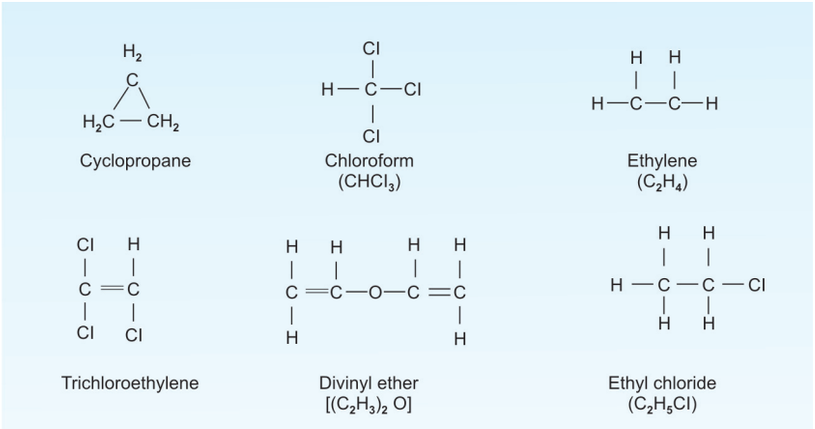


Fig. 15.7: Commercial anaesthetic agents

a closed circuit with sodalime, then toxic substances were formed. The most important toxic product of trichloroethylene in a closed circuit with sodalime is dichloroacetelene which is a very potent nerve poison and produced paralysis of the cranial nerves or even death. Also, it was decomposed into phosgene at a temperature above 125°C during cautery, and had caused death of many patients. But, cardiovascular stability provided by trichloroethylene was good, although dysrhythmias are seen. The heart was sensitized to adrenaline by trichloroethylene. It had an excellent analgesic property and was used in both surgery and in obstetrics, but was abandoned after the 1st half of twentieth century.

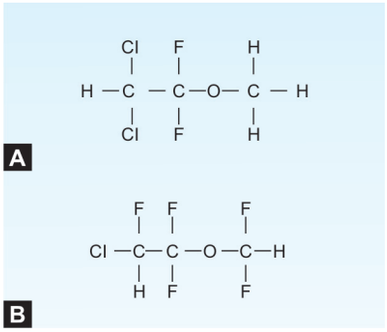
Cyclopropane was first synthesized in 1882, but nobody knew its anaesthetic property. Its anaesthetic property was first discovered in 1929. It was stored in orange cylinders as a liquid at a pressure of 5 bars without requiring any reducing valves during delivery. It was highly explosive and inflammable (Table 15.5).

Though, it had a powerful respiratory depressant effect, and also produced ventricular dysrhythmias with some deaths from ventricular fibrillation, still it was used for many years in the practice of inhalational anaesthesia since its introduction due to some advantages which are tabled. High incidence of PONV was common after anaesthesia with cyclopropane. Some anaesthetists found it immensly useful for very old, ill and shocked patients as it provides a strong haemodynamic stability. It was also popular for induction in children, till the 1980's (Figs 15.8A and B).

In 1950, Kety and Eger described the pharmacodynamics of inhalational anaesthetic agents, and determined the rate at which the arterial partial pressure of a volatile anaesthetic agent approached that of the inspired concentration of gas. During that period, occurence of diffusion hypoxia during emergence from N_2O anaesthesia was also described by Fink.

Table 15.5: Advantages of cyclopropane

1. Very rapid induction,
2. Cardiac output and arterial pressure are well maintained, even in very ill patients.



Figs 15.8A and B: (A) Methoxyflurane (B) Enflurane

Booth and Bixby, in 1932, observed that the greatest potential of an inhalational anaesthetic agent lay within its organic fluoride compound. This is because the substitution of fluoride ion for other halogenions in the compound reduced the boiling point, increased the stability and generally reduced the toxicity of the gases. Then, a large number of fluorinated volatile anaesthetic compounds were produced over the next 20 years. At last it culminated in 1950 with the development of fluroxene and then in 1952 with the synthesis of halothane, the first of the truly modern inhalational anaesthetic agents.

Then the first great jump-forwards in modern anaesthesia was the introduction of halothane into clinical practice with calibrated vapourisers in 1956. Then, the progress in the field of anaesthesia depended mainly on the pharmaceutical companies, developing the various inhalational anaesthetic agents. In 1960 methoxyflurane arrived. It had good analgesic properties, but had an unpleasant smell. It was non-inflammable and non-explosive. It had no reaction with sodalime. However, a significant amount of methoxyflurane was metabolised to fluoride which was toxic to the kidneys and caused high output renal failure. So, methoxyflurane was abandoned after its introduction.

Then came enflurane, in 1963, in USA. After that, isoflurane entered into the anaesthetic arena. It was a fluorinated methyl ethyl ether which was originally synthesised in 1965, but was first used in clinical anaesthesia in 1971. Then sevoflurane was first synthesised in the late 1960's at Baxter Travenol laboratory and was first used experimentally on animals in 1971 in North America. The first published record of its use in humans came out in the year of 1981. Then, the results of phase I trial of this drug on six healthy adults were published. It had two drawbacks. The metabolism of sevoflurane resulted in the production of potentially significant level of fluoride ions. And, it had also been found to be chemically unstable in the presence of sodalime. So, Baxter company decided not to develop this drug commercially. Then it had contracted with a Japanese pharmaceutical firm. There more extensive experiments were being done. After that, it was approved for clinical use in Japan in 1990 and eventually became the most popular inhalational anaesthetic agent there. Its success in Japan was subsequently followed by its introduction in Europe. But, the potential toxic degradation products of sevoflurane delayed its release in USA, until 1994.

Then came desflurane. It was first synthesized by Dr Ross Terrell who had also developed isoflurane and enflurane. But, due to its physical properties and some technical difficulties the subsequent research of desflurane was delayed. Later, a safer process of synthesis of desflurane was developed, and the result of the phase I trial was published in 1990. Subsequently it was approved for clinical use in USA in 1992 (Fig. 15.9).

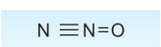


Fig. 15.9: Nitrous oxide

NITROUS OXIDE

History

N_2O was first prepared by Priestley in 1772. But, Humphry Davy first demonstrated its anaesthetic properties in 1800. At that time Davy was only 21 years old. However, from 1800 to 1844 it was absent from the anaesthetic practice, though the exact reason behind this is still not known. Then, on 10th December in 1844, Gardner Colton (Fig. 15.10) again demonstrated the anaesthetic property of N_2O in front of a big audience at Hartford. He was a lecturer in chemistry. Horace Wells (Fig. 15.11), a dentist, was among the audience. He was very much impressed by seeing the anaesthetic property of N_2O. So, this demonstration was again repeated on himself in the next day privately. In this demonstration, a local druggist's shop assistant, named Samuel Cooley banged the shin bone of Mr Wells and made it bleed, while he was under the effect of N_2O.

Then, Wells after recovery stated that he had experienced no pain. He also commented that N_2O could be used for tooth extraction painlessly. During this time, Mr Wells's wisdom tooth was producing trouble. So, he requested Mr Colton to extract it and try the N_2O gas on him during the dental surgery. So on 11th December in 1844, this experiment with N_2O was carried out, again where Colton was the anaesthesiologist, John M Rigg was the dental surgeon and Wells was the patient. It was also a big success, when Mr Wells had recovered from the anaesthetic effect of N_2O. Then he declared it as the new era of dental medical science. So, he asked for some N_2O from Colton and in the next day he used it on one of his patients for extraction of tooth. This procedure was also painless. By the middle of January, in 1845, Wells then performed 15 successful cases of painless extraction of tooth at his clinic. Next, Wells tried to demonstrate this technique at Massachusetts General Hospital in front of big audience. But, the patient complained of pain and Wells was dubbed as a fraud. The low lipid solubility of N_2O was the cause of this failure and it may be the cause of his suicide, at the age of 33 years.

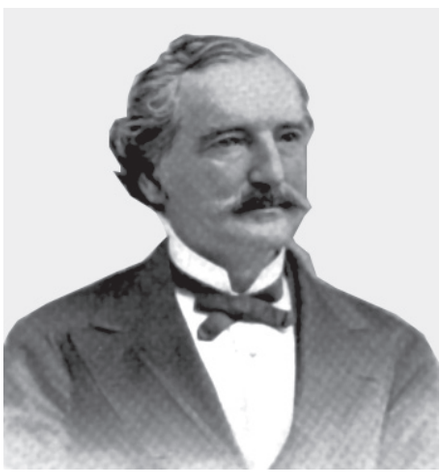


Fig. 15.10: Gardner Colton

Fig. 15.11: Horace Wells

These series of events antedates the first public demonstration of ether as an anaesthetic agent by only 21 months. So, at that time the introduction of both ether and N_2O delayed the full appreciation of the analgesic effects of the latter. Again, 20 years later Colton reintroduced it in dental practice.

So after a temporary period of its eclipse by ether, N_2O was reintroduced in anaesthesia practice and was widely used from 1867 onwards. By 1868 the gas was first available in London as a compressed gas in metal cylinders. Two years later, it was available as liquid nitrous oxide in metal cylinders. Then a reducing valve was attached in 1873 to the cylinder. During this period, the main difficulty was in the technique of administration of N_2O in its pure form as asphyxia was inseparable by this use. This difficulty was first overcome by Edmund Andrew, who in 1868 used N_2O with 20% O_2 for prolonged anaesthesia, avoiding asphyxia. Then in 1868, Clover first proved that N_2O had true anaesthetic properties. Subsequently, in 1876, he first introduced the N_2O-ether sequence in anaesthesia. N_2O is the only gas which has continued its use from the era of chloroform till the present day. In view of the large number of volatile anaesthetic compounds that have been used as anaesthetics and whose use has been discontinued after shorter or longer periods, it is remarkable that the use of N_2O still continues. More patients have been anaesthetized with N_2O than with any other inhalational agent and at present it still continues to be the most widely used agent than any other volatile anaesthetic.

Chemistry

Except xenon, nitrous oxide is the only inorganic compound which has been used to produce analgesia and general anaesthesia. This is not due to the some unusual pharmacological property of N_2O, but is due to the consequence of its degree of solubility in blood and lipid, and due to its chemical stability in the body. The structure of a molecule of N_2O is linear and asymmetrical, having a significant resonance feature: $N \equiv N =$.

Although biochemically N_2O is stable, but it is a thermodynamically unstable and is an endothermic compound. Because, it supports combustion by decomposing itself into its elements such as N_2 and oxygen. But a temperature above 450°C is required to initiate this reaction.

$$2\ N_2O \rightarrow 2N_2 + O_2 + 163\ kJ$$

Preparation

In laboratory, N_2O is prepared by allowing the reaction between iron and nitric acid. In this reaction nitric oxide is produced first which is then reduced to N_2O by excess iron.

$$Fe + 2NO \rightarrow N_2O + FeO$$

Commercially, it is produced by heating ammonium nitrate between 245°C to 270°C.

$$NH_4NO_3 \rightarrow N_2O + H_2O + 58.4\ kJ$$

The major part of the world's supply of N_2O gas is usually obtained by this method. In older plants, this was performed by heating solid ammonium nitrate. But, now in more modern plants an aqueous solution of 83% ammonium nitrate is being used. This is available as byproduct, during large scale manufacturing of ammonia.

Accurate temperature control during this process is essential. Because this reaction is exothermic and above 270°C the level of impurities increase. Again above 290°C, this reaction becomes very explosive. So, the control of accurate temperature is necessary. Serious explosions may also occur in a nitrous oxide manufacturing plant, if the temperature goes out of control. In the older type of plants where solid ammonium nitrate was used, the retort in which the exothermic reaction is occurred had to be externally cooled by ice-water. But, in newer plants, where ammonium nitrate solution is used, temperature control is done by the addition of more solution.

During the preparation of N_2O by heating NH_4NO_3 other higher components of nitrogen, such as ammonia, nitric acid, N_2, NO, and NO_2 are also produced. But, by different processes, adopted by different companies, N_2O is separated, dried and purified from this mixture. Then, pure N_2O is compressed to liquid form and filled in cylinders. However, during purification, a great care should be taken so that the content of higher oxide of nitrogen mixed with N_2O should not exceed 1vpm (volume per million). Greater care is also taken to prevent moisture from being included in the gas cylinder. Because water tends to freeze within the pipeline of anaesthetic machine as the N_2O passes through the reducing valves when the cylinder is turned on, and may lead to the obstruction of gas flow. About nine-tenths of a full cylinder is filled with the liquid form of N_2O. Nitrous oxide is stored and supplied in cylinders for anaesthetic purpose under a pressure of 5000 kPa at 20°C. A full N_2O cylinder at room temperature contains liquid N_2O. For this reason, cylinder should be kept upright when it is in use. When the cylinder is turned on and the gaseous portion above the liquid leaves the cylinder, then the liquid N_2O starts to vaporise. The pressure gauze on the N_2O cylinder cannot indicate the total content of liquid N_2O, until all the liquid is exhausted and cylinder is filled only by N_2O gas. Nevertheless, they do warn about the failure of gas flow when all the liquid is exhausted. For vaporisation of N_2O, during its flow from the cylinder, latent heat is obtained from the metal cylinder. So it rapidly cools, and water vapour of air outside the cylinder freezes on the cylinder forming a layer of ice.

Physical Properties

N_2O is a non irritating, odourless and colourless gas. Its molecular weight is 44. It is neither inflammable and nor explosive. Specific gravity of N_2O is 1.527 (air =1). At 50 atmospheric pressure and at 28°C, N_2O becomes a clear and colourless liquid with a boiling point of –89°C. It is stable in soda lime. Its partition coefficient at 37°C are : oil / water 3·2, water / gas 0·435, oli / gas 1·4, blood / gas 0·468. The critical temperature of N_2O is 36°C and the critical pressure of it is 72 bar. Its MAC value is 105.

Importance of N_2O as Anaesthetic Agent

This is remarkable that N_2O has stood the test for a long time since its inception as an anaesthetic agent. The other volatile anaesthetic agent which also stood the test of time with a contemporary history is only the diethyl ether. But, since the introduction of halothane, in 1950, ether has been of little use in Europe, and recently its production has also been stopped (Table 15.6).

Therefore, it is expected that N_2O would still have the considerable virtues as an inhalational anaesthetic agent which are tabled.

The speed of onset and the recovery from anaesthesia of any volatile anaesthetic agent is regulated by its blood solubility. The lower the blood solubility, the faster is the onset and recovery. The blood-gas partition coefficient of N_2O is only 0.46. This is the lowest for any inhalational agent that are currently used. This lowest blood-gas solubility of N_2O has another advantage. This makes it easier to control the depth of anaesthesia. Because any slight change in the inspired concentration of N_2O rapidly results in the change of its partial pressure in the blood and the brain, due to this less blood gas solubility of it. Thus, lightening and deepening of anaesthesia is quickly achieved, which is parallel to the partial pressure of this agent in the blood and the brain. So, after a few breaths the alveolar concentration of N_2O becomes equivalent to the inspired concentration of it, and the alveolar concentration or a partial pressure of N_2O (which is parallel to the partial pressure of the agent in blood and brain) reflects the depth of anaesthesia (Fig. 15.12).

So, now from the above discussion it is clear that the low blood gas solubility of

Table 15.6: Virtues of N_2O as an anaesthetic agent

1.	Have no irritant properties,
2.	Have good analgesic property,
3.	No metabolism in the body,
4.	Minimal adverse effects,
5.	Have advantages when used with other volatile agents,
6.	Low blood solubility,
7.	Accuracy of administration.

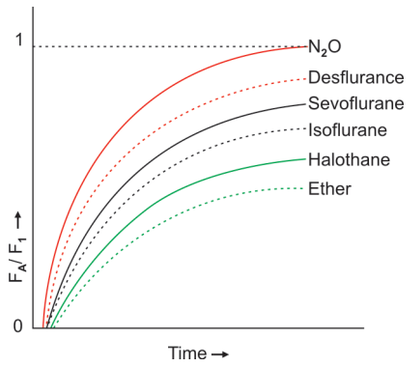


Fig. 15.12: FA /FI ratio of different volatile anaesthetic agents. In case of N_2O the alveolar fractional concentration (FA) rises rapidly and reaches the value of inspired fractional concentration (FI) quickly. Thus, the FA/FI ratio reaches to the value of 1 most rapidly with least soluble agent such as N_2O

any inhalational agent is a great asset for it. But, low blood – gas solubility is also associated with a low fat solubility, which indicates that the agent is of low anaesthetic potency. Because, it is known that anaesthetic potency of any volatile agent depends on its fat solubility. This is the disadvantage of N_2O or any such agent, and is the reason for the high MAC value of N_2O which is 104.

Impurities

During manufacturing of N_2O the main impurity in it is the higher oxide of nitrogen, i.e. NO_2. In addition to nitrogen dioxide (NO_2), atleast seven other oxides of nitrogen are also known to be present in it. But among these impurities those of importance as contaminants are – nitric oxide and nitrogen trioxide. This is because nitric oxide (NO) combines with air to form an even more toxic, nitrogen dioxide, which remains in equilibrium in the mixture and this point of equilibrium depends on the temperature of the mixture. The European and US standards for maximum permissible limit of NO and NO_2 in the medical preparation of N_2O is 5 ppm. The higher oxides of nitrogen in N_2O can be detected by smell at a concentration above 5 ppm. The consequences of inhaling higher oxides of nitrogen in concentrations above 50 ppm are: reflex inhibition of breathing, laryngospasm, cyanosis, methaemoglobinaemia, and pulmonary oedema. An insidious feature of these manifestations is the pulmonary damage, which may not become apparent until the development of pulmonary oedema and this usually occurs many hours later. If the patient does not die immediately, then chronic chemical pneumonities may follow with the resultant pulmonary fibrosis. Hypotension may be marked and results from the effect of nitrates on the vascular smooth muscles. Other impurities in N_2O, except the higher oxides of nitrogen are : ammonia, carbon monoxide and chlorine. So, after production scrubbing of N_2O with permanganate solution, sulphuric acid solution and water is important to remove all these impurities.

Pharmacological Actions

N_2O is very rapidly absorbed from alveoli into the blood if only remains in plasma as dissolved state. 100 ml of plasma can carry 45 ml of N_2O. It does not combine with Hb, nor does it undergo any chemical combination within the body tissue. It remains in blood just as physical solution. So, elimination of N_2O from body is as speedy as absorption through the lungs. It is 15 times more soluble in plasma than N_2, and 100 times more so than O_2. As far as anaesthetic action is concerned, N_2O is a weak anaesthetic agent. To produce a surgical anaesthesia (stage III) only with N_2O, a plasma partial pressure of 760 mm of Hg of N_2O is required. However 80% N_2O in mixture with O_2 at normal atmospheric pressure produces a partial pressure of only 600 mm of Hg in blood. So, surgical anaesthesia cannot be produced without hypoxia when N_2O is used alone. Only a 50:50 mixture of N_2O and O_2 at 2 atmospheric pressure can rapidly produce this surgical anaesthesia with complete saturation of arterial blood by O_2. Whereas, the same concentration of N_2O at 1 atmospheric pressure does not produce the loss of consciousness in a patient. So, in modern anaesthetic practice, N_2O alone at sea level is no longer used as the sole induction agent. But when accompanied by 33% O_2, it is used as an important supplement and carrier for other volatile anaesthetic agents.

1. Effects on CVS

N_2O is not a potent anaesthetic agent. It is also surprising that its adverse effects on CVS were overlooked, until the recent years. On the normal heart, the effect of N_2O is little and is entirely obscured by the sympathetic stimulation with concomitant rise in plasma noradrenaline concentration which is an important pharmacological action of N_2O. If there is no sympathetic stimulation or it is prevented then it reduces the cardiac output which is suggestive of its cardiac depression effect. It also causes the fall in heart rate and the decreases in limb blood flow. So, it is said that N_2O has a negative inotropic and chronotropic effect on heart and at the same time produces α–adrenoreceptor stimulation on the peripheral circulation which neutralises the depressive action on heart.

Inspite of this cardiac depression by N_2O, the normal arterial pressure appears to be maintained. This is because of the increased peripheral resistance by concomitant sympathetic stimulation by N_2O. It is also suggested that the depressant effect of N_2O on the heart is marked by the cardiac depressant effect of other anaesthetic agent, when they are used concomitantly. This N_2O induced myocardial depression may be offset by the concomitant increase in the sympathetic nervous system tone caused by it. 70 % N_2O decreases myocardial contractility to approximately the same extent as 1 MAC isoflurane. The negative inotropic action of N_2O may be more pronounced in the presence of pre-existing LV dysfunction. N_2O also produces LV diastolic dysfunction in a patient undergoing coronary artery bypass graft surgery. The N_2O induced depression of myocardial

contractibility is related to the decrease in Ca^{++} availability to the contractile element of myocardial tissue. But, it does not affect the myofibril sensitivity to Ca^{++} or in the Ca^{++} uptake and its release from the SR (sarcoplasmic reticulum).

N_2O increases the venous tone and decreases the venous capacitance. It modestly increases the pulmonary artery pressure and PVR. But in a normal patient this pulmonary artery pressure and pulmonary vascular resistance are not significantly affected by N_2O. When pulmonary hypertension is already present, then N_2O causes a marked increase in the mean pulmonary artery pressure and the pulmonary vascular resistance (PVR). Thus, the combined effects of enhanced venous return; elevated pulmonary vascular resistance and depressed myocardial contractile function, probably contribute to the increase in CVP during N_2O anaesthesia. Such an increase in PVR may adversely enhance the R to L atrial or ventricular shunt (if they are present) and compromises the arterial oxygenation in a patient with congenital heart disease. So, in such circumstances the use of N_2O is inadvisable.

The addition of N_2O to halothane lowers the threshold value in which halothane-induced arrhythmia occurs. This results from the combination of both the sympathetic nervous system stimulation by N_2O and myocardial sensitization by halothane. As the N_2O activates the sympathetic nervous system, it also causes the capillary dilation, diaphoresis, ↑SVR, and increased central blood volume. These findings suggest that the N_2O induced direct myocardial depression is partially offset by sympathetic nervous system stimulation, and may be partially responsible for the relative stability of hemodynamics during N_2O anaesthesia. The sympathomimetic action of N_2O on heart normally exceeds its direct depressant effect. The administration of drugs that tend to block this sympathetic stimulation, such as narcotics may reveal the underlying cardiac depressant action of N_2O. For this reason, the addition of N_2O to high-dose narcotic anaesthesia (to reduce the risk of awareness) has been found to cause depression of the cardiac function, which is not seen when either drug is given alone. However, this effect of N_2O is only of importance when cardiac performance is compromised by some cardiac disease. Thus, it is safe to conclude that in such conditions where there is need of strong sympathetic stimulation, such as hypovalaemia, then N_2O is considered as a cardio-depressant. Again in more complex situations its cardiac effects are not always predictable. This is because of an uncertain balance between its direct depressant and indirect stimulant action.

2. Effects on the respiratory system

Nitrous oxide is pleasant to inhale. Its pharmacokinetic properties make it very useful to act as supplement to other volatile anaesthetic agents, particularly during inhalational induction. This is done by increasing the uptake and reducing the MAC value of other volatile or inhalational anaesthetic agents. When given alone, N_2O has a minimal effect on ventilation. Like other inhalational agents, N_2O also increases the respiratory rate and decreases the tidal volume. However, this increase in respiratory rate is sufficient enough to compensate for the decrease in tidal volume. So that, despite the unfavourable change in the ratio of dead space to tidal volume during N_2O anaesthesia, alveolar ventilation is well maintained and $PaCO_2$ does not rise. This remains true even upto 2 MAC value of nitrous oxide, when the respiratory rate has been found to be two to three times greater than the normal value. N_2O does not alter the ventilatory responses to the changes in $PaCO_2$, but it significantly reduces the ventilatory response to hypoxia.

3. Effects on the CNS

When N_2O is used alone, it produces a significant increase in both CBF and ICP in normal, head injury and brain tumour patients. If N_2O is added to any volatile anaesthetic agent, there is also a significant rise in CBF and ICP. However, the interesting finding is that when the intravenous anaesthetic agents are administered in conjunction with N_2O, then these effects of N_2O on CNS may be greatly attenuated. N_2O also increases the cerebral metabolism. When the N_2O is used during neurosurgery, it should be kept in mind that it may diffuse into any air pockets, left within the skull following the closure of wound and may later increase the intracranial pressure. Despite all these potential disadvantages, the use of N_2O in patients undergoing neurosurgery remains an established and accepted practice (Table 15.7).

4. Analgesic properties

From the first observations of Humphry Davy it has been demonstrated that even when N_2O is inhaled at subanaesthetic concentrations, it has a strong analgesic action. The analgesic effect of 30% nitrous oxide has been found to be equivalent to that produced by 10 mg of morphine subcutaneously. So, the 50:50 nitrous oxide and oxygen mixture (Entonox) is widely used all over the world to alleviate labour pain and to facilitate minor surgical procedures. But it has a very weak anaesthetic property. Anaesthesia is likely to be inadequate when N_2O is used alone as a sole anaesthetic agent.

It is unclear why some inhalational anaesthetic agents have an analgesic effect at subanaesthetic concentrations and others do not. However, in the case of N_2O

Table 15.7: Advantages when N_2O is used in combination with a second volatile anaesthetic agent

1. It reduces the MAC of second agent.
2. It also reduces the amount of second agent required for effect.
3. It also increases the uptake and elimination of second volatile agent by second gas effect.
4. It increases the rate of induction and recovery.

(not other agents) there is evidence that the analgesic effect or at least a part of it is brought about by an interaction of N_2O with the opiate receptor. The chief evidence in support of this view is that the partial but significant reversal of analgesia produced by nitrous oxide is possible by naloxone. Also depletion of endogenous opiate stores may play a part in the acute tolerance to N_2O (Table 15.8).

However, the naloxone neither reverses the effect of anaesthesia, nor increases the MAC value of N_2O. In case of N_2O, although analgesia is partially reversed, but the ED_{50} of nitrous oxide as assessed by loss of righting reflex in mice (= MAC) is unaffected by naloxone. It is, therefore evident that the effect of anaesthesia is separable from analgesia in the case of N_2O.

Not only the naloxone does not affect the anaesthetic effect produced by other inhalational agent, but it also does not affect the analgesia produced by such volatile anaesthetic agents, other than N_2O. This shows the further evidence of the existence of other non-opiate pain control systems. It also suggests that the opiate receptor – endorphin system – is not directly involved in the mechanism of general anaesthesia.

Table 15.8: Adverse effects of N_2O

Harmful effects which have been clearly demonstrated

1. Adverse circulating effects,
2. Diffusion in close (compliant or noncompliant) spaces,
3. Oxidation of vitamin B_{12} causing :
   a. Abnormalities in haemopoietic system
   b. Abnormalities in nervous system

Harmful effects which are insignificant

1. Impaired wound healing,
2. Impaired leucocyte function,
3. Malignant hyperpyrexia,
4. Postoperative nausea and vomiting,
5. Teratogenicity,
6. Carcinogenicity,
7. Mutagenicity.

Metabolism of N_2O

N_2O is metabolised very minimally in the body. Hence, metabolites of N_2O in the liver has been detected, though in very low concentration. So, it can be concluded that with the probable exception to xenon, nitrous oxide is least metabolised in our body among all the anaesthetic agents.

The two small loci, responsible for the N_2O metabolism have been identified in the body. One is the reduction of this gas to nitrogen by bacteria, which is present in the gut. This has been estimated to be about 0.004% of the total quantity of N_2O taken by the body. It has also been shown that during this reduction of N_2O, free intermediate radicals may be formed. These compounds are potentially harmful, but there is no evidence of any toxic effects, resulting from these compounds due to their very low concentrations. Some bacteria in the gut may also synthesise N_2O themselves.

The other identified metabolic process of N_2O is the interaction between N_2O and vitamin B_{12}. The amount of gas taking part in this reaction is also too small to be of any significance. Interestingly, the reduction of nitrous oxide by intestinal bacteria may result, atleast in part, from the same chemical reactions in the body, since these organisms synthesise vitamin B_{12}.

Toxicity

N_2O has no direct toxic activity. However, its long term use can indirectly produce some hematological, neurological and gestational defects.

1. Haematological toxicity

Use of N_2O for a long period may cause pancytopenia (aplastic anaemia) and megaloblastic anaemia. Mild depression of bone marrow seen after exposure to N_2O for 6 hours may become severe after 24 hours of exposure. The mechanism of this response is probably due to the N_2O induced inactivation of Vit. B_{12}, which leads to an impaired synthesis of methionine and deoxythymidine, and also an impaired folate metabolism. However, all these are very essential factors for normal haemopoiesis.

2. Neurological toxicity

These have been found after long-term unintentional inhalation of N_2O by anaesthesiologist, OT assistant and habitual abuser. Neurological toxicity appears in the form of motor and / or sensory incoordination and / or reflex defects. This effects are due to the demyelination of posterior column, lateral spinothalamic tract and spinocerebellar tract of spinal cord. However, the mechanism of this toxicity is like the hematological toxicity, i.e, inactivation of Vit. B_{12}. The failure to synthesis S-adenosyl-methionine from methioxine and ATP leads to failure of methylation of basic protein in the myelin sheath.

3. Gestational toxicity

Increased incidence of gestational defects, abortion, foetal death etc., are found among OT personel who continuously inhales N_2O for prolonged period. Mechanism is similar to that of the hematological and neurological effects − inactivation of vit. B_{12}.

Interaction between N_2O and Vitamin B_{12}

The introduction of long-term IPPV by a ventilator, after 1952, facilitated the use of N_2O for long term sedation. Then several workers described granulocytopenia in cases where N_2O had been used continuously for several days. On long term administeration of N_2O, even at low concentration, leucopenia will occur after about 3 days which may develop into agranulocytosis in 5 to 7 days. However, if the patient does not succumb due to his or her primary illness, then the recovery of bone marrow from its depression effects of N_2O occurs within 4 to 5 days, after withdrawal of the N_2O. In such circumstances

the treatment with vitamin B_{12} was found to have no result.

In 1968, a paper was published describing the interactions between N_2O and vitamin B_{12}. Then in 1978, it was established that giving N_2O for 24 hours affects the DNA synthesis. Shortly after this, it was shown that the selective inhibition of synthesis of vitamin B_{12} by N_2O in due to inhibition of the action of an enzyme named methionine synthetase which is responsible for DNA synthesis. Thus it affects the DNA synthesis (Fig. 15.13).

Vitamin B_{12} is a cobalamine. The function of cobalt in the structure of vitamin B_{12} can be compared with that of the iron in Hb. The oxidation of cobalt in the vitamin B_{12} by N_2O is analogus to the oxidation of Fe in Hb by any chemical oxidizing agents to form methaemoglobin. In the case of cobalt, the N_2O converts the monovalent cobalamine to bivalent cobalamine, in which form it can no longer function as a methyl carrier. Methionine is a sulphur containing essential amino acid. It is available from food and also by metabolism of homocysteine. Folate which is also of dietary origin, is necessary for this conversion.

The enzyme methionine synthetase together with vitamin B_{12}, transfers the methyl group from methyl-tetrahydrofolate to homocysteine, and converts the later to methionine. At the same time, by losing its methyl group, methyl-tetrahydrofolate becomes simply tetrahydrofolate. Following this transmethylation, methionine and tetrahydrofolate take part in several reactions and result in the formation of deoxythymidine from deoxyuridine. Deoxythymidine is an essential component of synthesis of DNA. 90% of the deoxythymidine, incorporated into DNA, comes from the metabolism of deoxyuridine. Thus, inhibition of DNA synthesis by N_2O is thought to cause the hematological and the neurological toxicity effects of N_2O. The neurological effects may result from the depletion of methionine.

The duration of exposure of N_2O which is required to produce significant bone marrow depression is very clearly important. In man this time course is slower. No inactivation of methionine synthetase activity in human placenta was found, following N_2O administeration for upto 30 minutes during caesarean section. Presumably, this duration of exposure is inadequate. The intermittent exposure to N_2O such as Entonox during physiotherapy has been found to produce megaloblastic bone marrow.

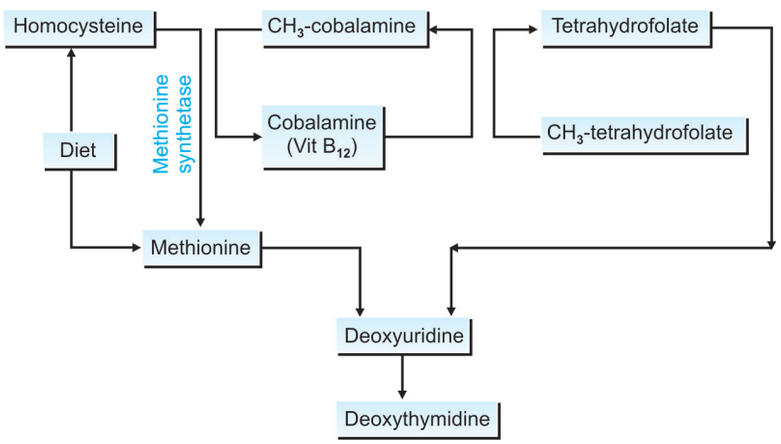


Fig. 15.13: The mechanism of synthesis of methionine from homocysteine with the help of vit B_{12} and folic acid

It is clearly important to discover the extent upto which the biochemical lesions produced by N_2O can be prevented or reversed by restoring the levels of deficient metabolites by folinic acid (5-formyl tetrahydrofolate, leucovorin, citrovorum factor etc). These compounds are freely available. They are used in chemotherapy as an antidote to folic acid antagonists, such as methotrexate. They are converted to methylene tetrahydrofolate and thus restores the metabolic pathway which leads to DNA synthesis. It is also seen that the two parenteral doses of 20 mg folinic acid, prevents the development of an abnormal deoxyuridine suppression test and megaloblastic changes in the bone marrow in 8 out of 10 patients, ventilated for 36 hours with 50% N_2O. It is also seen that in patients, subjected to N_2O anaesthesia for upto 12 hours, the abnormal deoxyuridine suppression test is corrected almost to the normal limit within 2 hour of giving of 15 mg folinic acid.

In addition to the impairment of DNA synthesis, a clinical feature of N_2O toxicity is vitamin B_{12} deficiency. This N_2O induced B_{12} deficiency is characterised by inability to synthesize myelin, causing a neuropathy. This usually develops insidiously in peripheral nerves and gradually progresses to involve the posterior and lateral columns of the spinal cord. But, it may be concluded that neuropathy is unlikely to be developed during clinical use of N_2O within the normal dose range in normal subjects.

The evidences regarding the effects of N_2O on chemotaxis, phagocytosis and wound healing are not entirely consistent. But, it seems likely that the stress metabolic responses due to surgery and anaesthesia on wound healing are more important than the effects of N_2O itself on it. The N_2O does not have any direct negative effect on wound healing.

Multiple reports have failed to show any carcinogenic potential of N_2O. The teratogenicity or other effects of N_2O on

the reproductive process is also less clear. The only agreed positive finding regarding the teratogenicity of N_2O is an increase in the rate of spontaneous abortion among the personnel who are exposed to N_2O for long duration. However, oocyte retrieval was carried out under N_2O anaesthesia, without any ill effects. Also no effect of N_2O on human spermatozoa and IVF success rate was found.

It is generally considered that N_2O is a weak triggering agent for malignant hyperpyrexia. So it is best to avoid its use, if it is suspected that the patient is susceptible.

N_2O and PONV

It is generally accepted that the use of agents that have sympathomimetic effects, such as cyclopropane or trichloroethylene results in more postoperative nausea or vomiting than the use of agents that lack such effects. For this reason and also due to the effects on middle ear (that is already described) it has been suspected that nitrous oxide might produce increased incidence of postoperative nausea and vomiting.

Methods of Administration of N_2O

1. By intermittent flow

This method of delivery of N_2O by intermittent flow is important for economy of the gas. For intermittent flow the two techniques are adopted. In the first technique a demand valve is commonly used where N_2O and O_2 coming from separate sources are combined in variable concentration in a mixing chamber and this is situated on the high pressure side of the demand valve. The characteristic of this demand valve is that it will deliver a flow of gas at low pressure, but upto the peak inspiratory flow rate in response to the slight negative pressure developed by the patient's own inspiratory effort. Since, as this type of valve is capable of delivering gas flows equal to that of the peak inspiratory flow rate, so no reservoir bag is needed. Sometimes a low resistance vapouriser, such as Goldman's, vapouriser may be placed between the valve and the patient if anaesthetist wants to use volatile anaesthetic agents to anaesthetise his patients. Such an assembly may be classified as an intermittent flow machine and these are commonly used for dental anaesthesia.

The second technique depends on the premixed cylinder, containing N_2O and O_2 under pressure with a demand valve which allows the gas to flow to the patient only during inspiration. In room temperature and at a certain pressure (2000 lbs/sq in) some N_2O remains in gaseous phase (25% in liquid form and 75% in gaseous) with O_2 due to the solvent action of later. This solvent action of O_2 is called the Poynting effect. In a premixed N_2O and O_2 cylinder with 50:50 proportion (Entonox) under pressure of 15000 kPa at 20°C, N_2O remains fully in gaseous phase (no liquid) due to this Poynting effect. Without O_2 it is not possible to keep this N_2O in gaseous phase under pressure. But, cooling of this cylinder to – 6°C causes part of the N_2O to become liquid, allowing a higher concentration of O_2 to be delivered first and exhausted. Then the cylinder will deliver a higher concentration of N_2O later and will cause hypoxia. Rewarming only can then help. So, delivery of a constant mixture of N_2O and O_2 from the cylinder can only be assured either by preventing cooling or should cooling occur, by briskly inverting the cylinder several times after rewarming.

2. By continuous flow

The continuous flow of N_2O is supplied from the Boyel's anaesthetic machine through a open, semi-closed (frequently used) or completely closed system. The semi closed technique is frequently used with CO_2 absorber to make the gas flow economical. The completely closed system with CO_2 absorber is not indicated when N_2O is used. Because, it is extremely difficult to ensure adequate oxygenation of the patient, if N_2O is used in a completely closed system. However, the development of an accurate oxymeter with a high and low alarm and also a digital display of FiO_2 has brought the completely closed circuit for N_2O delivery into the realms of clinical anaesthesia. In the absence of such sophisticated instruments the only safe way of the use of N_2O by continuous flow is to maintain a spontaneous respiration and to stop using N_2O once the system is completely closed.

In a completely closed circuit, if low gas flow (e.g. 1 lit flow of 75:25 N_2O/O_2) is used, then it will not render the patient unconscious, even after 10 minutes of breathing this mixture. This is because, the volume of air in lungs and the apparatus dead space is great enough and leads to the dilution of inspired N_2O to a level which is insufficient for narcosis. So, a high flow (e.g. 8 litres) of N_2O and O_2 gas mixture is used first. Then, when the consciousness is lost within a few minutes as the apparatus dead space is rapidly flushed out, it is switched over to a low flow technique. So, if low flow and a completely closed N_2O technique is to be used, it should always be started with a high flow for few minutes before reducing to low flow. Once, on a low flow and the circuit is completely closed, then we will have to keep in mind that the inspired O_2 concentration is not at the same level for certain constant flow, like in the beginning. Because, during every inspiration, O_2 will be taken up from the alveoli into the blood, while the N_2O will not be taken up (when body is completely saturated with N_2O). So, the O_2 concentration in the alveoli will gradually fall and N_2O concentration will gradually increase. This emphasizes the paramount importance of using an O_2 analyzer in the completely closed circle system, when a low flow of N_2O and O_2 mixture is being administered in the circuit. Provided that the concentration of O_2 in the inspired mixture does not fall below 25% and the total minute volume is adequate, then this technique can safely be used. It is best not

to use an inspired mixture containing less than 33% of O_2.

Diffusion of N_2O into Closed Space

The diffusion is defined as the physical process of intermingling of molecules, when the different gases and liquids are kept in close contact. This process results from the random movement of the molecules, present in the gases and the liquids. This is called the Brownian movement.

The factors which regulates the rate of diffusion are:

i. The concentration gradient or partial pressure of gases,
ii. The molecular size,
iii. The solubility of gases in the liquid when the passage of gas through liquid is involved.

Fick's law dictates that the rate of diffusion is directly proportional to the concentration or the gradient of partial pressure of the gases.

Graham's law dictates that the rate of diffusion of gases of identical partial pressure through some membranes is inversely proportional to the square root of their molecular weight. Therefore, a difference in gas density has only a small effect on the rate of diffusion. Finally, where the transfer of gas across the blood or water film is involved, the rate of diffusion is proportional to the solubility of the gas in that liquid. This is the principal factor for regulating the rate of diffusion of gases into or out of the spaces within the body, which can be seen from the Table 15.9.

The body is normally in equilibrium with the atmospheric nitrogen. So the N_2 present in the air of any closed cavity within the body will contain approximately the same concentration of N_2 as in the atmosphere. But, if the subject breathes a nitrogen-free gas mixture, containing 60 to 70% N_2O and 30 to 40% O_2, then it can be seen from the table that N_2O will diffuse into such spaces 25 times faster than the rate at which N_2 can diffuse out. But if the space is compliant, such as the gut, then there will be an increase in volume without an increase in pressure. But, If the space has rigid walls and is non-compliant, such as the middle ear, then there will be a rise in pressure without an increase in volume. Some cavities, e.g. the pneumothorax will fall between these two clearly defined cases, where there is both an increase in volume and an increase in pressure. Such an increase in volume and pressure may take place at the expense of other tissues, namely the lungs and mediastinal structures in the case of the pneumothorax.

Table 15.9: Diffusion of gases

Gas	*Density relative to O_2*	*Diffusion capacity relative to O_2*	*Water solubility relative to O_2*
O_2	1	1	1
N_2O	1·37	14	16·3
N_2	0.88	0.55	0.5

There are some sites within the body where the air filled cavities are normally present (such as the middle ear, sinus, etc.) or where air has been accidentally pushed or injected, (such as pneumothorax) or deliberately introduced (such as air encephalogram) and they cause an increase in volume and/or pressure, following the administration of N_2O. If the administration of N_2O is continued for a long time, then all the nitrogen of the body will diffuse out of the space, and the pressure and / or volume after having risen to a peak will return to normal. This is because, all the nitrogen would be replaced by the nitrous oxide and an equilibrium will be reached. Also, when the N_2O is withdrawn and air breathing is started, then the process goes into a reverse order and a subatmospheric pressure is created for a while in any cavity, until all the nitrogen diffuses back into the cavity. This low pressure phase during recovery is only seen in the case of the noncompliant middle ear (Table 15.10).

Table 15.10: Types of air filled cavities in our body

Non compliant
a. Nasal sinuses
b. Middle ear
c. Vitreous cavity
d. Intercranial – subdural, cisternal
Compliant
a. Stomach and gut
b. Pneumoperitoneum
c. Pneumothorax
d. Air embolus
e. Surgical emphysema

Stomach and gut

Under normal situations the volume of gas in the gut is not large enough. So, little to moderate increase in its volume due to diffusion of N_2O into the gut is not important in the absence of obstruction. But, when the intestinal obstruction is present, then the volume of gas within the lumen of intestine may be much greater and then even a little expansion of it by N_2O could cause problems. Imagining that no nitrogen is absorbed through the gut, so the theoretical increase in the volume of the gut that could result from the breathing of 66% nitrous oxide is almost 200%.

The effects of nitrous oxide on the motility of postoperative bowel have been extensively investigated. It is found that any excess of gas (N_2O) is absorbed long before the peristalsis of gut is re-established. So, the use of N_2O does not delay the return of gastrointestinal function or motility in patients undergoing bowel surgery.

Pneumoperitoneum

The gas which is most commonly introduced in the peritoneal cavity during laparoscopy surgery is CO_2. However N_2O anaesthesia does not produce any problem during this CO_2 pneumoperitoneum, because (i) N_2O and CO_2 have similar diffusing capacity, and (ii) the abdominal cavity is always vented out through some leak.

Pneumothorax

When GA is maintained by continuous flow of N_2O, then the risk of accumulation of N_2O in the cavity of pneumothorax,

producing tension pneumothorax has long been investigated. The similar risk is also applied when the sub-pleural blebs or lung cysts are present. Such cavities are non-communicating or communicate with airways only through a very narrow orifice, which becomes vulvular when there is an increase in the volume of cavity. But during breathing air, the volume of these cavities do not increase and do not cause any problem. However, the volume increases in the pneumothorax or in the subpleural blebs when N_2O is breathed in. It is found experimentally that during breathing of 70% N_2O, the volume of a pneumothorax is doubled in 15 minutes and tripled in 35 minutes.

Surgical emphysema

During maintenance of GA by N_2O, if surgical emphysema is produced, then air bubbles in the subcutaneous tissue will be expanded by N_2O, diffusing within it. But, problems have not been reported from this phenomenon, perhaps because even extensive surgical emphysema is not life-threatening.

Air embolism

It is predicted that during N_2O anaesthesia N_2O would enter and enlarge the venous air emboli, which may occur during neurosurgery and also open-heart surgery. In such situations, stopping the administration of N_2O should produce a rapid decrease in the size of such air bubbles.

Middle ear and nasal sinuses

The skull cavities such as the middle ear, frontal sinus, maxillary sinus, etc. are normally vented to the atmosphere via the eustachian tube or the various other ostia. These may be blocked by inflammatory processes or other lesions previously. Then, the pressure changes in these cavities following diffusion of N_2O during maintenance of GA by continues flow of N_2O may be expected. The nasal sinuses remain to be investigated. But, in the case of middle ear, the effects have been observed which is attributable to both the raised pressure during nitrous oxide administration and sub-atmospheric negative pressure, after its removal. These effects include: (i) rupture of the drum, (ii) graft displacement, (iii) stapes displacement, (iv) hematotympanum, and (v) temporary or permanent hearing loss. Low pressure in the middle ear after N_2O administration is particularly common in children. This is probably because the Eustachian tube is compliant and it collapses when ear pressure is sub-atmospheric. Thus, fails to maintain equilibrium of pressure on both sides.

Pneumoencephalos

The presence of air pockets or air bubbles any where within the brain or within the rigid skull raises the possibility of harmful pressure changes, due to diffusion of N_2O into these cavities if NO_2 is administered during GA. This is called tension pneumoencephalos. It is very common after posterior cranial fossa surgery, particularly in the sitting position. This condition is also found, if air is injected into the ventricle for radiological investigations, which is followed by general anaesthesia with N_2O. Intermittent drainage or aspiration of CSF from the ventricle during surgery via a shunt or ventriculostomy is also associated with this type of complication.

The eye

During surgery for retinal detachment, some ophthalmic surgeons may often inject gas bubbles into the vitreous cavity to tamponade the retina in place. So, it is desirable that this gas bubble remains in place for several days. For this purpose sulphur hexafloride (SF_6) and perfluroprofen (C_3F_8) gas have been used. They have very low blood-gas solubility. So, they are very slowly absorbed by the blood. A bubble of 40% SF_6 and 60% air maintains a constant volume for several days. But, if N_2O is given for maintenance of anaesthesia in such cases, then a considerable rise in intraocular pressure may occur due to diffusion of N_2O into this $C3F_8$ or SF_6 gas bubble. So, it is recommended that N_2O should be discontinued 20 minutes before the injection of the gas into vitreous cavity. However, practically the rise in intraocular pressure is not much, if N_2O is withdrawn simultaneously as the gas is injected.

Cuffs and Balloons and N_2O

The cuffs of endotracheal tube, balloons of Swan-Ganz catheters, and other balloons and cuffs which are used in anaesthesia are all permeable to N_2O gas. When these balloons and cuffs are in situ and filled with air, then they are subjected to pressure and/or volume changes in the same way, as other gas-filled cavities in the body during N_2O anaesthesia. These changes are clearly a complex one and many variables determine the rate of change of volume and pressure in these cuffs or balloons. These variables include the permeability of the material of the balloons or cuffs to N_2O, elasticity, contents of the cuff, its initial volume and pressure, the inspired N_2O concentration, temperature, etc.

Although sore throat is a common after effect of intubation, but serious problems do not commonly occur as a result of increased cuff pressure after routine N_2O anaesthesia. However, it is clearly undesirable to expose the tracheal mucosa to unnecessary pressure. Thus, care must be taken to inflate the endotracheal tube cuff to not more than the sealing pressure. We should also remember that the pressure may go on rising which need certain adjustments accordingly after every interval of 3 hours. The suggestions to minimise the pressure changes in cuffs include: inflating the cuff with the inspired gas mixture, (such as, with N_2O and air) or perhaps best of all with water and saline. Recently, several constant pressure inflating devices also have been developed.

Second Gas Effect of N_2O

When a high concentration of N_2O is given with O_2 and other accompanying

volatile anaesthetic agents, then N_2O quickly replaces the nitrogen, which was previously present in the alveoli. Then, though N_2O has a low blood-gas solubility compared to other volatile agents, still it is more soluble in blood than nitrogen. So, the volume of N_2O taken up by the blood is greater than the volume of nitrogen entering the alveoli from the blood. Therefore, the alveoli get smaller and the fractional concentration of the second volatile anaesthetic agent in the alveoli increases. This phenomenon is called the 'second gas effect'. After absorption of the N_2O in the blood, although the volume of N_2O in the alveoli decreases, but the concentration does not diminish to the previous level, because the volume of the alveoli also decreases.

At the end of anaesthesia, the opposite phenomenon occurs. Supply of the N_2O is stopped and the patient is allowed to breath air. At that time, N_2O diffuses back into the alveoli from the blood more rapidly, than the rate at which blood can take up nitrogen from the alveoli (as patient is breathing air). So, the concentration of N_2O in the alveoli increases with the volume of the alveoli. This increase in volume of the alveoli will cause a relative reduction of the concentration of the second volatile anaesthetic agent, which in turn will help in recovery.

Diffusion Hypoxia or Fink Effect

While a patient is breathing N_2O mixed with O_2 during anaesthesia, then a relatively large amount of this gas will replace the less soluble N_2 which is already present in the body tissues and fluids during breathing of air. Again, at the end of anaesthesia when the patient starts breathing air, then the alveoli soon become filled with N_2 and O_2 from air. But, there is still an appreciable quantity of N_2O dissolved in the blood and body tissues. Although N_2O is always referred to as an insoluble anaesthetic agent, it is 34 times more soluble than N_2. It means blood can carry much more N_2O than N_2. So, during the first few minutes after the end of anaesthesia, when the patient starts breathing in room air, then large quantities of N_2O leave the body tissue and enter into the alveoli and N_2 (now being breathed with air) diffuses from the alveoli back into the tissues. As the solubility of N_2O is much greater than that of N_2, so a relatively small amount of N_2 passes from the alveoli to the blood and tissues, but much larger amount of N_2O passes back from the tissues and blood to the alveoli. This mass movement of N_2O into the alveoli causes dilution of the alveolar O_2 concentration and reduces its tension. This is called the diffusion hypoxia or Fink effect. Normally in an alveoli, when the patient breathes in room air, then O_2 concentration is 14%. But, under these conditions, this O_2 concentration may drop to as low as 10% and result in a severe degree of hypoxia, which may be dangerous for elderly and critically ill patients. Clinically, diffusion hypoxia is only significant for N_2O anaesthesia, because N_2O is the only anaesthetic agent which is used in high concentrations and this diffusion hypoxia usually persists for about 10 minutes after the sttopage of flow of N_2O. However, it is of little significance in healthy patients and can be prevented by giving 100% O_2 for 5 minutes in the immediate postoperative period.

DIETHYL ETHER $(C_2H_5)_2O$ (FIG. 15.14)

History

It is commonly called as ether and was first prepared by Valerius Cordus in 1540. But, at that time it was not used as an anaesthetic agent and during this period it was called as the 'Sweet Oil of Vitriol'. Then, Sigmund August, a German chemist, botanist and physician, named it as ether. Previously, instead of being used as an anaesthetic agent, the vapour of it was being mostly used as a drug of amusement together with N_2O in both America and Europe. However, analgesic effects of ether were accidentally discovered in 1833 by an unknown chemist. He wiped freely the face of his wife with ether during her prolonged labour. Then, he observed that her distress passed away. So, he understood that ether had analgesic property. After that, ether was probably first used for clinical anaesthesia by Clarke, an anaesthetist, in January 1842 when a dentist named Elijah Pope extracted a tooth from his patient, named Miss Hobbie. But, this was not published by Clarke and did not attract attention during that period.

Crawford Williamson Long (Fig. 15.15), a general practitioner in Jefferson, Georgia was used to inhale ether frequently for amusement. Like Mr Wells, he also noted that he could acquire painless trauma on his body while under the influence of ether without remembering it later on. He applied this experience to remove one or two cysts from the back of his patient's neck, after administering ether from a towel. Thus, he used ether over the next few years for minor surgeries. But, even he did not publish his results.

During the period of 1843, Green Morton (Fig. 15.16), a specialist in dental

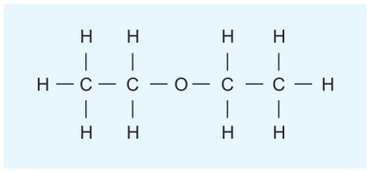


Fig. 15.14: Diethyl ether

Fig. 15.15: Crawford Long

Fig. 15.16: Green Morton

prosthetic works, had moved from Hartford to Boston and had set up his dental practice there. He had observed both Well's demonstration of N_2O and his failure at the Massachusetts General Hospital in 1845. He had also observed ether's anaesthetic effect on his patients, when they breathed the vapour of ether which was applied as a liquid to deaden the painful tooth sockets. Subsequently, Morton tried ether on himself, a dog and his two young assistants. But fortunately all were successful experiments. Then, Morton also gained further experience of anaesthesia from the administeration of ether in 50 cases of anaesthesia for a surgeon named Henry Jacob Bigelow, who was then a professor of Materia Medica. Morton then approached John Warren who was a senior surgeon of Massachusetts General Hospital for an opportunity to make a public demonstration of ether anaesthesia. However, this was arranged within two days and on 16th October in 1846 Morton successfully demonstrated the anaesthetic properties of ether publicly on a patient, named Gilbert Abott for removal of a congenital vascular malformation from the floor of the mouth under the tongue. It was operated by the surgeon, named JC Warren. The operation took place in what is now known as the 'Ether Dome' at Massachusetts General Hospital (Fig. 15.17).

Williamson Long also discovered the anaesthetic property of ether, even before

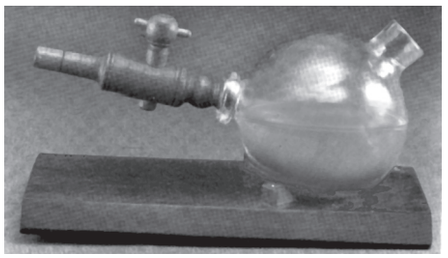


Fig. 15.17: Morton's inhaler

Morton. But he did not demostrate this in public. So, when Long reported his work in1849, Morton's fame was already well established. In science, ironically the recognition for the new discovery goes to the man who demonstrates, publishes and convinces the world first, but not to the man in whom the idea came first. Hence, as Morton convinced the world regarding the advantages of ether anaesthesia though late, so he bagged the crown.

Preparation

Ether is prepared by the reaction between ethyl alcohol and sulphuric acid at 140°C.

$C_2H_5OH + H_2SO_4 \rightarrow C_2H_5HSO_4 + H_2O$

$C_2H_5HSO_4 + C_2H_5OH \rightarrow (C_2H_5)_2O + H_2SO_4$

Physical Properties

It is a colourless, volatile liquid, with a very characteristic pungent smell. At room temperature (20°C) its vapour pressure is 425 mm of Hg. This vapour pressure helps to calculate the inspired concentration of ether, delivered to the patient by the bubble-through type of vapouriser (copper Kettle or Vernitrol). But this vapour pressure is not helpful for a blow-over type of vapouriser (Boyel's ether bottle) to calculate the inspired concentration of ether. If Boyle's ether bottle is converted to the bubble – through type of vapouriser by dipping the plunger into the liquid of ether, then also the constant change of temperature of the ether liquid due to the latent heat of vaporisation makes the calculation of the inspired concentration of ether difficult. On the other hand, in a copper kettle the temperature of ether is kept constant. Cooling of the Boyle's ether bottle due to the latent heat of vaporisation and freezing of the moisture outside the glass is prevented in a Oxford Vapouriser Mark II, where ether bottle is surrounded by a chemical crystal with a melting point more than ether and it helps ether to vaporise constantly. So, the ether vapour in Oxford vapouriser remain under pressure and emits spontaneously and continuously at a set concentration.

Ether and its vapour is highly inflammable and ignite at 154°C. Low concentration of ether vapour burns itself with a clear blue flame and at higher concentrations it explodes. Ether vapour is 2.5 times heavier than air and spreads like an invisible blanket over the floor. So, a spark from any electric point near the floor can ignite this ether blanket, causing a cold blue-like flame which is invisible in daylight. The zone of inflammability of ether vapour is usually confined to 25 cm around the exhalatory valve. So, if diathermy is kept outside this area and an efficient gas exhaust system is maintained in the OT, then there is little risk of explosion (Table 15.11).

The decomposition of ether is favoured by air, light and heat and it is prevented by copper and hydroquinone. So, ether is always kept in a dark, airtight bottle in a cool place. The main impurities due to decomposition of ether are: acetic aldehyde, ether peroxide, alcohol, sulphuric acid, SO_2, mercaptans, ethyl ester, etc. The systemic effects (toxicity) due to these impurities of ether in man are doubtful. The probable problems due to these impurities of ether on human body are gastric irritation (due to peroxide) and tachycardia with hypotension (due to mercaptans). During ether anaesthesia, the presence of mercaptans can be suspected, if the patient's expired air has a peculiar fishy odour.

Pharmacological Properties

Ether's blood/gas solubility coefficient is 12·1. So, it indicates that ether is highly

Table 15.11: Characteristic features of various anaesthesia

Agent	*Molecular Weight*	*Boiling Point (°C)*	*Vapour Pressure at 20°C (mm of Hg)*	*Blood-Gas Solubility*	*Oil-Gas Solubility*	*MAC*	*Metabolism*
Nitrous oxide (N_2O)	44	–88	–	0.42	1.4	105	0
Diethyl ether (C_2H_5-O-C_2H_5)	74	36.5	440	12.1	65	1.92	4
Halothane ($CF_3CHClBr$)	197.4	50.2	243.3	2.5	224	0.75	20
Isoflurane (CHF_2-O-$CHClCF_3$)	184.5	48.5	250	1.4	99	1.15	0.2
Sevoflurane (CF_3-CHO-CH_2F-CF_3)	200.5	58.5	160	1.69	50	2	4
Desflurane (CHF_2-O-CHF-CHF_2)	168	22.8	664	0.42	19	6	0.02
Xenon (Xe)	131.3	–107	–	0.11	–	71	0

absorbable in blood. Therefore, as it is constantly being removed from the alveoli by dissolving in plasma and without increasing its tension in plasma due to the high blood solubility, it takes a longer time to raise the plasma and alveolar tension. On the other hand, alveolar and plasma tension of any anaesthetic agent is synonymous with brain tension. So, induction of anaesthesia by ether will be slow (15 to 20 minutes) and may take a longer time to achieve deep anaesthesia than other volatile anaesthetic agents whose blood/gas solubility coefficient is very less. Similarly, recovery from ether anaesthesia will also be slow. The oil/gas solubility of ether is only 65, indicating that it is less potent than halothane and other volatile agents (halothane's oil/gas solubility 224). This is because potency of any volatile anaesthetic agent depends on its lipid solubility i.e. oil/gas solubility coefficient.

90% of inspired ether is excreted unchanged through the lungs. Rest is metabolised or excreted through the skin, body secretions and urine. About 4% of inhaled ether is metabolised in the liver to acetaldehyde and ethanol. Like phenobarbitone, ether is also a powerful inducing agent of hepatic microsomal enzymes. So, its prolonged exposure increases the rate of metabolism of other drugs in liver. Ether is an irritant to the mucosa of respiratory tract and increases the bronchial secretion. It also stimulates the vagal afferent fibres in bronchial tree, leading to an increased depth and rate of respiration. Ether itself is a bronchodilator. It does not affect the surfactant production. So, it does not reduce the surface tension of alveoli and does not help in the formation of atelectasis. Respiratory rate increases during ether anaesthesia, till a very deep level is achieved when the paralytic action supervenes with steady decline of minute volume, leading to apnoea. So, $PaCO_2$ level does not rise, till a very deep level of anaesthesia is reached with ether. Thus, in spontaneous respiration during ether anaesthesia, controlled or assisted ventilation is not needed till a very deep level is reached. Ether minimally depresses the ventilation than the other inhalational anaesthetic agents. It diminishes the ventilatory response to inhaled CO_2 at an anaesthetic depth at which $PaCO_2$ is maintained at normal levels. The action of ether on CVS is explained by an increased sympathetic activity caused by it. Ether anaesthesia produces a small alteration in BP and pulse rate. Very rarely it leads to cardiac irregularities, because it does not sensitize the myocardium to adrenaline. With a very deep anaesthesia, CVS is also depressed by ether. This is due to reduced catecholamine secretion from the exhausted sympathetic system and at this situation it should be used very cautiously with β-blocking agents.

Ether causes skeletal muscle relaxation by: depressing the CNS, affecting the motor end plate and affecting the muscle itself similar to tubocurarine. Ether is secreted through the saliva and passes to the stomach. It also stimulates the vomiting centre in medulla and is responsible for higher incidences of PONV. Smooth muscle motility of the intestine is depressed during ether anaesthesia. As ether stimulates the sympathetic activity, it leads to an increased release of catecholamines. So, glycogen is mobilized from both the liver and the muscles and a marked rise in blood sugar follows, due to the endogenous catecholamine-induced glycolysis. Ether reduces the tone of gravid uterus, even in slight concentration.

Clinical Uses

Ether is associated with lowest death rate in a properly conducted anaesthesia and lowest incidence of liver damage. Still it is gradually going out of vogue, because it does not attenuate the intubation induced sympathetic over activity, pungent odour, increased secretion, delayed induction and recovery, etc. It alone produces all the three major components of anaesthesia such as sedation, analgesia, and depression of reflexes. So, though modern anaesthetic techniques go far beyond this maxim, ether still remains the popular and most effective means of anaesthesia in many underdeveloped countries, mainly at rural area.

Guedel's Classification of Ether Anaesthesia

As the depth of ether anaesthesia increases, then gradually the respiratory pattern changes, more and more reflexes become suppressed and characteristic changes in the size of the pupil occur. So, in 1920

these slow progression of changes made it possible for Guedel to divide these various alterations in reflex activity during deepening of anaesthesia into four stages, after an exhaustive study of open-drop ether anaesthesia (Fig. 15.18).

GA by ether causes an irregular or a regular depression of the CNS in a descending order, i.e. higher functions are lost first and progressively the lower areas of the brain are involved. But, in the spinal cord lower segments are affected somewhat earlier than the higher segments. The vital centres located in the medulla are paralysed at last, as the depth of anaesthesia increases. However, these clear cut stages of anaesthesia are not seen nowadays with the use of muscle relaxants, faster acting inhalational anaesthetic agents, premedications and employment of many drugs together. These precise sequence of events also differs somewhat with other inhalational anaesthetics than ether. However, as still ether continues to

Fig. 15.18: Guedel

be widely used in India and so descriptions of these stages still serve us to define the level such as the light and deep anaesthesia (Fig. 15.19).

Stage I or stage of analgesia

It starts from the begining of inhalation of ether to the loss of consciousness. Pain is progressively abolished during this stage. Thus, it is named so. But the patient remains conscious or semiconscious. He can hear, see and feel a dream like state. The reflexes and respiration remain normal. Though some minor operations can be carried out during this stage, but it is rather difficult to maintain this stage. So its use is limited to very short procedures only.

Stage II or stage of delirium

It extends from the loss of consciousness to the beginning of regular respiration. Apparent excitement with irregular respiration is seen in this stage. The patient may shout, struggle or hold his breath. Muscle tone increases. Jaws are remained tightly closed. Breathing is jerky and vomiting, involuntary micturition or defaecation may occur. Heart rate and BP may rise and pupils may dilate due to the sympathetic stimulation. No stimulus should be applied or no operative procedure should be carried out during this stage. This stage can be cut short by rapid induction and premedication. However, this stage is

Stage		Respiration		BP	Sk muscle tone	Ocular movement	Pupil size	Reflexes				Heart rate	Uses
		Thor	Abd					Eyelid	Pharyngeal	Corneal reflex	Light reflexes		
I Analgesia				++	++	Normal						++	Delivery and minor surgery
II Delirium				++++	++++							++++	Nil
III	1			+++	+++	Roving eyeball		No eyelid reflex	No pharyngeal reflex	No corneal reflex	No light reflex	+++	Most of the surgical operations
	2			++	++							++	
	3			+	+	Fixed eyes						+	Occasionally reached
	4			+	+							+	Never attempted
IV Medullary paralysis		No respiration or very shallow		Pressure not record able	Fully relaxed		Non reacting fully dialated	No reflexes				No heart rate is recordable or severe bardycardia	Coma or death

Fig. 15.19: Stages of general anaesthesia

inconspicuous in modern anaesthesia due to the use of IV anaesthetic agents, muscle relaxants, very rapidly acting anaesthetic agents, etc.

Stage III or surgical anaesthesia

This stage extends from the onset of regular respiration to the cessation of spontaneous breathing. This has been again divided into four planes which are well distinguished as:

i. *Plane I* − moving eye balls. This plane ends when the eyes become fixed.
ii. *Plane II* − loss of corneal or laryngeal reflexes.
iii. *Plane III* − pupil starts dilating and light reflex is lost.
iv. *Plane IV* − intercostal paralysis, shallow abdominal respiration and dilated pupils.

In this stage as the level of anaesthesia passes on to the deeper planes progressively, so the muscle tone decreases, BP falls, pulse becomes weak and the heart rate increases. After that respiration gradually decreases in depth and later on in frequency.

Stage IV or stage of medullary paralysis

It extends from the cessation of breathing to the failure of circulation and death. In this stage pupil is widely dilated, muscles are totally paralysed, pulse is imperceptible and BP is very low to non-recordable.

However many of the above mentioned features described in different stages of ether anaesthesia may be masked by the use of atropine (pupil and heart rate), narcotics (respiration and pupil), muscle relaxant etc. So, during the use of many inhalational anaesthetic agents to determine the stages of anaesthesia, an anaesthetist may have to depend on several other observations.

i. If eyelash reflex is present and the patient is making swallowing movements, then stage II has not been reached.
ii. If incision of skin causes a reflex increase in respiratory rate and rise in BP or insertion of the endotracheal tube is resisted and induces coughing, vomiting, laryngospasm or tears appear in the eye during operation, then these indicate that the level of anaesthesia is in light plane.
iii. Fall of BP, HR and RR with cardiac and respiratory depression are the signs of deep plane of anaesthesia.

Now, modern multidrug anaesthetic technique is used in anaesthesia where combination of different drugs, each with more or less its distinct action is choised. It avoids the unnecessary depression of other parts of the body which is not under the area of action of that agent which occur occasionally, when a single agent with large doses is used. This type of multidrug anaesthesia is called the control or balanced anaesthesia, utilizing more than one agent to offset the disadvantage of another. Now, we choose a mixture of drugs that best fits with the anticipated needs of that operation.

Method of Administration of Ether

Ether can be administered mainly by three methods such as open, semiclosed and closed with CO_2 absorption. The open technique is used by a Schimmelbusch mask and ether is dropped from a Bellany Gardner dropper bottle. As the patient inspires only the mixture of air (which contains only 20% O_2) and ether vapour, so in this mixture the exact inspired O_2 concentration (FiO_2) falls which cannot be calculated accurately. Hence, extra O_2 supply by a catheter is mandatory to rise the FiO_2 > 33%. Patient inhales air and anaesthetic ether (ether vapour) mixture which is at low temperature. So, the respiratory tree is called upon to perform heavy task to raise the temperature of air – ether mixture to 37°C and also to saturate it with water vapour. It has also been estimated that there is heat loss of about 300 calories / minute from the patient, using ether (Fig. 15.20).

In a semiclosed technique, ether is used by blowing the mixture of N_2O and O_2 gas over it or bubbling through it, that is contained in a glass bottle vapouriser. The

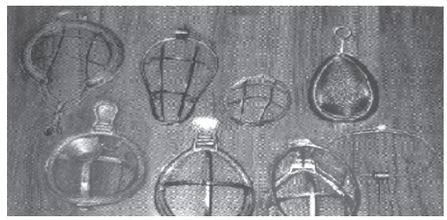


Fig. 15.20: Schimmelbusch masks

example of this technique is ether anaesthesia by Boyel's machine using Boyel's ether bottle vaporizer. Safety of this technique lies in the fact that, as vaporisation of ether increases, the temperature of the liquid and the bottle falls which in turn slows the rate of vaporisation from the bottle. Therefore, the control knob set to deliver a certain concentration of ether vapour, cannot perform this job. This is because after sometime, with the control knob still in the same position, there is reduction in the vapour concentration of ether due to the cooling of anaesthetic agent and bottle. In a circle system, higher concentration of ether is built-up very quickly (only if vapouriser is within the circuit), because the whole volume of expired gas passes through the ether bottle and vaporisation is assisted by heat, both from the patient and the canister (Fig. 15.21).

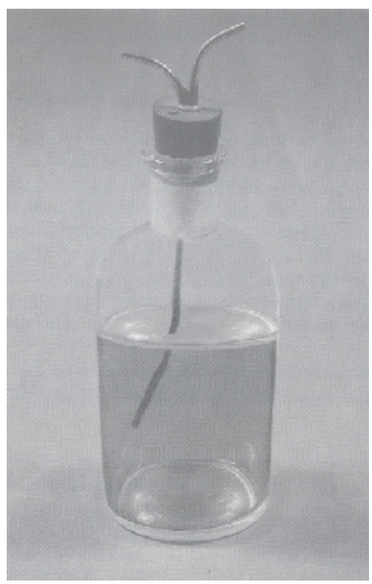


Fig. 15.21: Bellamy Gardner dropper bottle of ether

EMO vapouriser

Basically this is a draw-over or blow-over type of vapouriser, which is used to vaporise the ether. To deliver a required concentration of ether, the ether bottle is kept in a water bath which acts as a heat buffer and allows the delivery of a fixed concentration of anaesthetic vapour, set by the dial. This discussion is only for hitorical interest.

HALOTHANE

(2-bromo 2-chloro 1,1,1 trifluoroethane) (Fig. 15.22).

CW Suckling had first synthesized halothane in the laboratory of Imperial Chemical Industries at Manchester, in 1951. Then, Raventos studied its pharmacological properties in the succeeding years. After that, it was first used clinically in 1956 by Johnstone at Manchester and that was followed by Bryce-Smith and O'Brien at Oxford.

Physical Properties

Halothane is a colourless, non-inflammable, potent anaesthetic liquid with a sweet smell. Its commercial preparations contain 0.01% thymol for stability. Boiling point of halothane is 50.2°C and it does not react with soda lime. It decomposes to HCl, HBr, free chlorine, free bromine and phosgene gas, when exposed to bright light for several days. So, presence of thymol prevents this decomposition. It is suitable for vaporisation in a bubble-through vapouriser (copper kettle) or temperature and flow compensated vapouriser (flutec vapouriser).

If water vapour is present in the halothane vapour, then it can attack some metals like aluminum, brass and lead. But, copper and chromium is not attacked by halothane

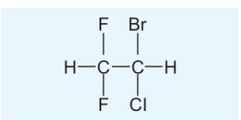


Fig. 15.22: Halothane

vapour. So, the previous metals are not used to build the halothane vapourisers. Halothane is readily soluble in rubber, but less so in polythene. Significant rubber solubility and the large amount of rubber used in anaesthetic delivery systems make the uptake of halothane by rubber very significant. The concentration of vapour of halothane in an anaesthetic gas mixture can be estimated by gas chromatography or by infrared analyser or by ultra-violet light analyser.

Pharmacology

The MAC value of halothane is 0.8. Its blood gas solubility co-efficient is 2.3 (N_2O is 0.46, Ether is 12.1, Isofluorane is 1.4, Sevoflurane is 0.69). So, the solubility of halothane in blood is of a medium range. Thus, as it is relatively insoluble (in relation to ether) in blood, so it is not taken up very rapidly from the alveoli. This means that alveolar concentration and tension of halothane can soon approach its inspired concentration and tension very rapidly. On the other hand, alveolar concentration and tension is virtually synonymous with the brain concentration and tension of volatile anaesthetic agent. So, a high concentration and tension of halothane is rapidly achieved in the brain. This means the induction of anaesthesia by halothane is relatively rapid in comparison to ether. During the first few minutes of halothane anaesthesia most of it goes to the heart, brain, liver, kidney, and later comes to an equilibrium with these tissues. After that, muscles tend to remove their quota from the circulation and take a few hours to come to an equilibrium. Then one of the principal reason for prolonged uptake of halothane by the body is the remarkable capacity of the human fat to absorb it due to its high solubility coefficient in fat (60 for halothane, 1 for N_2O). So, the fat is capable of removing almost all the halothane, received in the circulation. In this manner the body continues for almost indefinite pleriod to keep removing halothane vapour from the lungs. In fact, a complete equilibrium between the inspired and alveolar concentration of halothane is probably never reached, because a small amount of it is continuously lost through the skin.

Metabolism

Twelve percent of inspired halothane is metabolized in the body by liver through the oxidation and dehalogenation mechanism forming trifluoroacetic acid, bromide radicals and chloride radicals which are excreted through the urine. Then, the remaining part of inhaled halothane is expired through the lungs.

Pharmacological Actions

1. Effects on CVS

Halothane is a potent volatile anaesthetic agent. It reduces the myocardial contractile force, stroke volume, cardiac output and the heart rate by its direct –ve chronotopic action on the SA node and by its direct –ve inotropic action on the myocardium. Thus, during holothane anaesthesia BP goes down without any change in SVR. 2 MAC of halothane results in 50% decrease in blood pressure and cardiac output. As halothane attenuates baroreceptor reflexes, so HR does not change with the fall in BP that is normally expected in response to hypotension. At 1.1% end tidal concentration of halothane, the baroreceptor reflex is completely inhibited but SVR is very slightly affected. However, atropine can reverse this bradycardia, induced by halothane, but not the arterial hypotension or cardiac output. Thus, it indicates that hypotension during halothane anaesthesia is due to the direct myocardial depression effect and not due to bradycardia (Table 15.12).

The major cause of arterial hypotension during halothane anaesthesia is the fall in cardiac output, due to depression of the myocardial contractility. During halothane anaesthesia the limbs remain warm and dry with prominent peripheral superficial

Table 15.12: Mechanism of actions of hypotension due to halothane

1. It gradually blocks the action of noradrenaline at the effector sites in heart, CNS and peripheral tissues.
2. It gradually reduces the secretion and activity of nor adrenaline at the sympathetic nerve endings, in the myocardium.
3. It sensitises the parasympathetic nerve endings, leading to bradycardia.

veins, suggesting vasodilatation of both arteriolar and venular component of vascular tree. But, this does not cause reduction in SVR and hypotension. Plasma catecholamine levels are not raised during halothane anaesthesia. Decreased catecholamine level during halothane anaesthesia is due to the diminished release of adrenaline and noradrenaline from the adrenal medulla and the sympathetic nerve endings. Marked reduction of the coronary vascular resistance also occurs by halothane. So, although halothane is a coronary vasodilator, but coronary blood flow decreases. It is due to the drop in systemic arterial pressure. However, adequate myocardial perfusion is still usually maintained, as its oxygen demand also drops.

Arrhythmia and halothane

Most of the changes in cardiac rate and rhythm which occur during halothane anaesthesia may be explained on the basis of altered autonomic balance, i.e. preponderance of either vagal or sympathetic activity induced by halothane. The vagal stimulation produced by halothane causes slowing of sinus rate. If the SA node is sufficiently depressed, then the role of pacemaker activity of SA node may be taken over by the AV node. There may also be some independent activation of atria or ventricles, while intense vagal stimulation may lead to partial or complete SA block, bundle branch block, or even asystole. The relative sympathetic stimulation induced by halothane also causes sinus tachycardia or occasional ventricular extrasystole, although the actual plasma catecholamine level does not increase. When this relative sympathetic activation caused (Table 15.13) by halothane becomes more profound, then multifocal ventricular extrasystoles, ventricular tachycardia and VF may occur.

It has also long been known that the general anaesthetic agents which have a hydrocarbon structure in some form sensitize the myocardium to the effects of catecholamines. So like other hydrocarbons, halothane also sensitises the myocardium to the effects of catecholamines though the actual level of catecholamines does not increase. However, the manner by which halothane produces this effect (arrhythmia) is not clear, but it would seem that a reduction of HR and increase of ventricular automaticity plays an important role.

The halothane anaesthesia is accompanied with the shifting of pacemaker site, from the SA node to AV node. It is probable that these changes are mainly due to the increased vagal activity and can often be counter balanced by the action of atropine. It is believed that some form of re-entry mechanism is also likely the cause for production of halothane-induced arrhythmia. The respiratory depression and retention of CO_2 during halothane anaesthesia also may give rise to bigeminal rhythm, multifocal ventricular extrasystoles and VT. The higher degree of hypercarbia is required to provoke ventricular extrasystoles and their incidence is not related to the concentration of the inspired halothane. The correction of respiratory acidosis will often abolish these ventricular irregularities, even though the concentration of halothane is unaltered.

It is essential that the changes in heart rate and rhythm during halothane anaesthesia should not be treated indiscriminately with atropine. Because random abolition of any restraining vagal tone,

Table 15.13: Clinical pharmacology of inhalational anaesthetics

	N_2O	*Halothane*	*Isoflurane*	*Sevoflurane*	*Desflurane*
CVS					
Blood pressure	0	↓↓	↓↓	↓	↓↓
Heart rate	0	↓	↑	0	0/↑
SVR	0	0	↓↓	↓	↓↓
Cardiac output	0	↓	0	↓	0/↓
Respiratory					
Respiratory rate	↑	↑↑	↑	↑	↑
Tidal volume	↓	↓↓	↓↓	↓	↓
$PaCO_2$	0	↑	↑	↑	↑↑
Cerebral					
Blood flow	↑	↑↑	↑	↑	↑
ICP	↑	↑↑	↑	↑	↑
Cerebral mechanism	↑	↓	↓↓	↓↓	↓↓
Seizures	↓	↓	↓	↓	↓
Renal					
Renal blood flow	↓	↓↓	↓↓	↓	↓
GFR	↓	↓↓	↓↓	↓	↓
Urinary output	↓	↓↓	↓↓	↓	↓
Hepatic					
Blood flow	↓	↓↓	↓	↓	↓
Neuromuscular					
Non depolarizing blockade	↑	↑↑	↑↑	↑↑	↑↑
Metabolism	0.004%	15-20%	0.2%	5%	< 0.1%

No change = 0, Elevated = ↑, Reduced = ↓

may accentuate the severity of arrythmia and may even induce VF. It has long been suggested that if ventilation is adequate and the concentration and total dose of adrenaline is kept within prescribed limits, then SC injection of adrenaline may safely be given during halothane anaesthesia. It has been found that ED_{50} (the dose producing a positive response in 50% of patients) of epinephrine that produces arrhythmia during halothane anaesthesia is 2.5 µg/kg. So, it is considered that a maximum dose of 10 ml of 1:100000 epinephrine for 10 minutes period is safe. In the vast majority of patients, the incidence of arrhythmia can also be diminished, if isoflurane is substituted for halothane. The endogenous catecholamines are an important factor for the causation of arrhythmia, when their concentration is elevated during light anaesthesia by surgical stimulation. In such circumstances, the absorption of even a small amount of exogenous adrenaline which is injected may have serious consequences. It is, therefore, best to avoid the use of adrenaline for external sources during light halothane anaesthesia.

The mechanism of action of halothane on cardiac contraction

Halothane, like other inhaled anaesthetic agents, depresses the cardiac contraction by decreasing the free intracellular Ca^{2+} level by:

i. Interfering with the Ca^{2+} movement through the sarcolemma and by decreasing the release and availability of Ca^{2+} from the sarcoplasmic reticulum.
ii. Altering the sensitivity of the regulatory and contractile proteins to the available Ca^{2+}. The order of potency of inhalational anaesthetic agents regarding myocardial depression is halothane > enflurane > isoflurane > N_2O.

Halothane and pulmonary vascular resistance (PVR)

In the absence of underlying pathology, halothane have little affect on the pulmonary blood flow and pulmonary arterial pressure. However halothane in general decreases PVR and increases the left atrial pressure.

Halothane and hypoxic pulmonary vasoconstrictive response (HPV)

The mechanism by which halothane interferes the HPV response remains still a mystery. The possible theories are:

i. Halothane acts by interfering with the action of local vasoactive metabolic substances, responsible for vasoconstriction.
ii. Direct relaxing effect of halothane on vascular smooth muscles, counteracting the locally or systemically mediated vasoconstrictive response.
iii. Interfering with the Ca^{++} uptake by the cells of vascular smooth muscle.

Halothane and baroreceptors

Due to baroceceptor reflexes the changes in blood pressure result in an alteration in the peripheral vascular resistance, heart rate, venous tone and CO. Halothane (like other anaesthetics) depresses this baroreceptor reflex. So, hypovolaemic or CVS compromised patients are less able to compensate the hypotension, when they are anaesthetised by halothane. Another importance of this baroreceptor attenuation is that the clinical signs of hypovolemia or reduced CO are masked under halothane anaesthesia. So, sophisticated monitoring is required during halothane anaesthesia, specially when there is associated hypotension.

2. Effects on the respiratory system

Halothane is a non-irritating respiratory depressant and progressively decreases the tidal volume, rather than the rate of respiration. Actually, halothane increases the rate of respiration. But still the minute volume is reduced and this is due to the relatively much reduction of tidal volume. Halothane used in clinical practice produces bronchodilatation and this is probably not mediated through the β_2-adrenoreceptor stimulation. This is proved by the fact that this bronchodilating action of halothane is not inhibited by propanolol or β-adrenergic blocking agents. Halothane attenuates the airway reflexes and relaxes the bronchial smooth muscles by inhibiting the intracellular mobilization of Ca^{2+} within these bronchial smooth muscle cells.

Halothane is the most potent bronchodilator of all the available volatile anaesthetic agents. There may even be a decrease in the effective alveolar ventilation. It has no effect on the synthesis of surfactant of the lungs. In unstimulated airway, the resting muscle tone is minimal, so the bronchodilating properties of halothane is also nil (during normal condition). Only during bronchoconstriction, bronchodilating property of halothane is well demonstrated. Systemic administration of halothane via a bypass pump, does not cause bronchodilatation which suggests that halothane acts directly on the airway musculature and/or through the local reflex arc, rather than via the centrally controlled reflex pathways.

Halothane does not inhibit the release of histamine from the mast cells, causing bronchoconstriction. So, histamine level is not affected. Patients, resistant to other bronchodilators, promptly respond to halothane.

Halothane and mucociliary function of the respiratory tract

All the halothane like inhaled anaesthetic agents diminish the rate of mucous clearance by diminishing the ciliary movement and also by altering the quality and quantity of mucous production. Halothane anaesthesia decreases the mucous velocity by 7.7 mm/min. So no mucus movement seen after 90 minutes of halothane anaesthesia. So, prolonged anaesthesia could lead to the pooling of mucous which results in atelectasis and infection. Patients with a greater risk are those who are susceptible to excessive mucous production such as asthma, bronchitis, RT infection, cystic fibrosis, etc. So, the patients of COPD who

are anaesthetised by regional block, show less incidence of respiratory failure, than those who are undergone general anaesthesia with voltile anaesthetic agent.

Halothane and ventilatory response to CO_2

Measuring of minute ventilation in response to varying levels of $PaCO_2$, is a common method of measuring the effects of anaesthetic drugs on ventilatory drive caused by $PaCO_2$. Compensatory changes in ventilation secondary to alteration in $PaCO_2$ are believed to be mediated chiefly via chemoreceptors located in the medulla. In normal subjects, there is increase in ventilation by approximately 3 litre/minute for every mm of Hg increase of $PaCO_2$. It indicates a high gain from the central chemoreceptors in response to the variation in $PaCO_2$. All inhaled anaesthetic agents including halothane generally depress this CO_2 response curve. At sedating concentrations, halothane has little effect on this response curve. But, 1 MAC halothane has a profound depressant effect. At 2.5 MAC halothane level, there is no increase in ventilation in response to any altered blood CO_2 level. The slope of the ventilatory response curve during halothane anaesthesia usually returns towards normal after 6 hours of anaesthesia.

N_2O is a relatively weak inhaled anaesthetic and does not depress the ventilatory drive or response to CO_2, even at a concentration of 50%.

Halothane and ventilatory response to hypoxaemia

Increased ventilation in response to progressively lowered PaO_2 is also mediated entirely by the peripheral chemoreceptors. Ventilatory response curve to hypoxaemia is hyperbolic. This hyperbolic response curve rises most sharply at a PaO_2 of approximately 40 mm of Hg. At 1MAC level of halothane, significant depression of ventilatory responsiveness to hypoxia is observed. Synergistic effect of hypoxia and hypercarbia on ventilation is also profoundly attenuated by halothane. Peripheral chemoreceptors are remarkably sensitive to the depression effect of halothane. Patients with chronic respiratory failure, in whom the level of $PaCO_2$ may represent an important determinant of minute ventilation, may be drastically affected.

3. Effects on the cerebral blood flow and intracranial tension

Halothane decreases the cerebral vascular resistance by dilating the cerebral vessels. Thus it increases the cerebral blood flow, provided the systemic BP is maintained. Hence intracranial and CSF pressure increases, especially in a case of space occupying intracranial lesion. So, headache may occur following halothane anaesthesia. Cerebral blood flow is further increased by the addition of N_2O, because autoregulation of the cerebral blood flow is completely absolished by halothane. The net effect on ICP and cerebral perfusion pressure depends on the systemic blood pressure and brain compliance. CSF production is decreased by 30% by halothane. This increase in ICP and cerebral blood flow by halothane, can be prevented by hypocapnia. But, if there is any intracranial lesion, then this rise of ICP by mixture of halothane, N_2O and O_2 cannot be prevented by hypocapnia or hyperventilation. Halothane also reduces the cerebral O_2 consumption by 25%, with greatest reduction at an inhaled concentration between 0.5 to 0.8%. There is little further change in cerebral O_2 consumption with a further increase in halothane concentration, until the toxic levels are reached.

4. Effects on the GI tract

Halothane inhibits the motility of the stomach, jejunum, small intestine and colon like other inhalational anaesthetic agents.

5. Effects on the skeletal muscle

Halothane has direct neuromuscular blocking action and also potentiates the action of other neuromuscular blocking agents. Thus, halothane produces moderate skeletal muscle relaxation with increasing depth of anaesthesia. It is postulated that the post junctional membrane is the structure which is most sensitive to the neuromuscular blocking effects of halothane (Table 15.14A).

Shivering

Shivering is sometimes observed during the early post operative period after halothane anaesthesia. This is probably due to the vasodilatory action of drug and cool environment of operation theatre. This shivering and the muscle spasticity which occurs during emergence particularly from the halothane anaesthesia also occur with other halogenated volatile agents and is often referred to as the 'halothane shakes'. Due to this shivering, oxygen consumption and incidence of hypoxaemia are markedly increased. Its incidence may be as high as 80%. Patients are commonly hypothermic due to the cutaneous vasodilatation by halothane and the chilled OT enviornment. Thus, there is significant heat loss during anaesthesia, as the thermoregulatory response is also impaired by halothane. So, shivering is a normal physiological response during recovery (when muscle relaxation is gradually

Table 15.14A: Mechanism of action of relaxation of bronchial smooth muscles by halothane in asthma

1. Direct dilatation of the bronchial smooth muscles, involving increased cyclic AMP.
2. Blocking the effects of various bronchoconstricting mediators, by reducing the free Ca^{++} in the cytoplasm and suppressing the influx of Ca^{++} across the cell membrane. This action is also common to vascular smooth muscles for relaxation and cardiac muscles for depression by halothane.
3. Bronchodilation of halothane is not caused by β_2 stimulation.
4. Attenuation of centrally mediated bronchoconstricting reflexes by increasing the depth of anaesthesia (depresses the airway reflexes), which occurs in light anaesthesia.

withdrawn). However, this is not the complete explanation. There is also some central and spinal effects of halothane which may cause altered muscular activity during the emergence from halothane anaesthesia, producing shivering. A number of agents have been experimented to reduce this shivering, such as opiates, magnesium sulphate, muscle relaxants and clonidine, etc. But among these, meperidine is the most effective in reducing such shivering.

6. Effects on the uterus

Halothane relaxes the uterine muscles. It is due to the stimulation of uterine adrenergic β_2-receptors. But, uterine contraction is recovered twice as quickly as ether when halothane is stopped. So, it is not so liable to produce PPH as has been stated before. It readily crosses the placental barrier.

7. Effects on the liver

It is the most controversial issue. Although, no consistent abnormal histological pattern of liver parenchyma after exposure to halothane has emerged in the National Halothane Study, still it is appeared that some cases exhibited a lesion which simulate the fatal viral and drug-induced forms of hepatitis after exposure to halothane. It is more often than those associated with administration of other inhalational anaesthetic agents. It is written in details later in the chapter of 'liver diseases and anaesthesia'.

Clinical Use

Due to a high vapour pressure(243.3 mm of Hg at 20°C), low boiling point (50.2°C), high lipid gas solubility (224) and low blood gas solubility halothane can be regarded as a potent anaesthetic agent. So, a low concentration such as 0.4% halothane is capable of maintaining unconsciousness. Thus, it is widely used in anaesthesia for all types of surgeries, including general, ENT, orthopaedic, paediatric, neuro, etc. The reduction of blood pressure by halothane is used as an advantage in major surgeries. Halothane is also used to reduce the blood loss and to control the intubation-induced hypertension. It has a low incidence of postoperative nausea and vomiting (PONV). During abdominal surgery, if halothane is combined with muscle relaxant, then a very good relaxation is achieved without restoring to high concentration of halothane which prolongs the recovery.

Method of Vapourisation

High cost of halothane demands reasonable economy during its use. So, it cannot be used by open-mask method, pouring drop by drop on the Schimmelbusch mask. Halothane is used in a copper kettle (bubble through) vapouriser with a flow of 100 ml O_2 through the vapouriser at the room temperature. When this is added to 5 litres of N_2O : O_2 gas mixture, we get an inspired concentration of 1% halothane. Similarly 200 ml of O_2 will give 2% halothane concentration.

But, now a days halothane is used by a flutec vapouriser. It is temperature and flow compensated. It receives part of the inspired gas enroute to the patient and adds the predicted amount of halothane concentration to the gas mixture. It is now the most sophisticated and satisfactory vapouriser for halothane administration (Fig. 15.23).

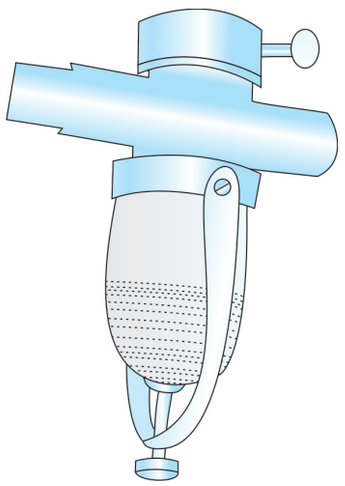


Fig. 15.23: Goldman's halothane vapouriser

A small, convenient, inexpensive Goldman vapouriser, which delivers a maximum of 2.3 volume % of halothane, is generally used in developing countries. It is not temperature or flow compensated.

ISOFLURANE (FIG. 15.24)

Chemically, isoflurane is a methyl-ethyl-ether and is an isomer of enflurane.

Physical Properties

It is a clear, colourless and non-inflammable liquid. Specific gravity of isoflurane is 1.52 at 25°C. Its boiling point is 48.5°C and vapour pressure is 250 mm of Hg (like halothane) at room temperature (20°C). It is non-corrosive and does not attack the metal, which are commonly used in the construction of anaesthetic apparatus and vapourisers. It has three fluorine atoms on the terminal ethyl carbon which makes it resistant to chemical and biological degradation. It is stable in warm soda lime and ultraviolet radiation. It can also be stored without any preservative at room temperature. Though, it is stable in sodalime, but like enflurane and desflurane it contains some moiety. So, it may undergo some degradation when exposed to sodalime or baralyme, resulting in the production of carbon monoxide, although not to the same degree as enflurane or desflurane.

Isoflurane has very pungent smell like ether. The pungent odour of isoflurane limits its speed of induction, due to coughing, breath holding, laryngospasm, etc. But, the low blood-gas solubility coefficient of isoflurane indicates its rapid induction like halothane. However, premedication, use of intravenous inducing agents, or

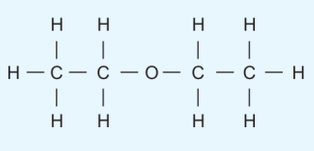


Fig. 15.24: Diethylether

step-by-step increase in the inspired concentration of isoflurane can overcome this problem. Low blood/gas solubility coefficient of isoflurane (isoflurane 1.4, halothane 2.3) suggests a swift induction and emergence from anaesthesia, compared to halothane. It takes only 4 minutes to reach a F_A/F_1 (ratio of the alveolar concentration to the inspired concentration) ratio of 0.5, compared to the 30 minutes required by halothane.

Greater chemical stability of isoflurane is reflected by its lesser metabolism in the body tissues(0.2%). This may in turn reduce the likelyhood of its toxicity due to low level of its metabolites. The rate of metabolism of isoflurane is considerably less (less than 1/5th of halothane) and near about 95% is excreted unchanged through the exhaled air. The metabolism of isoflurane is occurred in liver by oxidation through the hepatic cytochrome P_{450} system, with the production of inorganic fluoride and trifluoroacetic acid (TFA).

Pharmacology

The MAC value for isoflurane is 1·3. It decreases to 1 in elderly patients and decreases further to 0.6, when N_2O is used with it. For example, the addition of 70% N_2O roughly halves the MAC value of isoflurane, which further can be reduced by opioid analgesics. Premedicant drugs also reduce the requirement of isoflurane and its MAC value. Its oil/gas solubility coefficient is 98, which is much lower than that of halothane (halothane is 224). This suggests isoflurane is a weaker anaesthetic agent than halothane. Its vapour pressure is 250 mm of Hg at room temperature (halothane's vapour pressure 243 mm of Hg) and thus allows the delivery of desired concentration of isoflurane from the same vapouriser which is usually used for halothane. But, for obvious reasons this practice is not encouraged. Isoflurane is absorbed in the plastics and rubber used in the anaesthetic circuits, although not to the same extent as halothane.

Action on the respiratory system

Isoflurane is a potent respiratory depressant and this effect is more than halothane. For this reason, there is lack of increase in respiratory rate when a high concentration of isoflurane vapour is inhaled. This is in contrast to halothane, sevoflurane and desflurane anaesthesia where respiratory rate increases. However at a lower concentration of isoflurane respiratory rate is increased but the tidal volume is decreased with the net reduction of minute ventilation. Ventilatory responses to hypercarbia, progressively and linearly approaches to zero at about 2 MAC value of isoflurane. Ventilatory response to hypoxia disappears at 1 MAC concentration of isoflurane. So, reduction of the ventilatory response to hypercarbia and hypoxia may lead to a grossly impaired ventilation and gas exchange. Isoflurane produces a small drop in the total lung compliance and FRC. Bronchodilating effect of isoflurane is as good as halothane. As isoflurane is quite irritating (due to its etheral odour) to the airway, so it is not particularly suitable for inhalational induction of anaesthesia.

Action on the CVS

Isoflurane is less myocardial depressant than halothane, even upto the concentration of 2MAC value. But, the arterial blood pressure and peripheral vascular resistance (SVR) are much reduced in a dose related manner by isoflurane than halothane. It is due to the direct relaxation of vascular smooth muscles produced by isoflurane. However, cardiac output is maintained close to the control value by isoflurane. This well maintained cardiac output with isoflurane and sevoflurane is accompanied by or due to the dose related decrease in SVR by them. Whereas we have seen that there is little change in SVR, but a greater decrease in the cardiac output due to greater depression of the cardiac contractility with increasing doses of halothane. Thus, in contrast to isoflurane and sevoflurane, halothane lowers BP by reducing the myocardial contractility and cardiac output but not reducing the SVR. For this reason, deep isoflurane anaesthesia has been suggested as an appropriate technique for controlled hypotension (being preferable to halothane, in which hypotension is accompanied by decreased cardiac output and hence decreased perfusion).

Isoflurane depresses the baroreceptor function, but very less quantitatively than the other inhaled anaesthetics. This less depressed responsiveness of the baroreceptors probably better maintains the cardiac output in the face of hypovolaemia. So, there is wide margin of cardiovascular safety with isoflurane than with halothane. Isoflurane increases the HR in response to a lowered BP and maintains the cardiac output. This is because, the baroreceptor reflexes are relatively preserved. The isoflurane induced tachycardia is more pronounced in paediatric patients or in the presence of a vagolytic agent. This CVS stimulation and tachycardia by isoflurane may result from the sympathetic stimulation. It is achieved by the activation of tracheopulmonary and systemic adrenoreceptors by isoflurane, and can be attenuated by pretreatment with β_1-adrenoreceptor antagonist, α_1-adrenoreceptor antagonist or opioids.

Isoflurane is also a coronary vasodilator. Ventricular work and myocardial oxygen consumption are reduced by isoflurane. Thereby, it improves the oxygen supply-demand ratio of myocardial tissue. The coronary vasodilatation, produced by isoflurane, is mediated through the ATP-gated potassium channel (K_{ATP}). In the presence of adequate O_2, where intracellular level of ATP is high, these channels open and causes hyperpolarization. In turn this hyperpolarization reduces the cellular acitivity. Therefore, in vascular smooth muscles the muscle tone is reduced and blood flow is increased in the coronary vessels (also in other vessels). In myocardial cells activation of these channels

results in a reduced action potential duration, reduced calcium entry and a reduction in the myocardial contractility. But, this is very insignificant. Thus this helps to protect the myocardial cells from the effects of ischaemia. Although, isoflurane causes some slowing of the myocardial conduction, but it is less than halothane. So, cardiac rhythm is more stable during isoflurane anaesthesia.

Isoflurane preserves the regulation of autonomic nervous system on circulation to a greater extent than other volatile anaesthetic agents. During halothane anaesthesia there is a dose-related increase in the right arterial pressure and it is as a result of the direct negative inotropic action of halothane on the heart. Whereas, the pronounced venodilating properties of isoflurane and sevoflurane cause less increase in the right arterial pressure than halothane.

So, there appears to be a wide margin of cardiovascular safety with isoflurane. Cardiac index (ratio of doses producing circulatory arrest versus MAC) of isoflurane is 5.7, which is significantly higher than halothane which is only about 3. Isoflurane does not affect the cardiac rhythm and so dysrhythmia following injection of adrenaline is less likely with isoflurane than with halothane. This is a major advantage of isoflurane over halothane in plastic surgery, where there is a widespread use of adrenaline. The doses of epinephrine required to produce arrhythmia in patients receiving isoflurane is three times greater than the dose required in patients receiving halothane.

In normal doses and concentration, as isoflurane does not evoke sympathetic activity, so β_1-adrenoreceptor blocking agents are unlikely necessary. The vast majority of disorders of ventricular rhythm during isoflurane anaesthesia usually disappears when the concentration of inspired isoflurane is reduced and ventilation is improved. The use of β_1-adrenoreceptor blocking compounds should be reserved for the intractable tachyarrhythmias which is liable to progress to ventricular fibrillation. But, these drugs are contraindicated in the management of disorders of heart, arising from excessive vagal activity.

Isoflurane tries to maintain the myocardial contractility near normal and does not sensitize the heart to adrenaline. But, it maintains CVP very well. During isoflurane anaesthesia, the BP falls due to decrease in the systemic vascular resistance, but not due to myocardial depression and HR increases. It maintains the peripheral blood flow and tissue perfusion very well. Ventricular work is reduced due to reduction of after load. Pulmonary artery and wedge pressure remains normal.

Action on the CNS

Isoflurane produces a dose dependent depression of CNS activity. Concentration of isoflurane above 0.25 MAC produces amnesia. It does not promote convulsive activity. Cerebral metabolism is decreased which may lead to decrease in the cerebral blood flow. This property is very helpful in conditions where there is elevated intracranial pressure. Isoflurane does not increase the CBF in normocapnic patients, provided the mean arterial pressure does not increase. If MAP is allowed to fall, then ICP and CBF are both reduced. The increase in ICP, if occurs with isoflurane, is easier to reverse with hypocapnea than with halothane. Isoflurane with hypocapnea does not increase ICP associated with intracranial mass.

Neuromuscular effects

Isoflurane produces adequate muscle relaxation. It also enhances the action of suxamethonium. The neuromuscular effect of isoflurane is dose-related, but is more pronounced than that observed with halothane. Shivering also occurs during emergence from isoflurane anaesthesia like halothane, due to thermoregulatory response to hypothermia. But this can be suppressed with meperidine.

Effects on the uterus

As isoflurane relaxes the muscles of uterus in a dose-related manner and increases bleeding, so it is not recommended in obstetrical anaesthesia.

Metabolism and Toxicity

Isoflurane is physicochemically very stable which is reflected by its resistance to biodegradation. So, 95% of the administered dose of isoflurane is excreted unchanged in the exhaled air. Only less than 0.2% of the administered isoflurane (much less than halothane) is metabolised in liver and is excreted as urinary metabolites. Thus, the near absence of metabolism of isoflurane implies that the possibility of liver and kidney toxicity by the metabolites of isoflurane is remote. The main metabolities of isoflurane metabolism are trifluoroacetic acid and inorganic fluoride ions. The peak serum inorganic fluoride level after prolonged isoflurane anaesthesia was found to be only 4.4 μmol/lit, a concentration which renders the possibility of nephrotoxicity very little or almost nil. At a comparable anaesthetic exposure, there is ten times more production of fluoride ions with methoxyflurane which is known for nephrotoxicity. Production of trifluoroacetic acid, responsible for hepatoxicity, is also ten times less during isoflurane anaesthesia than during comparable exposure to halothane.

The Ames test which is widely accepted as a test for the mutagenicity and carcinogenicity for both the mother drug and its metabolites is negative for isoflurane, but positive for halothane and its metabolites.

Indications for Use of Isoflurane

The use of isoflurane is clearly of benefit in circumstances where:

i. The disturbance of cardiac rhythm is very likely.
ii. The neurosurgical patients who are known to have raised intracranial pressure.

iii. The patient presents with pre-existing renal and liver diseases.
iv. The patient who needs frequent exposure to an inhalational anaesthetic.

It is less useful, if an increase in the heart rate is not desirable, but would be deleterious in the presence of multivessel coronary artery diseases.

SEVOFLURANE

(1,1,1,3,3,3 hexafluro-2-fluromethoxypropane) Chemically, it is a halogenated (fluorine only) methyl-propyl-ether. As it does not contain any chlorine or bromine atom, so like halothane, isoflurane and desflurane it has no effect on the ozone layer of environment. The first report of this agent appeared in 1970. It has no asymmetrical carbon atom, so has no optical isomer. In this respect, sevoflurane is unique among all the currently available inhaled anaesthetics (Fig. 15.25A).

Physical Properties

Molecular weight of sevoflurane is 200.1(Da) and boiling point is 58.5°C. Its vapour pressure at 20°C is 160 mm of Hg. So, it can be administered by using a conventional temperature and flow compensated vapouriser. Rubber/gas partition coefficient of sevoflurane is 31(halothane 120, isoflurane 62). So, it is less soluble in rubber and plastic which are present in the anaesthetic circuits than halothane and isoflurane. The MAC value of sevoflurane with O_2 is 2 and with 70% N_2O is 0.8. The MAC value of sevoflurane also decreases with increase in age, like other inhalational agents. So, in neonates the MAC value of sevoflurane is 3.3, while in adults it is only 1.48. The MAC value of sevoflurane is also reduced with narcotics and hypnotics. No preservative is needed for sevoflurane for keeping it in bottles (in halothane, thymol is used as the preservative). Most of the administered sevoflurane is excreted unchanged by exhaled air through lungs and only 3 to 5% is recovered as metabolites (Table 15.14B).

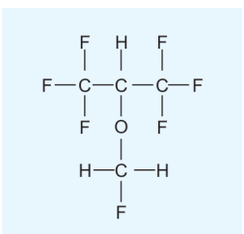


Fig. 15.25A: Sevoflurane

Blood/gas partition coefficient of sevoflurane is 0.6, which is substantially lower than other inhalational anaesthetic agents. So, the alveolar anaesthetic concentration of sevoflurane is very rapidly achieved which results in fast induction. Within 5 minutes, after the start of induction of anaesthesia, the F_A/F_I (ratio of the alveolar concentration to the inspired concentration) value for sevoflurane is 0.5, which is reached by halothane only after 30 minutes. This F_A/F_I ratio of sevoflurane is same as isoflurane, which indicates very quick induction of anaesthesia by it. However, sevoflurane blood-gas solubility, unlike that of halothane and isoflurane, does not alter with age. Sevoflurane has also lower distribution coefficient than other agents. So, elimination of it is very quick. Hence, it may prove ideal for outpatient anaesthesia due to its fast recovery. Sevoflurane is nonirritant to the upper airway. So, it is very suitable as an inducing agent for children. It is non inflammable.

Table 15. 14B: Effect of age on MAC of sevoflurane

Age (years)	*Sevoflurane with O_2*	*Sevoflurane with N_2O and O_2*
< 3	2.5-3.5	2
3-5	2.5	NA
5-10	2.5	NA
10-25	2.5	1.4
25-35	2.2	1.2
40	2	1.1
50	1.8	0.95
60	1.6	0.85
80	1.4	0.7

NA = Not applicable

Sevoflurane breaks down with sodalime. Metabolism of sevoflurane occurs in the liver by the cytochrome P_{450} system. It is broken down into inorganic fluoride ions and the organic fluoride compounds, such as hexafluoroisopropanol (HFIP). HFIP is conjugated with glucoronic acid to form HFIP glucuronide, which is then excreted through the bile and kidneys. There is no evidence of hepatic and renal toxicity associated with HFIP.

Pharmacological Actions

CVS effects

Sevoflurane has effects on the CVS which is similar to that of isoflurane, but it may cause less marked changes in the heart rate. That is, unlike isoflurane which cause tachycardia, sevoflurane causes minimal tachycardia or none. It causes decrease in the pulmonary arterial pressure and systemic arterial pressure, where decrease in diastolic pressure is more than systolic. This is due to the vascular smooth muscle relaxation and reduction of SVR, but not due to the much reduction of cardiac contractility and cardiac output, like halothane. It causes dose-related minimal decrease in myocardial contractility and cardiac output. Renal and hepatic blood flow is well maintained. Sevoflurane does not sensitise the myocardium to catecholamines.

Respiratory effects

Sevoflurane has no irritant effect on the airway like ether and isoflurane, and is very pleasant to inhale. So, these two qualities (nonirritant and pleasant smell) along with its low blood/gas solubility coefficient make the sevoflurane a very suitable agent for inhalational induction in children, infant and neonate. It is the least respiratory tract irritant among all the currently available inhalational anaesthetic agents. But, for induction it is less potent than halothane (MAC value of sevoflurane is 2, whereas MAC value of halothane is 0.75). This can be overcome

by using initially a higher inspired concentration of sevoflurane which is very well tolerated.

Like other halogenated volatile ether anaesthetics, sevoflurane is also a respiratory depressant. Tidal volume is reduced and respiratory rate is increased. But this increased respiratory rate cannot compensate the reduction in tidal volume. Thus it causes reduction of the minute volume. Both, ventilatory response to CO_2 (more than halothane) and hypoxia (30 to 40%) is depressed by sevoflurane. Sevoflurane also reduces the protective hypoxic pulmonary vasoconstriction reflexes in a dose-dependent manner. But, there is no change in the arterial O_2 concentration, when sevoflurane or isoflurane is used in anaesthesia during one-lung ventilation. Sevoflurane is also an effective bronchodilator, but is not as effective as halothane.

CNS effects

Sevoflurane may cause less cerebral vasodilatation than isoflurane. But the other effects of it on CNS are similar to isoflurane. Sevoflurane causes minimal increase in CBF in normocapnia, like isoflurane. Both sevoflurane and isoflurane reduce the cerebral metabolic rate. Cerebral perfusion pressure (CPP) is better maintained by sevoflurane, than isoflurane. Sevoflurane, like isoflurane causes a slight increase in ICP in normocapnic patients. The cerebrovascular response to CO_2 and cerebral autoregulation are both preserved under sevoflurane anaesthesia.

Metabolism and Toxicity

Sevoflurane is less significantly metabolised than halothane (but more than isoflurane and desflurane) by defluorination in liver and the plasma fluoride and HFIP concentration reaches a level of 15 to 25 μ mol/litre after 1 MAC exposure of the drug for 1 hour. But, it is much less than the nephrotoxic level. Approximately 3 to 5% of the inhaled dose of sevoflurane undergoes biotransformation in the liver. But this is 1/4 than that of halothane and 20 to 25 times more than that of isoflurane and desflurane. After prolonged anaesthetic exposure (13 to 14 hours) 5 out of 10 patients exceed the serum fluoride concentration more than 50 μ mol/litre (Fig. 15.25B).

This is a level which was previously thought to be nephrotoxic. But, still there have been no reports of renal failure. In vitro, sevoflurane undergoes extensive metabolism. But clinically (in vivo) it is not a problem, because it is very less soluble in blood. When sevoflurane is exposed to baralyme or sodalime, it breaks into methanol, formaldehyde, carbon monoxide, compund A and compound B. Both of these compounds are hepatotoxic and nephrotoxic. But, still there is no evidence of long term serious renal or hepatic injury after exposure to sevoflurane with baralyme or sodalime. Of the halogenated anaesthetic agents which are currently in widespread use, the sevoflurane is the only one which is not metabolised to trifluoroacetic acid (TFA), implicated in hepatotoxicity. Sevoflurane can also be degraded to hydrogen fluoride. This is due to the metal or environmental impurities which are present in manufacturing equipments. This hydrogen fluoride may produce an acid burn, when it comes in contact with the respiratory mucosa.

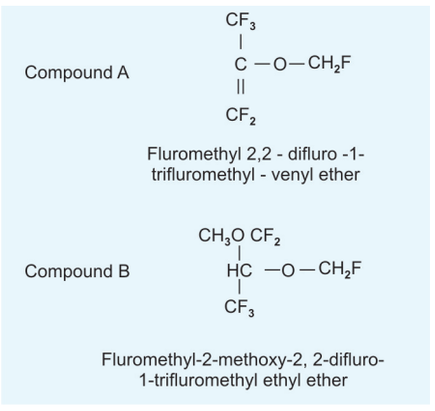


Fig. 15.25B: Sevoflurane compounds A and B

Potential Indications for Use of Sevoflurane

Sevoflurane has a definite place in paediatric anaesthesia practice for inhalational induction and maintenance. Though induction and recovery from sevoflurane is quick like isoflurane and has no pungent smell, so there is a definite advantage of sevoflurane over isoflurane. Sevoflurane offers good haemodynamic stability (like isoflurane) than halothane. As sevoflurane does not contain any chloride ion, so it is environment friendly. Although seveoflurane has fewer side effects than halothane, but there are some concerns about its hepatotoxicity (like halothane). There is also some concern about the renal toxicity of compound A, formed as a result of degradation of sevoflurane by CO_2 absorbers. But, this is not proved to be of any clinical problem.

DESFLURANE (FIG. 15.26)

After the appearance of sevoflurane in 1971, hundreds and hundreds of halogenated volatile anaesthetics agents were synthesized and analysed. Then, desflurane came in this effort. Initially, several factors had delayed the development of desflurane. These were: (i) the potentially hazardous process of utilizing only fluorine in the synthesis of desflurane (in desflurane there is no chlorine or bromine ion), and (ii) the peculiar vapour pressure of desflurane which is very close to the atmospheric pressure at room temperature. This is because the boiling point of desflurane is 22.8°C which is near about to the room temperature. So it starts to boil in the normal room condition. This precludes the use of conventional vapourisers for its administration. Later, a safer

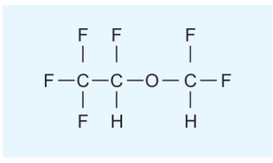


Fig. 15.26: Desflurane

process of synthesising desflurane was developed and there after the Aladin cassette vapouriser was invented for administration. Then, desflurane was subsequently approved for clinical use in USA in 1992. Desflurane is a halogenated (fluorine only) methyl-ethyl-ether. Structurally, it differs from isoflurane by the substitution of chlorine by fluorine on the α-ethylcarbon. The desflurane exists in different optical isomers and the drug for clinical use is a racemic mixture.

Physical Properties

The desflurane has very pungent odour. So, it makes desflurane very irritating and unpleasant to inhale like isoflurane.The molecular weight of desflurane is 168, boiling point is 22.8°C and vapour pressure at 20°C is 664 mm of Hg. Low boiling point of desflurane which is near about to the room temperature indicates that it cannot be administered by using a standard vapouriser. The MAC value of desflurane varies, depending on the stimulus and other co-agents used. It also decreases with age. MAC value of desflurane with O_2 is 6 to 9 and with 70% N_2O is 2.5 to 3.5. The blood/gas partition coefficient of desflurane is 0.42. It needs no preservative for storing and is stable in alkali, ultraviolet light and metal. Only 0.02% of the inhaled drug is recovered, as its metabolites. Desflurane has the lowest blood and other tissue partition coefficient, compared to other inhaled anaesthetics. So, it is unique as an agent for very fast induction and recovery than other inhalation anaesthetic agents. But, unfortunately, as it is an irritant to the upper respiratory tract and causes cough, breath holding, laryngospasm, etc. so induction by desflurane is automatically slowed. Hence, it is not the drug of choice for induction.

Desflurane is relatively less potent than other agents. It is extremely stable and is presented as a clear liquid in amber bottles without preservatives. Its physical properties (i.e, boiling point is around room temperature) donot allow its use by a standard vapouriser. So, special Tec-6 vapouriser is needed for its use. Like sevoflurane, as it is entirely fluorinated, so ozone depletion of the enviornment is minimal. Thus, it is environment friendly. Both sodalime and baralyme can degrade it with the production of carbon monoxide.

Pharmacological Action

CVS effects

The effect of desflurane on CVS is same as that of isoflurane. It causes the reduction of systemic vascular resistance, mean arterial pressure and increase in HR. The decrease in MAP by desflurane is due to the decrease in SVR, but not due to the much reduction of cardiac contractility like halothane. Therefore, there is a very small change in cardiac output. The arrhythmogenic potency of desflurane is like isoflurane. The decrease of SVR by desflurane is due to the peripheral vasodilatation. However the cardiac index remains unchanged or increased. The hepatic blood flow is maintained by desflurane. When desflurane is used for maintenance of anaesthesia there is no change in renal blood flow at concentrations upto 2 MAC. Desflurane is a direct coronary vasodilator. But, the potential improvement in coronary blood flow due to coronary vasodilation is offset by the tachycardia caused by desflurane and also by the fall of coronary perfusion pressure, resulting from peripheral vasodilatation caused by desflurane and hypotension. Like isoflurane, use of desflurane is associated with rapid increase in HR. But this can be reduced by small doses of opioids, esmolol, clonidine and N_2O. Desflurane does not sensitise the myocardium to epinephrine. It can slow the atrioventricular conduction or induce the junctional bradycardia.

Respiratory effects

Like other inhaled anaesthetic agents the ventilatory response of desflurane is accompanied by an increase in respiratory rate and decrease in tidal volume. But, ultimately there is reduction in the minute volume and an increase in $PaCO_2$. However, desflurane does not significantly reduce the minute ventilation, until a concentration of it greater than 1.6 MAC has been used. Thus, at higher concentrations of desflurane respiratory rate decreases, but less than halothane. At more higher concentrations, the respiratory depression effect of desflurane is similar to that of isoflurane and sevoflurane. Ventilatory response to CO_2 is also reduced. Intrapulmonary shunt fraction and the physiological dead space are also increased. Induction by desflurane is associated with coughing, salivation and laryngospasm due to its very pungent odour. This outweighs the benefit of its direct bronchodilating action and rapid induction. And, it is postulated that this causes early sympathetic stimulation. Thus, desflurane is unsuitable for inhalational induction, both for children and adults.

CNS effects

Desflurane decreases the cerebro vascular resistance. Thus, it increases the cerebral blood flow and intracranial pressure. But, it also decreases the cerebral O_2 requirement. Desflurane increases the CSF pressure to a greater extent than isoflurane. In a comparative study, carried out on patients with intracranial mass, 1 MAC desflurane or isoflurane was given. Then, it was observed that ICP increased progressively in the desflurane group, even with hypocapnia. Whereas there was no increase in ICP in the isoflurane group.

Of the commonly employed volatile agent, the order of cerebral vasodilating potency is as follows:

Halothane >> Enflurane > Isoflurane = Sevoflurane = Desflurane

Desflurane causes increased CSF production, under condition of ↑ICP and even in hypocapnia. To date, no clear advantage has been seen for any given inhalation agent over another in neurosurgical anaesthesia. But, the very rapid recovery

characteristic of desflurane may offer a definitive advantage for its use in neurosurgical patients in whom rapid postoperative neurological assessment is desirable. An EEG change caused by desflurane is comparable with that of isoflurane, but no epileptic form of activity is seen.

Effects on muscle

Like other inhaled anaesthetic agents, desflurane depresses the neuromuscular function and augments the action of both non-depolarizing and depolarizing muscle relaxants. Thus, it can provide sufficient muscle relaxation to allow tracheal intubation.

Metabolism and Toxicity

Desflurane has a very low blood-gas and blood-tissue solubility. So, it is very stable and undergoes minimal metabolism in body. These are the properties of desflurane that should favour its low systemic toxicity. However, still a very small amount of desflurane is metabolised with the production of difluoroacetic acid, which may interact with the hepatic proteins and may induce an immune response in susceptible patients. But, after a same concentration and same hour of exposure of desflurane, the concentration of toxic metabolites is 10 folds less than the levels, seen after exposure to isoflurane. So, its potential to cause organ toxicity is very negligible or nil. There is no evidence of renal toxicity with desflurane, even after prolonged exposure. Desflurane may trigger malignant hyperthermia. So, it is prudent not to use desflurane in susceptible patients.

Magnitude of carbon monoxide production in sodalime or baralyme absorber from greatest to least is :

Desflurane >> Enflurane > Isoflurane >>Halothane = Sevoflurane

Indications for Use of Desflurane

The recovery from desflurane anesthesia is more rapid and complete than following recovery from either propofol, isoflurane or sevoflurane-maintained anaesthesia. This suggests that it is very suitable for day-case anaesthesia. Insolubility of desflurane makes it eminently suitable for use in low-flow, closed circuit anaesthesia delivery systems. The lack of effect on the atmospheric ozone layer layer also makes desflurane environmental friendly. Though desflurane is metabolised in fraction to isoflurane, this advantage is theoretical than practical, as the use of isoflurane is not associated with significant incidence of organ toxicity.

XENON

This element was first discovered, in 1898, by W Ramsay and MW Travers. It is present in the atmosphere to the extent of about only one part out of twenty million part. Thus, the concentration of xenon in the atmosphere is only 0·0000087%. Before 1962, it was generally assumed that xenon and other noble inert gases were unable to form compounds with other elements. But, evidence has been mounting in the last few years that xenon and other zero-valency elements can form compounds with other elements. However, xenon is not toxic. But its compounds are highly toxic, because of their strong oxidizing characteristics.

By 1950, studies had proved that there was some hypnotic effect of this noble gas, xenon. Then, in 1951, xenon was first used as an anaesthetic agent by Cullen and Groaa and the patient was a 81 year old man, undergoing orchidectomy. They used 80% concentration of xenon. After that and till now different attempts has been taken to make it feasible to use in clinical practice. But due to different reasons which are described later it was not technically possible. At that time, different isotopes of xenon were also isolated and used in different industries, such as in X-ray tubes for high intensity lights and in many biological experiments such as measurement of cerebral blood flow and lung volumes etc. (Table 15.15).

Atomic number of xenon is 54 and its molecular weight is 131.3. It is a colourless, odourless, non-irritating gas and is four times heavier than air. It is more viscous than nitrogen. It freezes at −111.9°C and boils at −107.1°C It is non-inflammable and does not support combustion. As it is extremely inert, so it does not react with sodalime. It can diffuse readily through rubber. The MAC value of xenon is 71. It indicates that xenon is a more potent anaesthetic agent than N_2O. Therefore, it is possible to use xenon as the sole anaesthetic agent, at least in some patients. Its blood/gas partition coefficient is 0.115 and is lowest among all the available inhalational anaesthetic agents. So, it provides very rapid induction and very rapid emergence from anaesthesia. Its oil/gas partition coefficient is 0.14 to 0.2, which is lower than that of N_2O (0.47).

Xenon is extracted as a side product during air liquefaction (Linde process). Then, the gas is stored in cylinders, similar to those used to store O_2 or N_2O. As xenon only makes up a very small percentage of the atmospheric air, so it is extremely expensive to extract from it. It exerts analgesic effects independent of the α_2-adrenergic and opioid receptors. Although, the most intravenous general

Table 15.15: Advantages and disadvantages of Xenon (Xe) anaesthesia

Advantages

- Inert - has no metabolism,
- Nontoxic,
- Minimal CVS effects,
- Very low blood gas solubility coefficient,
- Very rapid induction and recovery,
- Does not trigger malignant hyperpyrexia,
- Non explosive,
- Environment friendly,

Disadvantages

- Very high cost,
- Low potency (MAC = 71),
- At present no commercially available anaesthetic equipment using xenon.

anaesthetics agents enhance the inhibitory activity of GABA receptors, but the action of xenon on these receptor is also negligible. Xenon potentially inhibits the excitatory NMDA (N-methyl-D-aspartate) receptor channels like ketamine like ketamine and this may account for the xenon's anaesthetic property. Though, xenon has more potent analgesic action than N_2O, but it is not always possible to use xenon as a sole anaesthetic agent. However, less supplementation by intravenous or inhalational anaesthetic agents is needed than N_2O. Like N_2O, xenon has the same potential for diffusion hypoxia during recovery and has the same implications regarding diffusion into gas-filled cavities within the body.

Xenon, being a chemically inert gas, does not enter into any metabolic process of the body, and therefore leaves behind no metabolic products. It is completely excreted through the lungs. Even in high concentrations, xenon is completely nontoxic. Xenon has no or minimal systemic and pulmonary effects. As xenon is odourless, so like N_2O, it is very useful for inhalational induction. Xenon is four times greater in density than that of nitrogen and 3 times denser than that of N_2O. Also it has a higher viscosity than that of both the nitrogen and N_2O. Thus, both the high density and high viscosity property of xenon have significant effects on the pulmonary mechanics, i.e. increasing airway resistance and airway pressure. So, xenon should not be used in patients with respiratory diseases, especially during obstruction of airway. Respiratory rate is slowed by xenon, but there is a compensatory increase in the tidal volume with little change in minute ventilation. It preserves the myocardial contractility in humans. Xenon attenuates the increased plasma epinephrine and cortisol level, associated with the surgical stimulus. It has a very minimal effect on LV systolic and diastolic functions of both the normal and cardiomyopathic heart. In conclusion, we can say that xenon provides good haemodynamic stability with mostly little change in myocardial contractility, SVR, PVR, blood pressure and heart rate (slight reduction of heart rate) than other inhalational anaesthetic agents.

Xenon causes an increase in the CBF and an increase in the ICP, but a reduction of CPP. So, xenon should be used with caution in patients who are at risk from raised ICP. Xenon does not cause malignant hyperthermia. S-100 is a protein that is found in high concentration in the nervous system of vertebratas. Any structural damage of the glia cells cause leakage of this protein S-100 into the extracellular compartment and finally into the serum, where the β-subunit of the protein S-100 can be measured. But, there is no increase in S-100 values during xenon anaesthesia. Thus, it can be concluded that xenon does not impair cerebral integrity.

When exposed to xenon, the patient loses consciousness within a very short period and the patient's state remains stable throughout the anaesthetic procedure. Pain is alleviated. Unlike other commonly used anaesthetic agents, patient's blood pressure does not drop. Patient becomes fully conscious without any side effects within two minutes of completion of the operation and cessation of the supply of xenon. The depth of anaesthesia is also sufficient at a xenon gas concentration of about 55%.

Till now, it is too expensive to use xenon gas in the routine anaesthesia practice. Only when the reuse of the gas within a low-flow, closed circle system becomes true, then the clinical application of xenon will become both possible and economical. At the end of the process of anaesthesia the xenon gas is recollected in a container, compressed and filled again into cylinders. Then it is returned again to the gas supplier to be prepared for reuse. Roughly, 15 to 20 litres of xenon gas is consumed during an operation, lasting for two to three hours. Xenon anaesthesia is mainly used in paediatric and cardiac anaesthesia. It is enviornmental friendly, as it is an atmospheric gas. Now, it is routinely used for anaesthesia in Germany, Netherlands, Sweden and Russia.

ANAESTHETIC DELIVERY SYSTEM OR CIRCUITS

History

The open-drop method of administeration of volatile anaesthetic agents was first introduced by Sir James Y Simson, in 1847, for chloroform. He first used a folded handkerchief as mask on the patient's face on which chloroform was instilled drop by drop. Later it was modified by different persons to ultimately schimmelbushch mask, which is still used now. But the disadvantage of this open-drop method was: (i) an uneven anaesthesia due to variations in concentration of the vapour of anaesthetic agent which was inhaled, (ii) risk of fire, wastefulness, and pollution of the atmosphere, (iii) fall in O_2 concentration under the mask (which could be remedied by giving O_2 under the mask via a small catheter) and (iv) the risk of damage to the eyes and skin of the patient from the direct contact anaesthetic liquid. Then, the administration of ether by a simple inhaler was developed by Morton. In 1846, he used a glass draw-over vapouriser for his public demonstration of general anaesthesia by ether. In 1862, Thomas Skinner, who was a general practitioner and obstetrician of Liverpool first invented a wire frame mask, covered with a domette which could be carried in the top of the hat. After that these masks gained wide acceptance. Then, in 1890 Schimmelbusch, a Berlin surgeon developed a trough shaped rim around this wire frame to prevent the anaesthetic liquid from flowing over directly on the patient's skin of face during open drop method of administration of volatile anaesthetic agent. It was used both for the ether and chloroform. During these first 80 years of general anaesthesia many

millions of patients were managed satisfactorily using this mask and dropping ether or chloroform on this mask (open drop method).

What is now called the anaesthetic mask was originally called the face-piece and was first invented by Cloquet and Sibson? Sibson's original mask was made of mackintosh (waterproof coat) and was lined with silk. Later, it was improved by Snow whose version was made of a thin lead sheet, covered with leather outside and velveteen inside. It was fitted with valves and was used with his newly invented ether inhaler. During that period nasal masks were also developed, instead of face masks for dental anaesthesia. In 1859, Faure of Paris gave chloroform vapour through a rubber tube inserted into one of the nostrils for oral surgery.

The history of anaesthetic machine dates back to 1880 when both the O_2 and N_2O were available as compressed gases in iron bottles for industrial purposes. From this period the development of the basic anaesthetic machine began. In the late nineteenth century, Sir Frederick Hewitt described a machine in which both the O_2 and N_2O from their cylinders was stored in two rubber bags and delivered in variable concentrations to the patient via a stopcock that he designed. Then in 1912, Cotton and Boothby developed a 'N_2O, O_2 and ether apparatus' with compressed gas cylinders where they also incorporated, reducing valves, bubble flowmeters and a bubble-through ether vapouriser. During that period many machines were also developed by many scientists. But the first World War had stimulated the major developments in anaesthetic machine.

In 1912, James Gwathmey of USA developed the first practical anaesthetic machine. Then, in 1917, Henry Boyle modified this American Gwathmey Apparatus and from that period his name became synonymous with this anaesthetic machine. One of Boyle's most important modifications of the Gwathamey Apparatus was the addition of reducing valves. During that time another modification of the Gwathmey's Apparatus was done by Marshall in London. Thus, a major advantage of this Marshall and Boyle's modification over the Gwathmey's Apparatus was the use of Hewitt stopcock to prevent rebreathing.

The original Boyle's machine of 1917 was rebuilt by an engineering firm named Coxeters for commercial use making a company. In its original form it housed two N_2O and two O_2 cylinders in a wooden box. There also was a water-sight flowmeter and an ether vapouriser. It had (Table 15.16) a pressure gauge on the O_2 cylinders and fine adjustment reducing valves. It also had a spirit lamp to warm these cylinders and to prevent the obstruction of gas flow from freezing of water vapour which remained as an impurity in early gas supplied in cylinder. A reservoir bag, a three way stopcock and a facemask completed the apparatus. A portable form of this Boyle's apparatus was also designed for the use of British army in France, and was then popularised very rapidly. However, the modern Boyle's apparatus bears little resemblance to this original model and subsequent modifications were included in the original one (Fig. 15.27).

In the mean time, many developments in anaesthesia had continued between the wars. For example, Jackson in UK introduced a circle system in 1915. Waters in USA developed CO_2 absorption system, in 1924, using granular sodium and calcium hydrate. At this time, watersight feed-meters and bubble bottles were used in industry to indicate the gas flow. In the early 1930's, Coxeter introduced the dry gas flowmeter. The rotameter which is still used today had been first designed by Kuppers in 1908 and was first widely used in the industry for gas and fluid. It was not until 1937, when it was introduced into the anaesthetic machines.

Table 15.16: Modifications of the Boyle's machine

1920 :	Addition of the first Boyle's vaporising bottle to flowmetres.
1926 :	Addition of a 2nd vaporising bottle and bypass controls.
1927 :	Addition of a 3rd watersight flow meter, for CO_2.
1930 :	Addition of a plunger device to the Boyle's vapourising bottle.
1933 :	Dry bobbin type of flowmetre instead of the water sight metre.
1937 :	Rotameters displaced dry bobbin flowmetres.
1952 :	Introduction of the pin-index system.

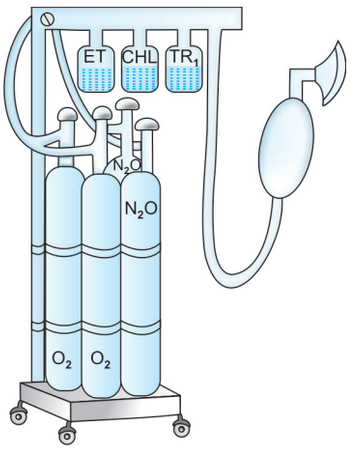


Fig. 15.27: Early Boyle's machine

After that during the next 50 years or more, much of the development of the Boyle's apparatus was focussed on patient's safety and standardization of its design. However, since the early 1990's the introduction of sophisticated electronic monitoring devices in anaesthetic arena has placed a new set of demands on the machine's design.

So, the design of an anaesthetic machine has now changed much for safety and monitoring purposes from its introduction at the end of the last century. However, the modern anaesthetic machine is a highly sophisticated piece of mechanical, pneumatic and electronic engineering tools which is built to maintain good safety standards and incorporate a state of the art monitoring and ventilator system. Now, the anaesthetic machine is called as

an anaesthetic work-station and is a part of a larger system incorporating : decision support, central monitoring and automated anaesthetic record keeping. Now, the most dangerous part of an anaesthetic machine is the operator. Therefore, it is the obligation of the manufacturer to make the new machines absolutely easy to use and also to help the anaesthesiologists to understand how to use them safely.

The Inhalational anaesthetic system has basically two parts:

i. Anaesthetic machine, itself, and
ii. Anaesthetic delivery system or breathing system.

The breathing system is defined as the conduit which is situated between a pressure-reduced and flow-restricted gas source or anaesthetic machine and the patient's airway. The term 'breathing system' is nowadays the preferred term, rather than the former term 'circuit'. Because the flow of gases does not necessarily circulate. Many breathing systems also incorporate the facility of artificially ventilating the patient, a system of humidification and also a facility of connecting the machine to a scavenging system.

Here, we will discuss only the anaesthetic delivery or breathing systems but not the whole anaesthetic machines. The whole anaesthetic machine is discussed in details in Chapter 1. All the anaesthetic delivery systems have some standard common features. These are:

i. Source of O_2 – may be atmospheric or compressed.
ii. Source of anaesthetic gases are compressed cylinders (N_2O) or vapourisers (for volatile anaesthetic agents).
iii. A method of CO_2 elimination – either by venting it to the atmosphere or by chemical absorption.
iv. A reservoir to meet the demand of high peak gas flow during inspiration.
v. A steady inflow of fresh gas both during inspiration and expiration.

The breathing system has three main functions. These are:

i. The supply of O_2 to patient,
ii. The supply of anaesthetic gases and vapours to the patient,
iii. The elimination of CO_2.

Classification of the Anaesthetic Delivery System

It is not possible to classify the anaesthetic delivery system in a completely logical or water-tight manner. Also, there is no justification in using the two near most similar terms – 'semiclosed' and 'semiopened' for confusion instead of one in a single test book. The term 'semiopen' is most commonly used in North America. Any system may function in different modes, according to the rate of inflow of fresh gas, pattern of ventilation, whether patient is in spontaneous or controlled ventilation and different interchanging position of the entry of the fresh gas, reservoir bag, expiratory valve, etc.

The main classification of the anaesthetic delivery system are:

i. Open or non-rebreathing system.
ii. Semi-closed or semi-opened system, where partial rebreathing may occur as there is no CO_2 absorber, such as Mapleson circuits.
iii. Circle rebreathing system with CO_2 absorption.

The main difference between the semiopen and the semiclosed system is that the semiopen systems are valveless and entrainment of room air can occur. But in modern anaesthesia this should not happen. On the other hand, a semiclosed system can not entrain room air. Because, it uses an APL valve and there is an airtight seal between the breathing system and the patient's face, either through a tight fitting mask or by a connection between the breathing system and an airway device such as an ET tube or LMA. In a semiclosed system the problem of peak inspiratory flow is overcomed by the incorporation of a reservoir bag. The bag collapses during inspiration to compensate the difference between the fresh gas flow (FGF) and the peak inspiratory flow. As long as the FGF is sufficient to replace the loss from the system which occurs through APL valve during expiration, the bag will return to its original full state after expiration.

(i) Open or non-rebreathing system

This system ensures that each breath gets full fresh gas flow and all the expired gas is vented out to the atmosphere. This classification includes:

i. Open drop mask,
ii. Insufflation,
iii. A non-rebreathing valve with or without an inspiratory reservoir bag.

Open drop mask

This is the simplest form of anaesthetic delivery system. If supplementary O_2 is not given under the mask, then some rebreathing does occur from the space under the mask which becomes an extension of the anatomical dead space. Schimmelbusch mask and Gardner ether bottle is the best example of this system.

Insufflation

Insufflation means the blowing of anaesthetic gases across the patient face or any part of the patient's airway. Although it is categorised as a breathing circuit, but actually it is considered as a technique that avoids the direct connection between a breathing circuit and the patient's face or airway. Children often resist the direct placement of facemask or an intravenous line before induction. In such circumstances, insufflation is particularly valuable for induction with inhalation anaesthesia. Insufflation avoids any direct patient contact. Therefore, there is no rebreathing of exhaled gases. But the inspired gas contains unpredictable amounts of volatile anaesthetic agents, entrained with the atmospheric air. Insufflation is also used to maintain the arterial oxygenation during a brief period of apnoea, such as during bronchoscopy and laryngoscopy (by oxyscope). In such situations, instead of blowing

gases across the patient's face, oxygen is directly directed and blowed into the the lungs through a device placed in the trachea. Insufflation is also useful during ophthalmic surgery. In ophthalmic surgery under local anaesthesia accumulation of CO_2 under the head and neck drapings is hazardous. So, insufflation of O_2 and air across the patient's face under the drape at a high flow rate (>10 L/min) avoids this problem.

Non-rebreathing valve

Non-rebreathing valve is a modification of semiclosed system. It prevents rebreathing by allowing the unidirectional flow of all the expired gases to the atmosphere. Thus, it enables the patient to inspire a constant proportion of fresh gas flow from the machine or the air, as there is no mixing of inspired and expired gases. Hence, any moment the anaesthesiologist can tell the exact proportion of gases that the patient is inspiring. The examples of this type of nonrebreathing valves are : frumin valve, ruben valve, demand valve etc.

Frumin valve

It can be used both for spontaneous and controlled ventilation. It is so designed that any sudden rise of pressure in the bag which is filled with fresh gases, like squeezing it during controlled ventilation, closes the expiratory valve and all the gases pass on to the patient. On release of pressure at the end of inspiration the expiratory gases escape fully to the atmosphere through the expiratory valve which open during expiration only. This valve can be used either with a facemask or with the ET tube. Resistance and dead space of this valve are minimal.

Ruben valve

The mechanism of action of this valve is same as that of Frumin valve, but it differs from the latter only by very little dead space. Like the Frumin valve, during inspiration this valve automatically closes in both controlled and assisted ventilation, but opens during expiration only allowing expiratory gases to escape fully to the atmosphere. The main advantage of this valve is the small dead space which is only 9 ml. Resistance is also very low in this valve. If it is used with a continuous gas supply, then an inspiratory reservoir bag must be incorporated into the system to supply the peak inspiratory flow rate and the gas flow into the system must be equal or should exceed the patient's minute volume (Fig. 15.28).

When the patient draws air from the atmosphere (i.e. when compressed gas supply is absent), then no reservoir bag is needed. But the system must have a low resistance to meet the peak inspiratory flow rate. Low resistance vapourisers, such as a EMO vapouriser, may be placed in the circuit to deliver the volatile anaesthetic agent and this constitutes a draw-over anaesthetic apparatus. This type of equipment is very useful in remote areas where compressed gas supply is absent. Useful addition to such a system is an extra inlet to permit O_2 enrichment of the inspired air and a bellows with additional valves to permit manual controlled ventilation when needed. The space between the non-rebreathing valve and the patient constitutes the apparatus dead space and for this reason the valve should be mounted as close to the patient as possible. The valve disc and the spring must be made as light as possible to reduce the resistance. The valve should be specially constructed to prevent the formation of water by condensation of its vapour which is present in the expired air. This is because the presence of water may prevent proper functioning of the valve due to sticking (back flow) and may cause serious accidents.

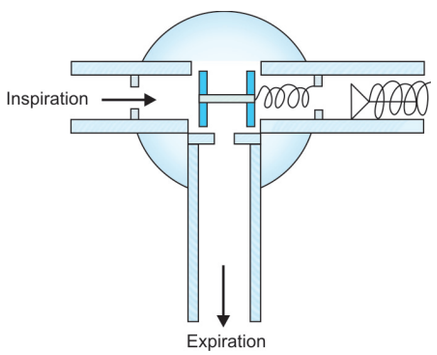


Fig. 15.28: Non-breathing Ruben's valve

Demand valve

This is a valve which is attached to a cylinder of a compressed gas and will deliver the gases at a low pressure up to the peak inspiratory flow rate in response to the slight negative pressure developed by the patient's inspiratory effort. Demand valve is commonly used in connection with the cylinder containing N_2O and O_2 mixture (Entonox). As the valve is capable of delivering gas flows equal to the peak inspiratory flow rate, so no reservoir bag is needed. Such an assemble is classified as an intermittent-flow machine because the valve allows the gas to flow intermittently, corresponding only with the patient's inspiratory effort.

(ii) Semiclosed system

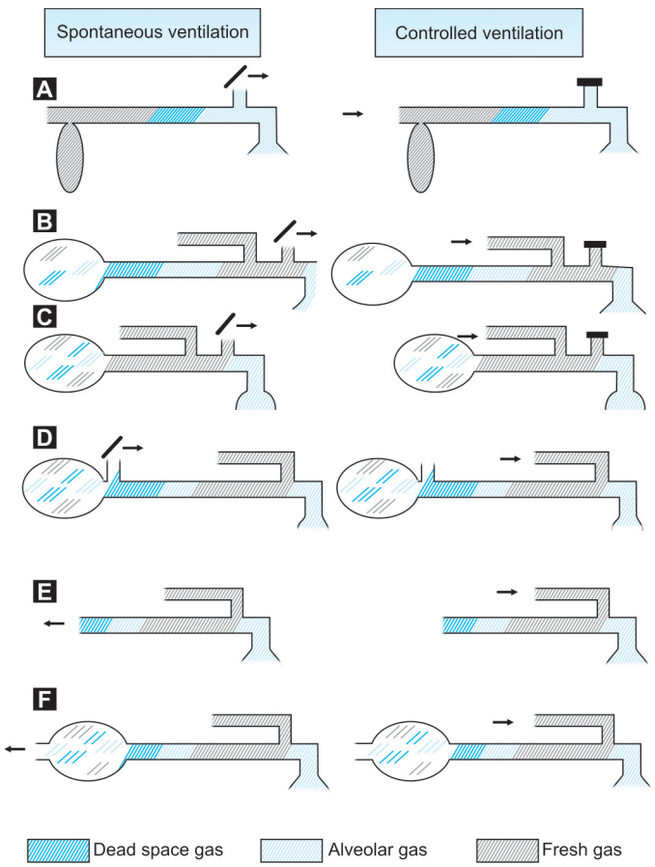
The best example of this breathing system is the series of Mapleson circuit. In 1954, Mapleson described and analyzed the five different types of semiclosed systems or circuits, depending on five different arrangements of the entry site of fresh gas flow, tubing, mask, reservoir bag and expiratory valve to prevent the rebreathing maximally during spontaneous and controlled ventilation. However, in general the elimination of CO_2 depends also on many other factors other than the above mentioned five factors. These are : the fresh gas flow rate, minute volume, tidal volume, the pattern of breathing (spontaneous or controlled), apparatus dead space, resistance of the circuit, the respiratory rate, the I:E ratio, the duration of expiratory pause, the peak inspiratory flow rate, the volume of the reservoir tube and the volume of the breathing bag.

The Mapleson semiclosed circuit is classified as A, B, C, D and E. Willis added an extra F-system to these original classifications. Recently these six types of Mapleson systems were grouped functionally into three. They included the: (i) group A, (ii) group B, C, and (iii) group D, E, F. The Mapleson A has a spring loaded pop-off valve, located near the face mask and the fresh gas flow enters from the opposite end of the system, distal to the reservoir bag. In the B and C groups the spring loaded pop-off valve is located near the face mask, but the fresh gas inlet is located near the patient, close to the APL valve but proximal to the reservoir bag. The reservoir tubing and the breathing bag serve as a blind limb where the fresh gas, dead space gas and alveolar gas can be collected. In the Mapleson D, E and F groups which is also called the T-piece group, the fresh gas enters near the patient end, proximal to the APL valve or an exhalation port, where there is no valve and the excess gas is popped-off at the opposite end of the circuit.

Mapleson – A

It is the most familiar breathing system to anaesthesiologists and is also known as the Magill's circuit. In this circuit the entry of the fresh gas flow is distal to the reservoir bag, opposite to the patient end of the circuit at a distant from the patient. The expiratory valve is near the patient's end. The type of expiratory value which is used in Mapleson circuit is the Heidbrink type. Rebreathing during spontaneous respiration in this circuit can be prevented by a relatively low fresh gas flow than any other Mapleson circuits. During anaesthesia with spontaneous respiration, the Magill's attachment is still the best in an adult for economy in total gas flow and for virtual elimination of rebreathing. During expiration, the first part of the expired gas comes from the anatomical dead space and contains no CO_2. It travels down the corrugated tube towards the reservoir bag and fills it, mixing with the fresh gas coming from the machine. In the next part of expiration when the volume of expired gas from the patient increase, then the pressure in the circuit also rises. Thus, the expiratory valve is lifted up (opening pressure of the Heid brink valve should not be more than 1 to 2 cm of H_2O) and expired gas escapes. Gas escaping at this expiratory part of respiratory cycle is the alveolar gas, containing maximum amount of CO_2. During spontaneous inspiration the fresh gas flushes the dead space gas (which collects in the tubing during first part of expiration) through the tubing towards the patient for rebreathing. But, rebreathing of this dead space gas by the patient poses no problem, as it does not contain any CO_2. If the fresh gas flow is adequate, then the dead space gas during expiration cannot go up to the reservoir bag, but meets with the fresh gas flow at the earlier part of the tube and escapes with the alveolar gas at the end of expiration, pushed by FGF. So, this circuit preferentially eliminates the alveolar gas first, and then the dead space gas later. If the fresh gas flow is gradually reduced, still then rebreathing does not occur, until the fresh gas flow falls below 70% of the minute volume, a figure (Figs 15.29A to F) which is approximately equal to the alveolar ventilation (2 to 4 liters/minute). So, during spontaneous ventilation the recommended fresh gas flow (FGF) rate through the Magill's circuit (Mapleson A) is one times of the minute volume which can prevent the rebreathing of CO_2.

But this Mapleson A circuit is inefficient during controlled ventilation. During controlled or assisted ventilation the



Figs 15.29A to F: Gas disposition at the end of expiration, during both spontaneous and controlled ventilation in Mapleson circuits

resistance of expiratory valve should be increased which will help to ventilate the patient. During expiration of controlled ventilation no venting of gas occurs through valve in the Mapleson A circuit. So, the total expired dead space gas and the alveolar gas are retained in the tubing and the bag. Venting of the gas from the circuit during controlled ventilation occurs only during inspiration by manual compression of the reservoir bag. During squeezing of the reservoir bag the alveolar gas with CO_2 which is retained during expiration in the tube is rebreathed first before the pressure in the system increases enough to force the expiratory valve open. Then this opened expiratory valve causes the dead space gas (without CO_2) with the fresh gas to vent in the last part of the inspiration through the pop-off valve. So adequate CO_2 elimination or prevention of rebreathing during controlled ventilation with Mapleson A system requires a fresh gas flow greater than 20 litre/minute or three times of the minute volume. Hence, in practice, controlled ventilation should be avoided with this system.

Mapleson – B

In this system the fresh gas inlet is near the patient, but just distal to the expiratory valve and proximal to the reservoir bag. But unlike Mapleson A, this system functions similarly both during spontaneous and controlled respiration. During the first part of expiration (both spontaneous and controlled), fresh gas with the dead space gas accumulates in the tube and the bag. Then the expiratory valve opens when the pressure in the circuit increases and a mixture of alveolar with fresh gas is discharged. Some CO_2 containing alveolar gas, dead space gas and fresh gas is also collected in the reservoir tube and the bag. During the next inspiration (in both spontaneous and controlled) patient receives the fresh gas flow from the machine and a mixture of retained dead space gas and alveolar gas from the tubing and reservoir bag. The composition of this inhaled mixture depends on the fresh gas flow rate. In this circuit rebreathing of expired gas (acceptable level of inspired CO_2 is 0.2 to 1%) can be prevented, if the fresh gas flow rate is greater than 2.5 times of the minute ventilation during both spontaneous and controlled ventilation. The amount of FGF needed for proper functioning of this circuit (i.e. prevention of rebreathing of CO_2) greater than D, E and F group of circuit.

Mapleson – C

This system is also known as the Water's circuit. It is also called the Westminister face piece. Arrangement of this system is similar to that of Mapleson B, except that the expiratory or reservoir tube is of large bore and very short. This change reduces the reservoir volume and allows a good mixing of the fresh gases with the exhaled gases. However, this system is less efficient than the Mapleson B system. Because, as there is no tube to maintain the separation of the alveolar and dead space portions of the expired gas, therefore the whole of the expired volume is mixed in the reservoir bag. So, the inspired mixture contains more the expired alveolar gas than the Mapleson B. Thus, a fresh gas flow more than 2.5 times of the minute volume is required to prevent rebreathing. It is, however, a very convenient arrangement for ventilating a patient before intubation or to assist chest physiotherapy in intensive care unit.

Mapleson – D

Actually this circuit looks like a T-piece. The T-piece has three way tubular connection − a patient connection port, a fresh gas port and a port for connection to the corrugated tubing with a reservoir bag and an APL valve for expiration. The Mapleson D system is popular, because the scavenging of excess gases is relatively easy in this circuit and it is the most efficient of all the Mapleson systems during controlled ventilation. For scavenging a large bore tube can be attached to the adjustable pressure limiting (APL) valve. The fresh gas inlet is located near the patient end of the circuit and the pop-off expiratory valve is close to the reservoir bag, i.e., away from the patient end. While in A, B and C Mapleson system the pop-off expiratory valve is situated close to the patient. The length of the expiratory tube is determined by the distance which the anaesthesiologist wants to maintain from the patient, but this length has minimal effects on the ventilation. The sensor or the sampling site for respiratory gas monitor may be placed between the bag and its mount, between the corrugated tubing and the T-piece or between the corrugated tubing and the APL or pop-off valve. In adults, it may be placed between the T-piece and the patient.

During the expiratory phase of spontaneous ventilation first the dead space gas, then alveolar gas and fresh gas, flow subsequently down the expiratory limb. As the pressure increases, the expiratory valve opens and a portion of the gas mixture containing dead space and alveolar gas is expelled. Patient receives a mixture of fresh gas and expired gas from the expiratory limb during next inspiration. The composition of this inspired gas mixture is determined by the rate of fresh gas flow, patient's tidal volume and the duration of expiratory pause. Slow respiratory rate with a long expiratory pause allows the fresh gas to drive out all the expired alveolar gas moving down the expiratory limb. High respiratory rate with a short expiratory pause provides inadequate time to flush out all the alveolar gas and allows rebreathing to occur. Rebreathing in this situation can be prevented by high fresh gas flows.

During the inspiratory phase of controlled ventilation, the alveolar gas and the dead space gas are also forced out of the expiratory valve, instead of the fresh gas like spontaneous ventilation. Therefore, this system also causes less rebreathing than Mapleson A, B and C systems during controlled ventilation. Recommended fresh

gas flow rates during spontaneous ventilation with Mapleson D system is approximately 2.5 times of the minute ventilation. The recommended fresh gas flow-rate for Mapleson D circuit are:

i. 2 to 3 litre/minute for patient weighing less than 10 kg.
ii. 3.5 to 4.5 litre/minute for patient weighing from 10 to 50 kg.
iii. 70 ml/kg/min for patient weighing more than 50 kg. In each of these cases, the recommended tidal volume is 10 to 15 ml / kg and the respiratory rate is 12 to 16 breaths/min.

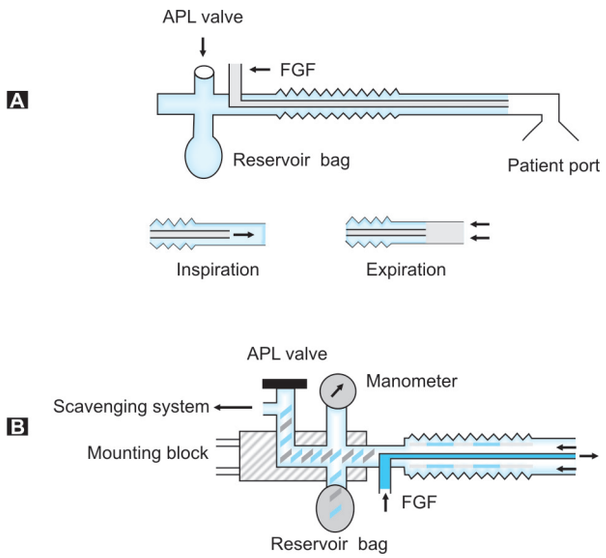
Bain's circuit

It is a modification of the Mapleson D system. It is also called the coaxial circuit, because the fresh gas flows through a narrow inner tube which is situated within the outer corrugated tube used for expiration and delivers fresh gas directly at the patient end of the circuit. The expired gas enters the corrugated outer large bore tube and is vented out through the expiratory APL valve, near the reservoir bag which is situated opposite to the patient end of the circuit. The expiratory gas does not enter the inner narrow tube, carrying the fresh gas because the pressure inside the narrow inner tube is high. The Bain's circuit may be used for both spontaneous and controlled ventilation. Like Mapleson D, to maintain normocarbia and to prevent rebreathing in the Bain's circuit, the fresh gas flow of 2.5 times of the minute volume is needed during spontaneous ventilation. But, only 70ml/kg of fresh gas flow will produce normocarbia in the Bain's circuit during controlled ventilation. Functional analysis of the Bain's circuit during spontaneous and controlled ventilation is like that of the Mapleson D circuit. In spontaneous ventilation during exhalation the expired gas mixes with the fresh gas and moves through the corrugated outer tube towards the bag. After the bag is filled with expired gas, the gas exists via the pop-off or APL valve. Then, during the expiratory pause the fresh gas also flows down the outer corrugated tubing from the narrow inner tubing and pushes the exhaled gas in front of it (Figs 15.30A and B).

In spontaneous ventilation then during inspiration the patient will inhale the fresh gas from the fresh gas inlet, the corrugated outer tubing and the reservoir bag. If the FGF is high, then all the gas which is drawn by patient during inspiration from the corrugated tube and the reservoir bag will also be fresh gas. If the FGF is low, then some exhaled gas which may be present in the outer corrugated tubing and the reservoir bag will be inhaled. So the ventilatory pattern, the FGF rate and the rate of breathing will also help to determine the amount of rebreathing.

In controlled ventilation during expiration the expired gas flows down the corrugated tubing from the patient's end. At the same time, fresh gas flow also enters the corrugated tubing. During the expiratory pause, the fresh gas flow continues and pushes the exhaled gas down the corrugated tubing towards the APL valve and the reservoir bag. During inspiration which is helped by squeezing the bag, the fresh gas and the expired gas from the corrugated tubing, enters the patient. If the fresh gas flow is low, then some exhaled gases may be inhaled from the corrugated tube with the fresh gas from the narrow inner tube. If the FGF is high, then it fills up the whole outer corrugated tube, driving out all the expired gas and the patient inhales only the fresh gas from the inner tube and the outer tube. Prolonging the inspiratory time, increasing the respiratory rate, adding an inspiratory plateau, etc., will increase the rebreathing. Rebreathing also can be decreased by allowing a long expiratory pause, so that the fresh gas can get adequate time to flush out all the exhaled gas from the outer tubing through the APL valve. When the fresh gas flow is high, there is little rebreathing. The $ETCO_2$ is determined mainly by the minute ventilation. The rate of FGF is the main factor controlling the CO_2 elimination. The higher will be the FGF, the lower will be the $ETCO_2$ level.

Bain's circuit (coaxial modification, i.e. tube within tube modification of Mapleson D system) is also available with a metal head and channels drilled



Figs 15.30A and B: Bain's modification of the Mapleson D system. The fresh gas supply tube is inside the corrugated tubing (coaxial version).FGF = Fresh gas flow, APL = Adjustable pressure limiting valve, (A) is the simple Bain's circuit, (B) is the ventilator compatible Bain's circuit permanently mounted on the anaesthetic machine

into it for permanent attachment with an anaesthetic machine. This provides a fixed position of the reservoir bag and the APL valve in relation to the anaesthetic machine. Some metal heads also have a pressure manometer. Mechanically the controlled ventilation can also be achieved by connecting the hose of an anaesthetic ventilator in the place of the reservoir bag and completely closing the APL valve. Excess gas is vented out through the ventilator.

PEEP valves or devices can also be applied with the Bain's system. A bi-directional PEEP device or valve may also be used between the APL valve and the corrugated tubing. This allows PEEP to be administered both during mechanical and manual ventilation. However, some PEEP valves close when a negative pressure is applied. So, spontaneous breathing is impossible, when such a valve is present in the system. The PEEP valve may be applied in the hose pipe leading to the anaesthetic ventilator. In this location it will only be effective during mechanical ventilation. An uni-directional PEEP valve can also be attached at the attachment site of the bag, using special connectors and unidirectional valves. Such an arrangement allows application of PEEP both during mechanical and spontaneous ventilation, but not during manual ventilation (Fig. 15.31).

Advantages of the Bain's circuit are: lightweight, convenient, can easily be sterilized, reusable and easy scavenging of the expired gases. The exhaled gases in the outer corrugated reservoir tube add warmth to the cold inspired gases passing through the narrow inner tube. In a patient weighing less than 40 kg the fresh gas flow should not be reduced below 3 litre/minute, otherwise higher $PaCO_2$ values will result. This is a reflection of the higher metabolic rate in children and infants. Hazards of the Bain's circuit include unrecognized disconnection or kinking of the inner fresh gas tube. So, the outer tube should be transparent for inspection of the inner tube.

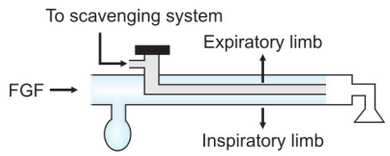


Fig. 15.31: This shows Lack's modification of the Mapleson A system

Another alternative arrangement of coaxial tubing is the Lack's circuit. Here, the fresh gas flows through the outer wide corrugated narrow tube and the expired gas flows down the central narrow inner tube. This central narrow tube runs from the connection at the patient's end to the APL valve at the machine end of the system. This makes it easier to adjust the valve and facilitates the scavenging of excess gas. However, it slightly increases the work of breathing. Actually, this is a modified configuration of Mapleson A (Magill) circuit, where a central inner tube extends from the patient's end to the APL valve. However, the same considerations like Bain circuit will govern the fresh gas flow, which is required to prevent the rebreathing in Lack's circuit. Diameter and length of the tube used in this circuit should be of low-flow resistance. The Lack circuit is suitable for spontaneous respiration and requires a lower fresh gas flow, than the Magill's circuit. The Lack system is also available in both 'dual tube'(or parallel arrangement) or 'tube within a tube'(or coaxial arrangement) arrangements, in which the narrow expiratory limb runs inside the outer wide inspiratory limb. For spontaneous ventilation, the APL or expiratory valve is kept in the fully opened position. Excess gas comes out of it during the later part of expiration. For controlled or manual ventilation, intermittent positive pressure is applied to the bag. Then, the APL valve is tightened accordingly, so that when the bag is pressed, sufficient pressure can be built-up which will be able to inflate the lungs. APL valve opens during inspiration and closes during expiration in controlled ventilation. It is opposite to the spontaneous ventilation.

Humphrey ADE System (Using Mapleson A, D and E Principle)

This is a recently described system or circuit which is available in both the coaxial and noncoaxial form. It is claimed that the Humphery system functions with the efficiency of the Lack's system for spontaneous respiration and of the Bain's system for controlled ventilation. But, it is heavier and less convenient to use. As the name implies, this ADE system works on the principle of Mapleson A, D and E circuits. In the A configuration, it acts similar to the Lack's modification of the Mapleson A system. In the D configuration, its action resembles to that of Bain's modification of the Mapleson D system. It also has a system which allows the APL valve to be bypassed in the D configuration, so that it resembles to the Mapleson E system. It has two levers and their positions determine the functioning of the system. There is a self locking mechanism which prevents the accidental displacement of any lever from their selected position. In the coaxial version, the expiratory limb runs inside the inspiratory limb (Lack system). In the noncoaxial or parallel version the inspiratory and expiratory tubes are held together at the machine end by a metal bridge. The expiratory limb consists of : a long tube which extends from the patient's end to the machine, an APL valve, a valve-bypass outlet and a lever that directs the flow of gases through either the APL valve or the valve bypass outlet. When the liver is kept at a vertical position, then the gases pass through the APL valve. On the other hand, when it is in the horizontal position, then the APL valve is isolated. Hence, gases flow through the valve-bypass outlet, like Mapleson E system. Both the outlets have a 30 mm external diameters for attachment to the scavenging devices. The valve-bypass outlet also has a 22 mm internal diameter for the attachment of a hose leading to a ventilator or a reservoir bag. A

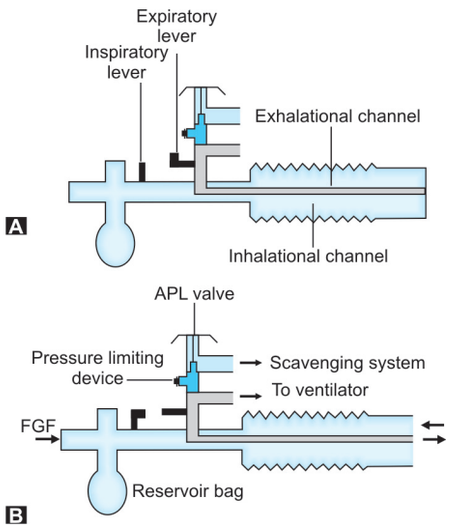
pressure limiting device may be fitted near the APL valve (Figs 15.32A and B).

The inspiratory limb consists of:

i. A fresh gas inlet,
ii. A reservoir bag,
iii. A lever
iv. A length of a corrugated tube that runs to the patient from the machine.

Gases can flow in and out of the bag when the lever is vertical. But, gas flow into the bag is blocked, when the lever is horizontal and thus makes the inspiratory limb a simple tube.

Later, a single lever Humphrey ADE system has also been developed. It is again available in both parallel noncoaxial and coaxial forms. Here, there is a single lever controlled rotating cylinder which passes through the inspiratory and expiratory limbs. When the lever is at an upright position, then the reservoir bag and the APL valve are in the circuit. Thus, the valve-bypass outlet is excluded from the circuit. On the other hand, when the lever is turned down, then the bag and the APL valve are excluded from the system. Thus, the valve-bypass outlet is connected to the system.



Figs 15.32A and B: Humphrey ADE system. The dual lever coaxial version of this system is shown here. (A) A mode ventilation, with vertical levers, (B) D and E mode of ventilation,with horizontal levers

Mapleson – E

The classical example of Mapleson E breathing system is the Ayre's T-piece with a modification of expiratory limb. Phillip Ayre first developed Ayre's T-piece in 1937 for use in paediatric patients, undergoing cleft palate repair and intracranial surgery. Mapleson E is the modification of this Ayre's T-piece with the addition of an expiratory limb. The picture shows the relationship between the fresh gas inlet, patient's end, expiratory limb and the gas exit point. It has minimum dead space, no valves, and exerts very little resistance. The expiratory limb constitutes or acts as reservoir, as there is no reservoir bag in this original Mapleson E system. If the volume of expiratory limb exceeds the tidal volume, then the breathing of room air through it does not occur and thereby prevents the dilution of anaesthetic gases with the room air, which can also occur in the original simple T-piece developed by Philip Ayre. On the other hand, if the volume of expiratory limb is less than the tidal volume of the patient, then the reverse will occur. If fresh gas inflow equals to two and half times of the minute volume of patient, then rebreathing will not occur. The actual length of the expiratory limb is irrelevant, provided it does not cause appreciable resistance to expiration and rebreathing. During expiration of spontaneous ventilation the fresh gas and the exhaled gas flows down the expiratory limb. Then, at the end of the expiration fresh gas accumulates at the patient's end of the expiratory limb. During the next breath, this fresh gas is drawn by the patient, both from the fresh gas inlet and the expiratory limb. The controlled ventilation can be accomplished by intermittent occluding of distal end of the expiratory limb (as there is no bag in this system). Squeezing of the bag attached to the end of expiratory limb (Jackson-Rees modification) can control the ventilation better.

Mapleson – F

This is the most commonly used T-piece system in anaesthesia practice. It is nothing but the Jackson-Rees modification of (Fig. 15.33) Mapleson E system. The Jackson-Rees modification is nothing but the addition of a reservoir bag at the distal end of expiratory limb of the Mapleson E system. The release mechanism is either by an adjustable valve at the distal end of reservoir

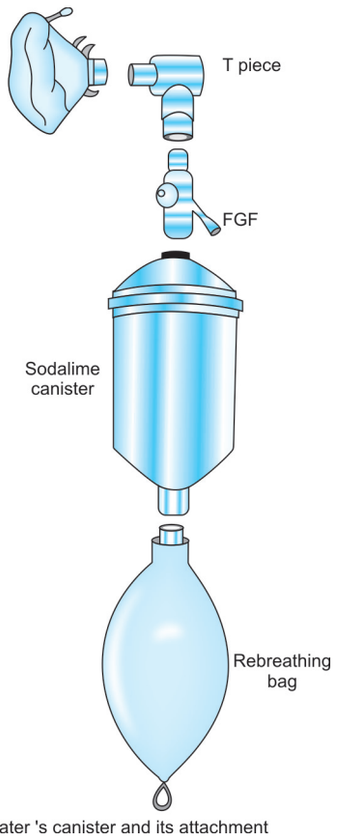


Fig. 15.33: Water's To and Fro T-piece system with carbon dioxide absorption canister which was first introduced in 1923, in clinical anaesthesia practice by Ralph Waters. It is discussed here only for its historical interest. In this system, a canister filled with sodalime was placed between the face mask and the rebreathing bag. Both inspiration and expiration took place through this canister.

This "To and Fro System" had some definite advantages. It was cheap, simple, easy to operate and easy to sterilise. It offered very low resistance and a low gas flow. Heat loss was also low as the exhaled gases were kept warm by the heat generated by a reaction during carbon dioxide absorption. It also helped in the conservation of moisture.

But, it also had some disadvantages. As the canister lay close to the head of the patient (especially a small baby), alkaline dust easily passed on to the patient. Also a heavy canister near the head of the patient was inconvenient

bag, or by an open tail (here lies the difference between Mapleson F and Mapleson E systems). Mechanism of action of this circuit is same as Mapleson D or E. The advantages of this Mapleson F system are : simple construction, inexpensive, minimal resistance and observation of the reservoir bag which allows one to inspect the respiratory excursion and also judge the depth of anaesthesia. Controlled ventilation can also be instituted easily by squeezing the bag if needed. Scavenging system of this circuit is easy. It is accomplished by enclosing the reservoir bag in a plastic chamber.

The disadvantage of this system is the lack of humidification. This problem can be overcome by allowing the fresh gas to pass through an online-heated humidifier. Another disadvantage of the Jackson-Rees modification of Mapleson E system is the need of high fresh gas flow. This system is used mainly in paediatric patients and for transportation of anaesthetized patients.

T-piece system

This is defined as a breathing circuit where the limb through which the fresh gas enters the circuit acts as the vertical limb of T and is placed between the patient's end and the expiratory end of a long tube which acts as the horizontal limb of the T. So, Mapleson A, B and C systems do not come under the T-piece system. But, this functional definition is sometimes confusing as there does not necessarily have a separate limb, leading to the expiratory port. It thus also includes some systems which physically do not look like the T-piece. As the T-piece breathing system is commonly used in paediatric anaesthesia, so resistance is of great importance. Highest resistance occurs at a peak expiratory flow, to which must be added the fresh gas flow.

T-piece system without expiratory limb

Devices of this sort of breathing circuit are mainly used with the endotracheal tube or tracheostomy tube. If the patient breathes spontaneously then no rebreathing occurs, as there is no expiratory limb where the expired gas can accumulate. So, the total amount of expired air is breathed out in the atmosphere. But, when anaesthesia is provided, then to prevent the breathing of room air due to the absence of the expiratory limb, the fresh gas flow must be equal or exceed the peak inspiratory flow rate. This is widely used for resuscitation purposes. If necessary for controlled ventilation, then intermittent occlusion of the expiratory orifice by the operator's finger affords a compact and convenient method of inflating the patient's lungs. But, in such conditions a pressure – relief valve with a water manometer is essential, as the pressure of fresh gas supply is applied directly to the patient's lungs.

Most of the T-pieces have a fresh gas entry port of narrow bore which enters the T-piece at right angles to the main respiratory channel. If high flow of fresh gas enters at an acute angle, within the T-piece then it is found that gases can be entrained in the main tube by the venturi principle. But this results in an impedance of expiration with dangerously high intrapulmonary pressure. This principle is used in a rigid bronchoscope to permit ventilation under general anaesthesia with muscle relaxants. A fine tube, mounted at the eyepiece of a rigid bronchoscope is used for O_2 delivery intermittently. The jet of O_2 entrains air and generates sufficient pressure to inflate the patient's lungs, which deflate as soon as the gas flow through the fine tube is stopped.

Now, at the end of discussion, we can conclude that the relative efficiency of different Mapleson systems with respect to prevention of rebreathing during spontaneous ventilation is like the following:

Mapleson A > D,E,F > B,C

and during controlled ventilation is like the following:

Mapleson D,E,F > B,C > A

The Mapleson A, B and C systems are rarely used now, but D, E and F systems are commonly employed. There is also some confusion regarding the recommendation of FGF in the different breathing systems with multiple variable predictions. So, monitoring of the end tidal CO_2 is the best method of determining the optimal fresh gas flow. But during monitoring it should be noted that the $PaCO_2$ to $ETCO_2$ gradient decreases with rebreathing.

PRESSURE LIMITING PROPERTIES OF THE RUBBER RESERVOIR BAG

The pressure/volume or elastic characteristic of the rubber bag which is commonly used as a reservoir in the anaesthetic circuit, constitutes a useful safeguard against the accidental build-up of dangerously high pressure in the patient's lungs which might occur if an expiratory valve is accidentally occluded. For examples if the gas flows into a BOC 2 litres rubber bag at the rate of 8 litre/minute, then the pressure rises quickly to a peak value of 30 mm of Hg and thereafter falls slightly, until it bursts after reaching a volume of more than 144 litres.

Tubing

Tubing in the anaesthetic system is usually made of corrugated walls, so that it can bend at acute angles without kinking. Regarding size 20 mm is the recommended minimum internal diameter of the tube. It must be sufficiently electrically conductive (by adding carbon to rubber) to prevent static charges to build up during anaesthesia which might produce sparking. Compliance of the tube may become an important factor. If the tube has high compliance, then a larger portion of the ventilator's stroke volume may be lost in the tubing. In patient with a very stiff lung , this may be a great problem.

The advantages of Mapleson system

i. The Mapleson system is most simple and inexpensive. In this system without the APL valve there is no moving

parts. The components of this system are easy to dis-assemble and disinfect or sterilize.

ii. This system has a buffering effect. So, any variation in the minute volume affects the end tidal CO_2 tension less than in a circle system.

iii. Rebreathing will result in retention of heat and moisture. In the coaxial system the inner inspiratory limb is heated by the warm exhaled gas in the large coaxial expiratory tubing.

iv. The resistance of this system is usually with in the recommended ranges at a given fresh gas flows which is usually used in clinical practice. So, the work of breathing during spontaneous ventilation is significantly less with these systems than with the circle system. However, this is not always true. The work of breathing increases, if the APL valve is not oriented properly.

v. These systems are of light-weight and not bulky. So, they are not likely to produce excessive pull on the endot – tracheal tube or cause accidental extubation.

vi. They are easy to position in relation to patient. A long Mapleson D system with an aluminium APL valve may also be used to ventilate a patient undergoing MRI investigation.

The disadvantages of Mapleson system

i. The Mapleson system requires a high gas flow. So, it results in higher costs, increased atmospheric pollution and difficulties in assessment of spontaneous ventilation.

ii. In this system it is difficult to determine the optimum fresh gas flow. On the other hand, it is necessary to change the fresh gas flow matching with respiratory rate from time to time during spontaneous ventilation and also while changing from spontaneous to controlled ventilation or vice versa.

iii. Anything that causes accidentally the fresh gas flow to be low then it presents a hazard, because dangerous rebreathing may occur. This has been reported with unnoticed emptying of the N_2O cylinder, a leak in the humidification device or leak of gas through a loose vapouriser-filler cap.

iv. If extra components, such as respiratory gas monitor, heat exchanger, moisture exchanger, etc, are placed between the fresh gas inlet and the patient, then a tremendous increase of the dead space area will occur. Therefore, this will cause dangerous rebreathing.

v. In the Mapleson A, B and C systems the APL valve is located close to the patient, where it is inaccessible to the user. In addition, scavenging is also difficult from this inaccessible APL valve. This disadvantage can be over – come by using the Lack's modification of Mapleson A circuit.

vi. The Mapleson systems are not suitable for a patient with increased CO_2 load, such as malignant hyperthermia. Because, it may not be possible to increase enough the fresh gas flow to remove the increased CO_2 load.

vii. Mapleson E system is notorious for air dilution. It is also difficult to scavenge the Mapleson E and F systems.

Respiratory Gas Monitoring and the Mapleson Systems

All the Mapleson systems, except the 'A' have the fresh gas inlet near the patient-connection port. This may make it difficult to get a reliable sample of exhaled gases for analysis of respiratory gases for monitoring (Fig. 15.34).

There are four possible sites from where the sampling of gases is done. These are :

i. At the junction of the breathing system and the elbow connector,

ii. At the corner of the elbow connector,

iii. 2 cm distal to the elbow conector,

iv. In the tracheal tube connector.

It is found that if the sampling is carried out at the two sites which are close to the patient, i.e. at the point 3 and point 4 of the table above, then the values are more accurate. Significant errors are noted when the samples are taken from the corner of the elbow connector (site 2). But this occurs only if a high fresh gas flow is used and not in low fresh gas flow. Significant errors are also noted when the sampling is performed at the junction of the breathing system and the elbow connector (site1), even if a low fresh gas flow is used. On the otherhand, a cannula that projects into the airway can be used to improve the sampling. In another study, involving infants and children, sampling at the junction of the tracheal tube and the breathing system resulted in a falsely low end tidal CO_2 values in patients weighing less than 8 kg. The accuracy of measurement can also be improved by inserting a small heat and moisture exchanger, between the breathing system and the tracheal tube connector. But, use of device at this site will result in an increase in dead space and may result in excessive resistance, so that spontaneous respiration cannot be used.

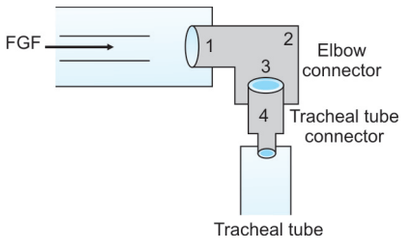


Fig. 15.34: Respiratory gas sampling site in a Mapleson system. Accurate values for expiratory concentration of gases is obtained by sampling at the sites of 3 and 4. Sampling at the site 2 will yield accurate values, only if the fresh gas flow (FGF) is not high. Sampling at the site 1 will yield inaccurate values, even at low fresh gas flows

Circle system

The circle system is the most popular breathing system in anaesthesia practice and is free from most of the drawbacks which are found in the to and fro Mapleson arrangements. It is so named, because its components are arranged in a circular manner. The circle system may be completely closed or semiclosed. The completely closed circle system prevents

rebreathing of CO_2 by the CO_2 absorber, but allows rebreathing of other exhaled gases. The extent of rebreathing of CO_2 in this system depends on the CO_2 absorption power of absorbent, component arrangement and the rate of fresh gas flow (Fig. 15.35).

In a semi closed system the APL valve is partially open and there is no rebreathing of expired gases and requires a very high fresh gas flow. Whereas a completely closed system is one in which the fresh gas flow exactly matches the volume being consumed by the patient. There is complete rebreathing of all other exhaled gases after absorption of CO_2, as all the valves are completely closed.

The circle system consists of seven components:

i. Entry site of fresh gas flow.
ii. Inspiratory and expiratory unidirectional valve.
iii. Inspiratory and expiratory corrugated tube.
iv. Y-piece connector.
v. An overflow or pop-off or damp valve, which is also called the adjustable pressure limiting (APL) valve.
vi. Reservoir bag.
vii. Canister, containing CO_2 absorbent.

Various circle arrangements are possible, depending on the relative position of these seven components. The possibilities

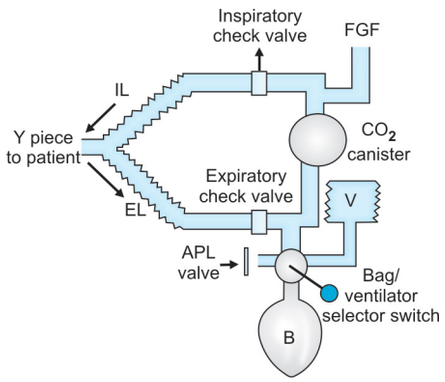


Fig. 15.35: Components of a simple form of circle system. B = Bag, V = Ventilator, FGF = Fresh gas flow, APL = Adjustable pressure limiting valve, IL = Inspiratory limb, EL = Expiratory limb

can also be reduced by considering the best possible arrangements of the 5 main components, such as unidirectional valve, APL valve, reservoir bag, CO_2 absorber and the site of fresh gas entry.

To prevent rebreathing of CO_2, three rules must be followed. They are :

Rule I

Unidirectional valve must be located both in the inspiratory and the expiratory limbs, between the patient and the reservoir bag.

Rule II

Fresh gas inflow cannot enter the circuit between the expiratory valve and the patient. Fresh gas inflow is best placed on the downstream side of the relief valve and after the canister containing CO_2 absorbent. This arrangement conserves the fresh gas which would otherwise be lost through the relief valve. It has been argued that placing the inflow site before the canister would allow the fresh gas to become humidified by the water, which is evolved with absorption of CO_2 by the CO_2 absorbent. However, this water is needed to ensure that the reaction takes place at a maximum rate. If the inlet of fresh gas is placed anywhere on the downstream side of the inspiratory valve, then the fresh gas will become mixed with expiratory gas during expiration and part of it will be ejected. If however, the inlet is placed on the upstream side of the inspiratory valve, then during inspiration any changes in the concentration of the anaesthetic gases are made effective immediately, while during expiration (when inspiratory valve is closed) the fresh gas fills up the reservoir bag. This is the position of maximum economy and efficiency.

Rule III

The over-flow (pop-off) valve cannot be located between the patient and the inspiratory valve, but must be located on the downstream side of the expiratory valve. If these rules are followed, then any arrangement of the other components does not increase the rebreathing of CO_2. The most efficient arrangement of circle system is shown in the picture, and this arrangement conserves the dead space gas and preferentially eliminates the alveolar gas. But, the more practical arrangements, used in all the contemporary anaesthetic machines, are less efficient, because it allows the alveolar and dead space gas to mix before venting. Even, with the fresh gas flow inlet fixed, there are several alternative options for position of the relief valve: (i) in the inspiratory limb, after the reservoir bag, (ii) in the expiratory limb, before the reservoir bag, or (iii) after the expiratory valve (Fig. 15.36).

There are two factors which determine the choice of position of the relief or APL valve. First, although the expired air will be blown-off in any of these three positions, but the closer the valve is to the patient, the more the gas will be pure alveolar air and also depends at the point in the respiratory cycle when the valve opens. Second, if the relief valve is placed before the expiratory valve, there is possibility of ejecting fresh gas, during the inspiratory phase of controlled and assisted ventilation. Thus, combination of these two conditions such as having the relief valve as close to the patient as possible and also on the upstream side of the expiratory valve, can be obtained if the inspiratory valves are a made part of the patient's T-piece. The practical disadvantage of this arrangement is that the

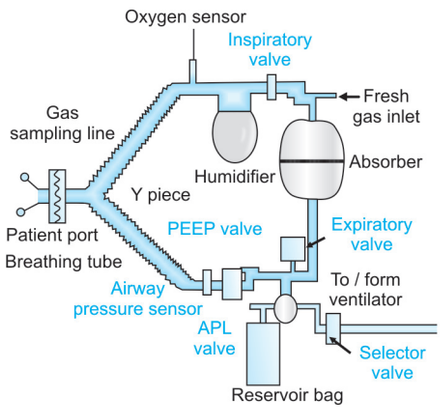


Fig. 15.36: Option for position of relief valve

connection to the patient becomes cumbersome and the operation of the valves may not be reliable, in practice. The alternative arrangement of retaining the relief valve on the T-piece connection to the patient, but moving the inspiratory and expiratory valves back to the anaesthetic machine, is economical only when the respiration is spontaneous. If the relief valve is also moved away from the patient, both alveolar and dead space gas is ejected, but the efficiency of the system is maintained only during controlled ventilation.

Circle system with low gas flow

In a circle system where components are arranged with optimum efficacy, then the expired alveolar gas is preferentially expelled from the circuit. Here, the circle system behaves like the Magill's circuit and rebreathing of CO_2 will not take place until the fresh gas flows falls below the alveolar ventilation. It is found that in the Magill's circuit the minimum fresh gas flow needed to prevent rebreathing in a spontaneously breathing patient is 3 to 4.5 litres/minute. Magill's circuit loses this efficiency when the above calculation is used for controlled ventilation. But, in an optimum arrangement of circle system the preferential elimination of the alveolar gas continues during controlled ventilation also with the same low gas flow which is sufficient to prevent rebreathing in Magill's circuit during spontaneous breathing. During commonly used conditions such as 'closed circuit with leak' and with a fresh gas flow of 4 litres/minute, it is unnecessary to have any sodalime in the canister at all. Under this condition the fresh gas flow takes over the role of the alveolar ventilation in controlling $PaCO_2$ without sodalime, even in controlled ventilation.

When the fresh gas flow is reduced to a level below the alveolar ventilation (or in some other arrangement of components where the system is not optimum) then sodalime is required in the circle system to prevent the rebreathing of CO_2. Without sodalime, when the fresh gas flow falls below the alveolar ventilation, then discrepancy develops between the inspired and delivered O_2 concentration in controlled ventilation. Calculation of the inspired O_2 concentration during the low fresh gas flow (N_2O:O_2 mixture), with considerable accuracy is possible only when a steady state has been achieved. For this reason, monitoring of the inspired O_2 concentration in the circuit is necessary.

Totally closed system

The circle system can also be used in a completely closed manner. After a period of about 10 minutes of breathing with high inflow of fresh gas, which brings about denitrogenation, the expiratory valve can be completely closed and the only fresh gas flow into the system is the patient's basal O_2 requirement together with the anaesthetic agent. Such a system was widely used when cyclopropane was in extensive use and if the O_2 (not N_2O) is the only gas which is flowing, apart from the other liquid anaesthetics. In such circumstances no monitoring is required, except for the usual close observation of the patient.

Advantages of the circle system (Totally closed or partially closed)

1. Reduction of atmospheric pollution

Once the expiratory valve is totally closed, then no anaesthetic gas escapes into the air to pollute the enviornment except a very small percentage which are lost through the different leaks. During totally closed halothane anaesthesia, concentration of halothane in the theatre does not rise above 0.03 ppm. In a partially closed system there is some atmospheric pollution, but this can be prevented by a scavenging system.

2. Economical

In a totally closed system the consumption of any volatile anaesthetic agent and fresh gas flow is very low. For example, the consumption of halothane in an adult patient is about 3.5 ml/hour and the fresh gas flow is about 250 ml O_2/minute. So, it is very economical.

3. Humidification

Intubation bypasses the normal physiological mechanism for humidification of the inspired gas. But, in the circle system with a CO_2 absorber, the inspired gas will be fully saturated with water vapour nearly at a body temperature.

4. Reduction of heat loss

Close circuit conserves the loss of heat of body. Because, the sodalime gets hot during use and thus the circuit actively assists in maintaining the temperature of inspired gas and thus the patient's body temperature.

5. Ease of monitoring

If O_2 is the only fresh gas flow into the completely closed circuit, then the patient's O_2 uptake is easily determined. Then, it is just the flow which is required to keep the volume in the circuit constant. Any change in this rate would be quickly noticed by the volume and movement of the bag. This would give an early warning of the onset of malignant hyperpyrexia. Patient's tidal volume can be assessed more accurately by the observation of the reservoir bag in a totally closed circuit, because there is no high flow of gas to affect the bag's movement.

Disadvantages of the circle system

The major disadvantage of the circle system stems from its complex design. Misconnections, disconnections, obstructions and leaks are the principle problems of this system. Malfunctioning of the valves can also cause serious problems. If the valves stick in an open position, then rebreathing occurs. On the other hand, if the valves are stuck closed, total occlusion of the circuit with high expiratory resistance occurs. In such circumstances, breath stacking and tension pneumothorax can occur.

N_2O in a Totally Closed System

The N_2O agent can be used in a totally closed system, but very cautiously and in a sophisticated manner. It is found that uptake of N_2O by body is about 500 ml/min in the first two minutes. Then, it falls to about 200 ml/min after ½ hour, and 100 ml/min after about an hour. After that, it tends to remain constant at about 50 to 100 ml/hour, due to inevitable losses through the skin and the wound. The complete saturation of body tissues by N_2O takes about 5 hours. At the end of a three hour operation, during which an inspired concentration of 70% N_2O has been used, an average adult will absorb 20 to 26 litres of N_2O, dissolved in his tissues. The fall in uptake of N_2O by the body from a closed circle system will be indicated by a gradual decrease in the inspired O_2 concentration, and the gradual increase in the inspired N_2O concentration in the circuit, which necessitates continuous readjustment of the O_2: N_2O ratio. So, N_2O should never be used in a totally closed circuit, without O_2 and N_2O analyzer.

CARBON DIOXIDE ABSORPTION

History

The idea of CO_2 absorption techniques in anaesthesia by the sodalime or other agents came from the submarine and chemical warfare. It was first applied during World War I, necessitating effective gas masks. Then in 1915, Wilson had patented the new sodalime with increased efficiency. But, CO_2 reabsorption technique in anaesthesia was slow to gain popularity, until the cyclopropane which was then an expensive gas was introduced in this discipline (Table 15.17).

Chemistry

Sodalime and baralyme are the two most important agents which are commonly used for CO_2 absorption in anaesthesia practice. The recently introduced chemical as CO_2 absorbent is calcium hydroxide lime. Of these three agents, the most commonly used is the sodalime. Calcium hydroxide lime consists primarily of $Ca(OH)_2$, $Ca(Cl)_2$ and two other setting agents such as calcium sulfate and polyvinyl pyrolidine. The latter two chemicals enhance the hardness and porosity of the granules of calcium hydroxide lime and increase its efficacy. The most significant advantage of calcium hydroxide lime over the other two agents used for absorption of CO_2 is its lack of sodium and potassium hydroxides as compositions. The absence of these two chemicals in calcium hydroxide lime eliminates the undesirable production of carbon monoxide and the nephrotoxic substance, such as: compound A by the reaction of halogenated anaesthetic agents with it.

Table 15.17: The desirable features of the agents for CO_2 absorption mechanism

1. Lack of toxicity with common anaesthetics,
2. Low resistance,
3. Low cost,
4. Easy handling,
5. High efficacy.

Sodalime consists of 94% $Ca(OH)_2$, 5% NaOH and 1% KOH. But, the precise proportion of these compounds differs for different manufacturers. The composition of best effective, 'high moisture' sodalime is 80% $Ca(OH)_2$, 15% H_2O, 4% NaOH and 1% KOH. Some silica is also added in it to produce the calcium and sodium silicate which makes the product hard and reduces the dust formation. But, the hardness and CO_2 absorption power of any agent varies inversely. In this CO_2 absorbent (soda lime) the NaOH acts as the active component for CO_2 absorption and KOH acts as an activator. In the first step, CO_2 reacts with water to form carbonic acid which then reacts with sodium and potassium hydroxide to form sodium and potassium carbonate. This chemical change requires the presence of some moisture which is provided by the patient's expired gases and at the same time produces heat. The $Ca(OH)_2$ then reacts with Na_2CO_3 and K_2CO_3 to form calcium carbonate and regenerate NaOH or KOH.

$$CO_2 + H_2O \leftrightarrows H_2CO_3$$

$$H_2CO_3 + NaOH \text{ (or KOH)} \rightarrow Na_2CO_3 \text{ (or } K_2CO_3) + H_2O + \text{Heat}$$

$$Na_2CO_3 \text{ (or } K_2CO_3) + Ca(OH)_2 \rightarrow CaCO_3 + 2\ NaOH \text{ (or KOH)}$$

Some CO_2 directly reacts with the $Ca(OH)_2$ to form (Table 15.18) calcium carbonate. But, this reaction is very slow. In the early days it was noted that sodalime could regenerate its efficacy automatically, even after being exhausted. But, the explanation for this regeneration is very complex and is of little clinical importance today. Regeneration is rarely seen nowadays, because of the improved quality of sodalime with less silica and addition of potassium hydroxide.

Water is required in every step of reaction. But, moisture which is provided to sodalime from the patient's expired air does not chemically combine with it. It is probably present as a thin film of NaOH solution on the surface of $Ca(OH)_2$. The sodium and potassium hydroxide is hygroscopic, but calcium hydroxide is not. The moisture threshold of both the sodalime and baralyme for the effective absorption of CO_2 is 10%, and the optimum efficiency of absorption of CO_2 in sodalime is obtained with a hydration of 14% to 19%. When the sodalime is exposed to room air, then it loses its moisture and subsequently efficacy falls rapidly. So, it must be stored properly.

Table 15.18: Specifications of sodalime

Contents	$Ca(OH)_2$	94%
	NaOH	5%
	KOH	1%
Moisture		More than 14%
		Less than 19%
Hardness		Greater than 75
Size of granules		4 to 8 mesh

Baralyme is composed of 80% $Ca(OH)_2$ and 20% $Ba(OH)_2$. It may also contain some KOH. It is more stable than sodalime and does not need any silica binder. But, it is 15% less efficient than sodalime, based on the weight basis. Baralyme contains water as barium hydroxide in the octahydrate form, $Ba(OH)_2\ 8H_2O$, on its surface. So, it may perform better in a dry climate. Because of this, the baralyme is more stable when exposed to dry atmosphere than sodalime. For this reason, baralyme is used to absorb CO_2 in the space capsule, despite it been less efficient than soda lime. The optimum water content for best reaction of baralyme is 11 to14%. The reaction of CO_2 with baralyme differs from sodalime in that more water is liberated during direct reaction of barium hydroxide with carbon dioxide. This CO_2 next reacts with water to form H_2CO_3.

$Ba(OH)_2 + 8H_2O + CO_2 \rightarrow BaCO_3 + 9H_2O$ + Heat

$H_2O + CO_2 \rightarrow H_2CO_3$

Then, by a direct reaction like with KOH and NaOH, Carbonic acid (H_2CO_3) reacts with $Ca(OH)_2$ to form a carbonate.

$H_2CO_3 + Ca(OH)_2 \rightarrow CaCO_3 + H_2O$ + Heat

Like sodalime, baralyme too has no regeneration capability. The granular size of the sodalime or baralyme used in anaesthesia practice varies between 4 and 8 mesh. This is an optimum size at which resistance to airflow is negligible. This is also the optimal size balancing between the resistance and the absorptive capability. The smaller the granules, the more is the surface area available for absorption of CO_2, but the airflow resistance will also increase. The larger the granules, the reverse occurs. Mesh refers to the number of openings per linear inch in a sieve through which the granular particles can pass. A 4 mesh screen means that there are four 0.25 inch openings per linear inch. An 8 mesh screen means that there are eight 0.125 inch openings per linear inch. The hardness number of the granules is 75.

Theoretically, the amount of CO_2 that should be absorbed is 26 litres per 100 gm of absorbent (sodalime or baralyme). However, this is not true in practise because the direct channeling of gas through the granules of the absorbent decreases its efficiency. Thus it actually allows only 10 to 20 litres of CO_2 to be absorbed with an average of only15 litres. The 100 gm of sodalime will absorb about 15 litres of CO_2 before the concentration of CO_2 in exit gas exceeds 1%. From this it can be calculated that 1 kg of soda lime is sufficient for 8 hours. On the other hand the absorptive capacity of calcium hydroxide lime has been reported to be 10 litres of CO_2 per 100 gm of absorbent (Table 15.19).

Indicators

The indicators are the chemical compounds which are used to assess the functional integrity of another channel compound. The pH indicators act on the principle of the changes in pH. The pH indicator which is commonly used for both the soda lime and baralyme to assess their functional integrity is the ethyl violet or triphenylmethane dye. The critical pH value of this indicator is 10.3. It means that above or below this pH level, the colour of this indicator will change. The pH of a fresh absorbent remains above the critical value and the ethyl violet indicator in this CO_2 absorbent exists in a colourless form. Ethyl violet changes from colourless to violet when the pH of the absorbent decreases below 10.3 as a result of CO_2 absorption. In such circumstances, base of the indicator reacts with the carbonic acid which is produced in the absorbent after absorption of CO_2 to form a soluble carbonate which is violet in colour. Indicators are not always reliable for functional status of the absorbent. Fluorescent light can also deactivate the indicator, so that the absorbent appears white even though it is exhausted.

Table 15.19: Different colours of indicators

Indicators	*Soda lime*	
	Fresh	*Exhausted*
Mimosa-Z	Red	White
Phenolphthalein	Colourless	Pink
Clayton yellow	Pink	Yellow
Methyl orange	Orange	Yellow
Ethyl violet	Colourless	Purple (violet)

The final proof of efficacy of a particular sodalime canister's contents can only lie in the periodic testing of the gases flowing through it for the possible presence and percentage of CO_2. Examples of other indicators are: methyl orange, phenolphthalein, clayton yellow, etc.

Canister

It is a container, made up of a transparent plastic to see the (Fig. 15.37) changes of colour of its contents such as sodalime or baralyme with indicators. It is mounted vertically in the machine. The size of the canister is no longer critical and it can be made considerably larger for a longer period of life. But, the optimum size of the canister which is commonly used clinically is 18 cm in height and at least 12 cm in diameter. The capacity of the canister is 2 litres and there is an annular ring which prevents the channeling of gas between soda lime and the canister wall.

The gas flow in the canister is from above downwards and the upper chamber is exhausted first. Once the upper chamber of the canister is exhausted, the lower chamber is placed up and fresh soda lime should be placed in the lower compartment, resulting in a highly efficient use of sodalime. To reduce condensation in the canister and to prevent the sodalime from becoming caked, air spaces are provided at the top and the bottom of the canister. The heat which is produced inside the canister due to the absorption of CO_2 is known as the 'heat of neutralization'. The rise in temperature of up to 60°C have been recorded inside the canister.

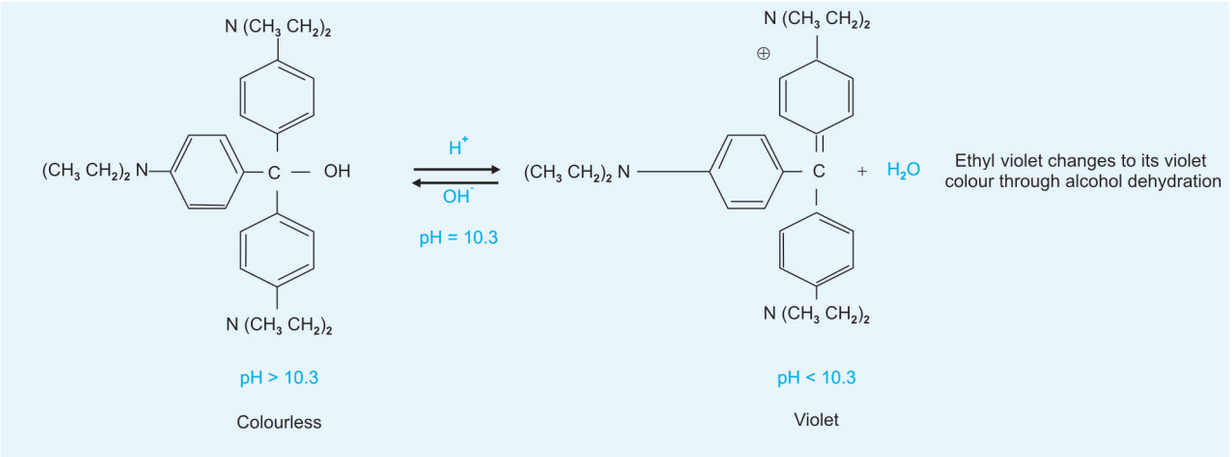


Fig. 15.37: Changes of coloured contents

The production of some heat is a sign that sodalime is functioning efficiently. There is also an overall increase in the weight of the contents of canister which amounts to about 33% when they are completely worn out.

Absorbents and Anaesthetic Agents

There is always some reactions between the CO_2 absorbents and the newer halogenated volatile anaesthetic agents. Halothane, isoflurane, sevoflurane and desflurane are all degraded to some extent by the CO_2 absorbants. But among them, the most extensive degradation occurs with sevoflurane and the degradation product is called 'compound A'. There are some factors which increase this degradation products. These are:

i. Higher concentration of sevoflurane,
ii. Low fresh gas flow,
iii. Higher temperature of the absorbent,
iv. Use of baralyme instead of sodalime,
v. Drying of the absorbent.

The significance of these degradation products is still controversial. The CO_2 absorbents also absorb the volatile anaesthetic of anaesthesia agents. So, they cause slower induction of anaesthesia and later subsequent exposure of the patient to these volatile anaesthetic agents when their use is stopped. Dry absorbents absorb more volatile anaesthetic agents, than the wet one. When volatile anaesthetic agents are used with absorbents, there is more production of carbonmonoxide CO. The concentration of CO increases in the following condition.

i. Increased length of time of use,
ii. Dry absorbents,
iii. Use of baralyme, instead of sodalime,
iv. Concentration of the anaesthetic agent,
v. Higher temperature of the absorbents.

The CO formation is maximum with desflurane which is followed by isoflurane. The amount of CO formed by sevoflurane and halothane is same and very little. Sevoflurane mainly produces 'compound A'. Moisture in the absorbant reduces CO formation. However, the respiratory gas monitors which are used currently cannot detect the CO directly.

Induction and Nitrogen Elimination

The elimination of body N_2 by O_2 during induction is very essential. So, for the first 3 to 5 minutes a high flow of 100% O_2 is necessary. This will reduce the nitrogen concentration in the lungs and breathing system to less than 5%. Fresh 100% O_2 flow can then be reduced. Only the N_2 is dissolved in the tissues, then is diffused back into the alveolar gas. The volume of the dissolved N_2 in an average adult is approximately 1litre and it takes about five hours for the entire body N_2 to be abstracted. In a low flow and semiclosed system, N_2 escapes through the release valve. In a totally closed system, N_2 will accumulate and may constitute as much as 15% of the circuit gas after an hour. However, this is of no consequence, provided N_2O is not given in a totally closed system.

VAPOURISERS

Introduction

Most of the inhalational anaesthetic agents which are used today are liquids at the normal atmospheric pressure and room temperature. So, they must be converted into gas or vapour, before they are used. A vapour is the gaseous phase of a chemical agent that is liquid at room temperature and normal atmospheric pressure. Thus, a vapouriser is an instrument which is developed to change a liquid anaesthetic agent into its vapour or gaseous form and deliver a controlled amount of this vapour or gas to the fresh gas flow. As many as three types of vapourisers are now commonly used and attached to an anaesthetic machine.

Simultaneously, with the development of different types of volatile anaesthetic agents different types of vapourisers also have been evolved. It has initially started from the rudimentary open-mask ether inhalers, and then passes through the EMO

and copper kettle vapouriser to finally reach (Table 15.20) the temperature-compensated, variable-bypass vapourisers. In 1993, with the introduction of desflurane in anaesthesia practice even more sophisticated vapourisers (Tec – 6 and Aladin cassette) were also introduced to handle the unique physical properties of this agent. But, operating principles of every vapouriser depends on the same physical characters of the volatile anaesthetic agents. These physical characters are : vapour pressure, latent heat, specific heat, thermal conductivity.

Physics

Vapour Pressure

When a volatile liquid is kept inside a container closed to the atmosphere, then few molecules of this liquid breaks away from the upper surface of the liquid and enters the space above. Thus, vapour of this liquid is formed. If the temperature of the container is kept constant, then a dynamic equilibrium is developed between the liquid and the vapour phase of this agent at that temperature. In that situation, the number of molecules in the vapour phase of this volatile agent remains constant and the pressure created by the bombardment of the molecules against the wall of container is also constant. Now, the pressure of this vapour is called the 'saturated vapour pressure' at that temperature and pressure. After that, if more heat is applied to the liquid, then the equilibrium is shifted more to wards the vapour phase, so that the more and more molecules enter the vapour phase from the liquid phase of this anaesthetic agent and the vapour pressure rises. On the contrary, if the heat is taken away from the anaesthetic liquid, then more and more molecules enter from the vapour phase into the liquid phase of the agent and vapour pressure falls. This causes a shifting of the equilibrium towards the liquid phase. During delivery of anaesthesia when a carrier gas is passed over a volatile anaesthetic liquid, then the equilibrium shifts to the vapour phase. The vapour pressure of a volatile liquid depends on the temperature and atmospheric pressure and the character of the lquid. So, it is useless to talk about the vapour pressure without mentioning the temperature and pressure. At the boiling point of a liquid, the vapour pressure and the atmospheric pressure is same at that temperature.

Boiling point

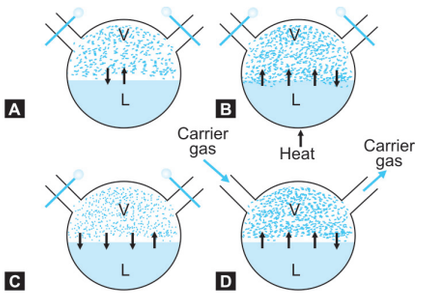
Boiling point of a liquid is defined as the temperature at which its vapour pressure becomes equal to the atmospheric pressure. Or conversely, during gradual increase in temperature of a liquid when the vapour pressure and atmospheric pressure becomes same, then this temperature will be called as the boiling point. The lower the atmospheric pressure, the lower will be the boiling point and higher the atmospheric pressure, the higher will be the boiling point (Figs 15.38A to D).

Concentration of gases

To express the concentration of gases or vapours, two methods are commonly used. These are : partial pressure in mm of Hg or volume in percent (%).

A mixture of many gases in a closed container will exert a total constant pressure on the walls of it. The part of this total pressure which is exerted on the wall of the container by the individual gas in the mixture is called the partial pressure of that gas in this mixture. Hence, the total pressure of the gas mixture is the sum of the partial pressures of each of the constituent gases.

Volume in percent to express the concentration of gas is defined as the number of units of volume of a particular gas in relation to the total 100 units of volume of the total gas mixture. In a mixture of gases each constituent gas exerts a pressure which is directly proportional to its percentage of volume of that gas in the total volume of the mixture. The volume percent expresses the relative ratio of volume of different gases in a gas mixture. Whereas, partial pressure of a gas expresses an absolute value.



Figs 15.38A to D: This figure depicts the changes in vapour pressure, with variations in temperature.
A: shows that the vapour and liquid phases are in equilibrium.
B: shows that the equilibrium shifts towards the vapour phase. Because, heat is applied and more molecules enter from the liquid into the vapour phase.
C: shows that the equilibrium shifts to the liquid phase. Because, cooling of liquid causes more molecules of vapour to enter the liquid and thus reduce the vapour pressure.
D: also shows that the equilibrium shifts to the vapour phase. This is because the carrier gas passes over the liquid. The liquid takes the energy for the molecules to break away and to form vapour. Thus vaporisation gradually removes the molecules from the liquid, which have more energy and the temperature of the liquid falls, as vaporisation proceeds. So, a gradient of temperature will be created between the liquid with the surroundings, and heat will flow from the surroundings to the liquid. This heat is called the heat of vaporisation. It is defined as the number of calories necessary to convert 1 ml of liquid into vapour

Table 15.20: Properties of common volatile anaesthetic agents important for vapourisers

Agent	*Boiling point (0°C)*	*Vapour pressure (mm of Hg)*	*Heat of vapourisation (cal/ml)*	*Specific heat of liquid (cal/ml)*	*MAC in O_2 (%)*
Halothane	50.2	243	65	0.35	0.75
Isoflurane	48.5	238	63	0.35	1.15
Sevoflurane	58.6	157	–	–	2
Desflurane	22.8	669	–	–	6.4

Partial pressure ÷ Total pressure = volumes percent ÷ 100

Although the concentration of a gas or a vapour in a mixture is most commonly expressed as volume in percent, but patient uptake or the depth of anaesthesia are directly related to the partial pressure of the gaseous phase of the agent.

Latent heat

Latent heat of vapourisation is defined as the number of calories required to change 1 gm of liquid into vapour, but without any change in the temperature. This latent heat for vaporisation comes from the liquid itself, or from an outside source. In the absence of outside energy (heat) sources the surrounding air gives the required heat to the anaesthetic liquid for its vapourisation. So, the water vapour in air condenses outside the Boyle's vapourising glass ether bottle and Goldman vapouriser which is not used now in modern anaesthetic machine. Thus, the temperature of the anaesthetic liquid falls and vapourisation is reduced.

Specific heat

The specific heat of a substance is the number of calories required to increase the temperature of 1 gm of a substance by 1°C. The concept of specific heat is important for the design and construction (metal) of vapourisers by the following two ways:

i. It indicates how much heat should be supplied to the liquid to maintain a constant temperature when the heat is lost during vaporisation,
ii. Manufacturers select the metal to build the vapourisers that have a high specific heat. Because it will supply more heat to minimize the temperature changes associated with vaporisation.

Thermal conductivity

The thermal conductivity of a metal is defined as the speed with which the heat flows through this substance. Vapourisers are made of metals of high thermal conductivity which helps to maintain a uniform temperature.

Types of Vapourisers (Table 15.21)

1. Open mask

The basic requirement of all the anaesthetic vapourisers is that they should convert the volatile liquid anaesthetic agents into a continuous flow of anaesthetic vapour of this liquid. Then, it is mixed with air or some other carrier gas under controlled conditions. The simplest form of vapouriser is a gauze pad which is usually fitted on a wire frame. It acts as the wick and a partial reservoir of the volatile anaesthetic liquid. The patient's respiration through the gauze pad, which is soaked with a liquid volatile anaesthetic agent, results in a flow of anaesthetic vapour which is at a saturated vapour pressure level near the gauze. But, it is subsequently diluted as air is entrained passing though the gauze. The temperature of the anaesthetic liquid in the gauze pad will drop below the atmospheric level, because the heat required for vaporisation will be greater than that available from the immediately surrounding air. Some control of the situation can be obtained by controlling the rate at which the anaesthetic liquid is dropped onto the gauze of mask, and the distance between the gauze pad and the patient's face (i.e., the amount of diluting air entrained). It is also fortunate that the main agent administered by open-mask is diethyl ether which does not dramatically depress the respiration (Figs 15.39A and B).

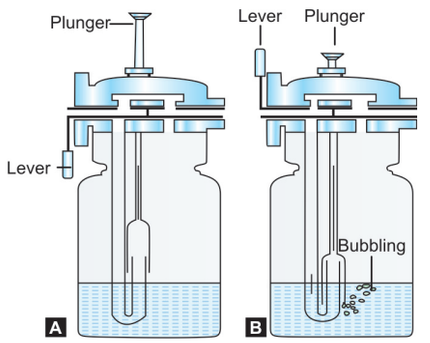
Table 15.21: Classification of different vapourisers

According to method of vapourisation
a. Open drop
b. Bubble through
c. Flow over
d. Injection
According to the regulation of output concentration
a. Concentration calibrated
b. Bypass flow calibrated
According to the compensation of temperature
a. Thermocompensation
b. Supplied heat

2. Uncalibrated vapourisers

When the use of compressed gas in metal cylinders was introduced into the practice of anaesthesia, then it became possible to contain the liquid anaesthetic agents in a bottle. Then, it also became possible to bubble the gas through the liquid anaesthetic agent, or blow it over its surface for vaporisation. Thus this bottle or container containing liquid anaesthetic agent is called vapouriser. This vapouriser is sometimes also called a plenum vapouriser. Because, gas is being forced into a chamber and plenum is a chamber in which the pressure is greater than outside.

In the Boyle's vapourising glass bottle used for anaesthetic liquid ether, the stream of fresh gas flow directed to the patient is divided into two. The main bypass stream passes straight without coming into contact with the anaesthetic liquid present in the bottle. The second carrier gas stream is passed over the surface or as bubble through the liquid anaesthetic agent kept in a bottle and reunited with the bypass stream. The ratio of the carrier gas to the bypass gas is determined by the position



Figs 15.39A and B: This figure shows uncalibrated vapourisers.
A: The cowl is not fully impinged in the liquid, so it is a Blow-Over type of vapouriser.,
B: The cowl is fully impinged in the liquid, so it is a Bubble-Through type of vapouriser

of the control knob. Again, the position of the plunger, controlled by the anaesthesiologist will determine how closely the stream of the carrier gas will pass over the surface of the liquid anaesthetic (blow-over) agent or whether it actually bubbles through the liquid. In a simple vapourisers of this kind the control of the splitting ratio of the carrier gas by the control knob, is not accurate. It is usually very non linear and there is wide variation between the different instruments. Also, as the latent heat of vaporisation is taken from the liquid anaesthetic agent, so there is also cooling of the liquid which reduces the resulting vapour concentration with passing of time. A number of factors, such as gas flow rate, volume of liquid in the bottle and the atmospheric temperature also influence the rate of vaporisation. So the resulting concentration of anaesthetic vapour received by the patient cannot be predicted with accuracy as it will not match with the indicator's number of control knob. Agitation of the bottle due to any cause will produce a big increase in vapour concentration, even without bubbling. Finally, when the bottle is not used for long time, then the total internal gas space over the volatile anaesthetic liquid becomes filled with the saturated anaesthetic vapour. Then, the initial concentration of the anaesthetic agent when the control lever is first turned on will be unexpectedly dangerously high. This happens particularly when the bottle is surrounded by a warm water bath which is sometimes done to avoid the reduction in anaesthetic concentration, produced by cooling of both the liquid and bottle.

Though, there are considerable draw backs, still the wide spread use of these uncalibrated vapourisers indicate their relative safety. Their safety feature lies in the fact that the anaesthetic vapour concentration falls with time, due to cooling of the anaesthetic liquid. Since, the concentration of vapour they produce is not accurately known, so its anaesthetic effect can only be estimated by noting the volume of anaesthetic liquid being used (vapourised) and close continuous observation of the patient.

The Goldman halothane vapouriser is another type of very simple uncalibrated vapouriser, which is most commonly used today for halothane in less sophinsticated machine and all the physics which is discussed till now should also be applied here. Actually, it was designed for use in an intermittent flow machine. It can also be used inside a circle anaesthetic system. It has a small volume. It offers a low resistance to gas flow, because it was initially intended for use during spontaneous respiration. It is an inefficient vapouriser without temperature compensation. The maximum halothane output of this vapouriser is about 3%. It has also been used successfully in a totally closed anaesthesia circuit.

3. Oxford vapouriser (Fig. 15.40)

This vapouriser is discussed here only for its historical interest. It was developed by Robert Macintosh in collaboration with Morris Motors for use by the Armed Forces in 1940. To increase the concentration of ether vapour the condensation of moisture outside the ether bottle during its vaporisation at the expense of latent heat can be prevented by placing a jacket of warm water around the ether glass bottle. Alternatively, the ether can be kept constantly above its boiling point (36.5°C), so that the ether vapour in the container is under pressure and is trying to escape. Then a fixed amount of ether vapour controlled by a knob is is allowed to come out mixed with the carrier gas to obtain a known percentage of ether vapour which is delivered to the patient. This principle was used in the construction of the Oxford vapourisers. Here ether was surrounded by chemical crystals of calcium chloride with a melting point above that of ether, which was again surrounded by warm water. Once these crystals melted due to the warm water, ether vapour would come out spontaneously (Fig. 15.41).

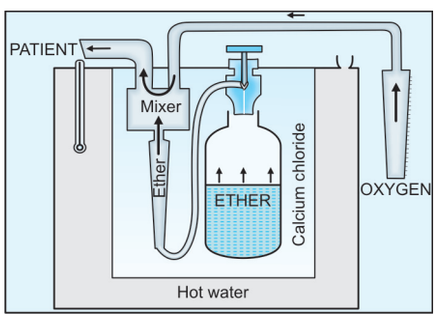


Fig. 15.40: Oxford vapouriser

4. Copper kettle vapouriser

This was commonly used in the past at North America. It is also discussed here for historical interest. In this type of vapouriser an O_2 supply, separate from the main supply, is metered and is passed through a copper vessel (for rapid heat transfer) containing a liquid anaesthetic agent. The gas passes through a fenestrated bronze disc which breaks it up into very fine bubbles. Thus, the gas becomes fully saturated during its passage through the anaesthetic liquid. The temperature of the anaesthetic liquid is measured by a thermometer. From the graph of saturated vapour pressure against this temperature, the concentration of the anaesthetic vapour coming out from the vapouriser can be calculated. Now the volume of gas passing through the vapouriser fully saturated with anaesthetic vabour is known. So, the final concentration of anaesthetic vapour in the mixture reaching the patient can be simply calculated. It may be adjusted finely as required by changing the gas flow rate through the vapouriser. This type of

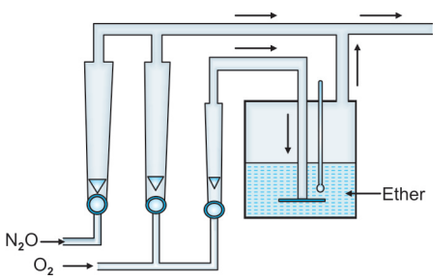


Fig. 15.41: A copper kettle vapouriser

vapouriser is capable of a high degree of accuracy than the simple Boyel's galss bottle vapouriser. The same apparatus may be used for all the types of volatile anaesthetic agents.

5. Draw-over vapourisers

Any vapouriser where the inspired gases is drawn over the surface of a volatile anaesthetic liquid which is kept in a container and offers sufficiently low resistance (1 to 2 cm of H_2O is a satisfactory figure) to gas flow at a normal respiratory flow rate, may be called as a draw-over (Fig. 15.42) vapouriser. The patient inspires air via the vapouriser and expiration is directed to the atmosphere by a nonrebreathing valve. A simple tin can, filled with an anaesthetic liquid may be used as a draw-over vapouriser. A vapouriser which has been specially designed for this purpose is the EMO (Epstein Macintosh Oxford) vapouriser. In this vapouriser ether is used as the anaesthetic agent. In this system a tank of water is used as a heat reservoir and the temperature compensation is made by a bellows filled with ether. It can be combined with an Oxford inflating bellows for intermittent positive pressure ventilation (IPPV). When the plunger is not dipped in the anaesthetic liquid, then the uncalibrated glass bottle vapouriser used in old Boyle's machine also acts as the draw over type of vapouriser.

Draw-over apparatus (Fig. 15.43)

This equipment was developed during the First World War, especially for field use

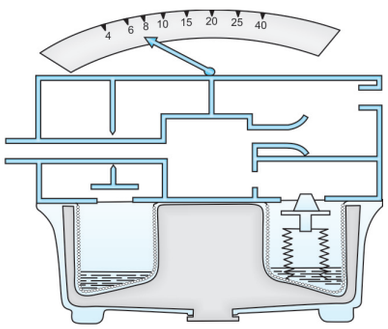


Fig. 15.42: EMO vapouriser

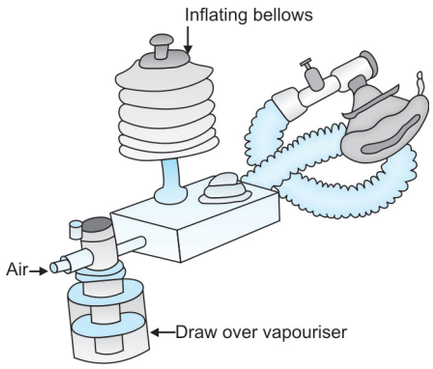


Fig. 15.43: Draw-over apparatus

where nitrous oxide was not available and portability was an important factor. In this apparatus, coffee jars, food tins, or any small cans were used as vapourisers keeping the volatile anaesthetic liquid. The patient who is intubated and under spontaneous ventilation breathed to and fro through this coffee jar used as vapouriser containing ether. Later, it was improvised and a control over the vapour strength coming out from the vapouriser was achieved. This draw-over device had a non rebreathing circuit to direct the expired gas to atmosphere and used ambient air as the carrier gas which enter from other side of the coffee jar (another end of the jar is attached to breathing circuit). Supplemental O_2 could be used, if available.

In its most basic application, air is drawn through a low resistance draw over vapouriser which may be made of a glass bottle or coffee jar, food tins or any small can which was used in First World War. For vaporisation, a suitable low resistance vapouriser, such as the EMO vapouriser may also be placed in the circuit instead of food tins. The device can be fitted with connections and equipments that allow IPPV, as well as CPAP and PEEP with a scavenging system. The N_2O can never be used with draw-over devices. Patients often manifest an oxygen saturation (SpO_2) < 90%. This can be treated with supplemental O_2, attached to a T – piece at the upstream side of the vapouriser. Across the clinical range of tidal volume and respiratory rate, an O_2 flow rate of 1 litre/minute gives an FiO_2 of 30 to 40% or with 4 litre/minute an FiO_2 of 60 to 80%. The greatest advantage of the draw-over system is its simplicity and portability. But the main disadvantage is the absence of a reservoir bag. So, the depth of the tidal volume is not well appreciated during spontaneous ventilation.

6. Variable bypass vapourisers

The variable bypass vapouriser is also called the concentration-calibrated, direct-reading, dial-controlled, automatic – planum, percentage-type and TEC-type (TEC type means Temperature Compensated) vapourisers. The other designation of these variable bypass vapouriser are blow-over, agent-specific and out-of-the breathing circuit vapourisers. Tec 3, Tec 4, Tec 5 and Tec 7 (different model of Ohmeda company) vapourisers are some examples of such vapourisers. They are such named, according to the improvisation of the model by the company. There are also such variable bypass vapourisers of other companies, such as Dragger of North America (vapour 19.1), Sigma and Penlon of UK, etc. However, the model of Tec 3 vapourisers of different companies (Flutec Mark 3, Fortec 3, Enfluratec 3, Sevotec III) are no longer manufactured at present.

The term 'variable bypass' refers to the method of regulating the output of the vapour of volatile anaesthetic agent in different concentration. When the delivered gas after the rotameter flows through the vapouriser's inlet, then the setting of the concentration control dial of vapouriser determines the ratio of flow that goes through the bypass channel without entering the vaporizing chamber that goes through the vaporising chamber. The gas which is channeled through the vaporising chamber flows over the surface of the liquid anaesthetic agent and becomes saturated with the anaesthetic vapour. So, the term 'blow-over' refers to this method of vaporisation (in contrast to the

bubble-through type of vaporisation in Copper Kettle). The term 'temperature-compensated' is applied to this type of vapouriser because every vapouriser is equipped with an automatic temperature compensating device that helps to maintain a constant vapouriser output concentration of volatile anaesthetic agent over a wide range of temperature variation. The mechanism is discussed in Chapter 1 and in this chapter. All these type of vapourisers are agent specific, because all the volatile anaesthetic agents have their own different vapour pressure at certain temperature. So, the control dial controlling the entry of carrier gas in the vaporising chamber and then thus subsequently controlling the concentration of output of anaesthetic agent is marked accordingly. Hence, they are designed to accommodate a single agent and any agent cannot be used in any vapouriser. However desflurane cannot be used by this variable bypass type of vapourisers the cause of which is explained later. These variable bypass vapourisers are usually calibrated using O_2 as the carrier gas. But, even if air is used instead of O_2 then there is no change in output also. On the otherhand, addition of N_2O as a carrier gas results in change of vapouriser output (Fig. 15.44).

These vapourisers are also called the level-compensated vapourisers. Because, one of the sources of variability of output from a simple vapourisers which are not level compensated is the change in the level of the anaesthetic liquid as it is used up. To prevent this variability of output with the change in the level of anaesthetic liquid these level compensated vapourisers use wicks. If the vaporising chamber contains wicks which are constantly wetted by contact with the anaesthetic agent, then not only the vaporisation will be more efficient, but it will also be constant (apart from the temperature effects) until the level of the liquid anaesthetic falls so low that the wicks are no longer wetted. The vapouriser using wicks in this way is described as the level-compensated vapouriser (Fig. 15.45).

The vapour pressure of a particular volatile anaesthetic agent depends on the temperature. For example, at 20°C the vapour pressure of isoflurane is 238 mm of Hg, whereas at 35°C the vapour pressure of isoflurane is 450 mm of Hg (almost double). So, at a fixed dial-setting with variation of temperature, the output of the anaesthetic gas will also vary. So, all the modern vapourisers should be temperature-compensated to keep the outflow constant by regulating the gas entry into the vaporizer. Actually, the temperature compensating devices are bimetallic strips. At an increased temperature this bimetallic strip change its shape and moves in one direction. This movement allows more flow to pass through the bypass chamber, and less flow to pass through the vaporising chamber. On the other hand when the temperature falls due to vaporisation of the liquid anaesthetic, the opposite occurs. Thus, the net effect is a constant vapouriser output. So, vapour pressure at a certain fixed temperature which is a physical principle of individual anaesthetic agents is important for a constant vapouriser output.

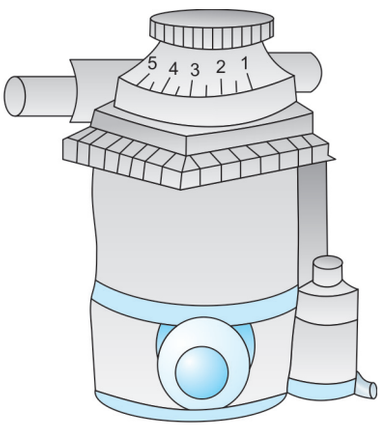


Fig. 15.44: Tec-3 halothane vapouriser

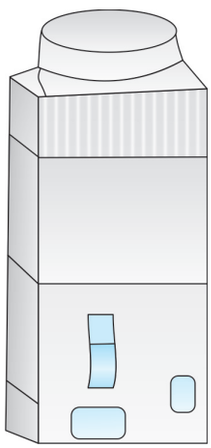


Fig. 15.45: Tec-5 vapouriser specific for isoflurane, halothane and sevoflurane

At 760 mm of Hg pressure (normal atmospheric pressure), the boiling point of desflurane, isoflurane, halothane and sevoflurane are approximately 22.8°C, 48.5°C, 50.2°C and 58.5°C, respectively. Desflurane boils at a temperature that may be encountered at normal room conditions. So, this unique physical characteristic alone mandates a special vapouriser (Tec 6) for desflurane to vaporise and control the delivery of that agent. From the above discussion it is clear that the output of an individual volatile agent depends on its vapour pressure and the temperature. Thus, the resetting dial is graduated accordingly depending on vapour pressure of that agent. So, every vapouriser is agent specific.

Though these variable bypass vapourisers have many advantages, but still they have some limitations. These limitations are: non-compensated for flow-rate, non-compensated for intermittent back pressure and dependent on the carrier gas composition. As these variable bypass vapourisers are not flow-rate compensated so the output variation of the volatile anaesthetic agent is particularly noticeable at the extremes of flow rate. The output from these type of vapourisers is less than the dial setting, when the flow rate is less than 250 ml/min. Similarly, at an extremly high flow rate (15 l/min) the output is also less than the dial setting.

Intermittent back pressure during IPPV or O_2 flushing can cause lower or higher vapouriser output than the dial setting. This phenomenon is called the pumping

effect. The pumping effect is more pronounced at low flow rates, low dial setting, low level of liquid anaesthetic agent in the vaporising chamber, high respiratory rate and high peak inspired pressure. The proposed mechanism for this pumping effect is the retrograde pressure transmission from the patient's circuit to the inside of the vapouriser during the inspiratory phase of positive pressure ventilation, i.e. when the bag is compressed.

However, this pumping effect can be minimized in a number of ways. These include the fitting of a small pressure regulating valve at the vapouriser output and keeping the vaporising chamber as small as possible. The Tec 3 model has a controlling resistance at the outlet of the vaporising chamber, so that the back pressure goes around the bypass and not through the vaporising chamber. In addition, a long inlet pipe to the vaporising chamber prevents vapour from the chamber to get back into the bypass gas stream by this route. This method to prevent the pumping effect is used in the Drager vapouriser.

Vapouriser output is also influenced by the composition of carrier gases that flow through the vapourisers. For example, when the carrier gas is switched over from 100% O_2 to 100% N_2O, then there is a rapid transient decrease in vapouriser output due to slow vaporisation of anaesthetic liquid followed by a slow increase to a new steady state value. This is because other than temperature, atmospheric pressure and character of anaesthetic liquid. The vaporisation of an anaesthetic liquid depends on the composition of gas that blows over it. Most vapourisers are calibrated using O_2 as the carrier gas. Generally, a little change in output occurs if air is substituted for O_2. Addition of N_2O to the carrier gas typically results in both a temporary and a long lasting effect on vapouriser output. The temporary effect is usually a decrease in vapour concentration. The duration of this effect depends on the gas flow rate and the volume of liquid in the vapouriser. The permanent effect may be an increase or decrease, depending on the construction of the vapouriser (Fig. 15.46).

7. TEC 6 Vapouriser

It is a different kind of variable bypass vapouriser and is only used for desflurane for its peculiar physical properties. Boiling point of desflurane is 22.8°C which is around normal room temperature. So, in normal room conditions it may start to boil and remains in a transitional phase between liquid and gas. Thus, its vapour pressure is 3 to 4 times higher than that of the other contemporary volatile anaesthetic agents at 20°C. That is why desflurane cannot be used in contemporary different models of variable bypass vapourisers (Tec 4, Tec 5 and Tec 7; Tec 3 model is obsolete now). Again, normal gaseous flow over desflurane in a traditional vapouriser would vaporise many more volume of desflurane than the dial setting. For example, at normal atmospheric pressure (1 atmosphere) and 20°C, passing over of 100 ml of a carrier gas for 1 min through the vaporising chamber will entrain 735 ml/min of desflurane vapour in comparison to 46 and 47 ml/min of isoflurane and halothane vapour, respectively. This is due to difference in vapour pressure at 20°C of desflurane, isoflurane and halothane which is 669, 240, 244 mm of Hg, respectively. Under the same condition, the amount of bypass flow to dilute the flow which is coming over the anaesthetic fluid and necessary to achieve 1% concentration of an anaesthetic desflurane output is approximately 73L/min compared with 5L/min for isoflurane, halothane and sevoflurane.

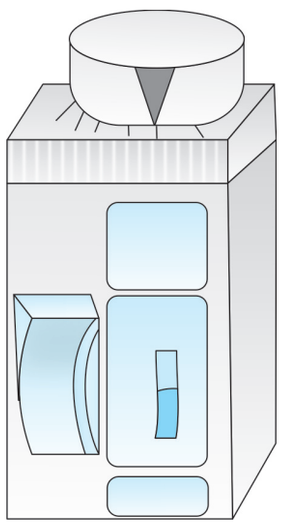


Fig. 15.46: Tec-6 vapouriser (specific for desflurane)

The MAC value of desflurane is 6 to 7 which is 4 to 9 times higher than the commonly used volatile anaesthetic agents. So, the absolute amount of desflurane needed over a given period of time is considerably higher than the other anaesthetic agents. Thus, the supplying of desflurane in higher concentration causes excessive cooling of the vapouriser. So, in the absence of an external heating source, the temperature compensation by using traditional temperature compensated variable bypass vapouriser where simple bimetalic strip is used is almost impossible. Hence, Tec 6 vapouriser requires an external electrical source for heat.

The Tec 6 vapouriser is also flow-compensated. So at a specific dial setting with different fresh gas flow rates, vapouriser output is constant (other variable bypass vapourisers are only temperature-compensated but not flow-compensated Actually the traditional vapourisers are flow compensated in certain limited range such as 250mL/min to 15 L/min). Thus, to conclude we can say that the Tec 6 vapouriser is an electrically heated, temperature and flow compensated, pressurized, electromechanically coupled, dual circuit vapouriser. This is not a blow-over type of vapouriser (other Tecs are all blow-over types).

In Tec 6 vapouriser, two circuits for gas flow are used (dual circuit). One circuit carries the main gas flow (carrier gas) without any bypass chamber. In another circuit there is a container which contains the desflurane in vapour phase. This is done by heating the desflurane electrically and controlling thermostatically at 39°C

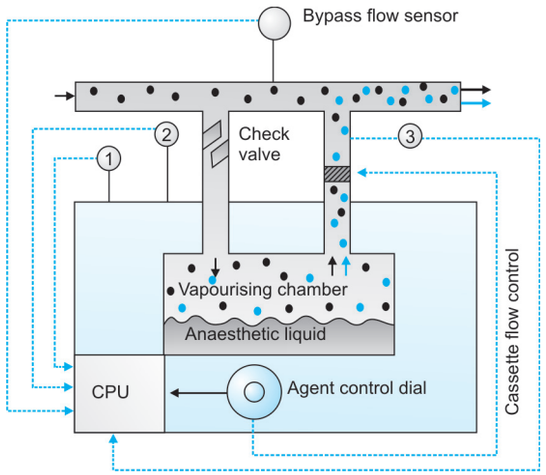


Fig. 15.47: Aladin's cassette vapouriser
1 = Cassette pressure censor,
2 = Cassette temperature censor,
3 = Cassette flow censor,
CPU = Central processing unit.

(a temperature well above the desflurane boiling point). Then the output flow and concentration of desflurane vapour is controlled electronically and is mixed with the main carrier gas flow at the main vapouriser outlet.

8. Aladin cassette vapouriser (Fig. 15.47)

It is a very sophisticated, electronically controlled vapouriser which is designed to deliver five different types of volatile anaesthetic agents, including halothane, enflurane, isoflurane, sevoflurane and desflurane. This type of vapouriser has two main components : a permanent internal control unit or anaesthetic delivery unit (ADU) and an interchangeable Aladin agent cassette unit that contains the volatile anaesthetic liquids

Aladin agent cassettes are colour coded, so that the control unit (ADU component) can identify the specific anaesthetic cassette which is inserted. The heart of the control unit has a electronically regulated flow-control valve, located at the vaporising chamber outlet. This flow-control valve is controlled by a computer (CPU) which receives information from the multiple sources such as agent's concentration control dial located by the side of the CPU, a pressure sensor located inside the vaporising chamber, a temperature sensor located inside the vapourising chamber, a flow measurement unit located in the bypass chamber, a flow measurement unit located at the outlet of the vaporising chamber and a gas analyser regarding the composition of the carrier gas. Using data from all these multiple sources, the CPU is able to precisely regulate the flow control valve to attain the desired vapour concentration of the anaesthetic agent.

Technically, the Aladin cassette vapouriser is a combination of Tec 4, 5 and 7 variable bypass vapourisers, along with the Tec 6 vapouriser and a computer. When desflurane is not used in the Aladin vapouriser, then the carrier gas passes over the anaesthetic liquid in the cassette and the vapouriser works like blow-over type (Tec 4, 5 and 7), but all the parameters are controlled by the computer. On the other-hand, when desflurane is used then Aladin works like a Tec 6 vapouriser, where carrier gas doesnot pass over the anaesthetic liquid. The bypass chamber is cut off from the cassette containing desflurane and the whole unit works as a dual circuit (like Tec 6). One circuit caries the carrier gas and another circuit carries the desflurane anaesthetic vapour from the cassette where like in Tec 6 the desflurane is always kept in a vapour form by a computer controlled electronically heating system at 39°C. The flow and concentration of desflurane is now under the computer control and at the outlet it mixes with the carrier gas.

16 Muscle Relaxants and their Antagonists

HISTORY

- The hint of the presence of these type of drugs such as curare or muscle relaxants first came to the ears of the world, in 1596, when Sir Walter Raleigh mentioned an 'arrow poison' in his book named 'Discovery of the Large, Rich and Beautiful Empire of Guiana'.
- Then 200 years later, in 1812, Sir Benjamin first showed that the life of animals could be maintained by artificial respiration, after they were paralysed or curarised by arrow poison. His source of curare was the bark, leaves, or vines of a tree named Chondrodendron Tomentosum, growing near Amazon. Also before that it had long been used by Amazonian Indians to poison the heads of arrow (arrow poison) for hunting of animals. Later on, they transported this poison to the different parts of the world in bamboo tubes, from where the name tubocurarine (curare in tube) was derived.
- Curare was first brought to the Europe by Charles Waterton. He also described a classic experiment, in which he kept alive a curarised she-ass by artificial ventilation with bellows and a tube introduced through a tracheostomy wound.
- Then, in 1850, the great French physiologist named, Claude Bernard had laid the most important scientific foundation stone. He demonstrated that curare acts by paralysing the myoneural junction. Later, this led to the discovery of concept of motor end-plate.
- During this period, George Harley also showed that curare can be used as an antidote to the convulsion of strychnine poisoning.
- After that, in 1858, a decade after the anaesthetic use of ether, Lewis Albert used curare and artificial verification through a tracheostomy to treat the muscular rigidity of tetanus in Newyork.
- Then, in 1862, curare was first used in American Civil War as chemical weapon.
- After that another foundation stone of anaesthesia was laid in 1864, when physostigmine was isolated from the calabar bean by Sir TR Fraser. But, at that time he was not aware of the anticurare action of physostigmine.
- Then, in 1900, the discovery of anticurare action of physostigmine by Jacob Pal had completed this basic foundation work, on which basis the relaxants are used later clinically in that century. Physostigmine was first used for animal experiment in 1909. Then, in 1912, curare entered the anaesthetic arena and was first used by Aurthur in an effort to reduce the amount of ether, employed for abdominal surgery. At that time the subparalytic doses of curare were used and produces only the relaxation of the abdominal wall, but did not prevent the respiratory movement of diaphragm.
- In 1931, Neostigmine was synthesised.
- In 1934, Dale demonstrated that acetylcholine (ACh) was responsible for the neuromuscular transmission and curare blocks its action.
- In 1935, pure d-tubocurarine was isolated from the crude drug.
- In January 23rd of 1942, at Montreol of Canada, appendisectomy was done under cyclopropane anaesthesia, where d-tubocurarine was first used through IV route, deliberately to give relaxation during surgery. This was a famous day in the history of anaesthesia. During this period the muscle relaxant was used with the idea to provide a greatly relaxed surgical field without the need for large doses of hypnotics and opiate drugs. Thus, the cardiovascular side effects of these anaesthetic agents could be minimised and allowed the very sick patients to get the benefit of surgery.
- The first reported use of curare in routine anaesthesia practice was from Britain in 1945.
- Gallamine was first used in 1948.
- In 1948, decamethonium was also described.
- In 1952, succinylcholine or suxamethonium was first used as muscle relevant and had revolutionised the anaesthesia practice.
- In 1958, alcuronium was first described and used in man.
- In 1967, pancuronium had first come into the anaesthetic arena.
- In 1980, atracurium and vecuronium had further revolutionised the clinical anaesthetic practice.
- The early 1990 had witnessed the introduction of pipercuranium and doxacurium.
- Mivacurium was introduced in 1993 and rocuronium in 1994.

CHEMISTRY OF MUSCLE RELAXANT

According to the chemical structure, most of the muscle relaxants have two positive charged N^+ atoms and so they mimic the quaternary nitrogen (N^+) atom of ACh which acts as the neuromuscular transmitter at the motor end-plate. This is the main reason for the attraction of these molecules of muscle relaxant agents to the cholinergic or acetylcholine receptors at the motor end-plate like acetylcholine. The cholinergic receptors are broadly classified as muscarinic and nicotinic type. In the peripheral nervous system the nicotinic receptors are found postsynaptically at the neuromuscular junction and at the autonomic ganglia. On the other hand muscarinic receptors are found only at the postganglionic parasympathetic nerve endings and some postganglionic sympathetic nerve endings such as sweat gland, erector pile, etc. Muscle relaxants act on the nicotinic receptors only at the neuromuscular junction and autonomic ganglion. Most modern muscle relaxants are specific for these nicotinic receptors with limited effects on other cholinergic receptors, found at the peripheral nervous system, the autonomic ganglia and the parasympathetic effector organs. As all the neuromuscular blocking agents have a quaternary ammonium structure containing nitrogen, so these are maximally ionised at the physiological pH and therefore penetrate the blood brain barrier poorly (Table 16.1).

The two positive charged N^+ atoms of a muscle relaxants are separated by a bridging structure which is lipophilic in nature. This bridging structure is different in size for different muscle relaxants and is the major determinant factor for potency and other pharmacokinetic properties of these group of drugs. Most of the muscle relaxants are highly water soluble. This is due to the positive charge of the molecule and contain various O_2 bearing group. Because of their water solubility, most of the muscle relaxants are easily excreted through urine by glomerular filtration and are generally not reabsorbed through the renal tubules. High water solubility of muscle relaxants also prevents its passage through the lipoid blood brain barrier, placental barrier and lipoid cell membrane of most of the cells, such as, renal tubular cells, hepatocytes, nerve cells, muscle cells, etc. Except few steroidal muscle relaxants, most are not metabolised by the liver due to two reasons: (i) water solubility of muscle relaxants which inhibits its uptake by the hepatocytes and (ii) cytochrome p – 450 oxidative enzyme system in the liver microsome which requires lipophilic substrates for their metabolism. The muscle relaxants used in anaesthesia practice are broadly classified under two heading according to their mode of action. These are: depolarising muscle relaxants and non-depolarising muscle relaxants. Among the depolarising group of muscle relaxants, there are many drugs, but succinylcholine is only and mostly used clinically.

SUCCINYLCHOLINE OR SUXAMETHONIUM (DIACETYLCHOLINE)

Succinylcholine is a quaternary ammonium compound. It is entirely a synthetic product. In contrast to the heavy bulky rigid molecules of non-depolarising muscle relaxants, the structure of this molecule is long, thin and flexible. It is made up of two acetylcholine molecules linked back to back. Like acetylcholine, it also depolarises the postsynaptic membrane. But, its effect on the motor end-plate is more persistant than that of acetylcholine. However, though the action of succinylcholine is like ACh, such as muscular contraction, but the prolonged action of it on the nicotinic receptor at motor end plate produces the muscular paralysis the mechanism of which is discussed in specific chapter. Now, succinylcholine is the only depolarising muscle relaxing agent which is still in clinical use. Though the demise of succinylcholine has been forecasted many times, but it is still widely used in clinical practice because of some unique properties such as earliest (still now) onset and shortest duration of action.

Succinylcholine produces depolarising block which is characterised by:

i. Absence of fade in response to train-of-four and tetanic stimulation (Fig. 16.1).
ii. The absence of post-tetanic facilitation,
iii. Increased intensity of block in the presence of anticholinesterase or cholinesterase inhibitors.

Table 16.1: The cholinergic receptors and its sites and the action of relaxants on it

Receptors	*Location*	*Function*	*Relaxant - interactions*
Nicotinic	Postsynaptic neuromuscular junction	Depolarisation of end-plate – muscle contraction	Succinylcholine – stimulates Non-depolarisation – block
Nicotinic	Presynaptic neuromuscular junction	Helps release of ACh	Succinylcholine – stimulates Non-depolarisers – block
Nicotinic	Autonomic ganglion	Depolarisation of ganglionic cell	Succinylcholine – stimulates Non-depolarser – block
Nicotinic	Postganglionic neurone terminal	Positive feedback for transmitter release	Succinylcholine – stimulates Non-depolariser – block
Muscarinic	SA node of heart	↓ heart rate	Succinylcholine stimulate – ↓ HR Non-depolariser block – ↑ HR
Muscarinic (M_1)	Autonomic ganglionic interneuron cell bodies	Inhibition of depolarisation	Non-depolariser block
Muscarinic (M_2)	Autonomic ganglia: Ganglion cell bodies	Depolarisation	Atropine blocks Non-depolarisers do not act

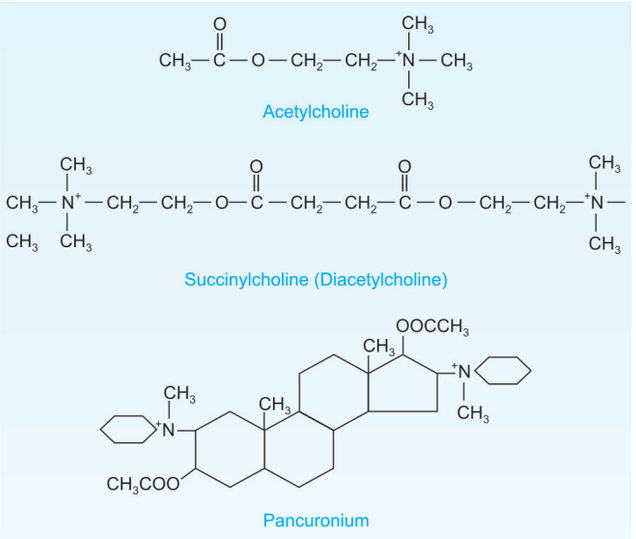


Fig. 16.1: The structural relationship between the acetylcholine, succinylcholine and pancuronium. The succinylcholine is simply a two molecules of acetylcholine, linked through the acetate methyl groups. So, it is called the diacetylcholine. Like acetylcholine, succinylcholine also stimulates the nicotinic cholinergic receptors at the neuromuscular junction, at the ganglionic sites and also on the muscarinic receptors at other autonomic sites. The pancuronium is also made up of acetylcholine like fragments, but properly oriented like a steroid nucleus. But, in contrast the pancuronium and other non-depolarising agents block the nicotinic receptors or inhibit the actions of acetylcholine at the motor end-plate (neuromuscular junction) and autonomic cholinergic sites

Mechanism of Action

Like acetylcholine (ACh) succinylcholine is not metabolised at the motor end-plate by true cholinesterase which are present there. So, the concentration of succinylcholine does not fall as rapidly as ACh in the synaptic cleft. Thus, it causes prolonged depolarisation of the motor end-plate and muscle relaxation, till it swept away from the synaptic cleft. The continuous depolarisation of the motor end-plate by succinylcholine causes muscle relaxation. This is due to the Na^+ channels which are present around the motor end-plate (perijunctional area) and have time sensitive lower gate which opens only during depolarisation for a fixed time period. During the passing of first wave of depolarisation from the motor end-plate to the whole muscle fibre (casing fasciculation) these perijunctional Na^+ channels are also depolarised and time sensitive lower gate opens that allows the passage of Na^+ which is a process of depolarisation. Then it closes after a fixed time period and enters in inactivated state and cannot further reopen until the end-plate repolarizes. The motor end-plate due to prolonged action of succinylcholine do not quickly repolarise after its depolarisation caused by it. Thus, the perijunctional Na^+ channel which make a baricade around the motor end-plate remains in inactive state. Hence, this line of Na^+ channel at the perijunctional area prevents the passage of subsequent impulse which comes through nerve fibre to spread on the surface of muscle fibre and prevents the contraction of it producing paralysis. On the otherhand, the muscle end-plate does not repolarise and continue depolarisation till the succinylcholine is present and thus maintain the muscular relaxation. This is called the 'phase I block'.

If the depolarisation of the muscle end-plate is prolonged further due to repeated injection and large dose of succinylcholine, then the ACh (or nicotinic) receptors at the motor end-plate undergo an ionic and conformational changes that result in 'phase II block' like non-depolarising muscle relaxant, i.e, ion channel in the ACh receptor close permanently with no flow of ions and becomes insensitive to ACh even in the absence of succinylcholine providing prolonged muscular paralysis. On the contrary, the non-depolarising muscle relaxants act on the ACh receptors and does not allow them to open the channel for ion movement from the very beginning and thus produce muscle relaxation. When the molecules of non-depolarising muscle relaxant are moved away from the receptor (nicotine) then ACh again acts on the receptor and resume muscular contraction. The site of action of non-depolarising agents is the ACh binding site of the α-subunit of the nicotinic ACh receptors. However, there are two binding sites of the non-depolarising muscle relaxant on the ACh receptor as there are two α-subunits in one ACh receptor. But, occupancy of only one subunit by non-depolarising agent is sufficient for their action.

This explains the difference in action or the effects of depolarising and non-depolarising muscle relaxing agents in different disease states. For example, during muscle denervation there is decrease in release of ACh. It stimulates the compensatory increase in ACh receptors on the muscle cell membrane. This upregulation of receptor causes an increased sensitivity of muscle to the depolarising agents as more receptors are being depolarized. But, the non-depolarising agents show a resistance in response, as more receptors are needed to be blocked. For another example, in myasthenia gravis there is fewer ACh receptors. This downregulation demonstrates a resistance to the depolarising agents and exaggerated response to the non-depolarising agents.

There are also some agents which act on the ACh (or nicotinic) receptors at the motor end-plate and block these receptors to produce neuromuscular paralysis but not like agonistic (succinylcholine) or antagonistic (non-depolarising) agents. They function by not disturbing the ACh binding sites of the ACh receptors. The example of such agents are: inhalational anaesthetics, local anaesthetics, ketamine, some antibiotics, neostigmine, quinidine, etc. There are

of two types of block of ACh (or nicotinic) receptor through which the above mentioned agents act. These are: close channel blockade and open channel blockade. In close channel blockade the molecules of the agents plug the mouth of ACh receptor channel and prevent the ion movement, whether or not the receptors are activated by ACh. In open channel blockade the neuromuscular blocking agents enter the ACh receptor channel after its opening and plug it preventing ion movement. So, it is use dependent and acts after the ACh activates the receptor and opens the channel. The significance of this channel blockade (closed or opened) is that such neuromuscular block cannot be overcomed by increasing the concentration of ACh by cholinesterase inhibitors. All these are discussed in more details in Chapter 4.

Pharmacokinetics and Pharmacodynamics

Succinylcholine is the only available depolarising muscle relaxing agent which is still used clinically and is very popular, though the popularity is under eclipse now. The popularity of it is due to: (i) very rapid onset of action (30 to 60 seconds), and (ii) short duration of action (5 to 10 minutes for the dose of 1 to 1.5 mg/kg IV). According to the initial bolus dose the duration of action of succinylcholine vary. For example, in dose of 0.5 mg/kg through IV the duration of action is only 3 to 5 minutes, though the onset of action remain same.

It is assumed that the rapid onset of action of succinylcholine is due to the relative large dose that is administered initially. As it is more water soluble and less lipid soluble, so this property prevents the drug to pass easily through the lipoid cell membrane and hence it needs the (Table 16.2) higher doses. After an initial IV bolus doses, a large portion of succinylcholine is rapidly hydrolysed by pseudocholinesterase present in plasma and then a small portion of it is distributed to the motor end-plate in the tissues. This also explains why large doses of succinylcholine is needed initially.

Plasma cholinesterase (pseudocholinesterase) is synthesized in the liver and has a half-life of 5 to 12 days. It hydrolyses or metabolises 70% of a 100 mg bolus dose of succinylcholine within 1 minute. Other drugs metabolised by plasma cholinesterase include mivacurium, cocaine and diamorphine. Only a small fraction of the injected dose of succinylcholine (10 to 15%) reach the neuromuscular junction. As there is no pseudocholinesterase at the motor end-plate, so the neuromuscular blockade by the action of succinylcholine at the neuromuscular junction is terminated only by its diffusion away from the end-plate into the extracellular fluid, where it is metabolised by the pseudocholinesterase. Only the action of acetylcholine is terminated at the motor end-plate by the action of cholinesterase (true) which is present there. Rapid hydrolysis of succinylcholine by pseudocholinesterase (synthesised by liver) in plasma is the cause of brief duration of action of it. Other than plasmacholinesterase the succinylcholine is also metabolised in liver. In the liver succinylcholine is metabolised first to the succinylmonocholine. Much of the succinylmonocholine have weak neuromuscular blocking effect and appear in urine.

The neuromuscular blocked produced by syccinylcholine can be prolonged by

Table 16.2: Drugs which cause the decrease of pseudo (plasma) cholinesterase level

i.	ACh E inhibitors	Neostigmine, pyridostigmine
ii.	Organophosphate use in glaucoma	Echothiophate
iii.	Cancer agent	Cyclophosphamide
iv.	MAOI	Phenozine
v.	β-blocker	Esmolol
vi.	Antiemetic agent	Metoclopramide
vii.	Oral contraceptive	Estrogen, progesterone
viii.	Non-depolarising muscle relaxant	Pancuronium, vecuronium, atracurium, etc.

the reduced quantity of normal or typical pseudocholinesterase enzyme (acquired cause) or by the normal quantity of atypical pseudocholinesterase enzyme (inherited cause). The acquired factors that cause lower typical pseudocholinesterase level in plasma are: liver disease, pregnancy, oral contraceptive pill (due to high oesterogen level), ecothiophate, neostigmine, edrophonium cytotoxic drugs, neoplasia, burns, metoclopromide, bambuterol (a prodrug of terbutaline), malnutrition and elderly, etc. The reduced typical plasma cholinesterase activity can also occur when some drugs which share the same metabolic pathway as succinylcholine (therefore compete with succinylcholine for the cholinesterase enzyme) are administered such as esmolol, MAOI, methotrexate, etc. However, the prolongation of neuromuscular block in these conditions is not very long. Very prolonged block is, however, associated with the presence of silent or atypical genes in homozygous individuals producing atypical pseudocholinesterase enzyme (inherited cause). The neuromuscular block in these cases (atypical enzyme) lasts for several hours, until the succinylcholine is broken down completely by the presence of little amount of normal enzyme (if present any) and eliminated very slowly through urine.

Ranitidine has no effect on pseudocholinesterase level. In a study, it is found that when the pseudocholinesterase level was reduced to 20% of the normal value, then the only duration of apnoea caused by succinylcholine is increased from 3 to 9 minutes.

Atypical Plasma or Pseudo Cholinesterase (Table 16.3)

Though a vast majority of the population possess the normal level of typical plasma or pseudocholine esterase enzyme, but rarely some patients are encountered who are either heterozygous or homozygous for the atypical gene. There are four principal autosomal dominant genes which are associated with

Table 16.3: Different genotype of plasma or (pseudo) cholinesterase

Genotype	*Figure*	*Action*
Usual\ (or typical)	E^u	Normal hydrolysis of succinylcholine
Atypical	E^a	Dibucaine resistant
Atypical	E^f	Fluoride resistant
Atypical	E^S	Complete lack of cholinesterase activity (silent)

Table 16.4: Incidence of Genotype

E^u E^u	Homozygous	95%
E^u E^a	Heterozygous	5%
E^u E^f	Heterozygous	0.5%
E^u E^s	Heterozygous	0.5%
E^a E^a	Homozygous	0.05%
E^a E^f	Heterozygous	0.005%
E^f E^f	Homozygous	0.0003%
E^f E^s	Heterozygous	0.0005%
E^s E^s	Homozygous	0.002%

Table 16.5: Different genotype and dibucaine number

E^u E^u	70-80
E^u E^a	
E^u E^f	50-60
E^u E^s	
E^a E^a	
E^a E^f	15-30
E^f E^f	
E^f E^s	
E^s E^s	0-5

the normal and atypical plasma or pseudocholinesterase enzyme. But more genes are also described recently. These four principal autosomal genes, responsible for plasma or pseudocholinesterase enzyme (normal and atypical) are designated as : E^u , E^a, E^f , E^s. Among these the only E^u gene is responsible for the typical pseudo or plasma cholinesterase enzyme and the normal hydrolysis of succinylcholine. Over 95% of the whole population have this normal genes and are homozygous who are designated as (E^u, E^u). Whereas the E^a, E^f, E^s genes are responsible for atypical type of pseudocholinesterase enzyme and cannot hydrolyse the succinylcholine or hydrolysis it partially. Normally, the succinylcholine is not resistant to inhibition by dibucaine and in homozygous person (E^u, E^u) the dibucaine number is 70 to 85. This is a method of assessment of the level or activity of typical pseudocholinesterase. The significance of which is discussed in more detail later. The duration of action of succinylcholine will be prolonged, if varieties of atypical genes are present and typical pseudocholinesterase is not produced in normal quantity. The commonest of these variation is the presence of atypical gene E^a in heterozygous form which is present in about 4% of the population. An individual who is heterozygous for this atypical gene (E^u, E^a) may have a slightly prolonged neuromuscular block following a bolus dose of succinylcholine (up to 30 minutes). But if the patient is homozygous (E^a E^a), he will remain paralysed for several hours after administration of succinylcholinne whose prevalence is approximately 1 in 2500 population (Table 16.4).

The atypical pseudocholinesterase produced by them is resistant to dibucaine and dibucaine number is 50 to 60 only. Other atypical genes are fluoride resistant gene (E^f) and silent gene (E^s). Fluoride resistant gene produces atypical pseudo or plasma cholinesterase enzyme which are not resistant to dibucaine, but is resistant to fluoride. Homologous persons with silent gene completely lack the cholinesterase activity. Persons may be homologous or heterologous of these type of genes which are responsible for atypical pseudocholinesterase enzyme with different dibucaine number. These are shown in Table 16.5.

The most variants of atypical pseudocholinesterase are due to the single amino acid substitution or error at or near the active site of the enzyme, e.g. substitution of glycine for aspartic acid at position 70 in atypical dibucaine resistant pseudocholinesterase.

The activity of plasma cholinesterase enzyme can be measured by using the spectrophotometric technique. Phenotype classification is also possible by adding different inhibitors such as dibucaine, sodium fluoride, etc. which cause different enzyme inhibition depending upon the type of enzyme present. Dibucaine inhibits the normal pseudocholinesterase enzyme to a greater extent than the abnormal enzyme. This observation had lead to the development of a test by dibucaine and had made possible to create a number. Dibucaine test examines the amount of inhibition of particular plasma cholinesterase (or pseudocholinesterase) activity by dibucaine. If a specimen has high normal (typical) enzyme content then it will be inhibited to larger extent by dibucaine. This percentage of inhibition can then be expressed as the dibucaine number. For example, if dibucaine inhibits normal enzyme about 80% and only 20% then the dibucaine number is 80 and 20 respectively. Thus, the dibucaine number indicates the genetic makeup of an individual patient with respect to typical pseudocholinesterase level in plasma. It does not measure the concentration of enzyme in plasma and nor does it indicates the efficiency of the enzyme (Table 16.6).

Fluoride test will also reveal a few instances where the samples may show a normal looking dibucaine number, yet an abnormally low fluoride number and prolonged duration of action of succinylcholine. The significance of fluoride test and its number is same as dibucaine. This is due to the some variants of gene which produces such plasma pseudocholinesterase which is inhibited by dibucaine but not by fluoride. Such a situation would be evident in the presence of E^f E^f genotype. The incidence of genotype will play an important part in the number of cases of prolonged response to succinylcholine. If it is accepted that the ensyme formed from E^u E^u genotype can hydrolyze the clinical dose of succinylcholine in about 4 minutes, then E^u E^a and E^u E^f genotype would take 10 to 20 minutes. However in E^a E^a, E^f E^f, E^s E^s genotype more prolonged muscular paresis will persist.

Table 16.6: Relationship between dibucaine number and duration of neuromuscular blockade by succinylcholine

Type of pseudocholinesterase	*Genotype*	*Frequency*	*Dibucaine number*	*Response to succinylcholine*
Typical homozygous	$E^u E^u$	Normal	70 to 80	Normal
Typical heterozygous	$E^u E^a$ $E^u E^f$	1/500	50 to 60	Slightly prolonged
A typical homozygous	$E^a E^a$ $E^s E^f$ $E^s E^s$	1/3000	20 to 30	Markedly prolonged

Doses

Succinylcholine is usually administered intravenously, but it can also be given though IM and SC route. However by IM or SC route, the onset of action of succinylcholine is delayed and duration of action is long lasting. By IV route, the arrival of succinylcholine at any group of muscle is heralded by brief fasciculation which represents this agent's acetylcholine like agonist activity. This usually happens within 30 to 40 seconds, with maximum effect of block occurring in 30 to 60 seconds, following administration of succinylcholine in the dose of 1 mg/kg through IV. This dose represents approximately the three times of ED_{95} value of this agent. The fasciculation following IV administration of succinylcholine is first observed in the eyebrow and in the eyelid group of muscles, passing later to the shoulder girdle and abdominal musculature and finally to the hands and feet. However, this muscle fasciculation is less obvious in deeply anaesthetised patient.

The average single bolus dose of succinylcholine in man is 1 to 1.5 mg/kg by IV with duration of action for only 5 to 10 minutes. For continuous infusion the dose of succinylcholine is 20 to 40 µg/kg/min. Repeated small bolus doses such as 10 mg at small intervals (when effects of relaxation of the previous dose wanes out) can also be used during short surgical procedures which require brief but intense muscle relaxation such as endoscopies, D and C, EUA, etc. When the succinylcholine infusion is used then sometimes methylene blue dye is used as an indicator in the drip. Because, it prevents the confusion between the solution of succinylcholine in bottle and other intravenous fluids. But in modern anaesthesia practice, the availability of short acting non-depolarising muscle relaxants such as mivacurium has decreased the popularity of this continuous infusion technique of succinylcholine. However, to avoid the overdose of succinylcholine by infusion it is essential to monitor the neuromuscular transmission continuously, whenever an infusion of succinylcholine or intermittent repeated bolus doses of it are used.

Adverse Effect

CVS

As succinylcholine is against to acetylcholine, so it stimulates all the cholinergic receptors which are constituted by both the nicotinic and muscarinic types. Action of succinylcholine on the nicotinic receptors of ACh at the neuromuscular junction produces fasciculation and subsequent muscular paralysis. Actions of succinylcholine on the muscarinic receptors of ACh on various tissues vary accordingly. Action of succinylcholine on muscarinic receptors of cardiac tissues produces sinus bradycardia, junctional rhythm, conduction block and ventricular arrhythmias ranging from unifocal premature ventricular contraction to ventricular fibrillation, etc. However, sinus bradycardia is more common after a second dose of succinylcholine and particularly it is found in children. This can be prevented by blocking the vagus or attenuating the muscarinic effect by atropine or by small dose of non-depolarising muscle relaxing drug. The higher incidence of bradycardia and other cardiac complications after a 2nd dose of succinylcholine suggests that hydrolysed product of succinylcholine (succinylmonocholine and choline) may sensitise the heart to the subsequent doses of it. However, bradycardia is not observed when suxamethonium is infused slowly.

Nodal rhythm, caused by succinylcholine is due to the greater activation of the muscarine receptor in the sinus node and thus suppressing the sinus mechanism and allowing the emergence of AV node as pacemaker. It is also common after 2nd dose and can be pervented by atropine or small dose of non-depolarising muscle relaxing agent.

Succinylcholine also induces the ventricular arrhythmias because:

i. It lowers the arrhythmia threshold of the ventricle.
ii. It increases the level of catecholamine and K^+ (due to fasciculation) which also increases the incidence of arrhythmia.
iii. Other associated autonomic stimulation due to intubation, hypoxia, hypercarbia, etc. also increases the incidence of arrhythmia, induced by succinylcholine.
iv. Different anaesthetic drugs such as, halothane (most common) also lower the ventricular threshold level for ectopic beat or increase the arrhythmogenic effect of catecholamines. When this effect of halothane combines with the arrhythmogenic property of succinylcholine, then the incidence of arrhythmia increases many fold. Glycopyrrolate is also effective in preventing the bradycardia and dysarrhythmia, produced by succinylcholine.
v. Other drugs which interact with succinylcholine and predispose ventricular arrhythmias are: digitalis, MAOI, tricyclic antidepressant, exogenous catecholamine, etc.

Hyperkalaemia

The administration of succinylcholine is associated with high rise of plasma K^+

level and it is believed to be due to the K^+ efflux from the muscle fibres during fasciculation. In normal patients this increase in plasma K^+ level is 0.5 m.mol/L and is of little significance. But, this may be significant for patients with pre-existing elevated serum potassium level. Under certain abnormal circumstances this rise of plasma K^+ level is very high and it is due to the spread of ACh receptors (nicotinic receptor) away from the restricted motor end-plate area to the whole outer surface of the muscle cell membrane. So, in these patients succinylcholine acts vigorously by binding with all the receptors and causing excessive fasciculation and tremendous rise of plasma K^+ level. The abnormal circumstances where this type of reaction occurs are: massive burn, massive muscle trauma, lower motor neuron lesion, upper motor neuron lesion, any lesion of the spinal cord, skeletal muscle (Table 16.7) diseases, bed ridden subjects, intra-abdominal infection, renal failure, etc. But, among these both the burn and the massive muscle trauma patients are most susceptible to hyperkalaemia following succinylcholine. This susceptibility to hyperkalaemia present for at least 60 days following burn or trauma or untill adequate healing of the damaged muscle occurs. So, in the above mentioned conditions succinylcholine should not be used, or if used then anaesthetist should be very cautious. Otherwise, subsequent cardiac arrest can occur which is quite refractory to the routine CPR.

Table 16.7: Conditions where succinylcholine causes more hyperkalaemia

- Massive trauma
- Massive burn injury
- Tetanus
- Stroke
- Spinal cord injury (haemiplagia or paraplagia)
- Encephalitis
- Severe Perkinson's disease
- Guillain-Barre syndrome
- Polyneuropathy
- Head injury
- Severe infection or septicaemia
- Prolonged immobilisation of whole body
- Multiple myopathies (Duchenne's dystrophy)
- Haemorrhagic shock with metabolic acidosis

If there is rise of plasma K^+ level due to any renal cause, then the use of succinylcholine is definitely contraindicated. Otherwise, the use of succinylcholine in renal failure is a controversial subject. Because many studies have failed to demonstrate the rise of plasma K^+ level by succinylcholine in renal failure patient. To them, succinylcholine is the muscle relaxants of choice, as it does not depend on the renal excretion. Since, a number of non-depolarising muscle relaxants are now available that depend little or not at all on the kidney for their elimination (e.g. atracurium, mivacurium, vecuronium), so they may be an alternative to succinylcholine as muscle relaxants in patient with renal disease.

Intraocular pressure

Succinylcholine causes tonic contraction of the extraocular muscles and thus increases the intraocular pressure (IOP). But, it has no clinical significance in most of the patients, where globe is not opened. IOP increases within 1 minute of administration of succinylcholine, reaches peak value at an interval of 4 minutes and its duration of action lasts for about 6 minutes. The mechanism of tonic contraction of the extraocular muscles by succinylcholine is discussed in the previous chapter. The use of non-depolarising drugs before the administration of succinylcholine to prevent the rise of IOP is controversial. But, the use of succinylcholine alone is not contraindicated, if the anterior chamber is not opened. Still, there are many studies where succinylcholine has been successfully used in penetrating eye injuries without any loss of global contents. Other than succinylcholine, additional factors such as cough, vomiting, bucking, etc. also raise IOP. So, to prevent a raised IOP the patient should be anaesthetised deeply and should not strain, which can be achieved by an adequate dose of IV anaesthetic drug, deeper level of inhalation anaesthesia, application of topical anaesthesia on trachea, additional muscle relaxants (non-depolarising), etc.

But, in conclusion, we can comment that in open globe eye surgery or lacerated globe injury the succinylcholine should be avoided. However, if for any reason the use of succinylcholine is mandatory for rapid sequence intubation due to full stomach or due to any other causes, then the above mentioned measures should be taken to prevent an increase in IOP.

Intragastric pressure (IGP)

The succinylcholine increases IGP maximum up to 30 cm of H_2O. But the rise of IGP up to 12 cm of H_2O is often normally found following the use of succinylcholine in adult. However, this effect is inconsistant, because many patient even show no rise of IGP after the use of succinylcholine. Again, this effect is insignificant provided the oesophageal sphincter mechanism is properly intact. The increase of IGP by succinylcholine is due to: (i) fasciculation of abdominal muscles, (ii) ACh like effect of succinylcholine which causes vagal stimulation and subsequently increase IGP (4 to 7 cm of H_2O). The increased IGP caused by succinylcholine can be prevented by prior curarisation and atropinisation. Normally, an increase in IGP is not important, as the opening pressure of the lower oespohageal sphincter also subsequently increases due to succinylcholine.

Usually, IGP above than 28 cm of H_2O is necessary to overcome the competence of gastro-oesophageal junction. But, except in few cases, normally this limit does not exceed by succinylcholine. However, only when the normal oblique entry angle of oesophagus into the stomach is altered or distorted due to pregnancy, abdominal distension by ascites or any cause, intestinal obstruction, obesity, hiatus hernia, etc. then the IGP required to cause incompetence of the gastro-oesophageal junction becomes frequently low and is less than

15 cm of H_2O. So, for the above mentioned causes precautionary measure should be taken to prevent regurgitation or the use of appropriate non-depolarising drug should be thinked. Succinylcholine does not increase IGP in infant and children. This is due to minimum or absent of fasciculation in this group of patients.

Muscle pain and fasciculation

The incidence of muscle pain which is most commonly observed as the side effects, following administration of succinylcholine varies from 25 to 89%. It develops mostly in chest wall, upper abdomen, shoulder and back. Sometimes, this muscle pain becomes very debilitating, necessiating analgesics and bedrest. However, it is more common after minor surgeries, in women and in ambulatory patients than the bed ridden patients. It is also more common in young and fit patients and in those who are mobilised early. Extremes of age and pregnancy are seemed to be protective. This muscle pain is due to the fasciculation and it can be substantiated by finding myoglobinaemia and increase in serum creatine phosphokinase (CPK) following the administration of succinylcholine, especially in children anaesthetised with halothane.

The subparalysing dose of non-depolarising muscle relaxant prevents this fasciculation and muscle pain and substantiates this hypothesis. But, the prior treatment with non-depolarising drug, mainly pancuronium, reduces the effectiveness of succinylcholine by about 30% and also cause the prolongation of effect of the depolarising drug by virtue of its anticholinesterase properties. However, due to the reduction of effectiveness a larger dose of succinylcholine (1.5 mg/kg) is then required. Muscle pain can also be reduced by premedication with diazepam, lignocaine, pentothal and bedrest. Raised CPK level due to rupture of muscle cell or fibre associated with muscle pain supports that fasciculation produced by succinylcholine is the cause of muscle pain.

So, it may be a better practice to use a small dose of non-depolarising muscle relaxants, before the administration of succinylcholine due to the following reasons: (i) fasciculation, which is the root of many problems can be prevented, (ii) postoperative whole body muscle pain, elevated IOP and increased IGP − all can be decreased or eliminated, (iii) succinylcholine induced increase in serum creatine phosphokinase (CPK) and myoglobinuria may be better attenuated. The relation between the muscle spasm and malignant hyperthermia is variable.

Masseter spasm

Succinylcholine may cause the spasm of certain group of muscles, especially masseters leading to masseter spasm, while other muscles are flaccid. Probably, this is an exaggerated response of succinylcholine at the neuromuscular junction of certain specific muscles and mainly found in children. Sometimes, this masseter spasm may be severe enough, making the laryngoscopy and intubation difficult. In such cases, the smaller dose of non-depolarising agent is not of much benefit. It is not the diagnostic sign of malignant hyperthermia, because it is not invariably associated with this syndrome, though it has been suggested that this is an early warming sign of the development of malignant hyperthermia.

Intracranial pressure

Succinylcholine transiently increases ICP, though the mechanism and significance of it is unknown.

Malignant hyperpyrexia

Succinylcholine often trrigers the mechanism of malignant hyperpyrexia in susceptible patient who is anaesthetised with halothane. Malignant hyperthermia is a hypermetabolic disorder of skeletal muscles. But, the signs and symptoms of it resemble those of neuroleptic malignant syndrome (NMS), though the pathogenesis is completely different. However, there is no need to avoid the use of succinylcholine in patients with NMS.

Allergic reaction

Of all the drugs used in anaesthesia, the frequency of allergic and/or anaphylactic reactions is probably highest with succinylcholine. If there is a history of previous allergic reactions, then the likelihood of further reaction is very high. Succinylcholine may also give rise to cross-sensitivity with other muscle relaxants in this respect.

Phase II block

It occurs if the ACh (nicotinic) receptors are exposed to succinylcholine either in excess doses or for prolonged period. The phase II block is nothing but like non-depolarising block with some exception. The transition from a depolarising or phase I block to phase II block is gradual and usually occurs after administration of large dose such as 7 to 10 mg/kg of succinylcholine intravenously. The recovery from phase II block is much slower and for it the cholinesterase inhibitor (anticholinesterase) should not be used. If used it may prolong the effects of succinylcholine and phase II block will be more intensed.

Interaction between Succinylcholine, Non-depolarising Muscle Relaxants and Neostigmine

Interaction between the succinylcholine and the non-depolarising muscle relaxants are antagonistic and/or additive, i.e. complex. These complex interactions are:

i. If succinylcholine is given first to facilitate the intubation, then it enhances the depth of block caused by subsequent dose of non-depolarising muscle relaxant and reduces the dose of it. But, there is no effect when the non-depolarising drug is given after the block from succinylcholine has dissipated.
ii. If the non-depolarising agent is given first, then it antagonises the depolarising phase I block produced by subsequent administration of succinylcholine. This

Table 16.8: Difference between phase I and II block by succinylcholine

	Phase I	*Transition*	*Phase II*
Train - of - four (TOF)	No fade	Moderate	Marked fade
TOF ratio	> 0.7	0.4 - 0.7	< 0.4
Tetanic stimulation	No fade	Moderate	Marked fade
Post-tetanic facilitation	No	Moderate	Marked present
Recovery	Rapid	Less rapid	Prolonged
ACh E - inhibitor	Increase (agonist)	Little effect	Decrease (antagonise)
Dose requirement (IV)	1 - 2 mg	3 - 4 mg	> 5 mg

is because, the non-depolarising agents occupy some of the ACh-nicotinic receptor at the motor end-plate and partially prevent the agonistic action of succinylcholine. An exception to this phenomenon is pancuronium. It augments the blockade of succinylcholine by inhibiting the pseudocholine esterase enzyme and increasing the concentration of succinylcholine.

iii. When succinylcholine is used after neostigmine, the duration of succinylcholine action is prolonged. This is due (Table 16.8) to the inhibition of pseudocholinesterase by neostigmine.

iv. If neostigmine (ACh E–inhibitors) is used to antagonise or to recover the phase I block produced by succinylcholine, then it markedly prolongs the effect of succinylcholine. This happens by two mechanism: (a) by inhibiting the acetylcholinesterase (ACh E) they cause the higher acetylcholine concentration at the motor end-plate which intensifies the depolarisation and phase I block. (b) They also reduce the hydrolysis of succinylcholine by inhibiting the pseudo (plasma) cholinesterase and potentiate the phase I block.

Difference between Phase I and Phase II Block

Train-of-four (TOF) is the best guide to detect the transition from phase I to phase II block. It helps to avoid the succinylcholine overdose by detecting the development of phase II block, observing the rate of recovery and assessing the effect of neostigmine on recovery from phase II block. Attempt to antagonise the pahse II block by neostigmine is controversial. If TOF ratio is less than 0.4, administration of neostigmine causes prompt antagonism of phase II block.

NON-DEPOLARISING MUSCLE RELAXANTS

Classification

Classification according to chemical structure

A. Steroidal Compound

Pancuronium, Pipercuronium, Vecuronium, Rocuronium and ORG 9487 (Rapacuronium).

Steroidal compounds have the following characteristics:

i. High potency,

ii. Lack of histamine release,

iii. Exhibits vagolytic property − moderate for pancuronium, slight to moderate for rocuronium, absent in clinical dose for pipercuronium and vecuronium,

iv. Excreted by kidney,

v. Duration of action depends on the balance between the lipophilic and hydrophilic activity of the molecule.

B. Benzylisoquinolinium Compound

d-tubocurarine (dTc), Metocurine, Doxacurium, Atracurium, Cisatracurium (51W89) and Mivacurium.

Benzyl isoquinolinium compound has the following characteristic (Table 16.9):

i. High potency,

ii. Lack of vagolytic effect,

iii. Tendency to release histamine − prominent for d-tubocurarine, moderate for metocurine, slight in atracurium and mivacurium, absent in dexacurium and 51W89 (cisatracurium)

iv. Excreted by kidney − also have unimportant biliary excretion for dTC and doxacurium,

v. Degradation by Hoffmann elimination (atracurium and 51W89) or hydrolysis by pseudocholinesterase (mivacurium) in plasma.

However, the choice of a particular drug during anaesthesia practice depends upon their unique characteristic which is related to their structures. This can be explained

Table 16.9: Summary of pharmacology of non-depolarising muscle relaxants

Drugs	*Chemical structure*	*Primary excretion*	*Histamine release*	*Vagal blockade*	*Autonomic ganglion block*
d-tubocurarine	B	Renal	+ + +	+	+ +
Gallamine	B	Renal	+ +	+ + +	0
Pancuronium	S	Renal	0	+ +	0
Pipercuronium	S	Renal	0	0	0
Vecuronium	S	Biliary	0	0	0
Atracurium	B	Insignificant	+	0	0
Cisatracurium	B	Insignificant	0 / +	0	0
Doxacurium	B	Renal	0	0	0
Mivacurium	B	Insignificant	+	0	0
Rocuronium	S	Biliary	0	+	0
Rapacuronium	S	Biliary	+ +	0	0

B = Benzylisoquinolinium compound, S = Steroid compound

by the fact that steroidal compounds tend to be more vagolytic, whereas the benzylisoquinoline compounds release more histamine. Again because of the same chemical structure allergic history to one group of muscle relaxants may precipitate allergic reactions to other group of muscle relaxants.

Classification according to duration of action

Long acting relaxants

It includes d-tubocurarine (dTC), metocurine, doxacurium, pancuronium, pipercuronium, gallamine and alcuronium. They have slow onset of action and maximum blockade occurs at 3 to 6 minutes, following an intubating dose which is 2 to 3 times of the ED95 dose. The average duration of action of these group of muscle relaxants is 80 to 120 minutes (measured as recovery of twitch response to the 95% of baseline) following an intubating dose. In clinical practice selection of these long acting muscle relaxant depends on their effect on CVS and the duration of surgery. Careful antagonism of residual paralysis at the end of operation is very important when these long acting muscle relaxants are used. All long acting agents are primarily excreted unchanged through urine with little or no-metabolism.

Intermediate acting relaxants

It invites vecuronium, rocuronium, atracurium, cisatracurium, (51W89). The onset of action of this group of drugs occur at 2 to 3 minutes following administration of an intubating dose which is 2 times of ED95 dose and the duration of action is 45 to 75 minutes (90% twitch recovery). The vecuronium and rocuronium have dual excreting pathway (liver and kidney). However, the atacurium and 51W89 have undergone Hoffmann elimination.

Short acting relaxants

It includes only mivacurium and rapacurium (ORG9487). Onset of action of these agents is 2 to 3 minutes following a tracheal intubating dose and clinical duration of action is 12 to 15 minutes. After intravenous administration of these agents 95% twitch recovery occur between 25 and 35 minutes. Mivacurium is destroyed spontaneously in plasma by pseudocholinesterase like succinylcholine, though it is non-depolarising drug. Only 5% is excreted unchanged in urine.

Pharmacokinetics and Pharmacodynamics of Non-depolarising Muscle Relaxants

The non-depolarising muscle relaxing agents act by competitive antagonism with the ACh at nicotinic ACh-receptor on the post-synaptic membrane of neuromuscular junction. The dose response relationship of this group of drug is sigmoid in shape. From the dose-response curve, like any other agent, the potency of any non-depolarising neuromuscular blocking agent also can be estimated (Fig. 16.2).

The potency of any agent is expressed as ED (Effective Dose) value. The effective dose or ED value that results in 50%, 90% or 95% neuromuscular block is termed the ED_{50}, ED_{90} and ED_{95} of muscle relaxant respectively. In general, a dose that is 2 to 3 times of the ED_{95} value is administered for facilitation of tracheal intubation.

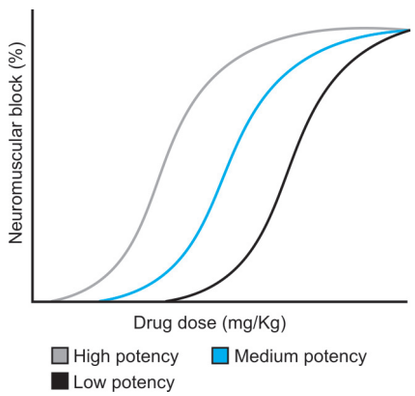


Fig. 16.2: This is a schematic representation of relationship between the dose of muscle relaxant and the percentage of neuromuscular block. A drug of high potency would be represented by pipercuronium, medium potency by atracurium and a low potency by gallamine

Clinically, the onset of neuromuscular block is the time which is taken for a drug to produce a depression of measurable response which is contraction of muscles for a muscle relaxant. During the onset of response, nearly 70% of the receptors must be occupied by the drug. The speed of onset of action of muscle relaxant depends upon the cardiac output, muscle blood flow, the potency, the dose, and some kinetic characteristic (e.g. clearance) of the relaxant. It is now established that drugs with low potency have a more rapid onset of action and potent drugs have slow onset of action. This is because as potency increases less amount of drugs (fewer molecules) are injected and the concentration gradient of the acting drug at the receptor site will be low causing delayed onset of action. For example, doxacurium is the most potent, but has slowest onset of action. Potent muscle relaxants also have high affinity for the receptors. So, their effects wear off very slowly, resulting in long duration of action.

The distribution profile of the currently used non-depolarising muscle relaxants can be described by two or three compartmental models. First, the relaxants are distributed from the central compartment (blood) to the peripheral compartment (tissue). Then, it is followed by one or two elimination phases when the drugs are metabolised in liver and excreted through urine. After IV injection the concentration of muscle relaxant in plasma (central compartment) rises rapidly. After that drug moves into the tissues from the plasma and the concentration of it in blood fall rapidly. When this fall in plasma level go beyond the tissue concentration level, then the drug again returns in the plasma from the tissues. Now plasma concentration depends on two factors: rate of re-entry from tissue and elimination from plasma by metabolism and / or excretion. Ultimately an equilibrium between the tissue and plasma concentration reaches and after that there is slow decrease in concentration of drug in plasma, constituting terminal elimination phase (Fig. 16.3).

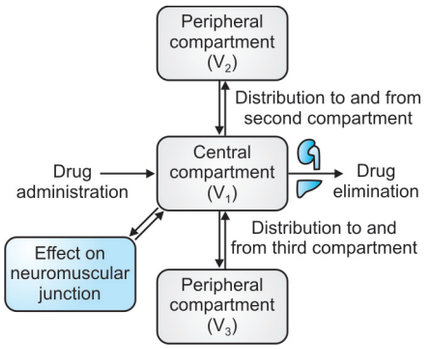


Fig. 16.3: This is a schematic representation of drug distribution into different compartments of body. These compartments are mathematical concepts only. It does not represent the real physiological space. The effect compartment in this case is the neuromuscular junction

After IV injection, the plasma concentration of muscle relaxants fall gradually. But in contrast the neuromuscular block begins to occur and does not recover even after many minutes of the gradual decrease of plasma concentration of muscle relaxant. This discrepency between the plasma concentration and the drug effect is because the action of muscle relaxants is not in the plasma, but at the neuromuscular junction.

The potency of non-depolarising muscle relaxants is increased by prior administration of succinylcholine. But, potency is decreased in patient with burn, injury, neonates and infants than the older children and adults.

Choice of non-depolarising agents for intubation

None of the recently available non-depolarising agent can fulfill the desire condition necessary for intubation, i.e. rapid onset and short duration of action which is provided by succinylcholine. But, succinylcholine is a depolarising agent and has many drawbacks which we do not want. So, there is continuous search for newer and newer non-depolarising agents which would have property like succinylcholine, i.e. quicker onset and short duration of action but should not have the drawback like depolarising agent. However, the onset of action of non-depolarising agent can be quickened by using a priming dose or a larger dose which is 2 to 3 times of ED_{95}.

The idea behind the priming dose is that if 10 to 15% of the recommended intubation dose is adminstered 5 minutes before induction, then it will occupy the enough receptors, so that paralysis will quickly occur when the balance or remaining 85 to 90% of the recommended dose is given after induction and before intubation. The use of this technique enables to perform intubation quickly within 60 to 90 seconds after administration of muscle relaxant. However, it is applicable mainly for short and intermediate acting non depolarising agents. Priming dose occupies usually 20 to 25% of the receptors. So, it does not produce clinically significant paralysis and its symptoms, before induction which requires 75 to 80% receptor occupancy. However, in some patients priming dose produces clinical paralysis manifested by dyspnoea or heavyness of breath, diplopia, muscle weakness, etc. In such instances patient should be reassured or induced quickly (Table 16.10).

ED_{95} is the dose when 95% of the effective block occur. But 2 to 3 times (some body uses 1 to 2 times) of the ED_{95} dose is usually needed for intubation. If the dose is increased more, then the intubation will be more rapid. But it exaccerbates the side effects and prolongs the duration of action. For example, pancuronium in high doses of 0.15 mg/kg (usual dose 0.08 mg/kg) produces an excellent intubating condition within 90 seconds and its irreversible duration of action lasts for more than 60 minutes, but at the cost of pronounced tachycardia and hypertension.

Table 16.10: Priming doses (mg/Kg)

Drugs	*Priming dose*
Atracurium	0.05
51W89	0.01
Rocuronium	None
Mivacurium	0.02
Vecuronium	0.01

It is also important to understand that the different muscle groups vary in their sensitivity to different non-depolarising muscle relaxants. Relaxation of laryngeal muscles are important for intubation. But, it recovers from blockade more quickly than adductor pollicies which is commonly monitored for neuromuscular paralysis.

Doses – the principle

i. The dose of non-depolarising muscle relaxants for tracheal intubation is 2 to 3 times than that of ED_{95} dose.
ii. If the patient has already been intubated, then the dose slightly less than that of ED_{95} dose is needed to produce the surgical relaxation.
iii. The maintenance doses for non-depolarisers ranges from 20 to 30% of the initial bolus dose.
iv. The intermediate and short acting non-depolarising muscle relaxants can be used by continuous infusion to keep the relaxation smooth. It also helps rapidly adjustment of the depth of relaxation according to the surgical needs and prompt recovery at the end.
v. Somebody thought that if the subparalysing dose of a non-depolarising agent is given 2 to 4 minutes before the final 2nd dose for intubation after induction, then the onset of action of this 2nd dose will be accelerated and intubation can be performed within 90 to 120 seconds. This procedure is called the 'priming'. When rapid tracheal intubation is performed by non-depolarising relaxants, then 'priming' is recomended. But long acting drugs are not advised for this priming and rapid intubation (Table 16.11).

Metabolism and elimination of non-depolarising muscle relaxants

The all non-depolarising muscle relaxants contain quaternary nitrogen atoms. So, they are positively charged cation. These characteristic nature conform them with a high (Table 16.12) degree of water solubility and only a slight degree of lipid

Table 16.11: Doses of rapid tracheal intubation in mg/Kg

Drugs	*Intubating dose*	*Clinical duration (minute)*	*Full recovery (minute)*
Atracurium	0.7 - 0.8	45 - 60	60 - 90
51W89	0.2 - 0.25	50 - 70	70 - 100
Rocuronium	0.6 - 1	30 - 60	60 - 120
Vecuronium	0.15 - 0.2	60 - 70	90 - 120
Mivacurium	0.25	15 - 20	20 - 30

Table 16.13: Doses of different nondepolarising agents when they are used by continous infusion

Continuous infusion	*(µg/kg/minute)*
Mivacurium	6 - 8
Atracurium	4 - 12
Cisatracurium (51W89)	1 - 2
Rocuronium	10
Vecuronium	0.8 - 2

solubility. So, this hydrophilic character enables the non-depolarising muscle relaxants to eleminate completely via kidney with no tubular reabsorption. Hence, they depend little or nothing for metabolism in the liver for exit from the body. Therefore, elimination of these drugs depend only on the glomerular filtration and make them long acting in renal disease (Table 16.13).

Effect on CNS

The non-depolarising muscle relaxants can hardly enter into CSF and their clinical significance is not clear. When inadvertently neuromuscular blocking agent is given in CSF (during spinal anaesthesia) then myotonia, autonomic changes, convulsion, etc. have been occurred. However, prolonged administration of rocuronium, atracurium and vecuronium in ICU results in entry of sufficient amount of these drugs in CSF. Laudanosine, a metabolite of atracurium crosses the blood barrier and causes CNS stimulation. In case of cisatracurium which is an isomer of atracurium and 5 times more potent than it, the measured quantities of laudanosine in CSF is 5 times lower than that of atracurium. However, the CNS effect of non-depolarising muscle relaxant due to prolonged use on morbidity and mortality in ICU is unclear.

Paediatric group of patient and muscle relaxant

At birth, the development of neuromuscular unit is immature. It becomes mature at 2 months of age. So, newborns are more sensitve to non-depolarising muscle relaxants than adult and a lower plasma concentration of it can achieve the desired neuromuscular block like adult. But, the dose of non-depolarising muscle relaxant should not be reduced due to its large volume of distribution in neonate and infant. Slower clearance by kidney also contribute to longer elimination half-life of the non-depolarising agents in children. In spite of these, the non-depolarising muscle relaxants can safely be used in neonates and infants.

Atracurium, cisatracurium, vecuronium, rocuronium are commonly used non-depolarising muscle relaxants in children due to their faster onset, intermediate duration of action, and minimum residual paralysis.

The mivacurium can safely be used in children and needs larger doses than adult. However, the duration of action of mivacurium is shorter in children than adult. It is best used by infusion in children for its shorter duration of action and infusion rate should be twice than that of adult.

The status of rocuronium in children is same as that of the adult. Rocuronium in the dose of 0.6 mg/kg has the earliest onset of action (60 to 90 seconds) among all the non-depolarising agents and produces an

Table 16.12: Doses, onset of action, duration of action and potency of different nondepolarsing agents

Drug	*ED_{95} (mg/kg)*	*Intubation dose (mg/kg)*	*Onset of action of intubating dose (min)*	*Duration of action of intubating dose (min)*	*Supplemental dose (mg/kg)*	*Potency*
Long acting						
Tubocurarine	0.5	0.5 - 0.6	1 - 2	30 - 60	0.1 - 0.2	7
Gallamine	3	4 - 6	2 - 3	90 - 120	0.5 - 1	40
Pancuronium	0.07	0.08 - 0.12	2 - 3	60 - 120	0.01 - 0.02	1
Pipercuronium	0.05	0.08 - 0.1	2 - 3	60 - 120	0.01 - 0.15	0.8
Doxacurium	0.025	0.05 - 0.08	4 - 5	90 - 150	0.01 - 0.05	0.4
Intermediate acting						
Vecuronium	0.05	0.1 - 0.2	2 - 3	45 - 90	0.01 - 0.02	0.8
Atracurium	0.23	0.5 - 0.6	2.5 - 3	30 - 45	0.1	3.5
Cisatracurium (51W89)	0.05	0.1 - 0.15	2 - 3	30 - 60	0.02	1
Rocuronium	0.3	0.6 - 1	1 - 1.5	30 - 60	0.1 - 15	6
Short acting						
Mivacurium	0.08	0.2 - 0.25	2.5 - 3	15 - 20	0.05 - 0.1	1.6
Rapacuronium (ORG9487)	0.75	1.5 - 2	1.5	14 - 20	0.05	–

excellent intubating condition for rapid tracheal intubation than vecuronium and atracurium, both for the adult and children. For rapid sequence intubation (within 30 to 60 seconds) in the presence of full stomach, rocuronium in the high dose of 1.2 to 1.5 mg/kg are also suggested.

The succinylcholine should be discontinued in paediatric group of patient, because of many side effects of it such as rhabdomyolysis, hyperkalaemia, acidosis and even cardiac arrest, particularly in patient with unsuspected muscular dystrophy of Duchenne type.

The antagonism of non-depolarising block in children is similar to adult.

Geriatric group of patients and muscle relaxant

The duration of action of most of the non-depolarising muscle relaxants is prolonged in older group of patients. This is due to many geriatric physiological changes which occur in the body and neuromuscular junction with increasing age.

The physiological changes in geriatric group of patients which affects the action of muscle relaxants are:

i. ↓splanchnic and renal blood flow,
ii. ↓GFR,
iii. ↓hepatic function,
iv. ↓total body water,
v. ↓cardiac reserve.

With increased, age the physiological and anatomical changes of neuromuscular junction which affects the action of muscle relaxants are:

i. ↑junctional cleft,
ii. flatening of folds of the motor end-plate,
iii. ↓concentration of ACh receptors,
iv. ↓ amount of ACh in vesicle.

In old age the sensitivity of nicotinic receptor to the muscle relaxants at myoneural junction is not altered. But, the decreased clearance of each drug from the plasma explain the prolonged duration of action in old age. The decreased clearance of drug in elderly is due to the ↑ volume of distribution. Atracurium and cisatracurium depends on ester hydrolysis and Hoffmann degradation for their clearance. So, the duration of action of atracurium and cisatracurium is not influenced by age.

The plasma cholinesterase activity of older patients is reduced by 26% than the younger ones. So, as mivacurium is metabolised by plasma cholinesterase, its activity is prolonged by 20 to 25% in the aged.

Obesity

The doses of the non-depolarising muscle relaxants should be precisely calculated in obese patient. In obese the dose of a drug would depend on the lean body mass rather than the actual body weight and will be 20% more. The recovery from atracurium does not depend on obesity. The duration of action of rocuronium is prolonged in obese, but the duration of action of pancuronium is unaffected by obesity.

Renal disease

The renal failure prolongs the duration of action of the non-depolarising muscle relaxants by causing decreased elimination of the drug or its metabolites via kidney or by decreasing the activity of enzymes which metabolise the drug. The long acting non-depolarising muscle relaxant such as pancuronium, pipercuronium, doxacurium, gallamine and metacurine are associated with decreased plasma clearance and increased elimination half-life with prolonged duration of action in renal failure. So, because of the prolonged duration of action and availability of intermediate and short acting muscle relaxants which depend much less on the kidney for their elimination, use of long acting drug in renal failure is not recommended now. The duration of action of atracurium is unaffected by renal failure. Vecuronium depends on both the liver and kidney for its excretion. So, its clearance is also reduced and action is prolonged in renal failure patient. In renal failure due to decreased activity of plasma cholinesterase, the duration of action of mivacurium is also prolonged by 50% (10 to 15 minutes). However, the duration of action of rocuronium is not prolonged and is not cumulative in renal failure. As only 16% of the total excretion of cistracurium depends on kidney (77% by Hoffmann degradation), so the renal failure has little impact on the duraton of action of cisatracurium.

Liver disease

Hepatobiliary diseases prolong the duration of action of pancuronium, doxacurium, vecuronium, rocuronium and mivacurium. The relationship between the liver disease and the pharmacokinetics of non-depolarising muscle relaxants is complex. Liver disease is associated with increased volume of distribution and decreased plasma clearance. As a result, there is apparent resistant to the effect of drug and prolonged action. So, the initial dose is increased to reach the desired level of effect in plasma and thus the subsequent recovery is slower. On the other hand, the decreased synthesis of plasma cholinesterase in liver disease causes prolonged action of mivacurium and almost is tripled. But the clearance of atracurium and cisatracurium is little affected by liver disease, and so also their duration of action.

Inhaled anaesthetics

In a dose dependent manner all the inhaled anaesthetic agents potentiate the action of non-depolarising muscle relaxants. But, the extent of potentiation is different for different inhaled anaesthetic agents.

The proposed several mechanisms for augmentation of neuromuscular block by inhaled anaesthetic agents are:

i. The increased blood flow by inhaled anaesthetic agent causes more availability of the injected muscle relaxants at the neuromuscular junction.
ii. Due to depressive action on CNS, the volatile anaesthetic agent itself often produces adequate muscle relaxation. Thus, this augments the action of muscle relaxants, without producing any neuromuscular block by itself.

iii. The decreased sensitivity of the post junctional membrane to depolarisation by inhaled anaesthetic agent.
iv. Some specific effects of inhaled anaesthetic on ACh receptor channel which reduces the average duration of opening of it during activation. The effect of inhaled anaesthetic on non-depolarising blockade is a pharmacodynamic one (i.e. blood concentration of muscle relaxants to produce paralysis is decreased) but not a pharmacokinetic one.

Temperature

Hypothermia invariably lengthens the duration of neuromuscular blockade produced by non-depolarising muscle relaxants.

Antibiotics

Some antibiotics enhance the neuromuscular blockade caused by non-depolarising muscle relaxants. The mechanism of potentiation of neuromuscular blockade by these antibiotic is prejunctional (depression of the evoked release of ACh) or postjunctional or mixed. Calcium is not used for reversal of this neuromuscular blockade caused by antibiotic for two reasons : (i) antagonism produced by calcium is not sustained and (ii) calcium antagonise the antibacterial effect of antibiotics also.

Antibiotics that potentiate the neuromuscular blockade are streptomycin, gentamicin, kanamycin, neomycin, tetracycline, polymycin A and B, lincomycin, clindamycin, etc.

Magnesium

Magnesium sulphate, used in the treatment of pre-eclampsia amd eclampsia, also have the neuromuscular blocking properties and enhances the action of non-depolarising and depolarising muscle relaxing agents. The mechanism of (Table 16.14) actions of magnesium in neuromuscular blockade are:

i. It reduces the amount of ACh, released from the presynaptic membrane at the nerve terminal,
ii. It reduces the depolarising action of ACh on the postjunctional membrane,
iii. It reduces the excitability of muscle fibre,
iv. It reduces the amplitude of motor endplate potential.

Enhancement of succinylcholine blockade by magnesium also involves the same mechanisms. Magnesium also inhibit the action of plasma-cholinesterase.

Local anaesthetic and antiarrhythmic agents

Local anaesthetic agents enhance the effect of neuromuscular block produced by both non-depolarising and depolarising muscle relaxants. So, when the local anaesthetic agent is given as antiarrhythmics in intraoperative or postoperative period then the muscular relaxation effect produced by muscle relaxant is prolonged. It acts by stabilising the postjunctional membrane and thus by blocking the ACh-induced muscular contraction. In addition, procaine inhibits the plasma cholinesterase action and enhances the effect of succinylcholine.

The antiarrhythmic agents (e.g. quindine) also augment the neuromuscular block caused by muscle relaxants. Any drug that influences the conduction of impulse and electrical properties of heart, e.g. β-blocker, Ca^{2+} channel blocker, etc. also influence the ion transport at neuromuscular junction and enhance the action of muscle relaxants. But, in clinical level these interactions are minor.

Antiepileptic agents

Antiepilepitic agents, e.g. phenytoin, carbamazepine, etc. reduce the action of both depolarising and non-depolarising muscle relaxants and accelerate the recovery from muscular paralysis. Patients receiving anticonvulsants are somewhat resistant to the blocking effect of muscle relaxants.

Diuretics

The diuretics in their clinical dose augment the effect of non-depolarising muscle relaxants. They inhibit the production of cyclic AMP → leads to ↓ATP → ↓output of neurotransmitter → ↑blocking effect. Mannitol and other osmotic and tubular diuretics have no effect

Table 16.14: Metabolism and elimination of muscle relaxants

Drug	*Duration*	*Metabolism*	*Elimination by kidney*	*Elimination by liver*
Succinylcholine	Ultrashort	Pseudocholinesterase (99%)	<2% metabolites eliminated in urine	None
Mivacurium	Short	Pseudocholinesterase (90%)	<10% metabolites eliminated in urine	None
Atracurium	Intermediate	Hoffmann elimination and esterase hydrolysis (60 - 90%)	10 - 40% metabolites eliminated in urine	None
51W89 (cisatracurium)	Intermediate	Hoffmann elimination (90%)	10 - 40% metabolites eliminated in urine	–
Rocuronium	Intermediate	None	40% relative excretion by liver and kidney	60%
Vecuronium	Intermediate	Liver (20 - 40%)	40 - 60%	60 - 40%
Pancuronium	Long	Liver (10 - 30%)	85%	15%
Pipercuronium	Long	None	>90%	<10%
Tubocurarine (dTc)	Long	None	80%	20%
Gallamine	Long	None	100%	0

on the non-depolarising muscle relaxants. Because the excretion of relaxants depend primarily on GFR. Mannitol, being an osmotic diuretic, exerts its effect in proximal tubules, so that the water is retained within the tubules, but does not ↑GFR and does not increase the excretion of non-depolarising relaxants.

Interactions between the non-depolarising drugs (change from short to long acting and *vice versa*)

The effects of some non-depolarising muscle relaxants may be potentiated by simultaneous or prior administration of other non-depolarising agents. This usually happens if the combinations of aminosteroidal and benzylisoquinolinium group of muscle relaxants are used together. In modern anaesthetic practice there is no reason to combine the drugs from different group of non-depolarising relaxants. But, sequential administration of long and short acting drugs can be considered. However, the general rule for change over from one non-depolarising agent to another is that 95% of the 1st drug should be cleared. If anybody wants to change from short to long acting drug (for example mivacurium to doxacurium), then the second drug should be given when the TOF response has begun to recover, i.e. two to three twitches are visible. Similarly, if any body wants to change from long to short acting drug for maintenance, then very small dose should be given.

Anaphylactic or allergic reaction

Due to the quarternary structure and previous natural sensitisation to such molecules, muscle relaxants are the most commonly responsible drug for allergic or anaphylactic reaction during anaesthesia. Manifestations of some reactions such as flushing, urticaria, tachycardia and hypotension may sometimes be severe enough and can lead to cardiac arrest. In some patients this reaction is manifested as severe bronchospasm. Succinylcholine is the most commonly implicated agent for allergic reaction, though any muscle relaxant may be responsible. Recently, rocuronium and cistracurium have also been implicated. However, the determination of causative preoperative muscle relaxant for anaphylactic or allergic reaction involves the demonstration of specific antibodies or skin testing by this agent.

Effects on autonomic ganglia and release of histamine

Within the therapeutic dose range, the different non-depolarising muscle relaxing agents differ in their effects on autonomic ganglia. The older agents like tubocurarine has marked ganglion (which also contain nicotinic receptor) blocking effect. Thus, it compromises the ability of sympathetic nervous system to increase the heart rate and the myocardial contractility in response to hypotension and other perioperative stresses. On the other hand, galamine and pancuronium have marked vagal blocking or vagolytic (muscarinic receptor) effect causing tachycardia. All newer (Table 16.15) non-depolarising muscle relaxants such as atracurium, cisatracurium, rocuronium, vecuronium, etc. are devoid of significant ganglion blocking effects in their recommended clinical dose range.

Many non-depolarising agents release histamine from mast cells causing bronchospasm, peripheral vasodilatation, hypotension, skin flushing, urticaria, etc. But, they are insignificant in recommended dose range, except atracurium and mivacurium where this incidence is high.

Other factors that may interfere with the action of muscle relaxants

(i) Acid-base state

Acidosis (respiratory or metabolic) augments the effect of non-depolarising block. So, antagonism of neuromuscular block is difficult in such situation. Administration of narcotics in recovery room to relieve pain may cause hypoventilation and respiratory acidosis → more augmentation of residual block → again more hypoventilation → more acidosis → vicious cycle.

(ii) Electrolyte imbalance

The low extracellular K^+ concentration increases the end-plate resting transmembrane potential (due to higher ratio

Table 16.15: Interactions of depolarising and non-depolarising muscle relaxants with other drugs

Other drugs	*Depolarising muscle relaxant*	*Non-depolarising muscle relaxant*
A. Antibiotics		
Streptomycin, kanamycin, neomycin, polymyxin, colistin aminoglycosides, tetracycline, clindamycin, lincomycin	Potentiation	Potentiation
B. Anticonvulsants		
Carbamazepine, phenytoin, valporate, primidone	Resistant	Resistant
C. Antiarrhythmics		
Ca-channel blocker, quinidine	Potentiation	Potentiation
D. Cholinesterase inhibitors		
Neostigmine, edrophonium, pyridostigmine	Potentiation	Resistant
E. Inhalational anaesthetics		
Halothane, isoflurane, sevoflurane, desflurane	Potentiation	Potentiation
F. Magnesium sulfate	Potentiation	Potentiation
G. Lithium carbonate	Potentiation	Not known
H. Ketamine	Not known	Potentiation
I. Local anaesthetics	Potentiation	Potentiation

of intracellular to extracellular K^+). This hyperpolarisation increase the resistance to depolarisation and neuromuscular transmission. Thus, hypokalaemia enhances the block produced by non-depolarising muscle relaxants. This also diminshes the ability of neostigmine to antagonise the block. Thus, K^+ imbalance due to other diseases also increases the response to muscle relaxants. The severe dehydration also concentrates the muscle relaxants present in the plasma, thereby increases the muscle relaxants activity.

(iii) Myasthenia gravis and muscle relaxants

In myasthenia gravis (autoimmune disease) as there is less number of postjunctional nicotinic receptor, so the patients are more sensitive to non-depolarising muscle relaxants and resistant to succinylcholine. However, not all the muscles are affected in the same way. So, only the short and intermediate acting non-depolarising muscle relaxants should be used in low dose, guided by the monitoring with nerve stimulator. About 1/5 to 1/10th of ED_{95} value should be given initially as test dose to estimate the patient's requirement.

If patients have already received pyridostigmine for the treatment of myasthenia gravis, it should be continued preoperatively. It modifies the response of muscle relaxants as follows: (i) the sensitivity to non-depolarising muscle relaxants will be diminished, (ii) the response to succinylcholine and mivacurium are lengthened, because pyridostigmine inhibit plasma cholinesterase, (iii) the reversal of block is ineffective as ACh E inhibitor already exist in plasma. So, it will probably be safer to allow the spontaneous recovery.

Eaton-Lambert Syndrome (Myasthenic Syndrome)

This syndrome resembles to myasthenia gravis and is associated with carcinoma and motor neuropathy. The patients with this syndrome are usually sensitive to both the non-polarising and depolarising muscle relaxants.

Upper and Lower Motor Neurone Disease

i. The lower motor neurone disease results in resistance to the non-depolarising muscle relaxants. It is because of the proliferation of acetylcholine (or nicotinic) receptors.
ii. In upper motor neuron lesion (hemiplegia and paraplegia) patient is more susceptible to succinylcholine.

(iv) Burns and muscle relaxants

Burn patient show abnormal response to depolarising muscle relaxants. Because after burn there is proliferation of extra junctional ACh (or nicotinic) receptor throughout the surface of the muscle cell membrane. Thus, massive stimulation of these receptors by normal dose of succinylcholine can cause massive release of potassium, producing ventricular tachycardia, ventricular fibrillation or cardiac arrest. So, succinylcholine can safely be administered within first 24 hours following burn injury or 1 to 2 years after the burn, when the skin has healed completely.

Burned patients also show abnormal response to non-depolarising muscle relaxant. Due to increased hepatic and renal clearance and due to hypermetabolic state, burn injury shortened the duration of action of non-depolarising agent. Dose requirement of non-depoalrizing agent is also increased. This resistant is due to the increased population of extrajunctional ACh receptors by burn injury.

INDIVIDUAL NON-DEPOLARISING MUSCLE RELAXANT

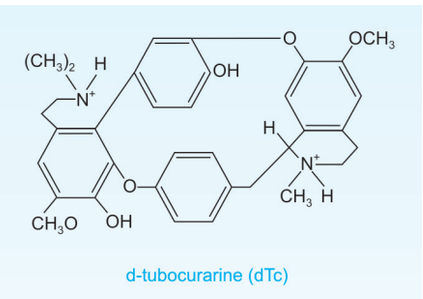
Tubocurarine (dTc)

d-tubocurarine is the first non-depolarising neuromuscular blocking agent found in the arena of anaesthesia. It was clinically first used by Griffith and Jhonson in 1942, at Montreal during an appendisectomy operation. It was first described by King in 1935 as bisquaternary compound. But, the correct formula of it is monoquaternary compound which is described recently. Despite many side effects, it was popular till 1970. But after that pancuronium and other short acting drugs like gallamine take the place of this long acting muscle relaxant. However, now it was only indicated for prolonged operation and where hypotension is desired which is due to the huge release of histamine by it (Fig. 16.4).

The release of histamine is profound by dTc than anyother non-depolarising neuromuscular blocking agent, when it is given in bolus. However, it can be prevented by slow administration, but not by H_1 & H_2 blockers. Histamine release may go up to 10 folds, causing severe hypotension (30 to 50% drop of BP). Though, theoretically it causes anaphylactoid reaction, but clinically is extremely rare, even in atopic individuals. Although, it was widely used in asthma without any adverse effect, still it may produce bronchospasm and should be avoided in these patient.

dTc has profound ganglion blocking effect as ganglion has the nicotinic receptors. But, this side effect is probably beyond the clinical dose range of it. Increase in HR by dTc is uncommon and may be due to the hypotension which is again due to the release of histamine.

As the hypotension by dTc is usually due to the release of histamine, but it also



d-tubocurarine (dTc)

Fig. 16.4: The chemical structure of d-tubocurarine

may be due to very slight ganglion blocking and cardiac depressant effect.

There is no active metabolism of dTc. It is mainly excreted unchanged through the urine. So, kidney is the primary and liver is the 2nd alternative route for elimination of it. In the presence of renal failure, biliary excretion of dTc is increased to provide a satisfactory alternative means of excretion. So, this drug is not indicated when both the renal and hapatic failure are present, at a time.

Clinical Use

dTc is not used now due to discovery of many other safe non-depolarising muscle relaxants. But the prolonged experience on this drug since 1946 has established its safety. It should be avoided in atopic and hypovolaemic patient. It should be avoided or used with caution in those patient in whom a modest fall of BP may endanger the cardiac function. The effective neuromuscular blocking dose of dTc is 0.3 to 0.5 mg/kg IV which provides good muscle relaxation for about 45 to 75 minutes.

Gallamine Triethiodide

Chemically, gallamine is a tribenzene triethiodide compound. In 1947, Bovet and his coworkers had first described the muscle relaxants properties of this synthetic product. It is the 1st synthetic neuromuscular blocking agent used in practice of anaesthesia. But, the effect of this muscle relaxant in man was first described in 1948 (Fig. 16.5).

Like dTc, it is a non-depolarising agent. Triquaternary structure of gallamine confers a strong vagolytic property on it and

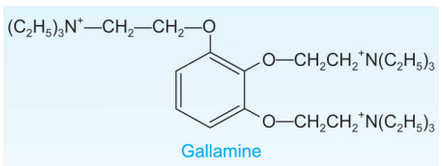


Fig. 16.5: It is a triquaternary ether of gallic acid. Its strong vagolytic property is probably due to the triquaternary structure of it. Gallamine is the only triquaternary compound, available in clinical anaesthesia

the degree of tachycardia goes up to 20 to 60% over the control value. This property of gallamine is useful when it is used in combination with halothane as halothane reduces the HR by stimulating the vagus. This tachycardia caused by gallamine can be accompanied by ↑BP and ↑CO. This may probably be due to increased release of catecholamines. Gallamine causes very little (1/2 to 1/5 quantity of histamine as campared to dTc) release of histamine and less block of autonomic ganglia. Therefore, it does not cause decrease in BP. It crosses the placenta in appreciable concentrations. It is not metabolised in the liver. So, it is entirely excreted by urine as unchanged form and has no biliary excretion. Thus, in the absence of renal function, there is no alternative way of lowering the blood concentration of this drug. The effective neuromuscular blocking dose of gallamine is 4 to 6 mg/kg through IV for intubation and 1 to 1.5 mg per kg of body weight through IV for maintenance of relaxation.

Pancuronium

It was introduced in clinical anaesthesia practice by Baird and Reid in 1964 by the addition of 2-acetylcholine like groups on the rigid nucleus of steroid molecule, at 2 or 3 and 16 or 17 position. Thus, pancuronium is a bisquaternary aminosteroidal non-depolarising muscle relaxing agent which was ultimately introduced in market in 1967. It is 10 times more potent than dTc with an ED_{95} value of about 0.06 mg/kg. High potency, lack of hypotensive effect, and mild to moderate vagolytic property, in contrast to then only available drug, i.e. dTc and gallamine at that time, make pancuronium an instant success in clinical practice. It was the first muscle relaxant introduced in clinical practice which did not have the ganglion blocking or histamine releasing properties, like d-tubocurarine and gallamine but has the long duration of action. So, its administration was ideally suited for longer operation, lasting for 3 to 4 hours and in which prompt extubation is not necessary. It is also suited for operation in which increased HR and BP is desirable as it has no ganglion blocking and histamine releasing property. Pancuronium also causes transient mild depression of pseudocholinesterase enzyme (Fig. 16.6).

CVS effects

Pancuronium stimulates the sympathetic nervous system by inhibiting the reuptake and increasing the release of catecholamines at nerve ending and by the muscarine receptor blockade action. Thus, catecholamines level increases by the use of pancuronium. All this effects results in tachycardia, ↑SVR, ↑CO, ↑after load, etc. So, pancuronium should not be used in patient with coronary artery diseases and myocardial failure. It may be associated with arrhythmias and cardiac ischaemia in susceptible individuals. So, the use of pancuronium is only advantageous in some situations where increase in HR, BP and CO is needed. Two such situations are when high dose of opium is used in cardiac surgery or in shock patients. Hence, the use of pancuronium has been decreased markedly following the introduction of other new short and intermediate acting muscle relaxants. But still it is a popular choice with many anaesthetists for use during cardiac surgery. This is because it tends to counteract the vagal effects which is found in high dose opiate anaesthesia. It causes very little release of histamine.

Metabolism and excretion

85% of the injected dose of pancuronium is cleared unchanged by the kidney and

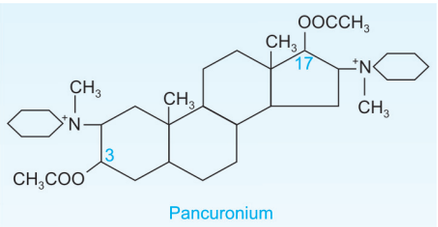


Fig. 16.6: The chemical structure of pancuronium

15% is metabolised in liver to 3-hydroxy or 17-hydroxy or 3,17-hydroxy compound to excrete throuh both kidney or bile. The first and principle metabolite of pancuronium is 3-hydroxy derivative whose potency is half than that of the mother compound. Due to the limited metabolism and limited biliary excretion its action is greatly prolonged in patient with severe renal disorder.

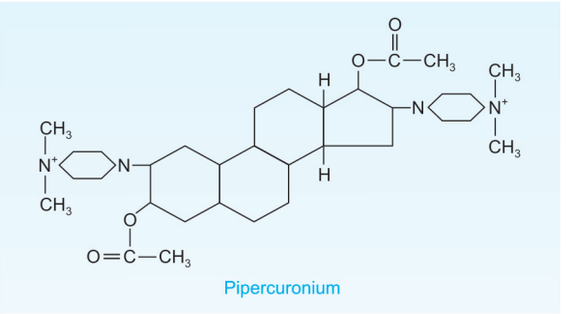


Fig. 16.7: The positive charge of the quaternary nitrogen atom in the pipercuronium molecule is separated by two carbon atoms from the carboxyl group in comparison to pancuronium. This chemical change reduces the vagolytic effect of pipecuronium by 10 times than pancuronium

Dose and clinical use

In clinical practice pancuronium is used in the dose of 0.07 to 0.1 mg/kg through IV (intubating dose) and the duration of action of this dose is 60 to 120 minutes. In this clinical dose (which is 1 to 1.5 times of ED_{95}) intubating condition only reach after 3 to 4 minutes of administration. However, higher doses have more faster onset and much longer duration of action. As pancuronium has the markedly cumulative action, so the top-up maintenance dose, only in the range of 0.01 to 0.015 mg/kg, should be used with duration of action of 30 to 40 minutes. With repeated administration progressive increase in the duration of action of pancuronium occur.

Pipercuronium

Chemically, pipercuronium is an aminosteroid compound. It is a pancuronium derivative, but vagolytic property is 1/10 of that of pancuronium. Pipercuronium is 20 to 30% more potent than pancuronium, but is free from cardiovascular side effects of the latter. Pipercuronium is a long acting drug with duration of action depending on the size of the dose. Spontaneous recovery from pipercuronium is very slow. It is only used when the early extubation is unnecessary and cardiovascular stability is required.

In the clinical dose range, pipercuronium does not release histamine. It has non-vagolytic action and does not block autonomic ganglia. The ED_{95} dose of pipercuronium during balanced anaesthesia is about 0.04 mg/kg. In comparison with pancuronium, increase in HR and cardiac index was observed only when the two times of ED_{95} dose of pipercuronium is administered. Haemodynamic changes are also minimal following pipercuronium up to the doses of 3 times of ED_{95} value (Fig 16.7).

No metabolism of pipercuronium occur in body. So, it is mainly excreted unchanged through the kidney. Liver is possibly a minor secondary pathway for elimination of pipercuronium. Intubating dose of pipercuronium is 0.08 to 0.12 mg/kg with duration of action 60 to 120 minutes. The onset of action of this intubating dose is 2.5 to 4.5 minutes and this dose is 1 to 2 times of ED95 value. The time of onset of neuromuscular block also decreases with increasing the dose. Maintance dose of pipercuronium is 0.005 to 0.01 mg/kg with the duration of action of 30 to 45 minutes. Like all other muscle relaxants renal elimination is also basic to pipercuronium. But the additional process of clearance shorten the duration of effect.

Vecuronium

Chemically, vecuronium is a 2-desmethyl analogue (or 16-monoquaternary derivative) of pancuronium with ED_{95} value of 0.04 to 0.05 mg/kg. However, the stereoisometric relationship of the 3-acetyl group on the molecule of vecuronium makes it structurally dissimilar from the pancuronium. It is more lipid soluble than pancuronium. This is because of the absence of methyl group in the molecule of vecuronium (Fig. 16.8).

The loss of quaternising methyl group at position 2, also destabilises the 3 acetyl group present in the molecule of it. As a result, the vecuronium compound in the form of solution has very short half-life and should be prepared in alkaline buffer solution shortly before its use. But, the powder of it does not need refrigeration. It is the first non-depolarizing agent with intermediate duration of action and the most popular muscle relaxant in clinical practice at present. The reason of popularity of vecuronium are: (i) it helps in more facile tracheal intubation, (ii) it causes easy administration by infusion for maintenance, (iii) it possesses intermediate duration of action, (iv) it has faster and more complete recovery, (v) it causes a remarkable lack of cardiovascular side effect, throughout a wide clinical dose range from one to eight times (0.05 to 0.4 mg/kg). It is more potent than pancuronium, because ED_{90} value of vecuronium

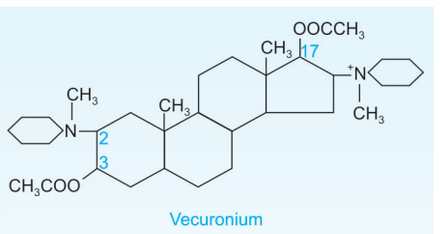


Fig. 16.8: The chemical structure of vecuronium

is 0.03 mg/kg, compared to 0.05 mg/kg for pancuronium.

It has 20 times less vagolytic action than pancuronium. It possesses no ganglion blocking, histamine releasing and cumulative effect. The drug is rapidly cleared from plasma. It has a short α-half-life, compared to pancuronium. However, its β half-life is similar to that of pancuronium (Fig. 16.9).

Vecuronium has two major routes of elimination. These are liver and kidney, and they are of approximately equal importance. 30 to 40% of the injected dose of vecuronium is deacetylated at 3 and 17 position by liver, producing 17-OH vecuronium, 3-OH vecuronium and 3,17-OH vecuronium. But, the major metabolite is 3-OH vecuronium which is as potent as the mother compound and is excreted through both urine and bile. For this reason, the effects of vecuronium are prolonged in patients with hepatic or renal failure. These metabolites may also be responsible for prolonged paralysis, seen after the long term administration of vecuronium in patients in ICU. Because of the lack of cumulative effect, vecuronium can be used as continuous IV infusion and rapid recovery is ensured after infusion has stopped.

Doses

The intubating dose of vecuronium is 0.1 to 0.2 mg/kg through IV route with duration of action of 45 to 90 minutes. It provides acceptable intubating condition within 90 to 120 seconds. However, both the onset and duration of action are dose related. The onset of action of vecuronium can also be accelerated by inducing anaesthesia with a potent volatile agent such as sevoflurane. The maintenance dose of vecuronium is 0.01 to 0.02 mg/kg IV, as intermittent bolus with duration of action only 15 to 30 minutes. The infusion dose of vencuronium is 0.8 to 2 mg/kg/minute.

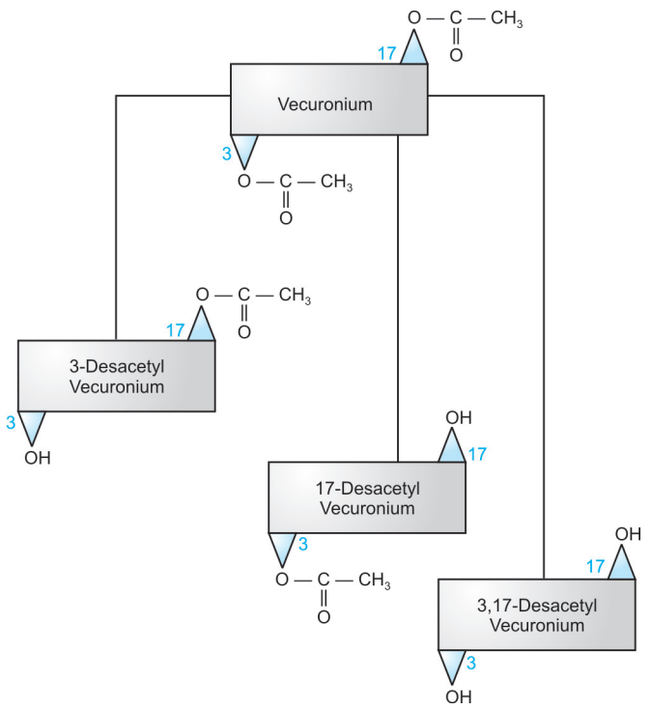


Fig. 16.9: Schematic diagram of metabolism of vecuronium. Metabolism of vecuronium occurs in the liver. About 30-40% is deacetylated at the 3 and 17 position. The major metabolite is 3 – OH vecuronium. Other metabolites are 17 OH vecuronium and 3,17 – OH vecuronium. All these metabolites are excreted in the urine and bile

Because of the safety factor, top-up dose of vecuronium can also be given in multiples of ED_{95} value for maintenance.

Of all the neuromuscular blocking drugs available, vecuronium is the most specific for neuromuscular junction and, therefore, has the least side effect. So, even when used in large doses, it is associated with extremely good cardiovascular stability. There is a wide separation between the vagal and neuromuscular blocking dose (68:1) of vecuronium. It has little sympathetic stimulation activity. Larger doses of vecuronium (1-4 × ED_{95}) can be administered to achieve a faster onset of action and good intubating conditions for rapid sequence intubation.

Atracurium (BW33A)

Like vecuronium, atracurium also has revolutionised the clinical anaesthesia practice due to the same reason.Chemically it is a synthetic bisquaternary benzylisoquinolinium ester and is of intermediate duration of action. It is the first non-depolarising muscle relaxant which is degraded in plasma by spontaneous chemical reaction, called the Hoffmann elimination, but not by the biological process, i.e. metabolism in liver and excretion through urine or bile.

The cardiovascular effects of atracurium are same as that of vecuronium, but it has a strong potential for the release of histamine. However, it is evident only when the higher doses (two times of ED_{95} value) are injected very rapidly. The release of histamine causes ↓BP and facial erythema. But the combined H_1 and H_2 receptor blocker effectively blocks the CVS manifestation of histamine, released by atracurium. The atracurium has no vagolytic action. It also does not block the autonomic ganglia. The pharmacodynamics of atracurium are unchanged with advancing age.

Atracurium is spontaneously degraded by (i) Hoffmann elimination, and (ii) ester hydrolysis. The Hoffmann elimination is

a pure chemical process, where the parent molecule of atracurium is fragmented by itself to laudanosine (a tertiary amine) and a monoquaternary acrylate at the physiological pH and temperature of plasma, i.e. at a pH of 7.4 and a temperature of 37°C. This spontaneous degradation is slowed down by the fall in pH (acidic condition) and temperature (hypothermia). Whereas degradation is accelerated by alkaline pH and rise in temperature of plasma. So, atracurium is stored at 4°C and is buffered to a pH of 3, where it is stable. Atracurium becomes unstable when it is injected in blood-stream and breakdown from itself in blood's normal pH and temperature. The alteration of pH and temperature of blood within its physiological range does not decrease the rate of Hoffmann's elimination of atracurium and does not cause clinically significant increase in the duration of action. Atracurium's duration of action is prolonged markedly by hypothermia. The ester hydrolysis which is a second pathway for degradation of atracurium may be of more importance than was originally thought. The steps of this hydrolysis is shown in figure. Laudanosine which is formed by Hoffmann's degradation is excreted through urine and bile. It can cross the blood brain barrier and enter the CNS. Very high doses of laudanosine can cause CNS excitation. But no clear cut cases have been noted in human (Fig. 16.10).

The duration of action of atracurium is not prolonged by the absence of hepatic and renal pathways for excretion. So, it is the relaxants of choice for patient with renal and hepatic failure. 90% atracurium is destroyed in plasma. Only 10% drug is excreted unchanged through urine. (Fig 16.11).

Doses

The intubating dose of atracurium is 0.5 to 0.6 mg/kg, with duration of action only 30 to 45 minutes. Actually, the ED_{95} value of atracurium is approximately 0.2 mg/kg and the onset of action of this ED_{95} value is 3 to 5 minutes. So, this onset of action can be reduced by increasing the intubating dose from 0.2 mg/kg to 0.5 mg/kg. The maintenance dose of atracurium is 0.1 to 0.15 mg/kg as intermittent bolus with duration of action only 15 to 20 minutes. The infusion dose of atracurium is 4 to 12 µg/kg/min. Repeated administration of atracurium does not lead to an increase in the duration of action. The unique type of metabolism of atracurium makes it suitable for use in the critically ill patient, as it is associated with rapid recovery.

Rocuronium (ORG – 9426)

Chemically rocuronium is a vecuronium derivative. It is a steroidal muscle relaxants with intermediate duration and faster onset of action than that of vecuronium. It is developed as a non-depolarising agent that would have an onset of action closer to that of succinylcholine. The basis for this development was the observation that potency and the speed of onset of action were inversely related. It means when potency decreases, the onset of action increases. This can be explained by the fact that to compensate the decreased potency, large volume of drug is needed which increases the onset of action (Fig. 16.12).

Though, rocuronium is a derivative of vecuronium, still it is stable in solution and formulated as an aquous ready to use form. It is 7 to 8 times less potent than vecuronium, with an estimated ED_{95} value of approximately 0.3 mg/kg. Due to the same molecular weight with vecuronium and larger volume is needed for initial bolus dose due to low potency, the large number of molecules of rocuronium reach the junctional nicotinic receptors within few circulation time, causing faster onset of action. The faster onset of action of rocuronium also can be improved by the addition of opiates, ketamine, or a small dose of ephedrine which maintain a better cardiac output and thus improves the rapid delivery of muscle relaxant to the neuromuscular junction. The weaker binding ability of rocuronium molecule with receptor allow repetitive binding and unbinding and thus easy diffusion of drugs away from the receptor site which limits the duration of action.

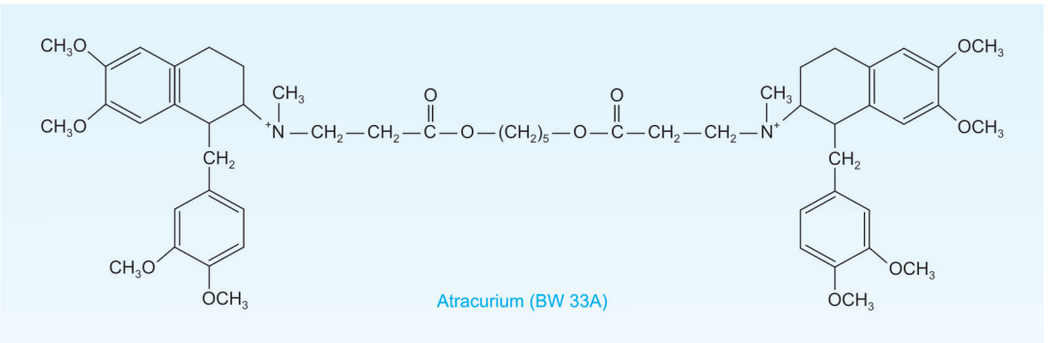


Fig. 16.10: It is a benzylisoquinolinium diaster and undergoes the Hoffmann elimination. This reaction is facilitated by the orientation of the ether oxygen of the carboxyl group toward the centre of chain

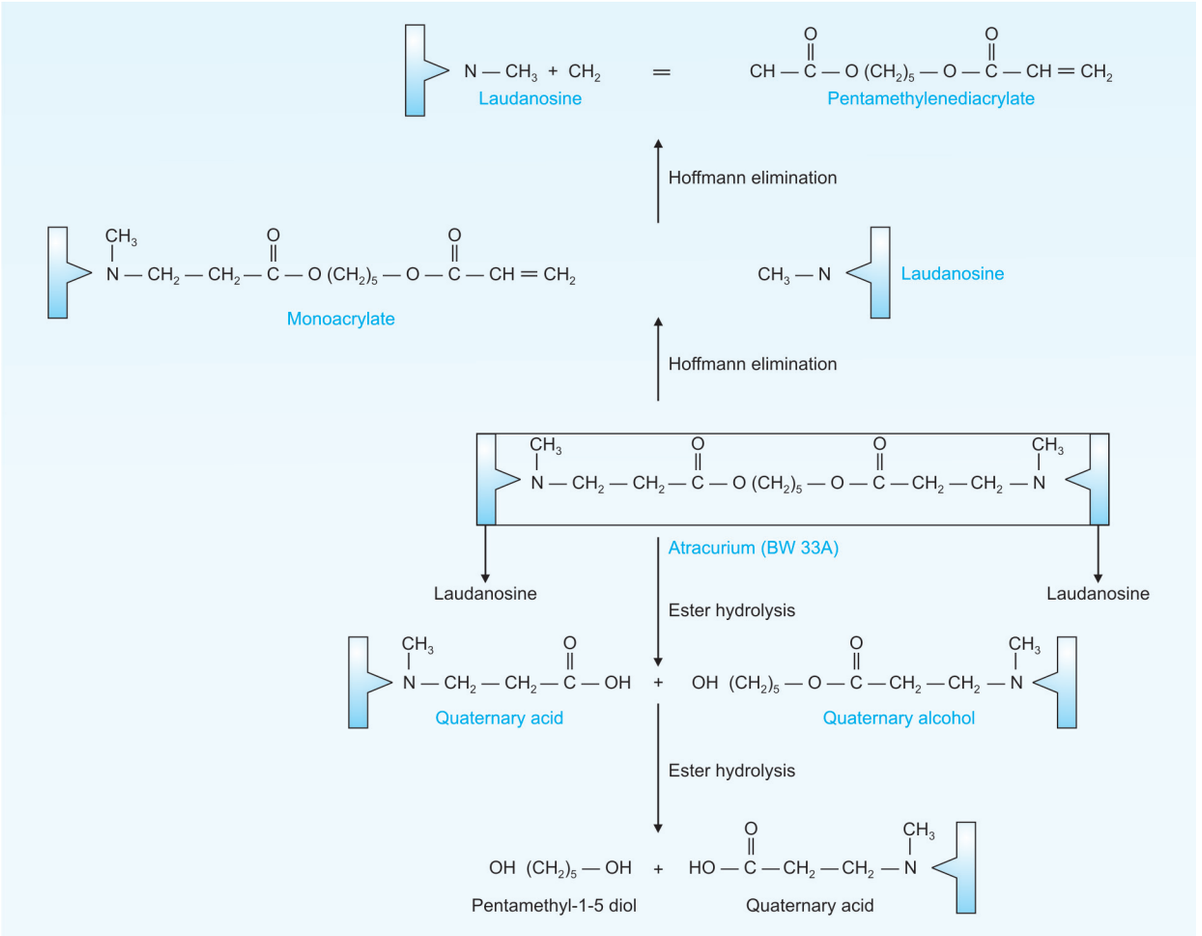


Fig. 16.11: Schematic diagram of metabolism of atracurium. The major metabolite of atracurium is laudanosine. It is excreted through urine and bile. Laudanosine may enter the CNS as it is a tertiary amine. Less than 10% of the atracurium is excreted unchanged as the parent compound

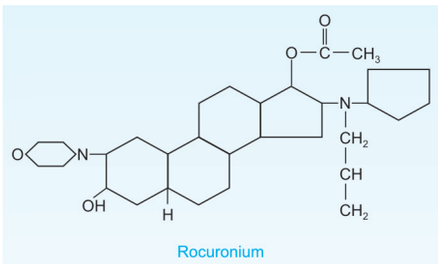


Fig. 16.12: A vecuronium derivative of faster onset and intermediate duration of action. The faster onset is conferred by lower potency. The lower potency is largely due to the D-ring substitutions with respect to vecuronium

Rocuronium is peculiar for its lower potency with faster onset of action. The onset of maximum block following an intubating dose of 0.6 mg/kg occurs in about 60 to 90 seconds, which is near similar to that of succinylcholine. More larger doses have a more rapid onset of action. However, a dose of about 1 mg/kg is required to obtain a good intubating conditions during a rapid sequence induction. The duration of action of rocuronium is similar to that of vecuronium and atracurium in comparable doses. The clinical duration of action of 0.6 mg/kg of rocuronium is 30 minutes. The repeated administration of it does not usually result in a prolonged effect. With adequate dose, rocuronium may enable tracheal intubation within 60 seconds and make it an ideal substitude for succinylcholine, during rapid sequence intubation.

It has no ganglion blocking effect and no histamine releasing property, but has mild vagal blocking effect, resulting sometimes in increase in heart rate. So, the commonly used doses of rocuronium are associated with cardiovascular stability, except only a small increase in heart rate.

Rocuronium does not undergo any metabolism. So, it is excreted unchanged through the bile and urine. Hence for elimination of rocuronium the dual renal and hepatic pathways exist. Unchanged drug has been recovered from bile and urine. Action of it is prolonged in severe

renal and hepatic dysfunction. The rocuronium is administered in an initial bolus dose of 0.6 to 1 mg/kg. The block can be maintained by repeated administration of bolus dose of about 0.1 to 0.15 mg/kg or by a continuous infusion in a dose of 10 µg/kg/minute. With the rapid onset of action, rocuronium is very useful for rapid sequence intubaion when succinylcholine is contraindicated. A useful dose in this situation is 1 mg/kg and it should be realised that this dose will have a clinical duration of action of about 1 hour. So, it is also very important to assess the airway carefully before intubation, if the use of rocuronium is contemplated in this setting.

Mivacurium

Like atracurium, mivacurium is a benzylisoquinolinium diaster and a non-depolarizing muscle relaxants. The beauty of mivacurium lies in its spontaneous hydrolysis in plasma by pseudocholinesterase like succinylcholine, but slightly at slower rate (at about 80% of the rate of metabolism of succinylcholine). This mechanism of metabolism (enzymatic hydrolysis) of mivacurium allows it to enjoy the shorter duration of action than vecuronium and atracurium, but 2 to 2.5 times than that of succinylcholine.

It has neither autonomic ganglion blocking action, nor any vagolytic action. Like atracurium, it has the potential to cause histamine release, causing facial erythema and ↓BP. Duration of action of mivacurium is 2 to 2.5 times longer than that of succinylcholine, but 1/2 to 1/3 times (Fig. 16.13) longer than that of atracurium. It can also be used by continuous infusion to maintain smooth relaxation of muscle for surgical procedure of intermediate length extending from 30 to 90 minutes. However, prolonged infusion of mivacurium may be given without any increase in recovery time. The recovery from mivacurium is not affected by the dose or by the duration of infusion. The neuromuscular block produced by mivacurium can also be antagonised by anticholinesterase (unlike succinylcholine) or by pseudocholinesterase enzyme (like succinylcholine).

90% of the injected dose of mivacurium is hydrolysed by pesudocholinesterase to mivacurium monoester and amino alcohol. The 10% of administered mivacurium is excreted unchanged through the urine. The Hydrolysed product of mivacurium is also excreted through the bile and urine. So, like succinylcholine, action of mivacurium is lengthened in patient, carrying atypical pseudocholinesterase enzyme. In heterozygotes, the duration of action of mivacurium is lengthened for 15 to 30 minutes. However, in atypical homozygotes (incidence 1 in 3000) the duration of action of it may be lengthened for 3 to 4 hours. Once the signs of recovery are begining to be noted, then antagonism by neostigmine should be initiated. If reversal is still inadequate then another dose of neostigmine is administer after ½ an hour. Alternatively, the pseudocholinesterase enzyme may be given through IV. Perhaps because of the inherent short duration of action of mivacurium, the reduction of duration of action by administering anticholinesterase is relatively small. Theoretically, anticholinersterase (neostigmine) may prolong the action of mivacurium like succinylcholine. But this has not been found to occur when the neostigmine has been administered to antogonise the neuromuscular block produced by mivacurium. However, previously administered neostigmine may prolong the effects of subsequently administered mivacurium (Fig. 16.14).

Doses

The ED_{95} dose of mivacurium is 80 µg/kg and like other non-depolarising muscle relaxant, the onset of action is dose dependent. It is the currently available shortest acting non-depolarising muscle relaxant and the duration of relaxation is only about 15 minutes, following a dose of 0.15 mg/kg ($2 \times ED_{95}$). The increase in the duration of action of mivacurium with increasing the doses is not as marked as with other non-depolarising relaxants. Intubating dose is 0.2 to 0.25 mg/kg with duration of action of only 15 to 20 minutes. The maintenance dose of mivacurium is 0.05 to 0.1 mg with duration of action of 5 to 10 minutes. Mivacurium is the most suitable agent for maintaing relaxation by infusion. Continuous infusion is the preferred method of administration of mivacurium

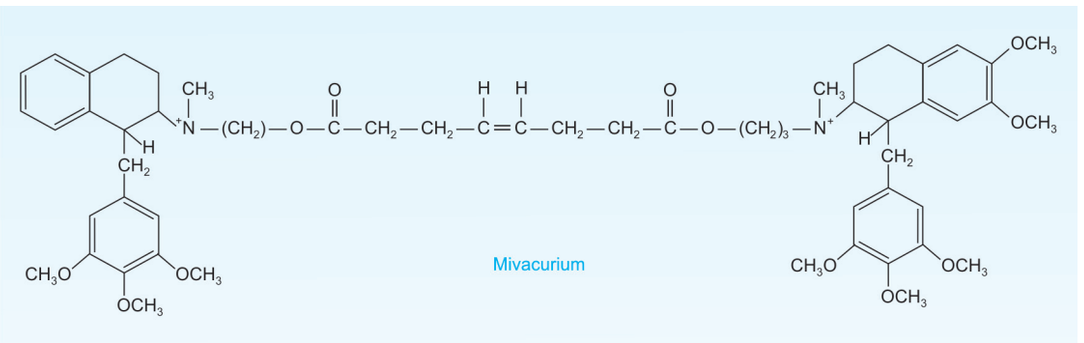


Fig. 16.13 : It is a benzylisoquinolinium disater which is hydrolysed by pseudocholinesterase at the rate of about 80% of succinylcholine. This hydrolysis is facilitated by the orientation of ether oxygen of the carboxyl group toward the quaternary nitrogen atom

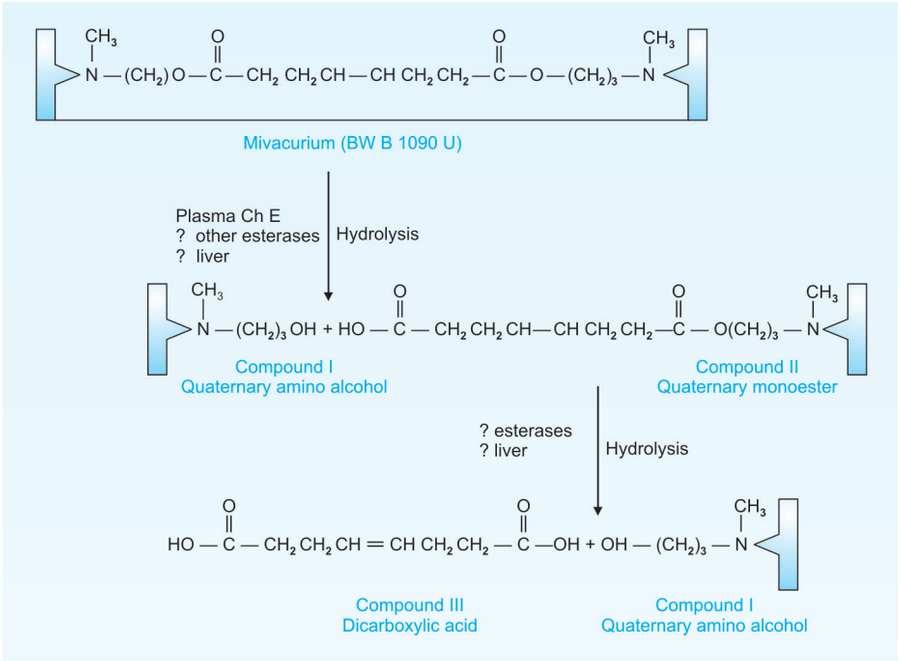


Fig. 16.14: Schematic diagram of metabolism of mivacurium. It is metabolised by plasma cholinesterase. The reaction occurs at the rate of about 70 to 80% of succinylcholine. These metabolites are inactive and carry positive charges. So their CNS enyry is minimal

for anything but brief surgical procedure. The recovery does not change significantly by repeated administration of bolus doses or infusion of varying doses and duration. It suggests minimal or no cumulative property of mivacurium. Infusion dose of mivacurium is 6 to 8 µg/kg/min.

There exist three isomers of mivacurium. Among these cis-cis isomer is hydrolysed by pseudocholinesterase very slowly, but fortunately constitutes only 5% of the commercial preparation. However, 95% of the commercial preparation is made up of cis-trans and trans-trans isomer of mivacurium which is hydrolysed very rapidly (t 1/2 β is 2 to 3 minutes). Another advantage of cis-cis isomer is that it is of less potent, about one-tenth of the neuromuscular blocking potency of other two isomers. It (cis-cis isomer) undergoes some renal excretion as well as is broken down by plasma cholinesterase. In renal failure the duration of action of mivacurium is prolonged. In hepatic failure the action of mivacurium is also prolonged due to the reduction of plasma cholinesterase activity. The same is true for elderly patient also.

Cisatracurium (51W89)

Cisatracurium constitutes about 15% of the commercial available preparation of atracurium. It is one of the 10 stereoisomers of atracurium and is very potent. It liberates only minimum amount of histamine than the parent compound. It is in clinical practice only for about last 6 years. In comparison to atracurium the ED_{95} value of cisatracurium is 0.05 mg/kg which indicates that it is 4 times more potent than atracurium (ED_{95} value of atracurium is 0.2 mg/kg). However, being more potent, the drug has slower onset of action. In the dose of 0.1 mg/kg (intubating dose 0.1 to 0.15 mg/kg) the onset of maximum neuromuscular block in cisatracurium takes about 3 to 5 minutes. Although increasing the dose (0.15 mg/kg) accelerates the onset of action, but it is still slower than that of atracurium. The duration of action of cisatracurium is 30 to 60 minutes at the initial bolus dose of 0.1 to 0.15 mg/kg and it depends on the dose. At equivalent dose, the duration of action of cisatracurium is slightly longer than that of atracurium. Cisatracurium can be used by intermittent bolus in the dose of 0.02 mg/kg with action lasting for 15 to 20 minutes or by continuous infusion in the dose of 1.5 µg/kg/minute for longer procedures (Fig. 16.15).

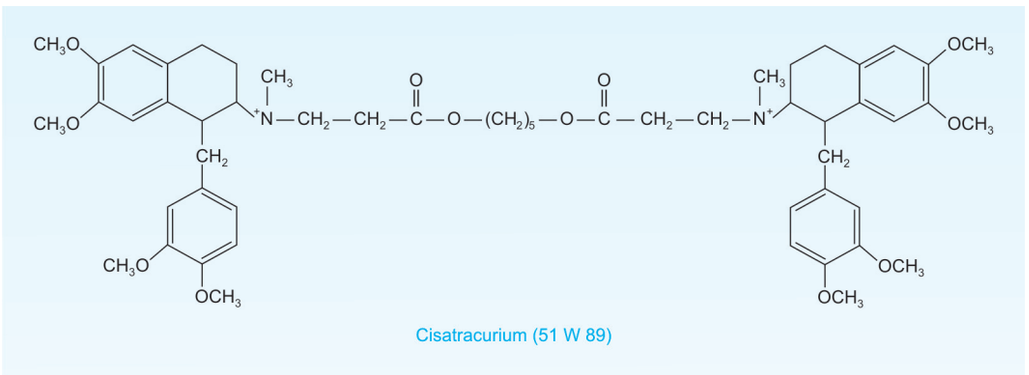


Fig. 16.15: This is the chemical structure of cisatracurium which is one of the isomers of atracurium. The R-cis and the R'-cis conformation of the structure provide greater potency and significantly reduces the side effects of release of histamine in comparison to atracurium

As cisatracurium releases the negligible amount of histamine, so it gives us a stable cardiovascular activity. Even, when administered in higher doses (eight times the ED_{95} dose), the cisatracurium does not give rise to any significant changes in arterial pressure and heart rate. It is eliminated predominantly by the Hoffmann degradation like atracurium. So, the pharmacokinetics of cisatracurium are independent of dose in healthy adult pateints. The renal clearance is responsible for 10% of total elimination of drug from the body. So, the recovery profile is not altered in patients with liver failure, but becomes slightly slower in renal failure patient. Compared with atracurium, the cisatracurium produces much less laudanosine, even when the drug is given by continuous infusion.

Rapacuronium (ORG – 9487)

Chemically rapacuronium is a steroidal non depolarising muscle relaxant. Introduction of rocuronium in clinical practice stimulates the search for muscle relaxants which have rapid onset, but short duration of action like succinylcholine. This is because rocuronium has rapid onset of action like succinylcholine, but does not have short duration of action. So, it has instigated the advent of rapacuronium which has both the rapid onset and a shorter duration of action (Fig. 16.16).

Rapacuronium is analogue of vecuronium and is of low potency with an ED_{95} value of about 0.75 mg/kg. In the dose of 1.5 mg/kg, rapacuronium produces complete block in 80 seconds, compared with 60 seconds for succinylcholine in the dose of 1 mg/kg. The rapid onset of rapacuronium is possibly due to its low potency necessiating higher doses and indicating a rapid access to the site of action. Though initially rapacuronium was thought to have short duration of action of only 8 to 9 minutes in the dose of 1.5 mg/kg, but recent studies reported this value to be about 14 to 20 minutes. The drug also showed cumulative properties − especially after repeated doses or administration by infusion. Rapacuronium caused higher rate of respiratory side effects − especially bronchospasm both in adults and children − though its exact cause has not yet been determined. Histamine release and muscarinic receptor stimulation by rapacuronium in the airways may be the probable explanation of bronchospasm. So, the drug was withdrawn from clinical use finally in March 2001, due to its higher risk of bronchospasm.

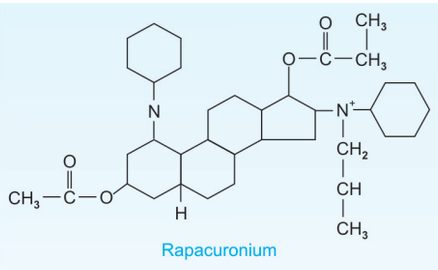


Fig. 16.16: The chemical structure of rapacuronium

ANTAGONISM OF NEUROMUSCULAR BLOCKADE

The neuromuscular blockade produced by non-depolarising muscle relaxant can be antagonized by temporary inhibition of true cholinesterase enzyme which is present in synaptic cleft and which inactivates the acetylcholine (ACh). Thus, anticholinesterase antagonize the true cholinesterase and increase the concentration of ACh and improve the neuromuscular transmission. The agents which inhibit this true cholinesterase enzyme are called the anticholinesterase or acetylcholinesterase enzyme inhibitor. The clinically commonly used cholinesterase enzyme inhibitors are edrophonium, pyridostigmine and neostigmine. They indirectly antagonise the non-depolarising block by: (i) increasing the concentration of neurotransmitter such as ACh at the motor nerve terminals, and (ii) blocking the neuronal potassium channels and thus preventing the hyperpolarisation.

Reversal of non-depolarising block by acetylcholinesterase (ACh E) inhibitor depends on five major factors.

(i) Depth of Block at the Time of Administration of ACh E-Inhibitor

The deeper the neuromuscular block will be the longer the time interval will be required between the administration of non-depolarising muscle relaxant and the administration of a standard dose of antagonist (ACh E–inhibitor) in restoring the twitch or TOF response to levels which is compatible with the clinically normal function of muscle. Usually the deeper block requires much longer time such as 15 to 30 minutes for adequate reversal. The relationship between the reversal time and the depth of block is hyperbolic. Maximum antagonistic effect of neostigmine is likely to be reached within 10 minutes after its administration.

(ii) Type of Antagonist Administered

Under standard condition and in moderate depth of block the order of rapidity of action of antagonist is: edrophonium > neostigmine > pyridostigmine. But, edrophonium is not as effective (or potent) as neostigmine in antagonising profound muscular blockade which is greater than 90% of twitch depression. As depth of block become more intense, edrophonium becomes less potent than neostigmine. The dose response curves between edrophonium and neostigmine are not parallel and become increasingly divergent as the depth of block intensifies. It indicates that edrophonium is less effective than neostigmine at very deep levels of block.

ACh E-inhibitor acts indirectly by increasing the level of ACh at synaptic cleft by inhibiting the true cholinesterase. ACh has both nicotine and muscarinic response as it acts on both the receptors. So, ACh E-inhibitors also has indirect both nicotinic and muscarinic effects. But, the nicotinic effect that is muscular contraction or

reversal of neuromuscular blockade is only desired. So, the muscarinic effect of ACh E inhibitor which is not desired should be blocked by anticholinergic agents such as atropine or glycopyrrolate. Atropine acts more rapidly than glycopyrrolate. So, atropine is better suited with rapid acting edrophonium, whereas glycopyrrolate is better suited with slower acting neostigmine.

It was initially thought that edrophonium is not suitable for antagonism of neuromuscular block, because of its too short duration of action. But, when it is used in standard large dose of 0.5 to 1 mg/kg, then a sustained action of antagonism results. Infact, elimination half-life of edrophonium in this dose is similar to that of neostigmine. So, use of edrophonium in this dose is more justified for faster onset of action, fewer muscarine side effects and standard duration of action like neostigmine.

The highly purified preparation of human pseudocholinesterase enzyme is also available. This enzyme antagonises the block produced by mivacurium and succinylcholine in patients with abnormal pseudocholinesterase activity and this antagonism may be 100%.

(iii) Dose of Antagonist

It is commonly thought that larger dose of ACh E-inhibitor can antagonise any level of depth of block more rapidly and more completely than smaller dose and this dose of ACh E-inhibitor is parallel to the depth of block. But, this is true up to a certain point i.e. maximum level of AChE-inhibitor, beyond which this is not true. For neostigmine, this maximum dose limit is 0.06 to 0.08 mg/kg (or 60 to 80 µg/kg) and for edrophonium this limit is 1 to 1.5 mg/kg. The maximum effect of both the drugs occur between 5 to 10 minutes. Further recovery that occur slowly beyond that period largely dependent on the rate of clearance of muscle relaxants from the body.

If 30 minutes after neostigmine administration adequate reversal of block does not occur, then a good rule of practice is: (a) continue the support of airway and ventilation, (b) wait for another 30 to 45 minutes which is 50% of the half live of both muscle relaxants and neostigmine, (c) administer another dose of same antagonist equal to the 50% of original dose (30 µg/kg of neostigmine). This repeat dose of ACh E-inhibitor would help to return the function of muscle power satisfactorily within subsequent 30 minutes. Neostigmine and edrophonium do not potentiate each other and should not be mixed and repeat dose should be of the original drug.

(iv) Concentration of Inhaled Anaesthetics

The inhaled anaesthetics retard the antagonism of neuromuscular block produced by ACh E-inhibitors.

(v) Rate of Clearance of Muscle Relaxants

The clearance Rate (CR) for different muscle relaxants are different. Usually for long acting drugs the CR is 1.2 to 2 ml/kg/min and reversal time interval is 20 to 40 minutes from deep depth of block which is about 95% of twitch depression.

CR of intermediate acting drugs is 3 to 6 ml/kg/min and reversal time interval is 12 to 15 minutes from 95% block. For mivacurium CR is 50 ml/kg/min and reversal time interval is 7 to 8 minutes from 95% block by neostigmine. So, higher the plasma clearance of muscle relaxant, shorter the time interval will be required for antagonism of block. If adequate reversal time interval from 95% block is not elapsed and neostigmine is administered, then after 10 minutes when the maximum antagonistic effect of neostigmine occurs, little amount of long acting drug is removed from plasma. Therefore, there is chance of recurization. So, in such circumstances restoration of adequate neuromuscular function depends entirely on the action of neostigmine, and large doses (50 to 70 µg/kg) is recommended for antagonism of long acting drug. This larger dose of ACh E-inhibitor maximally inhibit true ACh E but may cause a transient neuromuscular block by themselves.

INDIVIDUAL NEUROMUSCULAR ANTAGONIST

Neostigmine

Chemically neostigmine is an quaternary amine compound and is also an ester of an alkyl carbamic acid. It is a reversible (acid transferring) cholinesterase inhibitor. It acts by binding to the esteric site of acetylcholinesterase enzyme and thus temporary block and subsequently prevent the ACh from hydrolysis by this enzyme. Later the ACh E inhibitor is hydrolysed by the enzyme like ACh and make free the acetylcholine esterase (ACh E) enzyme but at a much slower rate than the acetylcholine. So, the ACh E enzyme remains engaged till the neostigmine is hydrolysed completely by it and cannot attack the ACh which will accumulate gradually. Thus, the accumulation of acetylcholine at the neuromuscular junction allows it to make competitive antagonism with any non-depolarising muscle relaxant that is present there. Hence, the mode of action of neostigmine is to let the accumulation of acetylcholine at the motor end-plate and the reversal of neuromuscular blockade (Fig. 16.17).

The pharmacological effects of neostigmine is indirect and is due to the accumulation of excess ACh which has both the nicotinic and muscarinic action. So, the nicotinic action of neostigmine caused by

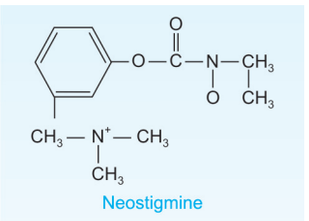


Fig. 16.17: The chemical structure of neostigmine

the nicotinic aciton of ACh is manifested as the removal of neuromuscular blockade or muscular contraction. Whereas, the muscarinic action of neostigmine caused by the muscarinic action of ACh is manifested on different organs where there is presence of muscarinic receptors such as heart, bronchial glands, intestine, blood vessels, etc. The effects of neostigmine on the cardiovascular system due to accumulation of ACh are variable and depend upon (Table 16.16) the prevailing autonomic tone. The drug may cause bradycardia, leading to a fall in cardiac output. It increases the duration of effective refractory period of cardiac muscle and decreases the conduction time in conducting tissue. In high doses, neostigmine may cause hypotension secondary to a central effect also. It increases the bronchial secretion and may cause bronchoconstriction. Miosis and failure of accomodation of the eye may be precipitated by the administration of this drug. Neostigmine increases salivation, elevates oesophageal and gastric tone, increases gastric acid output and increases gastrointestinal tract motility. Nausea and vomiting may occur. It increases ureteric peristalsis and may lead to involuntary micturition. Sweating and lacrimation are increased by neostigmine. All these effects are due to the muscarinic action of accumulated ACh caused by neostigmine.

The side effects of neostigmine are due to the excess manifestations of its pharmacological actions as described above. The cardiac arrest also has been reported after the use of large dose of neostigmine. In small doses, the drug has an indirect action on skeletal muscle leading to muscular contraction by accumulation of ACh. But in higher doses, neostigmine like other anticholinesterase may also block the neuromuscular transmission by allowing the accumulation of excess acetylcholine which acts like succinylcholine.

It is very poorly absorbed when administered orally and the bioavailability by this route is only 1 to 2%. This drug is highly ionised in solution and therefore does not cross the blood-brain barrier to any significant extent. Neostigmine is 6 to 10% protein bound in the plasma and the volume of distribution is 0.4 to 1 litre/kg. It is predominantly metabolised or broken down by plasma cholinesterases to a quaternary alcohol. Some, hepatic metabolism with subsequent biliary excretion may also occur. The 50 to 60% of an administered dose of neostigmine is excreted through urine. The rate of clearance of neostigmine is 5 to 10 ml/min/kg. and the elimination half-life is 15 to 80 minutes. The clearance of neostigmine is decreased and the elimination half-life is increased in the presence of renal impairment.

Table 16.16: Comparison between physostigmine and neostigmine

		Physostigmine	*Neostigmine*
1.	Source	Natural alkaloid, obtained from calabar bean	Synthetic
2.	Chemistry	Tertiary amine derivative	Quaternary ammonium compound
3.	Oral absorption	Good	Poor
4.	CNS effect	Present	Absent
5.	Topical action on eye	Good corneal penetration	Poor corneal penetration
6.	Direct action on cholinergic receptor	Absent	Present
7.	Prominent effect on	Autonomic target organ such as eye	Myasthenia gravis
8.	Important use	In glaucoma (miotic)	Myasthenia gravis

It is available for oral use as 15 mg tablet of neostigmine bromide and as a clear, colourless solution for injection in ampule, containing 0.5 mg/ml of neostigmine methylsulphate. A fixed dose combination, containing 0.5 mg of glycopyrrolate and 2.5 mg of neostigmine methylsulphate per 5 ml of injection, is also available for the reversal of neuromuscular blockade at the end of surgery. The adult oral dose of neostigmine is 15 to 30 mg at regular interval of 2 to 4 hours. The intravenous dose of neostigmine for the reversal of non-depolarising neuromuscular blockade is 50 to 70 µg/kg. It is administered slowly and in combination with an appropriate dose of an anticholinergic agent such as atropine or glycopyrrolate to counter act its muscarinic effect. The peak effect of the drug when administered intravenously occurs after 5 to 10 minutes of injection. A single dose of neostigmine has a duration of action for only 50 to 60 minutes.

Neostigmine prolongs the duration of the action of succinylcholine by inhibiting the plasma cholinesterase enzyme. There is also some evidence that the use of neostigmine to reverse the neuromuscular blockade is associated with an increased incidence of gastrointestinal anastomotic breakdown due to increased intestinal motility. Pyridostigmine resembles neostigmine in all these respects, but in dose-to-dose comparison it is less potent and longer acting. So, less frequent dosing of pyridostigmine is required in myasthenia gravis. The dose of pyridostigmine in myasthenia gravis is 60 to 180 mg orally and 1 to 5 mg IM or SC.

Neostigmine is used:

i. For the reversal of non-depolarising neuromuscular block,
ii. For the treatment of myasthemia gravis,
iii. For the treatment of paralytic ileus,
iv. In urinary retention.

Edrophonium

Chemically the edrophonium is a synthetic ammonium compound. Like neostigmine

it is also a prosthetic reverseble inhibitor of true acetylcholinesterase. So, it acts by competing with acetylcholine like neostigmine for the anionic site of the enzyme cholinesterase enzyme and reversibly binds to it. Thus, it left acetylcholine unbroken and accumulate to facilitate the neuromuscular transmission. A part of the effect of the drug also appears to be exerted through the prejunctional receptors and increase the liberation of ACh (Fig. 16.18).

Thus, the mode of action of edrophonium is like neostigmine, i.e. nicotinic and cholinergic. Nicotinic action improves neuromuscular transmission and prevent muscular paralysis. The cholinergic action is like ACh. So, the drug may cause bradycardia leading to a fall in cardiac output, increase in effective refractory period of cardiac muscle and decrease in conduction time. Like acetylcholine, edrophonium also increases bronchial secretion and may cause bronchoconstriction. For CNS effect, agitation and dreaming may occur by this drug and has a predictable miotic effect. Weakness of muscle due to fasciculation and paralysis may also occur due to accumulation of excessive acetylcholine when edrophonium is administered to normal subjects. The drug increases the salivation and lower oesophageal and gastric tone. It increases the gastric acid output and gastrointestinal tract motility. Nausea and vomiting may occur. Like neostigmine, edrophonium also increases the ureteric peristalsis and may lead to involuntary micturition. Lacrimation and sweating are increased by the drug.

Fig 16.18: This figure shows the chemical structure of edrophonium

The metabolic fate of edrophonium is uncertain. It is not hydrolysed by cholinesterase like acetylcholine or neostigmine. The volume of distribution of edrophonium in tissue is 0.9 to 1.3 litre/kg. The details of excretory pathways of this drug are unknown. The clearance rate of edrophonium is 6 to 12 ml /kg/minute and the elimination half-life is 110 minutes. The toxic effects of edrophonium are nothing, but only the exaggerated manifestations of its pharmacological actions which are described above. Cardiac arrest has also been reported after the use of edrophonium.

Edrophonium is usually administered intravenously. It has a more rapid onset (peak effect occurring at 0.8 to 2 minutes) and shorter duration of action (10 minutes) than neostigmine. The 'Tensilon Test' for the diagnosis of myasthenia gravis consists of the slow IV administration of 2 mg edrophonium, followed by further injection of 8 mg, if clinical deterioration does not occur. When it is used in the differentiation between myasthenic crisis and cholinergic crisis, then a dose of 2 mg of edrophonium is used first. If the weakness increases then the diagnosis is cholinergic crisis and if the weakness improves then the diagnosis is myasthenic gravis. An anticholinergic agent (e.g. atropine) must be immediately available when these tests are performed. In anaesthetic practice the dose of edrophonium for reversal of neuromuscular blockade is 0.5 to 0.7 mg/kg and is used by slow intravenous injection. This is preceded by an appropriate dose of an anticholinergic agent to counter the peripheral muscarinic side effects of this drug.

The potency of edrophonium is 12 to 16 times less than that of neostigmine. The muscarinic effects of this drug are relatively easier to counteract than those of neostigmine. Edrophonium is less predictable than neostigmine when used to reverse the profound competitive neuromuscular blockade.

Edrophonium is used:

i. For the reversal of non-depolarising neuromuscular blockade,
ii. For the diagnosis of suspected phase II block,
iii. For the diagnosis of myasthenia gravis (Tensilon Test)
iv. For the differentiation between myasthenia gravis and cholinergic crisis in myasthenic patient.

Pyridostigmine

It is an analogue of neostigmine. It was introduced for the treatment of myasthenia gravis. It has 1/4 of the potency of neostigmine. So, 10 mg of pyridostigmine in IV route is equivalent to 2.5 mg of neostigmine through same route. But the action of pyridostigmine on intestine and heart is less marked. The muscarinic action of pyridostigmine is less than equivalent dose of neostigmine. The action of pyridostigmine on neuromuscular junction is less reliable than neostigmine and takes long time near about 5 minutes to start its action. So, it is not used in anaesthesia practice (Fig. 16.19).

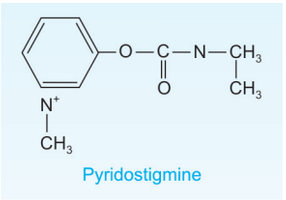


Fig. 16.19: The chemical structure of pyridostigmine

Physostigmine

It is also analogue of neostigmine and acts as cholinesterase inhibitor. But it is only used in ophthalmology as eyedrops. The difference between physostigmine and neostigmine is given below.

17 Pharmacology of Perioperative Arrhythmia

INTRODUCTION

The agents or drugs which are used to prevent the irregularities of cardiac rhythm are called the antiarrhythmic agents or drugs. Abnormal automaticity or impaired conduction of impulse or both underlie the cardiac arrhythmias. This may be paroxysmal or present continuously. It may cause sudden death, syncope, heart failure, palpitation or no symptoms. Arrhythmias are often a manifestation of underlying structural heart disease. But it may also occur in the context of an otherwise normal heart. The two most common form of abnormal cardiac rhythm is tachycardia and bradycardia. When the heart rate is more than 100/minute it is called tachycardia and when the heart rate is less than 60/minute it is called bradycardia. Tachycardia is caused by two mechanisms: Increased automaticity due to increased repeated spontaneous depolarisation or re-entry due to repeated nonspontaneous depolarisation by closed loop or re-entry circuit. But the most tachyarrhythmias are due to this re-entry mechanism. Bradycardia is also caused by two mechanisms: Reduced automaticity or abnormal slow conduction (due to block).

According to the site of origin the arrhythmias may also be supraventricular (sinus, atrial, junctional or nodal) or ventricular. Arrhythmias arising from supraventricular site usually produce narrow QRS complexes. This is because the ventricles are depolarized by impulses which pass normally through the AV node, bundle of His and Purkinje fibres. In contrast, ventricular arrhythmias produce broad bizarre QRS complexes. This is because the ventricles are activated by impulses which arise from any side of ventricular wall pass through an abnormal pathway such as myocardium. However, occasionally a supraventricular arrhythmias can produce broad or wide QRS complexes due to coexisting bundle branch block or the presence of accessory conducting tissue.

The incidence of perioperative arrhythmias varies and depends on: the definition (any minor caridac arrhythmia or any potentially dangerous arrhythmia), mode of surveilence, patient's characteristic and the nature of surgery. The factors that determine how a patient tolerates a cardiac arrhythmia usually include: The heart rate, duration of arrhythmia, the presence and severity of any underlying cardiac disease, etc. However, more or less the importance of a specific arrhythmia depends on the effects of it on the cardiac output and the possible interactions of the antiarrhythmic drugs which the patients are already taking with the drugs that are used in perioperative period for anaesthetic and analgesic purpose.

CLASSIFICATION

Perioperative cardiac arrhythmias are mainly divided according to their aetiology under two headings.

1. Disturbances of impulse formation.
2. Disturbances of impulse conduction.

Disturbances of Impulse Formation

i. Sinus rhythm: Sinus bradycardia, sinus tachycardia, sinus arrhythmia, sinus arrest, sick-sinus syndrome.
ii. Atrial rhythm: Paroxysmal supraventricular tachycardia (atrial tachycardia), atrial extrasystole, atrial flutter, atrial fibrillation.
iii. AV nodal rhythm: AV nodal extrasystole, AV nodal tachycardia, AV junctional escape rhythm.
iv. Ventricular rhythm: Ventricular extrasystole, ventricular escape rhythm, ventricular tachycardia, idioventricular tachycardia, ventricular flutter, ventricular fibrillation, torsades-de-pointes, ventricular asystole.

Disturbances of Impulse Conduction

SA block, AV block, WPW syndrome. The bundle branch block (right or left) does not cause any cardiac arrhythmia. So, it is not included in this classification.

MECHANISM OF ARRHYTHMIA (Fact file- I)

At rest in a cell there is potential difference of −70 to −90 mV across the cell membrane. This is known as the resting membrane potential (RMP). It is due to the Na^+-K^+-ATPase pump which brings out 3 Na^+ from the cell and pushes $2K^+$ inside the cell. So, there is high concentration of Na^+ outside of the cell and high concentration of K^+ inside of the cell. In this stage, the fast Na^+ channels are remained closed. But the K^+

FACT FILE- I

Genesis of resting membrane potential

The different distribution of ions across the cell membrane and the different nature of the ion channels on the cell membrane provides the explanation of the resting membrane potential. At resting condition the increased concentration gradient of K^+ inside the cell facilities its exit out of the cell via K^+ channels passively, without any help of a pump. But its electrical gradient is in the opposite direction (inward). Ultimately an equilibrium is reached when the tendency of K^+ to move out of the cell is balanced by its tendency to move into the cell. At that equilibrium, there is slight excess of cations on the outside and anions on the inside which is responsible for resting membrane potential (RMP) varing between –70 to –90 mv. This condition is maintained by Na^+-K^+ATPase pump which pumps three Na^+ out of the cell for every two K^+ pumps in. This pump is of electrogenic as it works against the electromotif force. It should be emphasised that the number of ions responsible for RMP is a minute faction of the total number present and also the total concentration of negative and positive ions are equal every where except along the cell membrane.

channels are remained opened. Therefore, the cell membrane in resting condition is relatively impermeable to Na^+ but permeable to K^+. Thus K^+ can also move passively into the cell by electromotive force other than Na^+-K^+-ATPase pump. When the cell becomes active by an impulse from outside or due to automaticity (explained later) the RMP rises to the threshold level, then the permiability of the cell membrane to Na^+ suddenly increases. This is due to the opening of fast response Na^+ channels and inactivation of Na^+/K^+ ATP are pump. Thus, Na^+ rapidly moves along the concentration gradient from outside into the cell, producing a rapid and complete depolarisation (phase 0). After this rapid and complete depolarisation, there is a short period of repolarisation or phase I. Deactivation of inward Na^+ current and activation of outward K^+ current are responsible for this short period of repolarisation or phase 1. Then, this phase 1 is followed by plateau phase (phase 2) during which complex ionic movement chiefly involving Ca^{2+} takes place. Ca^{2+} channels open during the phase 0. They remain open for 30 to 300 millisecond and account for this plateau phase. In this phase Ca^{2+} enters into the cell and balance the outward K^+ current maintaining the plateau.

After that a more rapid phase of repolarisation (phase 3) occurs. During this phase the slow inward Ca^{2+} current is inactivated and more K^+ channels open causing exit of more K^+ from the cell and restore the transmembrane potential to its resting state. But the nature of ionic (Fig. 17.1) distribution across the cell membrane is opposite to the resting state, i.e. K^+ outside of the cell and Na^+ inside the cell. At the end of this process or phase 3, the Na^+/K^+ ATPase pump is again reactivated and restores the resting ionic balance which have become already opposite during the whole action potential i.e. Na^+ is inside and K^+ is outside of the cell. This is called as phase 4. During this phase the Na^+/K^+ ATPase pump re-establishes the normal baseline concentration gradient of the relevant cations, with two K^+ ions moving into the cell for every three Na^+ ions moving out.

This sequence of events (RMP-depolarisation-repolarisation-RMP) is the pattern for nearly all the myocardial cells. But certain cells, particularly the specialized conducting tissues of the SA and AV node and the His-Purkinje system have the property of automaticity. In them, the RMP in phase 4 constantly drifts upwards until it reaches

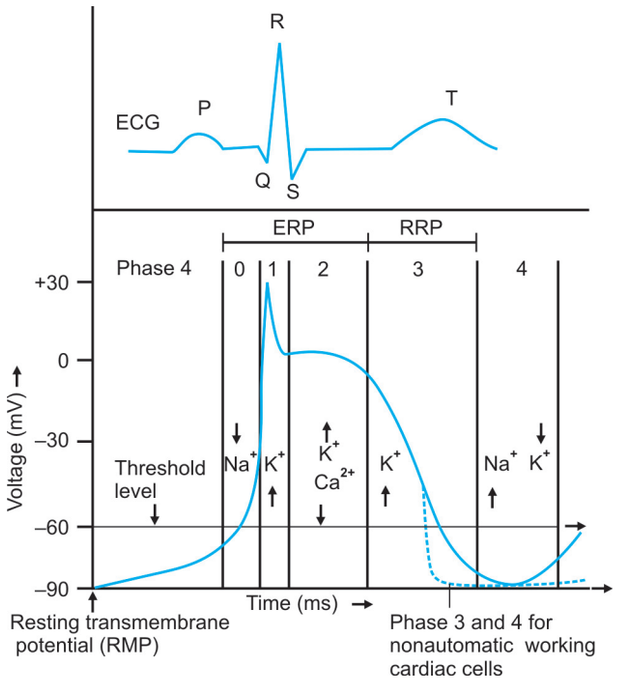


Fig. 17.1: Sequence of action potential of an automatic SA nodal cell (unbroken line) and a nonautomatic ventricular muscle cell (broken line) and its relation with ECG. Phase 4 undergoes spontaneous depolarisation from the RMP (–90 mV) until the threshold potential is reached which is the characteristic of an automatic SA nodal cell or any pace maker cell. Then, depolarisation (phase 0) occurs. Depolarisation of ventricle corresponds to QRS complex of ECG. Depolarisation of atrium corresponds to P wave. Phase 1, 2 and 3 represent repolarisation. Among them phase 3 of ventricular cell corresponds to the T wave on the ECG. The repolarisation of atrium is masked by QRS complex (depolarisation of ventricle) in ECG. The effective refractory period (ERP) is the time during which extra cardiac impulses can not be conducted, whatever may be the intensity of the impulses or stimulus. During the relative refractory period (RRP), a stronger than normal stimulus can initiate an action potential. The action potential of non-automatic working cardiac cells differ from an automatic cardiac cell such as SA node in that phase 4 of nonautomatic cardiac cell does not undergo spontaneous slow depolarisation during diastolic period which correspond with phase 4 of action potential. In the figure downward arrow indicates that the ion enters the cell and upward arrow indicates that, ion exits the cell

a threshold level (usually about −40 to −60 mV). So, the phase 4 of these cells is called the slow diastolic depolarisation phase. When RMP in slow diastolic depolarisation phase drifts to the threshold level, then the Na^+/K^+ ATP are pump is automatically inhibited and the fast response Na^+ channels reopen. This is responsible for the further massive influx of Na^+ ions into the cell and increases the transmembrane potential from −70 to −90 mV (RMP) to +20 mV (depolarisation or phase 0). Thus, again an active electrical and mechanical events of action potential are triggered off. It is thus however important to realize that this threshold level can be raised or lowered by drugs or injury and that automaticity in working cells also may be inhibited or induced by these influences (Table 17.1).

Thus, for cardiac arrhythmias five principle mechanisms have been identified. These are: enhanced automaticity, after depolarisation, re-entry, fractionation of impulse, and conduction block. Among these the first four factors are clubbed under the heading of disturbances of impulse formation and the last factor is put under the heading of disturbances of impulse conduction.

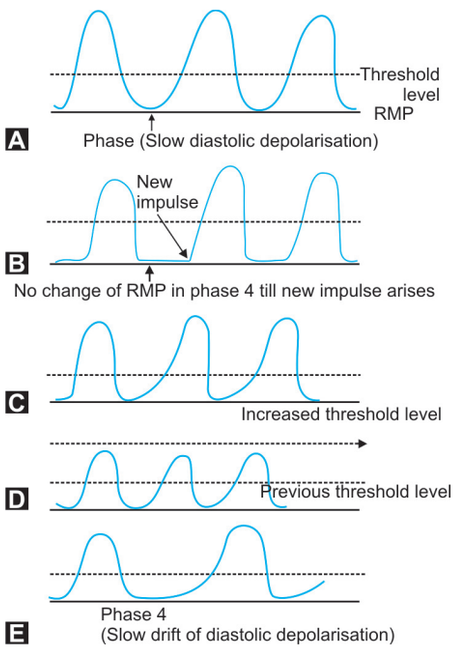
Table 17.1: Factors causing arrhythmias during perioperative period

Hypoxaemia
Hypercarbia
Electrolyte disturbances
Hypokalaemia
Hypomagnesaemia
Acid - base disturbances
Imbalance of autonomic nervous system
Increased stretching of myocardial fibre
Systemic hypertension
Valvular diseases
Congenital heart diseases
Cardiomyopathy
Myocardial ischaemia
Drugs
Catecholamines
Volatile anaesthetics
Coexisting cardiac diseases
Valvular diseases
Hypertrophy
Ventricular pre-excitation (WPW syndrome)
Prolonged QT interval syndrome
Hypo or hyperthermia
Types of surgery
Tracheal intubation

Enhanced Automaticity

The heart has many potential pace making cells and situated in SA node, AV node, bundle of His, Purkinje fibres, and Atria (atrial cells). The the SA node has the fastest inherent spontaneous discharge rate, which usually ranges around 80 beats per minute. The inherent automatic discharge rate of the potential AV nodal and the bundle of His pace making cells is about 60 and 50 beats per minute, respectively. The inherent automatic discharge rate of the Purkinje cells are about 40 beats per minute. Pacing or automaticity of cells is due to (Figs 17.2A to E) the phase 4 slow diastolic depolarisation. Decreasing the time to reach the threshold potential or increasing the slope of phase 4 (slow diastolic depolarisation phase) or elevating the resting membrane potential (i.e. making less negative) leads to enhanced automaticity and is, manifested as an accelerated heart rate. Hypoxia, hypercarbia, hypokalaemia, hyperthermia, mechanical stretching of cardiac muscle, catecholamines, sympathomimetic drugs, etc; increase the slope of phase 4 or decrease the time to reach the threshold potential. Thus, they induce or accelerate the pacemaking or automaticity, producing tachyarrhythmias. Whereas, acetylcholine, hyperkalaemia, hypothermia, etc, cause decrease in the slope of phase 4 or increase the time to reach the threshold potential. Thus, they reduce automaticity and produce bradyarrhythmia.

Hyperpolarisation, i.e. making the resting membrane potential (RMP) more negative also produces bradyarrhythmias. The automaticity also results from the sites that ordinarily lack the spontaneous pace making activity, e.g. ventricular cells. This is due to the ventricular myocardial cell damage by ischaemia causing depolarisation and automaticity. A current thus flows between these depolarized injured fibres and the normally polarised fibres (current of injury) and initiate an automaticity. Thus also arrhythmia results.



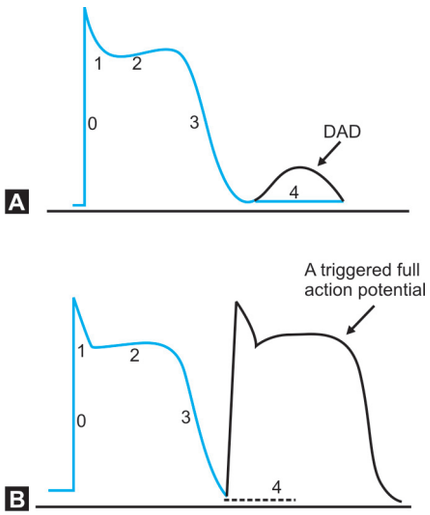
Figs 17.2A to E: The action potentials from different cardiac muscle cells with the property of automaticity (A) and without automaticity (B).
(A) SA node cell. In these cells the resting membrane potential (RMP) is continuously and spontaneously drifting in phase IV towards the threshold level. This explain the electrical basis of automaticity of the SA nodal cells or any pace maker cells.
(B) Normal working myocardial cell. In these cells RMP does not spontaneously drift to the threshold level. For the next depolarisation they wait for impulse coming from outside.
(C) Working myocardial cells damaged by injury. Like SA node, here also the RMP drifts spontaneously due to injury to the threshold level which represents a tendency to automaticity.
(D) Class Ia drugs reduce the peak of rise of the action potential. It also raise the threshold level by inactivation of Na^+ pump. This results in reduced automaticity.
(E) Class Ib drugs produce the same effect by slowing the rate at which the drift of phase 4 takes place, so that it takes longer time to reach the threshold level

After Depolarisation

Under some pathophysiological conditions, a normal cardiac action potential may be followed or interrupted by an sudden abnormal another premature depolarisation. If this abnormal premature depolarisation reaches the threshold level, then it may give rise to a secondary upstroke which then can propagate and create abnormal rhythm. Two major forms of secondary upstroke or after depolarisation are recognised. These are:

(A) Delayed after depolarisation

After an full action potential and attaining the resting membrane potential (RMP) a secondary premature deflection or depolarisation may occur at phase 4 which can reach the threshold level and initiate a single premature action potential. As this premature action potential is needed to trigger the arrhythmias and so this type of arrhythmias are called the 'trigger arrhythmias'. The examples of such trigger arrhythmias are some tachycardias, coupled beats, etc. (Figs 17.3A and B).



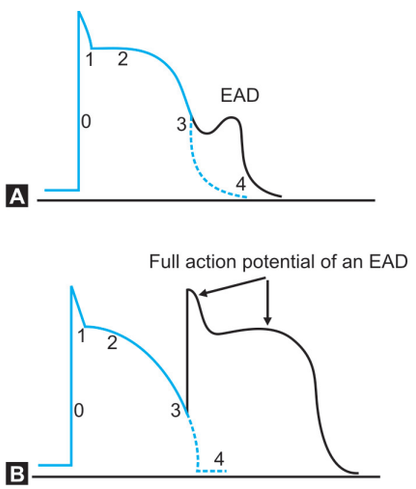
Figs 17.3A and B: A. Delayed after depolarisation (DAD), arising after full repolarisation. A DAD that reaches threshold results in a triggered upstroke and causes a full action potential B

(B) Early after depolarisation (EAD)

Sometimes phase 3 or repolarisation part of action potential is interrupted by an early premature depolarisation and thus the membrane potential oscillates. If the amplitude of oscillation of this membrane potential is sufficient enough, then a series of impulses are propagated and neighbouring (Fig. 17.4A and B) tissues are activated, causing arrhythmia. They are frequently associated with abnormally prolonged action potential such as bradycardia, low extracellular K^+ and certain drugs that prolongs the duration of action potential. When EAD is present, then subsequent sympathetic stimulation (α and β) can increase the likelihood of triggered beats. Again if the cardiac repolarisation is markedly prolonged, then ventricular tachycardia with long QT interval, known as 'torsades-de-pointes' syndrome may occur (Fig. 17.5).

Re-entry

Primarily due to some abnormality in conduction pathway, an impulse which is normally generated may recirculate in the heart muscle and can cause repetitive activation of it without the need for any new impulse to be generated. These are called the re-entry arrhythmias. It has also two mechanism: circus movement and micro re-entry.



Figs 17.4A and B: It shows early after depolarisation (EAD), interrupting the phase 3 part of repolarisation of action potential. Under some conditions EAD can not reach the threshold level and becomes unable to give a full action potential A. But sometimes EAD reaches the threshold level and initiates a full action potential causing arrhythmia B

Circus movement mechanism

When an impulse propagates by more than one pathway between two points of the heart, then part of the impulse may recirculate again and again in the heart muscle, causing repetitive activation of it without the need for any new impulse to be generated. These are called the circus variety of re-entrant arrhythmias. One of the example of this re-entry arrhythmia is WPW syndrome. In WPW syndrome there is an accessory conducting path between the atrium and the ventricle. With each sinus node depolarisation, the impulses can excite the ventricle via the normal structure (AV node) or the

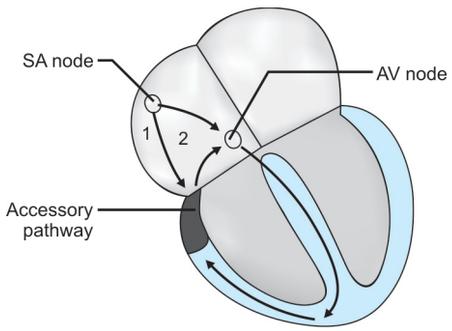


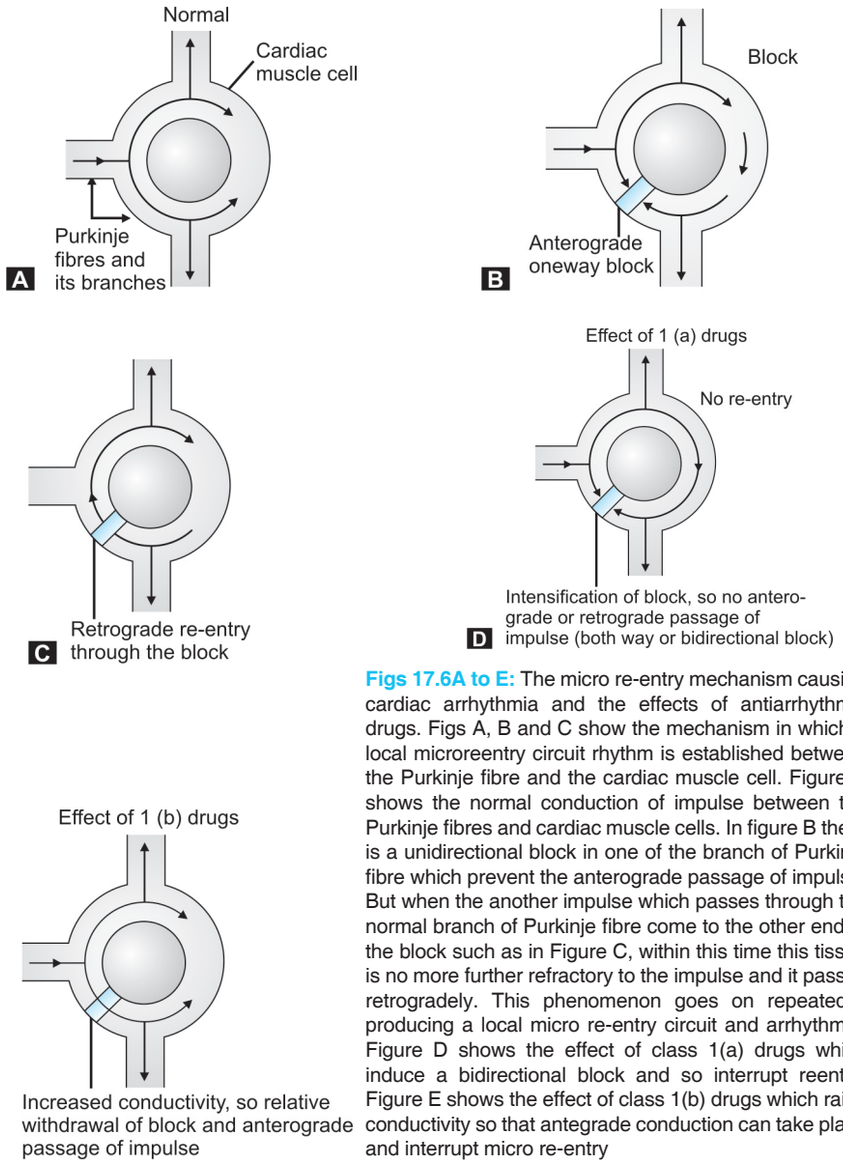
Fig. 17.5: In this patient, an accessory pathway connecting between atrium and ventricle is present and is shown by the black area. This picture explains a retrograde re-entry circuit mechanism of arrhythmia through accessory pathway. A normal or a premature atrial beat (1) cannot pass through the accessory pathway as it is refractory by the previous sinus beat. Thus the atrial beat propagates slowly through the AV node as usual. Then it reaches the accessory pathway through the Purkinje fibres and ventricular wall. Upon reaching the accessory pathway through the ventricular wall which is by now no longer refractory, the impulse re-enters the atrium (2). It then again re-enter the ventricle via the AV node and thus become a self-sustained circuit. AV nodal blocking drugs readily terminate this tachycardia or arrhythmia. Recurrences also can be prevented by drugs that prevent the atrial premature beats or by drugs that alter the electrophysiological characteristics of tissues in the circuit (i.e. they prolong the AV nodal refractoriness) or by nonpharmacological techniques that cut the accessory pathway

accessory pathway. But, the electrophysiological properties of AV node and the accessory pathways are different. Accessory pathways consist of fast response tissue, whereas AV node is composed of slow response tissue. Thus, with every atrial beat, conduction may fall both in the accessory pathway and the AV node. Then the impulse passing through the accessory pathway depolarise a part of the ventricle first (as it is fast conducting tissue) and produce delta waves. Then it meets the ventricular depolarisation caused by the impulse passing through the AV node and produce total QRS complex. During this period the accessory pathway is no longer refractory. Thus, the impulse which comes through the AV node re-enters the atrium via the accessory pathways and then it can again re-enter the ventricle via the AV node. It then re-enters again the atrium via the accessory pathways and such goes on again and again. Re-entry arrhythmia of this type is therefore, determined by: (i) The presence or absence of an anatomically defined accessory circuit, (ii) Heterogeneity in refractoriness among the regions of these circuits and (iii) the slow conduction in one part of the circuit than the other.

Similarly, an 'anatomically defined' re-entry circuit commonly occurs in the region of the (i) AV node causing AV nodal re-entry tachycardia and (ii) in the atrium causing atrial flutter. This is discussed in more details in chapter 6. The term paroxysmal supraventricular tachycardia (PSVT) includes the both AV re-entry and AV nodal re-entry tachycardia as both of them share the many same clinical features. In some of these cases, it is now possible to identify this re-entry circuit and to ablate the critical portions of this re-entrant pathways. It thus cures the patient nonpharmalogically and obviates the need for long-term drug therapy. This ablation procedure is carried out through a catheter advanced in the interior of the heart and requires minimal convalescence.

Micro re-entry mechanism

It is formed at the junction of Purkinje fibres with the ventricular myocardial fibres. The terminal Purkinje fibres divide into two branches or radicals which communicate directly with the myocardial cells. Usually the conduction of impulse down the each radical of these Purkinje fibres takes place at the same speed. But, if something happens and slow or unidirectionally block of conduction in one of the radical occurs, then the impulse reaches the myocardium by the second remaining radical. Then the impulse may reach from the myocardial cell to the blocked radical. In this circumstance, the retrograde conduction through blocked segment as the block is unidirectional is occured and the impulse crosses the block. Then the impulse passes again through the undamaged or unblocked radical (which is now nonrefractory) back to reach the myocardial cell, and again to the blocked radical. Thus, a self creating micro re-entry circuit is set-up, causing arrhythmia. The examples of this micro re-entry mechanism are ventricular ectopic, VT, VF, etc. (Figs 17.6A to E).



Figs 17.6A to E: The micro re-entry mechanism causing cardiac arrhythmia and the effects of antiarrhythmic drugs. Figs A, B and C show the mechanism in which a local microreentry circuit rhythm is established between the Purkinje fibre and the cardiac muscle cell. Figure A shows the normal conduction of impulse between the Purkinje fibres and cardiac muscle cells. In figure B there is a unidirectional block in one of the branch of Purkinje fibre which prevent the anterograde passage of impulse. But when the another impulse which passes through the normal branch of Purkinje fibre come to the other end of the block such as in Figure C, within this time this tissue is no more further refractory to the impulse and it passes retrogradely. This phenomenon goes on repeatedly, producing a local micro re-entry circuit and arrhythmia. Figure D shows the effect of class 1(a) drugs which induce a bidirectional block and so interrupt reentry. Figure E shows the effect of class 1(b) drugs which raise conductivity so that antegrade conduction can take place and interrupt micro re-entry

There is another re-entry mechanism which is called the functionally defined re-entry mechanism. This can happen in the absence of any anatomically distinct accessory pathway or certain block like micro re-entry mechanism. The example of this mechanism is VT in MI. Here the ischemic area is divided into two parts such as rapid longitudinal and the slow transverse segment which are electrophysiologically different. These two parts also have the different refractory period. Thus, the formation of these two different refractory areas results in alternate cyclical changes of refractoriness which allow the impulse to circulate repeatedly, among these two types of tissues with different refractory period causing arrhythmias.

Fractionation of Impulse

When the effective refractory period (ERP) of atrial or ventricular muscular fibre is brief and inhamogeneous, then a generated impulse is conducted irregularly over the atrium or ventricle. It means the impulse moves rapidly through the fibres with short ERP (which have recovered completely) or slowly through the fibres with long ERP (which have recovered partially) or does not move at all through the still refractory fibres. Thus an asynchronous activation of atrial or ventricular fibres occur, causing arrhythmia.

Conduction Block

Different types of block in the SA node and AV node, but not the bundle of His and Purkinje fibres, can also cause arrhythmia.

DRUGS USED IN THE TREATMENT OF CARDIAC ARRHYTHMIAS (Fig. 17.7)

Drugs used in the treatment of cardiac arrhythmias are mainly grouped under two headings. These are: (i) Drugs used to treat disturbances in impulse formation and (ii) Drugs used to treat disturbances in impulse conduction.

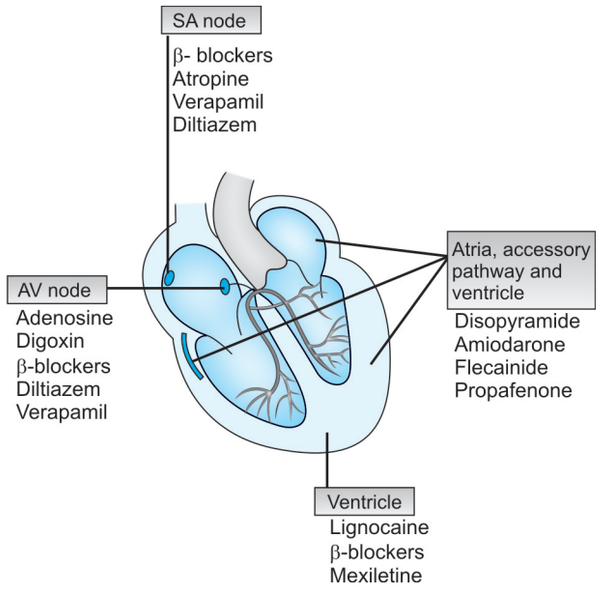


Fig. 17.7: Classification of anti-arrhythmic drugs by their site of action

A. Drugs Used to Treat Disturbances in Impulse Formation

Antiarrhythmic drugs used to treat disturbances in impulse formation act by different ways. These are by blocking : (i) different ionic channels (Na^+, K^+, Ca^{2+}), (ii) different receptors and (iii) different pumps. There are many classifications of antiarrhythmic drugs, but no one is satisfactory. Till now only the useful classification of antiarrhythmic drugs is William's classification. However, this classification also has a number of limitations in practice. This is because (i) many drugs have more than one mechanism of action, (ii) there is considerable variations in mechanism of actions of drugs in the same class and (iii) the distinct similarities between the drugs of supposedly different classes.

So, an alternative new classification of antiarrhythmic drugs such as 'Sicilian gambit' was introduced in 1990. Unlike William's classification which is purely based on the electrophysiological characteristic of the mechanism of action of drugs, this new approach is actually a gambit as in chess, rather than a finalized structure. It is based on the consideration of three factors which influences the antiarrhythmic (Table 17.2) effects of various drugs. These three factors are: (i) The molecular targets on which the drug acts, (ii) the mechanism of action, responsible for antiarrhythmic property of this agent and (iii) The clinical considerations.

However, this classification is a more complex and less easy to memorise than William's classification. But, it has the advantage of allowing better visualisation of some complex effects of newer drugs, which is unhindered by the constrants, imposed by the purely electrophysiological basis of earlier classification.

Arrhythmogenic Potentiality of Antiarrhythmic drugs

Most antiarrhythmic agents which are used clinically may themselves precipitate serious arrhythmias. Two multicentric trials have shown that the post MI patients, randomised to receive encainide, flecainide, moricizine and other antiarrhythmatic agents on a long-term basis, had higher incidence of sudden death, though initially

the same drugs had suppressed ventricular extra systole in these patients. It is possibly due to the marked intraventricular conduction slowing action of these drugs, resulting in VT and VF. It is, therefore not prudent to try and supress all the extrasystoles or arrhythmias with the drugs perioperatively (Table 17.3).

Class I : Membrane Stabilising Drugs

Drugs in this class are known as the membrane stabilisers. So, they act by blocking the fast Na^+ channels, across the cell membrane at 0 phase of action potential like local anaesthetic agents. Thus, they interfere with the onset of depolarisation and decrease the responsiveness to excitation. They also reduce the rate of phase IV slow diastolic depolarisation in automatic or pacemaker cells. There are pharmacologically diverse group of drugs in this class (Class I) which have been subclassified into IA, IB and IC. However, the primary antiarrhythmic effect of all these drugs is related to their effect on decreasing the maximum rate of voltage change during phase 0 of action potential. A number of other mechanisms may also be involved in this group of drugs, such as abolishing the re-entry currents.

Table 17.3: The 'Sicilian gambit' table

Drug	*William class*	*Channels*			*Receptors*				*Pump*
		Na^+	*K^+*	*Ca^{2+}*	α	β	*M_2*	*A_1*	*Na^+/K^+ ATPase*
Quinidine	1A	A	•		•		•		
Procainamide	1A	A	•						
Disopyramide	1A	A	•				•		
Lignocaine	1B	•							
Mexiletine	1B	•							
Tocainide	1B	•							
Propafenone	1C	A				•			
Flecainide	1C	A	•						
Propranolol	II	•				•			
Bretylium	III		•		PAG	PAG			
Amiodarone	III	I	•	•	•	•			
Verapamil	IV	•		•	•				
Diltiazem	IV								
Adenosine								AG	
Digoxin							AG		•
Atropine							•		

This is a new classification of anti-arrhythmic drugs. It is based on the activities of the membrane channels, receptors and pumps. This classification also offers a different perspective of the William's classification which only considers the electrophysiological effects

• High
• Medium
• Low

I - Inactivated state blockers
A - Activated state blocker
AG - Agonist, PAG - Partial agonist

Subclass IA

They are open state Na^+ channel blockers with moderate delay in channel recovery. Hence, they supress the A-V conduction and prolong the P-R, QRS, and QT interval and APD (action potential duration). The following drugs fall in this group.

Table 17.2: William's Classification

Class I	*Membrane stabilising drugs (fast Na^+ channel blockers)*
IA	Quinidine, procainamide and disopyramide. They block Na^+ channel and prolong action potential.
IB	Lignocaine and mexiletine. They block Na^+ channel and shorten the duration of action potential.
IC	Flecainide, encainide and propafenone. They block Na^+ channel with no effect on action potential.
Class II	β–adrenoreceptor antagonist, i.e. propranolol, metoprolol, esmolol, etc.
Class III	Drugs which increase the duration of action potential and the refractory period (antifibrillatory drugs), e.g. amiodarone, bretylium.
Class IV	Calcium channel blockers, e.q. verapamil, diltiazem, etc.
Others	Cardiac glycosides, Adenosine, Dofetilide, Ibutilide, Propafenone, etc.
For AV blocks	Anticholinergic - Atropine Sympathomimetics - Isoprenaline, etc.

NB: Some drugs have properties of more than one class. For example, amiodarone has actions of all four classes.

Quinidine

Chemically, it is a dextroisomer of quinine and an alkaloid which is available from cinchona bark. A dutch merchant had first noticed the beneficial effect of cinchona bark on irregular pulse, taken during malaria. Then, he demonstrated this to British cardiologist, Wenckebach in 1912 and subsequently quinidine was synthesized.

It reduces the rate of depolarisation or phase 0 of action potential and its overshoot, i.e. it decreases the membrane responsiveness. Thus, it depresses the cardiac excitability by (i) raising the threshold potential level, (ii) prolonging the duration of action potential and (iii) prolonging the effective refractory period (ERP) of His-Purkinje cells. Thus, it slows the intra-atrial, AV and intraventricular conduction of impulses. It extinguishes the extra systole and is

important in the prophylaxis of re-entrant arrhythmias. Quinidine has little effect on 'after depolarisation'. SA nodal automaticity is little affected by quinidine at therapeutic concentration. As ERP is prolonged, so tissue remains refractory even after the full repolarisation. The QT interval in the ECG is prolonged by quinidine. Therefore, the monitoring by ECG may provide a useful guide to the dosage of it. Prolongation of the QT interval with quinidine therapy may also has been associated with severe tachyarrhythmias.

The quinidine has anticholinergic effects. The cardiac anticholinergic effects include an increase in sinus rate. It has a variable effect on AV nodal conduction which may be depressed or enhanced, depending on the balance between the direct depression and the anticholinergic enhancement (Table 17.4).

Then anticholinergic effects of quinidine is also responsible for variety of non-cardiac effects. These are gastrointestinal irritation, nausea, vomiting, tinnitus and visual disturbances which are found in mild overdosage. Whereas, severe CNS symptoms such as confusions and psychosis may occur with major over dosage.

Table 17.4: Principles of use of anti-arrhythmic drugs

The drugs used to treat different cardiac arrhythmias are potentially toxic. So, they should be used carefully according to the following principles.

1. Many arrhythmias are benign and do not produce any haemodynamic instability. So, they do not require specific treatment and only need observation.
2. Always precipitating or causal factors for arrhythmia should be searched and corrected first, if possible. These may include: myocardial ischaemia, drug effect, hyperthyroidism, acidosis, hypokalaemia, hypo magnesaemia, excess alcohol or caffeine consumption, etc.
3. If the drug therapy is required at all, it is best to use as few drugs as possible.
4. In difficult cases, electrophysiological study may help to identify the optimum therapy.
5. Patients on long-term anti-arrhythmic drugs should be reviewed regularly. Always attempts should be made to withdraw the therapy, if the factors which precipitate the arrhythmias are no longer operative.
6. Non-pharmacological anti-arrhythmic therapy such as pacing or radiofrequency ablation of accessory path are often preferred to long-term drug therapy.

Mechanism of Action

Quinidine blocks the myocardial fast Na^+ channel in the open state. Thus, it reduces the automaticity by decreasing the maximal rate of depolarisation or phase of action potential. Some prolongations of AP by quinidine is also due to the K^+ channel blocking action. Lengthening of ERP by quinidine is due to the effect of it on the recovery of Na^+ and K^+ channels. As quinidine has some α-adrenergic blocking properties at higher doses, so it also directly dilates the blood vessels and causes the fall of BP.

Uses

Quinidine has been used to treat the atrial and ventricular arrhythmias, but is not in common use today. It is usually administered orally, because of the adverse haemodynamic consequences on parenteral use. Absorption from GI tract of quinidine is rapid and effective. Presently, quinidine is used only for maintenance and prophylaxis purposes, after AF and AFL which has been terminated by DC shock or by other measures. Recently, it is also used to prevent the recurrences of VT.
Dose: 200 to 400 mg TDS orally.

Procainamide

It is the amide derivative of local anaesthetic agent named procaine. Procaine was also found to have antiarrhythmic activity, but is not suitable clinically due to the rapid hydrolysis and marked CNS effects of it. So, in 1951, procainamide (analogue of procaine) was developed and had circumvented some of the limitations of procaine.

Like quinidine, it also decreases the rate of rise of depolarisation during phase 0 and phase IV of action potential. However, less prolongation of QT interval than quinidine is observed by procainamide. Procainamide also has the anticholinergic effect, but is less marked than quinidine. It has no α-blocking activity, so there is no fall of BP. It is better tolerated than quinidine when given intravenously.

Uses

It is orally active and is an alternative drug to quinidine, having the same spectrum of efficacy. Some patients not responding to others antiarrhythmic agent may respond to procainamide. Procainamide is more likely to increase the ventricular rate in patient with atrial fibrillation than quinidine. Thus, it is not used in the treatment of atrial fibrillation (AF) and flutter (AFL) like quinidine. Therefore, its use is usually confined to the treatment of ventricular extrasystole. In this respect it is usually used as a second line of drug after lignocaine and may be used for the treatment of multiple ventricular extrasystole, R on T phenomenon and ventricular tachycardia.

Initially, procainamide is used as IV loading dose and later with maintenance by intravenous infusions during the acute therapy of many supraventricular (except AF and AFL) and ventricular arrhythmias. But, long-term oral treatment by procainamide is often stopped, because of the many adverse effects.

Doses

For abolition of arrhythmia procainamide in the dose of 0.5 to 1 gm orally or IM is started fast. This is followed by 0.25 to 0.5 gm orally at every 2 hours interval. It can reduce the antimicrobial effect of sulfonamides, probably by generating PABA. Hypotension and marked slowing of conduction are the major adverse effects of procainamide at high concentration, especially during IV use.

Disopyramide

Like quinidine, it is also the drug of class Ia and has prominent cardiac depressant

and anticholinergic effects (which account for many of its adverse effects). It has no α-adrenergic blocking property. Disopyramide usually has no effect on sinus rate, because of opposing both the direct depressant and antivagal actions on SA node. It is used to treat both the supraventricular (atrial flutter and fibrillation) and ventricular arrhythmias (ventricular tachycardia and flutter). It may also cause atypical VT with prolongations of QT interval. Disopyramide may also be effective in slowing conduction through the accessory pathway in patient with WPW syndrome. It has marked negative inotropic effect on heart.

The anticholinergic effects of disopyramide include precipitation of glaucoma, constipation, dry mouth and urinary retention. The later is more common in males. Sometimes the negative inotropic effects of disopyramide may precipitate heart failure. It can also cause torsades-de-pointes.

It is orally active and is better tolerated than quinidine. The primary indication of use of disopyramide is the prevention of recurrences of ventricular arrhythmias. It may be better tolerated as the maintenance agent after cardioversion of atrial flutter and fibrillation.

Subclass IB

These group of drugs block Na^+ channels in both the activated and inactivated states, but do not delay the recovery of channel. They do not depress the A-V conduction. Also they do not prolong the duration of action potential (APD), effective refractory period (ERP) and Q-T interval. Class Ib group of drugs have virtually no autonomic effects. By these group of drugs the rate of rapid depolarisation or phase 0 of action and the slope of slow depolarisation in phase 4 is decreased in Purkinje fibres (PF).

Lignocaine

It is the most commonly used local anaesthetic agent and is also the most popular antiarrhythmic agent in ICU.

Lignocaine blocks both the open and inactivated cardiac Na^+ channels, but the recovery from this block is very rapid. So, it exerts greater effects on the depolarized (ischaemic) tissues. It is not useful in atrial arrhythmias. This is possibly because the atrial action potentials are so short that the Na^+ channel remains in an inactivated state only for a brief period as compared to the diastolic (recovery) times, which are relatively long.

The most prominent cardiac action of lignocaine is the suppression of automaticity of ventricular ectopic foci, but the SA nodal automaticity is not depressed. It has, practically, no effect on APD and ERP of atrial fibres. Atrial re-entry is also not affected. So, lignocaine is ineffective in treating the supraventricular arrhythmias. However, it can suppress the re-entry mechanism responsible for ventricular arrhythmias either by abolishing the one way block or by producing two way block. It also increases the threshold for ventricular fibrillation. So, lignocaine is used in the treatment of all forms of ventricular arrhythmias. The normal ventricular muscle fibres and conducting tissues are minimally affected, while depolarised or damaged fibres are significantly affected. This is due to the higher preferential distribution of lignocaine within the ventricular myocardium which has been shown to be damaged than the normal healthy ventricular myocardium and the concentration of lignocaine within the ischaemic arrhythmic areas of myocardium is the relevant factor for determining its efficacy. Lignocaine acts preferentially on the ischaemic myocardium and is more effective in the presence of high extracellular K^+ concentration. Thus, hypokalaemia must be corrected before the use of any class Ib drugs, other than phenytoin.

Lignocaine has minimal effect on normal ECG. It has no significant effect on PR interval or QRS duration. It causes little depression of cardiac contractility and no reduction of BP. There are no significant actions of lignocaine on autonomic nervous system. So, all the cardiac effects of lignocaine are due to the direct actions of it on the myocardial cells.

Lignocaine is well absorbed orally. But, because of his high first-pass metabolism in liver, adequate and constant blood levels of lignocaine are not attained by this route. So, it is not used orally. Actions of lignocane by IV bolus dose lasts only for 10 to 20 minutes. This is because of rapid redistribution of it in the tissues. On the other hand, therapeutic plasma concentration of lignocaine lies within the range of 1.5 to 5 µg/ml and plasma concentration above 9 µg/ml are likely to produce toxic effects. So, the normally accepted therapeutic scheme to maintain the desired therapeutic plasma level of lignocaine requires a loading IV dose of 1 to 1.5 mg/kg which is followed by an infusion of 150 µg/kg/min for 20 minutes and finally is maintained by infusion at the rate of 3 µg/Kg/min.

When rapidly large doses of lignocaine is administered intravenously, then seizures may occur. But during maintenance therapy, when the plasma concentration of drug rises slowly above the therapeutic level, then tremor, dysarthria, altered level of consciousness is occurred. Hence, it proves that the main toxicity of lignocaine is its dose dependent neurological effects. Other neurological symptoms of lignocaine are drowsiness, nausea, twitching, tinnitus, disorientation, nystagmus, etc. Only excessive dose of lignocaine causes cardiac depression and hypotension.

As it is ineffective in atrial arrhythmias, so lignocaine is used only in ventricular arrhythmias. It is also said that because of rapidly developing and titratable action, it is a good drug in the emergency setting like ventricular arrhythmias following acute MI, cardiac surgery and other acute conditions. Given prophylactically by infusion in acute MI, it also reduces the occurrence of ventricular fibrillation. However, a recent meta-analysis has shown that

prophylactic lignocaine fails to improve survival rate and may even increase the short term mortality. Therefore, it is no longer administered routinely to all the MI patients. This increased mortality may be due to the lignocaine induced exacerbated heart block or CHF.

Mexiletine

Chemically, it is a lignocaine analogue. So, like lignocaine, mexiletine is a local anaesthetic and an active antiarrhythmic agent. But, unlike lignocaine it is active orally. This is because the structure of mexiletine and tocainide which is also analogue to lignocaine are modified to reduce the first pass hepatic metabolism and to make them effective for oral therapy.

Pharmacologically, mexiletine is also similar to lignocaine. It increases the threshold voltage, reduces the rate of 'phase 0' of action potential or depolarisation and decrease the 'phase 4' slope. Thus, it converts the one way block to two way block. But, it has little effect on the heart rate, BP and ventricular function.

Mexiletine is almost completely absorbed orally. The incidence of adverse effects of mexiletine is relatively high than lignocaine. These adverse effects are bradycardia, hypotension, A-V block, etc.

Doses

Mexiletine is used orally as the loading dose of 400 to 600 mg stat and which is then followed by 150 to 200 mg thrice daily. Parenterally, it is used in the dose of 100 to 200 mg IV over 10 minutes, which is then followed by 1 mg/min through infusion. Parenteral mexiletine is effective in postinfarction ventricular arrhythmias, as alternative to lignocaine in resistant cases. Orally, it is used to keep the ventricular extra systole and ventricular tachycardia supressed over long duration.

Tocainide

Like mexiletine tocainide is also a lignocaine analogue and is active both orally and parenterally. It may be effective against severe ventricular arrhythmias which is refractory to other class I antiarrhythmic drugs. But, tocainide is rarely used now, because of the risk of severe agranulocytosis, thrombocytopenia (due to potentially fatal bone marrow depression) and pulmonary fibrosis.

Phenytoin and Dilantin

These are mainly antiepileptic drugs and are used very infrequently in cardiac arrhythmias. So, they are not discussed in details here.

Subclass IC

Class IC antiarrhythmic drugs are highly effective and are the most potent Na^+ channel blockers. It suppresses the 'phase 0' activity of action potential and causes a marked reduction in conduction velocity. It also prolongs the P-R interval and broadens the QRS complex. They have profound effect on HIS-Purkinje system and accessory pathways for conduction. They markedly retard the anterograde and as well as the retrograde conduction through accessory pathway in WPW syndrome.

However, recently it is discovered that this subclass of antiarrhythmic drugs have the ability to be proarrhythmic. Proarrhythmia is a phenomenon which is identified as the development of new arrhythmias or exacerbation of a pre-existing arrhythmias in response to treatment with an antiarrhythmic drug. Both the flecainide and encainide of the subclass IC drugs have been specifically implicated as proarrhythmic agent and sudden deaths occur. The precise mechanism for proarrhythmogenesis by this group of drugs is not fully understood, but it may be due to the decreased conduction in abnormal areas of myocardium which favour a re-entry mechanism.

Flecainide

Flecainide blocks the Na^+ current and delayed the rectifier K^+ current (IKr). It suppresses the 0 phase activity and increases the duration of action potential. Thus, it supresses the ventricular extra systole (VES), VT, WPW syndrome and prevent the recurrence of AF and PSVT. In recent study, it was found to increase the mortality in patient recovering from M1 and so has been withdrawn from the market in many countries. But in UK, still it is licensed for the treatment of AF and ventricular arrhythmias which are unresponsive to other therapy and in whom the structural heart disease is absent.

Encainide, a drug with very similar electrophysiological actions like flecainide, is no longer used and available.

Propafenone

It is a mainly Na^+ channel blocker. But, like flecainide it also blocks the K^+ channels. It also prolongs the PR and QRS interval, but its major action is to slow the conduction in fast response tissue. Propafenone is mainly used orally to maintain the sinus rhythm in patient with supraventricular tachycardia and atrial fibrillation. In ventricular arrhythmias it is modestly effective.

The adverse effects of propafenone therapy include increased ventricular response in patient with atrial fibrillation, increased frequency and/or severity of re-entrant VT and exacerbation of heart failure. It has β-adrenergic blocking effect and causes sinus bradycardia and bronchospasm.

Propafenone undergoes extensive first pass hepatic metabolism. It produces a metabolite, named 5-hydroxy propafenone which is equipotent like its mother compound as a Na^+ channel blocker, but is much less potent as a β-adrenergic receptor antagonist.

Class II - β - Adrenoreceptor Antagonist

The primary action of drugs in this class is to suppress the adrenergic induced automaticity by their specific membrane stabilising effect like local anaesthetic agents

which is mediated through the fast Na^+ channels blocking action.

The electrophysiological effects of β-adrenoreceptor antagonists are:

i. Decrease in automaticity.
ii. Increase in the duration of action potential, especially in ventricular conducting tissues.
iii. Increase in the effective refractory period in the AV node.

The latter effect is the most important for the antiarrhythmic effect of β-adrenoreceptor antagonists. Automaticity is decreased in both the SA node and AV junctional tissues. There is potent inhibition of catecholamine induced tachycardia and arrhythmia by this class of drugs.

In the clinically used dose range, antiarrhythmic action of this class of drug is exerted primarily through their β-adrenergic blockade. Only in very high doses, antiarrhythmic action of this group of drug is exerted by their membrane stabilizing property through fast Na^+ channel blocking action. Automaticity is decreased by this class of drug when it is due to the adrenergic influence, otherwise there is little or no action.

The most important ECG changes by the effect of this group of drug is the prolongation of PR interval. Depression of cardiac contractility and hypotension is less marked.

Individual drug in this class such as propranolol, metoprolol, esmolol, etc, are discussed elsewhere.

Class III

The characteristic actions of this group of drugs in class are: prolongation of repolarisation, widening of action potential, and increase in the effective refractory period (ERP). Tissue remains refractory even after full repolarisation. So, re-entrant arrhythmias would also be terminated. Drugs in this class are bretylium and amiodarone.

Bretylium

Bretylium tosylate is a quaternary ammonium compound. After IV injection, it produces biphasic response. Initially, it displaces or releases noradrenaline from the adrenergic nerve terminals and produces transient sympathomimetic effects. As a result initially, bretylium can produce transient hypertension and increased arrhythmias. But, this effect is rarely observed. Later, it produces adrenergic blockade and hypotension. The major direct action of bretylium is prolongation of AP and ERP and this is probably due to the action of K^+ channel blockade. It is not a Na^+ channel blocker and does not depress the automaticity. In theory, bretylium should be avoided in patients who are especially prone to the increased arrhythmias with norepinephrine release. In contrast, hypotension due to inhibition of noradrenaline reuptake is a common problem during bretylium therapy. Bretylium induced hypotension should be managed with judicious fluid replacement, but not by catecholamines. Since, bretylium effectively causes the sympathetic denervation, so the administration of normal doses of catecholamine such as dopamine may cause marked hypertension.

Oral absorption of bretylium is very poor. So, it is always used through IV route. It is excreted unchanged in urine.

Bretylium is mainly used in the treatment of VT and VF which is refractory to lignocaine and/or defibrillation. The first intravenous loading dose of bretylium is 5 to 10 mg/kg which is given over 10 minutes. Then, it is repeated up to a total dose of 30 mg/kg. The onset of action of bretylium is very slow. So, resuscitative measure for VT and VF should be continued for 20 to 30 minutes after administration of bretylium. An infusion of bretylium in the dose of 2 mg/min is used for maintenance of its action.

The efficacy of bretylium in the treatment of acute ventricular arrhythmia is still controversial, because of its slow onset of action. But, it is still regarded as a second line of drug after lignocaine for the treatment of VT and VF.

Amiodarone

Chemically, amiodarone hydrochloride is a di-iodinated benzofuran derivative and is a highly lipophilic agent. It is a long acting antiarrhythmic drug and is a structural analog to thyroid hormone. So, some of the antiarrhythmic actions and toxicity of amiodarone may be due to the interaction of it with thyroid hormone receptors. As amiodarone is highly lipophilic, so it is concentrated mainly in the fat containing tissues and is eliminated very slowly. Hence, the adverse effects of it may be very slow to resolve.

Amiodarone exerts multiple actions. It has been suggested that the amiodarone's main effects are mediated by the perturbation of lipid milieu of cell membrane in which all the ion channels are situated. On the otherhand, amiodarone is a potent inhibitor of abnormal automaticity and in most tissues it prolongs the APD and ERP.

The mechanism of actions of amiodarone are:

i. Block K^+ channels - prolong APD and ERP
ii. Block Na^+ channels - lignocaine like action - conduction is slowed and automaticity is depressed.
iii. Block Ca^+ channel and β-adrenergic blocking property.
iv. Also acts by partial antagonism of alpha and beta agonists by reducing the number of receptors and by inhibiting the coupling of agonists with receptors.

The SA node is depressed by amiodarone. So, sinus rhythm is slowed by 15%. It is secondary to the reduction of slow diastolic depolarisation in SA nodal cells by amiodarone. AV nodal automaticity is also depressed and AV nodal conduction is also slowed by 25% in the face of atrial tachycardia by amiodarone. It is due to the decreased speed of depolarisation of cells and increase in the duration of action potential. Amiodarone has no effect on the conduction through bundle of His, and Purkinje fibres and the ventricular myocardium. It has little effect on the blood

pressure and left ventricular contractility. The SVR is decreased and coronary blood flow is increased by it.

The SA node is affected slightly by amiodarone. The effect of oral dose of amiodarone on cardiac contractility and BP is minimal. But IV injection of it frequently causes myocardial depression and hypotension. There are clear differences in electrophysiological study when the drug is given IV and in chronic oral therapy. Following IV administration, the ERP is prolonged particularly in conducting and ventricular muscle tissue, but there is no prolongation of QTc interval. By contrast, during chronic oral therapy the refractory period is prolonged, chiefly in AV nodal tissue with the prolongation of QTc interval.

Amiodarone is now widely used to treat the supraventricular arrhythmias, pre-excitation syndrome such as the WPW syndrome and ventricular arrhythmias including VT, VF, etc. Its long duration of action makes it suitable for long term prophylactic use, but close monitoring is required.

Amiodarone is incompletely and slowly absorbed from the GI tract. So, by daily oral ingestion the action develops slowly over several days and weeks. But, on IV injection the action develops rapidly. Amiodarone has very poor and variable bioavailability (20 to 80%). It undergoes extensive enterohepatic circulation before entry into the central compartment, from where it undergoes extensive tissue distribution. This is due to the exceptionally high tissue/plasma partition coefficient of amiodarone. Its distribution half-life from the central to peripheral compartment may be as short as 4 hours. But, its terminal half-life is both long and variable (9 to 77 days). This is due to the result of slow mobilization of this highly lipophilic drug out of the adipose tissue. The main metabolites of amiodarone is mono-N-desethylamiodarone which also exerts antiarrhythmic effects and has a long terminal half-life.

Amiodarone is mainly used orally in the dose of 400 to 600 mg/day for few weeks and this is followed by 100 to 200 mg OD for maintenance therapy. In IV route 100 to 300 mg of amiodarone is given slowly over 30 to 60 minutes. For clinical action a therapeutic plasma amiodarone concentration in the range of 0.5 to 2 μg/ml has been suggested. However, the efficacy appears to depend as much as on the duration of therapy and on the plasma concentration of it. But the elevated plasma concentration are not useful in predicting toxicity. As because amiodarone accumulates in tissue, so initially a high oral loading dose is usually administered for several weeks and then maintenance dose is started. Maintenance dose is adjusted on the basis of adverse effects and the response of arrhythmias for which it is used. If the presenting arrhythmia is life-threatening, then the higher dose of amiodarone which is > 300 mg/day are also used, unless clear toxicity occurs. On the other hand, maintenance dose of amiodarone which is < 200 mg/day are used, if recurrence of arrhythmia is tolerated.

Amiodarone treatment may result in supratherapeutic level of iodine in plasma, which may result in either hyper or hypothyroidism. This is because amiodarone is a potent inhibitor of T_4 and thus it inhibits the peripheral change of T_4 to T_3, causing a dose and duration dependent increase in serum reverse T_3. This may account for many of the actions of amiodarone which are similar to those seen after thyroid ablation.

Amiodarone increases the concentration of serum transaminases, indicating hepatic damage secondary to phospholipidosis. A similar mechanism is also believed to account for the alveolitis (pulmonary fibrosis) which occur in about 5 to 7% of patients receiving amiodarone. This alveolitis (pulmonary fibrosis) produced by amiodarone may be insidious in onset and may present with cough, dyspnoea and diffuse pulmonary infiltration. It may occur acutely, especially after surgery in patients receiving high dose of IV amiodarone and may present as a postoperative adult respiratory distress syndrome.

Almost all patients receiving amiodarone develop corneal microdeposits and one third develop signs of CNS toxicity. Peripheral neuropathy, photosensitivity and GI upsets are also well-recognised complications of amiodarone. Hypotension, cardiovascular collapse and AV block have been reported after IV injection of it. Other dysarrhythmias may arise, especially in the presence of hypokalaemia due to the use of amiodarone.

Serious and prolonged hypotension has been described in patient who are pretreated with amiodarone alone or in combination with ACE inhibitor during anaesthesia. It is due to the decrease in systemic vascular resistance (due to vasodilation and myocardial depression) caused by chronic amiodarone therapy and is enhanced by the effects of ACE inhibitor. This exaggerated hypotensive effect produced by the combination of action of amiodarone and ACE inhibitor in mainly unmasked during the blood loss in surgery. Hypotension described in these cases is resistant to α-adrenoreceptor agonists such as metaraminol or phenylephrine and require high infusion rates of noradrenaline to maintain adequate arterial pressure. Hypotension associated with intravenous form of amiodarone is also partially due to the action of solvent which is used in its preparation.

Bradycardia and complete heart block which is resistant to atropine, adrenaline and noradrenaline also have been reported in patients who are receiving amiodarone and undergoing GA. So, it has been suggested that such patients may require temporary pacing in the perioperative period. The drug is contraindicated in porphyria.

Class IV: Calcium Channel Blockers

Calcium antagonists inhibit the inward flow of Ca^{2+} ions into the cell which

usually occurs during the mid and late phase (i.e late phase of 0, phase 1 and predominantly phase 2) of action potential.

The classification of Ca^{2+} channel antagonists recognises three subclasses. These are:

i. Papaverine derivatives (verapamil).
ii. Dihydropyridines derivatives (nifedipine, nicardipine, isradipine, felodipine, nimodipine).
iii. Benzothiazepines derivatives (diltiazem).

All the drugs in each subclass of calcium channel blocker have some specific activity on cardiac conducting tissue, cardiac muscle cells, and vascular smooth muscles. But, the dihydropyridine derivatives (nifedipine) and benzo thiazepine derivative (diltiazem) have some special activity profiles which render them ineffective as antiarrhythmic agents. So, only the verapamil is used clinically as antiarrhythmic agent. The comparisons of electrophysiological actions of these three subclass of main calcium channel blockers are shown in Table 17.5.

Verapamil

Of the many Ca^{2+} channel blockers, verapamil has the most prominant antiarrhythmic action. It predominantly acts on the SA and AV node as these tissues are mainly calcium dependent for their actions during the both phase 0 and phase 4 of action potential. It causes the competitive blockade of slow calcium ion channels of cell membrane leading to decreased influx of Ca^{+} into the cell. So, the rate of discharge in the SA node is reduced and the recovery is prolonged by verapamil. The AV nodal conduction is also strongly inhibited and the ERP is prolonged by it. Because of the powerful AV blocking effect, some drugs such as β-adrenoreceptor antagonist and halothane should be used very cautiously in patient receiving verapamil during anaesthesia (Table 17.5).

Verapamil is absolutely contraindicated in patient with digoxin toxicity. It also causes decrease in influx of Ca^{2+} into the vascular smooth muscle and myocardial cells. This results in inhibition of contraction and relaxation of cardiac and vascular smooth muscle fibres, leading to coronary and systemic arterial vasodilatation. So, the drug causes a decrease in the SVR and is a potent coronary artery vasodilator. Therefore, verapamil is used in the management of mild to moderate type of hypertension and angina.

Verapamil is mainly used in the treatment of supraventricular arrhythmias such as PSVT, AF, AFL, etc. By the effects of reduction of AV conduction, it also reduces the ventricular rate in atrial flutter and atrial fibrillation like digoxin. But the rapid action of verapamil makes it preferrable than digoxin in acute management of atrial flutter and atrial fibrillation or other causes of supraventricular tachycardia to reduce the ventricular rate. It also may be combined with digoxin for the treatment of AF to achieve a synergistic effect of low doses of both the drugs, with good control of HR and minimum undesirable side effects of both the drugs. Verapamil should not be used in the treatment of WPW syndrome associated with PSVT, because of increased risk of ventricular rate. It is only effective in treating the supra ventricular tachycardia when conduction is anterograde through the AV node and retrograde through the accessory pathways. In reverse condition verapamil is ineffective. It should never be used in broad complex tachycardia, because there is chance of VF. Adenosine is the best drug to distinguish between the broad complex tachycardia and supraventricular arrhythmias. Amiodarone is more effective in treating the broad complex tachycardia than the narrow complex tachycardia.

Intravenous administration of verapamil may cause negative inotropic effect and this may be due to synergistic effect with the hypotensive property of volatile anaesthetic agents such as halothane. Thus, profound hypotension and serious cardiac conduction disorders may occurs when verapamil and halothane or other halogenated volatile anaesthetic agents and used combinedly. Verapamil has poor efficacy in the treatment of ventricular arrhythmias. In contrast to β-blockers, verapamil prophylaxis does not reduce the mortality in post MI patients.

Table 17.5: Electrophysiological effects of three commonly used calcium channel blockers

	Verapamil	*Nifedipine*	*Diltiazem*
SA node automaticity	D	Nil	D
Ventricular automaticity	D	Nil	Nil
ERP : Atrial	Nil	Nil	Nil
: AV nodal	I	D/I	I
: Ventricular	Nil	Nil	Nil
: Bypass tract	I	Nil	Nil
ECG : RR interval	I	D	D/I
: PR interval	I	Nil	I

I = Increased, D = Decreased, Nil = No effect

Uses and doses

i. PSVT - Verapamil is the drug of choice for terminating an attack of PSVT. Only 5 to 10 mg of it though IV route over 2 to 3 minutes is effective in 80% cases. Adverse effects like bradycardia, AV block, cardiac arrest, etc., should be checked during the use of verapamil. For prevention of recurrence of PSVT, it is used in the dose of 60 to 120 mg thrice daily orally.
ii. To control the ventricular rate in atrial flutter and fibrillation, (as an alternative

to digoxin or an addition to it), verapamil should be used in the dose of 60 to 120 mg TDS.

Side effects

Verapamil can cause first or second degree heart block. Intravenous administration of it may precipitate heart failure in patients with impaired left ventricular function. It also precipitate ventricular tachycardia or fibrillation in patients with the WPW syndrome. The effects of volatile anaesthetic agents and β-adrenergic antagonists on myocardial contractility and conduction system of heart are syngergistic with those of verapamil. This drug increases the serum concentration of coadministered digoxin.

If verapamil and dandrolene are administered concurrently, then they may cause hyperkalaemia leading to ventricular fibrillation. So, these drugs are not recommended for use together in man. The drug decreases the MAC value of halotane. Chronic exposure to this drug may potentiate the actions of both depolarising and non depolarising muscle relaxants. Verapamil attenuates the pressor response to laryngoscopy and intubation.

Others Antiarrhythmic Agents

Cardiac Glycosides (digoxin)

It has been discussed in the heart failure chapter.

Adenosine

Adenosine and its physiological effects was first described in 1929. But, it has only recently been used as a therapeutic and diagnostic agent. In human body it is a naturally occurring compound (nucleoside) and composed of adenine (a purine base) which is bonded to D-ribose. It is formed in the body by two major mechanism such as the depolarisation of AMP and the breakdown of S-adenosyl homocysteine (SDH). The effects of adenosine in the CVS is mediated by its high affinity to some adenosine receptors such as A1 and low affinity to other adenosine receptors such as A2.

The activity of A1 receptor inhibits the adenyl cyclase and subsequently inhibits the production of cAMP. Thus adenosine causes depression of cardiac contractility. On the otherhand, activation of A2 receptor causes vasodilation throughout the body especially pulmonary, renal and coronary vessels producing hypotension. The pharmacological actions of theophylline, caffeine and methylxanthines are also mediated by their competitive antagonistic actions on A1 and A2 receptors. Part of the vasodilating effects of adenosine may be related to prostacyclin (PGI_2) synthesis. Though the main role of adenosine is as diagnostic and therapeutic tool in the management of supraventricular arrhythmias, but it may also have important roles as coronary and pulmonary vasodilator.

Mechanism of action of adenosine as antiarrhythmic agent

i. Action of adenosine on A1 receptor activates the acetylcholine sensitive potassium conductance in sinus, AV nodal and atrial cells. Thus it causes hyperpolarization of the cell membrane, and hence make slow or complete block the spontaneous activity of these cells.
ii. Adenosine also blocks the slow inward movement of Ca^{2+} current which is responsible for the upstroke (phase 0) of the action potential in sinus, AV nodal and atrial cells. Thus, it increases the refractoriness.
iii. Adenosine also inhibits the release of noradrenaline from the presynaptic terminals. Thus, it enhances the antiadrenergic effect.
iv. Adenosine also exerts its antiarrhythmic action by blocking the re-entry pathways, either through the AV node or through an accessory pathway.

Despite the availability of different types of sophisticated ECG machine, still now diagnosis of tachyarrhythmias is sometimes become very difficult. Because broad complex tachycardia may be due to ventricular tachycardia or supraventricular tachycardia with bundle branch block. If verapamil is used for the treatment of patient with VT mistaken for PSVT with broad QRS complex due to bundle branch block, then cardiac arrest may occur. Another therapeutic problem of verapamil is 15% of narrow QRS complex tachycardia is other than PSVT where it may can create problem. In such situation, if adenosine is injected rapidly in large peripheral veins, then it helps in differentiation between supraventricular and ventricular tachycardia with 90% accuracy, because VT remains unaffected by adenosine.

So, currently the only indication for the use of adenosine is the conversion of PSVT (including that associated with WPW syndrome), to sinus rhythm. Intravenous bolus administration of adenosine for PSVT may induce the onset of atrial fibrillation and thus should be administered only in an appropriate setting with cardioversion capability. Wide complex tachycardia arising from the ventricle, as opposed to the AV node, will not be affected by adenosine. Similarly, atrial arrhythmias (e.g. atrial fibrillation, atrial flutter, multifocal atrial tachycardia) will demonstrate only a transient slowing of ventricular rate.

Adenosine has no clinically important effects on blood pressure except transient hypotension, when administered in therapeutic dose by bolus. But continuous high dose of infusion may result in a decrease of SVR and BP. Thus, it causes a dose dependent reflex tachycardia and an increase in stroke volume and cardiac output. Adenosine also cause a dose dependent increase in myocardial blood flow which is secondary to coronary vasodilation and mediated via endothelial A_2 receptors. But this is without an increase in O_2 consumption and work load. However, the unfavourable changes in distribution of regional coronary blood flow (intracoronary steal) by adenosine have led to (Table 17.6) the myocardial

Table 17.6: Choice of drugs in the treatment of cardiac arrhythmias

Arrhythmia	*Acute*		*Chronic*	
	1st choice	*2nd choice*	*1st choice*	*2nd choice*
1. Atrial extrasystole	Not necessary		Quinidine	Propranolol Disopyramide
2. PSVT	Adenosine Verapamil	Digoxin Beta blocker	VerapamilDi-goxin	Betablocker Disopyramide
3. Atrial flutter and atrial fibrillation	Cardioversion Verapamil	Esmolol	Amiodarone Digitalis	Any of the previ-ous drugs
4. Ventricular extra systole	Lignocaine	Mexiletine Disopyramide Propranolol	Amiodarone	Mexiletine Propranolol
5. VT	Cardioversion-Lignocaine	Mexiletine Amiodarone	Mexiletine, Amiodarone	Disopyramide Quinidine
6. VF	Cardioversion	Lignocaine Bretylium	Bretylium Amiodarone	Same
7. WPW syndrome	Cardioversion	Amiodarone	Amiodarone	Propranolol

ischaemia in patient with coronary artery disease, which may greatly limit its usefulness during anaesthesia.

Adenosine also slows the AV conduction and increases the P-R interval. It can interrupt the re-entrant arrhythmias that involve the AV node. Large doses of adenosine depresses the SA node and ventricular automaticity, leading to brief periods of sinus pause, but it resolve spontaneously. Though adverse reactions of adenosine are rare and of brief duration, still it is best avoided in patients with second or third degree heart block or sick sinus syndrome.

The bolus administration of adenosine is associated with an increase in both the depth and rate of respiration. This is probably mediated by A_2 receptor, situated in the carotid body. It decrease PVR, increases intrapulmonary shunt and can lead to a drop in arterial O_2 saturation, as a result of the inhibition of pulmonary hypoxic vasoconstriction reflex. It may rarely cause bronchospasm in predisposed individuals.

Hypotensive dose of adenosine stimulate A_2 receptors, resulting in renal and hepatic arterial vasodilatation, although low doses have no effect on the glomerular filtration rate and urine output.

Adenosin has a very short half-life which is less than 10 seconds. It is due to rapid uptake of it by the RBC and endothelial cells where it is converted to 5 AMP and inosine. Almost complete elimination of adenosine occurs in a single passage through coronary circulation. Dipyridamole potentiates the actions of adenosine, while theophylline and caffeine antagonize the action of it by blocking the receptors. So, higher doses of adenosine are required for tea or coffee drinker.

The advantages of adenosine over verapamil for termination of PSVT are :

i. Efficiency of adenosine is greater than verapamil - 100% efficacy for adenosine compared with 73% for verapamil.
ii. Action of adenosine lasts < 5 sec. So, adverse effects of adenosine, even if cardiac arrest occurs - are transient and is infact the therapeutic goal.
iii. Adenosine causes no haemodynamic deterioration. So, it can be given to patients with hypotension or those receiving β-blockers. But, verapamil is contraindicated in these situations.
iv. Adenosine is safe in wide QRS tachycardia, while verapamil is unsafe in such condition.
v. Adenosine is effective in patients who are not responding to verapamil.

It may produce transient dyspnoea, chest pain and flushing. VF or ventricular stand still may occur in some patients, but it lasts only for few seconds. Bronchospasm may be precipitated in asthmatics. As adenosine has vary short duration of action, it is not suitable for recurrent cases. It is very expensive.

Dose: The therapeutic dose of adenosine is 6 to 12 mg through IV in bolus. Due to rapid metabolism in few seconds slow administration of adenosine results in elimination of the drug from the circulation prior to its arrival at the heart. So, adenosine is administered as a rapid intravenous bolus, followed by a saline flush. The initial adult dose of adenosine is 3 mg which is followed if necessary by 6 mg and then 12 mg bolus at 1 to 2 minute intervals, until the desired effects are observed. The paediatric dose of adenosine is 0.05 mg/kg, which is increased by 0.05 mg/kg to a maximum of 0.3 mg/kg. The drug acts within 10 seconds and has a duration of action of 10 to 20 seconds. No dose adjustment of adenosine is necessary in the presence of renal or hepatic impairment.

Dofetilide

It is a potent, specific and delayed rectifier K^+ current (IKr) blocker. So it acts only on heart without any extracardiac pharmacological action. Dofetilide is very effective maintaining sinus rhythm in AF. Use of dofetilide does not increase mortality in patient with advanced heart failure and acute MI.

Dofetilide is excreted unchanged by kidneys. So, in renal failure lower doses of dofetilide should be used cautiously. It is marketed first in 2000 and is currrently available only in few centres in the World. The incidence of adverse effects of it is still unknown.

Ibutilide

It also prolongs the duration of action potential by blocking the IKr and inward Na^+ current. For immediate conversion of atrial flutter and atrial fibrillation to sinus

rhythm, ibutilide is used as rapid infusion (1 mg in 10 min). The major drawback of ibutilide is toroades-de-pointes which required immediate cardioversion.

B. Drugs for AV Block (Disturbances for Impulse Conduction)

Atropine

Atropine sulphate (0·6 mg IV, repeated if necessary to a maximum of 3 mg) increases the sinus rate and sinoatrial and AV conduction. It is the treatment of choice for severe bradycardia and/or hypotension due to vagal overactivity. Atropine may also be of important value during the initial management of sympomatic bradyarrhythmias complicating the early stages of inferior myocardial infarction and cardiac arrest due to asystole. Repeated doses may be necessary because the drug disappears rapidly from the circulation after parenteral administration. Side effects include dry mouth, thirst, blurred vision and both atrial and ventricular extrasystole.

Sympathomimetics

Adrenaline

Discussed in the chapter of 'Autonomic Nervous System'.

Isoprenaline

Discussed in the chapter of 'Autonomic Nervous System'.

18 Hypertension: Pharmacology and Anaesthesia

INTRODUCTION

Any definition of hypertension is arbitray. Because in contrast to any specific disease it is often taken as a trait or chapacteristic and represents a quantitative rather than a qualitative deviation from the normal. It is the most common, asymptomatic, readily detectable and easily treatable disease which if untreated often leads to lethal complications. These complications depend also on other risk factors such as age, gender, weight, physical activity, smoking, family history, blood cholesterol, diabetes, etc. Therefore, effective management of hypertension requires a holistic approach which is based on all the identifiable risk factors and adoption of multifactorial intervention. Although, understanding of pathophysiology of elevated arterial pressure has increased but, still in 90 to 95 percent of cases the aetiology of elevated arterial pressure is largely unknown. So, the treatment of hypertension in most cases is nonspecific, resulting in large number of minor side effects and a high-compliance rate. Hence, in light of these observations, hypertension is now defined as the value of blood pressure at which level the benefit of treatment outweigh the cost and complications.

Classification of Hypertension (Based on Aetiology)

i. Systolic and diastolic hypertension
   a. Primary (essential),
   b. Secondary.
ii. Systolic hypertension
   a. Increased cardiac output
      Aortic regurgitation
      Patent ductus arteriosus
      Arteriovenous fistula
      Fever
      Thyrotoxicosis
   b. Rigidity of aorta
      Arteriosclerosis
iii. Diastolic hypertension

Classification of Hypertension (Based on Numerical Value)

Category	*Diastolic (mm of Hg)*	*Systolic (mm of Hg)*
Normal	< 85	< 130
High normal	85-89	130-139
Hypertension Mild	90-99	140-159
Moderate	100-109	160-179
Severe	110-119	180-209
Very severe	> 120	> 210

Essential or Primary or Idiopathic Hypertension

Arterial hypertension with no definite cause or explanation for its pathophysiology is said to be essential hypertension. Usually it constitutes 90 to 95% of the total cases of hypertension. Several abnormalities of varying systems that are mainly involved in the regulation of BP such as kidneys, peripheral resistance vessels, the sympathetic nervous system etc has been described in patients with essential hypertension. But it is still uncertain, whether these abnormalities of varying system which are mentioned above are responsible for development of hypertension (secondary) or are due to hypertension (primary) caused by an unknown aetiology. Also it may be the different expressions or pathophysiology of different organs to a single disease process or it may be the expressions of separate disease entities which is not known. However, the later is gradually getting ground. So, the distinction between the primary hypertension and secondary hypertension is gradually becoming blurred.

Individuals in whom the defect of any specific structural organ is responsible for the development of systemic hypertension are defined as having a secondary form of hypertension. In contrast, where the generalised functional abnormalities are the cause of hypertension (even if the abnormalities are very discrete), it is defined as the essential hypertension.

The probable theories of essential hypertension are:

Heredity

It is probably heterogeneous in nature and is multifactorial in origin. Monogenic defects (Liddle's syndrome) and susceptible genes (angiotensinogen gene) is also now reported.

Environment

Environments that is responsible for high BP includes excessive salt intake, obesity, occupation, smoking alcohol intake, etc. Blood pressure increases with age in more affluent societies and decreases with age in less affluent societies. This explains that enviornment has influence on the genesis of hypertension.

Sensitivity to salt

It is gradually receiving much attention, but pathophysiology of it is still

uncertain. This hypothesis explains that the sensitivity of individual to salt varies which is responsible for hypertension.

Renin

Renin-angiotensin-aldosterone system is an important contributory factor for hypertension. Renin is an enzyme which is secreted by the juxtaglomerular cell of kidney. It is linked with the secretion of aldosterone through a negative feedback loop. Variety of factors can modify the rate of secretion of renin. But the primary determinant is the circulatory volume status of the individual which is again particularly related to the changes in dietary Na^+ intake. The end product of the action of renin on its substrate (angiotensinogen) is the generation of angiotensin I and angiotensin II which is responsible for controlling BP by constricting blood vessels. The intake of Na^+ normally modulates the adrenal and renal vascular response to angiotensin II. With sodium (Fig. 18.1) restriction, the adrenal responses are enhanced and the renal vascular responses are reduced. Whereas the sodium loading has the opposite effect. Plasma renin activity is wider in hypertensive subject than in normotensive. As a consequence, some hypertensive patients have low-renin level and others have high-renin level.

Low renin essential hypertension

Approximately 20% of hypertensive patients have suppressed plasma renin activity. They show the features of hyper aldosteronism, manifested by expan-ded extracellular fluid volume, but not hypocalaemic (which is the feature of hyperaldosteronism). This so-called hyperaldosteronism (or pseudohyperaldosteronism) is responsible for low plasma renin level due to negative feedback mechanism. But due to some unknown reasons practically aldosterone level remains normal. So some atypical (unknown) mineralocorticoids is taken as responsible for low renin hypertension.

Nonmodulating essential hypertension

This type of hypertension constitutes about 25 to 30% of population. Here plasma renin level is normal to high and adrenal defect is opposite to that observed in low renin patients. In these patients, Na^+ intake does not modulate either adrenal or renal vascular responses to angiotensin II. So, this type of hypertension is named so.

High renin essential hypertension

Here plasma renin levels are higher than the normal range which suggests that plasma renin plays an important role in the pathogenesis of elevated BP. However, some investigators postulate that elevated renin and BP are secondary to the increase in activity of adrenergic system. It is proposed that angiotensin-dependent high renin hypertension is nonmodulating defect.

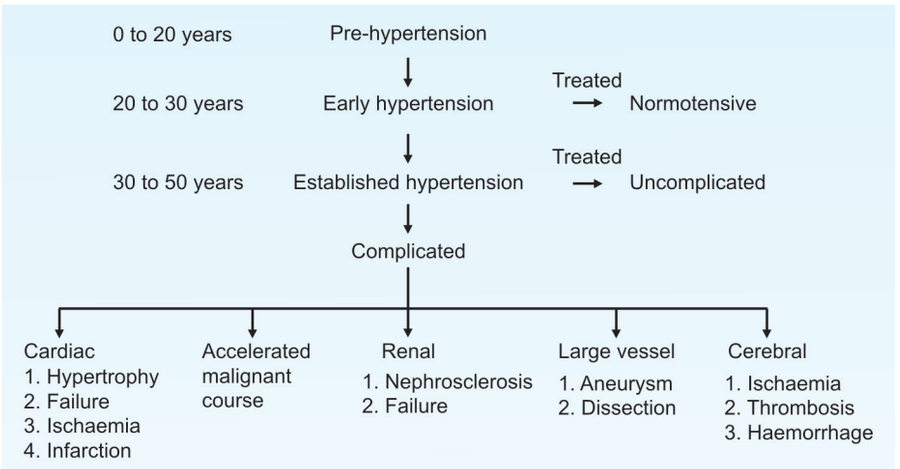


Fig. 18.1: Heredity-environment-age system

Cell membrane defect

Another postulated explanation for hypertension is generalised cell membrane defect, where there is both increase and decrease in the activity of different transport systems. Among these some abnorma-lities are primary and some are secondary. Abnormality in sodium transport reflects an undefined alteration in the cell membrane. This defect leads to the abnormal accumulation of calcium in vascular smooth muscle cells, resulting in higher vascular responsiveness to vasoconstrictor agents.

Insulin resistance

Insulin resistance and /or hyperinsulinaemia is one of the aetiological factors for hypertension. Insulin resistance is common both in NIDDM and obesity. Both obesity and NIDDM are common in hypertensive than normotensive subjects.

Hyperinsulinaemia elevates BP by the following mechanism:

i. Hyperinsulinaemia produces renal sodium retention and increases sympathetic activity which leads to increased BP.
ii. Vascular smooth muscle hypertrophy, secondary to mitogenic action of insulin is another mechanism.
iii. Insulin also modifies ion transport across the cell membrane. Thereby, it potentially increases the cytosolic calcium level in insulin sensitive vascular or renal tissue, thus leading to hypertension.

Secondary Hypertension

In minority of patients (5-10%) hypertension can be shown to be as the consequences of specific diseases or abnormalities which lead to sodium retention and/or peripheral vasoconstriction, causing elevated arterial

pressure. These are called the secondary hypertension. These specific causes have been identified and correction of this causes can cure the hypertension. The causes of secondary hypertension are:

(i) Renal

Acute and chronic glomerulonephritis, chronic pyelonephritis, polycystic renal disease, stenosis of renal artery, diabetic nephropathy, chronic renal failure, renin producing tumour, etc.

(ii) Endocrine

Acromegaly, oral contraceptive, pheochromocytoma, Cushing's disease, primary aldosteronism, congenital adrenal hyper- plasia, hyperthyroidism, etc.

(iii) Neurogenic

Increased intracranial pressure, psychogenic, polyneuritis, etc.

(iv) Miscellaneous

Coarctation of aorta, pregnancy induced hypertension, polyarteritis nodosa, increased intravascular volume, polycythemia, excess transfusion, etc.
Medications – glucocorticoids.

Effects of Hypertension

Hypertension is the most common cause of death. Patient dies prematurely due to hypertension. The adverse effects of hypertension mainly involve the CVS, kidney, retina, CNS which often can be detected by simple clinical means.

Effects on CVS

In hypertension heart has to work against excessive load due to increased SVR. So, the first compensatory change in heart is the concentric left ventricular hypertrophy to maintain the same CO. Then, gradually myocardial ischaemia develops and it damages the myocardium. Thus the function of left gradually ventricle deteriorates, cavity dilates and signs-symptoms of heart failure appear. During the compensatory phase angina may appear, and this is because of the combination of associated coronary arterial disease reducing O_2 supply and increased myocardial O_2 demand. Sound of aortic closure is accentuated and a faint murmur of aortic regurgitation is observed. Presystolic (4th heart sound) and protodiastolic (3rd sound) heart sound may be present. ECG and echocardiographic changes show left ventricular hypertrophy and ischaemia. Atrial fibrillation is common. It may be due to diastolic dysfunction, caused by LVH.

Effect on kidney

The most common renal vascular effects due to hypertension is arteriosclerotic changes in the affarent and efferent arteioles and in the glomerular tuft of capillaries. These changes cause decreased glomerular filtration rate, proteinuria, and microscopic haematuria. Renal failure contributes 10% of death caused by hypertension.

Retinal changes

Retina is the only tissue in which the arteries and arterioles can be examined directly. It also provides the opportunity to observe the progress and the effects of hypertension on vessels. When there is no arteriosclerotic change in retinal vessels, then gradually increasing severity of hypertension is associated with focal spasm and progressive general narrowing of the arterioles. After that there is appearance of haemorrhage, exudates (cotton wool) and papilloedema. These retinal lesions often produce scotoma, blurred vision and even blindness, especially when there is papilloedema or haemorrhage on the macular area. These hypertensive lesions may also develop very acutely. If therapy started immediately and results in significant reduction of BP, then the above mentioned retinal changes show rapid resolution.

If there are retinal arteriosclerotic changes which results from the endothelial and muscular proliferation, then it reflects the similar changes in other organs. These sclerotic changes do not develop as rapidly as hypertensive lesions, nor do they regress easily with therapy. As a consequence the increased wall thickness and rigidity, caused by sclerotic arterioles distort and compress the veins where the two types of vessels cross in their common fibrous sheath. Due to this arteriosclerotic changes the reflected light streak from the arterioles is changed by the increased opacity of the vessel wall.

Hypertensive retinopathy

Grade I

Arteriolar tortusity, thickening and increased reflectiveness (silver wiring).

Grade II

Grade I plus nipping or constriction at arteriovenous crossing.

Grade III

Grade II plus retinal ischaemia evidenced by flame shaped haemorrhage and cotton wool exudate.

Grade IV

Grade III plus papilloedema.

Effects on CNS

Common symptoms of patients with hypertension are headache, dizziness, vertigo, tinnitus, dimness of vision and syncope. The more serious manifestations of CNS for hypertension are due to the vascular occlusion, haemorrhage or encephalopathy. The pathogenesis of cerebral infarction (vascular occlusion) is secondary to the increased cerebral atherosclerosis. The pathogenesis of cerebral haemorrhage or stoke is the result of both elevated cerebral arterial pressure and the development of cerebral vascular microaneurysms. Stroke is the most common complication of hypertension and it may be due to cerebral haemorrhage or cerebral infarction. Hypertensive ence-phalopathy is a rare condition.

Some Terminologies Regarding Hypertension

Hypertensive emergency

It is defined as the elevation of both systolic and diastolic BP with the presence of any acute end organ disease. The organs at particular risk for hypertensive emergency are those that receive the greater proportion of cardiac output, that is the heart, brain and kidneys. So, the hypertensive emergencies include hypertensive encephalopathy, dissecting aortic aneurysm, cerebrovascular accidents, severe hypertension with progressive renal insufficiency and acute left ventricular heart failure. Hypertensive emergencies may also be caused by pheochromocytoma, pre-eclampsia, eclampsia. It may even be drug-related (MAO inhibitor and tyramine ingestion, withdrawal of α_2 agonist such as clonidine, use of sympathomimetic agents) or occur post-operatively. Hypertensive emergency is not distinguished by an arbitrarily chosen BP value.

Hypertensive urgency (or pseudoemergency)

It is described as an elevated BP (diastolic > 120 mm of Hg) with an absence of any acute end organ disease. Examples of hypertensive urgencies include perioperative hypertension, intractable nasal bleeding, hypertension associated with increased circulation of catecholamines and most commonly severe diastolic hypertension without any complications.

Hypertensive crisis

Hypertensive emergency and urgency are together encompassed in this term. Hypertensive emergencies are rare and treatment must balance the risks of lowering BP too rapidly against the persistent hypertension with continued end organ dysfunction. As for example, in case of LVF blood pressure should be reduced very rapidly, but in CVA reduction of BP should be over hours.

Malignant hypertension

In addition to marked elevation of blood pressure in association with papilloedema, retinal haemorrhages and exudates, the full blown picture of malignant hypertension may include the manifestation of hypertensive encephalopathy, such as severe headache, vomiting, visual disturbances, transient paralyses, convulsions, stupor and coma.

Accelerated malignant hypertension

Until recently, the term 'malignant' hypertension was used for the presence of papillaedema [grade IV Keith-Wagener (K-W) retinopathy], whereas the term 'accelerated' was used for the presence of haemorrhages and exudates in retina (grade III K-W retinopathy), both with markedly high BP (diastolic BP usually above 140 mm of Hg). But this funduscopic differences do not establish different clinical features or prognosis, so the term 'accelerated– malignant' hypertension is recommended and will be used from now on.

Hypertensive encephalopathy

In addition to the marked elevation of blood pressure associated with papilloedema, retinal haemorrhage and exudates etc, the full – blown picture of malignant hypertension may also include manifestation of hypertensive CNS disturbances, transient paralysis, convulsion, stupor and coma This is known as hypertensive encephalopathy. With or without structural defects of accelerated–malignant hypertension, progressively higher BP can lead to hypertensive encephalopathy.

The above mentioned manifestations have been attributed to spasm and dilatations of cerebral vessels and cerebral oedema. In some patients who have died, multiple small thrombi have also been found in cerebral vessels. CSF is clear but usually under increased pressure. MRI shows haemorrhage in and around the basal ganglia. However, the neurological deficit is usually reversible if the hypertension is promptly treated.

Mechanism of Hypertensive Encephalopathy

With changes in BP the cerebral vessels constrict or dilate to maintain a relatively constant level of cerebral blood flow (CBF). This is called the process of autoregulation and is regulated by sympathetic nervous activity. Cerebral vessels dilate progressively as pressure decreases and progressively constrict as pressure increases. When MAP reach a critical level, say around 180 mm of Hg, then the previously constricted vessels are unable to withstand such high pressure and become stretched and dilated. It occurs first in areas where the vessels are with less muscular tone, thus producing irregular sausage string pattern and later diffusely, producing generalised vasodilatation. This vasodilation allows an increase of CBF and hyperperfusion of the brain under high pressure. This causes leakage of fluid into the perivascular tissue, leading to cerebral oedema and the clinical syndrome of hypertensive encephalopathy. The figure relating the relationship between MAP and CBF demonstrates that CBF is constant between MAP of 60 and 120 mm of Hg in normotensive subject, i.e. the lower six curves. Of these lower six, upper two curves show breakthrough hyperperfusion when pressure is raised beyond the limit of autoregulation in normotensive subject. The autoregulation curve in chronic hypertensives, whose blood gradually vessels adapt to the chronically elevated BP with structural thickening mediated by sympathetic nerves, is shifted to the right (shown in the upper six curves). Even with this shift, breakthrough will occur if pressure is raised very high to levels of 170 to 180 mm of Hg.

These findings explain a number of clinical observations. At the upper portion of the autoregulatory curve of the previously normotensive people (lower six curves) who suddenly become hypertensive may develop encephalopathy at relatively low levels of hypertension. These include children with acute glomerulonephritis and

young women with eclampsia. On the other hand, chronically hypertensive patients less commonly develop encephalopathy and if so only at much higher pressure.

When BP is lowered by antihypertensive drugs too rapidly, then the chronic hypertensive patients are often unable to tolerate this reduction of BP without experiencing cerebral hypoperfusion (manifested by weakness, dizziness, etc.). These symptoms appear at levels of BP that are still above the upper limit of normal and that are well tolerated by normotensives. The reason is that the entire curve of autoregulation shifts to the right, so that the lower end is also shifted to the right with fall of CBF at levels of 100 to 120 mm of Hg of MAP (Fig. 18.2). If BP is lowered gradually then the curve shifts back toward its normal position, so that the greater reduction in pressure can eventually be tolerated. Unfortunately, chronic hypertensives may lose their ability to autoregulate and increase the risk of brain damage when BP is lowered acutely. In infracted brain tissue autoregulation is lost. Therefore, with high BP cerebral perfusion would be accentuated through the damaged tissue leading to oedema and compression of normal brain. Thus, hypertensive encephalopathy is a consequence of progressively rising arterial pressure that break through the protection of blood-brain barrier and the autoregulation of CBF.

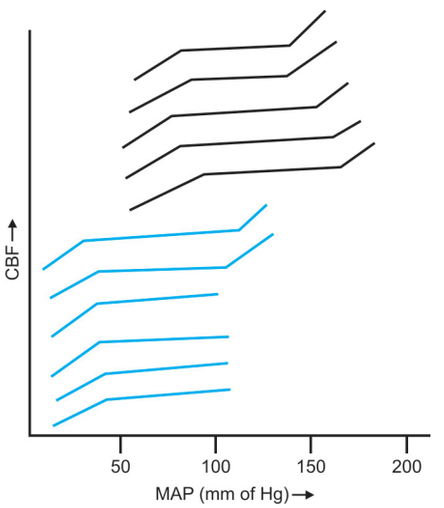


Fig. 18.2: The relation between cerebral blood flow (CBF) and mean arterial pressure (MAP) in both normotemive and chronic hypertensive patient

DIAGNOSIS OF PRIMARY AND SECONDARY HYPERTENSION

Primary hypertension is diagnosed by exclusion of secondary causes. But during the diagnosis of primary hypertension, we will have to keep in mind that the majority of abnormal signs are due to the complications of hypertension which may be mistaken as secondary causes. However, certain clues from history, clinical examination and routine laboratory tests may suggest secondary form of hypertension which dictates the need for special investigations for confirmation of it. For example:

i. Abrupt onset of severe hypertension under the age of 25 years or after the age of 50 years should lead to laboratory tests to exclude the renovascular hypertension and pheochromocytoma.
ii. History of headache, palpitation, sweating, hyperglycaemia and weight loss suggests pheochromocytoma.
iii. The presence of abdominal bruit suggests renovascular hypertension.
iv. Elevated creatinine, ↑BUN, proteinuria, haematuria, suggests renal insufficiency.
v. Therapeutic failure with initial drug therapy also suggest secondary hypertension.
vi. Characteristic facies and habitus suggests Cushing's syndrome. There are also many nonspecific findings which include: Left ventricular hypertrophy, accentuation of the aortic component of the 2nd heart sound, 4th heart sound, etc.

Pheochromocytoma

The easiest and best screening procedure for pheochromocytoma is the measurement of catecholamines or their metabolites in 24 hour urine sample, collected while patient is hypertensive. Measurement of plasma catecholamine levels is also useful.

Cushing's syndrome

A 24-hour urine test for cortisol. A urine cortisol level of less than 2750 nmol (100 µg) excludes Cushing's syndrome.

Administration of 1 mg of dexamethasone at bedtime followed by measurement of plasma cortisol at 7 to 10 am is the best screening test for Cushing's syndrome. Plasma cortisol level below 140 nmol/L (5 µg/dl) rules out Cushing's syndrome.

Investigations for All Hypertensive Patients

i. Blood glucose.
ii. Blood urea and creatinine.
iii. Blood electrolytes (hypokalaemic alkalosis is usually due to diuretic therapy, but it may indicate primary aldosteronism).
iv. Serum total and high density lipoprotein (HDL) and cholesterol.
v. Urine analysis for glucose, protein and blood.
vi. 12 lead ECG to diagnose LVH, coronary artery disease, etc.
vii. Microscopic urine analysis.
viii. White blood cell count.
ix. Serum calcium, phosphate and uric acid.

Investigations for Selected Hypertensive Patients

i. Ambulatory BP recording to assess 'white coat' or border line hypertension.
ii. Chest X-ray to detect coarctation of aorta, cardiomegaly, heart failure, etc.
iii. Echocardiography to detect and quantify the left ventricular function.
iv. Urinary catecholamine measurement to detect phaeochromocytoma.
v. Urinary cortisol measurement and dexamethasone suppression test to diagnose Cushing's syndrome.
vi. Renal ultrasonography to detect the possible renal diseases.

vii. Renal angiography to diagnose renal artery stenosis.
viii. Plasma renin activity and measurement of aldosterone to diagnose primary aldosteronism.

RENIN-ANGIOTENSIN SYSTEM (RAS)

To know the hypertension properly, renin-angiotensin system should be known in details. So, this system is discussed here. Initially, in 1970, inhibition of renin-angiotensin system was considered sensitive only for patients with high-renin hypertension. But, later it was found that ACE inhibitor was also proved to be effective in essential hypertension, with normal levels of plasma renin activity. Also recently ACE inhibitors gained widespread popularity for its use in congestive heart failure, myocardial infarction, diabetic nephropathy, renal failure, vascular disease and many other conditions associated with hypertension.

Overview

RAS control BP by short and long-term regulation. Factors that decrease the effective blood volume and reduce BP (e.g. use of vasodilators, diuretics, blood loss, low – Na^+ diet, liver cirrhosis, etc.) activate the release of renin from kidney. Renin is an enzyme that acts on angiotensinogen and catalyse this substrate to form a decapeptide, named angiotensin I from it. This decapeptide is then cleaved by angiotensin converting enzyme (ACE) to yield octapeptide named angiotensin II (A-II). This A-II acts via diverse and coordinated way to raise or maintain the arterial blood pressure. A-II causes vasoconstriction and increase peripheral vascular resistance. Thus, it contributes to the short-term regulation of arterial BP. A-II also inhibit the excretion of Na^+ and water by kidney. Thus A-II causes changes in renal function which play an important role in long-term stabilisation of BP.

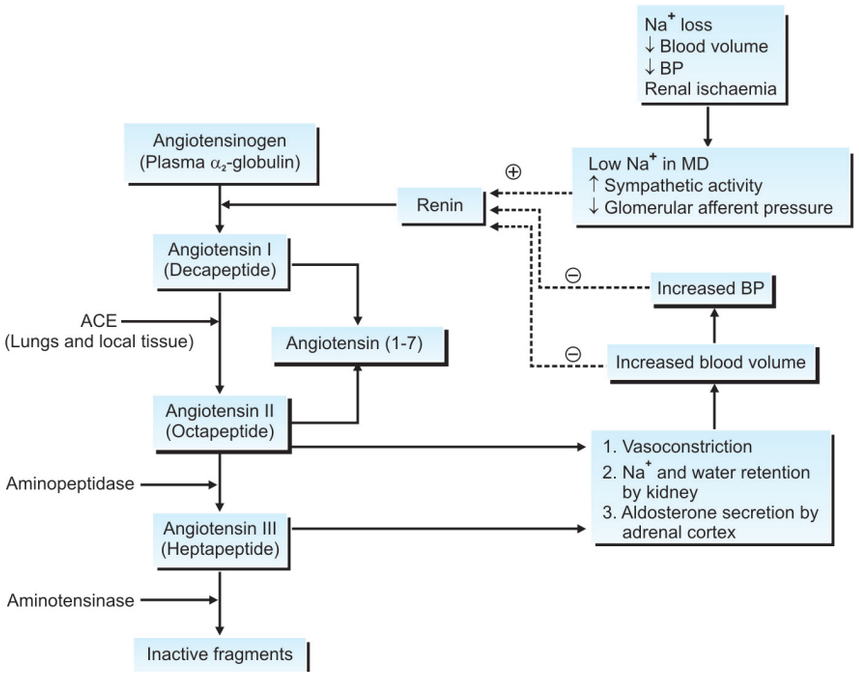


Fig. 18.3: Control of renin secretion

Renin

It is a glycosylated single chain polypeptide and is secreted by the granular juxtaglomerular (JG) cells which lie in the walls of the afferent arterioles as they enter the glomeruli. It is major determinant factor for angiotensin II (A-II) production. Its principal substrate is circulating α_2-globulin which is called angiotensinogen and convert it to angiotensin I (A-I). The first product during production of renin is preprorenin, which is processed in the ER of JG cells to prorenin. Prorenin then may be secreted directly from JG cells or packaged into immature granules where it is further processed to the active mature renin.

Control of renin secretion

The secretion of renin is controlled predominantly by three pathway. Among these the two pathways are locally acting within the kidney. The third is acting through the CNS and mediated by renal noradrenergic nerves. The locally acting two pathways within the kidney are: macula densa pathway and intrarenal baroreceptor pathway. The third pathway acting through CNS is the adrenergic receptor pathway (Fig. 18.3).

Macula densa pathway

It is composed of specialised columnar epithelial cells called the macula densa (MD). They are located in the wall of the thick ascending limb that passes between the afferent and efferent arterioles of the glomerulus, adjacent to JG cells. A change in the reabsorption of NaCl by MD results in the transmission of chemical signals to nearby JG cells of affarent arteriole that modify the release of renin from them. Increase in NaCl influx across the MD cells inhibit the release of renin and decrease in NaCl influx increase the release of renin. This chemical signal pathways involve both the adenosine and prostaglandin. Adenosine after being released when NaCl transport increases inhibits the secretion of renin. Whereas, prostaglandin after being released when NaCl transport decreases stimulates the secretion of renin.

Intrarenal baroreceptor pathway

The increase or decrease in BP in the preglomerular vessels inhibit or stimulate the release of renin respectively. It acts through PG pathway.

β-adrenergic receptor pathway

It is mediated by the release of norepinephrine from the postganglionic sympathetic nerve terminals. Then, the activation of β_1 receptor, situated on JG cells by norepinephrine enhances renin recreation.

These three pathways regulating the release of renin are embedded in a physiological network. Increase in renin secretion enhances the formation of angiotensin II (A-II). Subsequently, this A-II stimulates angiotensin subtype I (AT_1) receptors on JG cells and inhibit the release of renin. This feedback system has been termed the short loop negative feedback mechanism. Next, A-II also increases the systemic BP via stimulation of AT_1 receptor situated on the peripheral vessels of the body. This ↑BP inhibit the release of renin by: (i) activating the baroreceptors, thereby reducing the renal sympathetic tone, (ii) increasing the pressure in the preglomerular vessels and (iii) reducing the reabsorption of NaCl in the proximal tubule (pressure natriuresis), which increases the tubular delivery of NaCl to macula densa. This inhibition of release of renin due to A-II induced increase in BP has been termed as the long loop negative feedback mechanism.

Renin release also can be influenced by a number of pharmacological agents. These are:

i. Loop diuretics stimulate the release of renin by blocking the reabsorption of NaCl at MD.
ii. NSAID inhibit the formation of PG and decrease the release of renin.
iii. ACE inhibitor and AT_1 receptor blocker interrupt both the short and long loop negative feedback mechanism and increase the release of renin.
iv. Diuretics and vasodilators increase the release of renin by decreasing BP.
v. β-adrenergic receptor antagonists decrease the secretion of renin by inhibiting the β-adrenergic receptor pathway.

Angiotensinogen

The substrate for action of renin is angiotensinogen. It is glycoprotein in nature. It is continuously synthesised and secreted by liver. Its synthesis is stimulated by inflammation, insulin, estrogen, glucocorticoids, thyroid hormone, etc. During pregnancy the plasma level of angiotensinogen increases several fold under the influence of oestrogen. Renin converts angiotensinogen to angiotensin-I (A-I).

Angiotensin Converting Enzyme (ACE)

Although spontaneous slow conversion of A-I to A-II occurs in plasma, but the very rapid conversion of it occurs due to the activity of cell membrane bound ACE which is present on the luminal aspect of the endothelial cells throughout the whole vascular system. During conversion of A-I to A-II the two end amino acids such as histidyl and leucine of A-I are removed by ACE and form the 8-amino acid polypeptide angiotensin-II (A-II). Thus, conversion A-I to A-II occurs throughout the body, but particularly it occurs in lung. Angiotensin II is then converted to angiotensin III (A-III) by aminopeptidase.

Angiotensin Peptides

There are three angiotensin peptides. These are: Angiotensin-I (A-I), angiotensin-II (A-II) and angiotensin-III (A-III). A-I is less than 1% as potent as A-II on the vascular smooth muscle, heart and adrenal cortex. A-III is formed by the action of aminopeptidase on A-II. The A-II and A-III have qualitatively similar effects, but quantitatively A-III is only 25% and 10% as potent as A-II in elevating BP and stimulating the adrenal medulla, respectively. On the otherhand, A-III is as potent as A-II in stimulating the secretion of aldosterone.

A-I and A-II is metabolised to anginotensin (1 to 7). ACE inhibitors increases, rather than decreases, the tissue and plasma levels of anginotensin (1 to 7). This because A-I levels are increased and is diverted away from A-II formation to the formation of angiotensin (1 to 7). Unlike A-II, anginotensin (1 to 7) does not cause vasoconstriction, aldosterone release, or facilitation of noradrenergic neurotransmission causing elevation of blood pressure. Anginotensin (1 to 7) inhibits proliferation of vascular smooth muscle cells. Aminopeptidases, endo-peptidases and carboxypeptidases also cause degradation and inactivation of A-I and A-II to anginotensin (1 to 7).

The traditional view of the renin-anginotensin system is that circulating renin of renal origin acts on circulating anginotensinogen of hepatic origin and produce A-I in blood. Circulating A-I is then converted by plasma ACE and pulmonary endothelial ACE to A-II. A-II is then delivered to the target organ via blood stream and produces physiological responses. But actually this traditional view is oversimplification. It can be divided into Extrinsic Local R-A system and Intrinsic Local R-A system.

The conversion of hepatic anginoten-sinogen to A-I by renin and subsequently conversion of A-I (both circulating and locally produced) to A-II occur primarily within or on the surface of the blood vessel wall, but not in circulation. This is called the extrinsic local RA system because it depends on renal and hepatic based system.

Locally many tissues including brain, pituitary, blood vessels, kidney, adrenal gland, etc., express mRNAs for renin, anginotensinogen and ACE system. This system exists independently of the renal or hepatic based system and influences the local vascular, cardiac and renal's function and structure. This is called the intrinsic local RA system.

Angiotensin receptor

The effects of angiotensins are exerted through some specific receptors, situated on the cell surface. It is identifies as two types and designated as AT_1 and AT_2. Both AT_1 and AT_2 receptor are members of the G protein coupled receptor family. Most of the biological effects of A-II are mediated by the AT_1 receptor. Whereas, the functional role of AT_2 receptors are ill defined. AT_2 receptor is widely distributed in foetal tissues, but its distribution in adult is restricted. AT_1 receptor has high affinity for losartan (AT_1 receptor blocker) than AT_2 receptor. In adult some tissues contain primarily either AT_1 or AT_2 receptor. Whereas, other tissues contain these both receptor in similar amount.

Pre-eclampsia is associated with the development of agonistic autoantibodies against AT_1 receptor and thus produce exaggerated response causing hypertension. AT_1 receptor activates a large array of intracellular signal transduction system, including the intracellular Ca^{2+} release, influx pathways, phospholipases, mitogen activated protein kinase pathways, etc. Additional Ca^{2+} also enters the cell from outside due to opening of voltage sensitive Ca^{2+} channels, located on cell membrane. This Ca^{2+} binds to calmodulin and the Ca^{2+}/calmodulin complex activates a number of intracellular enzymes that contribute to the ultimate cellular responses. This is discussed in more details in ANS chapter (Table 18.1).

Function of Renin-Angiotensin System (RAS)

This RAS plays an important role in regulating the BP for both short and long-term basis. A-II is 40 times more potent than norepinephrine in respect to increase in BP. The rapid pressor response of A-II is due to the vasoconstriction and increase in the systemic vascular resistance. A-II also increases directly the cardiac contractility, acting through voltage gated Ca^{2+} channel and indirectly increase heart rate, acting by facilitation of sympathetic tone. It also enhances the noradrenergic neurotransmission and in crease the release of adrenal catecholamines. But, the increase in BP activates the baroreceptor reflex that decrease sympathetic tone and increase vagus tone. Therefore, in summary, the main function of RAS is: Alteration of SVR, alteration of renal function and alteration of cardiac function with structure.

Mechanism by which A-II increases the systemic vascular resistance (SVR)

A-II increases the SVR via direct effects on blood vessels and via indirect effect through CNS and adrenal medulla by catecholamines.

Direct vasoconstriction

A-II contracts the precapillary arterioles and postcapillary venules (lesser extent). This is caused by the activation of AT_1 retceptor by A-II which are located on the smooth muscle cells of blood vessels. But, the intensity of contraction is different in different vascular bed. Strongest contraction occur in kidney and somewhat lesser contraction occurs in other splanchinic vascular bed. A-II induced vasoconstriction is much less in the vessels of brain. It is more weaker in those of lung and skeletal muscle. But, in these regions the blood flow actually increases, because the relatively weak vasoconstrictor response is opposed by the elevated systemic blood pressure and the ultimate blood flow depends on the intensity of contraction and rise of BP.

Indirect enhancement of peripheral noradrenergic neurotransmission

A-II facilitates the peripheral noradrenergic neurotransmission and increases BP by: (i) augmenting the release of norepinephrine from the sympathetic nerve terminals, (ii) by inhibiting the reuptake of norepinephrine into the presynaptic nerve terminals and (iii) by enhancing the vascular response to norepinephrine.

Through effects on CNS

A-II increases arterial BP by its action on the CNS. This effect is mediated by increased sympathetic outflow (Fig. 18.4) from brain due to the effect of A-II on circumventricular nuclei that are not protected by a blood-brain barrier. The CNS is affected both by blood borne angiotensin

Table 18.1: Angiotensin II

Altered renal function	*Altered SVR*	*Altered CV function and structure*
1. Increased reabsorption of Na^+ from PT.	1. Direct vasoconstriction.	1. Increased proliferation, hyperplasia and hypertrophy of myocardium.
2. Increased secretion of aldosterone → increased reabsorption of Na and excretion of K+ from DT.	2. Indirect vasoconstriction through peripheral noradrenergic neurotransmission.	2. Increased fibrosis.
3. Increased renal vasoconstriction.	3. Increased sympatheitc discharge from CNS.	3. Increased extracellular matrix.
4. Increased noradrenergic neurotransmission in kidney.	4. Release of catecholamines from adrenal medulla.	4. Increased arterial wall thickness, ↑wall tension and ↑after load
5. Increased renal sympathetic tone through CNS		
↓	↓	↓
Slow pressure response	Rapid pressure response	Hypertrophy and remodelling of heart

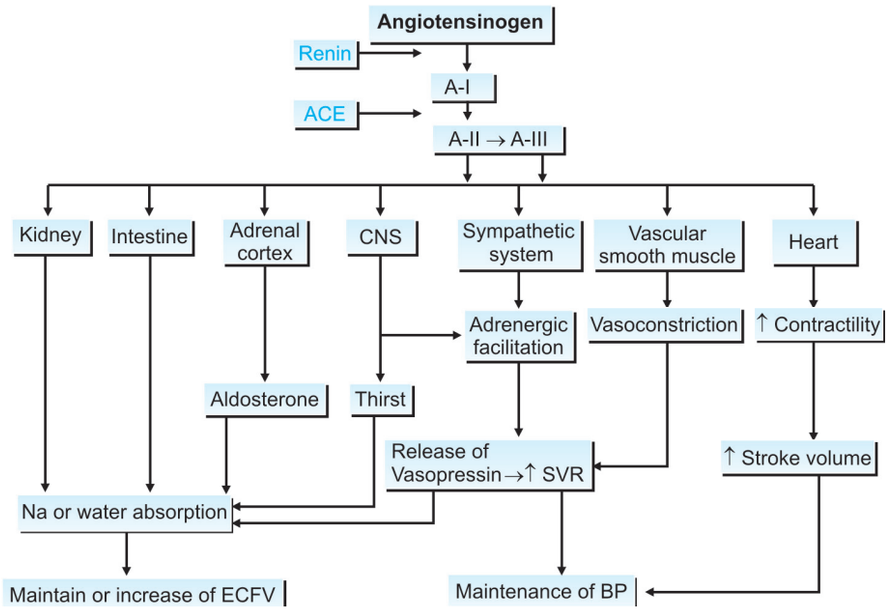


Fig. 18.4: The function of renin angiotensin system

II and by angiotensin II formed locally within the brain. The brain contains all the components of R-A system and here the A-II serves as a neurotransmitter or modulator.

Through release of catecholamines from adrenal medulla

A-II stimulates and release the catecholamines from adrenal medulla by depolarising the chromaffin cells.

Mechanism by which angiotensin II alters the renal function

A-II reduces the renal excretion of Na^+ and increase the renal excretion of K^+. It stimulates the Na^+/H^+ exchange in proximal tubule and increases the reabsorption of Na^+, Cl^-, HCO_3^-. The A-II also stimulate the secretion of aldosterone from zona glomerulosa of adrenal cortex which acts on the distal and collecting tubule to cause retention of Na^+ and excretion of K^+ and H^+. Aldosterone secretion increases under condition of hyponatraemia and hyperkalaemia and decreases in opposite condition. Such changes is due to alterations in the number of receptor for A-II at zona glomerulosa and adrenocortical hyperplasia in Na^+ depleted state.

A-II reduces the renal blood flow by directly constricting the renal vascular smooth muscle or by facilitating the renal noradrenergic neurotransmission. A-II influences the glomerulr filtration rate (GFR) in variable way by following mechanism: (i) constriction of affarent arterioles reduces GFR, (ii) contraction of mesangial cells reduces the filtration surface area and GFR, (iii) contraction of efferent arterioles causes increase in intraglomerular pressure and increases GFR.

The outcome of these opposing effects on GFR depends on the present physiological state. Normally A-II reduces the GFR slightly. But in hypotension, the effects of A-II on efferent arterioles predominate and increase the GFR. So, the blockade of renin angiotensin system cause renal failure in patient with renal artery stenosis.

Mechanism by which A-II alters the cardiovascular function and structure

Several pathological changes occur in cardiovascular structure and function by A-II and pose an increased risk of morbidity and mortality. These changes include: (i) increased wall thickness to lumen ratio in blood vessels, (ii) cardiac concentric hypertrophy, (iii) cardiac eccentric hypertrophy and fibrosis which is associated with congestive failure and infarction, (iv) thickening of the initial surface of the wall of blood vessel. All these changes are due to increased migration, proliferation, hyperplasia, and hypertrophy of smooth muscle cells, and increased extracellular matrix. The cells which are involved in these changes include vascular smooth muscle cells, cardiac myocytes and fibroblasts. All these changes in cardiovascular structure causes increase in cardiac contractility, stroke volume and BP.

Renal pressure – natriuresis curve

The intake of Na^+ and its excretion determines the arterial blood pressure. When the relation between the Na^+ intake, Na^+ excretion and the arterial blood pressure are drawn graphically, then this graph is called the renal pressure natriuresis curve. At a stable condition Na^+ intake is equal to Na^+ excretion. At some set point arterial blood pressure can be obtained from intersection of a horizontal line (representing Na^+ intake) with the renal pressure – natriuresis curve (Fig. 18.5).

When the dietary Na^+ intake is low, then renin release is stimulated and subsequent increased angiotensin II acts on the kidney to decrease the excretion of Na^+. Thus, the curve is shifted to the right to maintain the same blood pressure. Conversely, when

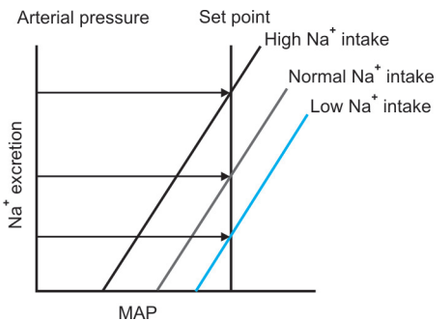


Fig. 18.5: Renal 'pressure-natriuresis' curve

the dietary Na^+ intake is high, then secretion of renin is inhibited and subsequently the withdrawal of angiotensin II causes increase in excretion of Na^+. Thus the curve is shifted to the left and blood pressure is maintained normal. The intersection of salt intake curve with the Na^+ excretion line remains near the same set point despite the large swings in dietary Na^+ intake (shown in curve as Na^+ excretion). If the curve does not shift then the arterial BP swings tremendously with different intake of Na^+. When pharmacologically the modulation of R-A system or the swings of the curve is prevented, then any changes in salt intake markedly affect the long term levels of arterial BP.

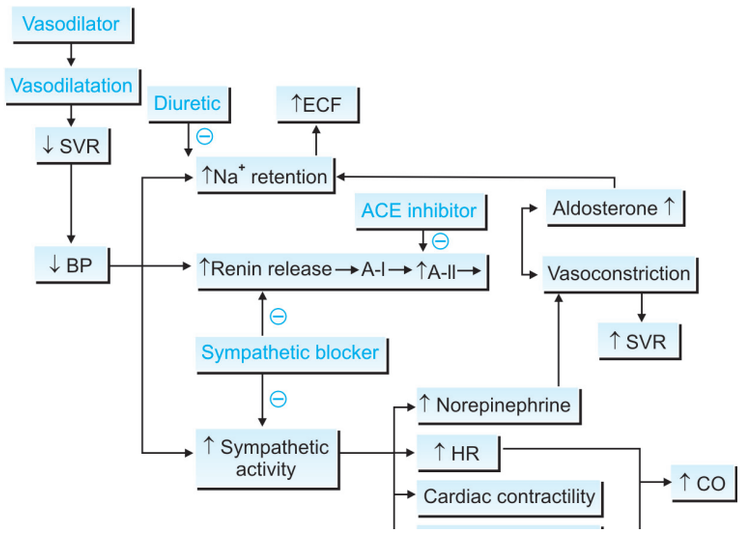


Fig. 18.6: The mechanism of secretion of renin and angiotensin

Inhibition of Renin-Angiotensin System

The inhibition of renin-angiotensin system is the main stay of the management of hypertension and its complication. It can be achieved by:

i. Decreasing the release of renin: This can be achieved by sympathetic blockers such as β-blockers and other adrenergic neuron blockers.
ii. Blocking the action of renin: This can be achieved by renin inhibitory peptides or renin specific antibodies. They interfere the rate limiting step producing A-I from angiotensinogen. But, they are not used clinically (Fig. 18.6).
iii. Blocking the action of angiotensin converting enzyme: These are called the angiotensin converting enzyme inhibitor (ACE-inhibitor) and prevent the generation of active principle A-II from A-I. These group of drugs are used extensively in clinical practice.
iv. Blocking the angiotensin receptor (AT_1): They block the action of A-II on the target cells.
v. Blocking the action of aldosterone: They block the mineralocorticoid receptors.

Angiotensin-Converting Enzyme Inhibitors (ACE-Inhibitors)

In 1960, Ferreria and his colleagues observed that the venom of pit vipers have some factors which increases the responses to bradykinin. These factors are called the bradykinin potentiating factors and reduce the BP. Following the discovery of these factors the teprotide was synthesised. It was a nonpeptide and inhibits the generation of A-II from A-I. It was found to lower BP in many patients with essential hypertension. It also exerts beneficial effect in patients with heart failure. But it had limitations of parenteral administration and brief duration of action. So, these observation lead to the search for other ACE inhibitor which could be active orally.

Then, in 1977, came captopril which was orally active dipeptide and had quickly gained wide usage. After that many ACE inhibitors was synthesised and out of that only six are currently available in India. These are captopril, lisinopril, enalapril, ramipril, benazepril, perindopril. But many others ACE inhibitors are also marketed in other countries such as quinapril, fosinopril, cilazapril, zofenopril etc. However, among all these the captopril is described as prototype, because most of its effects are common to all ACE inhibitors (Fig. 18.7).

Captopril

Chemically it is a sulphydryl containing dipeptide. It blocks the pressure action of A-I, but not that of A-II. It does not also block the AT_1 receptors. The main pharmacological action of captopril is reduction of BP by inhibiting the conversion of A-I to A-II. But the magnitude of this response in an individuals depends on the Na^+ status and the renin angiotensin activity. In individual with dietary Na^+ restriction and diuretics the response of ACE inhibitor is higher. It causes greater fall of BP in renovascular, accelerated and malignant hypertension.

Captopril decreases the SVR. It causes the arterioles to dilate. The compliance of large arteries are increased. Both the systolic and diastolic pressure fall and cardiac output increases. CVS reflexes are not impaired due to any ACE inhibitor and there is little dilatation of the capacitance vessels. So, there is no postural hypotension. The renal blood flow is not reduced, even when BP falls substantially. This is due to much dilatation of the renal vessels as A-II markedly constricts it. The coronary and cerebral blood flow are also not reduced by any ACE inhibitors or captopril.

Since, the conversion of A-I to A-II is blocked by captopril, so the plasma renin and A-I level is increased. A-I then

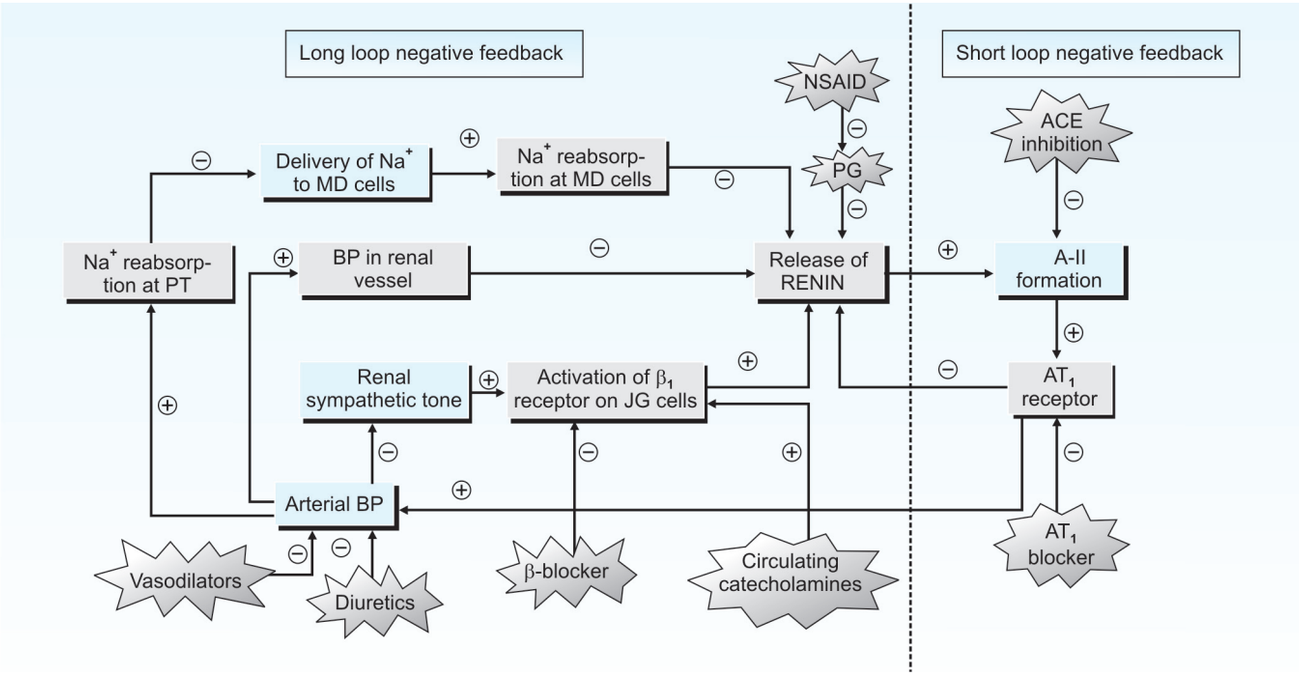


Fig. 18.7: The site of action of different antihypertensive

is redirected through another metabolic route, resulting in the increased production of peptides such as angiotensin (1 to 7). Some thought that it also contribute to the hypotensive effect of ACE inhibitors. It does not interfere the physiological secretion of mineralocorticoids (aldosterone) under the influence of ACTH, but abolish the reflex changes in plasma aldosterone mediated by A-II.

There is no strong reason to favour one ACE inhibitor over another. Because all the ACE inhibitors have (i) the same mechanism of action, (ii) the similar therapeutic indication and (iii) the same adverse effects profile and contraindications. But, they only differ in respect to the following three properties. These are the: (i) potency, (ii) whether ACE inhibition is primarily due to drug itself or to conversion of a prodrug to an active metabolites and (iii) pharmacokinetics.

Regarding the pharmacokinetics, all the ACE inhibitors differ markedly among themselves regarding their absorption, tissue distribution and elimination. This characteristic is exploited clinically to inhibit some local renin-angiotensin systems while leaving other relatively intact. Except fosinopril and spirapril which are eliminated by liver and kidney by equal proportion, other ACE inhibitors are eli-minated predominantly by the kidney. Therefore, the impaired renal function significantly reduces the plasma elimination of most ACE inhibitors. So, doses of these ACE inhibitors should be decreased in patients with renal failure. Increased plasma renin activity makes the patient hypersensitive to hypotension, induced by ACE inhibitor. So, the initial dose of it should be reduced in patients who have high plasma renin level such as salt depletion, heart failure, etc.

Captopril is well-absorbed orally (70%), but the presence of food is stomach reduces the bioavailability of it. It is mainly excreted unchanged through urine. Plasma half-life is about 2 hours. But, action usually lasts for 6 to 12 hours.

The usual doses of captopril is 25 mg twice daily which is increases gradually upto 50 mg thrice daily according to the response. Sometimes, it is wise to start with small doses such as 6.25 mg twice daily in such patients who are in diuretics and in CHF patients to avoid marked fall in BP initially (Table 18.2).

Adverse effects

The profile of adverse effect of all ACE inhibitors are same and serious untoward reactions are rare. Captopril is well-tolerated by most of the patients, especially if the daily dose is kept below 150 mg. Metabolic side effects of captopril are usually not encountered, even during

Table: 18.2: ACE inhibitor

Specially suited for:

1. Young, physically, intellectually and sexually active person
2. Left ventricular hypertrophy, LV systolic dysfunction
3. Diabetics, gout, dyslipidaemia
4. Nephropathy, high renin cases
5. Coexisting angina, peripheral vascular diseases
6. Potential MI
7. Chronic heart failure

Contraindicated

1. Pregnancy
2. Renal artery stenosis
3. Dry cough (relative)
4. Hyperkalaemia

prolonged use. All ACE inhibitors like captopril improve the insulin sensitivity in patients who are suffering from insulin resistance. They decrease the cholesterol and lipoprotein level in renal disease patients. The drug does not alter the plasma uric acid and Ca^{2+} level.

Hypotension

Sometimes, sharp fall of BP occurs after initiations of captopril or any ACE inhibitor therapy. This is particularly true for patients with persistant high renin activity such as diuretic treated and CHF.

Hyperkalaemia

Captopril or any ACE inhibitors may produce hyperkalaemia particularly in patients who is taking K^+ sparing diuretics, K^+ supplement, renal insufficiency, taking β-blocker or NSAID. But, significant retention of K^+ is rarely encountered in patients with normal renal function and who is not taking any medications.

Cough

In 10 to 20% patient captopril or any other ACE inhibitor may produce troublesome cough. It occurs within 1 to 8 weeks and is not dose related. Sometimes, the cough is so intense that it requires discontinuation of therapy. However, once the therapy is stopped, the cough disappears. This cough usually is due to accumulation of bradykinin and/or substance P and/or prostaglandin in lungs. Thromboxane antagonism reduces this captopril induced cough.

Acute renal failure

Sometimes, any ACE inhibitor or captopril may induce acute renal failure in patients with bilateral renal artery stenosis or renal stenosis in single remaining kidney or heart failure or dehydration. Normally A-II constricts the efferent arteriole and maintains adequate glomerular filtration when renal perfusion pressure is low. So, in the presence of above mentioned causes ACE inhibitors precipitate the acute renal failure.

Other less serious side effects

These are rashes, urticaria, angioedema, granulocytopaenia, proteinuria, headache, dizziness, nausea, vomiting, etc.

Foetal damage

ACE inhibitors are not teratogenic in first trimester of pregnancy. But, if it is continued during the second and third trimester of pregnancy, ACE inhibitors may produce different foetal anomalies such as IUGR, pulmonary hypoplasia, oligohydramnios, IUD, etc. These foetal anomalies are due to foetal hypotension. So, while ACE inhibitors is not contraindicated during reproductive age, but should be stopped once pregnancy is diagnosed.

FACT FILE- I

Advantages of ACE inhibitor as antihypertensive are:

1. It is safe for diabetic, asthmatic and peripheral vascular disease patient.
2. Renal blood flow is well maintained.
3. It is not associated with postural hypotension and electrolyte disturbances.
4. It prevents secondary hyperaldosteronism.
5. It prevents K^+ loss due to diuretics.
6. There is no rebound hypertension after withdrawal of ACE inhibitors.
7. It does not cause hyperuricaemia.
8. It does not produce any deleterious effect on plasma lipid profile.
9. It reverses left ventricular hypertrophy.
10. It also reverses the increased wall to lumen ratio of blood vessels that occurs in hypertensive patients.

Therapeutic Uses of ACE Inhibitors

Hypertension

In hypertension, ACE inhibitors lower the mean, systolic and diastolic blood pressure and systemic vascular resistance, except in case of primary aldosteronism. The change in the level of BP correlates well with the plasma renin-anginotensin level. There is variable vasodilator effect of ACE inhibitors at different vascular beds. But, kidney is the only exception where there is definite vasodilation and increased renal blood flow. Increased renal blood flow does not increase glomerular filtration rate. Because both afferent and efferent vessels dilates and effective filtration pressure does not increase. Blood flow in cerebral and coronary beds are usually well-maintained due to their powerful autoregulatory mechanism. Besides causing systemic arteriolar dilatation, ACE inhibitors increase the compliance of large arteries, which contributes to the reduction of systolic blood pressure and after load (Fact file- I).

Stroke volume and cardiac output increases in uncompromised heart. Baroreceptor and cardiovascular reflexes are well maintained. Still with substantial lowering of BP, the heart rate and concentrations of catecholamines in plasma increase only slightly if at all. This perhaps reflects slight alteration of baroreceptors function with increased arterial compliance and the loss of normal toxic influence of angiotensin II on the sympathetic nervous system.

Aldosterone secretion is normally reduced in hypertensive individuals, but is not seriously impaired by ACE inhibitors. Excessive retention of K^+ is encountered by ACE inhibitors only in patients who is taking supplemental K^+, renal impairment or taking other medications that reduce K^+ excretion. It has synergistic action with Ca^{2+} channel blocker, β-adrenergic receptor blocker or diuretics. Diuretics, in particular, augment the antihypertensive response of ACE inhibitors by rendering the patient's blood pressure renin-dependent.

All we have to consider that the goal of antihypertensive therapy (Table 18.3) is not just the lowering of blood pressure, but to diminish the patient's overall risk from cardiovascular complication. ACE inhibitors reduce this incidence of cardiac complication in hypertensive patients more than do other antihypertensive agents such as diuretics, β-blockers, Ca^{2+} channel blockers, etc. This is because other agents have their adverse metabolic effects and

Table 18.3: Pharmacokinetics of different ACE inhibitors

	Captopril	*Enalapril*	*Perindopril*	*Lisinopril*	*Ramipril*
Chemical structure	Sulphydryl	Carboxyl	Carboxyl	Carboxyl	Carboxyl
Activity	Active	Prodrug	Prodrug	Active	Prodrug
Peak action	½-1 hour	3 to 6 hours	3 to 6 hours	8 hours	3 to 6 hours
Elimination half-life	1 to 2 hours	12 hours	30 to 40 hours	12 hours	40 to 60 hours
Bioavailability	80%	60%	30%	30%	70%
Duration of action	6 to 12 hours	12 to 24 hours	> 24 hours	> 24 hours	> 40 hours
Mode of excretion	Renal	Renal	Renal	Renal	Renal
Daily doses (mg)	25 to 100	5 to 30	2 to 8	5 to 130	2.5 to 10

due to their inability to reverse the structural changes of heart and/or blood vessels that may be mediated by the circulatory catecholamines and/or renin-angiotensin system.

ACE inhibitors in left ventricular systolic dysfunction

The left ventricular systolic dysfunction ranges from asymptomatic reduction in systolic performance (cardiac output) to symptomatic severe impairment of left ventricular systolic function (Grade IV LVF). ACE inhibitors should be given to all these patients whether or not they are experiencing symptoms of overt heart failure. Inhibition of renin-angiotensin-aldosterone system by ACE inhibitors in patients with systolic dysfunction prevents or delays the progression of heart failure, decrease the incidence of sudden death and myocardial infarction.

ACE inhibitors commonly reduces the afterload and systolic tension. Both the cardiac output and cardiac index increase, as do the indices of stroke work and stroke volume in heart failure. Heart rate generally is reduced. This is due to the improvement of failure and withdrawal of sympathetic over activity. The excess volume of body fluids contracts, which reduces the excess venous return to right heart. This reduction of preload results from venodilation and increased capacity of the venous bed. The ACE inhibitors also reduce the pulmonary arterial pressure, PCWP, left atrial pressure and left ventricular filling volumes and pressure etc. Consequently, the preload and diastolic wall stress are diminished. The better haemodynamic performance caused by ACE inhibitors results in increased exercise tolerance and suppression of sympathetic nervous system. However, the role of ACE inhibitors on the diastolic dysfunction of left ventricle is still uncertain.

The ACE inhibitors reduce the overall mortality when the treatment is started during the peri-infarction period. Unless contraindicated (e.g. cardiogenic shock, severe hypotension) ACE inhibitors should be started immediately during the acute phase of myocardial infarction.

Myocardial infarction

ACE inhibitors definitely reduces the early as well as the long-term mortality from MI. However, this is true if it is administered while MI is evolving and then continued for another 6 weeks. But, during treatment it should be noted that hypotension should be avoided. ACE inhibitor is beneficial for MI, irrespective of the presence or absence of ventricular systolic dysfunction.

Diabetic nephropathy

ACE inhibitors also help to prevent or delay the progress of an end stage renal disease in insulin or noninsulin dependent diabetes. Albuminuria remains stable during therapy. Those patients who are treated with ACE-inhibitors require less dialysis, and have higher creatinine clearance. They have longer life expectancy also. So, all the patients suffering from diabetic nephropathy needs ACE inhibitors therapy, whether they are hypertensive or not.

MANAGEMENT OF HYPERTENSIVE EMERGENCY

Hypertensive emergency requires immediate reduction of BP to prevent or to minimise the end organ damage. It needs to be distinguished from severe hypertension or urgency where there is no possibility of acute end organ damage. Because aggressive therapy for hypertensive emergency and sudden reduction of blood pressure may result in potentially hazardous reduction in myocardial and cerebral perfusion with more end organ damage. So, the goal of treatment is to minimise the end organ damage due to sudden high rise of BP while preventing the complications due to sudden lowering of BP. Therefore, hypertensive emergency requires immediate lowering of BP in a controlled and predictable manner. The goal is to lower the mean arterial blood pressure (MAP) by approximately 20 to 25% of the previous value in the first hour, while maintaining adequate perfusion to the vital organs. Dropping of BP too quickly or too much can worsen the target end organ damage. With cerebral ischaemia when autoregulation is lost, then cerebral blood flow is directly proportional to the systemic blood pressure. Therefore, if BP is lowered too much, cerebral perfusion pressure in

ischaemic areas is also lowered, risking the further damage.

The recommendation for reduction of BP during management of hypertensive emergency are:

i. It should be reduced over 60 to 90 minutes to a mean BP of 120 mm of Hg
ii. 20 to 30% reduction in mean arterial pressure (MAP = diastolic BP + 2/3 pulse pressure)
iii. Reduction of diastolic pressure by one-third, but not to a level below 95 mm of Hg.

This goal should also be modified (i.e. more gradual reduction of BP) in those patients who are more susceptible to loss of cerebral blood flow (CBF), e.g. the elderly, patients with chronic hypertension and patients with atherosclerotic cerebrovascular disease.

The ideal drug for treatment of hypertensive emergency should have the following characteristics.

i. Rapid onset (controlled not precipitous) and rapid cessation of clinical effects.
ii. Predictable dose response relationship.
iii. Restoration of cerebral autoregu-lation.
iv. Lack of side effects.
v. Convenience to use.

Reasons against the use of oral agents in the management of hypertensive emergency include:

i. Unpredictable effect on MAP,
ii. Unpredictable time to peak effect,
iii. Higher failure rate than with parenteral therapy,
iv. Lack of ease in titration.

In addition, there is no less importance for the patient to be monitored vigorouslywith oral therapy, compared with the intravenous therapy. Institution of appropriate oral therapy may be required once hypertension has been controlled by parenteral agents and it is gradually withdrawn. The drugs used for control of hypertensive emergency are:

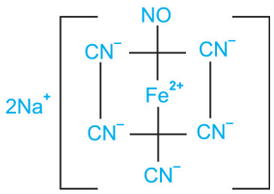


Fig. 18.8: Sodium nitroprusside

Sodium Nitroprusside

It is used primarily to treat hypertensive emergency. But the drug can be used in many situations where the, short-term reduction of cardiac preload and/or afterload is required. So, nitroprusside is used to:

i. Lower BP during acute aortic dis-section,
ii. Increase CO in congestive heart failure,
iii. Decrease myocardial O_2 demand after acute myocardial infarction,
iv. Induce controlled hypotension during anaesthesia (Fig. 18.8).

β-adrenergic receptor blocker should also be used along with nitroprusside. This is because:

i. It counteract the tachycardia due to hypotension induced by nitroprusside,
ii. Reduction of BP by nitroprusside alone can increase the rate of rise of pressure in the aorta as a result of increased myocardial contractility, thereby enhancing the propagation of dissection.

Mechanism of action

Na-nitroprusside is metabolised by the cells of the wall of the blood vessels to its active metabolite which is known as nitric oxide (NO). Then, this NO activates the guanylyl cyclase to form cyclic GMP which in turn cause vasodilatation. Thus, the mechanism of action of nitroprusside is same as nitroglycerin. But the metabolic activation of nitroprusside is catalysed by a different nitric oxide (NO) generating system which is not used for nitroglycerin. Hence, this probably

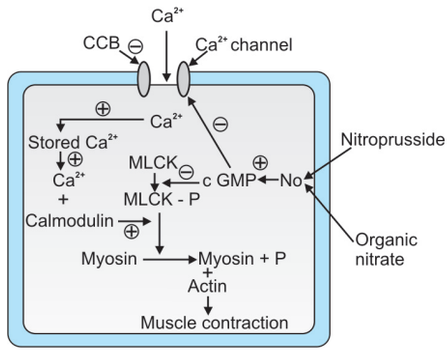


Fig. 18.9: Mechanism of action of calcium channel blocker (CCB), organic nitrates and nitroprusside. MLCK = Myosin light chain kinase

accounts for the difference in the potency of these drugs at different vascular sites. But, the fact is that tolerance develops to nitroglycerin, whereas not to nitroprusside (Fig. 18.9).

Pharmacological effects

Nitroprusside dilates both the arterioles and venules. Thus, the total haemodynamic response and CO produced by Na-nitroprusside depends on the combination of the reduction of venous pooling (↓preload) and reduction of arterial impedance (↓ afterload). In patient with normal left ventricular function, the effect of reduction of venous pooling which decreases the cardiac output is more than the effect of the reduction of afterload which increase CO. Thus, ultimately CO tends to fall. In contrast, for patient with severe impaired left ventricular systolic and diastolic function, the reduction of arterial impedence or after load is the predominant effect which leads to the rise in CO. Reduction of preload is also beneficial in this group of patient.

Nitroprusside is a nonselective vasodilator. So, the regional distribution of blood flow is little affected by this drug. Renal blood flow and glomerular filtration is maintained by nitroprusside. Plasma renin activity is increased due to hypotension and subsequent sympathetic stimulation. Unlike hydralazine, diazoxide, minoxidil

and other arteriolar vasodilators, the sodium nitroprusside usually causes only a modest increase in heart rate in respect to the reduction of BP. But, still there is an overall reduction in myocardial O_2 demand.

Absorption, metabolism and excretion

Onset of action of IV nitroprusside is 30 seconds. Peak hypotensive effect occurs within 2 minutes. When infusion is stopped, hypotensive effect disappears within 3 minutes. It is an unstable molecule and decomposes under alkaline conditions and when is exposed to light. Metabolism of nitroprusside occurs in the smooth muscle cells of blood vessel and is initiated by its reduction to cyanide and NO molecule. Cyanide is further metabolised in liver to thiocyanate and almost is eliminated through urine.

Metabolism of nitroprusside (NP)

$NP + OHbFe^{2+} \rightarrow NP^{-} + OHbFe^{3+}$

$NP^{-} \rightarrow$ 5 types CN^{-} + NO

i. $CN^{-} + HbFe^{3+} \rightarrow CNHbFe^{2+}$
ii. CN^{-} + Thiosulphate → Thiocyanate
iii. CN^{-} + Cytochrome oxidase → Cyanide toxicity

After injection, NP enter the RBC → it receives an electron from iron of oxyhaemoglobin ($OHbFe^{2+}$) → methaemoglobin ($OHbFe^{3+}$) and unstable nitroprusside radicle (NP^{-}) is formed → unstable NP^{-} spontaneously breaks into five cyanide ion (CN^{-}) and active NO group → the CN^{-} ion may involve in three reactions: (i) can bind with methaemoglobin to form cyanmethaemoglobin, (ii) can undergo in reaction with thiosulphate forming thiocyanate in liver and kidney, (iii) can bind with tissue cytochrome oxidase system, interferring normal oxygen utilisation.

Toxicity

The main side effect of nitroprusside is sudden excessive vasodilatation and severe hypotension. Hence, continuous close monitoring of BP is mandatory. So the use of sophisticated variable rate infusion pump will prevent this excessive haemodynamic response of the drug. Toxicity may also result from excessive conversion of nitroprusside to cyanide and thiocyanate. Excessive accumulation of cyanide, leading to severe lactic acidosis can occur, if sodium nitroprusside is infused at a rate of greater than 5 µg/Kg/min. But, concomitant use of sodium thiosulfate can prevent this accumulation of cyanide in a patient who receives more than usual doses of sodium nitroprusside. This is because the limiting factor in the metabolism of cyanide is the availability of substrate like thiosulfate. The risk of cyanide toxicity also increases when the nitroprusside is infused for more than 24 to 48 hours and especially if renal function is impaired. Plasma concentration of cyanide also should be monitored during prolonged infusion of nitroprusside and should not be allowed to exceed more than 0.1 mg/ml.

Nitroprusside may worsen the arterial hypoxaemia in patient who is suffering from chronic obstructive pulmonary disease. Because the drug interferes with the compensatory hypoxic pulmonary vasoconstriction reflex and therefore, promotes the mismatching of ventilation with perfusion. Rebound hypertension may also occur after abrupt cessation of short-term nitroprusside infusion. This may be due to the persistently elevated concentration of renin in plasma caused by hypotension.

Dose

Nitroprusside should be used in variable, controlled, continuous infusion according to patient's response. The usual dose of it ranges from 0·25 to 1·50 µg/Kg/min.

Organic Nitrites and Nitrates

The organic nitrates are the ester of nitric acid ($-C-O-NO_2$). On the otherhand, the organic nitrites are the ester of nitrous acid ($-C-O-NO$). The common organic nitrites and nitrates which are clinically used are: Amyl nitrite, nitroglycerine (glyceryl trinitrate), isosorbide dinitrate, isosorbide-5-mononitrate, erythrityl tetranitrate, etc. Glyceryl trinitrate is widely and officially accepted as nitroglycerin which has an explosive property. But, actually it is not nitrocompound. Because nitrocompound possess carbon-nitrogen bonds ($C-NO_2$) and is highly explosive. So, glyceryl trinitrate is erroneously called as nitroglycerin. For their actions the organic nitrates and nitrites are denitrated to release NO by nitric oxide synthetases. This NO synthetases are found in vascular endothelial and smooth muscle cells as well as in other types of cells throughout our body, including CNS. When the activity of NO synthetase and the production of NO is reduced, the individual suffer from atherosclerosis. This nitric oxide activates cyclic GMP in vascular smooth muscle cells and produce vasodilation like nitroprusside. So, the organic nitrates and nitrites are called nitrovasodilators. Normally, in vascular endothelial and smooth muscle cells endogenous NO is also formed by nitric oxide synthases, by converting L-arginine to citrulline.

Another organic nitrite such as amyl nitrite is highly volatile liquid and is administered by inhalation. This is because, usually the low molecular weight nitroglycerins are oily liquids and mode-rately volatile. Erythrityl tetranitrate, pentaerythritol tetranitrate, isosorbide dinitrate are solids and of high molecular weight without inert carrier such as lactose. Pure nitorglycerin is highly explosive.

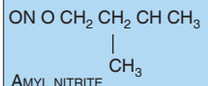
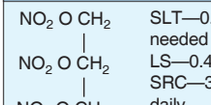
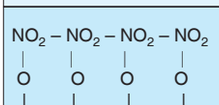
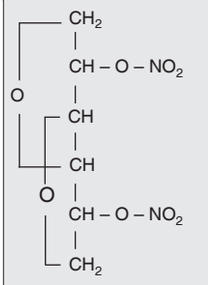
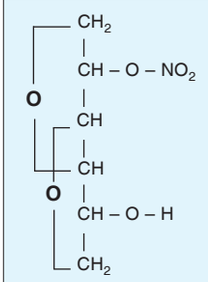
Mechanism of action of nitrates and nitrites

The organic nitrites, nitrates, nitrosocompounds and a variety of other nitrogen-oxide containing substances, including nitroprusside, etc. lead to the formation of reactive free radical such as nitric oxide (NO). This NO activates cytosolic guanylyl cyclase → increased cGMP → inhibition of cGMP dependent protein kinase → dephosphorylation of myosin light chain → relaxation →

vasodilation. Phosphorylation of the myosin light chain regulates and is responsible for the maintenance of contractile state of the smooth muscle of vessels. Raised intracellular cGMP may also reduces the Ca^{2+} entry into the cells and contribute relaxation smooth of muscles of vends.

Pharmacological action

Low therapeutic concentrations of nitroglycerin produce predominantly venodilation and reduce preload. Thus reduction of venous pooling causes reduction of end diastolic ventricular volume (Fig. 18.10) and pressure and reduction of CO. Whereas the effects of nitroglycerin on arterioles are minimal, causing little change in systemic vascular resistance. Hence, systemic arterial pressure may fall slightly. Pulmonary vascular resistance also fall slightly. As preload falls much more than the afterload, so CO falls. The doses of nitroglycerin which do not alter systemic arterial pressure, often produce arterial dilation of face, neck and meningeal vessels, resulting in flushing and headache. Enzymes which converts nitrates to NO is abundant in venous smooth muscle compared to arterial smooth muscle cells. This is the cause of predominant venoselective properties of nitrates. On the otherhand, higher doses of organic nitrates cause both the venous and arteriolar dilation which leads to the reduction of both systolic and diastolic blood pressure and increase or decrease of CO, according to the balance between the degree of reduction of preload and afterload. The resultant compensatory tachycardia and peripheral arteriolar vasoconstriction due to reduction of CO tend to restore the systemic vascular resistance. But, this is superimposed by sustained venous pooling. Thus, coronary blood flow may increase transiently as a result of coronary vasodilation. But it subsequently decreases if CO and BP fall sufficiently, causing severe reduction of coronary perfusion pressure.

Structure of organic nitrite and nitrates	Dose and route of administration
 Amyl nitrite	By inhalation 0·3 ml for each inhalation
 Nitroglycerine	SLT—0.3 to 0.6 mg as and when needed LS—0.4 mg per spray SRC—3 to 9 mg two to three times daily TDP-1 disc (2.5 to 15 mg twice daily) (Glyceryl trinitrate)
 Erythrityl Tetranitrate	SLT—5 to 10 mg as and when needed OT—10 mg two to three times daily
 Isosorbide dinitrate	SLT—2.5 to 5 mg every 2 to 3 hours OT—5 to 10 mg every 2 to 3 hours SRC—40 to 80 every 8 hours
 Isosorbide-5-mononitrate	SLT-10 to 40 mg two to three times daily. SRC-60 mg twice daily.

SLT = Sublingual tablet
LS = Lingual spray
SRC = Sustained release capsule
TDP = Transdermal patch
OT = Oral tablet

Fig. 18.10: The chemical structure of different organic nitrates and nitrites

Coronary blood flow

Ischaemia is the most powerful stimulus for coronary vasodilation. Regional coronary blood flow is adjusted by the local autoregulatory mechanism. Thus, blood flow is directed from the nonischaemic nondilating vessels to the dilated ischaemic areas. Organic nitrates does not impair this autoregulation. The small vessels which are responsible for about 90% of the overall coronary vascular resistance, nitrates does not dilate these small coronary arterioles. Therefore, organic nitrates do not directly increase the myocardial O_2 supply. Vessels larger than 200 µm in diameter which are responsible for 10% of overall coronary vascular resistance are highly responsive to the organic nitrates. But vessels less than 100 µm are not or minimally responsive. Thus, organic nitrates are only able to cause dilations and prevents constriction of large epicardial vessels. In fact, nitrates do not increase the total coronary blood flow in angina patients. However, it causes only redistribution of blood flow when coronary circulation is partially occluded and area is ischaemic. Collateral flow to ischaemic regions also is increased by nitrates. On the otherhand, due to redistribution there is disproportionate reduction in blood flow to the subendocardial regions of the heart which are subjected to the greatest extravascular compression during systole. Hence, practically, an important indirect mechanism for maintaining subendocardial blood flow is the nitroglycerin induced reduction in intracavitary systolic and diastolic pressure by reducing the preload that oppose the blood flow to subendocardium. Thus, indirectly the organic nitrates decrease the myocardial oxygen requirement. Increased blood flow in ischaemic regions are balanced by decrease flow in nonischaemic areas. An overall increase in coronary blood flow does not occur. Dilation of cardiac veins may result in an improvement in the perfusion of coronary microcirculation. In patients, suffering from angina due to coronary spasm, the capability of organic nitrates to dilate the epicardial coronary arteries and particularly at the regions which are affected by spasm may be the primary mechanism by which they are benefited.

Effect on myocardial O_2 demand

Organic nitrates reduce the myocardial O_2 demand. O_2 demand is directly proportional to the ventricular wall tension, heart rate and contractility of myocardium. Ventricular wall tension is again directly proportional with preload and afterload. Because according to Laplace's law:

Tension ∝ Pressure × Radius.

Preload is determined by the end diastolic ventricular filling, volume and pressure. Increased venous capacitance with nitrates decreases venous return to the heart and decreases ventricular end diastolic volume which in turn decreases the wall tension and O_2 consumption. Reduction of preload also increases the pressure gradient for perfusion across the ventricular wall and favours the subendocardial perfusion.

Afterload is the impedance against which the left ventricle contracts and ejects its contents. Thus, it is related to the systemic vascular resistance. Decrease of systemic vascular resistance by organic nitrites and nitrates reduces the afterload and thus reduces the left ventricular wall tension during myocardial contraction. Hence, myocardial O_2 demand is also reduced. An interesting finding is that angina occurs with or without nitroglycerin at the same value of the 'triple product' (aortic pressure × heart rate × ejection time) which is porportional to myocardial O_2 consumption. It suggests that beneficial effects of nitroglycerin is the result of reduced cardiac O_2 demand, rather than an increase in the delivery of O_2 to ischaemic regions of myocardium. But, it does not exclude the possibility that direct coronary vasodilation may be the major effect of nitroglycerin where vasospasm is the cause of angina. Organic nitrates have no direct positive inotropic or chronotropic effect on heart, but may affect indirectly. The main therapeutic uses of organic nitrites and nitrates are: angina, congestive heart failure, unstable angina, myocardial infarction, variant (Prinzmetal's) angina, etc.

Absorption, fate and excretion

The lipid soluble organic nitrates are metabolised to water soluble inorganic nitrates and denitrated compounds by nitrate reductase enzyme in the liver. The denitrated metabolites are less potent vasodilators than parent compounds. Since, the liver has enormous capacity for metabolism of organic nitrates, so oral bioavailability of it is much less.

Velocity of metabolism of erythrityl tetranitrate is 3 times faster than nitroglycerin. While isosorbide dinitrate and pentaerythritol tetranitrate are metabolised at the rate of one-sixth and one-tenth of that of nitroglycerin. After sublingual administration, peak concentration of nitroglycerin in plasma reaches within 3 to 4 minutes and half-life is 1 to 3 minutes. Onset of action is more rapid if nitroglycerin is delivered by sublingual spray. Sublingual administration of isosorbide dinitrate produces maximal concentration of drug in plasma by 6 minutes and half-life is 45 minutes. Its primary initial metabolites are isosorbide-2-mononitrate and isosorbide-5-mononitrate which have longer half-life (3 to 6 hours) and these are presumed to be responsible for the therapeutic efficacy and prolonged action of the isosorbide dinitrate. Isosorbide-5-mononitrate has excellent bioavailability after oral administration. It does not undergo significant first-pass liver metabolism. So, it has longer half-life and formulated as plain tablet or sustained release capsule, both of which have longer duration of actions.

Doses and route of administration

Nitroglycerin (or glyceryl trinitrate) is the most useful drug among the other organic nitrates that can be given sublingually. It is because of its rapid onset of action, long established efficacy and low cost. The onset of action of initial 0·3 mg nitrogly-cerin, administered through sublingual route is within 1 to 2 minutes and effects do not last for more than 1 hour after its administration. So, it can be used as needed. Other nitrates that can be used sublingually are not more effective and do not appear to be longer acting than nitroglycerin. But they are more expensive.

Oral nitrates are often used to provide prophylaxis against anginal episodes. They are given initially in higher doses to provide effective plasma levels due to first pass hepatic degradation. So, to obtain a continuous plasma therapeutic level of nitroglycerin the sustained release preparation of it should be used better. The effects of this sustained released form of nitroglycerin reach the peak level at 60 to 90 minutes and last for 3 to 6 hours. The dose of isosorbide dinitrate through oral route is 5 to 10 mg for every 2 to 3 hours and through sublingual route is 2.5 to 5 mg for every 2 to 3 hours.

Application of nitroglycerin ointment also relieves angina. The Nitroglycerin disc utilizes nitroglycerin impregnated polymer for transdermal use that permits gradual absorption and a continuous steady plasma nitrate concentration over 24 hours. But, the onset of action of nitroglycerin through this route is slow with peak effects at 1 to 2 hours. IV route for nitroglycerin is only used for the management of hypertensive emergency and the dose is 2.5 to 5 µg/m with increments of 2.5 µg/min.

Ca^{2+} Channel Blockers (CCBs)

Introduction

The Ca^{2+} channel antagonists or blockers are putative it means formerly thought as but not now coronary vasodilators, and possess negative inotropic and chronotropic effects that were not seen with nitroglycerin. The negative inotropic effect of CCB results from the inhibition of excitation and contraction coupling between the action and myosin filaments due to the reduction of movement of Ca^{2+} into the cardiac myocytes. They also alter the plateau phase (phase 2) of cardiac action potential that is due to entry of Ca^{2+} into the cells.

At present, all the CCBs are divided into 5 classes. In all these classes, there are many Ca^{2+} channel antagonists. But, out of them only ten CCBs are approved at present to be used clinically. This is depicted in below:

i. Phenylalkylamine: Verapamil
ii. Benzothiazepine: Diltiazem
iii. Dihydropyridine: Nifedipine, nicardipine, isradipine, amlodipine, felodipine, nimodipine, nisoldipine
iv. Diarylaminopropylamine: Bepridil
v. Diphenylpiperazine: No drug is approved in this class.

Among these, the dihydropyridine class is the most potent Ca^{2+} channel blockers and has proliferated exceptionally.

Practically there are three types of Ca^{2+} channels. These are:

i. Voltage sensitive channel: It acts through changes of membrane potential. Voltage sensitive channel is again subdivided into three types. These are: L-type, T-type and N-type.
ii. Receptor operated channel: These channels are independent of membrane depolarisation. They act through receptors.
iii. Leak channel: Small amounts of Ca^{2+} continuously enter into the resting cell and again are forced out by Ca^{2+} ATPase pump through some tiny channels which are called the leak channel. They does not act by membrane depolarisation or through receptor (Table 18.4).

Mechanism of action

The increased contraction of striated cardiac muscle cells and nonstratiated vascular smooth muscle cells are caused by the increased concentration of cytosolic Ca^{2+}. This increased intracellular or cytosolic concentration of Ca^{2+} is caused by the increased entry of extracellular Ca^{2+} into the cell and release of more Ca^{2+} from the intracellular storage, triggered by the entry of extracellular Ca^{2+}. Hence, cytosolic Ca^{2+} concentration can be increased by influx of Ca^{2+} from outside by various stimuli. Many hormones and neurohormones as stimuli act through receptor operated Ca^{2+} channel and increase Ca^{2+} influx. While some other stimuli such as high extracellular K^+ concentration and depolarising electrical stimuli works through 'voltage sensitive' or 'potential-operated' channels and increase the Ca^{2+} influx. Again small amount of Ca^{2+} continuously leaks into the resting cell through leak channel and are continuously pumped out through 'leak-channel' by Ca^{2+} ATPase pump.

Ca^{2+} channels are made up of many subunit such as α_1, α_2, β, γ, δ. Voltage sensitive Ca^{2+} channels have been divi-ded at least three subtypes based on their conductance and sensitivity to voltage. These are L, N and T subtypes, although P/Q and R type of voltage sensitive channels have also been identified. However, among these, only the L type of Ca^{2+} channel is sensitive to dihydropyridine group of Ca^{2+} channel blockers such as nifedipine. Large divalent cations such as Cd^{2+}, Mn^{2+}, etc. also block a wide range of Ca^{2+} channels. All clinically approved Ca^{2+} channel blockers bind to $\alpha_1$subunit of L-type channel, which is the main channel forming unit.

α_1 subunit share a common topology of four homologus domains (I, II, III, IV) and each of which is composed of six putative transmembrane segments (S_1-S_6). The phenylalkylamine group of Ca^{2+} channel blockers (verapamil) bind to transmembrane segment 6 of domain IV (IVS_6). The benzothiazepine group of Ca^{2+} channel blockers (diltiazem) bind to cytoplasmic bridge between domain III (IIIS) and domain IV (IVS). Dihydropyridine group of Ca^{2+} channel blockers (nifedipine) bind to transmembrane segments of both domain III ($IIIS_6$) and domain IV (IVS_6).

Table 18.4: Voltage sensitive Ca^{2+} channels

	L-type	*T-type*	*N-type*
1. Activation threshold	High	Low	High
2. Inactivation	Slow	Fast	Medium
3. Location and function	(i) Cardiac and smooth muscle excitation and contraction	(i) SA node pacemaker activity	(i) CNS, sympathetic and myenteric plexuses—release of transmitter
	(ii) SA and AV node—rate and conduction	(ii) Thalamus and other neurons	
	(iii) Endocrine cells hormone release	(iii) Endocrine cells—release of hormone	
	(iv) Neurons—release of transmitter		

Pharmacological properties

Action on vascular tissue

Although, there is some involvement of Na^+ current for depolarisation of vascular smooth muscle, but it primarily depends on influx of Ca^{2+} current which occurs through the voltage sensitive or receptor operated channel. Due to depolarisation these Ca^{2+} channels results in the hydrolysis of membrane bound phosphatidylinositol with the formation of inositol triphosphate which acts as a second messenger to release intracellular Ca^{2+} from sarcoplasmic reticulum. Then this increased intracellular Ca^{2+} binds to protein calmodulin $\rightarrow$ activates myosin light-chain kinase $-$ phosphorylation of light-chain myosin $-$ promotes interaction between actin and myosin $-$ contraction of smooth muscle. Calcium channel blocker (CCB) inhibit these 'voltage sensitive' Ca^{2+} channels in lower concentration than that are required to interfere the receptor operated Ca^{2+}

channels. Thus all the Ca^{2+} channel blockers relax arterial smooth muscle, but have little effects on venous smooth muscle. So, CCBs do not affect the venous return and cardiac preload does not decrease significantly (Table 18.5).

Action on cardiac cell

There is some differences in excitation – contraction coupling between the cardiac muscle cells and the vascular smooth muscle cells. The difference is that among the two inward currents one is carried through fast Na^+ channel, and the other is carried through the slow Ca^{2+} channel. In SA and AV node, the depolarisation is largely dependent on the movement of Ca^{2+} through this slow Ca^{2+}channel. In the cardiac myocyte troponin inhibit the actin and myosin interaction which cause contraction. Ca^{2+} binds to this troponin and withdraw this inhibition and initiates contraction. CCB thus acts to cause negative inotropic effect by preventing the binding of Ca^{2+} with troponin by decreasing the entry of Ca^{2+} into the cell.

The Pacemaker activity of SA node and atrioventricular conduction is dependent mainly on these slow Ca^{2+} channel. Nifedipine does not affect these slow Ca^{2+} channel. Thus it has no effect on heart rate and conduction through AV node. It mainly acts on peripheral smooth muscle in a dose dependent manner. In contrast, verapamil reduces the slow inward current and the rate of recovery of slow Ca^{2+} channel. Thus, verapamil and diltiazem both reduce the rate of sinus node pacemaker activity and slow the AV conduction. This is the basis for their use in the treatment of SVT. It also causes prolongation of the AV nodal effective refractory period and the prolongation of QT_C interval. In the presence of hypokalaemia, prolongation of QT_C interval may precipitate 'torsades-de-pointes' – a potentially lethal ventricular arrhythmia.

Table 18.5: Calcium channel blocker

Specially suited for:	
(i)	Asthma, COPD
(ii)	Pregnancy induced hypertension
(iii)	Physically and mentaly active
(iv)	Peripheral vascular disease (e.g. Raynaud's)
(v)	Isolated systolic hypertension
(vi)	Elderly with low renin
To be avoided	
(i)	CHF, conduction defects, sick sinus
(ii)	Receiving β-blockers
(iii)	Prostate enlargement
(iv)	LVH
(v)	Gastro-oesophageal reflux

Haemodynamic effect

CCBs decrease the coronary vascular resistance and increase the coronary blood flow. Among the CCBs nifedipine is more potent systemic vasodilator than verapamil and diltiazem. Nifedipine dilates arterial resistance vessels, but not the veins. This decrease in arterial BP stimulates sympathetic reflexes and produce tachycardia with positive inotropic effect (via sympathetic stimulation). Nifedipine relaxes the vascular smooth muscle at significantly lower concentration than those required for prominent direct effects (negative inotropic) on the heart. Arteriolar resistance and blood pressure are lowered, contractility and segmental ventricular function are improved. So heart rate and cardiac output are increased. After oral administration of nifedipine, arterial dilatation increases peripheral blood flow, but venous tone does not change. Because of the lack of myocardial depression and the lack of negative inotropic and chronotropic effect, nifedipine are less effective as monotherapy in stable angina than verapamil, diltiazem and β-blocker.

Therapeutic uses

Hypertension

Essential hypertension is the result of increased systemic vascular resistance, caused by the contraction of vascular smooth muscle mainly arteriole which is dependent on the free intracellular concentration of Ca^{2+}. Therefore all the CCBs decrease the BP by reducing SVR by relaxing the arteriolar smooth muscle. As a consequence of reduction of BP, CCB evokes a baroreceptor mediated sympathetic discharge. So, in case of nifedipine tachycardia ensues. Whereas tachycardia is absent with verapamil and diltiazem because of their direct negative chronotropic effect on the SA node of heart. The increased compensatory adrenergic stimulation of heart serves to counter the hypotensive effect of CCB. So, hypotensive effect of CCB is excessive when used concurrently with β-blocker. As a consequence of peripheral vasodilatation (more arterial dilatation than venodilatation) CCB increase venous return which will result in increased CO, except in case of verapamil and diltiazem which exert substantial negative inotropic effect. This increased venous return is beneficial for normal heart, but not for the patient with diastolic dysfunction due to hypertensive cardiomyopathy who are at increased risk of left ventricular failure. CCB does not improve the diastolic function of ventricle. So, it is not the first choice of treatment in hypertension with left ventricular hypertrophy. All CCBs are equally effective when used alone in the treatment of mild to moderate hypertension, like β-blocker or diuretics.

There is special set of concern regarding the use of CCB in presence of IHD with hypertension. CCB does not improve the survival rate in patient following myocardial infarction. Therefore, it is not the first or second drug of choice in the treatment of hypertension in patient who have a myocardial infarction. Sublingual administration of CCB does not achieve the maximum plasma concentration any more quickly than does oral administration. It is proved that nifedipine is not absorbed by buccal mucosa when used by sublingual route. With saliva it goes to upper GI tract and through stomach it is absorbed. Hence, oral or sublingual administration of standard formulation of

nifedipine (immediate release capsule) as an approach to urgent reduction of blood pressure has been abandoned. Only short acting, and parenterally administered agents should be used in the setting of hypertensive urgencies. In the treatment of emergency of hypertension, there is no place of standard formulation of immediate release capsule of nifedipine with short half-lives through oral route. Because, it causes great oscillation in BP and concurrent surges in sympathetic reflex activity at the interval of each dosage. Thus, nifedipine is a suboptimal choice for treatment of cardiogenic pulmonary oedema. In contrast, nitroprusside causes a greater reduction in left ventricular end diastolic pressure than equipotent doses of nifedipine and nitroprusside's pharmacological effect can be regulated more effectively. So, it is a better choice than CCB for treatment of cardiogenic pulmonary oedema.

CCB is especially effective in low renin hypertension. Long acting dihydropyridine group of CCB reduce the cardiovascular mortality. CCB should not be used in patient with SA and AV nodal abnormalities and overt CF. It can be used in hypertensive patient with asthma, diabetes, and renal dysfunction. Unlike β-blocker, CCB does not alter the exercise tolerance.

Variant angina

Variant angina is due to the reduction of blood flow in myocardium, rather than an increase in O_2 demand. So, CCB protect the variant angina by attenuating the coronary spasm and dilating the coronary artery, rather than alteration in peripheral haemodynamics.

Exertional angina

CCBs also are effective in the treatment of exercise or exertional induced angina. The effectivity of these agents may result from: (i) an increase in the blood flow due to coronary arterial dilation, (ii) from a decrease in myocardial O_2 demand (secondary to a decrease in arterial BP, heart rate and myocardial contractility) or (iii) from both. Numerous double-blind and placebo-controlled studies have shown that these drugs reduce the number of anginal attack and decrease the exercise induced depression of ST segment.

The 'double product' which is calculated from 'heart rate multiplied by systolic BP' is an indirect measure of myocardial O_2 demand. Since, these agents reduce the level of the double product, so O_2 demand is also reduced at a given external work load. The beneficial effect of CCB is primarily is due to the reduction of O_2 demand rather than the increase in coronary blood flow. The concurrent therapy of nifedipine with the β-adrenergic receptor antagonist has proven more effective than when the either agent is given alone. Because the β-blocker suppresses the reflex tachycardia produced by CCBs other than verapamil and diltiazem.

Beta Blockers

These drugs inhibit the adrenergic responses which are only mediated through β-receptors and are used in the treatment of hypertension, ischaemic heart disease, congestive heart failure and certain arrhythmias. All β-blockers are competitive antagonist at the level of these receptor. The β-blocker such as propranolol was first introduced in 1963 and was a great therapeutic breakthrough. Then, it remains the prototype to which the other β-blockers are compared. After that subsequently more and more β-blockers were developed and they are classified by some properties. These are relative affinity of them for β_1 and β_2-receptors, intrinsic sympathomimetic activity, additional blockade of α-adrenergic receptor, difference in lipid solubility, capacity to induce vasodilatation and general pharmacokinetic properties. Some of these characteristic have clinical significance. These help to guide the appropriate choice of β-blockers for an individual patient.

The main effectiveness of β-blocker is found in the treatment of exertional angina. This effectiveness is primarily due to the fall in myocardial O_2 consumption or demand during both rest and exercise and due to some tendency for increased flow toward ischaemic areas. The decrease in O_2 consumption and demand by β-blocker is again primarily due to the negative inotropic, negative chronotropic and reduction of arterial BP during exercise. Not all the action of β-blockers are beneficial for all patients. Because the decrease in HR and force of contraction cause an increase in the systolic ejection period and an increase in left ventricular end diastolic volume with pressure. This tends to increase the O_2 consumption. But the net result of the effect of β-blocker is reduction of O_2 consumption during exercise. On the otherhand, some patients with limited cardiac reserve are dependent on adrenergic stimulation. In these patients the use of β-blocker can result in the profound decrease of left ventricular function. Despite this, β-blocker definitely reduce the mortality in patients with congestive heart failure.

Classification

A. Nonselective (acting both on β_1 and β_2 receptors)
   i. Without intrinsic sympathetic activity: Propranolol, sotalol, timolol, nadolol.
   ii. With intrinsic sympathetic activity: Pindolol, oxprenolol, alprenolol.
   iii. With additional α-blocking property: Labetalol, carvedilol.

(Some β-blockers activate β-receptors in the absence of catecholamines. However, this intrinsic sympathetic activity of these drugs are less than that of full agonist such as isoproterenol. These partial agonistic effect of beta-blockers are said to have the intrinsic sympathetic activity.)

B. Cardioselective (acting only on β_1-receptors): Metoprolol, esmolol, ate-nolol, acebutolol, celiprolol.

C. Selective β_2 blocker: Butoxamine. It has no clinical application.

This classification of β-blockers is not absolute. Because, some β_1 antagonist, even

though selective for this receptor have some affinity for β_2-receptor, e.g. metoprolol, acebutolol, atenolol, etc. Therefore, selectivity of β-blockers is only relative and is lost at high doses. For this reason, though by blocking β_2 receptor, still the selective β_1-blockers have lower propensity to cause bronchoconstriction, these drugs should be avoided if possible in asthmatics. Acebutolol have some intrinsic sympathomimetic activity. Some β-blockers have the property of inverse agonism and decrease basal activation of β-receptor. Celiprolol is a β_1-selective blocker that acts on heart and a β_2 selective agonist that promotes vasodilatation. Some β-blockers have membrane stabilising or antiarrhythmic action, but this appears to be significant only at higher doses.

Pharmacological properties

Cardiovascular system

The β-blocker has relatively little effect on the normal heart at rest. But, it has profound effects when the sympathetic control on heart is dominant, e.g. exercise and stress. At rest usually the tonic stimulation of β-receptor is low, so the effect of β-blocker is correspondingly low or modest (Table 18.6).

But during exercise and stress when the sympathetic system is activated, then the effects of β-blockers are also increased. Therefore, in the presence of β-blocker exercise induced increase in HR and myocardial contractility is attenuated. However, CO is not affected due to decrease in HR. This is because of the increase in stroke volume corresponding with the reduction of heart rate. In hypertension propranolol decrease CO, ↑SVR. This increase in SVR by β-blocker is due to the blockade of peripheral vascular β_2-receptor which dilates the vessels The increased SVR in also due to compensatory increase in sympathetic activity due to lowering of BP and subsequent stimulation of vascular α-adrenergic receptor. Blockade of β_2-receptor also cause the α-receptor to take upper hand and increased SVR. However, labetalol and carvedilol which is both β-blocker and α_1-receptor antagonist maintain CO with greater fall of SVR.

β-blocker reduces the heart rate. This is due to the decrease in automaticity of SA node. The β-blockers also cause slow conduction in atria and AV node and increase in the functional refractory period of AV node. Although it has been thought that these effects are exclusively due to the blockade of β_1-receptor, but β_2 adrenergic receptors in small extent are also likely to be involved in regulating the heart rate in human beings.

The total coronary blood flow is reduced by β-blockers. This is due to the blockade of dilator coronary β-receptor, but these are largely restricted to the subepicardial region. While the subendocardial area which is the chief site of origin of ischaemia in angina is not affected. But, the overall effect of β-blockers in angina patient is improvement of O_2 supply/demand status and exercise tolerance by balancing the reduction of myocardial O_2 demand by decreasing the effect of catecholamine induced heart rate, cardiac contractility and systolic BP and increasing the O_2 demand by increasing the end diastolic pressure and systolic ejection period.

Table 18.6: β-blockers

Specially suited for:	
(i)	Tense young patients
(ii)	Coexisting anxiety and tachycardia
(iii)	Angina
(iv)	Post MI patients
(v)	High renin hypertension
(vi)	Nonobese
(vii)	Low cost
To be avoided	
(i)	Bradycardia, conduction block, elderly
(ii)	Asthma, diabetic
(iii)	Peripheral vascular disease, abnormal lipid profile
(iv)	LVF
(v)	Who need high physical and mental acitivity

As hypertensive agents

The β-blockers do not generally reduce the BP in normotensive patient, but lower it in patient with hypertension. On oral administration there is little acute change in BP. But, on prolonged oral administration BP gradually falls. Initially the total SVR is increased due to the blockade of β-mediate vasodilatation and CO is reduced with net little change in BP. But with continued treatment the resistance vessels gradually adapt to chronically reduced CO, so that SVR decreases and both the systolic and diastolic BP falls. But, all these are hypothesis and the actual cause of reduction of blood pressure by β-blockers is not known.

The probable hypothesis for antihypertensive effects of β-blockers are:

i. Decreased renin release from kidney (β_1 mediated) − Propranolol causes a more marked fall in BP in hypertensive individual who have high or normal plasma renin levels. Such patients respond at relatively lower doses of β-blocker than those with low plasma renin. However, pindolol does not decrease plasma renin actively, but is still an effective antihypertensive.
ii. Inhibition of presynaptic β-adrenergic receptor which cause the release of norepinephrine from sympathetic neurons.
iii. By acting centrally and reducing the sympathetic outflow from brain. However, the β-blockers which cannot penetrate the blood-brain barrier or poorly are also effective antihypertensive.
iv. β-blockers cannot decrease the contractility of vascular smooth muscle. But the long-term use of it can cause reduction of SVR (mechanism is not known), even in the face of persistent reduction of CO and appears to account for much of the antihypertensive effect of these drugs.

Some β-blockers have additional properties that may contribute to their ability to lower BP by peripheral vasodilatation. For example:

a. Labetalol and carvedilol directly block α_1-receptor and ↓SVR.
b. Celiprolol appears to have partial β_2-receptor agonist and cause vasodilatation.
c. Nonadrenergic receptor mediated vasodilatation by some β-blockers also contribute to decrease in SVR.

Respiratory system

In normal individual sympathetic β_2-receptor mediated bronchodilator tone is minimal. So, β-blocker has little effect on normal individual. However, in patient with asthma or COPD, such blockade can lead to life threatening bronchoconstriction. Propranolol which is both β_1 and β_2-receptor blockers is notorious for that. While the β_1 selective antagonist are less likely to increase airway resistance, but should be used very cautiously. Celiprolol with β_1-receptor selectivity and β_2-receptor partial agonism are of potential promise, but still now are of little clinical experience.

Metabolic effects

All the β-blockers modify the metabolism of lipids and carbohydrate. Although, insulin secretion is enhanced by β-adrenergic agonist, but β-blocker only rarely impairs insulin release. So, there is no effect on normal blood sugar. As catecholamines through β-receptor promote glycogenolysis and mobilise glucose from liver in response to hypoglycaemia, so nonselective β-blocker may adversely affect the recovery from hypoglycaemia and should be used cautiously in diabetic patient, receiving insulin. On the otherhand, all the β-blockers mask the tachycardia that is typically seen with hypoglycaemia.

Beta blockers block the adrenergically induced lipolysis and reduce the consequent increase in plasma free fatty acid levels. Plasma triglyceride level and LDL/HDL ratio is increased during β-blocker therapy.

Local anaesthetic effect

Propranolol acts as potent local anaesthetic agent like lignocaine. But, it is not clinically used for this purpose, because of its irritant property.

Uterus

Relaxation of uterus in response to β_2 agonist can be blocked by β-blocker. But the normal uterine activity in absence of B_2 agonist is not significantly affected by these group of drugs.

Individual drug

Labetalol

It is both α_1 and β (β_1+ β_2) receptor blocker. It has two optical isomers. So, the clinical formulation of labetalol contains four diastereomers and each of which displays different relative activities. This explains why the pharmacological activities of this drug is so complex. The resultant effect of the mixture of these isomers include selective blockade of α_1 (as compared to α_2-receptor) and blockade of $\beta_1$and β_2-receptor. There is also some partial agonistic activity on β_2-receptor and inhibition of neuronal uptake of norepinephrine. This is cocaine like effect. The potency of β-blocking mixture effect of labetalol is five fold higher than for α_1-blocker effect of it.

The antagonistic action of labetalol on both α_1 and β-adrenergic receptors result in fall of BP in hypertensive patient. The α_1-recep-tor blocked causes relaxation of arterial smooth muscle and reduction of BP by vasodilation. The β_1-receptor blockade also causes fall in blood pressure. This is caused by blocking of reflex sympathetic stimulation of heart. In addition to these the intrinsic sympathetic activity of labetalol at β_2-receptor may cause vasodilatation and reduction of BP.

It is available in both oral and intravenous form (for hypertensive emergency). The oral preparation of labetalol is completely absorbed from gut and goes through extensive first pass hepatic clearance, with bioavailability of only 20 to 40%. The elimination half-life of clinical formulation of labetalol is 8 hours.

Carvedilol

It is also a nonselective β (β_1+β_2) receptor and selective α_1-receptor antagonist and action is like labetalol. Bioavailability of carvedilol is only 20 to 30% and half-life is 10 hours.

Metoprolol

It is a selective β_1-adrenergic receptor blocker and is devoid of intrinsic sympathetic activity. After oral administration it is completely absorbed and due to first pass hepatic metabolism bioavailability is only 40%. The half-life of metoprolol is 3 to 4 hours. The use of metoprolol is contraindicated in patient with acute myocardial infarction with HR less than 46 per minute, heart block greater than first degree, systolic blood pressure less than 100 mm of Hg and moderate to severe heart failure. It is less likely to worsen the bronchial asthma, but is not entirely safe.

The usual initial dose of metoprolol is 100 mg once daily, but frequently it is used in two divided doses.

Atenolol

Like metoprolol it is also a selective β_1-antagonist, without intrinsic sympathomimetic activity. Atenolol is incompletely absorbed by oral route (50%) and half-life is 5 to 8 hours. The initial dose of it is 50 mg per day, given orally and can be increased to 100 mg per day. But, higher doses are unlikely to provide any greater antihypertensive effect. Atenolol in combination with diuretics is very effective for elderly patients with isolated systolic hypertension.

Esmolol

It is a selective β_1-receptor antagonist or blocker with little if any intrinsic sympathomimetic activity and without any membrane stabilising property. The beauty of esmolol is

that it can be administered intravenously and is of very short duration of action. The half-life of esmolol is 8 minutes. The drug contains an ester linkage and is hydrolysed rapidly by an enzyme named esterase present in erythrocytes. The onset of action of esmolol is rapid. The peak haemodynamic effects occur within 6 to 10 minutes after administration of a loading dose and the effect is substantially attenuated within 20 minutes of stopping the infusion. Strikingly, the esmolol has hypotensive effect on normal individual, but the mechanism of this action is unclear. In urgent setting, where immediate reduction of BP is needed, a partial loading dose is administered which is followed by a continuous infusion of the drug. The half-life of carboxylic acid metabolite of esmolol is much higher than that of the parent compound. So, it can accumulate in prolonged infusion but this metabolite has very low potency. Since, in urgent setting where immediate action is desired, esmolol is very helpful. The typical loading dose of esmolol is 0·5 mg/kg and for maintenance the infusion dose is 0·05 to 0·02 mg/kg/minute.

Therapeutic uses of β-blocker

β-blockers are extensively used in the treatment of hypertension, angina, acute myocardial infarction, congestive heart failure and arrhythmia. The other uses of β-blocker are: Thyrotoxicosis, pheochromocytoma, anxiety, migraine, glaucoma, essential tremor, etc.

Myocardial infarction

The use of β-blocker in the treatment of acute MI and for the prevention of recurrence has been well studied. It is confirmed that when the β-blockers are administered during the early phase of acute MI and is continued for long-term after recovery, then it may decrease the mortality by about 25%. The precise mechanism of it is still not known. But the favourable effects of β-blockers may arise from the decreased myocardial O_2 demand, redistribution of myocardial blood flow and its antiarrhythmic action. Thus, the β-blockers prevent sudden death from ventricular fibrillation during primary or subsequent attack of MI. However, there is likely much less beneficial effect, if the β-blockers are administered only for a short period. So, the β-blockers should be used for prolong period in high risk patients, except those who are not in shock, cardiac failure, have heart rate < 50/minute and with higher than first degree heart block.

Congestive heart failure

It is a very common clinical understanding that β-blockers can worsen or precipitate the congestive heart failure in a compensated patient. On the other hand, from the mechanism of action it is also clear that β-blocker might be effective in the treatment of heart failure. Again, it is clear that some but not all the β-blockers are beneficial in patient with mild to mode-rate heart failure. So, it is interesting to note how a class of a drug can move from being completely contraindicated to being almost the standard of modern care in many heart failure. The proposed mechanism of beneficial effect of β-blockers in heart failure is that the catecholamines are toxic to heart and inhibitions of its effects through β_1-receptor pathway may help to preserve the myocardial function. Again the β-receptor blocker in heart may attenuate cardiac remodelling, which might have deleterious effects on cardiac function. It also prevents the myocardial cell death, caused by continuous activation of β-receptor by sympathetic over activity in heart failure. Some β-blockers have α_1 antagonist properties and improve cardiac function by reducing the after load. So, the key point of the use of β-blocker in CCF is that it should be started with very low doses and should be increased slowly over time, depending on each patient's response.

Arrhythmias

β-blocker is also used in the treatment of arrhythmias. When arrhythmia is associated with hypertension, then α_1-receptor antagonist should be used before β-receptor antagonist. Otherwise, hypertension may be exacerbated. This is because of the loss of β_2-receptor mediated vasodilation.

There are many other therapeutic uses of β-blocker. But, there is no scope for discussion of these uses here.

Hydralazine/Dihydralazine

Hydralazine causes greater decrease of diastolic than systolic blood pressure. Because it is a directly acting arteriolar vasodilator, but without any effect on the venous capacitance vessel and coronary arteries. This hydralazine induced arteriolar dilatation is associated with powerful stimulation of sympathetic nervous system which causes tachycardia, increased myocardial contractility, increased plasma renin activity → increased aldosterone → increased Na^+ and water retention. Although most of the increased sympathetic activity is due to the baroreceptor mediated reflex, still hydralazine may stimulate the release of norepinephrine from sympa-thetic nerve terminals and augment the myocardial contractility directly. Thus, during the use of hydralazine a hyperdynamic circulatory state is present which may precipitate angina. There is no decrease in renal blood flow by hydralazine despite the fall in blood pressure (Fig. 18.11).

The sympathetic stimulation induced by hydralazine increases O_2 demand and precipitates myocardial ischaemia. Hydralazine does not dilate the coronary arteries. In the contrary, coronary arteriolar dilation produced by it may cause a

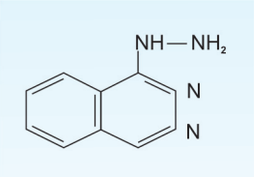


Fig. 18.11: Hydralazine

steal effect of myocardial blood flow away from the ischaemic region. So, hydralazine is contraindicated in hypertensive patient with coronary artery disease and age > 40 years. As it causes salt retention, hydralazine also may produce high output congestive heart failure. Tolerance to the hypotensive action of hydralazine develops, unless diuretics and β-blockers are given individually or together which block the compensatory mechanism.

Because of the preferential dilation of arterioles over veins, the postural hypotension is not a common problem of hydralazine. Although, hydralazine reduces the pulmonary vascular resistance, still the greater increase in CO can cause mild pulmonary hypertension. The exact mechanism of arteriolar smooth muscle relaxation by hydralazine is still not known. The probable mechanism may involve the generation of NO (Nitric Oxide) and stimulation of cGMP.

Hydralazine is also well absorbed orally, but the oral bioavailability is low. The peak hypotensive effect of hydralazine occur within 30 to 120 minutes after oral ingestion and half-life is 1 hour. The chief metabolic pathway of it is acetylation which is genetically determined. So, half of the population metabolise hydralazine rapidly (fast acetylator) and half of the population metabolise it slowly (slow acetylators). Therefore, oral bioavailability of it is higher in slow acetylators. Though the half-life of hydralazine in one hour, still its hypotensive effect lasts longer (12 hours). This is probably because of its persistent presence in the vessel wall.

Two types of toxicity of hydralazine develop. The first one is the extension of pharmacological effect of the drug itself which includes: hypotension, palpitation, angina, flushing, headache, etc. The second one is the autoimmune. So, lupus erythematosus or rheumatoid arthritis like syndrome can develop on prolonged use of hydralazine. Serum sickness, haemolytic anaemia, vasculitis, etc. also can develop and all these are immunological reaction.

Dose

The dose of hydralazine is 25 to 50 mg orally, once daily or thrice daily. For hypertensive emergency 10 to 20 mg of hydralazine is given very slowly through IV route.

Minoxidil

It is very effective in patient who is suffering from severe and some drug resistance forms of hypertension. Minoxidil itself is inactive *in vivo*. But it is metabolised in liver to minoxidil-N-O-sulfate which is the active form of it. Minoxidil sulphate like hydralazine is a very powerful arteriolar dilators but has very little effect on venous capacitance vessels.

The mechanism of action of minoxidil is like that it first activates the ATP modulated K-channel → opening of K^+ channel in arteriolar smooth muscle → K^+ efflux → hyperpolarisation → relaxation of arteriolar smooth muscle.

Like hydralazine the marked arteriolar vasodilation by minoxidil elicits strong compensatory elevated adrenergic activity, causing tachycardia and increased (Fig. 18.12) myocardial contractility with increased myocardial O_2 consumption. Thus, myocardial ischaemia can be induced by minoxidil in patients with coronary artery disease. Like hydralazine, as minoxidil dilates the arteriolar site only, so it increases the venous return to the heart and simultaneously increases CO.

Minoxidil has complex effect on kidney. Though, it dilates the renal vessels, but due to hypotension renal blood flow is actually reduced. As most of the renal dysfunction is due to hypertension, so the treatment of hypertension by minoxidil impress the renal function. The marked arteriolar vasodilation by minoxidil elicits strong compensatory increased sympathetic reflexes (as said before). Therefore, there are increased renin release → marked Na^+ and water retention → oedema and CHF. In case of minoxidil, the retention of salt and water is mainly secondary to reduced renal perfusion pressure and reflex stimulation of renal tubular α-adrenergic receptors. All these effects of minoxidil are like hydralazine and diazoxide. So, like hydralazine to offset these effects it is always practically used along with any loop diuretics and β-blockers. Used in this manner, it is effective even in severe hypertension which is resistant to combination of other drug. Thus, adverse effects of minoxidil is divided into three categories: CVS effects, salt and water retention, and hypertrichosis.

Hypertrichosis occurs in all the patients who receive minoxidil for an extended period and is particularly offensive to female patients. It is due to potassium channel activation. Growth of hair occurs in the face, back, arms and legs. Minoxidil is absorbed very well from GI tract and peak concentration in blood occur 1 hour after an oral administration. But maximum hypotensive effect of it occurs later. Because, this time is needed by liver to transform minoxidil to its active form. Its half-life is 3 to 4 hours, but action persists for 24 hours or more, as it accumulates in the walls of vessels.

Diazoxide (Fig. 18.13)

Like thiazide diuretics, chemically diazoxide is also a benzothiadiazine derivative

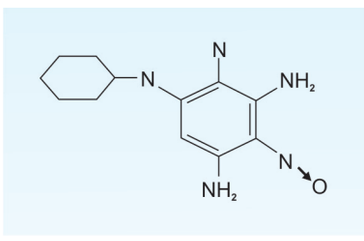


Fig. 18.12: Minoxidil

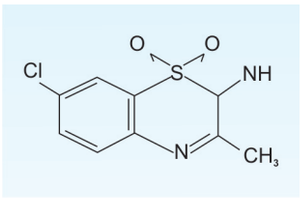


Fig. 18.13: Diazoxide

compound. But, it does not contain any diuretic effect, because it lacks the sulfonamido group. Only by IV injection it promptly decrease the tone of resistance vessels, but without any effect on capacitance vessels. So, though nitroprusside is the drug of choice, diazoxide is also used in the treatment of hypertensive emergency and had a definite place in some situation where accurate delivery of nitroprusside by infusions pump is not available and/or close monitoring of blood pressure is not possible.

Like minoxidil it also causes activation of ATP sensitive K^+ channel → increased influx of K^+ in the cell → hyperpolarisation of arterial smooth muscle cells → relaxation of arterioles. It also produces the reflex activation of sympathetic nervous system and increases the heart rate and myocardial contractility. Hence, it also increases CO. Sympathetic stimulation also cause → increase renin release → increased salt and water retention → increased level of angiotensin II. Thus, all these changes ultimately counter act the antihypertensive effect of diazoxide. Diazoxide increases the coronary blood flow. Renal and cerebral blood flow is maintained by autoregulation.

Although well absorbed orally, still diazoxide is only used intravenously in the treatment of hypertensive emergency. The initial recommended dose of diazoxide is 300 mg IV in bolus. But, this bolus dose sometimes cause severe hypotension with resultant cerebral and cardiovascular damage. So, this hypotension can be prevented by administration of diazoxide in minibolus dose of 50 to 150 mg at intervals of 5 to 15 minutes, until the desired blood pressure level is achieved. After IV bolus dose, the action starts within 30 seconds and maximum effect is achieved within 3 to 5 minutes. Diazoxide also can be given by slow intravenous infusion at a rate of 15 to 30 mg per minute.

The most common side effects of diazoxide are myocardial ischaemia, salt and water retention, and hyperglycaemia. This is because diazoxide inhibits insulin secretion from β-cells of pancreas. The myocardial ischaemia due to diazoxide results from the reflex adrenergic stimulation of heart and the increased flow to nonischaemic regions (steal phenomenon). Salt and water retention by diazoxide also cause increased plasma volume and cardiac load. But the routine use of diuretics with diazoxide in the management of hypertensive emergencies is not recommended, because these patients are frequently of volume depleted. The diazoxide solution is highly alkaline. So, pain and necrosis of tissues occur on extravasation.

It is partly metabolised and partly excreted unchanged through urine. Slow IV injection is less effective because it binds tightly to plasma proteins before bindings to vessels walls. The plasma half-life of diazoxide is 20 to 60 hours. The duration of hypotensive action of this drug is variable. It can be as short as 5 hours or as long as 20 hours.

Diuretics

Classification of diuretics as shown Table 18.7

Table 18.7: Classification of diuretics

A.	Inhibitors of Na^+ - K^+-$2Cl^-$ symporter (diuretics with high efficacy)
	(i) Furosemide, bumetanide (Sulphamoyl derivative)
	(ii) Ethacrynic acid (phenoxyacetic acid derivative)
B.	Inhibitors of Na^+-Cl^- symporter (diuretics with medium efficacy)
	(i) Thiazides: chlorothiazide, hydrochlorothiazide, benzthiazide, polythiazide, clopamide, Hydroflumethazide, etc.
	(ii) Thiazide like: Xipamide, indapamide, chlorthalidone
C.	Miscellaneous (weak efficacy)
	(i) Carbonic anhydrase inhibitor — acetazolamide
	(ii) Potassium sparing: Spironolactone (aldasterone antagomist), triamterene and amiloride (directly inhibiting renal epithelial Na^+ channel)
	(iii) Theophylline
	(iv) Mannitol—osmotic diuretics

Furosemide

It is a Na^+-K^+-$2Cl^-$ symporter (cotransporter) inhibitor and acts on the thick ascending limb (TAL) of the loop of Henle. So, it is also called the loop diuretics. Other diuretics in this group are bumetanide (like furosemide contain sulfonamide moiety), ethycrynic acid (phenoxyacetic acid derivatives) and torsemide (sulfonylurea). Diuretics acting on the Na^+-K^+-$2Cl^-$ symporter at TAL are highly effective, so they are often called as high-ceiling diuretics. This is due to: (i) as 65% of glomerular filtrate is absorbed in proximal tubule, so diuretics acting on proximal tubule have limited efficacy. The TAL reabsorbs most of the reject materials from proximal tubule and has a large reserved reabsorptive capacity. So, the diuretics which act on TAL are highly effective. (ii) Diuretics acting predominantly on post-TAL site have limited efficacy, because only a small percentage of the filtered Na^+ load reaches the post-TAL site and do not posses the reserved reabsorptive capacity.

Mechanism of action

Na^+-K^+-$2Cl^-$ cotransporter is a glycoprotein with 12 membrane spanning domains. It is only responsible for influx of Na^+, K^+ and $2Cl^-$ from the lumen into the epithelial cell of the TAL. This co-transporter captures the free energy from Na^+ electrochemical gradient which is established by the basolateral Na^+ pump and provides an 'uphill' for transport of K^+ and Cl^- into the cell. The presence of K^+ channels in the luminal membrane of the tubular cell provide a pathway for recycling of K^+ between the cell and the lumen. The presence of basolateral Cl^- channels provide a basolateral exit pathway for Cl^-. The movement of K^+ and Cl^- through their channels maintain a electrical gradient which is approximately 10 mV with the lumen positive in respect to the interstitial space. This positive potential difference

repels cations such as Na^+, Ca^{2+} and Mg^{2+} and thereby provides a important driving force for the paracellular flux of these cations into the interstitial space.

Furosemide acts as inhibitors of Na^+-K^+-$2Cl^-$ symporter. It binds to the Cl^- binding site, located on the symporter's transmembrane domain and block the symporter's function. Thus, it brings salt transport in this segment of the nephron to a standstill and causes diuresis. It prevents reabsorption of 25% of the filtered load that is absorbed in TAL. The inhibitors of Na^+-K^+-$2Cl^-$ symporter also inhibit Ca^{2+} and Mg^{2+} reabsorption in TAL by abolishing the transepithelial potential difference which is a dominant driving force for reabsorption of these cations. Thus, furosemide also causes the marked increases in the excretion of Ca^{2+} and Mg^{2+}. Furosemide has weak carbonic anhydrase inhibiting activity and increase the urinary excretion of HCO_3^-. It increases the urinary excretion of K^+ due to the increased delivery of Na^+ load to the distal tubule (increased Na^+ load in the distal tubule enhances the absorption of it and in exchange enhances the excretion of K^+ and H^+). However, K^+ loss by furosemide is less than that with thiazides diuretics. Increased HCO_3^- excretion may cause urinary pH to rise. But the predominant urinary anion is Cl^- whose excretion may increase in response to the action of furosemide. Acidosis does not develop by furosemide or causes minimum distortion of acid-base status. Mild alkalosis develops at high doses (Table 18.8).

Table 18.8: Diuretics

Specially suited for	
(i)	Renal disease with Na^+ retention
(ii)	Elderly, obese, volume overload
(iii)	Isolated systolic hypertension
(iv)	Low renin hypertension
(v)	Low cost
To be avoided	
(i)	Gout, diabetic
(ii)	Pregnancy induced hypertension
(iii)	Abnormal lipid profile

Furosemide tends to raise blood uric acid level by decreasing its renal excretion (increased reabsorption, decreased secretion). Increased uric acid reabsorption in the proximal tubule is the consequence of volume depletion caused by furosemide. However, reduced uric acid secretion is due to the competition between the diuretics and uric acid for their secretion through same secretory mechanism in PT as the furosemide is secreted at the PT, passes down the loop of Henle and acts at the TAL from luminal side. By blocking the active NaCl reabsorption in thick ascending limb, the inhibitors of Na^+-K^+-$2Cl^-$ symporter such as furosemide interfere with the critical step in the mechanism that produces a hypertonic medullary interstitium and help to concentrate the urine. Renal blood flow is transiently increased. There is redistribution of blood flow from outer to midcortical zone. Here prostaglandin may be suspected as the cause. NSAID dimi-nish the diuretic response of loop diuretics, most likely by preventing the prostaglandin mediated increase in RBF. Glomerular filtration rate generally remains unaltered due to compensatory mechanism, despite increased renal blood flow.

Furosemide also acutely increases the systemic venous capacitance and thereby, decreases the left ventricular filling volume and pressure, even before diuresis ensues. This is responsible for the quick relief of symptoms of LVF and pulmonary oedema by furosemide. These actions also may be mediated by prostaglandin. Furosemide also causes hyperglycaemia, but less marked than thiazides diuretics. It also causes hyperuricaemia which is lower than that of thiazide diuretics. The therapeutic uses of furosemide are: systemic oedema, acute LVF, pulmonary oedema, cerebral oedema, forced diuresis, hypertension, etc.

Pharmacokinetics

Furosemide is rapidly absorbed orally. Bioavailability of furesomide through this route is about 60%. As it is extensively bound to plasma proteins, so delivery of these drugs to the tubular cells by filtration is limited. On the otherhand for the action of furosemide it is effectively secreted by the organic acid transporter system in the proximal tubule and then it flows down through the tubular lumen with the tubular fluid to gain access to their binding sites on the Na^+-K^+-$2Cl^-$ symporter system of the luminal membrane of TAL. It is partly conjugated with glucuronic acid. Plasma half life is 1 to 2 hours.

Dose

Usually furosemide is used in the dose of 20 to 80 mg, once daily in the morning orally. In pulmonary oedema, 40 to 80 mg IV bolus may be given or according to the patient's response.

Toxicity, adverse effects and contraindications

The adverse effects of furosemide are rare and are mostly due to the fluid and electrolyte imbalance. So, the overzealous use of loop diuretics cause serious depletions of total body Na^+, resulting in hyponatraemia, extracellular fluid volume depletion, hypotension, circulatory collapse, etc. Increased delivery of Na^+ load to the distal tubule from TAL (due to reduction of reabsorption), particularly when combined with activation of the renin-angiotension system leads to increased urinary excretion of K^+ and H^+ causing a hypochloraemic alkalosis. Increased Mg^{2+} and Ca^{2+} excretion may result in hypomagnesaemia and hypocalcaemia. Due to reduction of circulation, furosemide may precipitate thromboembolic episode and hepatic encephalopathy in patient with liver disease.

Furosemide can cause ototoxicity; tinnitus, hearing impairment, deafness, etc. It can also cause hyperuricaemia (gout) and hyperglycaemia. Other Na^+-K^+-$2Cl^-$ symport inhibitors or loop diuretics are bumetanide, ethacrynic acid, torsemide. But individual discussion of these agents

is not possible here and furosemide should be taken as their prototype.

Thiazide diuretics

The primary site of action of these diuretics is the early DT. Here, they inhi-bit Na^+-Cl^- symporter system at the luminal membrane of the tubular cells. These groups of drugs also like furosemide gain access to their site of action at the DT after secretion in the PT. After secretion through the organic secretory pathway in the PT, they pass along the loop of Henle with the tubular fluid and finally bind to the specific receptor site i.e, Na^+–Cl^- symporter system located at the luminal membrane of DT. Like the Na^+-K^+-$2Cl^-$ cotransporter system, the Na^+-Cl^- (Table 18.9) symporter system is also a glycoprotein with 12 membrane spanning domains. But, it does not bind to furose-mide or any other class of diuretics except thiazides. Due to their action, increased amount of Na^+ is presented to the distal nephron where it is exchanged with K^+. So urinary excretion of K^+ is also increased in parallel to the natriuretic effect of these groups of thiazide diuretics, like furosemide. Nevertheless, they are moderately effective, because near about 90% of the glomerular filtrate has already been absorbed before it reaches their site of action. They have a flat dose response curve. Therefore, little additional diuretics occur when the dose is increased beyond their maximum dose. They do not cause significant alteration in acid-base balance of the body. They are not effective in patient with low GFR. They decrease the excretion of urate and Ca^{2+} by the same mechanism as furosemide and elevate blood sugar due to the decreased release of insulin.

All the thiazides and related drugs are well absorbed orally and their action starts within one hour. Their duration of action is variable. The more lipid-soluble agents have larger volume of distribution, lower rates of tissue clearance and therefore, are longer acting. Most of the thiazide agents undergo little hepatic metabolism and are excreted through kidney as such. This is because they are filtered at the glomerulus as well as secreted in the PT.

Thiazide diuretics are used mainly in the treatment of oedema, hypertension, diabetes insipidus, and hypercalcicuria. Mild to moderate oedema responses better. For mobilization of oedema fluid more effective diuretics are employed initially and thiazides are considered later for maintenance therapy. They are best for cardiac oedema and less effective for hepatic or renal oedema. They are not responsive in the presence of renal failure.

Most of the adverse effects of thiazide group of drugs are due to fluid and electrolyte changes caused by them. Among these, hypokalaemia is the most significant problem. But it is rare in low doses and short period of therapy. The consequence becomes grave if the thiazide therapy is prolonged and the dietary K^+ intake is low. The hypokalaemia associated with thiazide diuretics can be prevented by: (i) high dietary K^+ intake, (ii) supplement of KCl (24 to 72 mEq/day), and (iii) concurrent use of K^+ sparing diuretics. The last two measures are not routinely indicated, but only when the hypokalaemia is documented or in special risk situations such as cardiac patients, cirrhosis, etc. Other adverse effects of thiazide diuretics are hyponatraemia, hyperuricaemia, hyperglycaemia, hypercalcaemia, etc.

Table 18.9: Thiazide group of diuretics

Drugs	*Drug (Daily, in mg)*	*Duration of action (hour)*	*Relative efficacy*
Hydrochlorothiazide	50-100	10-12	2
Polythiazide	1-3	24-48	2.5
Benzthiazide	25-100	12-18	1.5
Hydroflumethiazide	5-100	12	1.5
Bendroflumethiazide	5-10	12	2
Chlorthalidone	50-100	48	2
Xipamide	20-60	24	1.5
Indapamide	2.5-5	24-36	1
Clopamide	10-60	12-18	2

Spironolactone

It is a K^+ sparing diuretic and is chemically related to aldosterone. Aldosterone acts on DT and CD by combining with a receptor which promotes the reabsorption of Na^+ and excretion of K^+. Spironolactone acts on this receptor and inhibits the action of aldosterone in a competitive manner. Therefore, it antagonises the loss of K^+ induced by other diuretics. Spironolactone is a weak diuretic becasue most of the Na^+ has already been reabsorbed proximal to its site of action. The K^+ retaining action of spironolactone develops over 3 to 4 days after its administration. It also increases the excretion of Ca^{2+} by direct action on renal tubules.

The oral bioavailability of spironolactone is 80%. It is highly protein bound and completely metabolised in liver. As it is weak in action, so is used only in combination with other more strong diuretics. It is more effective in cirrhotic and nephrotic oedema, because it breaks the resistance to thiazide diuretics that develop due to secondary hyperaldosteronism. Therefore, it is particularly employed in refractory oedema. Given together with K^+ supplements, dangerous hyperkalaemia can occur (Table 18.10).

Triamterene and amiloride

The most important action of these two diuretics is to decrease the excretion of K^+ along with the small increase in excretion

Table 18.10: Urinary excretion of electrolytes by some diuretics and their efficacy

Diuretic	Na^+	K^+	Cl^-	HCO_3^-	Efficacy
Furosemide	+++	+	++	+	High
Thiazide	++	+	+	+	Intermediate
Spironolactone	+	–	+	+ –	Low
Triamterene	+	–	+	+ –	Low
Mannitol	++	+	+	+	High
Acetazolamide	+	++	+ –	+	Mild

of Na^+. Therefore, their action is similar to spironolactone, but independent of aldosterone. Their site of action is the luminal side of the cells of late DT and CD. At this site of the cells there are distinct Na^+ channels through which Na^+ enters the cell down its electrochemical gradient which is generated by the Na^+-K^+-ATPase pump situated at the basolateral side of cell membrane. This Na^+ entry into the tubular cells from lumen promotes the secretion of K^+ into the lumen. Therefore, if there is more delivery of Na^+ to the distal nephron, there will be more absorption of Na^+ and more excretion of K^+. Thus, all the diuretics acting proximally such as furosemide, thiazides, etc., decrease the reabsorption of Na^+ and increase the load of Na^+ in DT and CD and so increase the excretion of K^+. Triamterene and amiloride act on these Na^+ channels and block the absorption of Na^+ and reduce the excretion of K^+.

Both these diuretics are used in conjunction with thiazide or other high ceiling diuretics to prevent hypokalaemia. They should not be given with K^+ supplements, because dangerous hyperkalaemia may develop. Triamterene is partly absorbed orally and largely metabolised in liver. Its duration of action is 6 to 8 hours. Amiloride is 10 times more potent than triamterene. It decreases the excretion of Ca^{2+} and increases the excretion of urate. Thus, the hypercalcaemic action of thiazides is augmented, but hyperuricaemic action is partly annuled. It is partly absorbed orally, not metabolized in liver and duration of action is 8 to 10 hours.

Mannitol

It is an osmotic diuretic with the following properties:

i. low molecular weight (182),
ii. freely filtered at glomerulus,
iii. limited reabsorption by the renal tubule,
iv. pharmacologically inert and does not metabolise in the body.

Mechanism and site of action

Mannitol acts both at the proximal tubule and loop of Henle (primary site of action). It mainly acts by (i) increasing the osmolality of plasma, (ii) increasing the osmolality of tubular fluid and (iii) reducing the medullary tonicity. Thus, it limits the tubular water and electrolyte reabsorption.

Mannitol extracts water from the intracellular compartment and expands the extracellular fluid volume. It decreases blood viscocity and inhibits renin release. All these effects cause increased renal blood flow (RBF) (both in cortex and medulla). Increased renal medullary blood flow removes NaCl and urea from the renal medulla and reduce medullary tonicity. Thus, corticomedullary osmotic gradient is dissipated. So, decreased reabsorption of water from DTL causes dilution of NaCl concentration in tubular fluid entering ATL and diminishes the reabsorption of NaCl with water in ATL. Osmotic diuretics also inhibit the reabsorption of Mg^{2+} and Ca^{2+}. Osmotic diuretics increase the urinary excretion of nearly all electrolytes, including Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^- and phosphate.

Administration

Mannitol is not absorbed orally and has to given IV as 10 to 20% solution. 80% of the drug is excretd as intact form by kidney. Next 20% is excreted after metabolism or is excreted as intact drug through bile. Plasma half-life of mannitol is 0.25 to 1.7 hours and in renal failure it may rise to 6 to 36 hours.

Adverse effects, indications and contraindications

As mannitol is distributed in the extracellular compartment, so water is extracted from the intracellular compartment and the extracellular fluid volume is expanded. In a patient with incipient heart failure and pulmonary congestion, this may cause frank pulmonary oedema.

Mannitol should never be used in the treatment of chronic oedema or as natri-uretic. Because loss of water in excess of electrolytes can cause hypernatremia and dehydration. If acute renal failure (anuria) has already set in, kidney becomes incapable of forming urine, even after an osmotic load by mannitol. So, mannitol is contraindicated in patients who are unresponsive to test doses of the drugs. In such circumstances large plasma volume expansion by mannitol may precipitate pulmonary oedema. Sometimes, 45% NaCl is as good as or better than either mannitol or furosemide for forced diuresis in protection against the acute tubular necrosis (ATN) which may lead to acute renal failure. It is not recommended to use mannitol repeatedly in case of non-responders (no urine formation). Nowadays, loop diuretic frusemide is more frequently used to convert oliguric to nonoliguric ATN than mannitol.

By increasing osmotic pressure of the plasma, mannitol extracts water from the eye (aqueous humour) and CSF (brain). So, it is frequently used in the acute attack of glucoma and increased ICP, during both preoperatively or postoperatively to control the intraocular pressure and the acute rise in intracranial pressure. It should not be used in intracranial haemorrhage.

Acetazolamide

It is a sulfonamide derivative compound and is the prototype of a group of agents which have limited diuretic effect, but greatly help to draw a fundamental picture of renal physiology. When sulfonamides are used as chemotherapeutic agents, they cause metabolic acidosis by inhibiting an enzyme named CAase (carbonic anhydrase). This leads to the enormous study and development of acetazolamide (sulfonamide derivative) as carbonic anhydrase inhibitor.

The main site of action of acetazolamide is proximal tubular epithelial cells, which is rich in CAase at its luminal side of cell membrane, basolateral side of cell membrane (type IV carbonic anhydrase) and in cytoplasm (type II carbonic anhydrase). At the luminal side of membrane Na^+ enter into the cell in exchange of H^+ which is excreted in lumen by Na^+-H^+ antiporter system (also called Na^+-H^+ exchanger) by free energy available from Na^+ gradient established by the basolateral Na^+-K^+-ATPase pump. H^+ in the lumen reacts with filtered HCO_3^- to from H_2CO_3 which rapidly breaks into CO_2 and H_2O by the help of CAase, present at the brush luminal side of cell membrane of proximal tubular cells. Due to lipophilicity, CO_2 is rapidly diffuses in the proximal tubular cells and in the cell CO_2 again reacts with H_2O to form H_2CO_3 by the help of cytoplasmic carbonic anhydrase.

$$CO_2 + H_2O \xleftrightarrow{\text{CAase}} H_2CO_3$$

Continuous use of Na^+-H^+ antiporter system causes low H^+ concentration in the cell which stimulates intracellular H_2CO_3 to ionise spontaneously to H^+ and HCO_3^-. Increased HCO_3^- concentration in the cell (simultaneously increased electrochemical gradient of HCO_3^-) is used by Na^+-HCO_3^- cotransporter system at the basolateral side of cell membrane to transport $NaHCO_3$ into the interstitial space. The net effect of this process is transport of $NaHCO_3$ from the tubule to the interstitial space followed by movement of water (isotonic reabsorption). Removal of water concentrates Cl^- in the tubular lumen and consequently Cl^- diffuses in interstitial space by its concentration gradient via paracellular pathway.

Acetazolamide, thus acting as car-bonic anhydrase inhibitors at cell membrane and cytoplasmic level, reduces the availability of H^+ to exchange the luminal Na^+ by the Na^+-H^+ antiporter system and results in nearly complete abolition of $NaHCO_3$ reabsorption which ensues alkaline diuresis. Secretions of H^+ in DT and CD is also inhibited. Though, H^+ is secreted at this site by an H^+-ATPase pump (proton pump), it is generated in the cell by the CAase-mediated reaction. Thus, this is a secondary site of action of CAase inhibitor or acetazolamide. In the distal tubule the absorption of Na^+ takes place in exchange of exeretion of H^+ and K^+. In the absence of H^+, the K^+ is lost in excess to preserve Na^+ producing hypokalaemia. Among all the diuretics, acetazolamide causes the most marked kaliuresis. Urine produced under acetazolamide action is alkaline and rich in HCO_3^- which is matched by both Na^+ and K^+. The fractional excretion of Na^+ may be as much as 5% and the fractional excretion of K^+ can be as much as 70%. Inhibition of transport mechanism in PT results in increased delivery of Na^+ and Cl^- to the loop of Henle, which has large reabsorptive capacity and captures most of the Cl^- and a portion of the Na^+.

CAase inhibitors also increase the excretion of phosphate. The effects of acetazolamide on renal excretion is self limiting. This is probably because as gradually metabolic acidosis develops, the filtered load of HCO_3^- decreases to the point that the uncatalyzed reaction between CO_2 and water is sufficient to achieve HCO_3^- reabsorption.

Extrarenal actions of acetazolamide

(i) Other extrarenal tissues such as eye, gastric mucosa, RBC, CNS, etc. are also rich in CAase. Ciliary process of eye is responsible for the formation of aqueous humour by the help of CAase. Acetazolamide, thus inhibiting CAase reduces the formation of aqueous humour and ↓intraocular tension.

(ii) CAase inhibitors also decrease gastric HCl secretion, but needs very high dose. So, it is not applicable therapeutically.

(iii) Due to interference with carbonic anhydrase activity in RBC, acetazolamide increases CO_2 levels in peripheral tissues and decreases CO_2 exhalation by lungs.

Oral bioavailability of acetazolamide is 100%. Plasma half-life is 6 to 9 hours and excreted unchanged in urine. Adverse effects of it are very infrequent like other sulphonamides. It may cause bone-marrow depression, skin reactions and allergic reaction in patients who are hypersensitive to sulphonamides. Adverse effects of acetazolamide are mainly due to secondary effects of urinary alkalisation and metabolic acidosis. So, there is a chance of precipitation of salt of calcium phosphate in alkaline urine and calculus formation. It also causes worsening of metabolic and respiratory acidosis. Thus, it is contraindicated in COPD patient. Precipitation of hepatic coma by interfering with urinary elimination of NH_3 (due to alkaline urine) may also occur.

Therapeutic uses of acetazolamide are: glucoma, alkalinisation of urine for urinary tract infection, acute mountain sickness (only as prophylactic), etc. The probable mechanism of action is by producing metabolic acidosis, or indirectly correcting a metabolic alkalosis, especially caused by decreased excretion of H^+ through urine.

ANAESTHESIA IN HYPERTENSIVE PATIENT

Perioperative management of patients with essential hypertension, scheduled for both elective or emergency surgery is same. During perioperative management of

patient suffering from hypertension it should be kept in mind that the raised intra-arterial pressure is due to either essential hypertension or secondary hypertension associated with the following conditions such as renal disease, coarctation of aorta, pheochromocytoma, Cushing's disease, etc. A severe intraoperative uncontrolled rise in blood pressure is particularly dangerous and may cause cerebrovascular injury or left ventricular failure with pulmonary oedema. If the intramural coronary arteries have been affected previously by the atheromatous process, the raised diastolic pressure may jeopardize the myocardial blood flow especially in the subendocardial region and produce ischaemic changes in ECG which is performed for monitoring during the whole perioperative period. Decrease of workload on the ventricle by lowering the systemic vascular resistance, may relief the failure and restore an adequate myocardial blood flow with reversal of the ECG changes.

Drugs that effectively control the systemic blood pressure in treated individual should be continued throughout the perioperative period. In general, hypertensive patients where BP is not controlled preoperatively should not be scheduled for outpatient or ambulatory (day-case) surgery under general anaesthesia, because of their tendency to haemodynamic fluctuation.

Preoperative Evaluation

The aim of pre-operative evaluation of patient suffering from hypertension is to determine the adequecy of control of systemic blood pressure. It is very general concept that hypertensive patient should be treated to normotensive before undergoing elective surgery. The point behind this concept is that the incidence of hypertensive emergencies, myocardial ischaemia and other complications increased in patients who remain hypertensive or not controlled prior to the induction of anaesthesia, although the increase in BP during intraoperative period occurs regardless of the degree of preoperative control of blood pressure. On the other hand, it is also evidenced that there is no increased incidence of perioperative complications when hypertensive patients with diastolic pressure as high as 110 mm of Hg undergoes elective operations, provided there is stringent perioperative control of BP. Therefore, from the above two statements it is clear that whatever may be the preoperative status of patient regarding the systemic BP, i.e. controlled or uncontrolled, it is the stringent immediate perioperative control of BP which is most important.

Pressure obtained in the hospital setting may not represent patients's usual levels. But, high blood pressure during admission of a hypertensive patient who was previously treated and controlled clearly can predict larger possible fluctuation of it intraoperatively. It is also very common that blood pressure increases during admission in hospital due to patient's anxiety. This is called 'white coat syndrome' and this group of patient also displays exaggerated pressure responses to direct laryngoscopy during tracheal intubation and surgical stimuli during intraoperative period.

Presence of end-organ disease due to long-standing hypertension should be evaluated pre-operatively by different investigations, e.g. ECG, renal function test, echocardiography, etc. Among them, the most important is the investigation for coronary artery disease. ECG for hypertensive patient with LVH, intraventricular conduction blocks or repolarisation abnormality should also be considered. Echocardiogram is more sensitive and informative than 12 lead ECG for diagnosis of LVH. Previous history of infarction has great significance. Essential hypertension is associated with the shifts of autoregulation curve of cerebral blood flow to the right. This shift suggests that cerebral blood flow is more dependent on perfusion pressure in hypertensive patient than in normotensive patient. Urgent revaluation and treatment of hypertension is necessary for patients with presence of fundal haemorrhage, exudates and particularly papilloedema on examination of the optic fundus.

Antihypertensive drugs used in the preoperative management usually do not alter the course and conduct of anaesthesia. But the abrupt discontinuation of antihypertensive drugs immediately in pre- or postoperative period causes rebound hypertension. This may be the another cause for continuation of antihypertensive drugs during the whole perioperative period. Despite acceptance of the concept that antihypertensive drug therapy should be continued throughout the perioperative period to reduce the morbidity and mortality, there is still risk that haemodynamic instability and hypertension or hypotension may occur during anaesthesia. During anaesthesia of a hypertensive patient exaggerated decrease in BP which are sometimes associated with increase in blood loss, excessive positive airway pressure or sudden change in body position could reflect impaired compensatory peripheral vasoconstriction due to inhibitory effect of antihypertensive drugs on the sympathetic nervous system.

Induction of Anaesthesia

There is a general agreement that all the hypertensive patients should receive an oral anxiolytic agent (e.g benzodiazepine) in addition to their normal morning doses of antihypertensive drugs as a pre-operative medication before induction of anaesthesia. There is also little evidence that any particular inducing agent or technique is better than other during induction of a hypertensive patient. Still it should be kept in mind that etomidate has the lowest cardiovascular effects, but thiopental is acceptable if administered carefully. Propofol may produce excessive hypotension in hypertensive patient. Induction of anaesthesia with rapidly acting intra-venous drug is the standard practice for hypertensive patient, but keeping in mind that exaggerated decrease

in BP may occur and this is due to excessive peripheral vasodilatation. This is because all the inducing agents cause widespread venodilation causing a large decrease in venous return and cardiac output, but a minor decrease in SVR. Ketamine is contraindicated as inducing agent in hypertensive patient.

Direct laryngoscopy and tracheal intubation is associated with exaggerated increase in BP for patient suffering from hypertension. This occurs even if these patients are treated with antihypertensive drugs and rendered normotensive preoperatively. Because hypertensive patients usually cause a greater increase in plasma catecholamine concentrations than normotensives during laryngoscopy and intubation. And it is also true that intravenous inducing agents cannot adequately and predictably suppress responses evoked by tracheal intubation.

This haemodynamic responses evoked during laryngoscopy and intubation can be attenuated adequately by:

i. increasing the concentration of inhaled volatile anaesthetic agents.
ii. by using adequate dose of IV opioids prior to initiating laryngoscopy and intubation. Intravenous opioid administration should be timed, so that peak effects of the opioids are predictably matched with the stimulus of laryngoscopy and intubation,
iii. by topical laryngotracheal administration of lignocaine, immediately prior to intubatioin,
iv. by administering lignocaine IV in the dose of 1.5 mg/kg about 1 minute before induction and intubation,
v. by using nitroprusside 1 to 2 µg/kg/IV just before laryngoscopy,
vi. by using esmolol 100 to 200 mg IV. As this haemodynamic response is primarily from sympathoadrenal axis to a noxious stimulus, it is most logical to use either opioids or β-adrenoreceptor antagonists to suppress the haemodynamics response and decrease the incidence of arrhythmias and myocardial ischaemia during and after intubation. Excessive autonomic activity may also be avoided when local anaesthetic techniques are employed as an adjunct to GA.

Regardless of the drugs which are used to blunt the circulatory effect of laryngoscopy and intubation, it is generally appreciated that excessive depressant effect of drugs producing hypotension during attempts to blunt or reduce the circulatory effect is more undesirable than the transient hypertension effect produced by direct laryngoscopy and tracheal intubation.

Maintenance of Anaesthesia

There is no evidence that any anaesthetic technique is better than others in hypertensive patient. However, also no limits for deviation of arterial pressure have been proven to be safe. But deviation not more than 20% from pre-operative MAP value is generally accepted. The goal during maintenance of anaesthesia in a hypertensive patient is to adjust the depth of anaesthesia and to minimise the wide fluctuations of blood pressure. Indeed, control of perioperative BP fluctuation with different anaesthetic techniques and agents is more important than preoperative control of hypertension.

Chronic hypertension is usually associated with hypovolaemia and IHD. Regional anaesthesia is an acceptable alternative method for hypertensive patient. But it should be kept in mind that sympathetic denervation proved by RA may unmask the unsuspected hypovolaemia (if present) and cause severe hypotension which may result in myocardial ischaemia. Untreated or poorly controlled hypertensive patient may suffer with greater decrease in BP and abrupt or dangerous bradycardia. The combination of α and β adrenoreceptor agonist or a vagolytic drug combined with α-adrenoreceptor agonist is better than α_1-adrenoreceptor agonist alone for treating hypotension after RA.

The intraoperative increase in BP is mainly due to sympathetic stimulation caused by painful surgical stimuli. The incidence of intraoperative hypertensive episodes is high in patient with history of essential hypertension. This is also evident even in patients who were previously rendered normotensive by drug therapy. Volatile anaesthetics are important agents to decrease the sympathetic activity which is responsible for intraoperative pressure response. It acts in dose-depended manner by decreasing SVR and to a lesser extent by decreasing the cardiac contraction and cardiac output. There is no evidence that one volatile anaesthetic agent is better than another in that respect. Poor blood solubility of desflurane and sevoflurane compared with isoflurane and halothane may permit more rapid changes in alveolar concentration and hence the depth of anaesthesia with good control of blood pressure. Intraoperative IV nitroprusside by infusion pump is a very good way of maintaining normotension in a hypertensive patient. There is no evidence that a specific muscle relaxant is better than another for intraoperative management of patient with hypertension. Pancuronium is not contraindicated in anaesthesia of a hypertensive patient but somebody avoid it in severe hypertension.

Hypotension often occurs during intraoperative control of high BP. This hypotension can be treated by decreasing the concentration of delivered volatile anaesthetic agents and decreasing the dose of antihypertensive drugs which are using intraoperatively. Intraoperative hypotension may be caused by a low circulating blood volume (in hypertensive patient blood volume is low). So a marked fall in arterial pressure may be produced by only a modest blood loss. The assessment of blood and other intravenous fluid requirements should be made from present circulatory status, rather than by

relying solely on the eye estimation of volume of blood loss. Measurement of pulmonary wedge pressure is of particular value in assessing intravenous fluid requirements in some patients with diseased left ventricle. Sometimes, sympathomimetic drugs can be used to restore the minimum perfusion pressure in vital organ. The response to sympathomimetic drugs should be both appropriate and predictable and can be titrated with hypotension. But care must be taken when vesopressor drugs are administered because they can interact with some antihypertensive agents.

Intraoperative monitoring of a hypertensive patient depends on the patient's condition and the complexity of surgery. The monitoring can extend from simple manual BP monitoring to intra-arterial BP monitoring to automatic NIBP, ECG, pulse oximeter, capnography, PAWP, transoesophageal echocardiogrphy, etc. Intraoperative myocardial ischaemia is usually evident from the conventional 12 lead ECG. But in some instances, only one lead can be monitored during anaesthesia and intensive therapy. In such situation the CM_5 bipolar lead would appear to be the best to show ischaemia changes in ST segment and give a good demonstration of P-wave and QRS complex. In this lead the reference electrode (right arm lead) is placed over the manubrium sterni. The exploring electrode (left arm lead) is placed on the V_5 position and the earthing electrode (right lower limb lead) may conveniently be sited on the left shoulder. The ECG may then be displayed by selecting the lead I position.

Postoperative Management

Extubation under light plane of anaesthesia or allowing the patient to cough on the tube during extubation can provoke a marked sympathomimetic response with undesirable tachycardia and hypertension. So, extubation should be done under adequate or deep plane of anaesthesia. Hypertensive patient usually responds with elevated BP during early post-operative period. It is usually due to exaggerated sympathetic activity due to post-operative pain. So, postoperative elevation of BP needs prompt assessment and treatment of postoperative pain to decrease the risk of myocardial ischaemia, cardiac arrhythmias, LVF, stroke, post-operative bleeding, etc., which may also be seen in postoperatieve period. When the intraoperative analgesia derived from the N_2O or opiates or others are wear off, the resultant increase in sympathetic acti-vity due to pain can cause a marked rise in systemic blood pressure and thereby heart failure. In addition, sometimes the intraoperative tendency toward pulmonary oedema may have been masked by IPPV, because of the raised intra-alveolar pressure. So, on return to the spontaneous ventilation, the LVF and pulmonary oedema may then become apparent and result in early post-operative collapse.

The Postoperative BP control can be done by the agents which are also used during the intraoperative period such as analgesics, GTN, nitroprusside, labetalol, hydralazine, etc. NSAIDs, though effective as postoperative analgesics, are one of the most common cause of acute renal failure. So, care should be taken in their use in hypertensive patients who are possibly at the risk of renal dysfunction. The use of vasodilator drugs to treat the patient with high systolic BP and normal diastolic pressure is not usually indicated.

If Hypertension Must be Treated and Controlled in Hypertensive Patient Before Operation

Till now it is the most debatable question, because a number of studies have failed to show that hypertension is an independent perioperative risk factor. The questions that centre around are:

i. Does adequate control of pre-operative hypertension could prevent perioperative complications?
ii. How much preoperative control of BP is needed?
iii. Should elective surgery be postponed due to preoperative elevated BP, so that treatment can be instituted for hypertension and patient can be optimised?

Now several schools of thoughts exist and several studies have been carried out. But unfortunately all the studies have failed to establish a definite answer. Prys-Robert's school believes that the preoperative management of hypertension lowers the incidence of perioperative morbidity and mortality. But others do not. Patients with astherosclerotic disease, who present with raised systolic pressure, but normal or low diastolic pressure, should not be considered as true hypertensive and should not have their surgery delayed (Prys-Robert-Brown).

Postponement of surgery due to hypertension is only necessary when there is an indication that the patient will benefit certainly from introducing antihypertensive therapy or modification of existing therapy (Prys-Robert-Brown). Only patients with severe hypertension with clear evidence of end-organ damage need postponement of surgery for further work up and treatment for optimisation unless minor surgery is planned (Prys-Robert-Brown).

The school represented by Goldman and Caldera views that the peri-operative management of patients presenting with untreated hypertension depends upon the level of the diastolic blood pressure and the surgical circumstances. For elective surgery, if the diastolic pressure does not exceed 110 mm of Hg, there is no evidence of increased cardiac and CNS complications. Patients with persistent diastolic blood pressure above this level should be referred to a physician for treatment. The occurrence of severe untreated hypertension (a diastolic pressure > 130 mm of Hg) in the perioperative period is known to be

associated with an increased morbidity and mortality.

Bedford, Feinstein, Wolfsthal and their supporters believe that fluctuation of blood pressure is the condition which is most frequently, predicts the rate of perioperative complications. So, according to their opinion by careful titration the fine control of perioperative BP is more important than only the preoperative treatment of hypertension. Despite the desire to render the patients normotensive before elective surgery, there is no evidence that the incidence of perioperative complication increases if fine control of BP is done when hypertensive patients (diastolic BP as high as110 mm of Hg) undergo elective operations (RK Stoelting and SF Dierdorf).

Conclusion

Although preoperative BP has been thought to be a significant predictor of the perioperative morbidity and mortality, no data establish definitly whether the preoperative control of hypertension reduces the perioperative risk. Preoperative treatment of patient suffering from hypertension is based on the following concepts that: (i) Patient should be educated regarding the importance of hypertension and its management which usually extends postoperatively and life-long. (ii) Incidence of perioperative haemodynamic fluctuations is less in treated than untreated group and (iii) Haemodynamic fluctuation has definitive relationship to morbidity.

The main aim of preoperative management of hypertensive patient is to search for end-organ damage secondary to hypertension, i.e. changes in CNS, coronary arteries, myocardium, aorta, kidneys, peripheral blood vessels, etc., and modulations of anaesthetic management accordingly.

19 Heart Failure and its Pharmacology

INTRODUCTION

The term myocardial failure is better than the term heart failure. On the other hand, the heart failure is though an unimpressive term, still it is most commonly used. It is a pathophysiological state in which due to some abnormality of cardiac function myocardium fails to pump out blood at a rate, corresponding to the requirement of the metabolising tissue and/or can do so (in compensated stage) only at the expense of an elevated filling pressure from an abnormally elevated diastolic volume. This failure of myocardium to pump out the required amount of blood which is needed for the body at that moment may be due to primary causes where myocardium itself is responsible, or may be due to secondary causes where the myocardium itself is not diseased (e.g. sudden increase of BP, pulmonary diseases, valvular diseases, arrhythmia, etc). In primary causes the abnormalities of heart muscle may be due to cardiomyopathies, viral myocarditis, myocardial ischaemia, infarction or abnormalities of heart valve where heart muscle have been damaged due to long standing haemodynamic burden. But, in secondary causes there is no detectable abnormality of myocardial function. In such circumstances, the normal heart is suddenly presented with an excessive mechanical load that exceeds its capacity. Secondary heart failure may also occur without any excessive load on myocardial function but there is chronic impairment of ventricular filling during diastole due to some mechanical abnormalities such as tricuspid stenosis, constrictivepericarditis, endocardial fibrosis, etc. which causes failure to pump out adequate amount of blood by heart according to the requirement of metabolising tissue. However, in maximum patients the combination of impaired myocardial function (or primary heart failure) and mechanical abnormality (or secondary heart failure) both coexist, because like vicious cycle they affect each other. For example, in one form such as with volume overload when the myocardium of ventricle without any pathology is called on to deliver an elevated cardiac output for prolonged periods (secondary failure), then it gradually develops myocardial pathology leading to primary failure. Similarly, systolic and diastolic failure (discussed later) affect each other and run in a vicious cycle.

In the mildest form of heart failure, cardiac output is adequate at rest, but becomes inadequate and is manifested only when the metabolic demand is increased such as during exercise or some other form of stress. In practice, heart failure or myocardial failure may be diagnosed, when-ever a patient with significant heart disease develops the signs and symptoms of a low cardiac output, pulmonary congestion or systemic venous congestion.

In summary, the causes of heart failure can be grouped under two headings:

i. Underlying or primary causes– Here, the pathology is within the heart muscle itself, e.g. CHD, long standing valvular lesion, ischaemia, infarction, myocarditis, arrhythmias, etc.
ii. Precipitating or secondary causes– Here, the pathology is not within the heart muscle itself, but away from it such as systemic hypertension, fluid overload, anaemia, thyrotoxicosis, etc.

In the presence of different underlying causes of heart failure, initially the heart usually remains in compensated stage with little additional reserve. So, later additional load imposed by precipitating or secondary causes results in further deterioration of cardiac reserve and manifested as frank or overt failure. In the absence of underlying primary causes, if the secondary factors become acute then the heart may also undergoes failure. Therefore, identification of such precipitating causes is of very clinical importance, because their prompt alleviation may be lifesaving. In the absence of underlying primary heart disease, the precipitating or secondary factors by themselves usually do not lead to heart failure, except in acute stage. The examples of some precipitating factors are anaemia, infection, pregnancy, thyrotoxicosis, emotion, physical exertion, fluid excess, pulmonary embolism, hypertension, etc. Precipitating causes of heart failure should also be recognised and treated more effectively than the underlying causes. Because the prognosis of heart failure where a precipitating cause can be identified, treated and eliminated, is more favourable than it is in patient in whom the underlying disease process is advanced enough to the point of producing heart failure (Table 19.1).

TYPES OF HEART FAILURE

The different types of heart failures are classified under the different headings. But

Table 19.1: Causes of heart failure

Primary	Secondary
Diseases primarily affecting the myocardium (PUMP)	Diseases of other cardiac and circulatory components except myocardium leading to secondarily myocardial failure
Causes	**Causes**
1. Ischaemic heart disease: Most common and very serious disease of the heart. It leads to myocardial damage, fibrosis or infarction.	1. Defects in control mechanism of heart, e.g. a. Valvular heart diseases b. Cardiac arrhythmias
2. Inflammation and toxic degeneration of myocardium—myocarditis	
3. Infiltration of myocardium fatty infiltration, amyloidosis, etc.	2. Defects in circulatory components, e.g. a. Systemic hypertension
4. Cardiomyopathies: a. Primary b. Secondary due to beri-beri, alcoholism, thyroid abnormality, etc.	b. Chronic lung diseases causing pulmonary hypertension. Both a and b cause increased cardiac work load.

↓
Loss of myocardial efficiency
↓
Initiation of compensatory mechanism
↓
More myocardial workload
↓
Further myocardial damage and loss of efficiency
↓
Failure of compensatory mechanism
↓
Heart failure manifested

this different classification of heart failure under different headings is only useful in its early pathophysiological course. Because late in the course of failure the difference between them often becomes blurred. The classification are :

Acute versus Chronic Failure

This two broad classification of heart failure depends on the suddeness of the onset or the rate of development of it. With this, the causative factors for their development and the effects of these two types of failure are also different. The acute heart failure develops instantaneously within hours to few days without giving any time for compensatory mechanism to develop. But, the chronic heart failure takes weeks or months to develop with the full blown compensatory pictures. The main causative factor of acute heart failure is acute coronary arterial occlusion with infarction and/or arrhythmia. The other aetiologies of acute heart failure are pulmonary embolism, acute toxic myocarditis, acute rise of BP (malignant hypertension), etc. On the other hand, chronic heart failure is the consequence of chronic hypertension, chronic valvular diseases, chronic lung diseases, chronic anaemia, myocardial fibrosis, etc. In acute conditions the system does not get enough time for the compensatory mechanism to develop. So, the patient suddenly present with acute symptoms and signs of failure without hypertrophy of myocardium, dilatation of cardiac chambers and systemic oedema, etc. which are found as compensatory mechanism. Whereas in chronic heart failure, compensatory mechanism has got time to develop with full force. So, there is always the presence of myocardial hypertrophy of atriums and/or ventricles, dilatation of cardiac chambers, chronic systemic venous congestion, oedema, etc.

Actually, the acute and chronic heart failure are the two opposite ends of a spectrum of a single disease. But, they merge with one another by the treatment procedures or the natural compensatory processes which is shown in Figure 19.1.

Systolic versus Diastolic Failure

In systolic heart failure there is impairment of myocardial contractile function during systole leading to reduction in stroke volume, inadequate ventricular emptying and gradually cardiac dilation. There is no abnormality of venous return and ventricular filling during diastolic period of cardiac cycle (preload). A decreased ejection fraction with normal preload diagnosed by end diastolic ventricular volume within normal limit is the hallmark of ventricular systolic failure. So, measuring the ventricular ejection fraction via echocardiography provides the quantification of severity of ventricular systolic function. An ejection fraction of less than 0.45 is often viewed as the evidence of ventricular systolic dysfunction. The example of systolic heart failure are IHD, cardiomyopathy, myocarditis, etc. In IHD, there is gradual loss of the number of myocyte, leading to localised defects in ventricular wall motion and impaired systolic contraction. Myopathies, especially the idiopathic dilated cardiomyopathy results in global ventricular

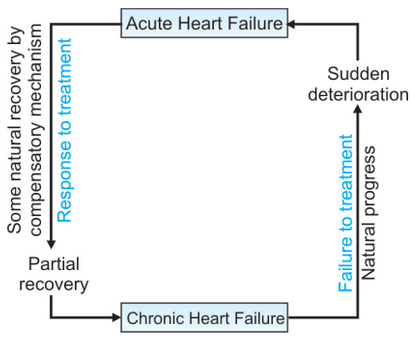


Fig. 19.1: Acute versus chronic failure

systolic dysfunction. Systemic hypertension, cardiac valvular disease, etc. also may produce systolic failure due to the chronic presence of increased afterload and gradual damage of cardiac muscle fibres.

But, they gradually produce the diastolic failure due to their subsequent effect, causing ventricular hypertrophy and leading to filling defect. However, actually in diastolic heart failure there is impaired relaxation and defect in filling of ventricle, leading to elevation of end diastolic ventricular pressure at any given diastolic volume or preload of the ventricle. The Failure of relaxation of ventricle in diastolic failure can also be caused by stiffened and/or thickened ventricle which impaired the filling of it. With diastolic heart failure, the ventricle has decreased compliance and can not adequately be filled up during diastolic period. Examples of diastolic heart failure are restrictive cardiomyopathy, infiltrative condition of heart such as amyloidosis, myocardial oedema, hypertrophic cardiomyopathy, constrictive pericarditis, ventricular hypertrophy due to essential hypertension or aortic stenosis, etc. The symptomatic congestive heart failure with normal ventricular systolic function is most likely due to diastolic dysfunction. In many patients cardiac hypertrophy and dilatation, i.e. diastolic and systolic failure can also coexist. Here, the ventricle both fills and empties abnormally.

Though, the systolic heart failure may result primarily from the abnormality of heart muscle such as in cardiomyopathy, but it may also result secondarily from the chronic excessive cardiac work load such as in hypertension or valvular heart disease. In ischaemic heart disease the systolic heart failure results from the loss in quantity of normally contracting myocardial cells.

The congestive heart failure is a condition which is coupled with multiple etiologies. These etiologies may be described as:

i. Abnormality in cardiac contraction (systolic heart failure, e.g. dilated cardiomyopathies),
ii. Abnormalities in diastolic filling (diastolic heart failure, e.g. restrictive cardiomyopathy, hypertrophic cardio-myopathy, constrictive pericarditis, cardiac tamponade),
iii. Pressure overload (afterload abnormalities, e.g. severe hypertension, aortic stenosis etc). Here the systolic and diastolic dysfunction work together. In acute form of hypertension the systolic failure is the cause. But, in chronic hypertension diastolic failure due to impaired filling for hypertrophy and systolic failure due to ischaemia caused by hypertrophy coexist.
iv. Volume overload (mitral regurgitation, aortic insufficiency).

High Output versus Low Output Failure

As the name signifies, the high output heart failure means there is an elevated cardiac output and the low output heart failure means there is decrease in cardiac output. The high output heart failure is seen in patient with hyperthyroidism, anaemia, pregnancy, beriberi, atriovenous fistula, transfusion overload, etc. In high output heart failure, though the cardiac output is high, still it is insufficient to maintain the body requirement. So, the heart has to work more and more to meet the tissue requirement and ultimately it fails like a tired horse.

On the contrary, the low output heart failure due to systolic or diastolic causes is seen in patient with ischaemic heart disease, hypertension, dilated cardiomyopathy, valvular diseases, pericardial diseases, etc.

In low output failure the A-V O_2 difference is widened, but in high output failure the A-V O_2 difference is normal or low.

Left Sided versus Right Sided Heart Failure

In human body, the cardiovascular system consists of two circulations, situated in series where the right and left heart act both as a pump in the connecting link for each of the series. The right ventricle acts as pump for the pulmonary circulation and the left ventricle acts as pump for the systemic circulation. The pulmonary circulation is the low pressure system. In it, the mean systolic arterial pressure is 15 mm of Hg and the pressure gradient between pulmonary artery and vein is 8 mm of Hg. Whereas, the systemic circulation is a high pressure system. In it, the mean systolic arterial pressure is 120 mm of Hg and the pressure gradient between the systemic artery and the vein is 90 mm of Hg. The ratio between the right ventricular mass with its coronary blood supply and the left ventricular mass with its coronary blood supply is 1:4.

The right-sided heart failure is referred to the conditions when the right ventricle fails to pump out the blood in the pulmonary circulation and the blood accumulates in and behind it. The causes of the right ventricular failure are :

i. Lung diseases, causing pulmonary hypertension such as emphysema, fibrosis, COPD, etc.
ii. Some form of cardiac valvular diseases, e.g. pulmonary stenosis, mitral stenosis, etc.
iii. Some congenital heart diseases with left to right shunt.
iv. As a consequence of left ventricular failure (Table 19.2).

The left-sided heart failure is referred to the conditions when the left ventricle fails to pump out the blood in the systemic circulation and the blood accumulates in and behind it. The causes of the left ventricular failure are :

i. The weakness of muscle of left ventricle due to IHD,
ii. Excessive workload due to systemic hypertension,
iii. Some valvular diseases such as aortic stenosis, mitral incompetence, etc.
iv. Some congenital heart diseases with right to left shunt.

The consequences or the effects of right or left-sided heart failure are mainly due to the low output and backward pressure.

Table 19.2: Causes of heart failure

1. Reduced ventricular contractility:

   Myocarditis, cardiomyopathy, IHD, myocardial infarction.
   Main features: Gradual ventricular dilatation, impaired ventricular wall motion.

2. Ventricular inflow obstruction :

   Mitral stenosis, tricuspid stenosis, constrictive pericarditis, myocardial fibrosis and other disorders that causes stiff myocardium (e.g ventricular hypertrophy).
   Main features: Small vigorous ventricle → dilated hypertrophied atrium.

3. Ventricular outflow obstruction :

   Hypertension and aortic stenosis (left heart failure), pulmonary stenosis, pulmonary hypertension (right heart failure).
   Main features: Concentric ventricular hypertrophy → try to maintain normal output → secondary changes in myocardium → ventricular dilatation.

4. Ventricular volume overload :

   Mitral and aortic reguritation (LV overload), pulmonary and tricuspid regurgitation (RV load), ASD, VSD, increased metabolic demand (high output).
   Main features: Hypertrophy and dilatation of ventricle → maintain normal output → secondary changes in myocardium → impaired contractility → dilatation of ventricle.

5. Arrhythmia:

   Atrial fibrillation, severe tachycardia, complete heart block.

In right-sided heart failure the low output to lungs from right-ventricle is usually not significant unless the right ventricular failure is a sequel to the left ventricular failure. On the other hand, due to backward pressure in RV failure the overfilling of right atrium, systemic veins and the capillaries produces the systemic oedema. Cyanosis in RV failure is the result of excess reduced haemoglobin in systemic capillaries and venules, but not due to the defective oxygenation at lungs. The measurement of pulmonary artery pressure is very important for the diagnosis of this two type of heart failure. The increase in pulmonary artery pressure may be the cause of RV failure or may be the effect of LV failure. But, in most of the cases the increased pulmonary artery pressure is due to the LV failure leading to the RV failure (combined failure). In mitral stenosis, RV failure is caused by this mechanism, but without LV failure. In chronic pulmonary diseases pulmonary hypertension and RV failure is the cause of death. In pulmonary stenosis, there is isolated RV failure which later leads to LV failure. Thus, the distinction between the right and left ventricular failure is valid and certainly useful from some clinical point of view.

However, when the heart failure exists for long time, then such classification of failing heart may no longer exist. For example, patient with long standing aortic valve disease may have ankle oedema, congestive hepatomegaly late in the course of this disease, showing the features of RV failure even though the abnormal haemodynamic burden initially was placed on the left ventricle. This occurs in part because of the secondary pulmonary hypertension and resultant right-sided heart failure arising from left-sided heart failure. But, this is also because of the retention of salt and water, characteristic of all forms of heart failure. On the other hand, the muscle bundles comprising both the ventricles are continuous and both the ventricles share a common wall—the intraventricular septum. So, failure of one of the ventricle precipitates the failure of another. Also, the biochemical changes that occur in heart failure and the factors that are involved in the impairment of myocardial function such as norepinephrine depletion and alterations in the activity of myosin ATPase, occur in the myocardium of both the ventricles, regardless of the specific chamber on which the abnormal haemodynamic burden is placed initially.

Backward versus Forward Heart Failure

The concept of backward heart failure indicates that one or other ventricle fails to discharge its full contents. As a consequence, the pressure on the atrium or venous system behind the failing cardiac chamber rises and by the result of which retention of sodium and water occurs. As a consequences of the elevation of systemic venous and capillary pressure, fluid transudates into the interstitial space. In contrast, the concept of forward heart failure indicates that one or other ventricle discharge inadequate blood into the arterial system. As a consequence, there is also salt and water retention due to diminished renal perfusion, excessive proximal tubular Na^+ reabsorption and excessive distal tubular water reabsorption through the activation of renin-angiotensin-aldosterone system.

A rigid distinction between the backward and the forward heart failure is not possible. Because, both the above explained mecha-nism appear to operate in varying extents at a given time in most of the patients with both of these type of heart failure. For example, in case of massive left ventricular infarction stroke volume, cardiac output and blood pressure is suddenly reduced due to myocardial damage which is manifested as forward failure and then the patient may succumb to acute pulmonary oedema which is a manifestation of backward failure.

COMPENSATORY MECHANISM IN HEART FAILURE

Before the development of signs and symptoms of heart failure, the myocardial reserve comes forward into action to increase or maintain the circulation of blood and to fulfil the increased or normal tissue O_2 demand. This myocardial

reserve comes forward by three different mechanisms which are called the compensatory mechanisms. These are: increased in pumping rate or heart rate, dilatation of ventricular chamber executing Starling law (dilatation of atrial chamber are ignored here) and hypertrophy of the musculature of ventricle executing increased contractility. In heart during pathological strain, all these three compensatory mechanisms come into action and try to cope for the considerable derrangement. This compensatory mechanism is mediated through activation of sympathetic and renin-angiotensin-aldosterone system (Fig. 19.2).

Heart Rate

Heart rate is an important determining factor of cardiac output because Cardiac output = Heart rate × Stroke volume. When stroke volume is reduced, then with increased heart rate cardiac output is maintained. This increase in heart rate is performed by the increase in activity of sympathetic system due to reduced cardiac output through baroreceptors, situated in the different parts of the body. Again this chronic long standing increased sympathetic activity gradually further deteriorates the ventricular function (discussed later) and accelerates the failure. So, what is beneficial and compensatory now, will be harmful later.

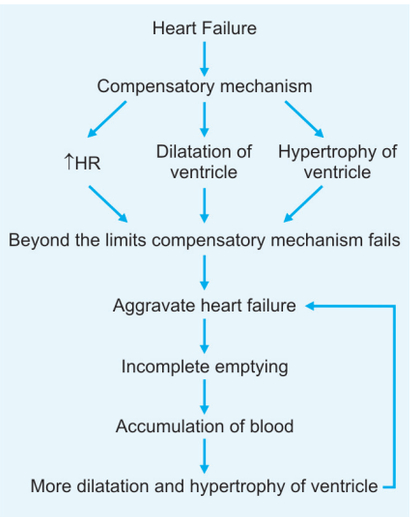


Fig. 19.2: Compensatory mechanism of heart failure

Dilatation

Under physiological condition and within a limit the volume of the ventricular chamber at the end of the diastole influences the pumping or contractile force of the ventricular musculature. The larger will be the chamber size, of ventricle due to filling by blood in diastole the longer will be the length of the ventricular muscle fibre before contraction. Again the longer will be the muscle fibre length, the greater will be the contractile force. This is called the Starling law. In this way the heart will try to maintain CO to its normal value before going to fail. Thus, the conditions where the Starling law mainly comes into action are early stages of valvular incompetence, valvular stenosis, fluid over load or other condtions where the venous return or regurgitation starts to increase. In the later stages when the end diastolic ventricular volume and the subsequent stretching of ventricular muscle fibre increases more and goes beyond the physiological limits, then the ventricular chamber starts to dilate permanently. The best example of this ventricular dilatation is valvular incompetence. In aortic incompetence the ventricular chamber dilates, because it has to accommodate the regurgitant blood from aorta as well as the normal input from the atrium. In valvular stenosis, the ventricular chamber also dilates because it has to accommodate the residual blood from present contraction and as well as from the normal input.

Hypertrophy

Ventricular hypertrophy is the another mode of compensatory mechanism of heart failure where the increase in number of muscle fibre comes into action and is able to deal with the greater workload. The only pure form of ventricular hypertrophy is best seen during the increased afterload. Left ventricular hypertrophy is most common in essential hypertension and aortic stenosis. Right ventricular hypertrophy is seen in pulmonary stenosis, pulmonary hypertension due to chronic lung diseases and also in mitral valve disease which secondarily causes pulmonary hypertension. But in clinical scenario, the both hypertrophy and dilatation come into action in different combination with their different magnitude to compensate the failure accompanying by the increased heart rate or not.

Failure of compensatory mechanism

The increased cardiac efficiency, deri-ved from all the three compensatory mechanism is limited. Beyond this limit, serious deficiency of compensatory mechanism ensures failure with definite signs and symptoms. Heart rate increases mainly in expense of duration of diastole. So, when the heart rate increases above 160 to 180/minute, then the period of diastole becomes very much shorter and ventricular filling is severely jeopardised and cardiac output does not increase. Similarly, Starling law also works within a physiological limit (plateau of the curve), beyond which further dilatation of ventricle or the stretching of muscle fibre does not increase the force of contraction. Then, the residual blood gradually accumulates in chamber which further helps in dilatation of ventricle and failure. Thus a vicious cycle sets up. Hypertrophy also fails to compensate beyond its maximum limit when the muscle mass has outgrown than its necessary blood supply, causing impairment of supply of nutrients, impairment of chemical and neural stimuli and inotropic activity. All these lead to further heart failure.

The effects of heart failure are principally seen in the peripheral organs. These are due to hypoxia and/or venous congestion. Hypoxia is well-exemplified in the acute form of left ventricular failure, where the cerebral function is seriously disrupted with transient loss of consciousness. In

chronic form of heart failure, the weakness and fatigue (which are so common symptoms) are probably the effects mainly of chronic hypoxia. But damage to organs due to chronic hypoxia is more difficult to define in chronic heart failure. This is because the effects of venous congestion and water retention in chronic heart failure are added to compensate the impaired circulation causing hypoxia. Venous congestion is responsible for oedema. Breathlessness or dyspnoea which is almost a constant feature of heart failure is essentially due to venous congestion and fluid retention within the lungs.

DETERMINANTS OF VENTRICULAR FUNCTION

Ventricular function is determined mainly by the three principle cardiac parameters. These are: Cardiac output, ejection fraction and ventricular end-diastolic volume or pressure.

Cardiac Output

The main single function of heart is to eject blood. It is measured in litre/minute and is the product of stroke volume and heart rate. Stroke volume is again determined by venous return (preload), myocardial contractility (force-velocity curve), afterload, myocardial size (hypertrophy and dilatation), wall motion abnormalities and valvular dysfunction. In addition, any alterations in sympathetic nervous system activity and humeral mediated response control the cardiac output. In the presence of mild heart failure, the resting cardiac output may be normal or adequate for the resting tissues, without any signs and symptoms of heart failure but unable to meet during stress. Whereas in severe heart failure, the resting cardiac output is even inadequate for resting tissues. When the cardiac output does not increase in heart failure corresponding with the demand of O_2 by tissues, then the usual O_2 extraction from blood by the peripheral tissues increases and lowers the O_2 content in the venous blood, producing an increased arterio – venous O_2 tension difference [$P_{a\text{-}v}$ O_2].

Venous return (Preload)

At any fixed level of contractile status of the ventricle (i.e. contractility) and afterload, the cardiac performance is profoundly influenced by the ventricular end diastolic fibre length or the end diastolic volume (EDV) which is closely related to the end-diastolic pressure (EDP). This end diastolic pressure or indirectly the end diastolic ventricular volume is called the preload. So, the terms such as EDV, EDP, venous return and preload are all interchangeable. Therefore, the cardiac performance is governed by the Frank-Starling law or principle. This Frank-Starling principle dictates the relationship between the initial fibre length of the muscle fibre of ventricle and the tension or force of contraction developed within it. It means that the stroke volume due to more forceful contraction of ventricular is increased when the tension developed in the muscle fibre before contraction is increased which is again increased when the resting length of that muscle fibre (or volume of ventricle) due to increased filling is increased. Therefore, preload is the intraventricular pressure which is closely related to the intraventricular volume at the end of the diastole and governed by the Starling law. On the otherhand, the other major determinants of ventricular preload are: Total circulating blood volume, distribution of blood volume in different organ and atrial contraction.

Total circulating blood volume

During severe haemorrhage or in hypovolaemic shock or in any other conditions where vasodilation occur, then there is absolute or relative reduction in circulating blood volume. It causes decrease in venous return → decrease in ventricular end diastolic volume (preload) → decrease in ventricular end diastolic pressure → decrease in length of ventricular muscle fibre → decrease in tension of muscle fibre before contraction → decrease in force of contraction → decrease in stroke volume → decrease in cardiac output for a given heart rate.

Distribution of blood volume

For any given blood volume the ventricular end diastolic volume or pressure which determine the cardiac output is influenced by the distribution of total blood volume between the intra- and extra thoracic compartments.

This distribution of total blood volume between the intra and extrathoracic compartment in turn is influenced by the following factors:

i. *Body position*: Upright position augments the extrathoracic blood volume and reduces the preload.
ii. *Intrathoracic pressure*: Increased intrathoracic pressure impedes the venous return and thus reduces the end diastolic ventricular volume and stroke volume, such as during valsalva manoeuvre, intense coughing, IPPV, etc.
iii. *Intrapericardial pressure*: During increased intrapericardial pressure such as in cardiac temponade, there is interference for cardiac filling and reduction of stroke volume.
iv. *Venous tone*: The smooth muscles of the walls of the veins respond to the variety of neural and humoral stimuli and control venous tone which in turn control the venous return, preload and cardiac performance, i.e. cardiac output.

Atrial contraction

Atrial contraction helps in ventricular filling and is of particular importance in patients with concentric ventricular hypertrophy. So, loss of atrial systole such as in atrial fibrillation tends to reduce the ventricular filling. Thus, the ventricular end diastolic volume and pressure (preload) and in turn the stroke volume is reduced.

Thus, now we have come to the conclusion that for all the striated muscle fibre

including the cardiac muscle fibre, the force of contraction depends on the initial length of the muscle fibre. The optimum sarcomere (cardiac cell) length associated with the most powerful contraction of the muscle fibre is 2.2 µm. At this length the actin and myosin are situated in such a fashion that they are able to provide the greatest area of their interaction and at this length the myofilaments are maximally sensitive to Ca^{2+} ion. When the sarcomere length is increased to 3.65 µm, then the thin actin filaments are entirely withdrawn from the myosin filament and no tension can be developed. Similarly, when the sarcomere are shorter than 2 µm, then the thin actin filaments will pass over one another and doubly overlapes. So, it reduces both the sensitivity of Ca^{2+} to the contractile sites and the capacity of force to develop. Therefore, the relation between the initial length of cardiac muscle fibres and the subsequent development of force is of prime importance for the functional integrity of myocardium which is stated by the Frank-Starling law.

Myocardial Contractility or Inotropic State of Ventricle (Force-Velocity Curve)

The state of mechanical contractility of all the striated muscle fibres can be expressed by relation between the velocity or the rate of shortening and the development of force during contraction within the muscle (Fig. 19.3).

The maximum velocity of contraction of muscle is written as V_{max} and in the presence of catecholamines when the inotropic state of heart is increased, the V_{max} will also increase. The contractility also depends on the intracellular Ca^{2+} concentration during systole and other neural, humoral and pharmacological factors. On the other hand, the myocardial contractility is depressed due to anoxia, acidosis, depletion of catecholamine stores and loss of functioning muscle mass as a result of ischaemia and infarction. Most anaesthetic and antiarrhythmic agents decrease myocardial contractility. Alternatively, the V_{max} will decrease when the myocardial contractility is impaired due to some factors which are responsible for heart failure. As for example, volatile anaesthetics decrease V_{max} and this effect is additive to the decreased contractility in the presence of heart failure. In clinical practice, the rate of decrease or increase of intraventricular pressure indicates the decrease or increase of V_{max} and is used as an important guide for the understanding of the inotropic state of heart.

At any given ventricular end-diastolic volume or pressure (preload) a number of factors described below determine the state of myocardial contractility or V_{max} and the level of ventricular performance, reflecting the change of ventricular function curve. All these factors act by modifying the myocardial force-velocity relation or curve and by altering the concentration of Ca^{2+} in the vicinity of the myofilaments which in turn trigger the cross-bridge between the actin and myosin.

These factors are :

i. *Adrenergic nerve activity*: Normally norepinephrine is released from the adrenergic nerve endings in the heart. Its action on the β-adrenergic receptor in the myocardium depends on the adrenergic nerve impulse traffic. This factor is most important for the myocardial contractility under physiological conditions.

ii. *Circulating catecholamines*: After adrenergic nerve stimulation of adrenal medulla, it releases catecholamines which reach the heart and augments the myocardial contractility.

iii. *Force-frequency relation*: The contractility of the normal (but not the failing) heart is augmented by the increase in frequency of adrenergic impulse.

iv. *Exogenously administered inotropic agents*: All inotrops improve the myocardial force-velocity relation and is used to stimulate the ventricular performance.

v. *Pharmacological depressants*: These incorporates calcium channel blocker, β-blockers, lignocaine, procainamide, etc.

vi. *Physiological depressants*: Hypoxia, ischaemia, acidosis electrolyte imbalance, etc. acting either singly or in combination depress the myocardial force-velocity curve or contractility and left ventricular performance at any given ventricular end-diastolic volume.

vii. *Loss of myocytes*: Ventricular performance or stroke volume is also depressed at a given end diastolic volume when there is loss of some myocardial cells as in myocardial ischaemia (transient loss), infarction

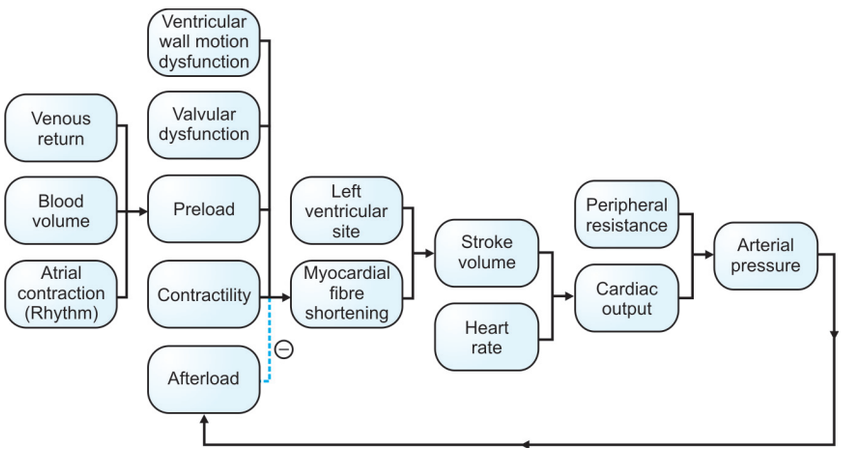


Fig. 19.3: Schematic representation of interactions among the various components that regulate the cardiac activity. Broken line represents an inhibiting effect

(permanent loss) and apoptosis (programmed cell death – can cause scattered loss of myocytes and when sufficiently widespread can impair ventricular function and cause heart failure), etc.

viii. *Intrinsic myocardial depression*: The fundamental mechanism, responsible for depression of myocardial contractility in most cases of chronic heart failure which is secondary to prolonged ventricular overload or cardiomyopathy is still unknown. It is now apparent that in this condition inotropic state of individual surviving myocytes is depressed and as a consequence the ventricular functional curve at any given ventricular preload and afterload is lowered.

Ventricular Afterload

Like venous return (preload) and inotropic state (contractility) of heart, cardiac output also depends on the afterload. But, it has negative effect on the cardiac output or stroke volume. In a contracting heart afterload is commonly equivalent to the mean aterial BP which produce impedance to ejection. At a given level of preload and myocardial inotropic state, the stroke volume or cardiac output is inversely related to the afterload i.e the load that opposes the shortening of the myocardial fibres (Fig. 19.4).

Due to any physiological cause (such as tension, anxiety, etc.) an increase in arterial pressure induced by vasoconstriction augments the afterload which opposes the myocardial fibre shortening and reduce the stroke volume and thus normalise the arterial pressure to the previous level (compensatory phenomenon). In essential hypertension, this physiological control is lost and the arterial pressure is not normalised by the previously described compensatory mechanism.

With age myocardial contractility is impaired, cardiac output falls and ventricle dilates. Then afterload or arterial pressure

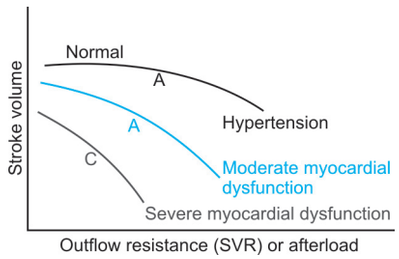


Fig. 19.4: The relationship between the stroke volume and the ventricular outflow resistance in patients with normal, hypertensive and systolic ventricular dysfunctional heart. Cardiac outflow resistance is a principle determinant of after load. An increase in SVR has little effect or stroke volume in normal heart (green curve A). In contrast, in patient with systolic ventricular dysfunction, an increase in outflow resistance or afterload is often accompanied by a sharp decline in stroke volume (curve B). With severe ventricular dysfunction the curve becomes more steeper (curve C). So, reduction of SVR, one of the component of outflow resistance, by vasodilator markedly increase the stroke volume in patient with severe myocardial dysfunction. The decrease of SVR is resulted by increase in stroke volume and subsequently prevent the fall of BP, which is caused by reduced SVR. Thus the increase in stroke volume offset the effect of reduced SVR

may rise as a result from the compensatory neural and humoral stimuli that occurs in response to a fall in cardiac output. This increased afterload may further reduce cardiac output while myocardial O_2 consumption are increased. This can set a vicious cycle.

There is some confusion regarding the afterload, systolic blood pressure and systemic vascular resistance. In the absence of any changes in size, shape, ventricular wall thickness and SVR, systolic blood pressure is usually taken as the afterload. Sometimes clinically SVR is considered as left ventricular after load which is calculated by the following formula:

$$SVR = 80 \times \frac{MAP - CVP}{CO}$$

MAP = Mean arterial pressure, CVP = Central venous pressure, CO = Cardiac output. The normal value of SVR is 1000 to 1500 dyn.s.cm^{-5}.

Right ventricular afterload is equivalent to the pulmonary vascular resistance (PVR). Like SVR, pulmonary vascular resistance also can be calculated by the following formula:

$$SVR = 80 \times \frac{PAP - PCWP}{CO}$$

PAP = Pulmonary artery pressure, PCWP = Pulmonary capillary wedge pressure. Normal value of PVR is 50 – 100 dyn.s.cm^{-5}.

Myocardial Size (Hypertrophy and dilatation)

Like the preload, contractility and afterload; the hypertrophy and dilatation of ventriclar wall also determine the amount of stroke volume. Initially, they represent the compensatory mechanism and help to maintain the cardiac output. But later they become the causes of further deterioration with reduction of output and heart failure. Hypertrophy helps to overcome the pressure overload. But it has limitations, because hypertrophied muscle functions at lower inotropic state than the normal cardiac muscle. Dilatations also leads to compensatory increase in output by Starling mechanism. But later both hypertrophy and dilatation is associated with increased O_2 requirement and decreased cardiac efficiency. Ventricular hypertrophy develops in response to chronic pressure overload such as aortic stenosis, systemic hypertension, mitral stenosis, pulmonary hypertension etc. Whereas the ventricular dilatation develops in response to volume overload such as aortic incompetence, mitral incompetence, etc.

Wall motion abnormalities

For adequate stroke volume, it requires all the ventricular muscle fibres to contract symmetrically at a time. But due to some abnormalities of muscle fibre such as ischaemia, hypertrophy, fibrosis, etc. all the portions of the ventricular walls do not contract symetrically and fully. So, ventricular emptying or output becomes impaired. The principal types of ventricular wall motion abnormalities found during echocardiography are:

akinesia (fully failure to contract), hypokinesia (decreased contraction), dyskinesia (paradoxical contraction). The severity of impairment of stroke volume depends on the size, number and the type of abnormality of the contracting areas of ventricular wall.

Valvular dysfunction

The types of valvular dysfunctions are stenosis, incompetence (regurgitation) or both and can involve any of the four valves. The stenosis of atrioventricular values such as the mitral and tricuspid valve causes reduction of stroke volume by reducing the preload, but not by altering the afterload. On the other hand, stenosis of aortic and pulmonary valve reduce the stroke volume by increasing the after laod which subsequently causes the compensatory ventricular hypertrophy, but not by altering the preload. Whereas the regurgitation of any valve decrease the stroke volume and increase the preload which subsequently causes compensatory ventricular dilatation.

Ejection Fraction

The ejection fraction is the ratio between the stroke volume and the end diastolic volume. It signifies the amount of blood filling the ventricle at the end of diastole, the amount of blood is stroked out and the amount of blood resides in the ventricle at the end of systole. Normally, the ventricle ejects 55 to 80% of its end diastolic volume during systole, resulting in ejection fraction of 0.55 to 0.8 (Fig. 19.5).

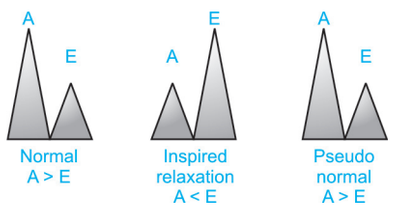


Fig. 19.5: Patterns of left ventricular filling, as recorded by diastolic doppler mitral flow velocities. A is the early diastolic filling and E is the late diastolic filling due to atrial contraction

During rest, even in the presence of heart failure, the value of cardiac output or stroke volume may be within normal limits due to compensatory mechanism, though it is depressed. Hence, the amount of stroke volume or cardiac output always cannot properly give the idea of cardiac performance. So, a more sensitive index of heart failure or cardiac activity is the ejection fraction than the cardiac output or stroke volume. In systolic heart failure, the ejection fraction is depressed, even when the stroke volume remain normal. It means with the increase of end diastolic volume (EDV) due to compensation, stroke volume may be normal, but the full amount of blood coming into the ventricle can not be ejected out and always some blood will remain in the ventricle after ejection. Alternatively, abnormally elevated EDV (normal value 70 ± 20 ml/m^2) in the presence of normal stroke volume signifies impaired left ventricular systolic function.

There are limitations in the isolated measurement of the stroke volume, cardiac output and ejection fraction for the assessment of the systolic performance of heart. The limitations are that these parameters are influenced strongly by some factors such as the ventricular filling conditions (preload) and afterload. Thus a decreased ejection fraction and low cardiac output may be observed in patients with normal ventricular function (contractility), but with reduced preload such as in hypovolaemia or with increased afterload as occurs during acutely elevated arterial pressure. So, the measurement of end systolic ventricular pressure and volume may be a useful index of ventricular performance than ejection fraction, since it is independent of both the preload and afterload. If the ventricular contractility declines, the end systolic ventricular presure and volume rises.

The diastolic performance is best assessed by continuously measuring the flow velocity across the mitral valve using the Doppler echocardiography. Normally, the flow velocity across the mitral valve is more rapid in early diastole (A) than during atrial systole (E). With impaired relaxation of the ventricle the rate of early diastolic filling declines while the rate of presystolic filling due to atrial contraction rises. With severe impairment of filling, the pattern is again pseudonormalised and early ventricular filling becomes more rapid.

End Diastolic Ventricular Pressure (EDP)

The end diastolic pressure of a ventricle runs parallel with the end diastolic volume (EDV) of it. It is also called the preload. It increases in the presence of heart failure. In the absence of failure, EDP can also increase in the presence of poorly compliant or stiff ventricle. In such circumstances, increase in EDP does not run in parallel to EDV of the ventricle which remains normal or decrease. The normal value of EDP of left ventricle and right ventricle are respectively 12 mm of Hg and 5 mm of Hg. In the absence of mitral valve disease the pulmonary artery pressure and the left atrial pressure is equivalent to left ventricular EDP. In ECG, manifestation of left atrial enlargement correlates well with the increased left atrial pressure and subsequently the increased left ventricular EDP (Fig. 19.6).

The analysis of heart as a pump has classically centered on the relation between the end-diastolic volume of ventricle (which is related to the length of the muscle fibres) and its stroke volume (Frank-Starling relation). The end diastolic pressure of the ventricle is sometimes used as synoname for end-diastolic volume. In the normal heart when the stroke volume remains within the limits, it correlates directly well with the end diastolic fibre length or volume of the ventricle (preload) and inversely with the arterial pressure (afterload). But, failed heart delivers a smaller than normal stroke volume from a normal or elevated end-diastolic volume.

So, the relation between the ventricular end-diastolic pressure and stroke work

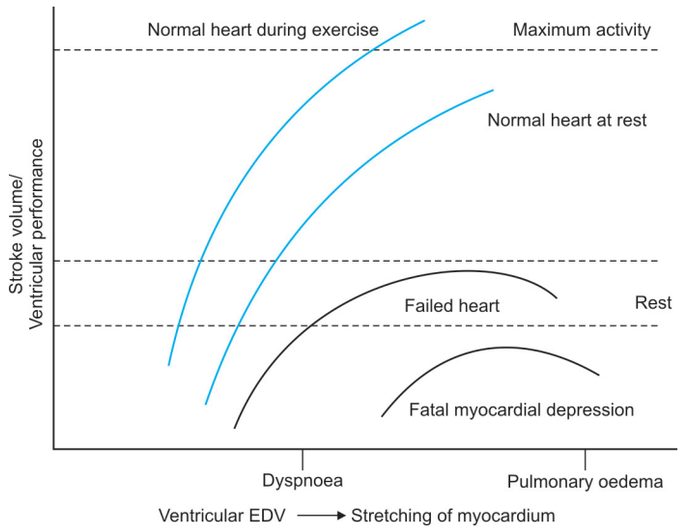


Fig. 19.6: Normal and abnormal ventricular function curve. It shows the inter-relations between the ventricular end diastolic volume (EDV) by stretching of myocardium and the contractile state of the heart. Ventricular EDV and resultant filling pressure are plotted on the abscissa and ventricular performance on the ordinate. Green lines indicate the performance or function of normal heart during rest and exercise. While red lines indicate the depressed performance of failing heart

(the ventricular function curve) needs a good and useful definition of contractility (i.e, the force of contraction) of the ventricle. An increase in ventricular contractility shifts the ventricular function curve upward and towards the left. It means, with increased contractility there is greater stroke volume at any level of ventricular end-diastolic pressure (or volume). While depression of contractility shifts the ventricular function curve to downwards and to the right. An example of shifting of the ventricular function curve to the left is exercise. During the adrenergic stimulation of myocardium, accompanying exercise, there is relatively little change in ventricular end-diastolic volume, while cardiac output, aortic flow velocity, stroke volume and the rate of ventricular pressure development are all augmented reflecting an increase in myocardial contractility.

Adrenergic stimulation of myocardium through adrenergic neurotransmitter such as norepinephrine has long been recognized. Norepinephrine activates the myocardial β-receptors and thereby increases the concentration of c-AMP. The latter in turn causes a more rapid forceful contraction by phosphorylating the Ca^{2+} channel in the myocardial sarcolemma and thereby enhancing the influx of Ca^{2+} into the myocyte which in turn, acts on the contractile apparatus.

ASSESSMENT OF VENTRICULAR FUNCTION

The assessment of ventricular function is divided into three parts: assessment of the systolic function, assessment of the diastolic function and assessment of the both ventricular systolic and diastolic function by ventricular function curve.

Assessment of Ventricular Systolic Function

The ventricular systolic function means the ventricular contractility and it is best assessed by the changes of intraventricular pressure over time during systole. It is designated as dP/dt. Measurement of this value is difficult and requires a high fidelity ventricular catheter. The usefulness of dP/dt is also limited. It may be influenced by preload and afterload.

Ventricular systolic function or contractility can also be assessed by the ejection fraction (EF), which is discussed before. In practice, this EF is the most commonly used parameter for assessment of contractility of ventricle by the formula:

$$EF = \frac{EDV - ESV}{EDV}$$

EDV = End diastolic volume, ESV = End systolic volume. The importance of this parameter is that it can be measured non-invasively by echocardiography. The limitation of importance of EF is that after a certain limit of increase in afterload, stroke volume decreases, but this reduction of EF does not indicate the reduction of contractility of ventricle, though output decreases.

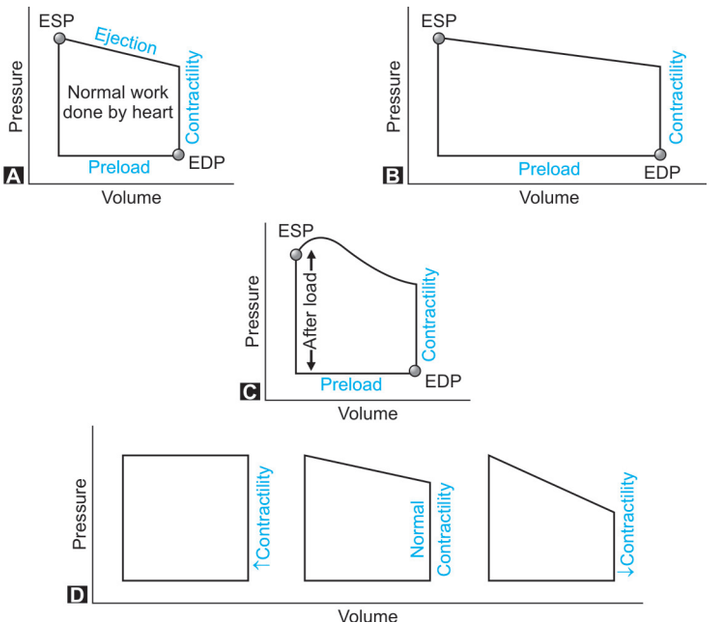
Assessment of Ventricular Diastolic Function

The ventricular diastolic function is also assessed by measuring the flow velocity of blood across the mitral or tricuspid value during ventricular diastole by Doppler echocardiography. The velocity of flow of blood across the mitral or tricuspid valve is measured or assessed by : Isovolumetric relaxation time (IVRT), the ratio of PEDF / PASF (PEDF = Peak early diastolic flow, PASF = Peak atrial systolic flow, discussed before) and the deceleration time of peak early diastolic flow (DTE) (Figs 19.7A to D).

The normal value of IVRT is 70 to 90 ms. It is greater than >100 ms means impaired relaxation and diastolic dysfunction of ventricle. The normal value of PEDF/ PASF ratio is 0.8 to 1.2. When this value is less than < 0.8, it also means impaired relaxation and diastolic dysfunction. The normal value of DTE is 150 to 300 ms, but the value above >300 ms means impaired relaxation.

Assessment of Ventricular Systolic and Diastolic Function by Ventricular Function Curve

The graph of Starling law which plots the stroke volume against the preload (described before) is useful for understanding



Figs 19.7A to D: Volume-pressure curve of single ventricular contraction
ESP = End system pressure, EDP = End diastolic pressure
A. Normal heart.
B. Increased preload with constant contractility (intraventricular pressure) and afterload.
C. Increased afterload with constant preload and contractility.
D. Increased and decreased contractility with constant preload and afterload.

the pathological states of heart and the effects of drug therapy on it. But the ventricular pressure volume curve is more useful than the previous curve. Because it dissociates the state of contractility from preload and afterload Fig. 19.7A shows the pressure volume curve of a normal ventricle. Fig. 19.7B shows the pressure volume curve with increasing preload where contractility and afterload (or intraventricular tension) is like normal. Fig. 19.7C shows the pressure volume curve with increasing afterload (or intraventricular tension) where preload and contractility is like normal heart. Fig. 19.7D shows the pressure volume curve with increased or decreased contractility where preload and afterload (or intraventricular tension during contraction) is constant.

PROBABLE THEORIES OF HEART FAILURE

There is no single unified theory which can explain the biochemical basis heart failure. Low-output cardiac failure (commonest form) due to coronary ischaemia, coronary atherosclerosis, hypertension, cardiomyopathy, valvular lesions, etc. is characterised by reduced external work done by heart in exchange of elevated O_2 consumption, i.e. the ratio of external work performed by heart and energy consumed by heart is depressed. The probable theories of heart failure are:

i. Myocardial energy which is stored in the form of creatine phosphate are depleted. Also, the activity of enzyme such as creatine kinase which is required for the shuttling of high energy phosphate between the creatine and adenosine diphosphate is reduced. So, it suggests that the reduction of myocardial energy reserves is one of the possible mechanism of heart failure.
ii. Another possible theory of heart failure is the reduction of myosin ATPase activity which could be caused by an alteration in the expression of troponin-T and/or of myosin light kinase2 activity. It could also be responsible for lowering the rate of interaction between the myosin and actin myofilaments.
iii. The third theory explains that in many forms of heart failure the delivery of Ca^{2+} to the contractile site is reduced, thereby impairing the cardiac performance. The abnormalities actually involved the sarcolemma, T-tubules or sarcoplasmic reticulum which is yet to be identified.

NEUROHORMONAL AND BIOCHEMICAL ADJUSTMENT OF HEART FAILURE

The reduction of stroke volume and the reduction of cardiac output in heart failure induce a series of neurohormonal adjustment, which may be considered to be the both adaptive (helpful) and maladaptive (not helpful). This neurohormonal adjustment involves the renin, angiotensin and aldosterone system and the adrenergic nervous system. In the face of reduction of CO though this changes are beneficial to maintain the CO and arterial perfusion pressure at the tissue level, but on the other hand, they increase the haemodynamic burden and O_2 consumption of the failing heart.

Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system is activated when CO declines due to heart failure. It causes the elevation of plasma level of renin, angiotensin I and II. Elevation of angiotensin II contributes to the excessive vasoconstriction and elevation of aldosterone which again lead to the retention of salt and water. All these compensatory changes are aimed to maintain the cardiac output and blood pressure. So, one of the principles of treatment of heart failure is the blocking of this system by ACE inhibitor or angiotensin II receptor blocker or by aldosterone antagonist.

Adrenergic Nervous System

The circulating norepinephrine level is markedly elevated in heart failure patient which reflects the increased activity of adrenergic nervous system. This increased adrenergic activity in one way is adaptive by supporting the ventricular contracti-lity in heart failure. In another way, it is maladaptive as the increased adrenergic activity increases the afterload by raising the vascular resistance and causing the further myocardial damage. This latter can be prevented by the cautious use of gradually increasing the doses of β-blocker (Fig. 19.8).

CONCLUSION

The density of the adrenergic receptor and therefore, the activity of norepinephrine on these cardiac adrenergic receptor (but not the circulating catecholamine or norepinephrine level) is reduced in heart failure. These changes leads to the reduction in the activity of adenyl α cyclase and lower the intracellular concentration of cAMP. The latter in turn reduces the activation of protein kinase and subsequently the phosphorylation of Ca^{2+} channel which then reduces the trans sarcolemmal Ca^{2+} entry and as well as the phosphorylation of phospholamban, a protein in the sarcoplasmic reticulum. Thereby it depresses the reuptake of Ca^{2+} by the latter. The changes in G-protein (or guanine receptor or GR), which make couple the β-receptor with the catalytic adenyl cyclase (which is responsible for the production of cAMP), may also occur in heart failure with increased inhibitory activity.

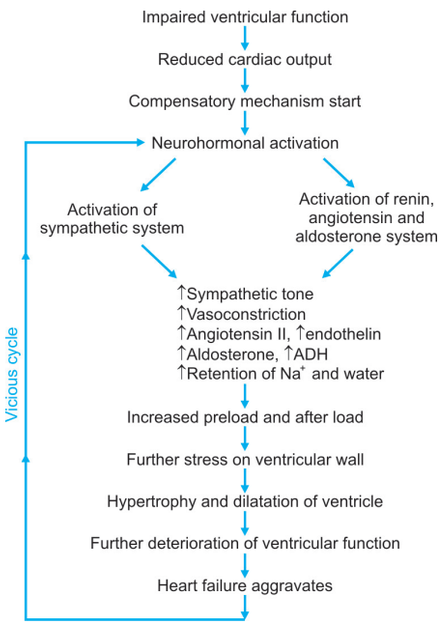


Fig. 19.8: The neurohormonal adjustment or compensatory mechanism of heart failure

Finally, we can tell that the basic problem of heart failure is the depression of myocardial contractility (or the force-velocity relationship) and the length tension curve (or the Starling law) reflecting the reduction of the contractile state of the myocardium. Usually, at rest the CO and ventricular performance is maintained within normal limits by an elevated ventricular end-diastolic volume and subsequently increased end-diastolic fibre length through the operation of Frank-Starling mechanism. This elevation of left ventricular preload is associated with elevation of pulmonary capillary pressure, contributing to dyspnoea experienced by patients with heart failure. During exercise the improvement of contractility of myocardium due to augmented adrenergic activity is attenuated by norepinephrine depletion and down regulation of the myocardial β-receptor which occur in severe heart failure. The factors that tend to augment ventricular filling during exercise in normal individual push the failing myocardium along its flattened part of the length tension curve. Although the left ventricle may perform somewhat better during exercise, but this occurs only as a consequence of an inordinate elevation of the ventricular end-diastolic volume and pressure, and therefore of the pulmonary capillary pressure. The latter intensifies dyspnoea and, therefore, plays an important role in limiting the intensity of exercise that the patient can perform. The left ventricular failure becomes fatal when the myocardial length tension curve is depressed to such a point at which the cardiac performance fails to satisfy the requirement of peripheral tissues, even at rest and/or the left ventricular end diastolic and pulmonary capillary pressure are elevated to levels that result in pulmonary oedema.

PHARMACOLOGICAL TREATMENT OF HEART FAILURE

The next part of this chapter will discuss the drug therapy of heart failure due to systolic and /or diastolic ventricular dysfunction. The systolic ventricular dysfunction due to idiopathic dilated or ischaemic cardiomyopathies is characterised by large dilated ventricular chamber. Contrary, the systolic failure due to infarction has the normal ventricular chamber. On the other-hand the diastolic ventricular dysfunction due to long standing hypertension, stenotic valvular disease or a primary hypertrophic cardiomyopathy generally leads to thickened hypertrophied poorly compliant ventricular walls with small ventricular volumes. In practice, many patients have both the abnormal haemodynamics, comprising of different degree of systolic and diastolic dysfunction. The treatment should, therefore, be according to the underlying pathophysiological process of the individual patient. So, the pharmacological treatment of heart failure can be described under two headings. The first heading describe the use of oral drugs in ambulatory patients. The second will describe the intravenously administered agents for the treatment of acute hospita-lised patients. We will only deal here the second heading. For the first heading dealing with only oral drug in an ambulatory patient suffering from chronic heart failure, you will have to consult any text book of medicine.

Primarily the treatment of any heart failure had three aims:

i. Removal of precipitating cause, e.g. treatment of hypertension, sepsis, etc.

ii. Correction of the underlying causes, e.g. mitral valvotomy, replacement of valve, etc.
iii. Control of the congestive acute heart failure state.

We will discuss here only the third component of the treatment of acute heart failure. This third component of the treatment again can be divided into three categories: (a) Reduction of cardiac work load, including both the preload and the afterload, (b) Control of excessive retention of salt and water and (c) Enhancement of cardiac contractility.

Diuretics

A variety of diuretic agents are available in practice and in patients with mild heart failure, almost all are effective. But, in patient with acutely decompensated heart with failure of sufficient severity, it is generally desirable to initiate an effective diuresis by using the intravenous doses of a loop diuretic. All the diuretics act by reducing the extracellular fluid volume or decreasing the ventricular diastolic filling pressure (preload). But usually they do not cause a clinically important reduction in CO except particularly in patient with very advanced heart failure. While, over treatment must be avoided, since the resultant hypovolaemia may severely reduce the preload and then CO and may impair the renal function. The examples of usual clinically used loop diuretics are fursemide, bumetanide, ethacrynic acid, piretanide and toresnide. They are extremely powerful and reversibly inhibit the absorption of Na^+, K^+, Cl^- through the renal epithelial cells of the thick ascending limbs of loop of Henle by inhibiting the specific protein, named the Na^+-K^+-$2Cl^-$ symporter. They depend for their adequate efficacy of action on adequate renal plasma flow and their proximal tubular secretion. Then, they are delivered to their site of action, i.e. the thick ascending limb of the loop of Henle through the lumen of renal tubule. These loop diuretics also induce renal cortical vasodilation and increase the rates of urine formation that may be as high as one-fourth of the glomerular filtration rate. These drugs also reduce the toxicity of medullary interstitial tissue by preventing the reabsorption of solute in excess of water through the thick ascending limb of the loop of Henle. The excessive use of loop of diuretics may also cause the development of hyponatraemia in heart failure patient. The increased delivery and absorption of Na^+ and fluid at the distal segment of nephron, i.e. distal and collecting tubule due to less absorption at the thick ascending limb of loop of Henle also markedly enhances the excretion of K^+, particularly in the presence of elevated aldosterone levels which is typically found in the case of heart failure.

While other diuretics loose their effectiveness when the blood volume is restored to the normal from higher levels, but the loop diuretics still remain effective despite the (Fig. 19.9) elimination of excessive amount of extracellular fluid volume. The major side effects of these loop diuretics

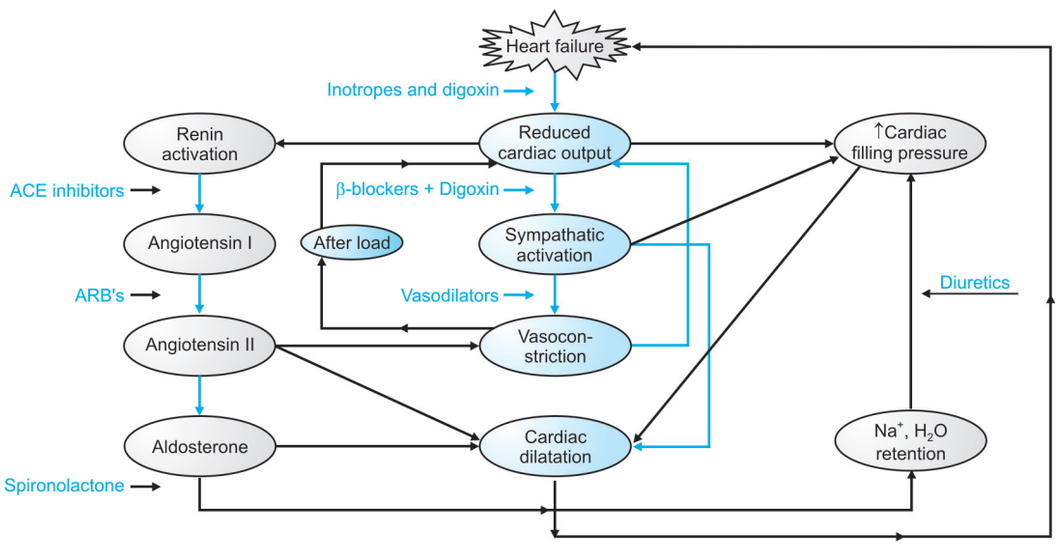


Fig. 19.9: The pathophysiological mechanism of heart failure and the different sites of action of different drugs used for its treatment. Initially heart failure is accompanied by compensatory (adaptive) neurohormonal response. It includes activation of sympathetic and renin-angiotensin-aldosterone systems. These responses initially help to maintain CV function by increasing systemic vascular tone and ventricular preload. But, with time decompensation (maladaptive) occur and the adaptive mechanism further helps to progress to the myocardial failure. Increased ventricular afterload (due to sympathetic vasoconstriction) and gradual cardiac dilatation (due to reduced cardiac output causing gradual elevated ventricular diastolic volume or filling pressure) cause a depression in systolic function. In addition, direct effect of epinephrine, norepinephrine and angiotension on the ventricular myocardium cause further dilatation and loss of contractile function. ACE = Angiotensin converting enzyme, ARB = Angiotensin receptor blocker

are due to their marked diuretic potency, which on rare occasions may result in contraction of plasma volume, circulatory collapse, reduction of renal blood flow, reduction of glomerular filtration rate and development of prerenal azotemia. The metabolic alkalosis and hypokalaemia produced by diuretics is due to large increase in the urinary excretion of Cl^-, H^+ and K^+ ions. Hyperuricemia and hyperglycemia are also sometimes observed in loop diuretics. These extremely effective loop diuretics are useful in all forms of heart failure, particularly in refractory condition and pulmonary oedema. They also produce diuresis in patient in whom thiazide diuretics and aldosterone antagonist, alone or in combination are ineffective (Table 19.3).

The loop diuretics may be administered as repetitive bolus doses which are titrated against the desired response or by constant infusion. The advantage of the latter approach is that the same total daily dose of diuretics, when given as a continuous infusion can result in a more sustained and continuous natriuresis due to the continuous maintenance of high drug levels within the lumen of renal tubules. A typical continuous furosemide infusion is initiated with 40 mg bolus IV injection, followed by a constant infusion of 10 mg/hour, with upward titration as necessary. When there is a poor response to diuretics due to reduced renal perfusion, then a short term administration of sympathomimetic drugs or phosphodiesterase inhibitors which act by increasing the CO may be necessary to achieve the response. Another useful approach for diuresis is the IV administration of dopamine at the so-called low renal doses (< 2 μg/kg/min) that can cause selective renal dopaminergic receptor stimulation and renal vasodi-latation. Therefore, it acts thereby causing a selective increase in renal blood flow without causing any systemic arterial and ven-ous constriction via α-adrenergic receptor stimulation which may occur at higher infusion rates of dopamine.

Table 19.3: Causes of resistance of diuretics in heart failure

1. Excess dietary Na^+ intake
2. Noncompliance
3. Decreased renal perfusion and glomerular filtration rate
   - (i) Hypotension or excessive intravascular fluid depletion.
   - (ii) Decline in cardiac output due to severe heart failure.
   - (iii) Aggressive diuretics and / or vasodilator therapy.
4. Primary renal pathology
5. NSAID agents

Thiazides and metolazone (thiazide related heterocyclics) diuretics are the agents of choice for the treatment of chronic ambulatory heart failure patient with severity of mild-to-moderate degree and when there is no contraindication of their use, e.g. hyperglycemia, hyperuricemia, hypokalaemia etc, or when complications are treated. When used alone, other diuretics such as spironolactone, amiloride and triamterene, etc. act as weak agent but they potentiate any thiazide and loop diuretics if they are already used. For heart failure with severe secondary hyperaldosteronism, spironolactone is very effective. In a very severe degree of heart failure which is refractory to common diuretics the combination of thiazides diuretics, loop diuretics and potassium sparing diuretics are also very effective.

Vasodilators

In a heart failure patient the left ventricular afterload is increased as a consequence of the several neural and humoral influences that tries to increase the BP by constricting the peripheral vascular bed for low CO as compensatory mechanism. These are due to the increased activity of adrenergic nervous system, increased circulation of catecholamines and increased activity of renin-angiotensin aldosterone system. In addition to the vasoconstriction the ventricular end-diastolic volume and end-systolic volume also rises in systolic heart failure. Vasoconstriction is a compensatory mechanism that tries to maintain adequate flow of blood to the vital organs. But this has no serious effect on cardiac function with normal heart, as for example hypovolaemia due to blood loss with increased sympathetic activities. But, on the other hand, in low cardiac output state due to impaired cardiac function, this vasoconstriction which increases the afterload may further reduce the CO and set a vicious cycle.

We know that afterload is a major determinant factor of cardiac output. With normal cardiac function moderate elevation of afterload does not reduce the cardiac output or stroke volume. But when the myocardial systolic function is impaired, then such increase in afterload can not maintain the stroke volume, instead it decreases. With the reduction of cardiac output there is increase in pulmonary capillary pressure leading to pulmonary congestion, oedema, dysponea, and all other signs and symptoms of heart failure. In heart failure, ventricle usually works at the peak flat portion of Frank-Starling curve. So, any additional increase in the afterload (aortic impedence) will reduce the stroke volume. Alternatively, the modest reduction of afterload in normal individual has no effect on stroke volume, but in patient with heart failure it tends to restore the stroke volume towards normal.

So, vasodilation and reduction of impedence to the left ventricular ejection i.e afterload is an important adjustment in the management of heart failure. This vasodilation is very helpful for patient with systolic heart failure. This approach is also helpful for diastolic failure by reducing the left ventricular end-diastolic pressure, left ventricular end diastolic volume and O_2 consumption, while raising the stroke volume and cardiac output, and causing only the modest reduction in systemic blood pressure. Vasodilator should not be used in patient with severe hypotension, because it may impair the tissue perfusion

and oxygenation which does not (Table 19.4) occur after a critical lower value of blood pressure in a hypertensive subject. When the chronic and acute heart failure patient is treated with vasodilators, then the cardiac output rises, pulmonary wedge pressure falls and a new steady haemodynamic state is achieved in which cardiac output increases and afterload decreases with no or only mild reduction of arterial pressure. Moreover, the reduction of elevated left ventricular end systolic pressure improves the subendocardial perfusion which further improves the myocardial contractility.

There are many available vasodilators which are used clinically. But they differ in their haemodynamic effects, site of action, duration of action and the mode of admininstration. Hydralazine, minoxidil and the alpha-adrenergic blocking agents (prazocin) act mainly on arterial system and increase the stroke volume. On the other hand, nitroglycerine and isosorbide dinitrate act mainly on the venous site of circulation and reduce preload. ACE inhibitors and nitroprusside are balanced vasodilators. They act both on the arterial and venous bed. Nitroprusside reduces the ventricular filling pressure by directly increasing the venous compliance and resulting in redistribution of blood volume from the central to the peripheral veins. It is also the most effective afterload reducing agent. It causes a fall in peripheral vascular resistance, as well as cause an increase in aortic wall compliance. These effects of nitroprusside decrease the left ventricular afterload, resulting in an increase in CO. Nitroprusside also dilates the pulmonary arterioles and reduces the right ventricular afterload. These combinations of reduction of preload and afterload by nitroprusside improves the myocardial function by reducing the wall tension, provided the blood pressure does not fall to the point where the diastolic coronary blood flow is compromised or there is no marked reflex increase in sympathetic nervous system tone causing tachycardia. Nitroprusside is particularly effective in patient with congestive heart failure due to mitral regurgitation or left to right shunt through the VSD. The increase in renal blood flow that accompanies an increase in CO, following initiation of administration of nitroprusside in patient with severe heart failure, may improve the glomerular filtration rate and increase the effectiveness of diuretics.

Nitroglycerine, like nitroprusside is also a potent vasodilator. But in contrast to nitroprusside, nitroglycerine is relatively selective for veins, particularly at low infusion rates. Thus, intravenous nitroglycerine is most often used in the treatment of acute heart failure when particularly decrease in ventricular filling pressure is desired. At higher infusion rates nitroglycerine also causes a decrease in the systemic and pulmonary arterial resistance, thereby decreasing the ventricular afterload.

Sympathomimetic Amines

The enhancement of cardiac contractility is the cornerstone of treatment of heart failure. Epinephrine, norepinephrine, isoprenaline, dopamine and dobutamine are the five sympathomimetic amines which are generally used to improve the myocardial contractility in various form of heart failure. Among them the dopamine and dobutamine are the most commonly used agents and effective in the management of heart failure, particularly in those patients who have undergone cardiac surgery, in some MI, shock, pulmonary oedema, etc. Their administration should also be accompanied by careful and continuous monitoring of ECG, arterial pressure, and if possible by PAWP (Fig. 19.10).

Table 19.4: Vasodilator drugs used to treat heart failure

Drug class	*Examples*	*Mechanism of action*	*Afterload reduction*	*Preload reduction*
ACE inhibitor	Captopril, enalapril, lisinopril	Inhibition of formation of angiotensin II	+ +	+ +
Angiotensin receptor blocker	Losartan, Candesartan	Blockade of anginotensin II receptor	+ +	+ +
Organic nitrates	Nitroglycerin, Isosorbide-di-nitrate	Nitric oxide (NO) mediated vasodilatation (nitric oxide)	+	+ + +
NO-donors	Nitroprusside	No-mediated vasodilatation	+ + +	+ + +
Direct acting on arterial smooth muscle	Hydralazine, Minoxidil	Unknown	+ + +	+
Phophodiesterase inhibitors	Milrinone, Amrinone	Inhibition of cAMP degradation	+ +	+ +
Ca^{2+} channel blocking drugs	Amlodipine, Nifedipine	Blocking of L-type Ca^{2+} channel	+ + +	+
Nonselective α-adrenergic receptors antagonist	Phentolamine	α-blocking vasodilatation	+ + +	+ + +
Selective α_1-adrenergic receptor blocker	Prazosin, Doxazosin	Selective α_1-blocking vasodilatation	+ +	+ + +
Vasodilating β/α_1 adrenergic receptor antagonist	Carvedilol, Labetalol	Selective β_1 and α_1 adrenergic receptor blockade	+ +	+ +

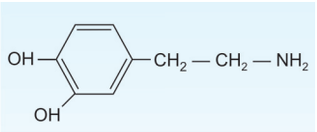


Fig. 19.10: Dopamine

Dopamine (3, 4, Dihydroxyphenyl Ethyl Amine)

It is an endogenous catecholamine and like dobutamine is a strongly positive inotropic agent which are most often used for the short-term support of circulation in advanced heart failure. Epinephrine, norepinephrine and isoprenaline are though strongly positive inotropic agent and useful in specific circumstances, but have little role in the treatment of most of the cases of severe heart failure.

Dopamine is a vary important natural central neurotransmitter and is an intermediate metabolic precursor for the synthesis of norepinephrine, epinephrine and other centrally mediated neurotransmitter. It possesses important intrinsic pharmacological properties. It is ineffective when administered orally, because dopamine is a substrate for both the MAO and COMT enzyme, present in the intestinal wall (Fig. 19.11).

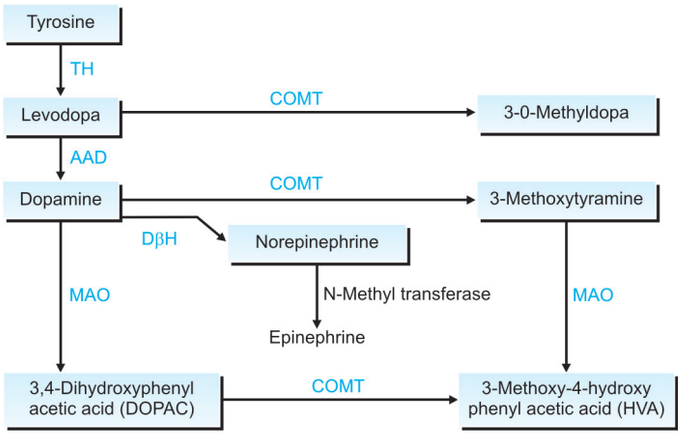


Fig. 19.11: Synthesis and metabolism of dopamine and levodopa. Levodopa is first synthesized from tyrosine which is transported into the cell by an active process present on the cell membrane. The conversion of tyrosine to levodopa is a rate limiting step and is catalysed by tyrosine hydroxylase (TH). Levodopa is then rapidly converted to dopamine by an enzyme, called aromatic amino acid decarboxylase (AAD). After that dopamine is taken up into the vesicles of dopaminergic nerve termjnals by transporter protein which can be blocked by reserpine. After its release in the synaptic cleft, the action of dopamine may be terminated by: (i) Reuptake which can be blocked by cocaine or (ii) Degradation by MAO or COMT enzyme. Metabolism of dopamine by MAO or COMT produces two metabolic products: DOPAC and HVA (Homovanillic acid). But in human beings, HVA is the primary product of metabolism of dopamine

Dopamine receptor

The action of dopamine is mediated by a family of dopamine receptors. Among them 5 subtypes of dopamine receptors are identified. These are designated as D_1, D_2, D_3, D_4, D_5. Of these the D_1 and D_5 receptor proteins have a long intracellular carboxy terminal tail and are the members of pharmacologically defined D_1 class. This D_1 class receptor stimulate the synthesis of intracellular second messenger, called cAMP and causes the hydrolysis of phosphatidyl inositol. The D_2, D_3 and D_4 receptor proteins share a common large third intracellular loop and are of the D_2 class. The D_2 class receptor inhibit the synthesis of cAMP as well as suppress the Ca^{2+} currents and activate the receptor operated K^+ currents.

All the dopamine receptors share the common structural features including the presence of seven α-helical segments capable of spanning throughout the cell membrane (Fig. 19.12). This structure identifies the dopamine receptors as the members of a large superfamily which includes other important receptors such as β-adrenergic receptors, olfactory receptors, etc. All the members of this superfamily act through the guanine nucleotide binding protein or G-protein and are discussed in more details in the autonomic nervous system chapter.

Cardiovascular effects of dopamine

Due to several distinct types of dopamine receptors and due to different affinity of dopamine to these receptors, the cardiovascular effects of dopamine vary with different doses. At low concentration (less than 2 µg/kg/min), the dopamine acts through its vascular D_1-dopaminergic receptors, especially in the renal, mesenteric and coronary beds. By activating adenyl cyclase and raising intracellular concentration of cAMP, D_1-receptor stimulation leads to vasodilation. So, infusion of dopamine in low doses increases the renal blood flow, GFR and Na^+ excretion. Thus, dopamine is often used in this small doses in the management of compromised renal function due to low CO in severe heart failure. At somewhat higher concentration (2 to 5 µg/kg/min), dopamine acts on β_1-adrenergic receptors and produce positive inotropic effect on the myocardium. In this dose dopamine also releases norepinephrine from the nerve terminals, and accounts for its effects on the heart. But, tachycardia induced by dopamine in this dose is less prominent than isoprenaline. At this level dopamine increa-ses systolic blood pressure, but has no effect on diastolic blood pressure and total peripheral resistance remains unchanged or reduce (probably because of the ability of dopamine to reduce regional arterial resistance in some vascular beds). At more higher concentration (5 to 15 µg/kg/min or higher), dopamine activates the vascular

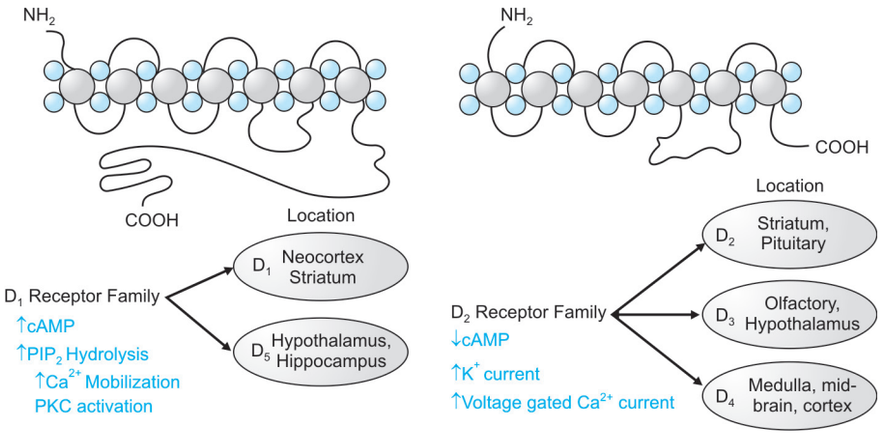


Fig. 19.12: Distribution and characteristic of different dopamine receptors

α_1-adrenergic receptor leading to peripheral arterial and venous constriction which sometimes may be desirable for the support of critically reduced arterial pressure. But this may further supress the ventricular systolic function, due to the increase in afterload.

As dopamine does not cross the blood-brain barrier readily, so it has no central effects, though there are specific dopamine receptors at the different area of CNS.

Precautions, adverse reactions and contraindications of dopamine

The adverse effects of dopamine is mainly attributable to excessive sympathomimetic activity of it. Tachycardia, anginal pain, arrhythmias, severe hypertension, headache, nausea and vomiting may be encountered during an infusion of dopamine. Hypovolaemia should be corrected by plasma, whole blood or appropriate fluids in shock patients before starting the dopamine infusions. Dopamine should be avoided in patients taking MAO inhibitors or tricyclic antidepressant compounds (Fig. 19.13).

Therapeutic uses and doses of dopamine

The indications where the dopamine is mainly used are: congestive heart failure with oliguria, low peripheral vascular resistance, cardiogenic shock, septic shock and during different cardiac surgeries.

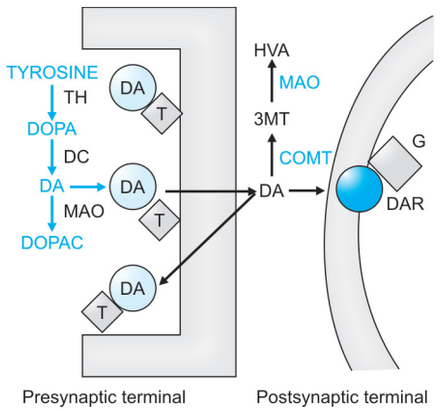


Fig. 19.13: The dopaminergic nerve terminal, where dopamine is synthesised from the precursor tyrosine by the sequential actions of the enzyme TH (tyrosine hydroxylase) producing DOPA (dihydroxy phenylalanine) and DC (decarboxylase) producing DA (dopamine). Dopamine is then transported into the storage vesicles situated in the presynaptic terminal by a transporter protein (T). Then, depolarization, entry of Ca^{2+} and release of dopamine by Ca^{2+} allows it to act on the postsynaptic dopamine receptor (DAR). Several distinct types of dopamine receptors present in the brain are discovered which explains the different action of it at different doses. The action of dopamine (DA) at the nerve terminal is terminated by sequential actions of the enzymes COMT and MAO or by reuptake of DA in the nerve terminal. DOPAC = Dihydroxyphenyl acetic acid

Initially, the dopamine infusion is usually started at a rate of less than 2µg/kg/min (low dose) and then gradually it is increased to 2 to 5 µg/kg/min (intermediate dose). The infusion rate of dopamine may be increased to 20 to 50 µg/kg/min or more as the clinical situation dictates. During the infusion of dopamine patients should be continuously monitored for the myocardial function, perfusion of vital organs, production of urine, arterial and venous pressure, ECG, etc. The reduction in urine output, tachycardia, development of arrhythmias indicate immediate termination of dopamine infusion. As the duration of action of dopamine is brief, so the rate of administration of it through infusion should be adjusted continuously to control the intensity of effect.

Usually an alteration of cardiac responsiveness to the catecholamines have been found in different stages of heart failure. So, the doses of infusion of sympathomimetic amines should be titrated according to the response of the patient. Increased sympathetic nervous system activity is observed in patient during the early part of congestive heart failure. At that stage, infusion of any β or dopa adrenergic agonist have been found to be toxic to the heart. Then, gradually the over expressions of β or dopa adrenergic receptor had lead to the dilated cardiomyopathy. After that a number of changes in β-adrenergic receptor signaling occur in myocardium in patient with long-standing heart failure. Decreased numbers and functioning of β_1-adrenergic receptor consistently have been found in chronic heart failure, leading to attenuation of β-adrenergic receptor mediated stimulation or positive inotropic response in the failing heart.

Dobutamine (Fig. 19.14)

The structure of dobutamine and dopamine is more or less same except a bulky aromatic substituent which is attached to the amino group in dobutamine. It is not a natural neurotransmitter, nor releases norepinephrine from the sympathetic nerve endings, and nor exerts their actions via dopaminergic receptors. The pharmacological effects of dobutamine are due to its direct effect on the α and β-adrenergic receptors. The

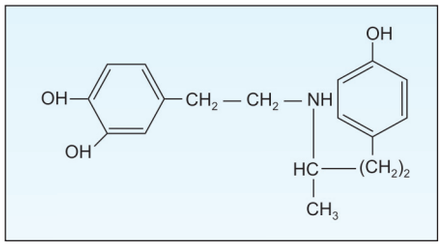


Fig. 19.14: Dobutamine

clinically used dobutamine is a racemic mixture of two enantiomers. The (−) isomer of dobutamine is a potent α_1-receptor agonist, causing marked pressure responses, whereas (+) isomer of dobutamine is a potent α_1-receptor antagonist, blocking the effect of (−) isomer (partial agonist). Thus, the mechanism of action of dobutamine is very complex. The positive inotropic action of dobutamine on myocardium is also due to its agonistic β_1-adrenergic effect. Here, the (+) isomer is about 10 times more potent than the (−) isomer of it.

In the peripheral vasculature, the α_1-adrenergic vasoconstrictive effect of (−) isomer of dobutamine is balanced by the partial antagonism of the α_1-receptor effect of (+) isomer and the vasodilatory effect is mainly due to the β_2-receptor stimulation by dobutamine. Thus, the net pharmacological effect of dobutamine is to increase the stroke volume and CO by positive inotropic action on myocardium (β_1-effect) and to decrease the systemic vascular resistance and venous filling pressure by both α, β effect. Dobutamine has no action on renal dopaminergic receptor, so it does not dilate the renal vessels. But the increase in renal blood flow and GFR by dobutamine is due to the increase in CO. Dobutamine causes no or little increase in heart rate. It has relatively more prominent inotropic effect than chronotropic effects on the heart. So, at doses that increase CO, there is little increase in heart rate than dopamine.

Dobutamine is used by infusion and is started with the dose of 2 to 3 µg/kg/min. Then, it is titrated upwards according to the patient's symptoms, and haemodynamic goals, which depends on the cardiac contractility, CO and peripheral vascular resistance. Depending on the vascular resistance and CO, the BP may increase, decrease or remains the same. In response to improved cardiovascular function by dobutamine, heart rate often declines due to withdrawal of reflex sympathetic tone. The measurement of PCWP and CO using pulmonary arterial catheter often allows the more effective use of dobutamine alone or in conjunction with other vasodilator and diuretics. However, continuous infusion of dobutamine over several days reduces its efficacy and it is due to the development of tolerance. When the tolerance develops to dobutamine after prolonged use, then it is necessary to switch over to an intravenous class III cyclic AMP phosphodiesterase inhibitory agent, e.g. amrinone or milrinone.

Like other sympathomimetic drugs, the side effects of dobutamine are also severe tachycardia, hypertension, arrhythmia, ventricular ectopic, etc. Patients with history of hypertension may be at greater risk of developing an exaggerated pressure response to dobutamine. As dobutamine facilitates AV conduction (enhancement of atrioventricular and intraventricular conduction by isoprenaline and dobutamine is same), so patients with atrial fibrillation are at increased risk of marked ventricular response rates. Dobutamine like other inotropic agents may also increase the size of myocardial infarct by increasing the myocardial O_2 demand. This risk must be balanced against the patient's overall clinical status. Infusion of dobutamine in a patient with receiving β-blocker fails to increase CO as the total peripheral vascular resistance is increased by it (Fig. 19.15).

The main therapeutic indication of the use of dobutamine is the short-term treatment of cardiac decompensation with severe hypotension that occur after cardiac surgery or in patient with congestive heart failure or in patient suffering from acute MI, because it increases the CO and stroke volume without increasing the heart rate. Half-life of dobutamine is 2 min. Onset of action of dopamine is rapid and so no loading dose is required. Steady state concentration of dobutamine is generally achieved within 10 min of starting of an infusion.

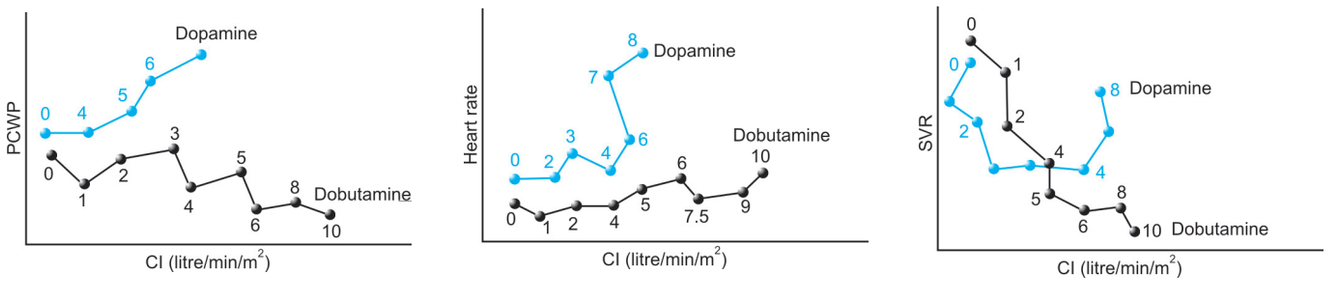


Fig. 19.15: The effects of dopamine and dobutamine on pulmonary capillary wedge pressure (PCWP), heart rate, and systemic vascular resistance (SVR) were shown in a patient with severe heart failure. Dobutamine increases both the cardiac output and cardiac index due to an increase in stroke volume. This effect of dobutamine is associated with decrease in both PCWP and SVR. It reflects both the direct vasodilation effect of dobutamine due to stimulation of β_2-adrenergic receptors and withdrawl of reflex sympathetic tone due to improved cardiovascular function. At infusion rates of dopamine exceeding 2 to 4 µg/kg per minute, it exerts a potent vasoconstrictor effect. It is evidenced by the increase in SVR and PCWP. It also decreases the left ventricular function caused by the increase in after load. The numbers shown on the figures are infusion rates in µg/Kg/minute

Phosphodiesterase (PDE) Inhibitors

Adrenaline in the form of physiological signals binds with adrenergic receptor on the cell surface and induce conformational changes of the receptor. This conformational changes of receptor permit interaction of it with stimulatory G-protein (G_S) at its binding site. This G_S-protein is now activated. The activated G_S protein now activates the enzyme, adenyl cyclase (AC), located on the cytoplasmic site of the cell membrane (cytoplasmic signalling protein). Activated adenyl cyclase now hydrolyses (not dephosphorylation) ATP to cAMP and its intracellular concentration increases. This cAMP inturn, then, phosphorylates and activate the protein kinase (PK_A) which again phosphorylates many other functional proteins including troponin and phospholamban so that they interact with Ca^{2+}, resulting in increased force of contraction. Intracellular Ca^{2+} is also made available for contraction by entry from outside by direct activation of the Ca^{2+} channel, situated on the myocardial cell membrane, by both G_S protein and phosphorylated active PK_A and as well as from intracellular stores in SR.

Now, the physiological signals outside the cell in the form of adrenaline, noradrenaline, acetylcholine, etc. are integrated within the cell as second messenger such as cAMP, cGMP, Ca^{2+}, inositol phosphates, nitric oxide, etc. and do all the cellular function. Normally, the cAMP is eliminated by hydrolysis which is catalysed by the cyclic nucleotide phosphodiesterase. Thus the phosphodiesterase inhibitors mimic the effects of adenyl cyclase activation by β agonist and act through increasing the level of cAMP by inhibiting the hydrolysis of it. Hence, the increased level of intracellular cAMP by PDE inhibitors increases myocardial contractility and causes vasodilation of both artery and vein. The first group of phosphodiesterase inhibitors, e.g. theophylline, aminophylline, etc, have been identified many years ago. But their use at haemodynamically effective dose for heart failure is plagued by side effects. In 1980 introduction of amrinone and subsequently later other phosphodiesterase inhibitor e.g. milrinone have become the cornerstone of the treatment of heart failure, alleviating the previous problems.

Amrinone and milrinone

Chemically, both these drugs are bipyridine derivatives and selective phosphodiesterase III (PDE III) isoenzyme inhibitors. Pharmacologically, they are distinct from digitalis and catecholamines and form a new class of inotropic drugs. By inhibiting the isoenzymes PDE III, which is specific for intracellular degradation of cAMP in heart, blood vessels, bronchial smooth muscle cells etc, both the amrinone and milrinone increases the intracellular level of cAMP and increases the transmembrane influx of Ca^{2+}. Thus, increased intracellular Ca^{2+} level causes direct stimulation of myocardial contractility. At the same time, they cause the balanced arterial and venous dilation with consequent fall in systemic and pulmonary vascular resistance and filling pressure of heart. Due to the stimulation of myocardial contraction and decrease of afterload the CO increases. As a result of these dual mechanisms of action (vasodilatation and increased cardiac contraction), the increase in CO with milrinone and amrinone is greater than the pure vasodilator agent such as nitroprusside when compared for a given decrease in systemic arterial pressure. Again the arterial and venous dilatation effects of these two PDE inhibitors are greater than arterial and venous dilatation caused by dobutamine when compared for a given increase in CO. However, amrinone and milrinone do not inhibit the Na^+K^+ATPase pump-like digitalis. Their actions are also independent of tissue catecholamines levels and adrenergic receptors (such as β receptor) concentration (direct action) (Fig. 19.16).

Both the amrinone or milrinone are commonly used as single agent or in combination with other oral and/or intra venous drugs for short-term treatment of patient with severe systolic right or left ventricular failure. Both the drugs are used intravenously, initially by a loading dose which is then followed by a continuous infusion. For amrinone, the initial IV bolus dose is 0.75 mg/kg and is given over 2 to 3 minutes. Then it is followed by 2 to 20 µg/kg/min through continuous infusion. As milrinone is 10 times more potent than amrinone, so the initial loading dose of it is 50 µg/kg IV which is followed by 0.25 to 1 µg/kg/min by continuous infusion. The IV action of both these drugs starts within 5 minutes. The half-lives of amrinone and milrinone in healthy subjects are 2 to 3 hours and 30 to 60 minutes respectively. This half-live becomes doubled in patient with severe heart failure.

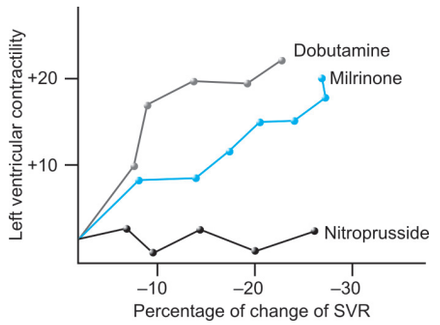


Fig. 19.16: Comparative effects of nitroprusside, milrinone and dobutamine on the gradual reduction of SVR. Among these compounds, dobutamine and milrinone (but not nitroprusside) also increases the ventricular contractility with reducing the SVR

Thrombocytopenia is the most common and prominent dose related side effect of amrinone. But it is mostly transient and asymptomatic. However thrombocytopenia is rare with milrinone (Fig. 19.17).

Milrinone is now the agent of choice among the currently available PDE inhibitors for short-term parenteral inotropic support in severe heart failure. This is because of greater selectivity of milrinone for inhibition of isoenzyme PDE III, shorter half-life and fewer side effects of it. Hence, in chronic heart failure (CHF)

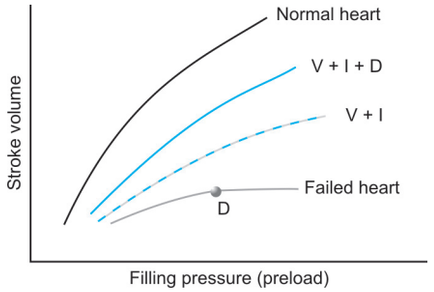


Fig. 19.17: The haemodynamic responses of the failed heart to different pharmacological interventions. V = Vasodilators, I = Inotrops. D = Diuretics. Black line represents the normal heart and red line represents the failed heart due to systolic dysfunction, with the effects of diuretics (D) alone. The other two curves show the effect of V + I and V + I + D on the failed heart. The combination of drugs produce the synergistic effect on haemodynamic responses more towards the normal heart. The diuretics alone improve the symptoms of congestive heart failure by reducing the only filling pressure of heart, but not improving the cardiac output with same ventricular function curve. Use of inotropic agents such as dobuta-mine, glycosides, etc. move the patients to higher ventricular function curve (black line)

these inotropes have no role for long-term use, but even increase the mortality.

Cardiac Glycosides

Chemically, glycosides are compound which contain both a carbohydrate (sugar) and a noncarbohydrate (nonsugar) part. It is particularly found as natural product in plants. It can be converted by hydrolytic cleavage into a sugar (glycone) and nonsugar (aglycone) component. They are also named specifically according to the type of sugar component present in it such as glycoside (glucose), pentoside (pentose) or fructoside (fructose) etc. The glycosidic compounds which have cardiac inotropic effects are called the cardiac glycosides (Fig. 19.18).

All the cardiac glycosides have a common molecular structure, i.e. a steroid (cyclopentanophenanthrene) nucleus and an unsaturated lactose nucleus (or ring) attached to the steroid nucleus at C 17 position. This steroid nucleus and the lactose ring together form the aglycone part. One or more sugar residue is attached to the

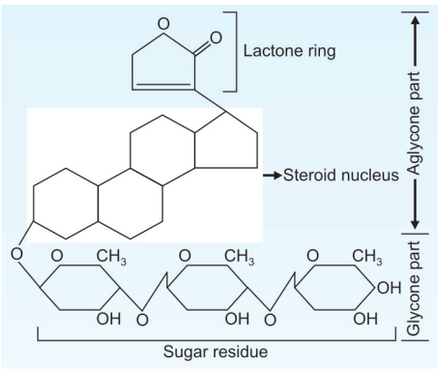


Fig. 19.18: Structure of digoxin

steroid nucleus and constitutes the glucone part of the glycoside molecule. The pharmacological properties of cardiac glycosides reside on the aglycone part. But, sugar or glycone part modifies the water solubility and the cell membrane permeability of it. There are many cardiac glycosides, available in practice. But among them only the digoxin and digitoxin are orally active, and between them only digoxin is in the widespread clinical use today. Digitoxin differs from digoxin only by the absence of hydroxyl group at C_{12} position, resulting in a less hydrophilic compound with altered pharmacokinetic property (but same pharmacodynamics) compared to digoxin.

The beneficial effects of cardiac glycosides in heart (Fig. 19.19) failure is derived from: (i) the positive inotropic effect of it on failing myocardium, (ii) the efficacy in controlling the ventricular rate in response to atrial fibrillation and (iii) the modulating sympathetic nervous system activity of it which may be an additional mechanism and contribute significantly to their efficacy in heart failure.

Mechanism of action of glycosides (digitalis)

Cardiac glycosides selectively bind to the specific site of extracytoplasmic part of the α-subunit of Na^+K^+ATPase pump situated on the cell membrane and inhibits it. As a result, there is reduction in the rate of active Na^+ extrusion and rise in intracellular Na^+ concentration.

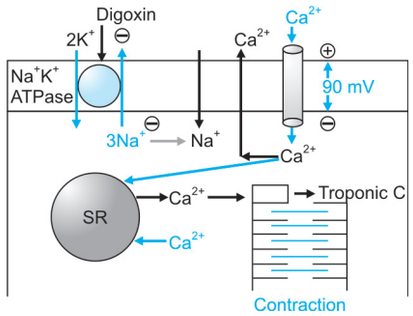


Fig. 19.19: Mechanism of positive inotropic action of digitalis (cardiac glycosides). Digitalis increases the force of cardiac contraction by not acting through catecholamine's receptor, but by its direct action on the Na^+-K^+-ATPase pump. It binds selectively with the Na^+-K^+-ATP system on the cell membrane and inhibits it. Then, inhibition of this system causes gradual accumulation and increase in concentration of Na^+ intracellularly. By the side of the Na^+-K^+-ATPase system, there is Na^+-Ca^{2+} exchange protein which extrudes Ca^{2+} in exchange of influx of Na^+. Incresed intracellular con-centration of Na^+ inhibits the further influx of Na^+ and extrusion of Ca^{2+} through this Na^+Ca^{2+} exchanger and indirectly increases the intracellular concentration of Ca^{2+} which gradually store in the SR. During depolarisation, Ca^{2+} further enters the cell through the voltage sensitive Ca^{2+} channel (A). This triggers the more release of stored Ca^{2+} from SR and thus helps in more forceful contraction. The more of intracellular Ca^{2+} concentration, the more in the force of muscular contraction. After contraction is over, Ca^{2+} is further taken back by SR. The portion of Ca^{2+} which enter the cell from outside during depolarisation is also extruded by 3 Na^+-1Ca^{2+} exchanger. This excess Ca^{2+} remains in cytosol and is taken up by SR. Thus, SR is progressively loaded with more and more Ca^{2+} and subsequently Ca^{2+} store is augmented

The relationship between the intracellular Na^+ and Ca^{2+} concentration is such that a small percentage of increase in intracellular Na^+ concentration results in large percentage of increase in intracellular Ca^{2+} concentration. Thus, the resulting increase in intracellular Ca^{2+} interacts with troponin-C and activates the cross-bridge interaction between the actin and myosin filaments that results in forceful contraction and sarcomere shortening. Moreover, the raised intracellular Ca^{2+} concentration induces a greater re-entry of Ca^{2+} through the voltage sensitive Ca^{2+} channel of 2 and 5, during plateau phase. Hence, this increased intracellular level of Ca^{2+}

is taken up by SR and its storage capacity is increased which is to be made available for the contractile elements during the subsequent depolarisation of myocytes. Thus, the contractility of myocardium is augmented and this is the mechanism of action of digitalis.

Binding of glycosides to Na^+K^+ATPase pump is slow. So the Ca^{2+} loading in SR occurs gradually and the inotropic effects of digitalis takes hours to develop even after IV administration. As the digitalis inhibit the Na^+K^+ATPase pump activity, so there is gradual depletion of intracellular K^+ (as K^+ does not enter) and this is responsible for the mechanism of all toxicities of digitalis. So, the toxicity of digitalis is partially reversed by K^+ supplementation. Excessive Ca^{2+} loading in SR results in spontaneous cycles of Ca^{2+} release and reuptake by it, producing oscillation after contraction or depolarisation. So, both the therapeutic and toxic effects of digitalis are due to this myocardial Ca^{2+} loading. These are inseparable and also explain the low therapeutic index or window of digitalis.

Electrophysiological effects of glycosides (digitalis)

The electrophysiological effects of digitalis on different types of cardiac tissues such as atrial muscle, ventricular muscle, pacemaker cells and conducting fibres are different due to their different action potential, different sensitivities and different responses to glycosides (Fig. 19.20). The Purkinje fibres and the other specialised automatic and conducting tissues in atria and ventricle are more sensitive to cardiac glycosides. The resting membrane potential (RMP) of all these tissues is progressively reversed, i.e. shifted away more from the isoelectrical level. So, the rate and amplitude of O phase depolarisation is reduced, primarily as the result of less negative value of RMP. The duration of action potential is also reduced (primarily at phase 2). Amplitude of action potential is also diminished.

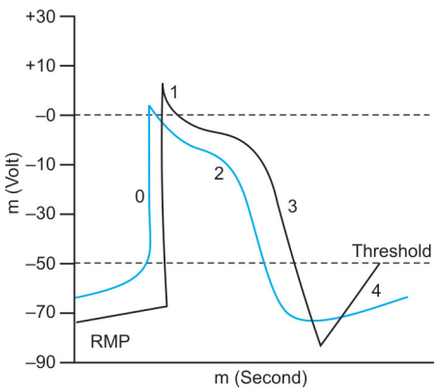


Fig. 19.20: Effects of digitalis on the action potential (AP) of Purkinje fibres (PF). Red line - digitalis untreated fibre, green line - digitalis treated fibre. RMP - resting membrane potential. The effects of digitalis differ qualitatively and quantitatively according to the types of cardiac muscle fibres. PFs, SA node and other conducting tissues are more sensiive to cardiac glycosides. For the action of glycosides, direct action and indirect autonomic influences are both important. RMP gradually shifts to the isoelectric level (i.e. decreased). So, excitability or automaticity increases due to reduction of gap between the RMP and threshold level. But this occurs in higher doses. At therapeutic concentration, automaticity is reduced (SA and AV node) by indirect vagal action which hyperpolarises these cells. In therapeutic concentrations, the slope of phase 4 also reduces that is becomes more flat which explains the reduction of automaticity in SA and AV node. In toxic doses RMP also decreases, i.e. becomes less negative. This is due to depolarisation running below the critical potential value which inactivates the fast Na+ channel. In therapeutic concentration the height of 0 phase of AP is also reduced by digitalis. This is due to more negative value of RMP at which excitation occurs. This reduction of height of AP is responsible for slow conduction and is most marked in AV node and bundle of His. In high doses the slope of phase 4 is increased in PFs which is responsible for enhanced automaticity and ectopic focus

The action of digitalis on cardiac muscle is mediated by its direct action on cells and also by the indirect action through vagus and sympathetic nervous system. At therapeutic concentration, digoxin reduces the automaticity, increases the diastolic resting membrane potential, prolongs the effective refractory period and decreases the conduction velocity or time, predominantly of the atrial and AV nodal tissues. All these are due to the increased vagal tone and decreased sympathetic nervous system activity. At higher or toxic serum concentration, the digoxin causes sinus bradycardia and /or prolongation of AV conduction, resulting heart block or arrest. On the other hand, paradoxically at more higher concentration of digoxin, sympathetic activity increases. This increases the automaticity of cardiac muscle cells that contributes to the generation of atrial and ventricular arrhythmias. Both the increased intracellular Ca^{2+} concentration and increased sympathetic activity by glycoside result in an increase in the spontaneous rate of diastolic depolarisation (phase 4) leading to ventricular ectopic, tachycardia and fibrillation. Nonuniform simultaneous increase in automaticity and depression in conduction through bundle of HIS and Purkinje system by glycoside causes arrhythmias which may lead to ventricular tachycardia and fibrillation.

Pharmacological action of cardiac glycosides

All the cardiac glycosides have similar pharmacodynamic actions. But they differ only in quantitative and pharmacokinetic properties. Digoxin is the prototype of all the cardiac glycosides and is so described here. By convention the term 'digitalis' is applied as a collective name to the whole group of cardiac glycosides (Fig. 19.21).

Digoxin has positive inotropic action and causes does dependent increase in the force of contraction of failing heart which is exquisitely sensitive to it. Systole is shortened and diastole is prolonged. When a normal cardiac muscle fibre is subjected to increased impedence to outflow, then

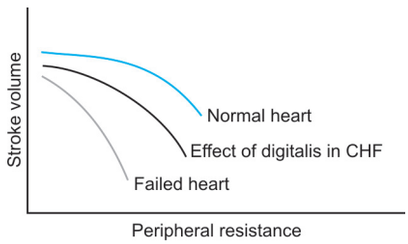


Fig. 19.21: Relationship between the peripheral resistance and the stroke volume in normal and failing heart. The figure also shows the effect of digitalis on the failed heart

by Starling principle incresed tension is generated in it so that the stroke volume is maintained considerably up to a certain higher values of impedence. While the failing heart where limitation is crossed, will not be able to do so and the stroke volume progressively decreases. But under the influence of digoxin the failing heart regains some of its capacity to contract more forcefully, when it is subjected to increased resistance for ejection. Therefore, there is more complete emptying of failing and dilated ventricles and cardiac output is increased (Fig. 19.22).

The Digoxin also increases the force of contraction in normal heart. But this is not translated into increased output, because the normal heart empties almost completely (even otherwise) and therefore further reduction of end-diastolic volume is counter productive.

The Digoxin causes decrease in HR and it is due to the improved circulation. This is more marked in failing heart where heart rate is increased as a mechanism of compensation. The improved circulation reduces the compensated sympathetic activity and thus decreases the heart rate. The direct vagal mimetic action of digoxin is also cause for bradycardia. The digoxin has direct action on SA and AV node which is also responsible for reduction in heart rate. The vagal action of digoxin manifests early and can be blocked by atropine. Whereas, the extravagal action of digoxin becomes prominent later and cannot be reversed by atropine.

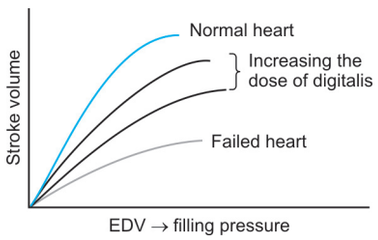


Fig. 19.22: Relationship between the filling pressure and stroke volume in normal and failed heart. It also depicts the effect of increased dose of digitalis which shifts the curve towards normal

ECG

At therapeutic level, the effect of digoxin on the ST segment is characteristic. It is one of the main effects of all the changes of digitalis on ECG. The characteristic ST segment depression seen with digoxin is described as a reverse tick and is most obvious in leads with tall R wave.

Therefore the effects of digoxin on ECG at therapeutic levels are:

i. ST-segment depression due to interference with repolarization.
ii. Reduction of T-wave size or inversion of T-wave.
iii. Shortening of QT interval – reflecting shortening of systole.
iv. Increased P-R interval due to slowing of AV conduction.

At toxic level of digoxin, the changes in the picture of ECG seen are : (i) T-wave inversion, (ii) Arrhythmias almost of any type, but especially of sinus bradycardia, paroxysmal atrial tachycardia with block, AV block, ventricular ectopic, ventricular bigeminy, ventricular tachycardia, etc.

The abnormal QRS complex of WPW syndrome under the influence of digoxin is widened, because conduction through the normal AV bundle is slowed but not through the aberrant pathways.

Pharmacokinetics

The most oral preparation of digoxin available in market have 70 to 80% oral bioavailability. Presence of food in stomach delays its absorption. Bioavailability of oral preparation of digoxin differ considerably for different manufacturers. So, it is advisable to stick to one brand. Liquid filled digoxin capsules have greater bioavailability than tablets and require dose adjustment, if a patient switches over from tablet to liquid filled capsule. Parenteral digoxin is also available for intravenous use when only oral route is impractical. Intramuscular digoxin administration causes pain and necrosis as all the glycosides are irritant to local tissues. It gets bound to muscle tissues after the IM injection and so the absorption from injection site is erratic as well as poor. Hence, the IM route for digoxin is not recommended.

All the cardiac glycosides have cumulative properties. Elimination half-life ($t_{½}$) of digoxin is 36 to 48 hours in patient with normal renal function. So, digoxin is given once a day and the steady state level with full therapeutic effect is attained after ($4 \times t_{½}$) 7 days of initiation of maintenance therapy.

Another glycosides, named digitoxin is primarily metabolised in liver which is partly to digoxin and partly undergoes some enterohepatic circulation. It is primarily excreted unchanged by the kidney, mainly by glomerular filtration. Rate of excretion of digoxin through kidney is altered in renal disease, but is parallel to the creatinine clearance. So, half-life of digoxin is prolonged in elderly and renal failure patient. Thus, the dose of digoxin has to be reduced, but is not greatly altered in renal failure.

Doses

The dose and route of digoxin administration depends on the speed of action, desired by the clinician. In many patients, the therapeutic response can occur at doses well below the maximum tolerated dose, but in some patients the reverse is observed. Generally, higher doses of digoxin is needed for severe heart failure patient. According to the therapeutic need any digitalis can be used by three methods. These are : slow oral digitalisation, rapid oral digitalisation and emergency IV digitalisation.

Slow Digitalisation (oral)

In mild-to-moderate heart failure digoxin is started orally in the dose 0.125 to 0.250 mg/day, depending on the lean body mass, as digoxin concentrates mainly in heart, skeletal muscle, liver and kidney; but not in the fat. Full theraputic response develop 5 to 7 days after initiation of therapy. If adequate response is not seen after one week, the dose is increased to 0.375 mg/

day and then to 0.5 mg/day after another 1 week.

The relief of signs and symptoms of heart failure and reduction of HR is the best guide to judge the response of action of digitalis.

Rapid digitalisation (oral)

It is done when the result is expected within few hours. It is started in the dose of 0.5 to 1 mg start, followed by 0.25 mg every 6 hours interval, with careful monitoring of toxicity, till the response occurs. It generally takes 6 to 24 hours and the total dose needed is about 0.75 to 1.5 gm. But this is seldom practised now.

Emergency IV digitalisation

This is also rarely practised now. It is only taken as a desperate measure in acute heart failure or in atrial fibrillation producing acute symptom. In such situation, digoxin is used in the dose of 0.25 mg IV stat, followed by 0.1 mg IV slowly at the interval of every hour with close ECG, BP and CVP monitoring, till response occurs. Usually, IV digitalis takes 2 to 6 hours for its full action and the total dose needed is 0.5 to 1 mg.

Current Status of Clinical Use of Digitalis

Before introduction of high ceiling IV loop diuretics, different specific arterial, venous and mixed vasodilators such as nitroprumide, nitroglycerine, ACE inhibitors, phosphodiesterase inhibitors, etc, digitalis were thought as an indispensable agent for the treatment of heart failure. But, its importance has been gradually waned away in cardiac failure. All acute, mild and moderate heart failure are treated now by diuretics and ACE inhibitors and vasodilators. Emergency IV use of digoxin is practically in extinct now. But as there is no oral inotropes for prolonged use in chronic heart failure, digitalis is still a prominent drug in chronic heart failure patients, those are not controlled by diuretics and ACE inhibitors.

Only one question exists during the prolonged use of digitalis in CHF is after decompensation how long it should be used. The answer is with the availability of diuretics, vasodilators and ACE inhibitors, there has been a trend to discontinue digitalis once compensation has been restored, specially in mild-to-moderate cases. Thus if stable clinical state has been maintained for 2 to 3 months, withdrawl of digitalis may be attempted and early reinstitution of digitalis is recommended if cardiac status declines again. There is no coincidence that digitalis prolongs the survival of CHF patients. The two major limitations for the use of cardiac glycosides are the low margin of safety and inability to reverse or retard the process which causes the heart to fail. Based on all these discussions, the international recommendation is that digoxin should be reserved for patients with CHF who have AF or for patients with sinus rhythm who remain symptomatic despite adequate treatment with diuretics, ACE inhibitors and β-adrenergic receptors antagonists.

Adverse Effects or Toxicity of Digitalis and its Management

The adverse effects or toxicity of digitalis is very high and the margin of safety is low. The adverse effects of digitalis are divided into:

Extracardiac effect

These are anorexia, nausea, vomiting, fatigue, malaise, mental confusions, restlessness, disorientation, psychosis, visual disturbances, etc.

Cardiac effect

Almost all types of arrhythmias can be produced by digitalis. These are pulsus bigeminus, ventricular extrasystole, ventricular fibrillation, ventricular tachycardia, AV junctional ectopic, partial to complete AV block, severe bradycardia, atrial extra-systole, atrial filtration and flutter, etc.

However, management of all this complications often require only dose adjustment and appropriate monitoring. Sinus arrest, second or third degree AV block are usually treated by atropine IV injection. In extreme cases temporary ventricular pacing may be needed. Even when serum K^+ level is in the normal range, still potassium supplementation should be considered for completely digitalised patients with AV junctional and ventricular ectopic beats, unless higher degree AV block is present. Extracellular K^+ promotes the dephosphorylation of $Na^+ K^+$ATPase enzyme and decrease the affinity of this enzyme for binding with cardiac glycosides. This provides one explanation for why increased extracellular K^+ reverses some of the toxic effects of digitalis. As extracellular K^+ depletion precipitate digitalis toxicity, this toxicity again causes high plasma K^+ level.

Lignocaine is used for the treatment of ventricular automaticity of digitalis toxicity which threaten haemodynamic compromise. But it does not accentuate the AV block. Electrical cardioversion carries increased risk of inducing severe rhythm disturbances in patient with overt digitalis toxicity and it should be used with particular caution.

Recently for the treatment of digitalis toxicity, antidigoxin immunotherapy is very promising and is now a great breakthrough. Purified Fab fragment from ovine antidigoxin antisera is an effective antidode for digoxin toxicity. The Fab fragment has been marketed in Europe as 'digibend' (40 mg/vial). It is nonimmunogenic. Given by IV infusion it markedly improved the survival of digitalis intoxicated patients. The total neutralizing dose of Fab is calculated from either the estimated total dose of drug ingested or the total body digoxin burden. This antidigoxin antisera can be administered intravenously with saline solution over 30 to 60 minutes. The digoxin – Fab complex is rapidly excreted by kidney. However, it is very expensive.

20 Management of Airway

HISTORY

The tracheal intubation in animals was first described by Vesalins of Padua, in 1543 and by R. Hooke of UK, in 1667. But after that there was prolonged silence and nobody had tried for intubation. Then, after a long interval, the end of the eighteenth century had again seen a flurry of researches and publications on tracheal intubation. It was triggered by the humanitarian factor for the resuscitation of drowned persons by mouth to mouth breathing. Because during that period mouth to mouth resuscitation of drowned person was condemned due to unhygienic ground. So, there was continuous search for alternative way to resuscitate a drowned person other than this unhygienic mouth to mouth artificial ventilation. Then, again after a century, in 1776, John Hunter described tracheal intubation by a metal tracheal tube. After that, in 1788, C. Kite had also described an oral and nasal intubation for resuscitation of a apparently drowned person. This is followed by James Curry who also described several different metal endotracheal tube in 1792. But, in 1827, Leroy had first showed that pneumothorax may result from high intrapulmonary pressures during artificial ventilation by tracheal tube. Then, John Snow used a tracheal catheter to resuscitate a newborn baby.

All these works described above was directed with an aim, either for resuscitation of a drowned person, or for the relief of an upper airway obstruction. Then, from 1848, passage of a metal tube or a catheter into the trachea was also routinely practised to resuscitate only the anaesthetic casualities, but not to administer sole anaesthesia. Gradually, there was a significant technical advancement to contemplate for deliberately administering anaesthetic vapours through this tracheal tube for sole anaesthetic purpose. So, John snow in 1852 had made a historical leap by intubating animals via a tracheostomy wound and providing anaesthesia through this tube. After that, in 1871, Friederich Trendslenburg of Rostock used this method in human while he was a surgical assistant to surgeon named Dr Langenbeck in Berlin. He used this method for operation in mouth. After performing a tracheostomy, he introduced a tube into the trachea and inflate the cuff for administering anaesthesia.

At that time, it had been assumed that if a tube was passed through the larynx it would not be tolerated, except tracheostomy. So, they were used to do tracheostomy for intubation. But in 1878, William MacEwen of Glasgow had first decided and try to avoid tracheostomy for intubation, if otherwise inevitable. So, after practising on the cadever, he passed a flexible metal tube through the mouth into the trachea, using his fingers as a guide in a conscious patient. Through this tube he gave choloroform and air mixture for the removal of carcinoma from the base of the tongue. A sponge was packed by him around the tube at laryngeal inlet to protect the lungs from contamination. He had also previously used rubber and gum elastic catheters into the trachea for the relief of obstruction in laryngeal diphtheria. Next in 1901, Franz Kuhn of Kassel had extended and developed this technique by using a flexible metal tube and introducing it through larynx with the help of curved wire guide after palpating the epiglottis with the fingers of his left hand. His preference was for inhalation anaesthesia and the patient was breathing to and fro through the tube. Then in 1907, Berthelemy and Dufour of Nancy, in France, blew the mixture of chloroform vapour and air into the lungs from a Vermon Harcourt inhaler through a rubber catheter which was guided into the trachea by hand, as laryngoscope was not invented at that time. It was the first kind of endotracheal insufflation technique of anaesthesia and was subsequently widely used in the forth coming World War I in 1914.

Largely after that due to their experience as anaesthetist during World War I, Mr Gillies, Mr Rowbotham and Mr Magill first used ether inhalation through one narrow gum elastic tube passed via larynx with the help of laryngoscope. During that period laryngoscope had already been invented which is described later. After that the first blind nasal intubation was performed by Rowbotham. Then, Magill also published his results of blind nasal intubation by using a wide bore rubber catheter during the years following 1928. This technique revolutionised the use of endotracheal tubes in anaesthesia, because not only it provides anaesthesia, but also

gained early control of the airway and protect it. Inflatable cuffs had been used for many years but were again reintroduced by Guedel and Waters in 1928. A pilot ballon had been described first in 1893 by Eisenmenger. It was also described in 1906 by Green and was reintroduced by Langton in 1939.

While the methods of intubation by Magill and Rowbotham had earned the support and approval of the surgeons with whom they worked, but many other surgeons discouraged the use of intubation through larynx. This was partly because of the possibility of tissue damage and partly due to conservatism. Thus, it took many years before the intubation was accepted by the all anaesthetists. Those who learnt how to perform blind nasal intubation soon realised its great advantages, especially due to the fact that it would enable a patient to be taken to the necessary level of anaesthesia very quickly by the use of relaxant and IPPV than by the use of only volatile anaesthetics which at that time was the rule. In addition, they also realised that intubation provides a clear airway, prevents laryngeal spasm and enables the lungs to be proteced against aspiration of foreign materials.

During the previous period, intubation was performed only by deepening anaesthesia by volatile anaesthetics such as ether or chloroform which was only available at that time. After that, when the muscle relaxants became available, then it was possible to perform oral intubation easily and rapidly by direct laryngoscopy. Because intubation by only inhalational anaesthetic agent was difficult and need a long time to reach the necessary deep plane of anaesthesia for it. The use of muscle relaxants to facilitate intubation in UK was pioneered by Bourne. This turning point in anaesthesia was long over due. So, the credit was given to Bourne for convincing the postwar generation of anaesthetists of the value of relaxants for rapid and easy intubation.

The traditional tubes for either nasal or oral intubation were Magill endotracheal tubes, made of mineralised rubber. The red colour of the tube is due to the presence of preservative. The oral tubes had thicker walls than the nasal ones. The angled oxford tube was thicker in the pharyngeal part and thinner in the tracheal part. Then Polyvinyl chloride (PVC) tubes had started to replace the red rubber tube, progressively from 1950. The toxicity of the PVC tube was tested by implantation test in rabbit muscle (IT = Implantation Test) or by cell culture. The Z79 was the committee in USA that originally approved anaesthetic equipment to maintain a standard and was formed first in 1956. RAE preformed tubes were first developed in 1980.

During the evolution of direct laryngoscope, indirect laryngoscopy was also evolving. The indirect laryngoscopy with mirror was first introduced by M Garcia who was a teacher of singing in london. Then, it was widely used for diagonostic purposes. But, direct laryngoscopy was pioneered in 1895 by Alfred kirstein. After that Jackson himself designed a laryngoscope which was later modified by Magill in 1926 and by Miller and Macintosh in 1932. The light was originally powered from the electric mains. But later the light was supplied by a 3 volt battery which was incorporated into the handle of laryngoscope or by a fibreoptic cable. The Macintosh blade was shorter, curved and Z shaped on cross section. Its tip entered the valecula, lifted the base of the tongue and with it the epiglottis, so that the cords could be visualised. It does not generate so much laryngospasm as it does not pass over and stimulate the posterior surface of the epiglottis. Then, it was an immediate success and has continued to be so, as it can be used in lighter planes of anaesthesia. Macintosh also developed a laryngeal forcep which bear his name and is used for directing the nasal tubes under direct vision into the larynx.

Without using muscle relaxant, cocaine was first used to supress the laryngeal reflexes during general anaesthesia by Rosenberg in 1895 and by Magill in 1928 to aid intubation. Then many sprays also have been described such as applying local anaesthetic to the larynx to supress the reflexes for intubation. But lignocaine is now generally preferred because of its lower toxicity.

To remove the different disadvantages of endotracheal intubation, initially a small mask had been tried in the pharynx, but it was rejected. Then, the invention of laryngeal mask airway (LMA) had completed the cycle of history of airway management in anaesthesia. It was first developed by an anaesthetist, named Mr A Brain and was later manufactured by an equipment company, named Colgate Medical. After that improved materials and different designs of the laryngeal mask airway, coupled with the timely arrival of propofol which deeply supresses the pharyngeal and laryngeal reflexes allowed a successful outcome of it.

INTRODUCTION

An airway is defined as the passage through which air passes into and out of the lungs during respiration. Any artificial device with a lumen inside of it and which serves as a conduit, connecting between the atmosphere and lungs is also considered as an airway. These include oropharyngeal airway, nasopharyngeal airway, LMA, other supraglottic airways, endotracheal tube (ETT), ventilator's breathing circuit etc. It is estimated that about 600 patients die each year in a developed country from complications, related to the airway management. This picture in the under developed countries is further grimmer. On the contrary, about 98% of difficult airway in relation to mask ventilation or ET intubation can be predicted by proper preoperative evaluation or assessment of patient (Table 20.1).

Table 20.1: Preoperative evaluation of patient

1.	Facial anomalies
	Maxillary hypoplasia
	Apert syndrome, Crouzon disease.
	Mandibular hypoplasia
	Pierre-Robin syndrome,
	Treacher-Collins syndrome,
	Goldenhar syndrome.
	Mandibular hyperplasia
	Acromegaly, Cherubism.
2.	Affection of temporomandibular joint
	Ankylosis, rheumatism, trauma, infection, previous surgery, etc.
3.	Problems with teeth
	Loose teeth, false teeth, protruding incisior, edentulous.
4.	Problems with tongue
	Macroglossia due to Down syndrome, hypothyroidism, haemangioma, lymphangioma, tumour, scarring, etc.
5.	Problems with mouth
	Microstomia due to burns, trauma, scarring, etc.
6.	Problems with palate
	Cleft palate, narrow arched palate, palatal swelling, haematoma etc.
7.	Problems with pharynx
	Hypertrophic tonsils, large adenoids, pharyngeal tumours, abscess, retropharyngeal or para pharyngeal abscess, etc.
	Supraglottic-epiglotitis, tumour, injury etc.
8.	Problems with larynx
	a. Glottic—Laryngomalacia, granuloma, foreign body, papillomas.
	b. Infraglottic—Congenital stenosis, traumatic stenosis, oedema due to inflammation.
9.	Problems with nose
	Choanal atresia, hypertrophic turbinates, deviated nasal septum, polyp, foreign bodies, etc.
10.	Problems with trachea
	Tracheal stenosis, tracheal webbing mass of neck deviating trachea, mediastinal mass deviating trachea, trachea esophageal fistula, tracheomalacia, foreign bodies, etc.
11.	Problems of neck and spine
	a. Neck - large goiters, skin contractures.
	b. Spine - Klippel-Feil syndrome, surgical fusion, fracture of cervical vertebrae, traumatic subluxation, etc.

The difficult airway is defined by American Society of Anaesthetist (ASA) as the clinical situation in which a conventionally trained anaesthesiologist experiences difficulty during mask ventilation or difficulty during tracheal intubation or both. *Difficult mask ventilation* is defined by ASA as the clinical situation in which it is not possible by an unassisted trained anaesthesiologist to maintain O_2 saturation more than 90%, using 100% oxygen and mask for ventilation, provided preventilation O_2 saturation level was within the normal range. *Difficult laryngoscopy* is defined by ASA as clinical situation in which it is not possible to visualise any portion of the vocal cords with conventional laryngoscope. ASA also defines *difficult endotracheal intubation* as a situation when insertion of ET tube in the larynx requires more than 3 consecutive attempts or more than ten minutes with conventional laryngoscope and experience. The later definition of ten minutes provides a margin of safety for preoxygenated patients who are undergoing elective intubation in the operating room. Because such patients in stable circumstances can usually tolerate 10 minute of attempts without any bad consequences. *'Zero class airway view'* is defined as unability to see any portion of the epiglottis after opening the mouth and tongue protrusion. Approximately 1.8% patient of the total population belongs to this class of airway view. *Failed intubation* is defined as the condition when the placement of ET tube fails after multiple attempts of intubation.

The airway is divided into an upper and lower airway. The upper airway is comprised of oral cavity, nose, pharynx (nasopharynx, oropharynx and laryngopharynx) and larynx. The nose is again comprised of external nose and nasal cavity. The lower airway includes the trachea, bronchi, bronchiole, and its subsequent divisions and subdivisinos which terminate in the alveoli. The upper airway serves to warm, humidify and filter the air or gases before it enters the lower airway. Bypassing these structures by endotracheal intubation or tracheostomy makes an anaesthetist essential to provide warm, humidified and filtered air to the patient. Among the two airways, upper airway is more vulnerable to obstruction during anaesthesia. This is because in anaesthetised patient there is loss of muscle tone which allows the tongue to fall back on the pharynx, the pharyngeal wall to collapse and occlude the upper airway at the level of laryngo pharynx and then subsequently allows the epiglottis to occlude the airway at the level of larynx.

There are many different accquired and congenital conditions which affect the upper and lower airways and cause the difficult management of it. These are listed in the Table 20.1.

ANATOMY OF THE UPPER AIRWAY

Nose

Nose consists of external nose and nasal cavity.

External nose

It is a pyramid like projection on the face. It presents a free tip or apex and a root at its junction with the forehead. The rounded boarder between the tip and the root of the nose along with adjoining area is known as the dorsum of the nose. The inferior surface of the external nose presents a pair of pyriform apertures which is called the nostrils or nares. Each nostril is bounded medially by the mobile part of nasal septum and laterally by the ala of nose (Fig. 20.1).

The frame work of the external nose is formed by some bones and cartilages. Among them the upper part is supported by bones and the lower part is supported by cartilages. The upper part is supported by the following bones such as nasal bone, frontal process of the maxillary bone and nasal part of the frontal bone.

The lower part is contributed by the following cartilages:

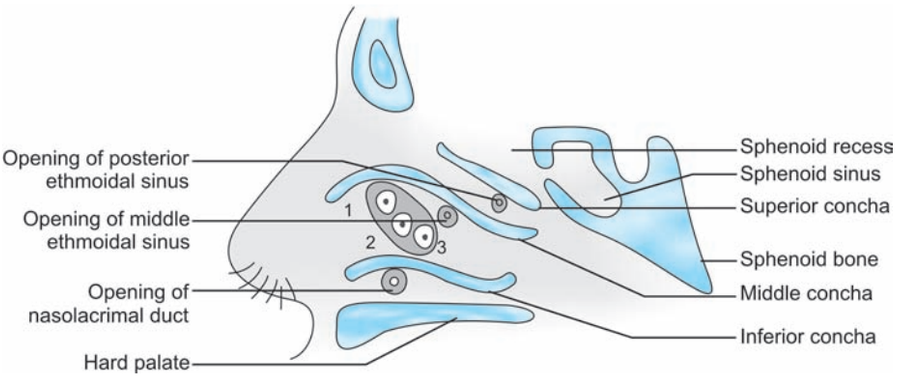


Fig. 20.1: The structures which open on the lateral wall of the nose. The cut margin of conchas are seen. 1. Opening of frontal sinus, 2. Opening of anterior ethmoidal sinus, 3. Opening of maxillary sinus

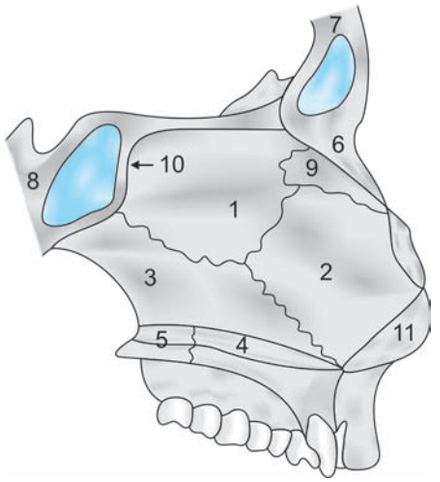


Fig. 20.2: The formation of nasal septum
1. Perpendicular plate of ethmoid
2. Septal cartilage
3. Vomer
4. Nasal crest of maxilla
5. Nasal crest of palatine bone
6. Nasal spine of frontal bone
7. Frontal bone
8. Sphenoid
9. Nasal crest of nasal bone
10. Rostrum of sphenoid
11. Septal process of inferior nasal cartilage.

i. anterior border of the septal cartilages,
ii. superior nasal cartilages, which is continuous with the septal cartilages,
iii. inferior nasal cartilage (or alar cartilage) which presents a septal process to form the mobile part of nasal septum,
iv. a few minor alar cartilages,
v. fibrofatty tissue in the lower part of the ala.

The skin overlying the bones at the root of the nose is thin and mobile. But it is thick and adherent to the underlying cartilages and fibrofatty tissue. The skin of nose is provided with multiple sebaceous glands.

The sensory nerves of external nose are derived from (i) the external nasal and the infratrochlear branches of opthalmic nerve and (ii) the infraorbital branch of maxillary nerve.

Nasal Cavity

The nasal cavity is triangular in shape and has an irregular surface. It is divided into right and left halves by the nasal septum. Each half of the nasal cavity extends anteriorly from the mucocutaneous junction of anterior nares to the nasopharynx posteriorly (posterior nares and choanac). Each nasal cavity has a roof, a floor, a lateral wall and a medial wall. The roof of the nasal cavity slopes downwards both in front and behind from the middle horizontal part. The middle horizontal part of the roof of the nasal cavity is formed by the cribriform plate of ethmoid bone. The anterior slope of the roof is formed by the nasal part of the frontal bone, nasal bone and the nasal cartilages. The posterior slope of the roof is formed by the inferior surface of the body of sphenoid bone. The floor of nasal cavity is formed by the palatine process of maxilla and the horizontal plate of palatine bone. The area of the nasal cavity close to the nostrils or anterior nares is known as the vestibule. It is lined by skin and provided with coarse hairs, sebaceous glands and sweat glands. Except vestibule, rest of the nasal cavity is lined by the mucous membrane (Fig. 20.2).

The lateral wall of the nasal cavity is irregular due to the presence of three shelf-like or scroll-like bony projections. These projections increase the surface area of the nose and ensure effective conditioning (warming and humidification) of the inspired air. Lateral wall separates the nasal cavity (i) from the orbital cavity above while the ethmoidal air sinuses interven between them, (ii) from the maxillary sinus below and (iii) from the lacrimal groove with lacrimal sac and the nasolacrimal canal with nasolacrimal duct in front (Fig. 20.3).

The lateral wall of the nasal cavity is formed by some bones. These are: nasal,

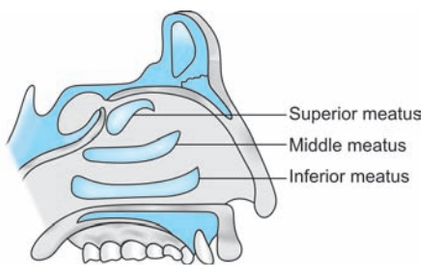


Fig. 20.3: The lateral wall of the nose

frontal process of maxilla, lacrimal, labyrinth of ethmoid with superior and middle conchae, inferior nasal concha, perpendicular plate of palatine and medial pterygoid plate of sphenoids. There is a shallow depression which is situated just in front of the middle meatus and above the vestibule of the nose. This is called atrium (Fig. 20.4).

The bony lateral wall of the nasal cavity is convoluted by three turbinates. The superior and middle turbinates are formed by the medial aspect of the lateral mass (or labyrinth) of the ethmoid bone. The inferior turbinate is formed by

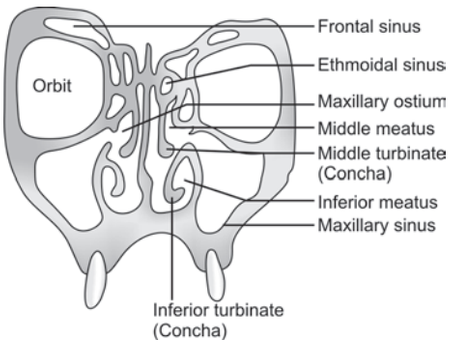


Fig. 20.4: The coronal section through nose and sinuses at the plane of maxillary ostium

separate bone called inferior nasal concha which is attached to the maxilla. In cross section, as the bones of turbinates look like whorl (turbinate) or scroll (concha), so they are named like that. Each turbinate hangs over a meatus or channel and the meatuses are named according to the name of the turbinate. The highest space in the nasal cavity above the superior turbinate is called the spheno-ethmoidal recess and sphenoidal sinus opens in this recess.

The olfactory cleft of nasal cavity is the area which lies between the superior turbinate, cribriform plate of ethmoid and the corresponding area of the septum. It is lined by specialised olfactory epithelium.

Several ducts drain on the lateral wall of the nose at the meatuses under the respective turbinate. The nasolacrimal duct open into the inferior meatus. The frontal, maxillary and anterior ethmoidal sinuses drain into the middle meatus. The posterior ethmoidal sinuses drain into the superior meatus. Sphenoethmoidal recess receives the sphenoidal sinus.

The nasal septum is situated in the midline and seperates the two nasal cavities. Posteriorly, it is bony in structure and anteriorly it is cartilagenous. Bony part of the nasal septum is formed almost entirely by vomer and the perpendicular plate of ethmoid bone. However, its margins are contributed by the nasal spine of frontal, the rostrum of sphenoid and the nasal crests of nasal, palatine and maxillary bone. The cartilagenous part of nasal septum is formed by the septal cartilage and septal process of inferior nasal cartilage. The attachement of the cartilagenous part of nasal septum are inferiorly to the maxillary crest, posteriorly to the vomer, posterosuperiorly to the perpendicular plate of the ethmoid. The nasal septum is rarely strictly in midline. It is usually deflected to one or the other side and the deflection is produced by the overgrowth of one or more of the constituent parts of it.

Mucous membrane

The mucus membrane of the nose is initially adherent to the periostium or the perichondrium with the exception at the olfactory area. At the olfactory area it is loosely attached. The nasal mucous membrane is subdivided into three parts: vestibular part, olfactory part and respiratory part.

Vestibular part

This part of the mucous membrane lies just inside the aperture of the nostril. It is lined by skin with coarse hairs, sweat glands and sebaceous glands. The hairs (vibrissae) which are curved forward here are moistened by the secretion of the sebaceous gland and arrest the foreign particles, carried by the inspired air.

Olfactory part

This part of the mucuous membrane contains the olfactory cells and its hairs. From the olfactory cells 15 to 20 olfactory nerves start which pass through the cribriform plate of the ethmoid bone and end in the olfactory bulb of cerebrum.

Respiratory part

The rest part of the mucous membrane of nose except the vestibular and olfactory area constitute the respiratory part. It is lined by thick, vascular, ciliated, columnar epithelium. The ciliated columnar epithelium is interspersed by goblet cells. It is thickest and most vascular over the lower aspect of the septum and the turbinates. Actually, over the inferior concha the mucous membrane contain masses of the erectile tissues with numerous arterio-venous shunts. It permits vascular engorgement to regulate the temperature and humidity of the inspired air. The secretion from the sub-epithelial thin walled vessels, serous glands and mucous glands contribute to the formation of mucous in the nose.

The mucous secreted in the nose has two phases – the gel phase and the sol phase. The sol phase is less viscous and is closely applied to the columnar cells of mucous membrane. The gel phase lies over the solphase and is more viscous. It moves backwards by the hooks of the beating cilia which are situated at the end of the ciliated columnar cells. The cilia beat the mucous of the nose back to the nasopahrynx. The mucus and nasal vibrissae (hair) helps to trap the contaminants or foreign particles from the inspired air. The vascularity of the nasal mucosa helps in warming and moistening of the inspired air.

Arterial supply of nose

The arterial supply of nose consists of the arterial supply of medial wall (or nasal septum) and the arterial supply of lateral wall.

A. Arterial supply of medial wall or nasal septum

The nasal septum is supplied by the following arteries.

i. Mobile part of the septum is supplied by the septal branches of superior labial artery which is the branch of facial artery (Fig. 20.5).
ii. Antero superior part of nasal septum is supplied by the anterior ethmoid artery, branch of ophthalmic artery.
iii. Postero inferior part of nasal septum is supplied by the sphenopalatine and greater palatine artery, branches of ophthalmic artery.

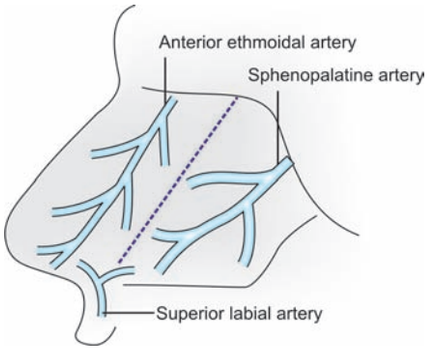


Fig. 20.5: The arterial supply of the nasal septum

An area on the antero inferior part of the septum is highly vascular and known as the Little's area of epistaxis. Because this is the common site for profuse arterial haemorrhage from nose. Here, the septal branch of facial artery, long spheno palatine and terminal branches of greater palatine arteries anastomose.

B. Arterial supply of lateral wall

Similar to the nasal septum, the lateral wall of nose is supplied by the branches of ophthalmic, maxillary and facial arteries. The branches are arranged into four quadrants.

i. Antero superior quadrant: It is supplied by the anterior ethmoid artery, branch of ophthalmic artery.
ii. Postero superior quadrants: It is supplied by the post ethmoidal artery branch of ophthalmic artery and sphenopalatine artery branch of maxillary artery.
iii. Anteroinferior quadrant: It is supplied by the alar branch of facial and terminal branches of greater palatine arteries.
iv. Postero inferior quadrant: It is supplied by greater palatine artery (Fig. 20.6).

Nerve supply of nose

Nasal septum

1. General sensory nerves – comes from the ophthalmic and maxillary divisions of trigeminal N and supply the whole septum.

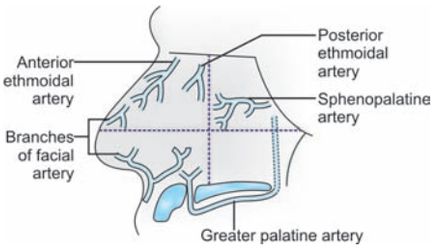


Fig. 20.6: The arterial supply of the lateral wall of the nose

   i. Anterosuperior part of septum – supplied by the intrernal nasal branch of anterior ethmoidal N – branch of opthalmic N – branch of trigeminal N.
   ii. Postero-inferior part of septum – supplied by the spheno-palatine branch of pterygopalatine ganglion – branch of maxillary N – branch of trigeminal N.
   Mobile part: supplied by the external nasal nerve, branch of the ophthalmic division of trigeminal nerve.
2. Special sensory olfactory nerves – supply the upper olfactory area (Fig. 20.7).

Lateral wall of nose

1. General sensory nerves: Like nasal septum the nerve of the lateral wall comes from the trigeminal nerve and distribute to the whole portion of it.
   a. Anterosuperior quadrant–supplied by the anterior ethmoidal nerve – branch of opthalmic nerve–branch of trigeminal nerve.
   b. Anteroinferior quadrant–supplied by the anterior–superior alveolar nerve – branch of maxillary nerve–branch of trigeminal nerve.
   c. Posterosuperior quadrant–supplied by the posterior–superior lateral nasal nerve–comes from pterygo–palatine ganglion–branch of maxillary nerve–branch of trigeminal nerve.
   d. Posteroinferior quadrant–supplied by the anterior palatine nerve–comes from pterygopalatine ganglion–branch of maxillary nerve–branch of trigeminal nerve.
2. Special sensory olfactory nerves – supply to the upper part just below the cribriform plate of ethmoidal bone up to the superior concha (Fig. 20.8).

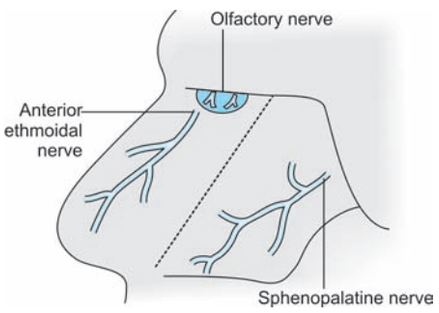


Fig. 20.7: The nerve supply of nasal septum

Functions of the nose

The nose does the following important functions.

(i) Respiration

An adult patient usually takes inspiration through the nose, provided there are no obstructions. Then, the inspired air passes through a wide curve which begins at the nostril and continues through the upper part of the nose to end at the posterior choanae. The inspired air is laminar in flow by character. However, the expired air does not follow this laminar flow like the inspired air. But, it is broken up by the turbinates into turbulent and eddies flow and then passes out through the nostrils. It has been

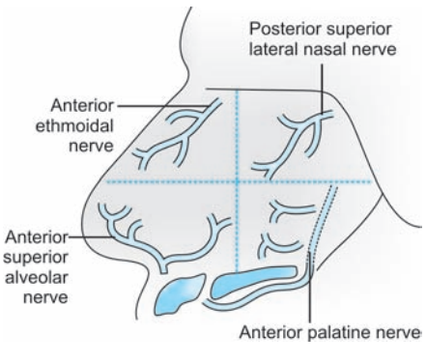


Fig. 20.8: The nerve supply of the lateral wall of nose

postulated that this is because the outlet is smaller than the inlet as the posterior choana is much larger than the nostril. Inevitably, always there is also certain degree of recirculation of air.

In a normal adult subject, the resistance for air to flow through the nose is one and half times greater than the mouth and accounts for nearly 2/3 of the total airway resistance. This explains why a patient takes mouth breathing when high air flow rates are necessary. So, it is always advisable to taste the patency of nasal passage before the nasal intubation is performed. Deflection of nasal septum sometimes become severe and diminishes the lumen of the respiratory airway. Thus, it prevents the passage of all, but the smallest of endotracheal tube.

(ii) Defence

The presence of stiff hairs in the anterior part of nasal fossa (vestibule), the thick and highly vascular (spongy) mucous membrane, the ciliated colmnar epithelium, the extensive lymphatic supply and the bacteriocidal property of the secreted mucous provide a powerful defensive action of nose against the invasion of any organism directly from air. Intermittent flushing action of the watery secretion of nose by sneesing also lies in the reserve of defence action of it.

(iii) Warming and humidification

The most important work that the nose has to perform is the warming and humidification of the inspired air, which is about 10,000 litres in 24 hours in a normal healthy adult. This is only possible due to the high vascularity of nasal mucous membrane. For example, if the temperature of the inspired air is 17°C which is equivalent to the normal room temperature is raised to 37°C which is equivalent to the normal body temperature during its passage through the nose and upper airway. The inspired air temperature also may vary from 25°C to 0°C according to the temperature of the enviornment. But, its passage through the nose produces more or less 1°C difference than that of the body temperature, when it reaches the laryngeal inlet or alveoli (Fig. 20.9).

When the air passes through the air passages, then with rising of temperature also the qauantity of water, needed to saturate the air by water vapour increases. As for example, at room temperature of 17°C the air normally contains 2 volume percent of water to become fully saturated. But, at body temperature of 37°C the air should contain 6 volume percent of water vapour to become fully saturated. The nose and the respiratory tract, therefore, have to perform this heavy task of warming and humidification of the inspired air by adding large quantities of heat and water vapour in the inspired air to make it warm and saturated with water vapour. Warming and humidification of inspired air is achieved by the dilatation of vessels of large vascular mucosal beds of the turbinates of nose. They normally change their volume after every 4 hours of interval (nasal cycle) and each side alternates.

The humidification of inspired air in the air passage is done by the supply of moisture (or water vapour) which comes as transudation of fluid from the mucosal epithelium of nose, pharynx and larynx, and to a lesser extent from the secretion of mucous glands and goblet cells, present in the nasal and pharyngeal mucous membrane. The daily volume of nasal secretions is about 1 litre. Of which about 3/4 is used to humidify the inspired air. Nose also collects the moisture from the expired air to prevent the excessive loss of water from the body.

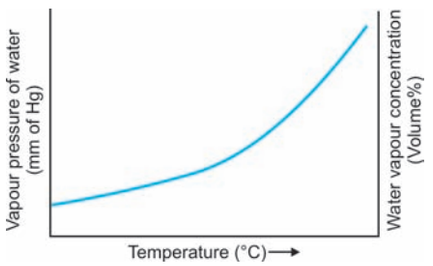


Fig. 20.9: The relationship between the tension of water vapour and the temperature

During intubation and tracheostomy, relatively dry and cool anaesthetic gases or air reach the trachea directly. Because nose and pharynx is bypassed and so proper warming and humidification of inspired air is not done. This compell the mucosa of the trachea and bronchus to perform the heavy duties of nasal and pharyngeal mucous membrane. Therefore, the mucosa of lower airways becomes dry and ciliary activity ceases in such circumstances. Later the tracheal and bronchial mucosa adapts itself to this changed condition. So, endotracheal anaesthesia is frequently followed by tracheitis and bronchitis.

In the most anaesthetic machine, compressed-dry-cooled gases are used. But, these gases are warmed itself to the room temperature before entering into the body during their passage through the long flexible breathing tube. On the other hand, by the 'to and fro' breathing system which occurs in the canister and which is situated near the patient's mouth, the temperature of the inspired gases can be raised upto 37°C (body temperature). So, this system provides (canister which is not used now) very efficient method for warming and humidification of the inspired air. But it has other disadvantages which is discussed in appropriate chapter. But during the passage of expired air through CO_2 absorber in circle system the expired air gains some heat and water vapour produced during absorption of CO_2. In non-rebreathing valve system such as if Ruben and Frumin valve is attached with the circuit, the inspired air is always at room temperature (17°C) and contains only 2 volume percent of water vapour at full saturation which is the normal content of air. But as there is no rebreathing, so the expired air at 37°C containing 6 volume percent of water vapour at full saturation passes out through the valve. In the absence of rebreathing heat with

water vapour is also lost from the body to the atmosphere. Thus it does not help to warm and humidify the inspired air.

In the circle absorption system, the inspired gas mixture contains fresh dry gases coming from cylinder and pipelines and also some expired gases containing water vapour at room temperature. The expired gas leave the patient at body temperature containing water vapour. But by the time they have traversed the breathing tube of the apparatus, they become cool to the room temperature and so have lost the major part of their water content in the apparatus. Dry, cool, fresh gas is again added to the system for inspiration and is mixed with the expired gas coming from the absorber. So, the circle absorption system does much help in warming and humidifying the inspired gases.

(iv) Resonance

Nose as surrounded by multiple air cavities, so gives some resonance to the voice and helps in talk. It also protects the transmission of sound of one's own speech to his own ears. It also equalises the pressure during respiration between internal and external pressure.

(v) Filter

Nose also helps in filtering and clearing the suspended particles from the inspired air. It also transports the mucus posteriorly to lubricate the pharynx.

(vi) Olfaction

Nose also acts as an integral part of the olfactory system.

Some methods of humidification of Inspired air

The inspired air can be humidified by various ways. These are:

(i) Direct instillation of water

Inspired air can be humidified by direct fine drop by drop instillation of normal saline into an endotracheal or tracheostomy tube.

(ii) Water bath

Here, inspired air is passed over the surface of water, kept in a thermostatically controlled and heated water bath. This type of humidifier should be placed on the inspired limb and the gases will flow from the water bath to the patient by the shortest possible route. The tube in shortest route should be insulated to prevent the heat loss with consequent water condensation during the passage of heated and humidified inspired air through the tube. Another method to deliver the inspired gas at body temperature with full saturation by water vapour but without condensation in the breathing circuit is to raise the temperature of the water bath few degrees above the body temperature for compensation to loss which occurs during passage through inspiratory limb. The exact temperature setting of the water bath depends on the surface area of the water, flow rate of gases and the amount of cooling and condensation which take place in the inspiratory limb after the water bath. This type of humidifier should always be kept below the level of the patient to prevent the water being blown accidentally into the patient (Table 20.2).

(iii) Moisture exchanger

It is also called the 'artificial nose'. It is mainly consists of replaceble condenser that can be taken out and cleaned. It is very light and a moderately efficient method of humidification of inspired air. As this system works at room temperature which is much below the body temperature, so part of the water vapour of expiratory gases is condensed on its inner surface and this condensed water again humidifies the dry inspired gases. It can not, of course, achieve full saturation owing to the lower temperature. There are two demerits of this system. One is the colonisation of bacteria and another is the increasing of airway resistance due to the condensation of moisture. These disadvantages can be overcome by using disposable and sterilised unit.

Table 20.2: The percentage of humidity of inspired gases in different anaesthetic system

Anaesthetic system	*% of humidity*
Nose	100
Close circuit	40 - 60
'To and fro' system	60 - 100
Non-rebreathing valve	0
T-piece	0

(iv) Mechanical nebuliser

This is operated by pneumatic power and breaks up the drops of water into small particles. In this system the water passes up through a capillary tube to its summit where it is crushed by the jet of air into microparticles. In this type of nebuliser 80% of the water particles are in the range of 2 to 4 microns and the remainder are smaller. So most of these particles are deposited around the bronchial level and for many patients this is sufficient. Contrary, the water particles which are less than 2 micron reach the small bronchi and alveoli. Those water particles which are above 4 microns do not float. They coalesce and fall back in the reservoir. This type of nebuliser for humidification of inspired air can be used pre and post-operatively with the face mask to improve the lung function.

(v) Ultrasonic nebuliser

This is the most efficient instrument for humidification of inspired air. Here the drops of water is passed through a capillary tube, and completely nebulized to aerosal by a vibrating transducer head which is activated by a high frequency ultrasonic energy. Here, 70% of the water particles get the size of 0.8 to 1 micron. So usually, most of the particles of less than 1 micron are deposited in the lower airways and alveoli of the lungs. At the maximum rate of 12 drops of water/ min falling on the transducer head and with a ventilator delivering of 10 litres of gas/min, 72 ml of water as vapour can be provided with each litre of gas . This corresponds to the relative humidity of 160% at 37°C.

Among all the methods of humidification of inspired air, ultrasonic nebuliser produces the most satisfactory humidification. It can also be used for the administration of water soluble aerosal drugs. The two demerits of this instrument are: (i) over hydration, due to extreme effeciency and (ii) difficulty to sterilise by conventional method.

Ciliary Activity of Airway

Throughout the upper and lower respiratory tract the continuous ciliary activity of mucous membrane plays a very important function. This is the prevention of accumulation of mucous secretion which is needed for the efficient functions of nose, pharynx and larynx. By ciliary action in the nose, the mucous secretion are swept posteriorly towards the pharynx and in the bronchial tree the mucous secretions are carried upwards towards the larynx (Fig. 20.10).

The Cilia are fine hair like structures. They are 7 µm in long and 0.3 µm in width. The tips of cilia are always bend towards the direction of the flow of mucous. In the shaft of the cilia which are occupied by cytoplasm there are microtubules containing dyenin arms. The longitudinal fibrils or microtubles in the shaft of the cilia are arranged in a fashion like that a pair of microtubles is situated in the centre and it is surrounded by nine pairs of microtubles at the periphery. The activity of the cilia depends mainly on the mucous blanket, covering it. The covering mucous blanket consists of two layers. The outer gel layer is thick and viscous. It is designed to entrap the floating particles from inspired gas such as dust, soot, microorganisms etc. The inner sol layer is thin serous like fluid. It is designed to lubricate the action of the ciliary movement. The tips of cilia come just in contact with the outer gel layer with each beat. Acting in union, the cilia set the outer gel layer in motion. Thus gathering momentum, the mucous flows towards the pharynx from nose and towards the larynx from the bronchus and trachea. They beat forward in an effective stroke pulling the gel phase by the action of hooks at the end of the cilia and then beat backward in a recovery stroke. Their action is reminiscent of a corn field being blown by the wind. This movement is called metachrony, as opposed to the synchrony where all the cilia beat together. At 37°C, the cilia of the nasal mucosa beat about 10 to 16 times per second. The average estimated speed of movement of mucous blanket over the mucous membrane is 0.25 to 1 cm/min. Thus, the entire mucous content of the nose take 20 to 30 minute to be emptied into the pharynx (Fig. 20.11).

In some conditions, ciliary action may be defective, for example, Kartagener's syndrome. This is a genetic disorder in which there is defect in the ultrastructure of the cilia. This is due to the failure of synthesis of protein which form the dyenin arm of cilia. The congenital absence of this dyenin arms which normally contain ATP and power the cilia makes the cilia immobile. So, these patients have a constantly running nose, secretory otitis media, chronic sinusities, bronchiectasis and often situs inversus. The tail of sperms have the similar structure like cilia. So that in this syndrome there is also male infertility due to reduced sperm motility.

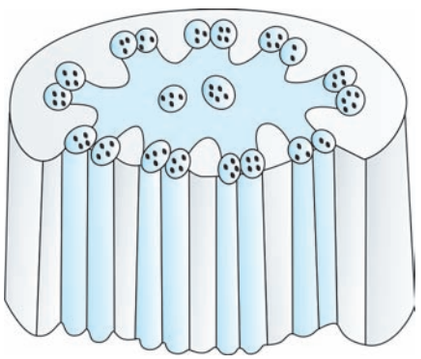


Fig. 20.10: The transverse and longitudinal section of a nasal cilium at the middle of the shaft of it

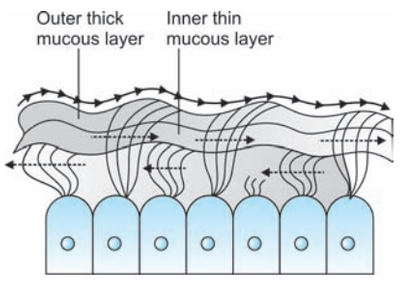


Fig. 20.11: The ciliary movement

Factors influencing ciliary activity

The factors which influence the ciliary activity are: temperature, mucous, changes in pH and drugs.

Temperature

There is a definite range of temperature when the cilia acts optimally. This is 28°C to 35°C. Ciliary activity ceases when the temperature of the mucosa falls from 7°C to 10°C. It is also depressed when the temperature of cilia rises above 35°C, while the average nasal temperature is about 32°C. Actually the direct effect of temperature on ciliary action is minimal and the effect is largely caused indirectly by alterations in the amount of mucus secreted.

Mucous

Cilia cannot work without the optimum temperature and the blanket of mucus. Drying out of the mucus blanket over them can stop ciliary activity, though the temperature is maintained at optimum level. So, excessive dry and cool air, volatile anaesthetics, atropine, etc; decrease mucus secretion and subsequently stop the ciliary activity.

Changes in pH

Cilia acts better in alkaline media. They become paralysed in acid solutions at pH 6.4 or less. A rise of pH to 8 or more also causes depression of the ciliary activity.

Drugs

All volatile anaesthetics, opiates, atropine, etc, also depress ciliary activity. But, N_2O has no effect on it.

Pharynx

The pharynx or the pharyngeal airway is a fibromuscular structure. It extends proximally from the base of the skull at the posterior aspect of the nose to distally upto the level of the 6th cervical vertebra or cricoid cartilage where it becomes continuous with the oesophagus and the larynx. Anteriorly the pharynx communicates with the nasal cavities, the oral cavity and the larynx from above downwards. Thus, pharynx is divided anatomically into nasopharynx, oropharynx and laryngopharynx (hypopharynx). Soft palate separates the nasopharynx from the oropharynx and the plane drawn at the upper border of epiglottis separates the oropharynx from laryngopharynx. Except the nasopharynx which is covered by ciliated columnas epithelium, the oropharynx and laryngopharynx is covered by the stratified squamous epithelium. The middle fibrous layer of pharynx consists of the pharyngobasilar fascia. The outer muscular layer of pharynx is comprised chiefly of the three constrictor muscles such as superior, middle and inferior constrictor muscle of pharynx and overlap one on another from below upwards.

Nasopharynx (Fig. 20.12)

It extends above from the base of the skull to below upto the level of hard palate and soft palate. Anteriorly nasopharynx communicates with the nasal cavities through the posterior nares and posteriorly it is bounded by the body of C_1 and C_2 vertebrae. Nasopharyngeal isthmus is the aperture situated between the nasopharynx and oropharynx and is surrounded by the free margin of the soft palate anteriorly and the posterior wall of the pharynx posteriorly. This opening is closed during the 2nd stage of deglutition by the soft palate. At the junction of the roof and the posterior wall of the nasopharynx and at the base of the skull, there lies a small mass of lymphoid tissue, embedding in the mucous membranes called the pharyngeal tonsil or adenoids. By the side of

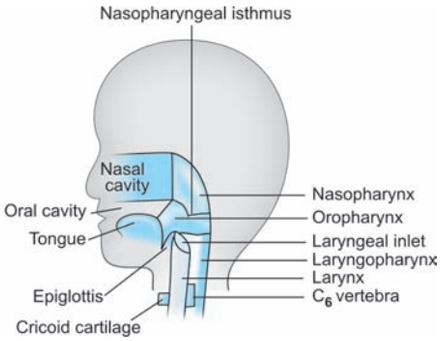


Fig. 20.12: The sagittal section of head showing the different parts of pharynx

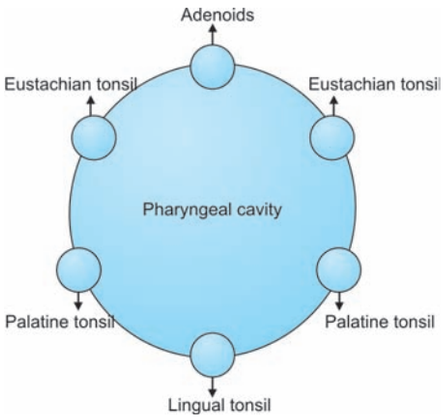


Fig. 20.13A: The ring of Waldeyer

adenoid, there is an opening of Eustachian tube, which connect the middle ear cavities with the nasopharynx. It is also lined by ciliated columnar epithelium and is continuous with the nasopharynx. There is also a collection of lymphoid tissue around the Eustachian tube opening and is called the Eustachian tonsil. Lying close to the base of the adenoids there is a small recess, called the pharyngeal bursa which often impedes the passage of a nasal endotcheal tube. If force is applied, the tube may then penetrate the bursa and can create a false passage. This may lead to the collection of blood and postoperative sepsis. As the pharynx is riched with the lymphatic supply, so the enlargement of these lymph glands and the swelling of the overlying mucosa may lead to the partial obstruction of the airway. All the lymph glands of nasopharynx are arranged in a circular fashion, called the Waldeyer ring. It consists of adenoids (A), Eustachian tonsil (E), palentine tonsil (P) lying between the pillars of the fauces, and the small lingual tonsil (L) at the base of the tongue. The motor nerve supplying to the constrictors muscle of pharynx comes from vagus. The sensory nerve supply of pharynx comes from the trigeminal nerve (Fig. 20.13A).

Oropharynx

This part of the pharynx extends from the level of hard palate and soft palate above to the level of the hyoid bone below. It is bounded above and infront by the soft and hard palate; below and infront by the dorsal surface of base of the tongue up to the upper border of epiglottis. It is bounded posteriorly by the bodies of C_2 and C_3 vertebrae. The free edge of the soft palate forms the palatine arch. From the centre of the palatine arch uvula hangs downwards. From the side of the arch, on either side, two folds of mucous membrane run downwards. These two folds of mucous membrane are raised up by the bands of muscle fibres, named the palatoglossus and palatopharyngeus muscle. They form the pillar of the fauces and between which lies the palatine tonsil. The glossopharyngeal and trigeminal nerve supplies the sensory of the oropharynx.

Hypopharynx

It is a part of the pharynx lying below the oropharynx. It extends from the plane drawn at the upper border of the epiglottis above to the lower border of the cricoid cartilage or C_6 vertebrae below, where it is continuous with the larynx in front and the oesophagus at behind. The inlet of larynx, posterior surface of cricoid and arytenoid cartilage lie in front and 4th, 5th and 6th cervical vertebrae lie behind the hypopharynx. Laterally, the hypopharynx present the pyriform fossa on each side of the inlet of larynx. Pyriform fossa is bounded medially by the eryepiglottic

fold and laterally by the thyroid cartilage and the thyrohyoid membrane. Beneath the mucosa of the pyriform fossa lies the internal laryngeal nerve which is a branch of superior laryngeal nerve (Fig. 20.13B).

The motor supply of hypopharynx comes from the cranial accessory nerve through the pharyngeal branches of glossopharyngeal nerve. Vasomotor of pharynx is supplied by the superior cervical sympathetic ganglion. The vagus nerve supply the sensory to the airway below the level of epiglottis. The superior laryngeal nerve, a branch of vagus, divides into an external (motor) nerve and an internal (sensory) laryngeal nerve that supply sensory to the hypopharynx and larynx between the epiglottis and vocal cord. Another branch of vagus, the recurrent laryngeal nerve, supply the larynx below the vocal cord and trachea.

Larynx

Larynx acts as an organ of voice, air passage and inlet valve for the lower respiratory tract.

It extends from the base of the tongue above to the trachea below. It lies opposite to the body of C_3 to C_6 vertebrae. In children it lies more anteriorly and at more higher level than adult. Larynx is consist of cartilages, ligaments, muscles and membranes. The cartilages are total 9 in number. Among them 3 are paired (arytenoid, corniculate and cuneiform) and 3 are unpaired (epiglottis, thyroid and cricoid). The epiglottis is a leaf-shaped cartilage with broad and free upper margin. The lower end of it is pointed and attached to the angle between the two laminae of the thyroid caritlage. Anteriorly the epiglottis is connected to the base of tongue by 3 mucosal folds – a median glossoepiglottic fold and a pair of lateral glossoepiglottic folds. The depression between the median and lateral glossoepiglottic fold is called the vallecula and this is the site where the tip of the blade of Macintosh laryngoscope rests. The epiglottis projects into the hypopharynx and overhangs on the laryngeal inlet. Sealing of the laryngeal inlet by epiglottis during swallowing and deglutition is not absolutely necessary. The lateral margins of the epiglottis is attached to the quadrate membrane which extends from the arytenoid cartilage (situated posteriorly) to the margins of the epiglottis (situated anteriorly). The lower free border of this quadrate membrane forms the vestibular fold and the upper free border forms the aryepiglottic fold. Arytenoid is a small pyramidal shaped cartilage and situated at the upper border of the lamina of cricoid caritlage. The Apex of arytenoid cartilage again articulates with corniculate and cuneiform cartilage.Vocal cord is attached to the vocal process of this arytenoid cartilage. Corniculate and cuneiform cartilage lie in the posterior part of aryepiglottic fold (Fig. 20.14).

The thyroid cartilage is a V-shaped cartilage and is made up of two quadrilateral laminae. They are fused > 90° angle in male and > 120° angle in female anteriorly. The line of junction of these two laminae forms in male the Adam's apple. The Posterior border of the thyroid cartilage is free and projects both upwards and downwards as superior and inferior cornu. The Inferior cornu articulates with the cricoid cartilage. On the outer surface of the laminae of thyroid cartilage there is an oblique line which gives attachment to sternothyroid, thyrohyoid and inferior constrictor muscle of the pharynx. The Upper border of the thyroid cartilage gives attachment to the thyrohyoid membrane

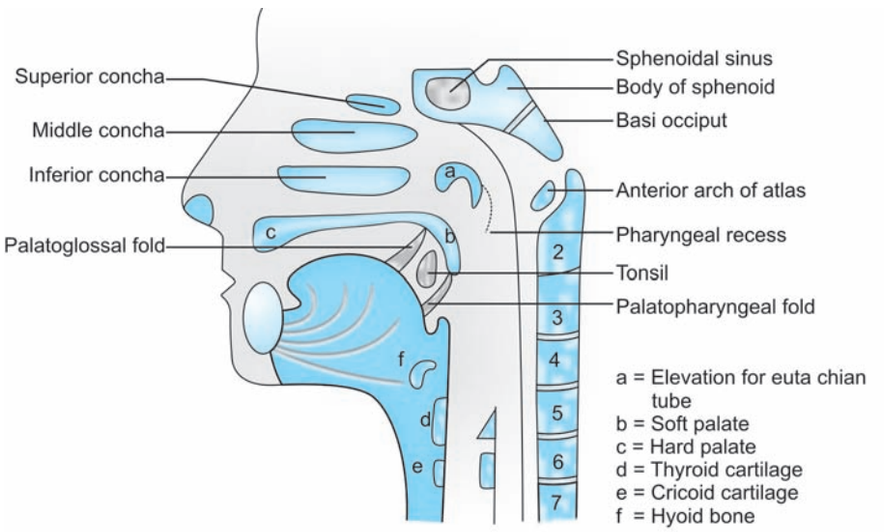


Fig. 20.13B: The sagittal section through the pharynx, nose, mouth and larynx

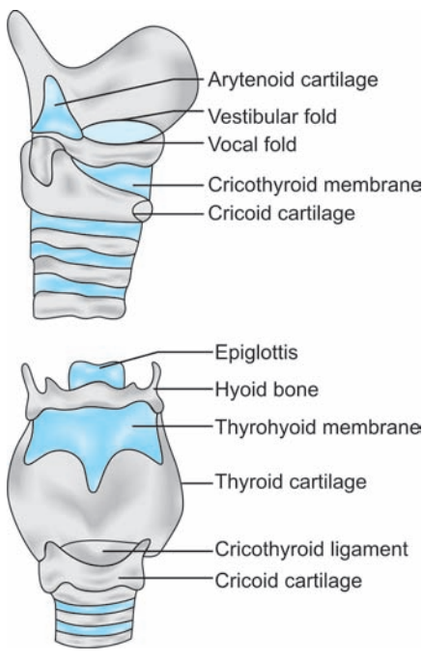


Fig. 20.14: Cartilages and ligaments of larynx

which is pierced by the internal laryngeal nerve and superior laryngeal vessels (Fig. 20.15).

The cricoid cartilage is looked like a signet shaped ring and encircles the larynx. The narrow anterior part of this ring shaped cricoid cartilage is called the arch and the broad posterior part is called the lamina. Superiorly the lamina is attached with arytenoid cartilage and at the side with the inferior cornu of the thyroid cartilage. A membrane named the conus elasticus or cricovocal membrane extends upwards and medially from the upper border of the arch of cricoid cartilage to the thyroid cartilage in front and the vocal process of the arytenoid cartilage behind. The anterior part of this membrane is thick and is known as the cricothyroid ligament. The upper free border of this conus elasticus membrane forms the vocal cord (Fig. 20.16).

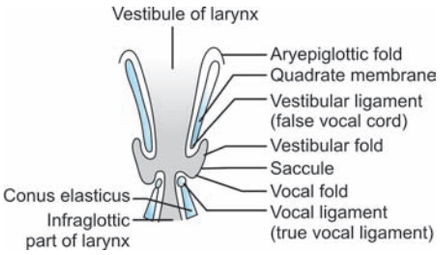


Fig. 20.16: Coronal section showing the parts of the cavity of larynx

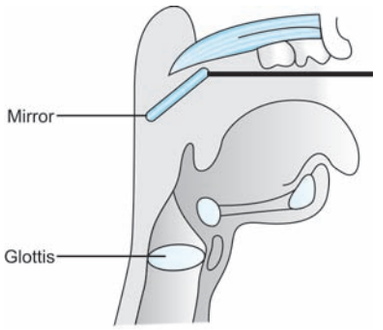


Fig. 20.17: Indirect laryngoscopy by mirror

Cavity of larynx

The cavity of the larynx extends above from the inlet of the larynx to the lower border of the cricoid cartilage below where it is continuous with the trachea. The inlet of larynx opens above in the laryngopharynx or hypopharynx and bounded anteriorly by the epiglottis; posteriorly by the interarytenoid fold of mucous membrane and on each side by the aryepiglottic fold which is the upper border of the quadrate membrane (Fig. 20.17).

Within the cavity of the larynx, on each side there are two folds of mucous membrane. The upper folds are called the vestibular folds and the space between these two vestibular folds is called the rima vestibuli. The lower folds are called the vocal cords and the space between these two vocal cords is called the rima glottis.

The vestibular fold and the vocal fold divide the cavity of the larynx into three parts. The part of the larynx above the vestibular fold is called the vestibule of larynx. The space between the vestibular folds and the vocal folds is called the sinus of the larynx and the part below the vocal folds is called the infraglottic part of the larynx. The anterior part of the sinus of larynx is prolonged upwards as a diverticulum between the vestibular fold and the lamina of thyroid cartilage. This extension of the sinus is called the saccule of larynx and contains mucous glands which helps in lubrication of the vocal folds (Fig. 20.18).

In the vestibular folds, under the mucous membrane, a narrow bands of fibrous tissue passes from the anterolateral surface of the arytenoid cartilage to the angle of the thryoid cartilage at the point of attachment of the epiglottis. This is called the vestibular ligament. On the otherhand, in the true vocal folds under the mucous membrane a tough fibrous vocal ligament extends from the vocal process of arytenoid cartilage to the angle of thyroid cartilage. Since, as there is no true submucous layer with the usual network of blood vessels within it, so the true vocal cords or folds have the characteristic pale appearance.

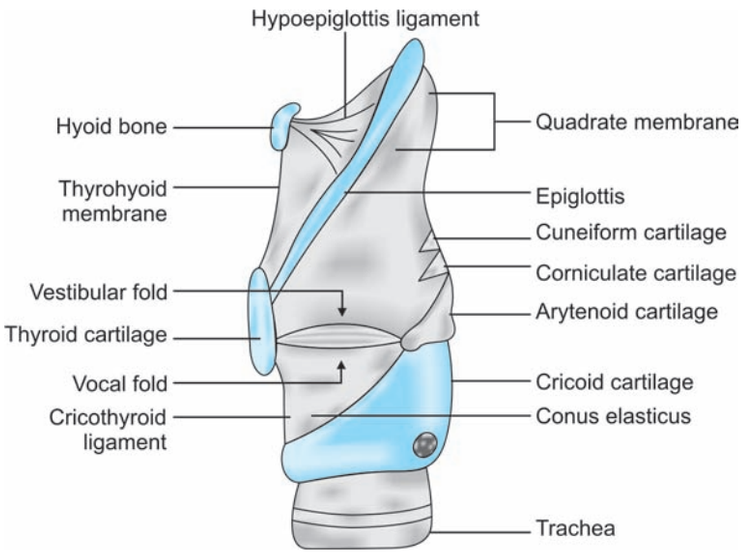


Fig. 20.15: Ligaments and membranes (mainly quadrate membrane and conus elasticus) of larynx

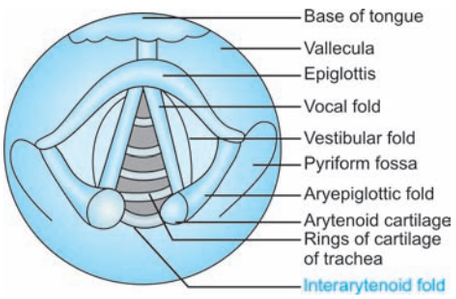


Fig. 20.18: The laryngeal image on mirror during indirect and direct laryngoscopy

In an adult the narrowest part of the laryngeal cavity is the area which is situated between the vocal cords. But in children, under ten years of age, the narrowest part of the larynx is just below the vocal cords at the level of the cricoid cartilage. The clinical significance of this anatomical difference in larynx between an adult and child is found, when small children are intubated. The significance is that in children an endotracheal tube which can be passed between the vocal cords may yet be too large to pass beyond the cricoid cartilage.

Mucous membrane of larynx

The total anterior surface of the epiglottis, upper ½ of the posterior surface of epiglottis, the upper parts of aryepiglottis folds and the vocal folds are all lined by the stratified squamous epithelium. Otherwise, the rest of the laryngeal mucous membrane is covered with the columnar ciliated epithelium. All parts of the mucous membrane of laryngeal cavity are loosely attached to the cartilages, except over the vocal ligaments and posterior surface of the epiglottis where it is thin and firmly adherent to the underlying structure. So, this prevents further spread of laryngeal oedema and accumulation of tissue fluids downwards in the larynx causing suffocation. Mucous glands are absent over the vocal cords. But they are plenty over the anterior surface of the epiglottis, around the cuneiform cartilages and in the vestibular folds. In other parts of the larynx this mucous glands are scanty.

Nerve supply of larynx

Both the superior and the recurrent laryngeal nerves which are branches of vagus supply the sensory and the motor of the larynx. The superior laryngeal nerve descends on the lateral wall of the pharynx, passes posteriorly to the internal carotid artery and at the level of the greater cornu of hyoid bone it divides into an internal and external laryngeal branch (Fig. 20.19).

The internal laryngeal branch is entirely sensory, apart from a few motor filaments

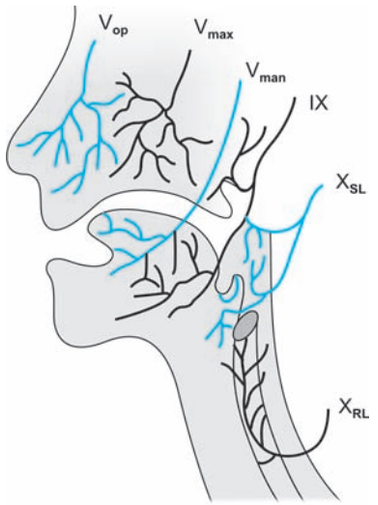


Fig. 20.19: Sensory supply of airway.
V_{op} = Ophthalmic division of trigeminal nerve (anterior ethmoidal nerve)
V_{max} = Maxillary division of trigeminal nerve (sphenopalatine nerve)
V_{man} = Mandibular division of trigeminal nerve (lingual nerve)
IX = Glossopharyngeal nerve
X_{SL} = Vagus superior laryngeal nerve
X_{RL} = Vagus recurrent laryngeal nerve

to the arytenoid muscles and descends on the thyrohyoid membrane. It pierces this membrane above the superior laryngeal artery and then again divides into two branches. The upper branch supplies the mucous membrane of the lower part of the pharynx, epiglottis, vallecula and the vestibule of larynx. The lower branch passes medial to the pyriform fossa beneath the mucous membrane and supplies the aryepiglottic fold and mucous membrane of the posterior part of the rima glottis. The external laryngeal branch, carrying only the motor fibres, innervates the cricothyroid muscle (Table 20.3).

The recurrent laryngeal nerve travels upwards deep to the lower border of the inferior constrictor muscle of the pharynx, accompanying with the laryngeal branch of the inferior thyroid artery. Apart from the sensory fibres which supply the mucous membrane of the larynx below the level of the vocal cords, this nerve innervates all the muscles of the larynx except the cricothyroid and a small part of the arytenoid muscles.

Summary

The upper airway derives its sensory supply from cranial nerves. This can be summarised as follows. Anteriorly the nose gets its sensory supply from the anterior and posterior ethmoidal branch of the opthalmic division of the trigeminal nerve (Vth cranial nerve). Posteriorly the nose is supplied by the sphenopalatine branch of the maxillary division of trigeminal nerve. The soft and hard palate get its sensory supply from the palatine nerve which is branch of the trigeminal nerve. The lingual nerve, a branch of mandibular division of the trigeminal nerve supply the sensory of anterior 2/3 of tongue. The glossopharyngeal nerve or the 9th cranial nerve, supply the sensory of posterior 1/3 of the tongue. Facial and glossopharyngeal nerve provide the sensation of taste of anterior 2/3 and posterior 1/3 of the tongue respectively. The glossopharyngeal nerve also provides the sensory supply to the roof of pharynx, the tonsils and the under surface of the soft palate. The vagus nerve or the 10th cranial nerve, supplies the sensory of the airway below the epiglottis through its superior

Table 20.3: Laryngeal innervation

Nerve	*Sensory*	*Motor*
Superior laryngeal (anterior or internal branch)	Base of tongue, epiglottis and supraglottic mucosa	None
Superior laryngeal (posterior or external branch)	Only anterior subglottic mucosa	Cricothyroid (tensor of vocal cord)
Recurrent laryngeal	Whole subglottic mucosa	Posterior cricoarytenoid (abductor), lateral cricoarytenoid (abductor), interarytenoid (abductor), thyroarytenoid (abductor)

laryngeal (divides into internal and external branch) and recurrent laryngeal branch which is described above (Fig. 20.20).

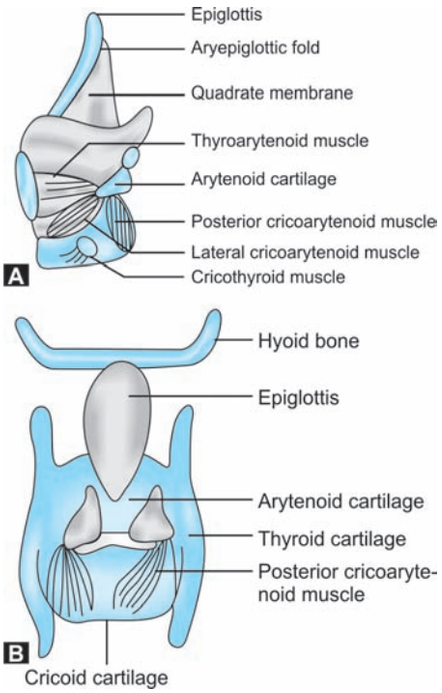
Actions of the intrinsic muscles of the larynx

i. Muscles for closing and opening of the laryngeal inlet.
   a. Closing – aryepiglottic
   b. Opening – thyroepiglottic
ii. Muscles for closing and opening of the rima glottis.
   a. Closing – lateral cricoarytenoids, transverse arytenoid, cricothyroid, thyroarytenoids.
   b. Opening – Posterior cricoarytenoids.
iii. Muscles which tense and relax the vocal cords.
   a. Tense – cricothyroid.
   b. Relax – thyroarytenoids and vocalis.

Movements of the vocal cords

Movements of the vocal cords affect the shape and size of the rima glottis as follows:

i. During quiet breathing (in resting condition), the inter membranous part of the rima glottis is triangular and the inter cartilagenous part is quadrangular in shape.
ii. During forced inspiration the both parts of the rima glottis (intermembranous and intercartilagenous) are triangular, so that the entire rima is lozenge-shaped and the vocal cords are fully abducted.
iii. During phonation (speech), the rima glottis is reduced to a chink by adduction of the vocal cords.
iv. During whispering, the intermembranous part of the rima glottis is closed, but the intercartilagenous part is widely open (Fig. 20.21).



Figs 20.20A and B: The intrinsic muscles of larynx

Applied Anatomy

i. Damage or block of the internal laryngeal nerve which is a branch of superior laryngeal nerve produces anaesthesia of mucous membrane of the supraglottic part of larynx. So, any foreign body can readily enter into the laryngeal inlet as reflexes do not work. But the function of vocal cord is not jeoparadised.
ii. Damage to the external laryngeal nerve which is an another branch of superior laryngeal nerve causes some weakness of phonation. It is due to the loss of tightening effect of the cord by paralysis of the cricothyroid muscle which is supplied by it. On the contrary bilateral damage of the superior laryngeal nerve result in hoarseness and easy tiring of voice. But airway control by vocal cord is not jeoparadised through reflexes of laryngeal inlet is impaired like the injury of internal laryngeal nerve.
iii. When both the recurrent laryngeal nerves are interrupted or blocked, then the vocal cords lie in position of complete adduction due to the unopposed action of cricothyroid muscle. So, patient suffers from stridor and respiratory distress. But airway problem is less frequent in chronic bilateral recurrent nerve interruption. This is because of various compensatory mechanisms which always develop. When only one recurrent laryngeal nerve is paralysed, the vocal cord of opposite side compensates for that. Then there is no difficulty in respiration but only deterioration of voice quality occurs. Bilateral interruption of vagus nerve affects both the superior and recurrent larngeal nerve. Thus it produces flaccid, midpositioned vocal cord as seen after administration of muscle relaxants.
iv. Larynx can be seen directly by a laryngoscope (direct laryngoscopy) or by a laryngeal mirror (indirect laryngoscopy). By these procedures one can see the base of the tongue, valleculae, epiglottis, aryepiglottic folds, pyriform fossae, vestibular folds and the vocal cords.
v. Since glottis of larynx is the narrowest part of the respiratory passage in adult, so if foreign body enters the respiratory passage, it usually lodged at glottis. Once it crosses glottis, it would easily pass through the trachea to lodge in some peripheral narrow bronchus or bronchiole.
vi. Laryngeal oedema may occur due to variety of causes which may be traumatic, allergic or infective, etc. This produces inspiratory stridor, dyspnoea and symptoms of hypoxia.
vii. Laryngismus stridulus is a condition which is characterized by attacks of laryngeal spasms in children, usually during night. In between the attacks, the child is normal.

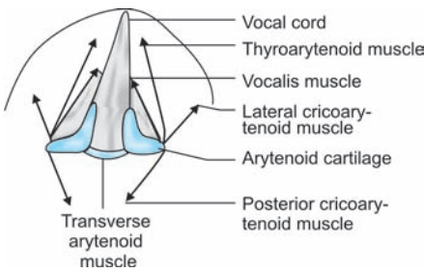


Fig. 20.21: The different directions of movement of muscles of vocal cord

Physiology of Airway Protection

The pharynx, epiglottis and the larynx protect the lower airway from aspiration of foreign bodies. An important mechanism for expelling or preventing the entry of foreign bodies into the lower respiratory passage below the vocal cord is cough. Although epiglottis covers the laryngeal inlet, but it is not always absolutely essential for the airway protection. Closure of the vocal cords by reflex mechanism is the most vital mechanism for lower airway protection, which also produces the protective laryngeal closure during deglutition. The physiological exaggeration of this reflex closure of vocal cord is called the laryngospasm. Therefore, laryngospasm consists of prolonged intense glottic closure in response to the stimulation by inhaled agents, foreign bodies or stimulation from visceras. Laryngospasm is associated with sound ranging from high peached squeaky to total absence, depending on the degree of spasm. Complete laryngospasm is usually silent and should be diagnosed and treated immediately.

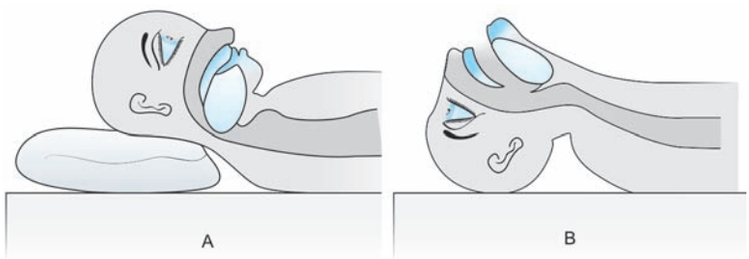
The ideal treatment for complete laryngospasm is the use of muscle relaxant and mask ventilation or intubation. But before muscle relaxants, forward displacement of the mandible, and IPPV by mask and bag with 100% O_2 should be tried. In most of the cases it is effective, because strong pressure applied manually with the help of a bag which is full of O_2 can force the gas effectively through the adducted cords. Thus, tracheal intubation can be avoided. In such situation the traditional view regarding limiting the pressure to avoid barotrauma of lungs are not important and stomach should be watched closely for if air is entering the oesophagus forcefully or not. Another way of management of laryngospasm is IV administration of propofol or thiopentone, making the patient deeply sedated, provided airway is clear of any foreign body. A patient who is scheduled for elective surgery, but experiences repeated intermittent laryngospasm and arrhythmia is a poor candidate for continued attempt of intubation.

Upper Airway Obstruction

One of the foremost duties of an anaesthetist is to maintain an unobstructed airway in an unconcious patient. This obstruction of airway may be total or partial. Partial obstruction is associated with diminished tidal volume (but not completely absent), retractive movement of the rib cages and neck muscles, tugging movement of diaphragm and snoring sound. If the obstruction is near the laryngeal inlet, then there will be inspiratory stridor. The total obstruction of airway is characterised by complete lack of movement of air in and out of the lungs or zero tidal volume which is recognised by no movement of breathing bag and paradoxical movement of the chest and abdomen. The air entry and exit from the lungs should be perceived by the feeling with hand placed over the nose and mouth, looking the non-paradoxical movement of chest and abdomen, and seeing the movement of the bag. An inexperienced person, usually wrongly interprete this retractive movement of chest, abdomen (see-saw paradoxical movement) and neck as a breathing affort. So, recognition of airway obstruction depends on the close observation of the movement pattern of the chest and abdomen and high index of suspicion (Fig. 20.22).

Upper airway obstruction is commonly due to the soft tissue obstruction byfalling back of the tongue on the posterior pharyngeal wall. It may also be due to the tumour, foreign bodies or laryngospasm, etc. But here we will only discuss the obstruction of upper airway by the base of the falling tongue (obstruction of airway by laryngospasm is discussed before). Because it is the commonest cause of upper airway obstruction during anaesthesia and is due to the relaxation of the tongue and jaw muscles. This occurs as soon as the consciousness is lost and the muscles supporting the tongue relax. So, the tongue falls back on the posterior wall of the oropharynx or hypopharynx or on the inlet of the larynx. If the tongue is brought forward by manipulation, then the laryngeal opening once again is cleared and opened. This can be achieved by the following methods.

i. Simple extension of the neck will clear the airway in 75% of cases. It causes the forward movement of mandible and the stretching of anterior tissues of the neck which, in turn, produces the forward traction of the tongue. Thus simple extension of neck release the airway obstruction.
ii. Extension of the neck also causes the mouth to fall open due to down ward pull of the neck tissues. In such condition, simple closing of the mouth in extended position of neck will often improve the airway by straightening the anterior tissues of the neck still further. Thus the resultant changes in head position have been shown to modify the upper airway resistance significantly.
iii. If there is still obstruction, airway can be restored by preventing the mandible from falling back with the tongue. This



Figs 20.22A and B: A. The fall of tongue on the posterior pharyngeal wall and the collapse of pharyngeal wall due to the relaxation of muscles of the airway (mainly genioglossus). B. Extension of neck and elevation of the angle of mandible removes the falling base of the tongue from posterior pharyngeal wall and maintains a clear airway

can be done by drawing the mandible forward and upward by placing the fingers behind the angles of the jaw and exerting an upward pressure towards roof.

iv. If the above mentioned procedures also fail, then the removal of obstruction of the airway can be accomplished with some mechanical contrivnaces, termed the oropharyngeal or nasopharyngeal airway, though other types of airways are discussed later. The idea behind both the oropharyngeal or nasopharyngeal airway is to lift the base of the tongue from the posterior wall of the pharynx and thus to remove the obstruction. The nasopharyngeal airway is better tolerated in light plane of anaesthesia than the oropharyngeal airway. But, the mere placement of any of the above mentioned airway does not gurantee unobstructed air flow. This is because these airways do not get any support from the relaxed mandible due to the relaxation of jaw muscles and is displaced. So, it is often necessary with the oropharyngeal or nasopharyngeal airway to support the mandible further by forward traction or by pressing upward at the angles of it. In the anaesthetised patient, pharyngeal and laryngeal reflexes are obtunded. If these reflexes are still active, then insertion of any airway to prevent the obstruction may precipitate further gagging, emesis or laryngeal spasm, causing more obstruction (Fig. 20.23).

Oral airways are generally made up of plastic and its size ranges from 0, 1, 2 (50 to 60 to 70 mm) for children to 3, 4, 5 (80 to 90 to 100 mm) for adults. It is inserted first with the upside down direction while passing through the oral cavity and then is rotated 180 degrees into the position of function. During insertion of oral airway teeth can be injured and the airway itself can pushes the base of the tongue into the pharynx. Thus it can actually increase the airway obstruction instead of removing it. Hence, an anaesthetist must be careful during insertion of airway.

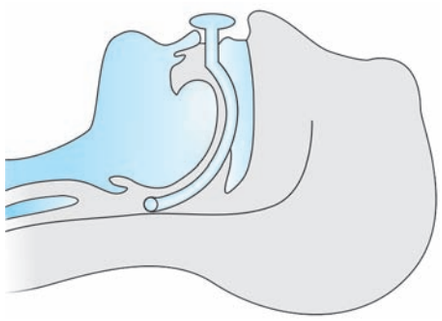


Fig. 20.23: Oropharyngeal airway elevating the tongue

To remove obstruction of upper airway by falling tongue soft nasal airways are useful for patients who are not deeply anaesthetised. However, contraindications to the use of nasal airways include coagulopathy, basilar skull fracture, large adenoids, nasal infections, nasal deformities, etc. Introduction of nasopharyngeal airway can be facilitated by phenylephrine nasal drops (causing vasoconstriction of nasal mucosa) or by lubricating the airway with lignocaine or K-Y gel. During introduction, tip of the nasal airways should be perpendicular to the face and is advanced slowly along the floor of the nasal passage. At any circumstances the tip of the airway should not be directed upward towards the cribriform plate. The length of the nasopharyngeal airways is roughly estimated by the distance from the tip of the nose to the meatus of the ear. When such manoeuvres and the use of artificial airways provide inadequate relief of upper airway obstruction by soft tissues, then the insertion of an endotracheal tube or other methods to by pass the upper airway obstruction should be comtem-plated.

EVALUATION OF THE AIRWAY

Introduction

One of the most important thing that an anaesthetist has to learn is the efficient management of airway. On the otherhand, proper evaluation of an airway is an essential part of the efficient management of airway. So, before every induction for anaesthesia, the airway of a patient should be evaluated or assessed properly by an anaesthetist. Thus, the discussion regarding the assessment and evaluation of airway has been widely accepted in anaesthesia for long time. Although, multiple predictive methods and scoring system for evaluation of airway has been suggested, but nothing can give 100% correct prediction. So, we will take only true scientific predictive protocol that all anaesthesiologists can depend upon it. This is because still now sometimes the unanticipated difficult airway in apparently normal patients sends us the signals for our inability to solve this problem.

The questions in these predictors tell us about the different terms which are frequently used such as difficult airway, difficult ventilation or difficult intubation. Because the answers to these questions are different. These three different technical skills are: unable to expose the glottis by conventional laryngoscope (difficult airway), unable to ventilate the patient maintaining $SPO_2 > 90\%$ (difficult ventilation) and unable to insert a ET tube into the larynx (difficult intubation). The former is generally termed difficult if one gets a poor view of the target organ i.e glottis (Cormack Lchane grade 3 or 4). The second is termed difficult if one without any assistance can not maintain $SPO_2 > 90\%$ by ventilating with 100% O_2. The third is termed difficult if after an arbitrary number of attempts (usually 3), the ET tube cannot be placed into the trachea (difficult intubation). All these three should be evaluated together or separately based on the history, clinical examination and radiological diagnostic tests. For easy and quick intubation good view of larynx is mandatory. So difficult laryngoscopy and bad view of larynx (difficult airway) is associated with difficult intubation. Hence, the assessment

of difficult airway and difficult intubation should be discussed together. The assessment for difficult ventilation is discussed under separate heading.

Airway can be classified on the basis of predictions and ultimate difficulties or outcome into three categories.

i. A predicted normal airway.
ii. A predicted abnormal airway.
iii. An unpredicted difficult airway.

Among them, the patients of group three are the most dangerous. Even, among the patients of group three, those which have failed intubation and mask ventilation is also not adequate, actually presents the life threatening condition.

Evaluation of airway can be performed under three headings.

Table 20.4: Common congenital syndrome causing difficult airway and intubation

(i)	Pierre-Robin syndrome:
	Micrognathia, macroglossia, cleft palate.
(ii)	Treacher-Collin's syndrome:
	Auricular and ocular defects, mandibular hypoplasia.
(iii)	Down's syndrome:
	Poorly developed nasal bridge, large tongue, small mouth.
(iv)	Klippel-Feil syndrome:
	Fusion of vertebra, restricted neck movement.
(v)	Goldenhar syndrome:
	Mandibular hypoplasia, cervical spine abnormality, occipitalization of atlas, auricular and ocular defects.
(vi)	Goitre:
	Compression and deviation of trachea.

There are many other diseases such as rheumatoid arthritis which may progress gradually and may cause airway problem during present anaesthesia which might have no airway complication during previous anaesthesia.

History

One of the most important point during history taking for evaluation of the airway is if there is any difficulty during previous general anaesthesia, more specifically during mask ventilation or ET intubation. This history should be properly documented and passed on to the next anaesthesia caregiver.

History of other previous and present diseases such as infection, trauma, neoplasia and inflammation which may affect the airway and subsequently the mode of anaesthesia should be taken properly. Some other present conditions that could predispose to difficult airway are: oedema of the face and neck, burn, active bleeding in the oral cavity, tracheal and oesophageal stenosis or aspiration of gastric content etc. There are many other congenital syndromes which are associated with airway problem and intubation difficulty during anaesthesia should also be kept in mind.

These common congential syndrome causing difficult airway and intubation are given in table (Table 20.4).

Physical Examination

After history taking, every patient should be properly examined physically to predict any difficulty of airway management during anaesthesia. Many additional clinical tests to predict difficult laryngoscopy and difficult intubation have also been described, but none of these tests is totally reliable. Their use may complement each other and also the routine physical examination of the airway. The routine physical examination of air way should start from the simple inspection of head and neck of patient to identify any obvious problem such as massive obesity, cervical collars, external injury, burns, contracture, restricted jaw movement, reciding mandible, bucked teeth, etc. to whole body inspection to some comprehensive scoring system. For example, congenital presence of some ear and hand abnormalities suggest associated presence of some congenital cardiovascular disorders and abnormal airway. Adequate nasal airway should also be evaluated before any nasal intubations (Table 20.5).

Regarding teeth; loose teeth, protuberant upper incisors, false teeth and other dental works such as crown, bridges, braces, etc. should be noted. Edentulous patients presents seldom difficulty to intubate unless other associated problems are severe. Protuberant upper incisors may make laryngoscopy difficult and can cause damage to the teeth. Severe loose teeth should be removed or fixed by ligature before laryngoscopy to avoid aspiration of it. Artificial dentures should be removed (Table 20.6).

Table 20.5: Wilson has identified five risk factors on the basis of which 0, 1, 2 points are awarded and a scoring system has been developed. A score of 5 to 10 would predict severe laryngoscopy and intubations difficulty

	Risk factors	*Scoring*
Weight	< 90 Kg	0
	90 - 110	1
	> 110	2
Head and neck	> 90°	0
	± 90°	1
	< 90°	2
Jaw movement (Inter incisor gap = IG)	IG > 5 cm	0
	IG = 5 "	1
	IG < 5 "	2
Receding mandible	Normal	0
	Moderate	1
	Severe	2
Bucked teeth	Normal	0
	Moderate	1
	Severe	2

Table 20.6: Conditions associated with difficult airway and intubations

Tumours	
	Large goitre, cystic hygroma, lipoma, haemangioma, haematoma, adenoma, papillomatosis, any tumours of pharynx or larynx etc.
Arthritis	
	Rheumatoid arthritis
	TM joints ankylosis, restricted spine.
	Ankylosing spondylitis
	Cervical spine ankylosis, restricted cervical spine mobility.
Infections	
	Abscess (peritonsilar, retropharyngeal submandibular etc), Ludwig's angina, epiglottitis, trismus, laryngeal oedema, laryngitis etc.
Trauma	
	Maxillary fracture, mandibular fracture, basilar skull fracture, cervical spine fracture, inhalation, burn, laryngeal fracture, oedema of airway, etc.
Foreign body: Anywhere in pharynx and larynx	
Obesity	
	Short neck, sleep apnoea, extra tissue in oropharynx.
Acromegaly	
	Macroglossia, prognathism.
Other anatomical variations	
	Micrognathia, high arched palate, prominent upper incisor, scleroderma, sarcoidosis.
Congenital syndrome	
	Discussed before

Next, opening of the mouth should be assessed and it depends on the function of the temporomandibular joint. Any previous and present disease of the temporomandibular joint make the mouth opening difficult and visualization of any pharyngeal and laryngeal structure is impossible. Normally, an adult should be able to open their mouth, so that there is 50 mm distance between the upper and lower incisor teeth (Figs 20.24 and 20.25).

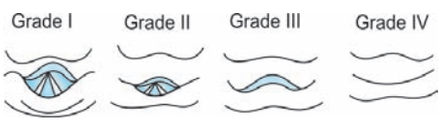


Fig. 20.24: Grading of the laryngeal view (Cormack-Lehane)

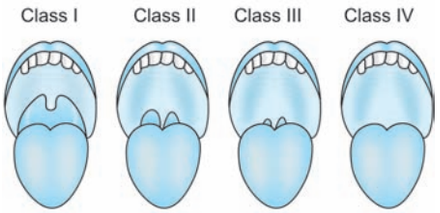


Fig. 20.25: Mallampati classification or test of oral opening

After assessment of mouth opening, oral cavity should be examined for large tongue, high arched palate, long narrow mouth, etc., which may cause difficult laryngoscopy and intubation. In 1983, Mallampati has evaluated a scoring system by observing the structure of the oral cavity through opened mouth by which difficulty of laryngoscopy and subsequent difficult intubation can be assessed or predicted. This is based on the visualisation of soft palate, uvula and faucial pillar. This test is performed with the patient sitting upright, head in neutral position, mouth opened as wide as possible and tongue protruded as far out as possible. Originally, there was three grades in Mallampati scoring system. The scoring system of Mallampati predicts approximately 50% difficult intubation. Then in 1987 Sampson and Young in their modification of Mallampati scoring system further added grade IV (Table 20.7).

Another way of assessing the difficulty in laryngoscopy or visualization of glottis and subsequent difficult intubation is to measure the distance from the symphysis of mandible to the hyoid bone. This distance should be at least 2 large finger breaths in adults. The space between the mandible and the hyoid bone is important, because during laryngoscopy the tongue is displaced into this place for visualization of glottis. If this space is narrow, glottis cannot be seen properly.

Then, the neck should be examined for its mobility, particularly for extension. A thick short muscular neck may result in difficult mask ventilation and as well as laryngoscopy and intubation. The normal amount of neck extension is 35 degrees. The measurement can be made by simple visual estimation or more accurately with goniometer. Any reduction in extension of neck is expressed in grades (Table 20.8).

Cervical spondylosis, ankylosis, rheumatoid arthritis of cervical vertebral joint etc; may restrict the flexion and extension of the inter cervical vertebrae or atlanto-occipital joint and cause difficulty in visualization of glottis by laryngoscope. Thus difficult intubation may precipitate. Extension of the neck also can be quantified by measuring the distance from the symphysis of mandible to the thyroid notch (thyromental distance) with the head fully extended. If the distance is more than 65 mm (3 large finger breaths), then visualization of the larynx and intubation will not be difficult. If this thyromental distance varies between 60 and 65 mm (or 6 and 6.5 cm) then visualization of larynx would be slightly difficult. The thyromental distance below 60 mm definitely suggests that laryngoscopy would be more difficult. The explanation of this observation is that if the thyromental distance is short then the laryngeal axis will make a more acute angle with the pharyngeal axis and it will be difficult to achieve alignment between the laryngeal and pharyngeal axis. This scoring system is developed by Patil, Sterling and Zanden. These three specific tests such as Mallampati, thyromental distance and extension at the atlanto-occipital joint together have

Table 20.7: Mallampati grading

Grade I	Anterior and posterior faucial pillar, soft palate and uvula is visible.
Grade II	Only soft palate and uvula is visible.
Grade III	Only soft palate is visible.
Grade IV	Soft palate is not visible.

Table 20.8: Mallampati grading for neck extension

Grade I : > 35 degree
Grade II : 22 to 34 degree
Grade III : 12 to 22 degree
Garde IV : < 12 degree

almost 100% reliability in predicting airway difficulty. Another way of assessment of neck mobility is the measurement of sternomental distance. If the sternomental distance is less than 12.5 cm, then intubation will be difficult. Lesser the distance greater will be the difficulty. This distance should be measured with head in full extension and mouth closed (Fig. 20.26).

It should be noted that the combination of several minor physical anomalies may result in a difficult laryngoscopy and difficult intubation even when no single factor or test is severely abnormal. Difficult intubation may occur occasionally for reasons that are currently unexplained and none of the available indices predicts it. Even though the airway may look normal on external assessment, one may come across difficulty during laryngoscopy and intubation due to the variations in internal anatomy of upper airway. Cormack and Lehan have defined four grades of laryngoscopic view and predict subsequent difficult intubation which is given below.

Grade I : Visualization of entire laryngeal aperture including full length of vocal cord and arytenoid cartilage.

Grade II : Visualization of epiglottis, aryte-noid cartilage and posterior part of vocal cord only.

Grade III : Visualization of epiglottis only.

Grrad IV : Epiglottis not visible.

Comparison of Mallampati and Cormack-Lehan grading.

Grade I Grade I

Grade IV, Grade III and IV

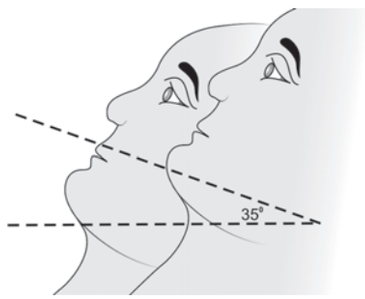


Fig. 20.26: Assessment of neck mobility by measuring sternomental distance

Grade II and III Relatively uniform distribution in all grades

The application of external pressure can reduce the incidence of grade III view from 9% to between 5 and 1%.

Investigations

The other ways of assessing the airway are laboratory investigations such as X-ray, CT scan and MRI of head and neck. Lateral X-ray of the head and neck along with distance marking between the bony land marks have been used to predict the difficult laryngoscopy and difficult intubations. In radiology plate the measurement of atlanto- occipital distance and interspinous gap between C_1 and C_2 vertebrae may also have a predictive value. Other radiological examinations for airway assessment include: decreased posterior depth of the mandible (PDM) and increased anterior depth of mandible (ADM). A ratio of more than 3.6 between the mandibular length and posterior mandibular depth has also been shown to indicate the difficult intubation by White and Kander (Fig. 20.27).

Some Rules and Laws

What is lemon law?

LEMON law stands on:

L = Look externally,
E = Evaluate the 3-3-2-1 rules,
M = Mallampati scale,
O = Obstruction,
N = Neck mobility.

Look externally

It is the external indicators of either difficult laryngoscopy or difficult ventilation or difficult intubation. It includes: presence of huge beard or large moustache, abnormal facial shape, extreme nourishmentmal or over, a person without teeth, facial trauma, obesity, large front teeth, high arched palate, receding mandible, short bull neck, severe contracture, etc.

Evaluate 3-3-2-1 rule

i. 3 finger mouth opening. The normal interincisor distance is 4.6 cm or more. While < 3.8 cm of interincisor distance predicts difficult airway and < 3 cm indicates TM joint dysfunction. If the distance is < 2.5 cm, it indicates the difficult laryngoscopic view and < 2 cm indicates laryngoscopy and intubation is impossible.

ii. 3 fingers is the normal distance between the tip of the jaw and the begining of the neck (hypomental distance), while it is fully extended. Alignment of the laryngeal and pharyngeal axis is difficult if this distance is less than 3 fingers breath (or < 6 cm) in adult. If the length varies between 6 and 6.5 cm then alignment is less difficult and while the distance is > 6.5 cm it is normal.

iii. 2 fingers breath is the normal distance between the thyroid notch and the floor of the mandible. When this distance is < 2 fingers breath, then difficult airway and intubation is predicted. (Fig. 20.28)

iv. 1 finger is the normal subluxation of lower jaw anteriorly.

Mallampati scale

Grade I: 80 to 100% easy intubation.

Grade II: Intubation is possible with proper positioning and optimal laryngeal maneuver technique.

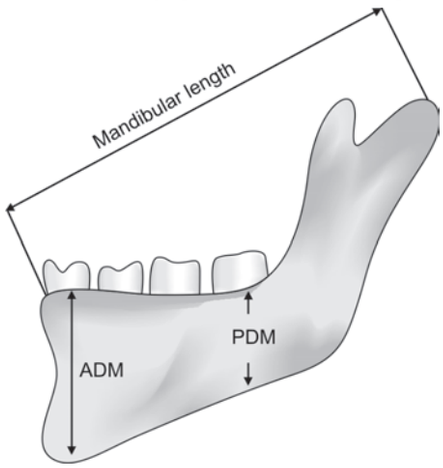


Fig. 20.27: ADM = Anterior distance of mandible
PDM = Posterior distance of mandible

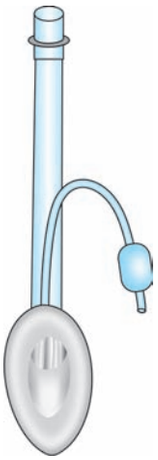


Fig. 20.28: Laryngeal mask (classic)

Grade III: Intubation is still possible with special laryngeal blade or with the use of gun elastic bougie.
Grade IV: Intubation is almost impossible.
This test should be repeated twice to avoid the false positive and false negative results.

Obstruction

For obvious difficulty during laryngoscopy and intubation anaesthetist must consider the obstruction of airway with foreign body, tumour, abscess, epiglottitis or expanding haematoma, etc.

Neck mobility

(Movement of atlanto-occipital joint and flexion-extension of the neck)
Normally the atlanto-occipital (A-O) joint movement ranges arround 35°. Limited A-O joint movement is present in cervical spondylosis, rheumatoid arthritis, halo-jacket fixation, etc. The grading of A-O joint movement is done as follows.

Grade I : > 35 degrees
Grade II : 22-34 degrees
Grade III : 12-21 degrees
Grade IV : < 12 degrees

Airway assessment based on LEMON law or method is able to stratify, successfully, the risk of difficult laryngoscopy and subsequent intubation or ventilation by mask.

What is LMMAP rule of airway assessment?

It stands for :
L = Look for external deformity of face and neck,
M = Mallampati,
M = Measurement 3-3-2-1 or 1-2-3-3 fingers,
3– fingers mouth opening
3– fingers hypomental distance
2– fingers distance between the thyroid notch and the floor of the mandible
1 – finger subluxation of lower jaw
A = Atlanto-occipital (A-O) extension
P = Pathological airway obstruction

What are the 4Ds?

The following 4Ds also suggest the difficult airways:

- Dentition filtered = Prominent upper incisors, receding chin, etc.
- Distortion filtered = Oedema, blood, vomits, tumour, infection, etc.
- Disproportion filtered = short chin to laryngeal distance, bull neck, large tongue, small mouth, etc.
- Dismobility= TM joint and cervical spine

What are the Magboul 4 Ms?

There is another easier way to memorize the prediction of difficult laryngoscopy and intubation. This is described as Magboul 4 Ms with STOP sign. The 4 Ms are:
a. Mallampati
b. Measurement
c. Movement of neck
d. Malformation
The STOP signs are
S = Skull (hydro and microcephalus)
T = Teeth (buck, protrud, loose)
O = Obstruction
P = Pathology
(cranio-facial abnormality and syndrome: Treacher-Collins, Pierre-Robin, Goldenhar's Waardenburg syndrome, etc).

Cass and James risk stratification

In 1965, they summarised 6 common anatomical causes of difficult intubation and stratification of risk. These are:

i. Short muscular neck.
ii. Receding jaw with an obtuse mandibular angle.
iii. Protruding upper incisor teeth.
iv. Long and high arched palate.
v. Poor mobility of mandible.
vi. Decreased distance between alveolar and mental ridge which is required for wide opening of mandible for introduction of laryngoscope.

Rapid assessment of airway by "1-2-3 rule"

Rule 1: Ability to insunate at least one finger in front of the tragus when the patient opens his mouth. This establishes the integrity of movement of TM joint.
Rule 2: Determing the adequacy of the opening of mouth by measuring the interincisor gap. This should be at least 2 finger breadths.
Rule 3: Measurement of thyromental distance. It should be at least 3 finger breadths.

Type variable score

i. Receding chin or temporomandibular distance less than 7 cm. 3 points
ii. Mallampati Grade IV. 2 points
iii. Restricted head extension. 2 points
iv. Protruding teeth. 2 points
v. Mouth opening < 4 cm. 2 points
vi. Vertical neck length < 7.5 cm.1 point
vii. Neck circumference > 33 cm. 1 point

The study reveals that a score of 6 or more correctly identify 22 out of 23 difficult intubation.

AIRWAY MANAGEMENT BY MASK VENTILATION

In emergency situation where the patient is apnoeic after giving muscle relevant and patient is unintubated or we fail to intubate then ventilation by mask and bag is life saving. Usually anaesthetic face mask is employed for ventilation by administering air or O_2 and/or anaesthetic gases.

The rim of the face mask is contoured or conformed to a variety of facial features to create a airtight seal with the patient's face. The 22 mm orifice of these face mask is attached to the breathing circuit of the anaesthetic machine through a right angle connector. These face masks are made of different materials which vary from rubber or plastic to silicon. It is also available in different shapes and sizes for newborn to large adult face. The transparent masks are more advantageous because they are less frightening and facilitate observation of the patient for cyanosis and vomiting.

Mask can be held with one hand or both the hands (if necessary, to fit the mask tightly over the face). If both the hands of anaesthetist are used to fit the mask on the patient's face, then an assistant is needed to ventilate the bag or anaesthetic ventilator can be used to supply the positive pressure breaths. By the thumb and the first finger of anaesthetist's left hand the mask should be held tightly on the patient's face, while the other three fingers of the hand will displace the mandible upward by giving upward thrust on the angle of it. Care should be taken that fingers should be kept on the ramus of the mandible, but not on the soft tissues of the neck and the floor of the mouth. Because pressure on the soft tissues of neck by fingers produces discomfort and push the base of the tongue towards the posterior pharyngeal wall, causing more airway obstruction. Mandibular upward displacement along with the upper cervical extension and lifting of the chin upward by fingers tend to pull the tongue and soft tissues away from the posterior pharyngeal wall. Thus, it relieves the upper airway obstruction that occurs in the paralysed and anaesthetised or unconcious patient.

But this mask ventilation is difficult for obese patient, thick neck, short neck, big face, endentulous patients, etc. In endentulous patients, the mask ventilation can be helped by leaving the dentures in place or by using packs or employing the mask strap to pull up the sagging cheeks. Mask ventilation in paediatric patients are more easier than adult patients, provided there is no laryngospasm. Though mask ventilation is very helpful in emergency condition and more easier than ET intubation, but the most serious problems with mask ventilation include failure, distension of stomach by air, pulmonary aspiration and pressure damage to the eyes.

How Do we Predict Difficult Mask and Bag Ventilation ?

Langeron et al suggested five recognised criteria as independent predictors of difficult bag and mask ventilation and that can be summarised as the word OBESE. It is a simple visual way to remember what to look for when evaluating and assessing the airway for difficult mask and bag ventilation.

O = Obese (Body mass index > 40 Kg/m^2)
B = Bearded
E = Elderly (older than 55 years)
S = Snorers
E = Edentulous

The presence of any two of these criterias is best indicated as difficult mask and bag ventilation with a sensitivity of 0.72 and specificity of 0.73.

Obesity is asociated with decreased posterior airway space behind the base of the tongue. This is due to the accumulation of fat in the pharyngeal soft tissue. Thus, it causes more impairment of airway patency during sleep due to fall of tongue on posterior pharyngeal wall and is a risk factor for obstructive sleep apnoea syndrome. Upper airway obstruction can occur early after induction of anaesthesia with the posterior displacement of soft palate, base of the tongue and epiglottis in morbidity obese patients (BMI > 40 Kg/m^2). Age is also closely related to the increased pharyngeal and laryngeal resistance to airflow and is more common in men than women. Lack of teeth and the presence of beard are also associated with difficult mask ventilation. It is due to the decrease in airtight seal of facemask and increased air leak around the mask with more difficult positive pressure ventilation.

AIRWAY MANAGEMENT BY LARYNGEAL MASK AIRWAY (LMA)

Laryngeal mask airway is a new device whose status regarding the management of airway is lying somewhere between the face mask with oropharyngeal airway and the endotracheal tube (ET). This is because it provides more definite airway than the former, but not the more reliable air way protection and maintenance than the later. It sometimes acts as an essential airway device to provide emergency airway and ventilation when conventional mask ventilation and attempts to intubation fails. Therefore, although LMA was originally developed for airway management in routine cases with spontaneous ventilation, but it is now listed in the ASA difficult airway algorithm at 5 different places as a ventilatory device or as a conduit for endotracheal intubation. It is a new device designed to maintain a seal around the laryngeal inlet for spontaneous ventilation and also permits positive pressure controlled ventilation at modest level of pressure (up to 15 cm H_2O). But because of the limited ability of LMA to seal off the laryngeal inlet tightly, the elective use of this device is contraindicated in any of the condition where there is an increased risk of aspiration and where ventilation under high pressure is needed. In patients without these predisposing factors, the risk for pharyngeal regurgitation appears to be low and the use of LMA is safe (Fig. 20.29).

Now, LMA is available in seven different sizes for neonates to large adults. LMA classic is a reusable device. It is made of medical grade silicone and is free from latex. It is to be discarded after 40 autoclaving. There are three main components of a LMA classic: an airway tube, a laryngeal mask with inflating cuff and a cuff inflating pilot catheter with balloon. The

Fig. 20.29: Proseal LMA (PLMA)

airway tube is of large bore with 15 mm standard male adaptor which can be connected with breathing circuit. Its other end is fitted to the mask which has an inflatable cuff. The cuff can be inflated or deflated via a valve located on the pilot catheter. Two aperture bars guard the distal end of the large bore airway tube. The mask of the LMA is specially designed to conform to the contours of the hypopharynx. Now, several new variants of the LMA except classic are available. These are : LMA Flexible, LMA Unique (disposable LMA, Sizes 3, 4, 5), intubating LMA or LMA Fastrach and most recently LMA Proseal. All variants of LMA, except unique variety, are made of silicone or latex free rubber. Unique variety of LMA is made of medical grade PVC. Just enough air to seal the laryngeal inlet can raise the intracuff pressure around 60 cm of H_2O. During cuff inflation, after the introduction of LMA the tube should not be hold by hand as this prevents the mask from setting into its own correct location from itself in hypopharynx. A small outward movements of the tube is often noted during inflation of the cuff as the device seats and adjusts itself in the hypopharynx.

The Proseal Laryngeal Mask Airway (PLMA) is the latest addition to the various modification of the original LMA. Like LMA, the PLMA is also made of latex free silicone and is reusable. The mask and the inflation assembly of this variety of LMA is identical to the classic variety of it. Here, the original larger ventral cuff is fixed to a second cuff which is attached to the dorsal surface of the first cuff. The dorsal cuff, when inflated, improves the seal by pushing the ventral cuff more firmly on the periglottic tissues. So a properly placed PLMA can withstand a leak pressure of approximately 35 cm of H_2O, as against 25 cm of H_2O offered by the LMA classic. The PLMA airway tube is flexible, wire reinforced and double lumened. One lumen is used as airway tube for ventilation and another lumen is used as gastric drainage tube for aspiration of gastric contents during regurgitation. The rationale to place the two tubes side by side, except at the level of the mask is to give greater stability to the device, while once placed in the oral cavity. The PLMA bowl is deeper through which traverses the drainage tube and open most distally. This drainage tube in the bowl helps to eliminate the aperture bars. However, the main purpose of the drainage tube is : to facilitate the gastric tube insertion, to divert the regurgitated fluid away from the respiratory tract and to prevent gastric insufflation. The PLMA comes with a reuseable introducer which is an easily clip-on / clip-off device. A built in bite block has also been added at the proximal end of the two tubes which prevents the patient from biting and collapsing the airway tube. It also helps to bond the two tubes firmly. Introduction of LMA needs adequate depth of anaesthesia, but not so deep as required for tracheal intubation. So, it is not suitable for conscious emergency room patients (Fig. 20.29).

LMA insertion requires an anaesthetic depth which is slightly greater than that required for the insertion of an oral airway, but lighter than ET tube intubation.Under an adequate depth of anaesthesia, an appropriate size of LMA is gradually introduced into the mouth and then into the cavity of laryngopharynx with the aperture facing towards the base of the tongue. It is performed by pressing the cuffed tip of LMA against the posterior pharyngeal wall and guided by the index finger of the dominant hand. The LMA is pushed in hypopharynx till a resistance is felt which indicates that the tip of it has reached the upper esophageal sphincter. Some anaesthetists prefer to introduce LMA with deflated cuff and some with fully inflated. But, it is better to introduce LMA with partially deflated cuff and when the tip felt the resistance, then the cuff is fully inflated again with the addition of appropriate volume of air and is secured with tape.

The correct position of the cuff should be checked by auscultation of lungs and capnography. The other signs of correct placement of LMA cuff include one or more of the following : (i) the slight outward movement of the tube after the inflation of LMA cuff, (ii) the presence of a smooth oval swelling on the neck around the thyroid and cricoid area, (iii) no portion of cuff should be visible in the oral cavity. Before taping the LMA in place, a bite block should be inserted. It not only stabilizes the LMA, but also prevents the occlusion of tube from bitting. Reinforced flexi LMA are more prone to biting and bite block should be placed, until LMA is removed.

One of the principal cause of obstruction during the use of LMA is the downward displacement of epiglottis by LMA or curling up of tongue on the laryngeal inlet. An ideally positioned cuff of LMA is bounded by the base of the tongue superiorly, the pyriform fossa laterally and the upper oesophageal sphincter inferiorly. If the inlet of oesophagus lies within the rim of the cuff, then gastric distension and reguritation become a distinct possibility. The anatomic variations of hypopharynx prevent adequate functioning of LMA in some patients. So, if an LMA is not functioning properly after attempts to improve the condition, most anaesthetists will try another LMA which is one size larger or smaller. However, introduction of LMA under direct vision with the help of laryngoscope or fibreoptic scope may prove beneficial in difficult cases (Fig. 20.30).

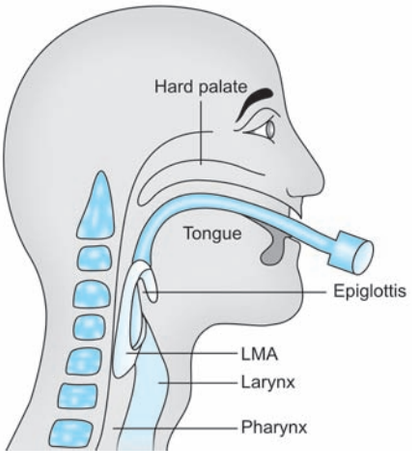


Fig. 20.30: LMA in position

The main advantages of LMA are:

i. It provides an emergency airway in patients, where either mask ventilation or tracheal intubation is difficult or has been failed.
ii. In case when intubation is not mandatory and operation can simply be done by spontaneous face mask ventilation, but airway cannot adequately be maintained by simple Guedel's oropharyngeal airway and face mask.
iii. Introduction of LMA eliminates the presence of a relatively large face mask and anaesthetist's hand on the patient's face that may interfere with surgical access, especially when the surgical site is situated over the head and neck. On the otherhand, availability of new flexible LMA provides an easy connection with the anaesthetic machine at any angle from the mouth, while resisting kinking and displacement.
iv. LMA also provides an emergency airway in awkward position, such as in the lateral and prone position of the patient and in emergency settings when laryngoscope and other equipment for intubation are not available. Instead of mouth to mouth breathing, mouth to larynx breathing through LMA in emergency condition is a better alternative.
v. LMA sometimes provides a conduit to facilitate fibre optic guided or gum-bougie guided or blind oral tracheal intubation during difficult situations of intubation. LMA, specially designed to facilitate such tracheal intubation, is now available and is called intubating LMA.

Disadvantages of LMA are: pulmonary aspiration, laryngospasm, failure to function in the presence of pharyngeal and laryngeal disease, failure to provide high inflation pressure during decreased compliance of lungs and thorax and also due to resultant leak around the cuff by high pressure ventilation. Therefore, the contraindication of use of LMA are: full stomach (e.g. pregnancy, hiatal hernia, intestinal obstruction, etc.) pharyngeal pathology (e.g. tumour, absces, etc.), pharyngeal obstruction, low pulmonary compliance (e.g. asthma, COPD, etc.) requiring peak inspiratory pressure greater than 30 cm of H_2O, etc.

AIRWAY MANAGEMENT BY COMBITUBE

Like LMA, combitube is another supraglottic airway device that provides an emergency airway when tracheal intubation is failed and mask ventilation is not effective or fails. It is a double lumen tube that combines the features of both a conventional tracheal tube and that of an esophageal obturator airway. Both the lumens of tube are connected at its proximal (outer) end with a 15 mm connector that helps it to be attached with the main anaesthetic machine. It is especially useful for patients in whom direct visualization of the vocal cords is not possible as in patients with massive airway bleeding or regurgitation, limited access to the airway and in patients in whom neck movement is contraindicated. As combitube is made of natural rubber or latex, so it may cause allergic reactions. It has two latex cuffs or balloons – one is oesophageal and another is oropharyngeal. The pharyngeal cuff or balloon is blue in colour and larger in volume (100 ml) than the oesophageal cuff or balloon (15 ml). The longer lumen is blue in colour and ends at the patient's side with multiple apertures between the two cuffs while the shorter lumen ends at the most distal end of this device (Fig. 20.31).

Combitube can function effectively whether is placed in the trachea or much more commonly in the oesophagus when it is introduced blindly. Ventilation is usually started first through the blue longer tube. This is because, placement of the distal end which proximally begin with shorter tube is usually in the oesophagus when combitube

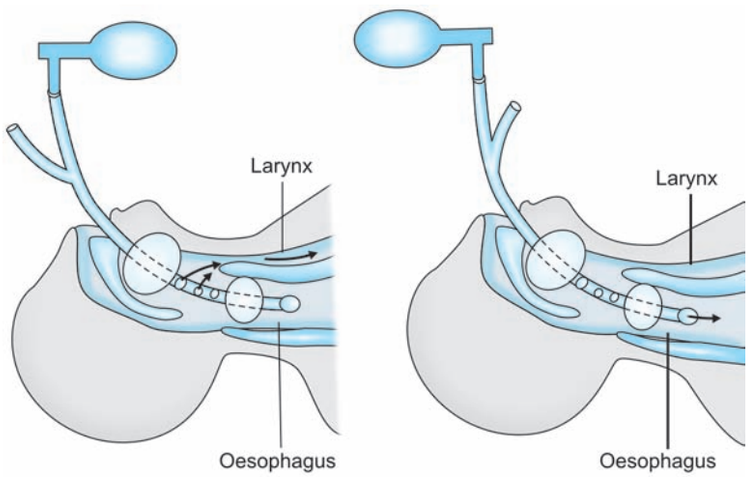


Fig. 20.31: The mechanism of action of combitube

is introduced blindly through oral cavity. Then, if auscultation of the breath sound is positive and auscultation of gastric insufflation is negative, ventilation is continued. In this situation, multiple apertures which are continuous with the longer blue lumen is situated at the laryngopharynx between the two cuffs and air passes from the laryngopharynx through the laryngeal inlet into the lungs. Under this condition, the shorter tube which ends at distal aperture and now is in the oesophagus may be used to remove the gastric fluid with a suction catheter. In such circumstances if inflation of lung is absent and the stomach is being insufflated, then ventilation should be started through the transparent shorter tube which communicate with the distal single aperture beyond the oesophageal balloon. Under this situation, the multiple apperture which are continuous with the longer blue tube and through which ventilation was done before are situated above the laryngopharynx and distal end which is connected with the transparent shorter tube is situated in the trachea. So, the air is passing from blue tube through oropharynx and oesophagus to the stomach. Then, ventilation should be continued through the transparent shorter tube which can be confirmed by auscultation of breath sound and absence of gastric insufflation.

The combitube has also been successfully used during emergency cardiopulmonary resuscitation and in such circumstances esophageal balloon provides protection from aspiration which may represent an distinct advantage of it over the LMA. But, care must be taken to avoid excessive deep placement of combitube in the oesophagus, which can further obstructs the glottic opening by the pressure of distal cuff from oesophagus. Though, it is listed in the management of difficult airway in advanced life support algorithm, still combitube is rarely used by anaesthetists now. Because they prefer LMA or other device in such difficult situations.

AIRWAY MANAGEMENT BY ENDOTRACHEAL (ET) TUBE – INTUBATION

The introduction of an ET tube into the tracheal lumen through glottic opening is called intubation. This is the best way of airway management, but not without any disadvantages or complications.

There are many indications for endotracheal intubation, but the principle head lines are:

i. maintenance of unobstructive airway,
ii. protection of airway from aspiration,
iii. application of positive pressure ventilation,
iv. adequate oxygenation and delivery of anesthetic gases.

Equipment for Intubation

The main equipment needed for intubaton are: endotracheal tube, laryngoscope and some accessories in difficult situations such as stylate, bougie, light weight, etc.

Endotracheal (ET) tube

In present practice, the commonly used ET tubes are now made of clear polyvinylchloride (PVC) with high volume low pressure cuff, though red rubber tubes with low volume and high pressure cuffs are still manufactured. The distinct advantage of a clear PVC made ET tube is that it helps to obseve the condensation of water vapour in expired air which occurs during expiration and confirm the ET-tube in the trachea. They are numbered according to their internal diameter (ID) measured in mm, as for example the internal diameter of 7 no. ET tube is 7 mm. The external diameter of ET tube varies with the thickness of the tube's wall which again varies according to the different manufacturers. Less commonly, some ET-tubes are numbered in the French scale which indicates external diameter in mm multiplied by 3. The choice of diameter of a ET tube for a particular patient always runs through a compromise between maximizing the flow of gases through a large size and minimizing trauma with a small size. Tubes are manufactured in 0.5 mm ID increments from 2.5 to 9 mm. A radioopaque line is impregnated into the wall of the tube which aid its later visualisation by X-ray in case of displacement or aid in determination of tube position after intubation. The radiopaque barium sulphate stripe also significantly lowers the temperature at which ignition of the tube occurs and thus decreases the risk of fire during laser surgery (Fig. 20.32).

An ASTM (American Society for Testing and Materials) standard for manufacturing of tracheal tube recommends the following things which include: the material from which the tube should be constructed, inside diameter, length, inflation system, cuff, radius of the curvature of the tube, markings, Murphy eye, packaging and labeling, etc. A separate standard also covers the testing of the shaft of tracheal tube for laser resistance.

The standard specifies that the radius of curvature of a conventional ET tube should be 140 ± 20 mm. The internal and external walls should be circular. A tube whose lumen is oval or elliptic in shape is more prone to kinking than one that is circular. The machine end of the ET tube receives the connector and projects from the patient mouth or nose. By cutting with scissors it should be possible to shorten this end if necessary. The patient end of the ET tube is inserted into the trachea. It usually has a slanted opening which is

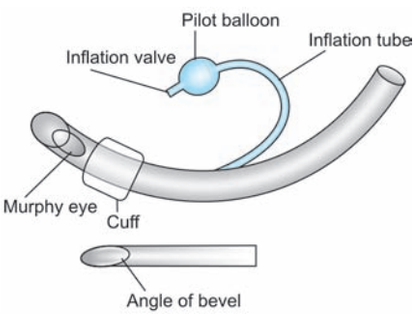


Fig. 20.32: The cuffed Murphy eyed endotracheal tube

called the bevel. The angle of this bevel is acute which is formed between the axis of the bevel and the longitudinal axis of the tracheal tube. A standard tracheal tube has a bevel angle of 38 ± 10°. The opening of the bevel looks left when viewing the tube from its concave aspect. This is because most often the ET tube is introduced in the larynx from the right side of the patient. So as the bevel faces left, it facilitates better visualization of the larynx when the tube is being inserted.

Sometimes, there is a hole on the side opposite to the bevel. This is known as the Murphy eye and an ET tube with this feature is called the Murphy-type tube. The purpose of this eye is to provide an alternate pathway for gas flow, if the bevel is occluded sometimes due to any reason. Some anaesthetists think that having such an eye is a disadvantage, because secretions may accumulate there and forceps, tube changers, fibrescope, etc, which are sometimes used for different purposes through the ET-tube may inadvertently advance through this Murphy eye instead of passing through the bevel. Some tubes have a second eye on the bevel side. This Murphy eye may also provide a measure of safety, if the tube accidently advances into the right mainstem bronchus. The endotracheal tubes lacking Murphy eye are known as Magill type tubes. Lack of Murphy eye allows the cuff to be placed closer to the tip. This may decrease the chance of inadvertent bronchial intubation.

The result of IT (implantation test) and Z-79 seal is usually stamped upon the tube. This means that the tube is compatible with human tissues, free of toxins and have no irritant properties. There are other various markings on the tube which include: (a) whether or not it is designed for nasal or oral use and (b) the distance in cm between the tip of the tube and the place where that tube is emerged either at the nose or at the mouth.

The pressure in the cuff of the tube is important. This is because high pressure in the cuff is transmitted to the tracheal mucosa and can cause ischaemic injury. So the cuff should be inflated to such a minimum volume and pressure that there is just no leak of air on positive pressure ventilation through the gap between the cuff and the tracheal mucosa. This will allow for reasonable airway protection from aspiration without excessive lateral wall pressure on the tracheal mucosa that may cause ischaemic injury and subsequent complication later. The cuff pressure that afford good protection from aspiration is 20 to 25 mm of Hg and it is just below the perfusion pressures of the tracheal mucosa which is about 25 to 35 mm of Hg. Therefore, this 20 to 25 mm of Hg cuff pressure does not cause ischaemic injury to the tracheal mucosa. The N_2O used during the maintenance of anaesthesia can also diffuse into the cuff and can increases the cuff pressure which in turn can increase the risk of ischaemic tracheal mucosal injury. But, if high volume and low pressure cuff is used for less than 24 hours, it is of no clinical significance or importance. On the otherhand, tubes with high volume and low pressure cuff produces more difficulty during insertion, because the cuff often obscures the (Fig. 20.33) view of the tip of the tube and larynx. So, the trauma to the airway by this tube is more common. The otherways to avoid this problem is to remove the air from the balloon intermittently, guided by the tension of the pilot balloon. Alternatively, cuff should be inflated by N_2O of clinical concentration or N_2O should be totally avoided from the maintenance of anaesthesia. Inflation of the cuff by 5 to 10 ml of air would be sufficient to achieve an effective seal if the selection of ET-tube is correct. If the amount of air required is more than 10 ml, then the ET tube should be changed to a size of 0.5 to 1 mm ID larger than that had already passed. High volume – low pressure cuff also increase the incidence of sore throat (due to larger mucosal contact area), aspiration, spontaneous extubation and difficult insertion due to floppy cuff. But still because of low incidence of mucosal injury, high volume-low pressure cuff are more commonly recommended now.

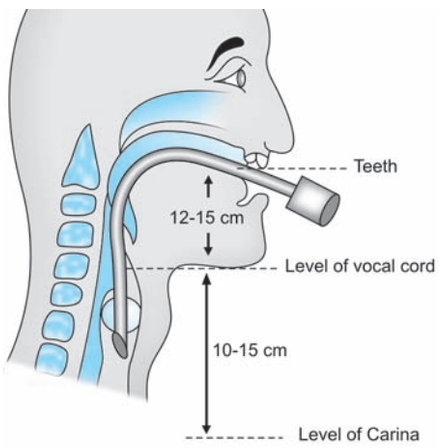


Fig. 20.33: The distances relating to the ET tube position

In younger children below the 8 years of age uncuffed tubes have generally been used. This is because the narrowest subglottic area is believed to limit the use of a cuffed tubes due to difficulty in introduction and in paediatric patients tacheal mucosa is more sensitive to ischaemic injury. In such circumstances endotracheal tube leak pressure is a clinically useful guide to confirm the proper selection of the uncuffed tube size in childrean. Leak should occur in a properly selected tubes at 15 to 20 cm of H_2O pressure and above. Below this pressure there should be no leak if the tube's size is properly selected. In this pressure there is no ischaemic injury of tracheal mucosa and aspiration.

Now, the use of a cuffed ET tube in paediatric group of patients has brought new discussion, keeping in mind the following advantages of it: require low fresh gas flow, reduce waste gas exposure to OT personal and avoide repeat laryngoscopy without any increased incidence of croup.

Generally, larynx is smaller in female than male. So, in an adult male an ET tube of 8 mm ID is appropriate, whereas for female a 7 mm ID tube is appropriate. In

adult, the glottic aperture limits the size of an ET tube, but in children the subglottic area (cricoid cartilage) is the narrowest part of larynx and limits the size of ET tube. The tube size or the internal diameter (ID) of on ET tube for children up to the age of 14 years is calculated from the formula: {(16 + age) ÷ 4}. But practically, a tube of 0.5 to 1 mm ID size, smaller or larger than the estimated must be immediately available. There are other two popular formulae for calculating the probable size or ID of ET-tube to be used for paediatric patients are:

A. For children up to 3 years or less: Age/3 + 3.5 = ID of tube in mm.
B. For children 4 years and above : Age/4 + 4.5 = ID of tube in mm.

However, a crude clinical guide to calculate the outer diameter of the ET-tube, appropriate for a paediatric patient, is that of his little finger.

A special type of ET tube is used in head-neck surgery, neurosurgery or other surgeries where there is every possibilities of kinking of it. This type of ET tube is called the armoured tube. Here, the wall of the tube is reinforced with a spiral wire to reduce the chance of kinking and collapse. This armoured ET tube is also useful when it is placed through a tracheostomy or laryngectomy stoma to provide an clear airway.

Another type of special ET-tube, called RAE (Ring-Adair-Elwin) tube, is sometimes used which is available as both oral and nasal versions. It is best used when it is necessary to keep the tube out of the respective surgical fields. The curvature of these tubes are predefined to facilitate surgery over the head and neck. There is a preformed bend in the tube that helps the outer portion of it to pass directly over the chin (oral version) or forehead (nasal versions). It may be temporarily straightened during intubation and again takes its preformed shape automatically after the introduction in trachea. Like nasal and oral versions, they are also available in cuffed and uncuffed versions. As the diameter of this type of tube increases, simultaneously the length or distance from the distal tip to the curve also increases. Usually, there is a mark at the bend. In the majority of cases when this mark is at the teeth or naris, it is assumed that the tube is correctly positioned in the trachea, provided the proper size of tube for that patient is selected. However this mark is taken only as a guide but should not be used as the sole criteria for confirming the correct positioning of the tube in trachea.

The nasal preformed RAE tube has a curvature opposite to the curvature of the oral RAE tubes. It is because when this nasal version is in place the outer portion of the tube is directed over the patient's forehead. This helps to reduce the pressure on the nares. Thus, RAE tube may be useful for oral intubation of patients who are to be placed in the prone position or is scheduled for otolaryngologic procedures. The oral preformed RAE tubes are shorter than nasal ones. The external portion of the oral RAE tube is bent at an acute angle. So, when in place it rests on the patient's chin.

These RAE tubes are easy to secure. Their use may reduce the risk of unintended extubation. The curvature of the tube allows the breathing system to remain away from the surgical field during operation, especially around the head and neck without the use of any special connectors. It also helps to protect against kinks. The long length of RAE tube may also make them useful for insertion through an LMA.

The main disadvantage of preformed RAE tubes is difficulty in passing a suction catheter through them. When necessary, suctioning can be accomplished by cutting the tube at the preformed curvature and reinserting the connector of anaesthetic machine into the cut end. They offer more resistance to airflow than conventional ET tubes of comparable size. As the length of these tubes are designed to fit the average group of patient, so a tube may be either too short or too long for a given patient. When selecting the tube size, the reference to the height and weight of a patient may be more useful than the age in years, and the user should always be alert to the possibility of bronchial intubation or accidental extubation.

Other varieties of ET tubes are : microlaryngeal tube, double lumen tube, Parker Flex Tip tube, Cole tube, spiral embedded tube, Carden bronchoscopy tube, Carden laryngoscopy tube, injectoflex tube, different laser resistant tubes, etc. Detailed discussion of these tubes is not possible here.

Laryngoscope

A laryngoscope is an instrument which helps to see and examine the larynx and also helps to facilitate the intubation of trachea. It is of two types: rigid and flexible fibreoptic. Standard rigid laryngoscope consists of two parts: detachable blade with bulb and handle containing batteries. Each standard laryngoscope blade has: (i) a spatula which compresses the tongue in the submandibular space, (ii) a flange for displacing the tongue to one side, and (iii) an open side for visualization of the larynx by elevating the epiglottis indirectly by pressing on the glossoepiglotic fold or directly by pressing on the posterior surface of epiglottis. The batteries in the handle light the bulb at the tip of the blade. Alternatively, it powers a fibreoptic bundle that terminates at the tip of the blade and acts like a bulb. This light, emitting from the end of this fibreoptic bundle, is less diffused, more intense and more direct. This rigid laryngoscope with fibreoptic bundle in the blade also can be made MRI compatible.

According to the different shapes of blade, laryngoscope may be of different types which is not possible to discuss in detail here. However, among these few are discussed below.

Macintosh Laryngoscope

It is the most popular laryngoscope for use in adult. Its blade is curved and Z-shaped

on cross section. Its tip lies beneath the pharyngeal (or anterior) surface of the epiglottis. Sizes of blade ranges from 1(smallest blade) to 4 (largest blade). Among these no 3 blade is most frequently employed for the adult use. But the no 4 blade is reserved for the unusual large or different patients. The smaller size blades are used for the paediatric patients. Tip of the Macintosh blade enters the valeculla and lifts the base of the tongue and the pharyngeal subtissues from the front of epiglottis. Thus, it elevates the epiglottis indirectly, so that cords can be visualized (Fig. 20.34).

Miller Laryngoscope

Unlike Macintosh laryngoscope its blade is straight with slight curved tip. The size of the blade ranges from 0 (smallest blade) to 4 (largest blade). Here, the tip of the blade elevates the epiglottis directly from behind and thus the cords are visualized. Another commonly used straight blade laryngoscope is Wisconsin blade which has a straight tip. Although, the straight blades may be advantageous in younger children, but the choice of blade in older children and adults is really a matter of familiarity and taste of an anaesthetist. Sometimes, in adults this straight blade Miller laryngoscope is also recommended for use in patients with a more anteriorly placed larynx. But, an anaesthetist should have a habit of using both the curved and straight blade, because when laryngoscopy becomes difficult with one type of blade, use of other type may permit adequate visualisation of glottis. For neonates and babies another type of straight blade such as oxford infant blade – is also very useful (Fig. 20.35).

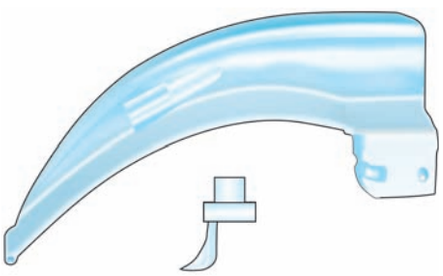


Fig. 20.34: Macintosh laryngoscope

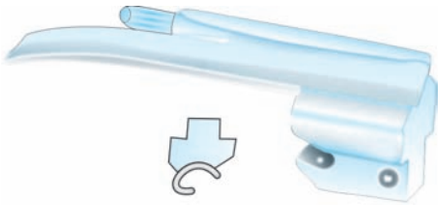


Fig. 20.35: Miller laryngoscope

McCoy Laryngoscope (Flexi – tip laryngoscope)

The peculiarity of this laryngoscope is that it has a hinged tip, assembled by lever which is positioned alongside the length of the handle on the opposite side of the blade. After insertion, once the tip of the blade is in the valeculla, pressure on the lever elevates the hinged tip with the epiglottis. This becomes specially useful for grade 3 intubation (of course in combination with cricoid pressure).

Bullard Laryngoscope

Bullard intubating laryngoscope is useful when the neck is immobile and mouth opening is very restricted. It has a long curved blades with fibreoptic illuminating system, suction port and intubation channels. It is made as both adult and paediatric versions (Fig. 20.36).

Wu-laryngoscope

Like Bullard laryngoscope, it has also a curved blade with elongated tip, fibreoptic light source, suction port, oxygen port and intubating channels through which tracheal tube is passed. It is designed to help to see the glottis in patient with very large tongue or whose glottis is very anteriorly placed. Anaesthetists should gain experience in using this Bullard and Wu-laryngoscope in normal patients, before using it urgently on patient with difficult airway. Many anaesthetists thought that these devices are preferred in patients where difficult airway is anticipated. But, others are not as they have no experience (Fig. 20.37).

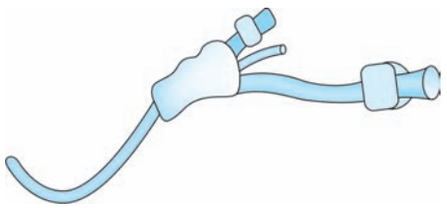


Fig. 20.36: Bullard laryngoscope

Stylet and Bougie

Stylet

It is made up of a flexible metal and is inserted into an ET tube in order to maintain a chosen shape of it. This will facilitate the intubation when visualisation of glottis is minimal or absent. It should be remembered that the tip of the stylet should not cross the tip of ET tube. Otherwise, it will injure the trachea. The other uses of stylet are: rapid sequence intubation and when the haemodynamically stressfull time for laryngoscopy should be minimised, e.g cardiac patients. During use, stylet should be lubricated to facilitate its movement

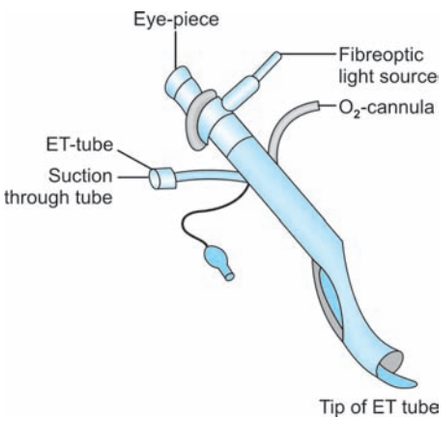


Fig. 20.37: Wu-laryngoscope

within the ET tube. The stylet should be removed as the tip of the ET tube enters the larynx to avoid undue trauma.

A special type of Stylet with a light source at the tip is called light-wand. The advantage of this light wand is that it can be guided with the ET tube into trachea by observing the movement of light under the skin of the neck from outside. Generally the room should be dark as the light can be seen adequately from the surface. The ET tube is placed over the light wand and is then introduced in the midline through the hypopharynx with the patient in standard sniffing position. The wand is then manipulated until a flare of light down the trachea is seen illuminating the neck. When the ET tube with the light wand is correctly positioned above the vocal cord in the midline, a distinct glow is seen in the anterior neck. Then, the tube is gently pushed into the trachea and the light wand is withdrawn. A special type of light wand is called 'Trachlight'.

Bougie

It is most commonly known as the gum-elastic-bougie. But, it is neither gum, nor elastic, and nor a bougie. It is actually called the Eschmann introducer and is such designed that it provides both stiffness and flexibility. The length of this introducer is 60 cm and the external diameter is 5 mm. It has a 35° bend, 2.5 cm from the patient's end which is inserted into the trachea.

Like stylet, it is also a very useful instrument to facilitate intubation when the laryngoscopic view of glottic is very poor. It is also very useful in limiting the degree of necessary neck movement during intubation with potential cervical spine injuries. It can also be used as tube exchanger. When the bougie is used, the tip of it is introduced first into the larynx through the glottic inlet blindly under reduced vision by laryngoscope. Then, keeping the laryngoscope in place, the ET tube is glided over the bougie upto the laryngeal inlet. After that 90° anticlockwise turn facilitates the glottic passage of ET tube, by presenting the bevel posteriorly. Then, bougie is withdrawn.

Technique of Intubation

In the technique of intubation the usual sequences are: pre-oxygenation, induction by administering rapid acting intravenous or volatile inducing agent, administration of rapid acting neuromuscular blocking agent, cricoid pressure, mask ventilation, laryngoscopy and followed by intubation. Both laryngoscopy and intubation are noxious stimuli and are sometimes more powerful than the surgical stimuli. So, deeper level of anaesthesia is required to blunt the stress response of laryngoscopy and intubation. This stress responses have deleterious effects on respiratory, CV and neurological systems. Thus, during laryngoscopy and intubation, these stress effects should be blunted to whatever degree if possible, especially when the patient falls into a high-risk category (e.g hypertension, CAD, ↑ICP, cerebral aneurysm, asthma, etc).

Before giving neuromuscular blocking agent, every anaesthesiologist must assesses his or her own patient, if mask ventilation will be possible or not when the patient will be fully paralysed. Therefore, if there is any doubt regarding the maintenance of patient's airway and ventilation by mask after induction and paralysis, then a conscious intubation with sedation and/or local anaesthetic agent should be considered before paralysis.

The general view regarding the pre-oxygenation is that breathing of 100% O_2 for 3 minutes or 4 vital capacity breaths with 100% O_2 before induction of anaesthesia provides added margin of safety. So, routine pre-oxygenation is optional, but strongly recommended before induction of anaesthesia and intubation for high risk group of patients. In patients with full stomach, where 'rapid sequence' intubation is chosen, there pre-oxygenation and cricoid pressure (Sellick maneuver) is mandatory and mask ventilation is not provided before intubation after administration of muscle relaxant unless unsuccessful intubation necessitiates it. Pre-oxygenation also can be omitted in patients : (i) who object to accept face mask, (ii) who are free of pulmonary diseases and (iii) who do not have any difficult airway.

Once the decision for induction of anaesthesia and intubation is taken, varieties of drugs can be used for induction and muscular paralysis and a variety of methods can be chosen to achieve the acceptable intubating conditions. For induction of anaesthesia intravenous, inhalation or oral route can also be used. But, usually intravenous route for adult and inhalation route for paediatric group of patients for induction of anaesthesia are chosen. For intravenous induction thiopental and propofol are most widely used now. But, other rapidly acting barbiturates (methohexital, thiamylal), benzodiazepines, narcotics, ketamine, etomidate, etc, also can be used. However the choice of inducing agents depends on the status of CVS, the status of CNS, effects on bronchomotor tone, presence of allergy, pharmacokinetics and pharmacodynamics of the agent etc. But among these the most important is the experience of the clinicians.

Both the depolarising and non-depolarising muscle relaxants are used for muscular paralysis, needed for intubation. But, due to some disadvantages such as masseter spasm, malignant hyperthermia, hyperkalaemia, burns, ↑IOP,↑ intracranial pressure, etc, the choice of succinylcholine for intubation has recently been questioned. However, still it is routinely used in many centres due to some of its advantages such as excellent intubating condition within a minute, rapid offset of action by ester hydrolysis if airway cannot be secured, and the patient's own ventilation will return much more quickly than any of the currently available nondepolarising muscle relaxants. So, still it is the relaxant of choice in many potentially difficult intubation cases, unless there are

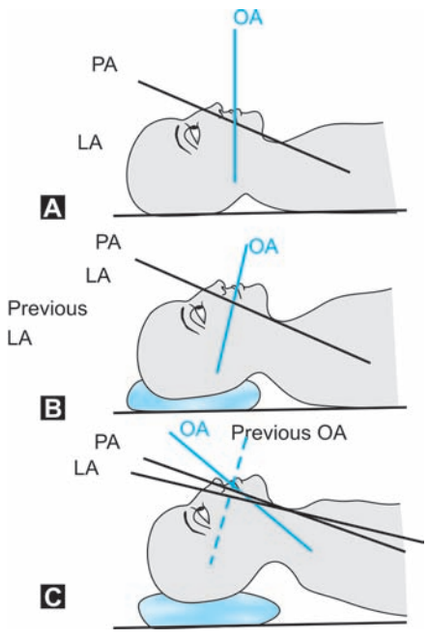
contraindications. However, recently rapid onset and excellent intubating condition produced by a nondepolarising drug such as rocuronium is achieved instead of succinylcholine. Other alternative non-depolarising drugs such as atracuronium, vecuronium, cisatracuronium etc. are not quite as rapid in onset of action as rocuronium.

Intubation may also be accomplished with only intravenous or inhalation anaesthetic agent without muscle relaxants when there is any doubt of difficult airway and failed intubation. But, this approach posses difficulties such as the potential for laryngospasm. So, a very deep level of anaesthesia should be achieved to avoid untowards laryngospasm if one wants to intubate only by intravenous or inhalational anaesthetic agents. In practice, the majority of clinicians employ lesser degree of muscle relaxation by reducing the dose of muscle relaxants (1/4th of the usual dose for quick recovery) to facilitate intubation in such circumstances.

Oral intubation

For successful oral intubation, position of the head is also very important. Unless there is contraindication for oral intubation, the head and neck is maintained in the classical 'sniffing position' to align the oral, pharyngeal and the laryngeal axes in a straight single line. Elevation of head by a small pillow with the shoulders remaining on the table first causes alignment of the pharyngeal and laryngeal axes. It causes flexion of the neck by about 25 to 35°. Then subsequent extension of the head at the atlanto-occipital joint (85°) causes alignment of oral axis with the pharyngeal and subsequently with the laryngeal axis. Thus, it serves to create the shortest possible distance and most nearly straight line from the incisior teeth to the glottic opening. But no such head elevation is required in paediatric age group (< 8 years) as their large head circumference produces the neck in flexion (Fig. 20.38).

Usually, the laryngoscope is held by the left hand of an anaesthesiologist and by the right hand mouth of the patient is opened. Then the blade of the laryngoscope is gently inserted into the patient's mouth from the right side of it and the tongue is kept left by the flange of the laryngoscope. During this procedure pressure on the teeth, gums or lips by the blade of laryngoscope should be avoided. After visualization of the epiglottis, the tip of the curved blade (Macintosh) is inserted into the vallecula and the laryngoscope is pulled forward and upward to elevate the epiglottis indirectly which expose the glottis. During that period gentle downward pressure on the cricothyroid cartilage from outside by an assistant may bring a non-visualised larynx into view. Then, the ET tube is inserted through the right side of the mouth and is pushed into the trachea between the paralysed,



Figs 20.38A to C: A. The oral axis (OA), pharyngeal axis (PA) and laryngeal axis (LA) in usual position. B. Elevation of head about 10 cm by a pillow with the shoulders remaining on the table aligns the LA with the PA. C. Extension of head at the atlanto occipital joint aligns the OA with the PA. So, these three axis more or less come on a single straight line

opened and abducted vocal cords under the direct vision. Instead of curved blade, if the straight blade is used then the tip of the blade is usually advanced behind the epiglottis, so that the epiglottis is included within the structures which are lifted up by the laryngoscope blade. Choice of the blade of laryngoscope depends on the clinicians preference and peculiar anatomy of the individual patient. When one blade does not become successful, then other types of blade become. So, skill should be developed in the use of different types of blades by an anaesthetist.

The cuff of the ET tube should lie in the upper part of trachea above the carina, but beyond the larynx or vocal cord. The cuff should be inflated with the least amount of air which is just necessary to create a tight seal in the trachea during positive pressure venitlation and minimize the injury of tracheal mucosa caused by the pressure transmitted to it from the cuff. Feeling of the pilot balloon is not a reliable sign of determining the adequacy of cuff pressure. After intubation, the chest and epigastrium are immediately ausculted. Capnographic tracing is also monitored to ensure the intratracheal location of the ET-tube. Because the persistent detection of CO_2 by capnograph is the best way of confirmation of tracheal placement of a ET-tube. But, it cannot exclude the bronchial intubation. The bronchial intubation is best diagnosed early by an increase in peak inspiratory pressure. The proper placement of an ET tube in the trachea also can be confirmed by palpating the cuff on the suprasternal notch, while compressing the pilot balloon with the other hand. The cuff of an ET-tube also should not be kept above the cricoid cartilage. Because prolonged intralaryngeal location of the cuff between the vocal cord may result in postoperative hoarseness of voice and increase the incidence of accidental intraoperative extubation. The true position of an ET tube can also be documented by X-ray. But, this is rarely needed except in ICU. If there is still any

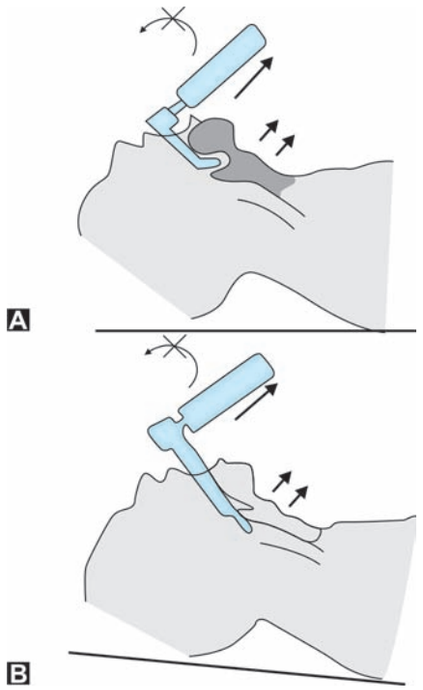
doubt, whether the tube is in the oesophagus or trachea, then it is prudent to remove the tube and ventilate the patient with a face mask (Fig. 20.39).

Under normal conditions the common causes of non-visualisation of vocal cords are mainly due to the wrong head position, or wrong blade position that is too far advanced, or not enough advanced, or reluctance to apply the adequate upward force.

The ET tube is usually inserted into the trachea by keeping the lip 23 cm away from the tip of the tube in adult male for correct position of cuff in trachea. In that position the tip of an ET tube lies 4 cm above the carina. In adult female this distance from the lip to the tip of the tube is 21 cm. Too far advancement of tube in trachea causes endobronchial intubation (usually right), whereas inadequate advancement of tube causes protrusion of the cuff through the vocal cords of larynx leading to risk of accidental extubation. In children, the distance (in centimeter) between the lips and the tip of the tube can be estimated from the formula: 12 + age/2 (Table 20.9).

There is also another simple formula to calculate the probable distance of ET tube from the mouth opening or from the external nares to the carina, which is as follows:

A. Mouth opening to carina = 0.16 × Height of child (cm) + 2.5 cm.
B. External nares to carina = 0.16 × Height of child (cm) + 4.5 cm.



Figs 20.39A and B: The proper position of the curved and straight blade of the laryngoscope during exposure of glottic opening. In figure A, the tip of the curbed laryngoscope blade (Macintosh) is placed in the space between the base of the tongue and the pharyngeal surface of the epiglottis (vallecula). In figure B, the tip of the straight laryngoscope blade (Miller or Jackson Wisconsin) is placed on the laryngeal (posterior) surface of the epiglottis. Irrespective of the type of blade, forward and upward force shown by the arrow should be applied along the handle of the laryngoscope to elevate the epiglottis and to expose the vocal cord

Table 20.9: Magboul et al scoring system

Score	*1*	*2*	*3*	*4*
Mallampati	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*
Measurement	3 fingers mouth open	3 fingers hypomental	2 fingers thyromental	1 fingers subluxation
Movement of neck	Left	Right	Flexion	Extension
Malformation	Skull hydrocephalus	Buck teeth, Loose teeth Macro and micro jaw	Obstruction, obesity, neck swelling	Syndrome and pathology

If the patient scores 8 or higher, he is likely to be a subject of difficult intubation. Mogbul et al reported 100% correct prediction from this score, but obviously more multicentre study and data will be needed to support this opinion.

When a patient is at particular risk for aspiration due to full stomach, intestinal obstruction, gastric paresis, etc; then rapid sequence intubation is employed. Like the general principles of intubation during rapid sequence, if there is sufficient doubt about the ability to intubate such patient, then a concious intubation with judicious use of topical (Table 20.10) anaesthesia with or without sedation, should also strongly be contempleted. For rapid sequence intubation, pre-oxygenation is mandatory. Normally 4 vital capacity breaths with 100% O_2 is suffiient for nearly complete denitrogenation of healthy lung. But diseased or aged lungs require longer period of preoxygenation (3 minutes) to ensure adequate washout of N_2 from body. During very urgent surgery, where every second is counted, then four vital capacity breaths with 100% O_2 are adequate. After pre-oxygenation, intravenous rapid acting inducing agent and rapid acting muscle relaxant (usually succinylcholine) are administered. When the patient becomes unconscious, proper cricoid pressure is

Table 20.10: ET tube size and length calculated based on patient's age

Age	*ID (mm)*	*French unit*	*Distance from teeth to tip of tube in trachea (cm)*
Premature	2.5	10	10
Newborn	3	12	11
1-6 months	3.5	14	11
6-12 years	4	16	12
1-2 years	4.5	18	13
2-4 years	5	20	14
4-6 years	5.5	22	16
6-8 years	6	24	17
8-10 years	6.5	26	18
10-12 years	7	30	20
12-14 years	7 (Female)	30	22
	7.5 (male)	32	
> 14 years	7.5 (female)	32	24
	8 (male)	34	

applied to prevent aspiration whether muscle relaxant is administered or not. Proper cricoid pressure (or sellick manouvre) is applied by giving gentle downward pressure with thumb and first finger on the cricoid cartilage. This downward pressure on the cricoid cartilage occlude the esophageal lumen behind the cartilage. Because only the cricoid cartilage form a complete ring or have a posterior cartilagenous bar that can press and occlude the oesophagus and thus prevents regurgitation. But this pressure cannot prevent the regurgitation resulting from forceful vomiting. Only the force of vomiting is blunted by the muscle relaxant. Laryngoscopy and intubation in this setting are then performed without any preceding manual mask bag ventilation, if possible. If intubation is not possible in first attempt then only, mask ventilation should be started and continued while cricoid pressure is maintained. It is important to say that the cricoid pressure should be correctly applied such that it actually does not impede the visualisation of the glottis or passage of tube through it by any means. Cricoid pressure also decreases the flow of gas in the stomach and inturn limits the regurgitation.

Nasal intubation

In the operating room, oral intubation is the usual method. But, in some conditions when the surgery is performed in the oral cavity or on the mandible, or in any where on the face when both the surgeon and anaesthetist struggle for the space, then the nasal intubation is the choice. Nasal intubation is usually performed under direct vision. But, it also can be accomplished in difficult airway condition blindly or with the help of fibre optic scope under sedation and topical anaesthesia. Blind or fibre-optic nasal intubation is also chosen, where direct laryngoscopy is impossible.

However, there are certain contraindications for nasal intubation. These are: Coagulopathy, severe intranasal pathology, basilar skull fracture, the presence of CSF leak from the base of the skull, etc.

In any case when both the oral and nasal intubation has one or more contraindication, then anaesthetist must take any one decision, after discussing the relative risks and benefits of tracheostomy, oral intubation and nasal intubation with the surgeon to arrive at an acceptable compromise. Nasal intubation is sometimes chosen, because it may be quicker and more comfortable than oral intubation in the topicalised and less sedated patient (Table 20.11).

Technique of nasal intubation

Nasal intubation may be blind or under direct vision. It will be helpful if phenylephrine as a vasoconstrictor is applied on the nasal mucosa before nasal intubation. After the induction of anaesthesia and administration of muscle relaxant and mask ventilation, ET tube is introduced into the nose in a plane, perpendicular to the face up to a certain length when the tip of the tube reaches the oropharynx. Then, direct laryngoscopy is performed (in case of under direct vision nasal intubation) in the usual fashion. After that the tip of the ET tube which is seen in the oropharynx is directed into the glottis by holding and manipulating the machine end of the tube from outside of the nose.

Table 20.11: Risks factors for aspiration of gastric contents

Full stomach
< 8 hours fasting in solid food
< 6 hours fasting in milk
< 4 hours fasting in breastfeeding
< 2 hours in clear fluid
Pregnancy, obesity
Trauma
Intraabdominal pathology Intestinal obstruction
Gastric paresis (peritonitis, infection, diabetes, drugs, uremia)
Oesophageal diseases
Symptomatic reflex
Motility disorders
Uncertainty about intake of food and drink

If this is not possible then a Magill forcep may be used through oropharynx to direct the tip of the ET tube into the glottis, often with the help of an assistant who will push the nasal end of the tube. If the glottis can not be visualised by direct laryngoscopy, then the Magill forcep can still be used to guide the tip of ET tube blindly into the area of the glottis.

Blind nasal intubation is usually done in an anaesthetised spontaneously ventilated patient where spontaneous respiration facilitate the intubation blindly. This is described below. While the patient is taking spontaneous respiration, under deep sedation or anaesthesia (to prevent laryngospasm) or proper topical anaesthesia the tube is gradually inserted through the nasal cavity and then through the nasopharynx, oropharynx and laryngopharynx until the maximum breath sounds are heard from the outer end of the tube. It implies that the tip of the tube is just above the glottis. The tube is then inserted blindly into the glottis during next inspiration which tend to be deepest immediately following a cough. During forward movement of ET tube through laryngopharynx. If breath sound through the tube disappears, then it should be thought that the tube has passed into the oesophagus or pyriform fossa and must be withdrawn slightly above the level of the glottis. It is then reintroduced blindly into the larynx again and such several attempts can be tried. If still the tube does not enter the glottis, the patient's head should be extended, flexed or turned to guide the tip of the ET tube into the glottis. Usually, the tip of the tube enters into the oesophagus and extension of head is useful. If still, intubation is not possible, then help of direct laryngoscopy or bronchoscopy should be taken. As in blind procedure the entry of ET tube into the glottis is not seen directly, so it is helpful to have capnographic or bronchoscopic confirmation for endotracheal placement of the tube. Because at times, all the indirect signs of intubation may be misleading.

Blind nasal intubation in anaesthetised, apnoeic and paralysed patient may also be attempted. But as in this case there are no spontaneous breath sounds to help the placement of tube in the larynx, so this is only guided by the external observation of the tip location in the larynx.

INTUBATION FAILURE

Despite the most meticulous preoperative assessment of the airway, sometimes few patients present sudden and great difficulty during intubation. No matter how skilled, every practitioner have to encounter such patients in his practising life. So, induction of anaesthesia and use of muscle relaxant should be approached with this possibility in mind, as if a clear plan of action can be persuaded without unnecessarily panicking, if intubation failed.

These patients may be of elective or emergency cases. Failed intubation in emergency case is potentially life threatening. Because, there is a greater possibility of hypoxia both from regurgitation with aspiration (as these patients are not properly prepared by restricting the intake of food) and failed intubation. The cardinal rule under such condition is oxygenation first and everything else, i.e. regurgitation, aspiration, etc. are secondary. In such cases the majority of opinion is that, it would be wiser to allow the patient to come back to spontaneous respiration or even better to regain consciousness. Then, as the surgery is emergency and unavoidable, so one can review, rethink, plan and proceed again. The objective for these difficult patients should be not to use muscle relaxant producing apnoea until intubation has been successfully accomplished at the beginning of any anaesthesia or intubation has failed and patient is backed to spontaneous respiration. For such patients, conscious or 'awake' intubation by topical / infiltration local anaesthesia or intubation under spontaneous respiration under deep sedation or GA is ideal.

Indications for awake intubations are: (i) previous history of difficult or failed intubation, (ii) findings on physical examination that can indicate difficult or failed intubation and (iii) severe risk of aspiration. Actually, the term 'awake intubation' is applied to intubation on nonanaesthetised conscious emergency patient outside the operating room. But, this term is misnomer in OT where it is used after appropriate sedation, topical anaesthesia and/or nerve blocks to avoid laryngeal reflexes. If awake intubation has to be performed due to severe risk of aspiration, then narcotics and other IV sedatives should be used sparingly (Fig. 20.40).

Promoting local anaesthesia for awake intubation, the nerves that need to be blocked are trigeminal (nasal cavity and oral cavity) glossopharyngeal (nasopharynx, oropharynx, and laryngopharynx), vagus (supraglottic and infraglottic region). Woods and Lander describe a technique of glospharyngeal nerve block that only anaesthetizes the sensory supply

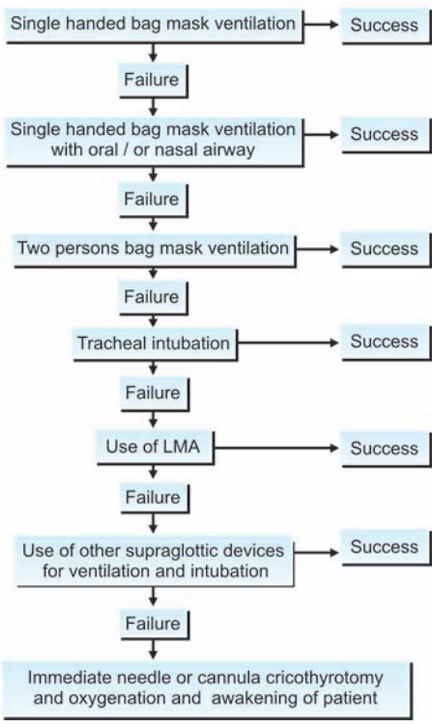


Fig. 20.40: Strategy in case of predicted or unpredicted difficult bag-mask ventilation

over the area of the back of the tongue which is innervated by this cranial nerve (glossopharyngeal IX). For this technique, by a 24 G needle, 2 ml anaesthetic drug is injected at the junction where the base of the tongue opposes with the palatoglossal fold. This causes local anaesthesia of the base of the tongue and does not appear to affect the airway integrity when performed bilaterally. This block is acceptable with full stomach also. This type of local anaesthesia allows a more comfortable laryngoscopy with lower doses of sedation. It has also been seen that if larger volume of local anaesthetic is given at that site then superior laryngeal nerve (SLN) which is the branch of vagus will also be blocked with glossopharyngeal nerve, because both the nerves lies in the same tissue plane. SLN innervates the epiglottis, aryepiglottic fold and the laryngeal structure up to the false vocal cords. This nerve can also be blocked isolatedly by giving injection of 2 to 3 ml local anaesthetic agent percutaneously between the greater cornu of the hyoid bone and the thyroid cartilage. But this block is contraindicated in full stomach patient as it impairs the protective mechanism of airway and cannot prevent the regurgitation and aspiration of stomach contents, if vomiting occurs. So, in full stomach where regurgitation and aspiration have possibility, then surface anaesthesia and analgesia of larynx (both supraglottic and infraglottic area) is the rule. For surface anaesthesia, 'spray-as-you-go forward' technique or certain variations of it, with or without cricothyroid puncture can be employed. The specific nerve blocks associated with surface anaesthesia is restricted only to the superior laryngeal nerve which can either be blocked percutaneously near the greater cornu of the hyoid bone where internal branch traverses the pyriform fossa before entering the larynx. A cricothyroid puncture for surface anaesthesia below the vocal cord is usually performed with the patient in semirecumbent position and local anaesthetic solution is

injected or sprayed in the trachea usually at the end of expiration.

The difficulty of glottic exposure in laryngoscopy can be graded ranging from 1 to 4 : in grade 1, no difficulty of viewing the glottis; in grade 2, only posterior extremity of glottis is visible; in grade 3, only epiglottis is seen; in grade 4, no recognisable structure. When intubation fails by initial attempt, mask ventilation (if muscle relaxant is used) should be resumed and situation is reassessed. As long as oxygenation is maintained by mask ventilation, the problem is not an emergency one except if the patient is not in full stomach. During mask ventilation, cricoid pressure should be maintained if the stomach is full. However, in case of topical anaesthesia and / or nerve block if awake intubation is failed, then patient's spontaneous respiration is maintained only by giving 100% O_2. After that slight sedation can be added and fibre-optic intubation can be tried.

During reassessment of upper airway after a failed intubation in first attempt, the following things that should be brought in mind and correction should be done are: Head position, laryngoscopy technique, change of the shape (curved to straight) and size of blade, etc. If repeated laryngoscopy by an experienced practitioner is unsuccessful, then the first aim should be efficient mask ventilation (obviously in paralysed patient) to prevent hypoxia and attempts to bring back the patient to the spontaneous ventilation. If mask ventilation is efficient then before bringing back to spontaneous ventilation the anaesthesiologist can also again try intubation by the help of stylet, bougie, flexi tip laryngoscope, lightwand (trachlight), etc. LMA aided intubation, indirect rigid fibre-optic laryngoscope assisted intubation, pharyngeal airway Xpress aided intubation, etc. also can be tried. If all the previous methods are failed then patient should be brought back to the spontaneous ventilation. After resumption of spontaneous ventilation, there are three options: One, the patient may be allowed to awaken and the procedure is postponed if the case is not emergency; second, the patient is awakened and intubation is further attempted with topical anaesthesia if the case is emergency; three, after resumption of spontaneous respiration, not awakening the patient, try again to intubate the patient by previously described methods such as using styllate, bougie, fibre-optic bronchoscope, blind oral or nasal intubation, etc. then the muscle relaxant can be used if the operation is emergency. Actual life threatening emergency condition arises when after the use of muscle relaxants the tracheal intubation is failed and mask ventilation is also ineffective. The management of this extremely emergency condition is discussed later.

All anaesthetist should develop skill for conscious oral intubation with direct laryngoscopy. Blind nasal intubation that avoids the discomfort of laryngoscopy is also equally important to learn.

Intubation Failed – Mask Ventilation is Effective or Patient is Breathing Spontaneously (No Hypoxia – Oxygenation is Maintained) Operation is Urgently Needed

This group of patients can be managed by the following way:

i. If the manual mask ventilation is effective enough and the anaesthetist think that he will be able to carry on the operation by only mask ventilation with muscle relaxation (if that operation needs relaxation), then he can procede.
ii. Operation also can be carried out in anaesthetised spontaneously ventilated patient through mask if muscle relaxant is not needed to complete that surgical procedure. So after muscle relaxation and failed intubation, when spontaneous respiration is re-established, the anaesthesia can be continued with volatile inhalational agents by mask without muscle relaxant.
iii. After re-establishment of spontaneous respiration in anaesthetised patient, if the patients fall in the group where operation is urgent and the full muscle relaxation is required for completion of the surgical procedure and mask ventilation is though effective, but cannot be carried out for prolonged period or the surgical site does not allow the mask ventilation, then the patients should be managed by intubation first after re-establishment of spontaneous respiration and later followed by full muscle relaxation. Intubation in this group of patients is tried first with the help of different intubation accessories. In such situation there is another option that is use of LMA. By LMA we can maintain anaesthesia by spontaneous ventilation with the inhalational agents or we can ventilate if muscle relaxant is needed. Mask ventilation or ventilation with LMA (spontaneous or IPPV) is usually satisfactory for short minor procedures, such as cystoscopy, EUA, inguinal hernia repair, etc. but not for long complicated procedures or where high pressure for IPPV is needed.

Accessories for Intubation

(a) Using stylet

Difficult orotracheal or nasotracheal intubation can be performed by employing direct laryngoscopy and using stylet which is passed though the ET tube. ET tube is directed anteriorly with the stylet.

(b) Difficult oral intubation using bougie

Difficult oral intubation may also be attempted by gliding ET tube over a long flexible 'bougie', inserted blindly into the glottis under direct laryngoscopy. Sometimes, the subsequent passage of an ET tube by gliding over the bougie is difficult. In such situation, laryngoscope should be kept in position and the tracheal tube is rotated 90° anticlockwise, in order to prevent the 'fork' created by the bevelled end

Table 20.12: Recognition of correct placement of ET-tube

- Direct visualisation of tube passing through the larynx.
- Auscultation of chest.
- Asucultation of epigastrium.
- Observation of chest movement.
- Observation of abdominal movement.
- Tension of CO_2 in expired air, confirmed by capnography.T
- Observation of condensation of water vapour in expired air in PVC ET-tube.
- Movement of reservoir bag in up paralysed spontaneously breathed patient.

of the tube and the bougie, from impacting on the posterior rim between the aryteroid cartilages. A white (Table 20.12) plastic bougie with a soft metal core is said to be easier most to place in the glottis than the older gum elastic bougie. Advancement of the distal end of the bougie over the tracheal rings produces a clicking sensation and confirms its placement in trachea. If the bougie is hollow, then jet ventilation can also be done through this channel or capanography can be attached with it which will show the characteristic pattern of PCO_2 in expired air associated with the breathing.

(c) Using light wands

Light wand was originally introduced for blind intubation, but it can be used with direct laryngoscope also (semi-blind technique). If the light at the distal end of the tracheal tube is seen to transilluminate brightly through the cricothyroid membrane, then it is confirmed that the endotracheal tube is in the larynx. If no transillumination is seen, then the tube is considered to be in the oesophagus. The advantages of light wand or trach light are: easy technique, relatively inexpensive, useful adjunct in difficult airway, does not require much neck manipulation, useful in cervical spine injury, useful in patient with limited mouth opening, less traumatic than blind nasal intubation, presence of secretion is of no problem etc. The disadvantages of light wand are: should not be used with laryngeal or tracheal polyps, tumours, inflammation, retropharyngeal abscess, foreign body, etc. In morbidly obese patients, the ability to see the glow of light may be diminished. On the contrary, in thin and frail patients some transilluminations may also occur, even when the tube tip with the light source is in the oesophagus and will confuse the anaesthetist.

(d) Blind nasal intubation

For blind nasal intubation the patient should normally have the head and neck, placed in the classical 'sniffing the morning air' position. The anaesthetist will have to first decide which of the nasal passage is to be used. Then as a first step a well lubricated nasal tracheal tube is gradually passed along the floor of the nose into the nasopharynx, oropharynx, and hypopharynx (as the patient is breathing spontaneously). After that it is ultimately introduced blindly into the trachea. But unfortunately this is very uncommon, and commonly these tubes end up in either of the pyriform fossae or in the oesophagus. In such circumstances several blind attempts with or without the help of any accessories are tried. Occasionally, they can also cause various degrees of haemorrhage. Chances of successful blind nasal intubation can be increased by the following methods :

i. Listening to the proximal end of the nasal tube and feeling the air being breathed out of the tube.
ii. Using capanography to guide the distal end of the tube into the larynx.
iii. Using the light wand which can be manipulated, so that the long shaft of the wand follows the contours of the upper nasal passage and enter the larynx.
iv. A fiber-optic laryngoscope or bronchoscope can be passed through the nasal tube to guide it into the larynx.

(e) Using LMA

LMA has also been used on many occasions for difficult intubation. It has enabled effective oxygenation by spontaneous ventilation or manual positive pressure ventilation. LMA has also enabled the passage of bougie and/or fibre-optic scope into the trachea which is again followed by the passage of an ET tube in trachea with the help of these bougies or fibre-optic scope. There is also a special type of intubating LMA (ILMA) which is called 'Fastrach LMA'. It consists of an anatomically curved, short, wide bore tube and a laryngeal cuff with a guiding stainless steel handle. It has a single moveable epiglottis elevation bar in the place of fixed aperture bars. It is available in 3 sizes and can accomodate 7, 7.5 and 8 mm ET tube within its wide bore tube for intubation (Fig. 20.41).

(f) Combitube

The most recent method of accomplishing emergency intubation–or more correctly ventilation–is the use of combitube. This is the modern version of the older oesophageal obturator airway. The principle of combitube is that this tube is inserted blindly and artificial ventilation is started through any one of the distal two ports. Depending on the results of auscultation,

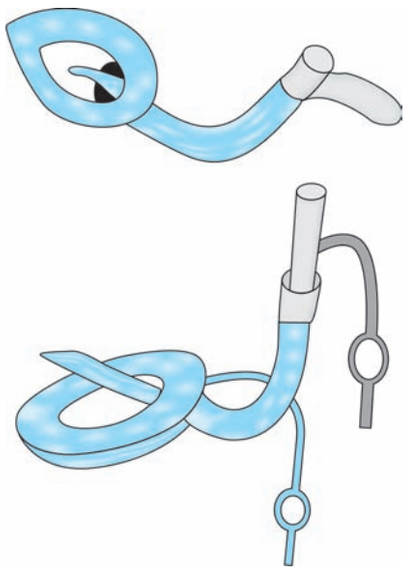


Fig. 20.41: Intubating LMA (ILMA)

any one of the two tubes is selected to ventilate the lungs.

(g) Fibre-optic instruments

Recently fibre-optic laryngoscope or bronchoscope have become an extremely important piece of instrument in the management of difficult airway. Due to their extreme flexibility, they easily can be passed either through the nose or through the mouth into the trachea and assist in intubation. The observer can also see the tip of the ET tube in trachea with the help of fibre-optic scope and confirm intubation.

When used for nasal intubation, the fibre-optic laryngoscope or bronchoscope with an ET tube can be passed through the nose into the larynx followed by the tracheal tube. Alternatively, the nasotracheal tube or airway can be passed into the pharynx and the fibre-optic scope is passed through it into the larynx, followed by the tracheal tube. The latter technique is used to prevent the tip of the fibrescope from toileting with blood, secretions or water vapour condensation to get a clear view. By contrast, the usual practice of fibre-optic scope through the oral route is to pass it first using the conventional laryngoscope, followed by an endotracheal tube. Once the intubation has been accomplished by either of these two routes or methods, the fibre-optic scope can also confirm the ET tube in the trachea by observing the tip of the tube against the tracheal ring or wall.

One of the disadvantages of fibre-optic techniques for intubation is that the instrument is delicate and expensive and can be quite easily damaged. Even in experienced hands, an intubation using these instruments can take duration which is three times longer than that of the conventional method and may be associated with marked cardiovascular resposes to intubation. It is reported that blood pressure and heart rate remain higher for a considerably longer period compared with following a normal intubation.

When Intubation is Failed and Also Ventilation By Mask is Ineffective or Not Possible

The patient who is a truly impossible candidate for mask ventilation after failed intubation presents really a life threatening emergency condition. Always the best treatment of such condition is prevention, like the other branches of medicine. So, an anaesthetist must always carefully evaluate the airway to determine the safest plan for intubation and the plan if both intubation and mask ventilation failed, before instituting muscular paralysis and general anaesthesia. In the patient who has been thoroughly de-nitrogenated by pre-oxygenation, there should be adequate time to institute one of the following procedures before serious O_2 de-saturation and consequent haemodynamic deterioration happen if such condition appears. In reality, when such circumstances will arrive, then everybody has to thought that he is often dealing with a severely anoxic patient who has suffered or is near to the brim of cardiac arrest. So, it is critical to start one of the following procedures before irreversible cardiac arrest or brain damage has ensured. The interventions during failed to intubate and failed to ventilate by mask conditions are the followings:

i. Establishment of emergency non-surgical airway and ventilation:
   After mask LMA or combitube will probably become the next non-surgical airway intervention for emergency ventilation.
ii. Establishment of emergency surgical airway and ventilation.

Emergency surgical airways can be established by many ways. These are: needle cricothyroidotomy, cannula cricothyroidotomy, surgical cricothyroidotomy, percutaneous tracheostomy (PCT), conventional surgical tracheostomy (ST), etc. Among these, the needle and cannula cricothyroidotomy is done during emergency condition when an anaesthetist 'cannot intubate and cannot ventilate by mask' the patient. Through these needle or cannula of cricothyroidotomy jet ventilation is performed for oxygenation of patient. So, this procedure may be called as the transtracheal jet ventilation (TTJV). Actually, the term 'jet ventilation' means introduction of gas (oxygen) into the tracheobronchial tree under high pressure and speed and has been used in different forms. For example, this technique may also be used during anaesthesia for bronchoscopy or laser surgery on the larynx. During anaesthesia for bronchoscopy as laser surgery on the larynx, jet ventilation via a needle, placed within the lumen of an otolaryngological laryngoscope permit oxygenation of patient without a tracheal tube intubation.

Trans-tracheal jet ventilation (TTJV) through needle cricothyroidotomy

In such TTJV a 12 to 18G needle (12 or 14G for adults and 16 or 18G for paediatric patients) is inserted through the cricothyroid membrane and is attached to a high pressure O_2 source via a low compliance circuit. For high pressure O_2 source, anaesthetic machine can also be used. For that an adaptor of ET tube of 5 mm ID which is attached to the low compliance O_2 supply tubing is inserted to the fresh gas outlet of the anaesthetic machine. At the other end of the low compliance O_2 tube (i.e. between O_2 tube and 16 G or 14 G cannula) a three way stop-cock is attached and then this stop-cock is connected to the translaryngeal 16 G or 14 G cannula. The three way stop-cock helps by preventing excessive pressure to build-up by releasing the aperture to the air in between jet inspiration. Before starting artificial jet ventilation, it is wise to fix the tube. Otherwise, high pressure through a narrow tube will tend to force the tube out of its position. It is essentially a blind technique and incorrect placement or excessive pressure can produce pneumothorax, pneumomediastinum, pneumotrachea, pneumolarynx, or pneumomediastinum. In this era

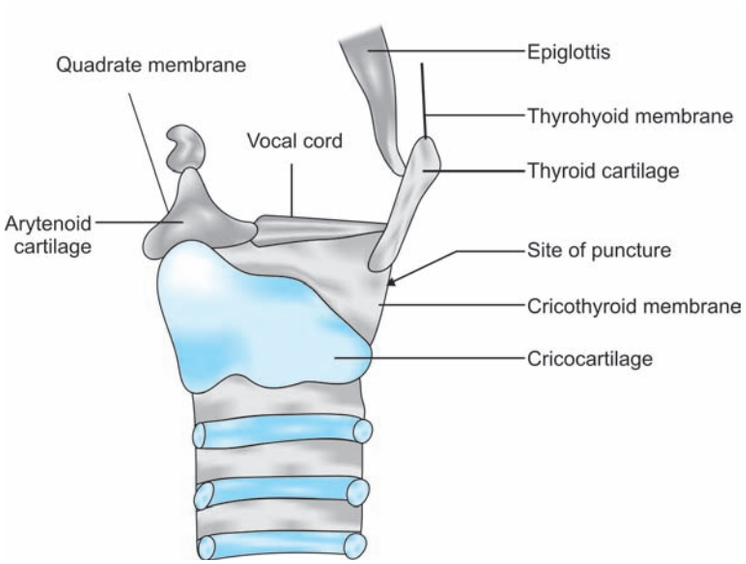


Fig. 20.42: The anatomy of cricothyroid membrane

of technological advances, flexible fibreoptic endoscope, Bullard laryngoscope, noninvasive light wand and different intubation guides are also recommended (Fig. 20.42).

This needle TTJV provides adequate ventilation as well as oxygenation and serves as an alternative emergency procedure for those who are planning to assemble a standard TTJV system through cannula cricothyroidotomy by modified Seldinger technique. TTJV, either by needle or cannula, only provides emergency oxygenation. So, always the successful TTJV should be followed up by provision of making a definite airway and ventilation by tracheotomy (precutaneous or classical) or endotracheal intubation or waking up the patient and resumption of the normal airway. In the technique of cannula cricothyroidotomy, after a needle is introduced into the tracheal lumen, a wire is passed downwards. Then the needle is withdrawn and a dilator is passed over the wire which is followed by an cannula. The advantages of this technique are that it is quick and relatively easy to perform. It is important to comment that neither TTJV or cricothyroidotomy can relieve obstruction which occur below the first few tracheal cartilages.

Surgical Cricothyroidotomy

In the 'cannot ventilate, cannot intubate by mask' condition, a classical tracheostomy cannot be performed quickly enough to save the life. In such situation emergency surgical cricothyroidotomy can also be employed to insert a small endotracheal or tracheostomy tube. Truly speaking, this surgical cricothyroidotomy is also time consuming (more than 5 minute) and may not be able to save the apneic patient's life.

For surgical cricothyroidotomy a stab incision by a short scalpel blade is made through the skin and cricothyroid membrane and the trachea is opened. Then, the incision is enlarged by using hook to pull the cricoid cartilage caudally. This helps to insert an ET tube of 5 to 6 mm ID (Table 20.13).

FIBREOPTIC SCOPE

There are some elective situations where direct laryngoscopy with a rigid laryngoscope is undesirable or impossible or if possible still the laryngeal inlet is completely out of view with this type of rigid laryngoscope. Examples of few such situations are: patients with unstable cervical spines, very poor range of motion of the temporomandibular (TM) joint, severe burn contracture of neck, certain congenital or acquired upper airway anomalies, etc. In such situations direct visualisation of larynx by fibreoptic scope and intubation with the help of it is the only answer. But, in contrast to conventional laryngoscope, its use needs intense practice. Intubation by fibre-optic scope requires longer time. So, it has no role in emergency situation where airway has to be established rapidly in the face of severe hypoxia. When the fibreopticscope aided intubation is anticipated for the elective management of a more difficult airway, then the fibre scope should be employed first, before visualisation of larynx is obscured by oedema, secretions and / or haemorrhage due to previous repeated attempt and failed intubation.

The fibre-optic scope is consist of a collection of thin glass fibres whose diameter vary between 5 to 25 µm. These collection of thin glass fibres are divided into two groups each containing 10,000 to 15,000 fibres. Among these two groups

Table 20.13: Difficult airway algorithm

1. Assessment
   - Assessment for difficult mask ventilation.
   - Assessment for difficult intubation.
   - Assessment for difficulty for patient cooperation and consent.
   - Assessment for difficulty for tracheostomy.
   - Assessment of opportunities for delivery of supplemental oxygen throughout the process of difficult airway management.
2. Consider the relative merits and demerits of the basic choices of management
   - Preservation of spontaneous ventilation vs Ablation of spontaneous ventilation.
   - Awake intubation vs Intubation after induction of GA.
   - As an intial approach for intubation taking the help non-invasive technique vs Invasive technique.
3. Difficult airway-recognised or unre-cognised.
4. Develop some other primary and alternative strategies.

one group transmits image from the target object to our eyes and another transmits light from a powerful source. In addition to all these fibreoptic scope consists of: (i) wires which control the angulation of the tip of fibres and (ii) ports for suction, injection of local anaesthetics and delivery of oxygen.

The keys to successful elective intubation by fibreoptic scope include control of secretions, adequate topical anaesthesia, proper sedation, proper defogging of lens and aligning of the scope in midline. As during any manipulation of airway, pulse oximeter is also mandatory during this procedure to detect hypoxia. During the use of fibre-optic scope aided intubation, the use of anticholinergic is strongly recommended, because excessive secretions in the upper airway may obscure the view. The tip of the scope should be defogged intermittently and frequently with warm soapy water and the entire length should be lubricated by K-Y jelly to facilitate the passage of scope through the ET tube. A patent suction port is important and a 10 ml syringe filled with 1% lignocaine solution can be attached for further topical spray through the scope. If O_2 insufflation is desired, then an appropriate source adaptable to the bronchoscope port should be available. This is useful in keeping the secretions off the tip of the fibre-optic scope and diminishing fogging as well as providing a source of 100% O_2. Preventing hypoxia during the fibreoptic scope aided intubation.

The elective intubation by fibre-opticscope may be oral or nasal and can be employed on conscious or anaesthetized patient. But among the oral or nasal route, the nasal route and among the sedated unparalysed and paralysed patient, the intubation in unparalysed patient by fibre-optic scope is technically more easier. On the otherhand, through oral route on a sedated paralysed patient fibre-optic intubation is the most difficult of the four possible technique such as oral or nasal fibre-optic intubation in sedated unparalysed or paralysed patient.

During oral intubation by fibre-opticscope on a sedated unparalysed patient, an endoscopic oral airway or a bite block should be used to protect the scope from biting by teeth. Among the oral airway PatilSyracuse airway or Williams airway or ovassapian airway has some advantages. It prevents the dorsal displacement of the tongue and keeps the instrument in midline and guides the scope past the epiglottis into the larynx (Table 20.14).

As a first step, the base of the tongue, the oropharynx and the laryngopharynx is anaesthetised topically by 10% lignocaine spray or by nebulisation of 4% lignocaine. This is done in a completely conscious patient or with minimum sedation. Then an intubating airway is inserted through mouth after topicalisation. After that the ET-tube is inserted into the mouth about 8 to 10 cm through this airway and fibre-optic scope is passed through the ET-tube. The base of the toungue, epiglottis and finally glottis is visualised in proper sequence. If tip of the scope is obstructed by the posterior pharyngeal wall (which is diagnosed by pink blurr vision), it should be turned down to visualise the glottis. If the epiglottis obstructs the vision, then the scope should be manipulated, so that the vocal cords can be seen. After visualisation of the vocal cord, the ET tube is introduced into the glottis.

Table 20.14: Possible contents in an emergency difficult airway unit

1.	Rigid laryngoscope blades of different sizes and designs.
2.	Endotracheal tube of different sizes and shapes.
3.	Different ET tube guides, such as stylets of different sizes with or without hollow inside for jet ventilation, gum elastic bougies, light wands, forceps to manipulate the patient's end of the tube in the larynx.
4.	Various supraglotic airway devices : LMA of different sizes and types Combitube
5.	Fibre-optic intubation device.
6.	Set of a transtracheal jet ventilation.
7.	Set for emergency cricothyrotomy and ventilation.
8.	Set for retrograde intubation.
9.	Capnometer for detection of CO_2 in expired air.

Fibre-optic intubation in anaesthetised patient may also be done under spontaneous or controlled ventilation in a nonparalysed and paralysed patient respectively. It is obvious that the fibre-optic intubation under spontaneous ventilation in an anaesthetized patient is more technically easier and advantageous than the controlled ventilation. But, in spontaneous ventilation, diminished anaesthetic level causing cough, vomiting, laryngospasm, bronchospasm, etc. is the definite disadvantage. On the other hand, fibre-optic intubation under controlled ventilation, apnoea is the major headache. Patient should be ventilated with 100% O_2 by mask in between the intubation attempts by fibre-optic scope or patient should be ventilated with special endoscopic mask with a sealing port (through which endoscope is introduced) that allows for the continuous use of mask and ventilation during the attempts of intubation by fibre-optic scope. During endoscopy, additional O_2 from the separate source can be administered through the injection port of the fibre-optic scope.

Nasal intubation by fibre-optic scope has the advantage that the instrument can easily be positioned directly through nasal route into the hypopharynx to visualise the glottis. If the patient is not anaesthetized, tongue causes less interference when this route is used. On the contrary, anaesthetized intubation by fibre-optic scope through nasal route is less difficult due to less soft tissue upper airway obstruction caused by anaesthesia. In anaesthetized patient a standard nasal airway or a split nasal airway can be used to keep the tongue away from the posterior pharyngeal wall. Usually, the patient is not anaesthetized for fibre-optic scope to visualise the glottis. But, only anaesthesia is employed where patient is un-cooperative

and keeping in mind that intubation by fibre-optic scope under anaesthesia is usually more difficult. This is because of the development of the upper airway obstruction by falling tongue. If there is any doubt about the ability to maintain ventilation by mask during fibre-optic laryngoscopy under anaesthesia and paralysis, then fibre-optic aided intubation should always be preceded with conscious sedation and/or topical anaesthesia instead of full anaesthesia. In topical anaesthesia, for nasal fibre-optic intubation the supraglottic, glottic and tracheal areas may be anaesthetized with 1% lignocaine, sprayed through the injection port. After awake sedation, and application of topical anaesthesia and vasoconstrictor on nasal mucosa, an nasal ET tube or split nasal airway is passed through any nares into the nasopharynx and oropharynx. Then fibre-optic scope is passed through it. Thus, in vast majority of cases glottis can be seen by this scope with minimal tip manipulation. After visualisation of glottis, it is very easy to push the tip of ET tube in the larynx with the tip of fibre optic scope inside it.

OTHER SURGICAL AIRWAY TECHNIQUE

Other surgical airway techniques except the needle cricothyroidotomy, modified cricothyroidotomy by Seldinger technique (cannula cricothyroidotomy) and surgical cricothyroidotomy are percutaneous tracheostomy (PCT) and conventional surgical tracheostomy (ST). But none is performed under emergency 'cannot ventilate and cannot intubate' (CVCI) condition. Because all these procedures are time consuming (more than 5 minutes) and may not be able to save the apnoeic patient's life. By these above mentioned cricothyroidotomy techniques (including needle, cannula and surgical cricothyroidotomy) O_2 can be provided on a short-term basis until a definite airway can be placed or the patient resumes spontaneous breathing or wakes up. So, for a definite airway PCT is most commonly performed in ICU on patients who need prolonged ventilatory support for more than 3 weeks by ET tube.

Chevalier Jackson in 1909, first defined the method of surgical tracheostomy. Before that a patient remains intubated through larynx till he becomes conscious and cannot maintain his own airway. But, prolonged intubation through larynx has many disadvantages. So, if one thinks that a prolonged intubation is needed (more than 10 days) or if it is apparent that the patient is unlikely to maintain his airway independently within 3 weeks, then tracheostomy should be done. Usually, there are two types of tracheostomy – PCT and ST. The PCT has several advantages over conventinal surgical tracheostomy. These advantages are: (i) reduced wound complications such as haemorrhage and infection, (ii) improved cosmetic results, (iii) can be easily done at the bed side in ICU, (iv) reduced duration of the procedure and (v) it can be performed by non surgeons. The disadvantages of PCT over ST is that due to narrow tract and lack of formal stoma formation in PCT, there is increased risk of delayed airway loss. Without a formal stoma and with only a narrow tract between the airway and the skin, tracheostomy tube may be displaced which can lead to death.

First PCT was reported in 1955 by Sheldon. But because of high complication rate in this technique adopted by Sheldon, Ciaglia in 1985 modified this technique and called it as percutaneous dilatational tracheostomy (PDT). PCT differs from conventional ST in that in PCT a puncture is made on the trachea in between cartilages (usually between 1st and 2nd or between 2nd and 3rd) by needle or scalpel and subsequently the puncture is dilated over a flexible guiding catheter to intorduce a small tracheostomy tube or a small endotracheal tube. Whereas in conventional ST the tracheal cartilages are dissected and cut by the scalpel. On the other hand, in cricothyroidotomy the site of puncture is cricothyroid membrane and not the tracheal cartilages. Other different techniquees of performing PCT are : Grigg's technique, White tusk / Blue Rhino technique, Pere Twist technique and Trans Laryngeal Tracheostomy Technique (TLT).

PCT is performed in the intercartilagenous area between the 1st and 2nd tracheal rings or 2nd and 3rd tracheal rings. There is increased incidence of subglottic stenosis when it is performed above the first ring. The area below the third ring is generally avoided to minimise the potential trauma of the isthmus of thyroid and to prevent the accidental injury of the inominate artery.

In conventional ST the tracheostomy tube should be placed so that it does not erode the ring and press against the cricoid cartilage. In addition, the opening should not be placed too low, so that the tip of the tube or its cuff will be too close to carina. Low placement of tracheostomy tube is also hazardous, because the innominate artery crosses anterior to the trachea low in the neck. During ST any segment of trachea should not be removed, because this might lead to greater loss of tracheal wall stability and predispose to stenosis, once healing is accomplished after removal of the tube.

SUPRAGLOTTIC AIRWAY DEVICES

These are the devices which lying above the glottic opening help in ventilation and avoid the 'tube within tube' situation that is produced by intubating the trachea by an ET tube. It provides a better unobstructed airway during spontaneous respiration than the oropharyngeal or nasopharyngeal airway. It also help in controlled ventilation if needed. LMA is such the first supraglottic airway device and has been in practice nearly 20 years, since Dr. Archie Brain in UK had first introduced it. The LMA has been used for more than 150 million times world wide, but without a single death attributed to its use. So now, LMA has a well established role in the management of patient with normal or difficult airways.

Thus, the amazing success trail of LMA has spurred the introduction over a dozen of different supraglottic airway devices other than LMA to remove the disadvantages of it. But, only some have stood the test of time, while others have dwindled into the oblivion. Some of the supraglottic airway devices which have stood the test of time include: Combitube, soft seal and laryngeal airway device, laryngeal tube suction (LTS), cobra perilaryngeal airway (cobra PLA), pharyngeal airway Xpress (PAX), streamlined linear of the pharyngeal airway (SLIPA), cuffed oropharyngeal airway (COPA), glottic aperture seal airway (GOS airway).

All the supraglottic airway devices produce minimal to nil haemodynamic instability during their placement in larynx as they avoid stimulation of the infraglottic structures. They offer minimum resistance to the patient's airway. Other advantages of supraglottic devices are: Easy insertion and smooth awakening, no inadvertent bronchial intubation, no vocal cord injury, no translocation of oral or nasal bacterial colony and no secretions into the lower respiratory tract. Among all the above mentioned supraglottic devices, LMA and combitube have been recommended as the rescue of airway in 'cannot ventilate, cannot intubate' situations. Again LMA has been recommended at five places in the ASA Task force Algorithm for the management of difficult airway, either as a ventilating devices or as a conduit for endotracheal intubation.

However, today these devices (LMA and combitube) are not only used during emergency situations, but also during elective management of the patient's airway. Ambulatory or day case surgery for patients of ASA I and II grade (ASA I patients only according to some anaesthetist) are one of the most suitable candidates for the use of these supraglottic devices. These include short procedures, not requiring controlled ventilations with muscle relaxant such as surgeries of the upper and lower limb, ear and nose surgeries, ophthalmic surgeries, short gynaecological procedures, etc. These devices are also recommended in patients with ischaemic and other heart diseases, coming for short surgical procedures under general anaesthesia, as their use is associated with lesser haemodynamic changes compared to tracheal intubation. At the end of neurosurgery, but prior to termination of anaesthesia, ET tube can be replaced with LMA as a preventive strategy against hypertension, coughing, bucking, etc. which are associated with extubation and smoother emergence. For these reasons, supraglottic devices also are used during ophthalmic surgery to prevent risk from sudden rise in IOP during intubation and extubation. The supraglottic devices are also extremely popular in patients, undergoing minor therapeutic and diagnostic surgical procedures outside the OT complex. These include: Radiotherapy, diagnostic and interventional radiology, endoscopy, ECT, cardioversion, etc. In the ever expanding horizons of the supraglottic devices, more and more number of the routine general anaesthesia, lasting for 2 to 3 hours are now also being administered using these devices. Even surgeries associated with increased intra-abdominal pressure (Laproscopic surgeries) are now being safely done using proseal LMA, LTS or combitube.

Factors which prevent the use of supraglottic airway devices include: Small oral opening and any pharyngeal pathology which prevents the proper fitting of it at the laryngeal inlet. For example, pharyngeal mass and oesophageal pathology including caustic injury contradicts the use of supraglottic airway devices like combitube and laryngeal tube suction. All the supraglottic airway devices do not offer reliable protection against regurgitation and aspiration of stomach contents, except combitube and LTS. So, they should not be used in patients with the possibility of reflux of gastric contents and aspiration of it or where retained gastric contents may be present.

These conditions include:

i. When fasting is not confirmed
ii. Morbid obesity
iii. Pregnancy where there is delayed gastric emptying
iv. Others conditions associated with delayed gastric emptying such as history of gastroesophageal reflex, hiatus hernia, etc.
v. Multiple or massive injury.
vi. Acute abdominal or thoracic injury.

But, we have to keep in mind that these above mentioned conditions are not the absolute contraindications for the use of supraglottic devices.

Supraglottic airway devices also have the limited value in patients with poor lung compliance as they cannot withstand the high inflation pressure. But, it is noted that only the proseal LMA can withstand the peak inflation pressure of 35 to 38 cm of H_2O without leak from sides.

Individual Supraglottic Device

There are many supraglottic devices, among them which are commonly used are described below.

LMA

Previously it has been already discussed.

Soft seal and laryngeal airway devices

both the soft seal and the laryngeal airway device are quite similar to the LMA of unique variety in regards to structure and single use concept. But, one major difference between the LMA of unique variety and the soft seal or laryngeal airway device is the removal of the aperture bars from both of these later devices and a softer cuff of the soft seal. So, the latter confers a better periglottic seal, which can withstand the higher inflation pressure than the LMA classic.

Laryngeal tube suction (LTS) device

LTS is basically a shorter version of combitube. It is a newly developed, multiuse, latex free, double lumen, silicon tube. Like combitube, it has both oropharyngeal and oesophageal low pressure cuffs, a ventilation outlet in between them and a second

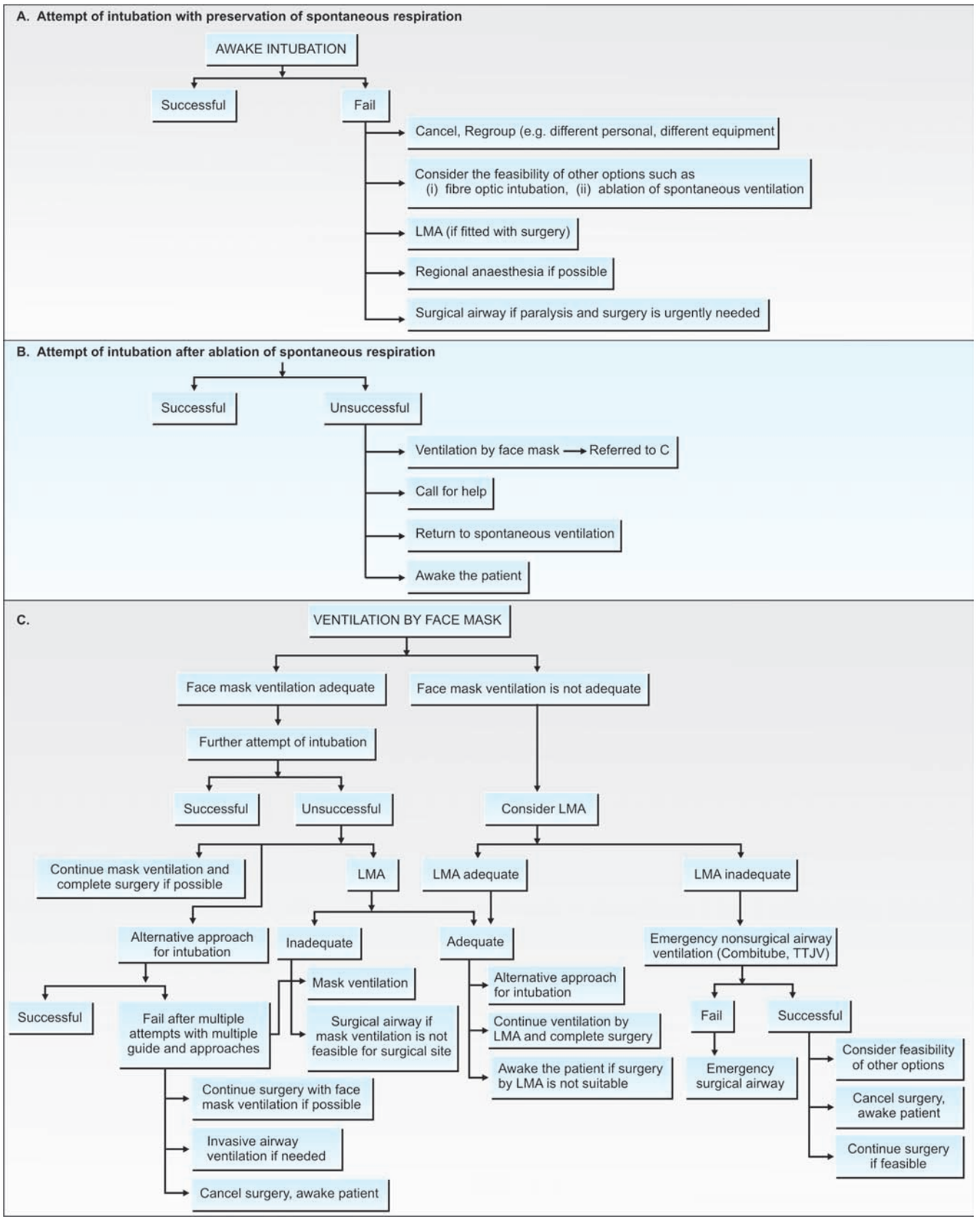


Fig. 20.43: Algorithm of airway management

tube placed posteriorly. The second tube is situated posterior to the respiratory lumen. The same inflation assembly inflates the two cuffs at a time. When correctly placed, the distal tip along with its opening and the cuff lies in the oesophagus. This effectively separates the oesophagus from the rest of the airways. Being shorter and blunder, the possibility of the oesophageal portion of the tube entering the trachea is non-existent. Laryngeal tube (LT) which is precursor to LTS has no second tube. So, it has now been replaced by LTS. Method of insertion of LTS is same as combitube. Due to the specially designed inflation line, the proximal cuff is inflated first and stabilizes the tube. Then once the proximal cuff has adjusted to the anatomy of the pharynx of the patient, the distal cuff will be inflated automatically. It is usually recommended to use a cuff pressure below 60 cm of H_2O. Like combitube there is no need to connect both the lumen alternatively for confirmation of ventilation. If ventilation is not adequate, then position of the tube can be changed by pushing it either distally or pulling it proximally according to patient size. The fine drained tube allows the insertion of a gastric tube.

Cobra Peri-laryngeal Airway (Cobra PLA)

It is a new device in the field of supraglottic airways. It consists of a tube, a cuff and a 15 mm standard adaptor for attachment with the anaesthetic machine. Distally, the tube ends at an opening with cobra head design which holds both the soft tissues and the epiglottis out of the way. Thus, it facilitates the ventilation though the slotted opening. The cuff when is inflated gently seals off the upper airway and allows improved positive pressure ventilation. Cobra PLA is usually used as an alternative to face-mask and certainly does not protect the airway from the effects of vomiting, regurgitation and aspiration.

Pharyngeal Airway Xpress (PAX)

PAX is a sterile, latex free, single use supraglottic airway device. It is used as an alternative to face-mask, LMA, Cobra PLA. The PAX supra glottic device consists of a tube, a cuff and a soft-flexible-gilled tip and is made of medical grade PVC. The tube has a standard 15 mm connector at its proximal end for attachment with anaesthetic machine. The soft, flexible, gilled tip is tapered to guide the device and help to rest the device within the cricopharyngeal recess, above the oesopharyngeal sphincter. The gilled tip is made of thermoplastic elastomer. A high volume, low pressure cuff which volume is 60 ml stabilizes the PAX within the oropharynx. Approximately, placed cuff lies just below the uvula and pushes the tongue forward for improved ventilation. An open hooded window is situated between the cuff and the gilled tip for aligned to the glottic opening. The hood is designed to lift the epiglottis forward. An anatomically curved tube can accept 7.5 mm ET tube if tracheal intubation is indicated.

Streamlined Linear Pharyngeal Airway (SLIPA)

The SLIPA is a hollow, preformed, boot-shaped airway. It is made of soft plastic and blow molded to the shape of the pressurized pharynx. As it is fitted tightly in the pharynx, no cuff is provided to seal the device in the pharynx. SLIPA is looked like a boot with 'toe bridge and heel' prominences. It is used as an inexpensive single use alternative to the LMA and to decrease the risk of aspiration if limited volume regurgitation should occur. It is available in different sizes to match the patient size (Fig. 20.43).

21 Mechanical Ventilation

INTRODUCTION AND HISTORY

For centuries, it has been felt that failure to breathe should not be allowed to proceed to death. So, expired air ventilation (mouth-to-mouth resuscitation) has been used throughout the ancient history in an effort to revive the apparently dead person especially from drowning. So, in the Second Book of Kings there is a vivid description of such a successful mouth-to-mouth breathing by the Prophet Elisha. He performed this on a child who appeared to be dead from drowning. But, the actual date of this event is not known. Then during the period of 12th and 13th century tracheostomy was usually used to perform ventilation for the treatment of drowned persons instead of by mouth-to-mouth breathing. After that between 1493 to 1541, Paracelsius and Vesalius were credited for the introduction of bellows and a pipe to ventilate the lungs through this tracheostomy wound. But only for ventilation tracheostomy was not accepted by the people during this era. Then, Elisha's mouth-to-mouth breathing was rediscovered by Tossach, in 1743. But that method of ventilation was later condemned as an unhygienic manoeuvre by the newly founded Royal Human Society. After that in 1763, the 'Society for the Recovery of Drowned Persons' was formed in Amsterdam. They declared to offer medals and prizes for new ideas and apparatuses for ventilation other than mouth-to-mouth breathing. Hence, many designs of pumps, bellows and tubes were introduced to ventilate the lungs through larynx or tracheostomy wound. In 1811, Brodie and Waterton employed the 'curare plus bellows' principle for positive pressure ventilation on the experimental animals and also suggested that artificial breathing by bellows could be used to treat severe respiratory depression in opium poisoning. Then, in 1827, Leroy demonstrated the dangers of this positive pressure ventilation such as rupture of alveoli, pneumothorax, etc. which was later confirmed by Magendie's report in 1829. So, after that positive pressure ventilation for resuscitation using bellows fell into disrepute. In 1837, Royal Human Society also criticised positive pressure ventilation by bellows and recommended the manual compression of chest (negative pressure ventilation), if artificial ventilation was necessary. So, for the next century, positive pressure ventilation by bellows went into oblivion but mouth-to-mouth resuscitation and chest compression for ventilation continued. Then again 100 years later, bellows for resuscitation or ventilation reappeared, when Kreiselman introduced his own apparatus during the second World War. Within this period of 100 year (1840–1940), most of the mechanical aids for artificial ventilation were depended on the application of subatmospheric pressure from outside the thorax (negative pressure ventilation).

During this period using the principle of subatmospheric pressure from outside the thorax for ventilation, the tank ventilator and cuirass ventilator were invented which were later claimed as a very successful apparatus for the treatment of respiratory paralysis, and respiratory failure due to poliomyelitis. First tank ventilator was patented in America in 1864. After that, different modifications to this basic design of tank ventilator were introduced over the next few years. In 1929, Drinker and his colleagues first introduced their tank ventilator for prolonged artificial respiration. This apparatus subsequently was known as the 'iron lung'. The first patient to be treated with the iron lung was a victim of paralytic bulbar poliomyelitis. The tank ventilator, introduced by Dinker and his colleagues, was also the first ventilator driven by power. In this tank ventilation the patient was placed on a mattress inside an air tight cabinet, from which only his or her head is protruded. A padded collar around the neck formed an effective air tight seal. The pressure inside the cabinet was lowered rhythmically by a system of pumps or a set of bellows during inspiration and was next allowed to return to the atmospheric level slowly during expiration. There were portholes at the sides of the tank, through which the patient could be observed and sealed ports to allow the use of manometers, blood pressure cuffs and stethoscopes. The two main disadvantages of these tank ventilators were: (i) access to the patient for nursing care and physiotherapy was restricted and (ii) the air way was not usually protected. So, vomiting and regurgitation are particularly hazardous in respect to the chance of aspiration, during this intermittent negative pressure ventilation (INPV) by tank

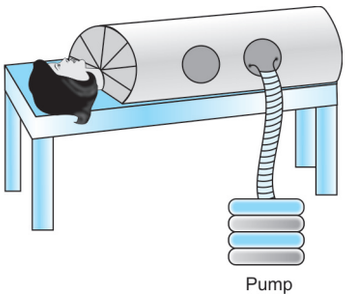


Fig. 21.1: The tank ventilator. Inside the ventilator the patient is placed in a body shaped shell. Head is outside the tank

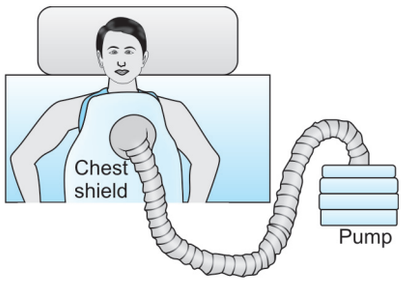


Fig. 21.2: Cuirass ventilator with chest shield (red) which is connected with pump

ventilators, even for patients who have normal laryngeal and pharyngeal reflexes. If vomiting occurs, then an emergency port should be opened immediately to equalise the pressure between the inside and the outside of the tank and thus reduce the risk of aspiration (Fig. 21.1).

Cuirass ventilator was named after the piece of a 15th century body armour, used during war. It is consisted of a breast plate and a back plate which were joined together at both side forming a rigid shell around the thorax. This rigid shell was fitted over the thorax and upper abdomen and a padded rim at the periphery around the neck and upper abdomen made contact with the skin to form an air-tight seal. A bellow was connected by a flexible tubing to the airspace situated between the skin and the shell. The expansion of bellow was able to create a subatmospheric pressure in the airspace between the chest wall and the armour plates during inspiration and allowed the chest wall to inflate and the air to rush into the lungs through airways. During expiration the pressure in the air space again became atmospheric and the chest wall deflated with the lungs and the air came out. Cuirass ventilators though work on the same principle as tank ventilator, but left patient's arms and legs free and caused less circulatory embarrassment than tank ventilators. But they were less efficient than tank ventilators and the tidal volume obtained by a given subatmospheric pressure was smaller. So, Cuirass ventilators were used as an assistants for patients who was suffering from chronic respiratory impairment with some respiratory efforts but not had complete respiratory paralysis or who were recovering from some acute episode of paralysis (Fig. 21.2).

After 1940, due to multiple disadvantages of tank and cuirass ventilators positive pressure ventilation again resurfaced by the work of Krliselman during the Second World War in 1939. During that period Krliselman's work was also supported by the development of non-depolarising neuromuscular blocking agents by Griffith in 1942. He was the first to use curare in anaesthesia. This development initiated the need for new positive pressure ventilators in anaesthesia which could be combined with newly developed endotracheal intubation techniques by Magill and Macintosh. These were more convenient for operating theatre enviornment and also solving the problem of oropharangeal and gastric secretions entering the trachea. Another cause for loosing the popularity of negative pressure ventilations by tank ventilators was that these were large and awkward devices. The poliomyelitis epidemic which occured in Copenhagen in 1952 also had enormous influence on the development of newer positive pressure ventilation techniques and ventilators. By this time, controlled positive pressure ventilation was well established in anaesthesia. During that epidemic of poliomyelitis, an eminent anaesthetist named Ibsen was called in by Prof. Lassen to help him for the ventilatory management of polio patients in the Blegdam Hospital. Then Ibsen developed the method of positive pressure hand ventilation through the tracheostomy tube and almost all the students of the medical school were appointed to help with this manual ventilation. So, medical teaching activities were temporarily suspended until polio epidemic was over. After that, Lassen and Ibsen established some basic principles for long-term positive pressure ventilation. These were careful airway control and protection, humidification of inspired air, avoidance of high inspired O_2 concentration for ventilation and meticulous physiotherapy. Once the acute phase of poliomyelitis disease was over, then weaning was accomplished by a forerunner of IMV. Then the adequacy of ventilation was assessed by oximetry and end tidal CO_2 concentration measurement. So, after the second World War in 1939, there were two stimuli for the further development of positive pressure mechanical ventilation. The first was the introduction of curare into anaesthesia. The second was the fear of health authorities that if another epidemic of poliomyelitis occured, then large number of patients might require artificial ventilations which in turn need huge manpower. So, in 1940, the first commercial automatic mechanical ventilator for anaesthesia was manufactured in Sweden for IPPV.

A dramatic fall in the mortality from polioepedemic was occured after this new technique of automatic ventilation (IPPV) had been introduced for its management and this ensured that IPPV would become the standard method of artificial ventilation than negative pressure ventilation made by tank and cuirass ventilator. Later the superiority of automatic IPPV was also confirmed by Stockholm polioepidemic in the following year and New England polioepidemic in 1955. After the intorduction

of poliomyelitis vaccine (Salk and Sabin), the incidence of poliomyelitis fell sharply. So, the ventilation skill which had been developed to fight polio epidemic were diverted to other good uses, such as anaesthesia, and for management of polyneuritis, drug over doses, trauma, asthma and complicated surgeries, etc. where prolonged artificial positive pressure ventilation was needed. After that in 1960, the indications for IPPV were broadened further and its cardiovascular effects were also investigated. The value of mechanical positive pressure ventilation in anaesthesia was also soon recognised simultaneously in Sweden, Britain and many other European countries. But during this period it was still disputed in USA, where the reliance on manual IPPV was persisted. However later, the more stringent ventilatory requirements for cardiac surgery changes this view.

After successful establishment of automatic IPPV as the ideal mode of treatment for respiratory failure, a group of patients went on to develop a lung condition, which were characterised by certain radiological changes and severe impairment of gas exchange due to prolonged ventilation. At that time such changes in lung condition was called by many names such as shock lung, ARDS, respirator lung, etc. But in 1970, the pathophysiology of such lung condition was studied intensively and PEEP was introduced. The PEEP was added to IPPV to aid better gas exchange in patients with shock lung or ARDS. But, gradual recognition of the adverse effects of PEEP on the circulation started the quest for an ideal PEEP level which would balance the respiratory advantages against the circulatory disadvantages of it. The year of 1970 also saw the development of extracorporeal circulation techniques which could ensure the adequate gas exchange for several weeks. At that period, high frequency ventilation (HFV) was also developed, but its true role in long-term mechanical ventilation was not established. In 1960, pulmonary oxygen toxicity was also blamed for the pathology of ARDS or shock lung, because toxic effects of pure oxygen on lung at standard atmospheric pressure was known for over 50 years. Hence, an inspired O_2 concentration of 50% or less was considered safe. So, after 1960, most ventilators which are in use in North America employed a venturi device to entrain air and to mix it with the principal gas flow of O_2. This evidence together with the experience which was, already gained from polio patients, established that IPPV with modest level of O_2 in the inspired gas and modest level of inspiratory and expiratory pressure may be continued indefinitely, without any adverse effects on the lungs. Then the subsequent evolution of ventilators had taken two paths. One was to fulfil the need for cheap, simple and reliable method which could be used for anaesthesia and for the majority of patients needing short-term ventilation. The other was to provide increasingly sophisticated and versatile ventilators with the facilities, necessary for treating patients with severe respiratory failure or suffering from other life threatening condition.

ARTIFICIAL INTERMITTENT POSITIVE PRESSURE VENTILATION (AIPPV)

After the Second World War, in 1939, positive pressure ventilation was established which certainly was artificial and intermittent. So this artificial intermittent positive pressure ventilation (AIPPV) can be employed and classified by three ways:

1. AIPPV requiring no apparatus – expired air ventilation (e.g. mouth-to-mouth resuscitation).
2. AIPPV using simple devices or apparatuses.
3. AIPPV using sophisticated instruments manual ventilation Boyle's machine or automatic ventilation by ventilators.

1. AIPPV by Using No Apparatus or Mouth-to-mouth Resuscitation

It was previously described that Elisha's mouth-to-mouth positive pressure ventilation which was gone out of vogue today due to development of tracheostomy and bellows, was rediscovered by Tossach in 1743. But, again as the mouth-to-mouth method of breathing was unhygienic, so Royal Human Society had condemned it and recommended some other methods of ventilation, described below. But in 1954, Elam and in 1958, Safar showed that the other methods of non mouth resuscitation, (recommended at that time by Royal Human Society), such as Holger-Nielsen method, Schafer's method, or Sylvester's method failed to provide adequate ventilation. So, since that time mouth-to-mouth breathing or expired air resuscitation had again become the method of choice when equipments are not available, except for those who have inhaled toxic gases or who are the victims of cyanide poisoning (Figs 21.3 and 21.4).

2. AIPPV by Using Simple Devices

Many simple devices had made the positive pressure ventilation through mouth more easy, more acceptable, more hygienic and more effective than mouth-to-mouth ventilation. This devices are so simple that it can be carried in pocket. AIPPV using these simple devices are of the following types. This may be expired air ventilation or fresh air ventilation, enriched with O_2.

Mouth ventilation by mask

Here, the device is nothing but a simple transparent Laerdal pocket face mask. The angle piece is replaced by a short, straight tube to which the resuscitator's lips can be applied for forceful blow. A nipple can be added on the body of the mask, so that through it O_2 can be added to the inspired gas. This device makes the IPPV procedure more hygienic and O_2 enriched expired air can be used to ventilate the patient (Fig. 21.5).

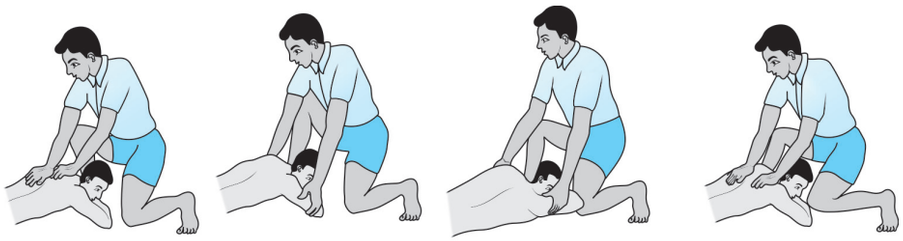


Fig. 21.3: Holger-Neilson's manual method for artificial respiration.

Fig. 21.4: Schafer's manual method for artificial respiration

Mouth ventilation by air-way devices

Here, different types of airways are used for expired air ventilation by mouth. The different types of airways are: Safar S-tube, Brook airway, oesophageal obturator airway, etc. Safar S-tube is a double Guedel airway and is used both as a pharyngeal airway and for ventilation. Brook airway is slightly sophisticated where a non return value in used which allow the expired air from patient to pass out. In oesophageal obturator airway, a large cuffed tube is designed to obstruct the oesophagus which prevents the reflux of gastric contents during ventilation (Fig. 21.6).

Bag-valve-mask ventilation

Here, resuscitator's mouth is not used for expired air ventilation. Instead a self refilling bag is used to ventilate the patient by mask. Between the bag and the mask, a non rebreathing valve is incorporated which help the expired air from patient to pass out. O_2 can be administered, if available, through a side tube, but a reservoir tube is necessary to deliver 100% O_2. Example of one such ventilation is by Ambu bag (Fig. 21.7).

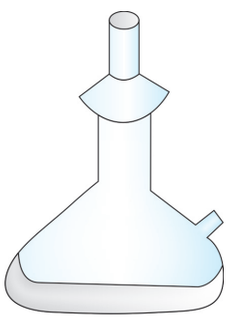


Fig. 21.5: Laerdal pocket mask

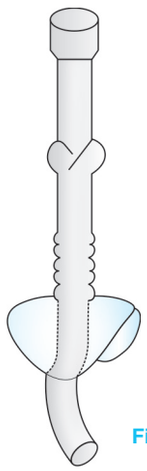


Fig. 21.6: Safar-S-tube

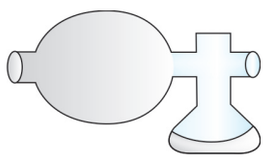


Fig. 21.7: Ambu-bag with mask

3. AIPPV Using Sophisticated Instrument

AIPPV using sophisticated instrument can be conducted manually or automatically. When it is conducted maunally, the best example is bag-mask ventilation by Boyle's apparatus. Automatic artificial intermitent positive pressure ventilation also can be performed by ventilators.

The power mechanism (electric or pneumatic) forms an important part of the driving system of an automatic ventilator. The only electrically driven ventilator uses only electrical source for its complete working. Here both the electronic and mechanical components which are incorporated in this type of only electrically driven ventilator, is such designed that this ventilator uses only the electrical source for its complete working. Except the anaesthetic ventilator which uses the anaesthetic gas mixture from Boyle's machine, the air is sucked inside the other type of ventilators (which are used in critical care unit) from the atmosphere, and this is blended then with the external source of O_2 to meet the desired FiO_2. During inspiration, the air is pushed by the ventilator through the bellow system into the patient's airways. These only electric driven ventilators find a good application typically during transport of a patient.

On the other hand, both pneumatically and electrically operated ventialtors need a source of highly compressed, pressurised air to operate the mechanical components of the ventilator, in addition to the electrical source for the complete control of it. The source of compressed air can be provided from external or internal sources. The external source of compresed air is available either from a cylinder or from an air compressor which is permanently build in the ventilator or through an air compressor available for the use of hospital. Some ventilators incorporate piston assembly or turbine technology in their system as the internal source of compressed air. This turbine compresses the room air, after

it is sucked inside the ventilator. In such ventilator systems, there is no need for an external source of compressed air for their function.

An automatic positive pressure ventilation has four stages:

i. Inspiration – inflation of lungs.
ii. Changing over from inspiration to expiration – cycle.
iii. Expiration – deflation of lungs.
iv. Changing over from expiration to inspiration – trigger.

The term 'cycling' is referred to the changing over from inspiration to expiration and the term 'triggering' is referred to the changing over from expiration to inspiration (Table 21.1).

Inspiration

In positive pressure ventilation, inspiration can be instituted by presenting a preset pressure or a preset volume of air to the patient's upper airways. So, as a result of difference between the upper airway pressure and the alveolar pressure, gas flows into the lungs of patient. This cause of flow results in delivery of fixed (in VCV) or variable volume of air (in PCV) in the patient's lung.

So, according to the preset pressure presentation or preset volume presentation the ventilators can be first classified into:

Table 21.1: Classification of ventilators

1.	According to power and control mechanism
	i. Pneumatically driven and operated
	ii. Electrically driven and operated
	iii. Both
2.	According to cycling mechanism
	i. Time cycling
	ii. Volume cycling
	iii. Flow cycling
	iv. Pressure cycling
	v. Combinational cycling
3.	According to trigger mechanism
	i. Time or ventilator triggered
	ii. Patient triggered

i. Pressure controlled (or generated) ventilator (PCV)– Here, ventilator applies a fixed pressure set by operator to the upper airway during inspiration. So due to this fixed pressure pattern, the volume of air delivered to the patient during inspiration may vary according to the condition of lungs.
ii. Volume or flow controlled (generated) ventilator (VCV) – Here, ventilator delivers a fixed volume of air set by operator to the lungs during inspiration. Like PCV, as fixed volume of air is delivered to the patient, so the pressure in the airway may vary according to the conditions of the lungs.

Pressure controlled ventilation (PCV)

In pressure controlled or generated or pressure limited ventilation (PCV), the peak inspiratory pressure or P_{max} is preset by operator and is maintained for the whole set inspiratory time. So, the flow or volume of air entering the patient's lungs will depend on the set pressure pattern, lung compliance, airway resistance, and the time allowed for inspiration. The flow of air in alveoli decreases as the alveolar pressure gradually increases with the increasing alveolar volume and ceases when the alveolar pressure equals to the applied set airway pressure. So, the delivered tidal volume will depend on all the factors which affect the flow. In PCV, the normal airway pressure is typically set in the range of 15 to 30 cm of H_2O, while pressure above 50 cm of H_2O can be associated with an increased risk of barotrauma. However, High pressure (even above 50 cm of H_2O) is sometimes set in cases of ARDS, to inflate the stiff lungs and here the PCV is preferred mode of ventilation. The PCV is also used for obstructive lung diseases, where resistance for airflow into the lungs is very high. In neonatal and paediatric patients PCV is also indicated, since the peak airway pressure is controlled and barotrauma can be avoided.

Advantages of pressure controlled ventilation are

i. As the flow rate or volume varies depending on the patient's lung compliance and airway resistance, so there is no flow or volume starvation.
ii. It protects against barotrauma. So, it is essentially used for neonatal and paediatric group of patients.
iii. Since the fixed peak airway pressure is maintained throughout the inspiration, so it ensures that not only the healthy alveoli do not over inflate but also, the non participating alveoli are recruited resulting in better gas exchange.

Disadvantages of PCV are

i. The tidal volume may decrease, if the compliance deterioates or the resistance increases. In such situations the setting of pressure should be changed, as if the delivered tidal volume can be adequate.
ii. Required tidal volume delivered to the patient cannot be assured.
iii. Minute ventilation should be closely observed to ensure adequate alveolar ventilation.

In pressure controlled ventilation, adequate alveolar ventilation and oxygenation can be achieved by the manipulation of various ventilator settings. Patient's alveolar ventilation depends on minute volume. Minute volume depends on tidal volume and respiratory rate. In PCV tidal volume cannot be controlled directly by knob. Tidal volume depends on pressure (PIP-PEEP) and time constant. Time constant depends on resistance and compliance. Time constant cannot be controlled by knob, while only preset pressure is controlled by knob, thus controlling the tidal volume indirectly. Respiratory rate depends on inspiratory time and expiratory time and I:E ratio, all of which can be controlled by knob. So, in PCV ventilation is controlled by controlling the knob of pressure (PIP – PEEP), respiratory rate, inspiratory time, expiratory time and I:E ratio, according to

the resistance and compliance of airways and lung tissues. The last four parameters are integrated and when any two of these four is changed, then other two will change automatically. Oxygenation can be improved by increasing FiO_2. In PCV, pressure is the independent variable and volume is the dependable variable. In lung pathology when compliance decreases and resistance increases, then the pressure is set such that an adequate volume of air is delivered according to that set pressure. The ultimate arterial oxygenation and $ETCO_2$ is maintained by setting the knob of pressure, inspiratory time, expiratory time, I:E ratio, FiO_2, PEEP and flow pattern.

Pressure controlled ventilation differs from pressure cycled ventilation and pressure support ventilation (PSV). In pressure cycled ventilation, the inspiration is terminated when the peak set pressure level is reached, whereas in pressure controlled ventilation, the peak pressure is held constant in the form of plateau until the inspiratory time has elapsed. Difference of pressure controlled ventilation from PSV will be discussed later in the next paragraph. The most salient feature of PCV is that the maximal airway and alveolar pressures are controlled. Whereas the tidal volume and subsequently the minute volume and alveolar ventialtion cannot be controlled which depend on compliance, resistance and ventilatory pattern. The effective tidal volume is the result of the product of compliance and P_{max}. The level of P_{max} which is the necessary inspiratory pressure level are chosen or set, depending on the tidal volume required, but the pressure exceeding 35 cm of H_2O should generally be avoided.

In both, pressure controlled and pressure support ventilation, a set or fixed pressure is controlled by the machine. But the difference between the two involves the inspiratory time which is machine controlled in the former and patient controlled in the latter.

The special advantages of PCV for its decelerating flow are:

i. Since the flow of air during PCV is decelerating, so the peak airway pressure due to airway resistance occurs early in inspiration, and the peak airway pressure due to elastic recoil resistance does occur at the end of inspiration. This produces less variability of peak airway pressure than during volume – controlled ventilation.
ii. Effective ventilation in cases of distribution disorders in lungs. The decelerating inspiratory flow characteristic of PCV reduces overinflation of well ventilated 'faster alveoli'.
iii. Improved gas exchange due to characteristic of decelerating flow.
iv. PCV like pressure – support ventilation is also especially suited for ventilation during losses due to leakage (e.g. fistulla, uncuffed tracheal tube) as an increased flow to maintain the preselected pressure can automatically compensate these losses to a certain degree.

In reality, PCV or PSV refers to how the different type or mode of breaths are modified by pressure, rather than specifying it as a particular mode or type of breath. PCV can be delivered in conjunction with CMV, ACMV, SIMV, etc. It was actually been available for many years in conjugation with IMV in neonatal ventilators. A number of variants of PCV have recently been introduced into the clinical practice which include PC-IRV, APRV, intermittent mandatory pressure release ventilation and bilevel positive airway pressure ventilation.

The initial settings for PCV include FiO_2, air way pressure level (P_{max}) and the end expiratory pressure, as well as back up mode and rate. P_{max} is adjusted to ensure adequate tidal volume. Back-up mode and rate is chosen to provide adequate minute ventilation in the event of decreased intrinsic respiratory drive and may be supplied either in pressure control or SIMV mode.

Volume controlled ventilation (VCV)

In a volume controlled or limited ventilation (VCV), a preset amount of minute volume is delivered to the patient in a fixed inspiratory time set by the respiratory rate and the tidal volume in machine. The breath (inspiration) is triggered on by the timing interval determined by the set respiratory rate. Then, it cycles off into the expiratory phase when the inspiratory time has elapsed. By controlling the respiratory rate and tidal volume knob the minute volume should be fixed or preset. That prefixed minute volume should be delivered during fixed inspiratory time. The alveolar and upper airway pressure that is developed due to this inspired volume will depend on the volume and flow pattern of gas delivered by the ventilator, lung complainace, airway resistance and the time allowed for inspiration.

Volume (or flow) controlled (or generated) ventilators are thought as strong ventilators than PCV, because the minute volume (set by the tidal volume and respiratory rate) delivery will not change with the patient's lung characteristic, i.e. compliance and resistance. Here the minute volume is independent or fixed factor and the airway or alveolar pressure is dependent factors which are affected by the changes in lung compliance and airway resistance. If lung compliance decreases and resistance increases, then airway or alveolar pressure will also increase as ventilators will try to ventilate the preset volume of gas within the preset time. So, barotrauma can happen. Thus to avoid barotrauma, minute volume (by tidal volume and respiratory rate) should be set carefully according to the compliance and the resistance of lungs and should not be used in paediatric patients (mainly neonates and infants) and pathological lung conditions. Here as the pressure is variable so it cannot be controlled directly according to wish. Indirectly it can be controlled by adjusting the preset

tidal volume level and inspiratory time (independent variable). In normal lungs with normal compliance and resistance, if volume is set wrongly, then barotrauma can also occur.

In contrast, pressure controlled ventilators are thought as weak ventilators, because the minute volume will change as the patient's lung characteristic changes. So, to maintain the adequate ventilation independent variable such as pressure should be controlled accordingly. In this ventilators airway pressure is the independent variable, volume is dependent variable (cannot be controlled directly, can be controlled through pressure) and are affected by changes in lung compliance and airway resistance.

The main indications of volume controlled ventilation are: intraoperative IPPV, restrictive lung diseases, patients weighing more than 10 kg (where lung's compliance and resistance are thought to be normal). Adequate ventilation and oxygenation can be achieved in volume controlled ventilation by manipulation of minute volume (tidal volume and respiratory rate) and FiO_2. Tidal volume can be set according to patient's body weight (10 to 12 ml/kg) and minute volume can be set by controlling tidal volume and respiratory rate knob. After setting a minute volume if airway pressure goes to the allowable maximum limit (not causing barotrauma) and still oxygenation is not adequate, then oxygenation can be improved by increasing the FiO_2. In volume controlled ventilation oxygenation cannot be improved by further increasing the minute volume in fear of barotrauma. In such situation for better oxygenation PEEP can be used with increasing FiO_2.

Advantages of VCV are:

i. Pressure time waveform of a volume controlled ventilation (VCV) should be ramped one. Because the ramped pressure time waveform helps to maintain minimum mean airway pressure.
ii. Guaranteed preset volume is delivered during each breath which ensures proper ventilation.

Disadvantages of VCV are:

i. The resulting high distending peak airway pressure can cause barotrauma.
ii. Distending or peak airway pressure will increase, if compliance of lung decreases and resistance of airway increase. So, it is mandatory to correctly set the high pressure alarm limit.
iii. Unequal ventilation of different alveoli with different resistances and time constant can occur. The flow of air takes the path of least resistance. Hence, the alveoli with lower resistance and short time constant will be overinflated. Whereas the alveoli with higher resistance and long time constant will be under inflated.
iv. Since, the flow and subsequently the volume is fixed in VCV, so an improper flow setting can cause flow hunger for the patient. This may cause discomfort and hypoxaemia to the patient. In VCV, if lung's characteristics change frequently, then you will have to keep eye continuously on pressure gauge and according to that you have to control or preset the minute volume by controlling the tidal volume knob and respiratory rate knob for avoidance of barotrauma (Fig. 21.8).

Whereas in PCV if lung's characteristics change frequently you will have to keep eye continuously on the computer screen giving tidal volume/minute volume data or breathing bag of ventilator or SPO_2 level for tidal volume and according to that you have to adjust the pressure setting knob for proper ventilation and oxygenation. In some volume control ventilator

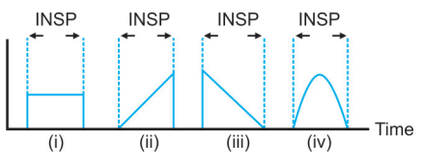


Fig. 21.8: (i) Constant flow, (ii) Accelerating flow (ramp), (iii) Decelerating flow, (iv) Sine flow

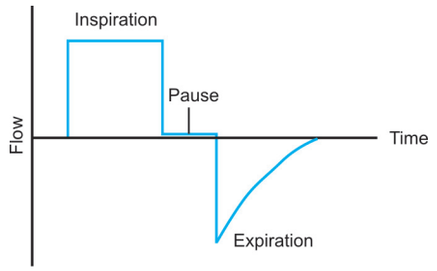


Fig. 21.9: Flow time waveform (square pattern) with end inspiratory pause

there is no pressure gauge. In such circumstances an idea of airway pressure, produced by preset volume on the background of certain compliance and resistance of lungs should work in mind (Fig. 21.9).

In a ventilator, the distinction between the pressure generated and volume or flow generated is important. A cheap and simple ventilator use a weighted concertina bag to generate a constant volume during inspiration. Even today these ventilators remain adequate for the majority of patients who require artificial ventilation during anaesthesia. The more sophisticated modern ventilators are fitted with devices which measure the instantaneous flow of gas during inspiration. This information can be incorporated into the feed back loop of ventilator to ensure the delivery of some predetermined volume and flow pattern. As a result, there is now greater emphasis on the flow pattern, produced by a ventilator during inspiration. In theory, ventilator can produce any flow pattern or waveform. But the four main waveforms are: sine wave, ramp or accelerating flow, top hat or constant flow, reverse ramp or decelerating flow. No matter, what flow pattern is chosen, but the inspiratory flow in any pattern can be modified further by adding an end inspiratory pause (EIP). Towards the end of inspiration, the flow of gas ceases, but the lungs are held inflated for a variable period which is called the 'pause time'.

Changing over from inspiration to expiration

Changing over form inspiration to expiration may be: Time cycled, volume-cycled,

pressure-cycled, flow-cycled or combination of them.

In time-cycled ventilation, expiration occurs after a predetermined duration of inspiraton. It is most popular. The time cycle may be of electronic, mechanical or pneumatic controlled. If a ventilator is time cycled, the change from inspiration to expiration will occur after a fixed time interval, no matter what airway pressure has been reached or tidal volume has been delivered. But in volume controlled and time-cycled ventilator, minute volume is preset by tidal volume and respiratory rate. So, inspiratory time (time cycled) is fixed by I:E ratio, leaving the airway pressure is only variable. Sometimes confusion arises by seeing the excursion of the inflating bellows, which create the optical illusion of being volume cycled, though infact they are time cycled and volume controlled. To ensure delivery of a preset volume in a preset time, the ventilator must have sufficient power to overcome the circumstances where there is increase in airway resistance or decrease in lung compliance.

In volume-cycled ventilators, there is some confusions as to what volume cycling really means. Ideally, a volume cycled ventilator would change over to expiration when the desired tidal volume had been delivered to the patient's lung, whatever may be the time needed. Unfortunately, lung expansion is not easy to measure and volume-cycled ventilators rely on measuring the volume of gas leaving the ventilator. So, if there are leaks in the apparatus or if the connecting tubes are distensible, then the volume leaving the ventilator may be very different form the volume which reaches the lungs. It has been suggested that the meaning of true volume cycling should apply to those ventilators which measure the gas volume leaving the ventilator and compare it with the volume which the patient exhales. This would be better regarded as a form of volume cycle during ventilation. But, unfortunately very few ventilators have these facilities.

Others forms of cycling, such as flow cycling, pressure cycling and combination cycling are also possible. But, neither of these are commonly used. In flow cycling, the end of inspiration will depend on the inspiratory flow. The moment when the inspiratory flow reaches the level of a predetermined flow, then the inspiration is terminated and the expiratory phase begins. Flow cycling is generally used for pressure support ventilation. In pressure cycling, when the airway pressure reaches a preset peak inspiratory pressure (PIP), set before hand by the operator, then the ventilator will end the inspiratory phase. Other parameters such as inspiration time, tidal volume and flow are variable. The time taken to reach the peak pressure level will depend on the airway resistance and lung compliance. In such circumstances before adequate inspiratory volume expiration will start. It is important to note that pressure cycling must be differentiated form pressure control ventilation. If an adjustable pressure safety value is set to low value, the change over from the inspiration to expiration may become pressure cycled in some ventilators that would otherwise be time cycled or volume cycled.

The present day ventilators offer the facility to use a combination of the above four cycling mechanisms. One cycling mechanisms is used as the basic mechanism and the second one is used as a secondary back-up. PSV is an example of combination cycle. In PSV, flow cycling is the primary, whereas time and pressure cycling forms the secondary back-up.

Expiration

The majority of ventilators allow passive expiration to atmosphere and the pressure created in the upper airway at the end of expiration is atmospheric. But, this atmospheric pressure at the end of expiration can be modified by applying: (i) Negative end expiratory pressure (NEEP), (ii) Espiratory retard (ER), or (iii) Positive end expiratory pressure (PEEP).

During the early development of ventilators, the use of negative pressure (subatmospheric) at the end of expiration was advocated to expediate the expiration. But this NEEP is not used now, though many ventilators still provide this facility. The main disadvantage of NEEP is that it causes early closing of the bronchiole of smaller diameter and subsequently air trapping in alveoli. So, in the second phase of evolution of ventilator, to prevent this peripheral airway collapse in chronic lung disease with obstructive airway, a variable resistance is placed in the expiratory limb of ventilator which reduce the expiratory flow rate. This is called expiratory retard. It tries to maintain a pressure above the atmospheric level in alveoli and peripheral airways and so prevents their early closure. Thus, the idea of positive pressure during expiration had developed.

Positive end expiratory pressure (PEEP) is the positive pressure above the atmospheric level (atmospheric level is regarded as baseline or '0' cm of H_2O) which is presented artificially in the expiratory phase of respiratory cycle. This above atmospheric pressure level (positive pressure) is preset by operator and is generated by the ventilator. This set positive pressure during expiration prevents the early closure of alveoli and peripheral airways. Thus, they try to maintain a patent airway with inflated alveoli and gaseous exchange. The ideal level of this PEEP does offer no resistance to expiratory flow. The PEEP can be used as a stand-alone mode or in combination with other modes. The physiological level of PEEP is 0 to 5 cm of H_2O. PEEP $\geq$ 10 cm of H_2O can be used in the treatment of ARDS. PEEP improves ventilation and thus oxygenation. But, the disadvantage is it reduces the cardiac output.

The mechanism of action and advantages of PEEP

i. It helps to prevent the collapse of smaller airways and alveoli and also try to inflate the already collapsed alveoli.

Thus, it helps in the better participation of gas exchange. It reduces the dead space to tidal volume ratio.

ii. It prevents atelectasis as positive pressure is maintained at the end of expiration and increases the expiratory time.

iii. It gradually lowers the alveolar distending pressure due to more and more alveolar recruitment.

iv. It helps to improve the functional residual capacity.

v. It reduces the left to right shunt by increasing the pulmonary arterial pressure and PVR.

vi. It improves the V/Q ratio.

The disadvantages of PEEP

i. Increased levels of PEEP can cause barotrauma.

ii. If higher PEEP level is maintained, then it causes increased intrathoracic pressure. This high intrathoracic pressure, in turn, impedes the venous return and reduces cardiac output. So, PEEP should be maintained at a level balancing between the need for better oxygenation and the reduction of cardiac output.

iii. It decreases renal perfusion (from increased renal venous pressure).

iv. Since higher level of PEEP reduces the venous return, so it causes the increased intracranial pressure.

v. It increases hepatic congestion (from increased hepatic venous pressure).

vi. It worsens the right to left intracardiac shunts (Fig. 21.10).

Sometimes, in few circumstances positive airway pressure is developed automatically at the end of expiration. This is called auto-PEEP. Auto-PEEP is also known as the intrinsic PEEP. It occurs due to air trapping in the alveoli, caused by inadequate expiratory time due to high respiratory rate or severe airway obstruction with high expiratory airway resistance. The auto-PEEP means the presence of PEEP that is automatically created at the end of expiration due to any obstruction (spasm) in conducting part of airway or due to inadequate expiration for high respiratory rate. The difference between auto-PEEP and extrinsic PEEP is that in auto-PEEP there is peripheral airway closure first (due to airway spasm) resulting air trapping in alveoli and positive end expiratory pressure in alveoli. These trapped air does not help in gas exchange. But in extrinsic PEEP, which is created by machine artificially, airway pressure is maintained above the atmospheric level at the end of expiration and thus prevents the closure of peripheral airway and alveoli (with positive pressure in alveoli) which helps in gas exchange.

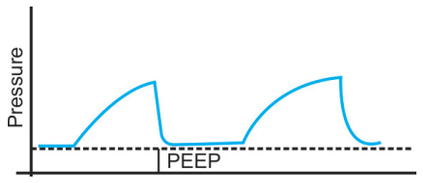


Fig. 21.10: Pressure - time curve shows PEEP in mechanical ventilation

Auto-PEEP is not reflected or detected in the ventilator manometer which will continue to show either zero (if extrinsic PEEP is not applied) or set PEEP level (if extrinsic PEEP is applied and in such case if auto-PEEP is again developed). To monitor the level of auto-PEEP, the expiratory port of ventilator should be occluded before the start of inspiration in next breath. Auto-PEEP can increase the work of breathing, since the patient has to overcome the auto-PEEP level to trigger the ventilator. It also more increases the intra thoracic pressures, leading to more reduction of venous return and cardiac output. Auto-PEEP can be eliminated or kept under control by increasing the expiratory time or by reducing the inspiratory time or by reducing the airway obstruction by bronchodilator.

In extrinsic PEEP, when used correctly, the peak airway pressure may significantly be less than the predicted sum of peak end inspiratory pressure measured prior to application of PEEP and positive airway pressure applied. If positive end expiratory airway pressure (PEEP) is applied in a situation where additional alveolar recruitment cannot or does not occur, then it can have detrimental effects on both haemodynamics and lung mechanics. A decrease in lung compliance still with the addition of PEEP indicates that additional gas exchanging units or alveoli are not being recruited and that the PEEP is unlikely to be of clinical benefit. The useful effect of PEEP is exhausted at about 15 cm of H_2O. At pressure exceeding 15 cm of H_2O, the alveolar diameter does not increase more with increasing PEEP level. The alveolar tissue cannot be stressed further by applying more and more high pressure, so that there is a danger of overdistension and alveolar rupture (barotrauma). This effect begins at the level of PEEP which is about 15 cm of H_2O. When addition of PEEP results in improvement in lung compliance and oxygenation, but a decrease in cardiac output, then it may be that the intravascular volume depletion is present. The PEEP level should be selected such that sufficient oxygenation is provided with FiO_2 not exceeding 0·6 (or 60%) and is most commonly employed when an $FiO_2 \geq 0{\cdot}5$ (50%) is needed for more than few hours to avoid hypoxia. During its application as PEEP is increased in small steps, titrated against the effect, similarly it should also be decreased slowly. Abrupt termination of PEEP therapy can result in pleural effusion, in addition to hypoxia. The extubation of patient is usually done at the PEEP level of 3 to 5 cm of H_2O, because 'physiological PEEP' is held at this level by the closure of the glottis.

Changing over from expiration to inspiration

Changing over of ventilation from expiration to inspiration needs some trigger factors which determine the start of inspiration after a period of expiration. This changing over is called trigger and is either determined by ventilator (ventilator triggered and can be preset) or by patient (patient

triggered). In a ventilator triggered breath, inspiration starts depending on the timing (time triggered), set on the ventilator by the clinician. Ventilator triggers inspiration after a preset duration of expiration or after a preset duration of the entire respiration (inspiration + expiration). This should not be confused with the time-cycled change over from inspiration to expiration (I → E = cycling, E → I = triggering). If the entire respiratory cycle is used for triggering, then any increase in the inspiratory time will lead to corresponding decrease in the expiratory time. This change may have a profound effect on inspiratory/expiratory ratio and results in auto-PEEP. In a ventilator triggered the time is preset (time triggered) and the patient is completely paralysed. There is no patient's effort to inspiration and this type of time trigger is used in CMV mode of ventilation. On the other hand, in patient triggered, the breath is initiated by the patient's effort and then immediately ventilator changes over from expiration to inspiration. Assisted ventilation provided by ventilator is not possible without patient triggering.

Patient triggered ventilation has the following advantages:

i. It reduces the duration of ventilatory support
ii. It reduces the weaning time
iii. It improves the level of blood gases
iv. It lowers the oxygen dependency.

Patient trigger mechanism are of various types, such as: Pressure triggering, flow triggering, chest wall impedence triggering and abdominal wall motion triggering. The last two patient triggering mechanisms are not commonly used. The two most common types of patient triggering mechanisms are: pressure triggering and flow triggering. Whereas in ventilator trigger, time triggering is the most commonly used mechanism.

Pressure triggering

The pressure triggering is used when the patient tries to take breath spontaneously. When the patient tries to take breath, then there is drop in the airway pressure. This drop in airway pressure is sensed by the ventilator and results in start of inspiration which is delivered by the ventilator. The trigger level on the ventilator is set as pressure unit of cm of H_2O. The ventilator continuously monitors and senses the airway pressure. For the ventilator to be triggered and deliver a breath, it is essential that the drop in airway pressure by the patient's own respiratory effort must exceed the set trigger or sensitivity level. If the pressure drop in the patient's airway which is transmitted to the ventilator's circuit is not sufficient enough, then the ventilator cannot sense it and will not be triggered to deliver a breath.

In the commercially available ventilators, the sites for pressure sensing are: (i) inside the ventilator, (ii) At the patient's airway (proximal triggering) or (iii) At the carina (distal triggering). The proximal and distal triggerings are more sensitive as compared to the drop of pressure being sensed inside the ventilator. The commonly used values for pressure triggering are in the range of −0·5 cm of H_2O to −3 cm of H_2O. It must be noted that the negative value indicates the drop in pressure below the zero or atmospheric level, when PEEP is not set. But, when PEEP is applied then this negative triggering pressure should be calculated from the set level of PEEP pressure. For example, if PEEP is set at +10 cm of H_2O and pressure trigger sensitivity is set at −3 cm of H_2O, then patient must generate a drop of pressure upto +7 cm of H_2O (10 − 3 = 7) from +10cm of H_2O to trigger the ventilation by ventilator.

The triggering sensitivity is referred to the negative pressure which is generated by the patient to stimulate the ventilator to deliver a breath. Trigger sensitivity is reduced means at more negative pressure, ventilator will be stimulated and this will increase the work of breathing of patient. On the other hand, trigger sensitivity is increased means at slight negative pressure, ventilator will be stimulated. When the trigger sensitivity is increased then as the ventilator delivers the breath at slight initiation of patient's effort to take breath, so the patient's capability of taking its own full breath will be diminished and wearing from ventilator will be delayed. If the trigger is set at maximum sensitivity level, then the ventilator will often perform at autocycle. So, the trigger should be set at such maximum sensitivity level that does not cause autocycling and usually this pressure is −0.5 to −3 cm of H_2O.

Flow triggering

In flow triggering, a continuous flow is present in the ventilator circuit during the expiratory phase. Due to continuous flow in the ventilator circuit during expiration, there is also a continuous flow at the exhalation valve. But when the patient makes a spontaneous effort for inspiration, then the flow is suddenly interrupted at the exhalation valve of the ventilator. Hence, the machine senses this interruption of flow and initiates a delivery of breath. For flow triggering to be functional, the anaesthetist needs to set a flow sensitivity setting in litres per minute. When the patient breaths spontaneously, the generated flow gradient must be higher than the flow trigger level, set by the clinician for the ventilator to sense and to initiate a breath delivery. The commonly used values of flow triggering are in the range of 0.6 to 4 litres per minute. In some ventilators, the trigger flow may need to be set, whereas in some ventilators there is a fixed preset flow to trigger the machine.

However, it is very important to note that triggering is not just a method, but rather the application of a method that affects the patient's work of breathing and ventilator synchrony. The trigger sensitivity setting must be optimized after proper assessing the patient's own ability to trigger. In the initial stages of the ventilatory support, the trigger must be set at more sensitive level. It means at less negative

value as for example −1 cm of H_2O for pressure triggering or 0.5 litre per minute for flow triggering. As the patient's condition improves, the trigger sensitivity should be decreased, because the patient will gradually try to take breath by himself.

Inspiratory/Expiratory Time Ratio (I : E)

The I : E ratio have an important effect on the removal of expired gases and on the mean intrathoracic pressure which again have an implication on oxygenation and cardiac output. Usually, an adequate time is required for the removal of expired gases without any air trapping. So, the expiratory time is greater than inspiratory time. Normally, the I:E ratio is about 1:2, i.e. the duration of expiration is twice than that of inspiration. It limits gas trapping and optimises the mean intrathoracic pressure. In obstructive lung disease, this I:E ratio is less than 1:2, i.e. the expiration becomes more prolonged than normal. In such circumstance there also occurs gas trapping due to spasm of peripheral airways and reduction of cardiac output. For volume cycled ventilators, I : E ratio can be achieved by adjusting V_T , respiratory rate and inspiratory flow rate. Whereas, in time cycled ventilators, the I : E ratio is adjusted by controlling the respiratory rate and inspiratory time.

While setting respiratory rate on ventilator for a spontaneously breathing patient the following points should be kept in mind; These are: (i) The patient's actual rate demand, (ii) The patient's anticipated ventilatory requirement, and (iii) The impact of rate setting on breathing time. The ventilators are not capable of varying inspiratory time and flow which is set by the operator. For example, with machine back up at a rate setting of 12 breaths / minute, the total cycle time (T_{Tot}) for each breath is 5 sec. If the I:E ratio is set at 1:2 or if V_T and flow have been set at 0·5 litre and 0·34 litre/sec, respectively, then T_I (inspiratory time) is fixed at 1·5 sec and expiratory time (T_E) will be 3·5 sec. If the patient actually triggers at 24 breaths/min, then T_{Tot} declines to 2.5 sec. T_I remains fixed at 1·5 sec, because it is determined by the preset machine (back up) rate, the I : E ratio or the inspiratory flow settings. The T_E must now decrease from 3·5 sec to 1 sec and the actual I:E ratio will increase from 1:2 to near about 2:1. At a rate of 40 breaths / min (T_{Tot} = 1.5 sec), T_E becomes '0' and then 'fighting with the ventilator' must result. For these reasons, the machine back up rate should always be set close to the patient's actual respiratory rate. If the actual respiratory rate initiated by patient is very high that effective ventilation cannot be achieved, then the patient needs additional sedation and possibly neuromuscular blockade.

Tidal volume (V_T)

It is generally accepted that V_T should be in the range of 10 to 15 ml/kg of body weight for most of the patients. Because small tidal volume (6 to 8 ml/kg) promotes the development of microatelectasis. While very large tidal volume can cause barotrauma and cardiovascular decompensation.

However, in some conditions such as obstructive lung disease, ARDS, etc; it is probably safer to choose a relatively low tidal volume (5 to 7 ml/kg) to avoid complications. While setting V_T, it is important to consider the role of compliance of the connecting tube of the ventilator circuit. This is approximately 3 to 4 ml/cm of H_2O during peak pressure. So, during inflation certain amount of tidal volume will not be delivered to the patient. But as the airway pressure falls and the tubes return to its original size, then this volume will be measured as exhaled volume, if a spirometer is attached on the expiratory limb of ventilator circuit.

Inspiratory flow

The inspiratory flow rate is the measurement of velocity at which the breathing gas is supplied to patient. It is an important determinant of patient's work of breathing. If the ventilator's inspiratory flow rate is chosen less than the patient's flow demand, then the patient will increase his inspiratory efforts in an attempt to improve his gas delivery. Thus, it will increase the patient's work of breathing. So, to minimize this work of breathing, the ventilator's inspiratory flow rate should be fixed above the patient's peak flow demand. On the other hand, if the inspiratory flow rate are very high during volume controlled ventilation, then it can lead to increased inspiratory peak pressure. Thus, over inflation of healthy lung leads to an impaired V/Q ratio and increased intrapulmonary shunt. So, a balance has to be reached. Constant flows of 60 to 70 litres/min are well tolerated in ventilator dependent patients and it does not manifest significant levels of auto-PEEP. Flow rates may require modification in certain circumstances such as COPD or asthma. Here higher flow rates (70-100 litres/min) are often used to shorten the inspiratory time and to lengthen the expiratory time. Thus, potentially it reduces the degree of auto-PEEP and hyperinflation.

Pressure control and pressure support ventilation can deliver the high initial flow rates. This may be advantageous for patients with high initial flow demands or those with severe lung disease and high minute ventilations.

FiO_2

FiO_2 should be selected as high as necessary to save the patient's life when emergency condition arised and as low as possible to prevent O_2 toxicity when patient's condition is stable. The increased inspired O_2 concentration to maintain P_aO_2 should always be understood as symptomatic treatment. In case of respiratory failure, it is common practice to initiate ventilatory support with an FiO_2 of 1 (i.e. 100% O_2). In such circumstance It is advised to ignore the potential for oxygen toxicity during the first few hours of ventilatory management

by 100% O_2. Then, it should be decreased gradually. One instance, where clinician must minimise FiO_2 at all costs, is a patient who has received bleomycin or amiodarone. Because, these drugs make the lungs extremely susceptible to injury (oxygen toxicity), mediated by O_2 radicals.

DIFFERENT MODES OF MECHANICAL VENTILATION

The mode of mechanical ventilation is defined as the configuration of flow, pressure and volume of gas which is delivered to the patient in a specific characteristic manner, coupled with cycling and triggering mechanisms. Thus, the ventilation mode also specifies the manner in which the ventilator breaths are controlled, cycled and triggered. The controlled factors are operator specified values, such as : airway pressure, volume and flow that cannot be exceeded during inspiration and expiration. If the specific values of any of the parameter are exceeded, then inspiratory flow is immeidately stopped and the ventilator circuit is vented to atmospheric pressure or to the specified PEEP value. Cycle refers to the factors that determine the end of inspiration and trigger defines what the ventilator senses to initate an inspiration.

The mode of ventilations are:

i. Controlled Mechanical Ventilation (CMV) − It may be of two types VCV or PCV.
ii. Assisted Mechanical Ventilation (AMV).
iii. Assist Control Mechanical Ventialtion (ACMV).
iv. Intermittent Mandatory Ventilation (IMV)
v. Synchronised Intermittent Mechanical Ventilation (SIMV).
vi. Positive End Expiratory Pressure (PEEP).
vii. Continuous Positive Airway Pressure (CPAP).
viii. Bilevel Positive Airway Pressure (Bi-PAP).
ix. Pressure Suport Ventilation.
x. Inverse Ratio Ventilation.
xi. Airway Pressure Release Ventilation (APRV)
xii. Spontaneous Ventilation.
xiii. Apnoea Back-up Ventilation.
xiv. Dual Mode Ventilation.

Controlled Mechanical Ventilation (CMV) – VCV or PCV

Here, all the breaths delivered to patient are totally controlled by the ventilator and ventilatory pattern is totally independent of patient's breathing effort. In CMV mode, the ventilator is totally nonresponsive to the patient's spontaneous respiratory efforts and requirements, still if the patient starts to take breath. So, CMV is usually used in totally paralyzed patient. If this mode is used in a partially paralysed patient or the patient starts to take breath spontaneously, then there will be a fight between ventilator and patient (i.e. breath stacking or starvation – anyone can occur). So, this mode is not useful for spontaneously (even slightly). In this controlled mode of ventilation, the breath is delivered to the patient by ventilator at a preset fixed respiratory rate and pattern (volume or pressure), determined by the ventilator controls. Here, every breath is time cycled and time triggered. For volume controlled breaths or ventilation (VCV), the set volume is delivered to the patient in the set inspiratory time, irrespective of the developed airway pressure which are determined by the lung mechanics. The fixed minute volume is totally controlled by the ventilator. Since, very high pressure (if it develops due to altered lung mechanics as pressure is dependent variable) can cause barotrauma. So, to ensure patient's safety the volume controlled ventilators should be equipped with a pressure release valve and high pressure alarm to alert the clinician. Whereas in pressure controlled breaths or ventilation (PCV) the set pressure plateau is maintained for the set inspiratory time for each breath. Like volume controlled ventilation, PCV is also time cycled and time triggered. During inspiratory phase, a given pressure is immediately imposed at the airway opening and this set pressure remains at this user specified level throughout the inspiration. Since, the inspiratory airway pressure is specified by the operator, so the tidal volume and inspiratory flow rate are dependent variables and are not user specified. PCV is the preferred mode of ventilation for neonates and infants and for patients with increased risk of barotrauma and for postoperative thoracic surgical patients in whom the shear forces across a fresh suture line should be limited. When using PCV, minute ventilation and tidal volume must be monitored by seeing the amount of gas delivered to ensure adequate ventilation (whereas in VCV airway pressure should be monitored). Inadequate or over adequate minute ventilation can be altered through changes in respiratory rate or through changes of the set pressure by pressure control knob (Fig. 21.11).

The PCV mode is used as a control mode with a normal I:E ratio or with increase I:E ratio. It could also be used in combination with PSV mode of ventilation. At present, the primary indication for PCV is ARDS patient to whom the conventional IPPV with PEEP is not effective, i.e. specifically those patients: Who are on an FiO_2 of 1, have a positive inspiratory pressure (PIP) of > 50 cm of H_2O, higher PEEP levels of > 15 cm of H_2O, higher assist control rates > 16 respiratory rate, have low PaO_2 and low lung compliance. Now a special form of CMV, i.e. the pressure regulated

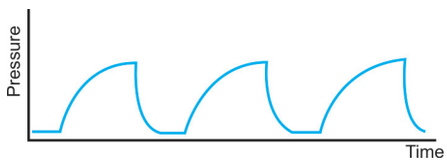


Fig. 21.11: Controlled mechanical ventilation (CMV) and time cycled

volume control mode (PRVC) of ventilation is available on many sophisticated ventilators. This mode has advantageous features of both the VCV and PCV mode of ventilation. It incorporates tidal volume as a servo parameter to ensure adequate volume delivery in PCV mode. Usually in our anaesthesia practice, we administer constant flow, pressure limited or regulated, volume controlled, time cycled ventilation that is often regulated up to 35 cm of H_2O to prevent barotrauma.

Some common indications for the use of CMV mode of ventilations are:

i. Neuromuscular paralysis – drug induced as in general anaesthesia (commonly the volume controlled ventilation), or neuromuscular pathology such as myasthenia gravis, paralytic poliomyelitis, etc.
ii. Prolonged apnoea.
iii. Severe central nervous system depression – such as high dose narcotic, brain trauma, spinal cord injury, etc.
iv. Postoperative patients with complete paralysis.
v. Patients who have fatigue of respiratory muscles and need for maximal rest of it.

Some complications or disadvantages associated with CMV mode are :

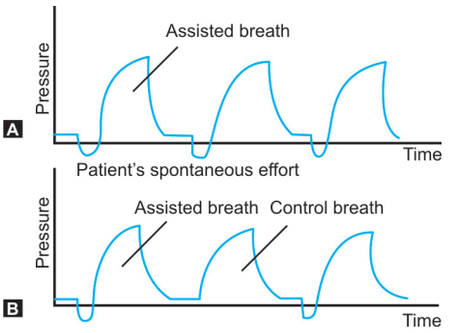
i. During incomplete paralysis as the patient's trigger efforts are not sensed and supported by the ventilator, so it can cause patient's discomfort and agitation during recovery.
ii. This CMV mode is unresponsive to the changing minute ventilation and airway pressure requirements of the patient.
iii. Total controlled mechanical ventilation for a longer period can inhibit the contraction of respiratory muscles which are then prone to atrophy. Because this mode is generally used in patients, who are fully paralyzed with muscle relaxants or in patients with poor or no spontaneous attempts to respiration. It is also used when the patient's respiratory drive is suppressed with heavy doses of narcotics and sedatives due to any reasons.

Assisted Mechanical Ventilation (AMV)

Here, every breath of patient is assisted by mechanical ventilator, but breath rate is completely controlled by the patient. Ventilator only supplements the patient initiated or triggered breath during changing over from expiration to inspiration (E → I). But initiation of expiration (I → E) is time cycled. The initiation of breath by ventilator (inspiration) occurs as a consequence of a sensing device which detects patient's initiated breath as a fall in airway pressure below the end expiratory pressure (pressure triggered). This amount of fall in patient's airway pressure required to trigger a breath by ventilator is reffered to as trigger sensitivity, which can be adjusted. So, for the proper functioning of this mode, it is essential to set optimum trigger level sensitivity, so that all the patient's efforts to inspiration are recognised by the ventilator. Thus, every recognised patient's effort is assisted by the ventilator, either by a volume controlled breath or by a pressure controlled breath. As this ventilatory mode is time cycled, so the spontaneous respiratory rate of the patient must exceeds the control back-up repiratory rate of ventilator or the ventilator's set respiratory rate should be kept below the patient's spontaneous effort rate. In this mode, ventilator does not respond to patient's apnoea, as there is no system for control or mandatory breath (Figs 21.12A and B).

Assist Control Mechanical Ventilation (ACMV)

Assist control mechanical ventilation is a combination mode where 'assist' refers to the ventilator's supplementation of patient initiated breaths and 'control' refers to the mandatory preset (back-up) ventilation when there is no patient's initiation of breath. An inspiratory cycle is initiated



Figs 21.12A and B: A. Assisted mechanical ventilation (AMV) B. Assist control mechanical ventilation (ACMV)

either by the patient's inspiratory effort or by the ventilator, if patient's effort is not detected within a specified time window by a timer signal. If the breath which is delivered by ventilator is due to the patient's spontaneous efforts, then it is called the assisted ventilation and if the breath delivery is due to the set respiratory rate in the ventilator in the presence of apnoea, then it is called the controlled ventilation. As every breath (assisted or controlled) is a mechanical breath, hence volume or pressure controlled delivery will be as per the ventilator's settings. It is important to set the proper trigger sensitivity and back up respiratory rate, matching with the patient for proper working of this mode. An insensitive trigger setting will inadvertently change the ACMV mode to CMV mode. If the spontaneous respiratory effort rate of the patient exceeds the control back-up rate, then no control breaths are delivered and the ventilator will function completely in assisted mode. However, if the patient's spontaneous effort is less than the control back up rate, then the volume or pressure control breaths will be provided at appropriate intervals. As compared to control mechanical ventilation mode (CMV), in patient with slight spontaneous efforts, this ACMV mode allows for better synchronomy between the patient and the machine. So, it can be applied to both awake, sedated or fully paralyzed unconcious patients. Since, it

has been shown that CMV mode used for more or less than 48 hours results in reduction in diaphragmatic muscle mass and a decrease in the diaphragmatic twitch tension, so it has been suggested that minimal amount of work is required to prevent the reductions in diaphragmatic strength and endurance. During ACMV mode with optimum ventilator settings, the load faced by the inspiratory muscles should not be enough to cause fatigue of the inspiratory muscles or respiratory distress, but should be sufficient enough to prevent muscle atrophy.

With assisted ventilation on optimal ventilator settings, the pressure-time product of inspiratory muscles which is the measure of work of breathing will be average 50% of that obtained during spontaneous breathing. While when SIMV mode is used as a primary mode of ventilation and SIMV rate is set such that 50% of the minute ventilations is delivered by the mechanical ventilator, then the pressure-time product per minute will be average 80% of the values obtained during spontaneous breathing. This workload may not be sustainable in many patient. Therefore, it is desirable to increase the level of ventilatory support, until the patient appears comfortable.

ACMV is the recommended mode for primary initiation of mechanical ventilation. Because, it ensures a back-up minute ventilation in the absence of an intact respiratory drive and also allows for synchronization of the ventilator cycle with the patient's inspiratory effort. However, it never allows the patient to take a full breath by himself (difference from SIMV). Problems can arise when ACMV is used in patients with tachypnoea due to nonrespiratory or nonmetabolic factors such as anxiety, pain, or airway irritation, etc. In such situation, respiratory alkalemia due to high respiratory rate (which is due to full ventilatory assistance for each patient initiated breath) and excessive washout of CO_2 may produce trigger myoclonous or seizures. Also COPD patients who are tachypnoic may develop auto-PEEP on ACMV mode of ventilation, with potential for barotrauma. Auto-PEEP also limits venous return, decreases cardiac output and increases airway pressure. ACMV mode is not effective for weaning the patients from mechanical ventilation, because it provides full ventilator assistance for each patient initiated breath.

Indications for use of ACMV mode are:

i. Patients who are earlier put on CMV mode for complete muscular paralysis or apnoea but now is gradually initiating spontaneous respiratory efforts.
ii. Patients who have own stable respiratory drive with any capability of triggering the ventilator.
iii. The ventilator should be set to achieve minimum 80% of the minute ventilation. This is a prove to be a good setting of the ACMV mode.
iv. Postoperative patients coming out of the effects of complete muscullar paralysis and anaesthesia.

Advantages of ACMV mode are:

i. Atrophy of respiratory muscles seen in CMV and AMV mode can be prevented in ACMV mode. This is due to the spontaneous efforts, being assisted and supported by the ventilator.
ii. It avoids patient agitation. This is because the patient can now get assisted ventilation for his or her spontaneous efforts from the ventilator.
iii. As the patient is allowed to control his or her respiratory rate, so the minute volume, and the P_aCO_2 of patient can be normalized.

Complications of ACMV mode are:

i. If the patient's respiratory rate increases in ACMV mode, then the auto-PEEP will develop. This will cause the mean intrathoracic pressure to increase, affecting the venous return and cardiac output.
ii. Increased respiratory rate will increase the minute volume and subsequently the mean alveolar presssure causing barotrauma.
iii. If the patient respiratory rate is high and is being assisted at higher rates, then it can result into hyperventilation causing hypocapnia and repiratory alkalosis.

Intermittent Mandatory Ventilation (IMV)

In IMV the ventilator delivers intermittent mandatory breaths in a predetermined pattern (volume or pressure controlled ventilation, time cycled with set respiratory rate) and allow the patient to breath spontaneously in between the mandatory breath. This mode is a combination of control mechanical ventilation mode (CMV) with a facility to support the patient's spontaneous efforts fully. The point where IMV differs from CMV is that in between the ventilator's breath, the breathing circuit is open and patient can breath fresh gas at his own rate and tidal volume. There is no option of synchronisation between the ventilator's breath and the patient's breath. All spontaneous breaths are fully patient's controlled or all controlled breaths are ventilator's control. So, ACMV = CMV + AMV (not a single full spontaneous breathing is allowed). But IMV = CMV + full patient's spontaneous breathing (not a single spontaneous breathing is assisted). In ACMV, all the ventilation is machine controlled, but some are triggered and some are not triggered. But, in IMV there is no trigger and all or none principle is followed (i.e. if patient breaths he will take the full breathe, otherwise machine will force him to take breathe).

'Breath stacking' is the major limitation of this IMV mode. This is because as the ventilator is allowed to deliver some mandatory breath, the rate of which is set by operator and the patient is also permitted to breath spontaneously, so at times it is seen that the patient is fighting with the ventilator. This is due to sometimes patient's

exhalation is superimposed by the ventilator's inspiration. Hence, the patient faces a high expiratory resistance which is called the 'breath stacking'. So, due to the problems of breath stacking, the IMV mode is now replaced with a mode which deliver the mandatory breath when necessary and synchronises the ventilator's breaths with patient's efforts, i.e. SIMV. IMV can be used as a full ventilatory support mode or as a weaning mode.

Advantages of IMV mode are:

i. Decreased requirement of sedation and muscle relaxation,
ii. Better ventilation to perfusion (V/Q) matching,
iii. Lower mean airway pressure,
iv. Avoidance of respiratory alkalosis,
v. Expediated weaning,
vi. Prevention of respiratory muscle atrophy or discoordination,
vii. Reduced likelihood of cardiac decompensation.

Disadvantages of IMV mode are:

i. Increased risk of CO_2 retention,
ii. Increased work of breathing and respiratory muscle fatigue,
iii. Stacking of breath.

Setting of this mode include: mandatory rate, mandatory tidal volume/minute volume, I:E ratio, trigger sensitivity, high and low pressure alarm, respiratory rate, tidal volume display.

Synchronised Intermittend Mandatory Ventilation (SIMV)

SIMV = CMV + AMV + patient's full spontaneous breathing or ACMV + patient's full spontaneous respiration. In SIMV mode the patient spontaneously breaths and intermittent ventilator's breaths are synchronised and if there is no spontaneous breath ventilator takes over the whole reponsibility producing mandatory ventilation (CMV). Synchronisation means ventilator waits for patient's spontaneous inspiration. If the inspiration is not sufficient enough (measured by triggered sensitivity), then machine assist the ventilation (AMV). In between CMV and AMV, patient takes full spontaneous respiration if he can. In SIMV, it is important to set an optimal trigger sensititivity level, so that the patient can have optimum amount of spontaneous respiration and this optimum amount of ventilation is assisted and the next optimum amount is fully controlled. So, to achieve this the ventilator must creates a timing window which divides the expiratory time into non-synchronisation interval and synchronization interval. Synchronisation interval is responsible for mandatory breath and nonsynchronisation interval is for assisted spontaneous breath. If the patient's spontaneous efforts occur in the synchronization interval, then the next schedule mandatory breath will be shifted accordingly and will be delivered as assisted ventilation to the patient in response to the patient trigger. In the absence of patient's effort during synchronization interval the mandatory breath is delivered as per the set breath rate interval. On the otherhand, any patient's effort in the nonsynchronization interval will result in a ventilator assisted breath which is completely patient controlled (Fig. 21.13).

The mandatory breaths, which are delivered to the patient will not exceed the set SIMV rate. Usually the mandatory rate in SIMV is set such that even if the patient has no spontaneous attempts, still adequate minute ventilation is delivered to the patient. Usually, a minimum rate of 8 to 10 breaths per minute with a tidal volume of 8 to 10 ml/kg is set for mandatory breaths. When the spontaneous attempts are rigorous and adequate, the patient is weaned off this mode.

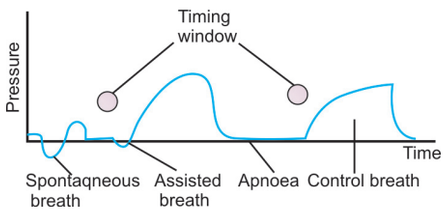


Fig. 21.13: Synchronised intermittent mandatory ventilation (SIMV), volume controlled

The major difference between SIMV and ACMV is that in former the patient is allowed fully to breathe spontaneously i.e without ventilator assistance, in between the delivered breaths by ventilator (assist or control). However, mandatory breaths are delivered in synchrony with the patient's inspiratory efforts at a frequency, determined by the operator. If the patient fails to initiate a breath, the ventilator delivers a fixed tidal volume breath and resets the internal timer for the next cycle of respiration. SIMV also differs from ACMV in that only the preset number of breaths is ventilator assisted.

SIMV allows patients with an intact respiratory drive to exercise inspiratory muscles in between the assisted breaths. This characteristic makes the SIMV a very useful mode of ventilation for both supporting and weaning of an intubated patient. SIMV may be difficult to use in patients with tachpnoea, because they may attempt to exhale during the ventilator programmed inspiratory cycle. When this occurs, then the airway pressure may exceed the inspiratory pressure limit, or the ventilator's assisted breath will be aborted or minute volume may drop below that programmed by the operator. In such setting, if tachypnoea occurs in response to the respiratory or metabolic acidosis, then a change to ACMV will increase minute ventilation and help to normalize the pH, while the underlying pathology is further evaluated.

Advantages of SIMV mode:

All the advantages and disadvantages of SIMV are like IMV mode of ventilation.
Advantages are:

i. It reduces the work of breathing,
ii. It lowers the mean airway pressure,
iii. It expediates weaning,
iv. It prevents respiratory muscle from atrophy, because the patient can breathe spontaneously,

v. It reduces ventilation – perfusion mismatch,
vi. It aviods breath stacking.

Limitations of SIMV mode

Sometimes, the mandatory respiratory rates which are set in the ventilator does not provide adequate minute ventilation, if the patient develops apnoea. In such circumstances, respiratory rates delivering lower than the adequate minute ventilation should be closely monitored. Otherwise, the ventilator is set with an appropriate apnoea back-up ventilation mode if available on the ventilator.

Mandatory Minute Ventilation (MMV)

This is also a servo contolled (i.e. feedback controlled) ventilation mode similar to SIMV. But, it differs from SIMV in that instead of predetermined respiratory rate (as in SIMV respiratory rate is preset), a predetermined fixed minimum amount of minute volume that the ventilator is bound to deliver to patient is the criteria for the mode of this mechanical breath. So, this mode of ventilation also can be called as SIMMV. Like SIMV, the MMV mode is also useful for spontaneously breathing patients. During MMV, the ventilator continuously measures the actual patient's spontaneous minute volume that he or she inhales and compares it with the clinician set minimum minute volume. If the patient's spontaneous minute ventilation goes below the set mandatory minute ventilation, then the ventilator automatically takes over the responsibility and the difference between the two volumes is then delivered as mandatory breaths by the ventilator. If the patient's spontaneous minute ventilation is higher than the set mandatory minute volume, then no ventilator breaths will be delivered.

MMV may be a useful method of ventilation for patients with fluctuations in ventilatory drive or who are being weaned from the mechanical ventilation. During weaning as the patient can contribute gradually more control over the spontaneous portion of the tidal volume, so the mandatory minute volume can be decreased automatically gradually. A good strategy of MMV mode is to set the MMV value as little as below the desired minute ventilation of the patient. If the patient experiences the apnoea episode, the ventilator automatically takes over the responsibility and delivers additional mandatory breaths. In some ventilators, MMV function is replaced by 'apnoea back up' mode which works on the criteria of low minute volume alarm limit.

The advantages of MMV is that it is useful in preventing hypoventilation and simultaneously permits complete spontaneous breathing. The disadvantages of MMV is that under distress the patient may have a breathing pattern of rapid respiratory rates and shallow tidal volume. This rapid breathing pattern of the patient may be identified by the ventilator as the predetermined minimum minute ventilation is met. Thus, this rapid shallow respiration causes inadequate alveolar ventilation and muscle fatigue.

Pressure Support Ventilation (PSV)

The pressure support ventilation combines the advantages of pressure control ventilation with spontaneous breathing. As the breathing is spontaneously maintained in PSV, so the patient himself determines the respiratory rate, inspiratory time and tidal volume. Each inspiratory effort of the patient is assisted by the ventilator at a preset level of inspiratory pressure. So, PSV is a patient triggered and pressure or flow cycled ventilation. Because as the chosen pressure is constant, so the flow decreases as more and more the lungs are filled (decelerating flow). Thus, when flow comes to zero against a certain elevated pressure, inspiration ends and expiration starts. Flow cycling forms the primary criteria for termination of breath in PSV. The other safety back up criteria are time and pressure. During PSV the inspiratory phase is terminated when inspiratory air flow falls below a certain level. In most ventilators this flow rate cannot be adjusted by the operator. If PSV is used, patient receives ventilatory help, only when the ventilator detects an inspiratory effort (patient triggered) (Fig. 21.14A and B).

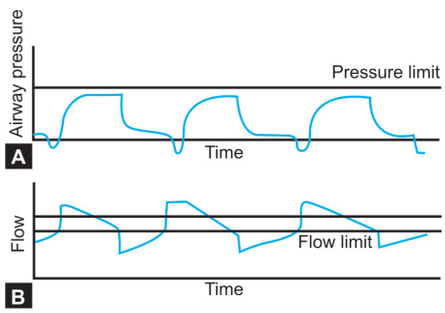
Thus patient initiates a pressure support when

i. There is fall in pressure of airway,
ii. The spontaneous inspiratory flow touches the value of certain limit (for example between 1to15 litre/min),
iii. The inhaled volume is less than 25 ml during spontaneous breathing.

PSV can be used as an independent mode or in combination with SIMV and CPAP modes. In combination with SIMV, it ensures volume cycled back up for patients whose respiratory drive is depressed, either spontaneously or as a result of various therapeutic manoeuvres.

The pressure support stops when

i The inspiratory flow goes back to zero or the patients actively exhales,
ii. The inspiratory flow goes below 25% of the maximum flow,
iii. Both the above criteria become inoperative or when the time of exhalation takes more than 4 seconds − a safety mechanism.



Figs 21.14A and B: Airway pressure and airway flow versus time during PSV. All the breaths are patient triggered and flow cycled. Inspiration is cycled off when the inspiratory flow drops below a predetermined threshold level which is internally set in the ventilation circuit

The advantages of PSV are:

i. Maximally reducing the work of breathing this mode enhances the patient's comfort on ventilator.
ii. Maximize patient's control on respiration.
iii. No haemodynamic consequences.
iv. With the change in work of breathing, pressure support can be adjusted (decreasing the level of pressure support during weaning and increasing the levels of pressure support when patient gradually deteriorates). Normally, to overcome the airway resistance (including the tubing system of ventilator, ET tube, etc.) a pressure suport of 5 to 10 cm of H_2O is required.
v. A preferred mode of weaning from mechanical ventilator. PSV is well tolerated by most of the patients who are being weaned. PSV parameters can be set in such a way that it can provide a full or a nearly full ventilatory support and can be withdrawn slowly over a period of days in a systemic fashion where gradually load is applied on the respiratory muscles.
vi. Provide an insight of the patient's repiratory status i.e. if patient is in the state of normal work of breathing (weaning) or not. For example, a patient with COPD, exhibiting good clinical status and normal gas exchange with normal pressure support (3 to 7 cm of H_2O) is a good candidate for tracheal extubation.

It is observed that addition of PSV mode to the spontaneous breathing pattern causes increase in tidal volume and decrease in respiratory rate. Increased tidal volume and decreased respiratory rate cause increased alveolar ventilation. Increased tidal volume (V_T) produces a decrease in the ratio between deadspace and tidal volume (V_D / V_T) and thus better gas exchange. Studies have demonstrated that addition of PEEP can increase the efficacy of PSV and much reduces the work of breathing in patients with COPD, presenting with intrinsic PEEP. So, combination of PSV with PEEP may be the optimum way to support the ventilation.

The limitations of PSV mode are :

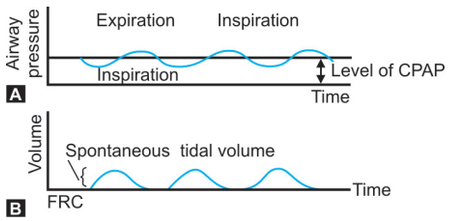
i. It is applied only to the patients who breath spontaneously.
ii. When high pressure support is needed then PSV mode is not good. Then, PCV is far better mode.
iii. As PSV is a flow-cycled ventilation, so if there is any circuit leak, then it causes continuous flow and continuous delivery of airway pressure, even during patient's spontaneous expiration. This can lead to severe haemodynamic compromise. Thus, autocycling caused by circuit leak allows inspiration to be triggered.
iv. With this mode, patient with unreliable inspiratory effort may receive inadequate ventilation.
v. High airway pressure, if there is high level of pressure support.

Continuous Positive Airway Pressure (CPAP)

Like PEEP, it is not a true mode of ventilation, because patient is already breathing spontaneously with full effort. The ventilator provides fresh gas flow to the breathing circuit during the whole cycle of respiration and produces in the circuit a constant operator specified pressure that can range from 0 to 25 cm of H_2O. Basically, CPAP is like PEEP (which is maintained only at the end of expiration), but it differs from later in that CPAP is applied continuously both during inspiration and expiration and only during spontaneous breathing. Unlike PEEP, CPAP cannot be applied during controlled ventilation, whereas PEEP can be applied both during controlled and spontaneous ventilation. CPAP can also be administered to the patient non invasively by using a mask attached to the patient's face with harness. It is also a popular weaning mode (Figs 21.15A and B).

Bi-Level (or Phasic) Positive Airway Pressure (BIPAP)

BIPAP is a unique ventilatory mode which covers the entire spectrum from complete mechanical ventilation to full spontaneous



Figs 21.15A and B: Airway presure and lung volume versus time profiles during CPAP. Breathing is spontaneous and no ventilator assist is provided. The spontaneous profile is superimposed on an elevated mean airway pressure that the user specifies

breathing. It is a variation of PCV, but differs from it that in BIPAP spontaneous breaths is possible. BIPAP ventilation indicates two levels of positive presure and thus it is named so. Among the two levels of positive pressure, one level is maintained during inspiration (inspiratory positive airway pressure – IPAP) and the other level is maintained during expiration (expiratory positive airway pressure – EPAP). IPAP is always greater than EPAP in BIPAP. But when IPAP is equal to EPAP it results in CPAP, otherwise EPAP is similar to PEEP. Patient can breathe spontaneously at both IPAP and EPAP. BIPAP is available on ventilators or as separate BIPAP machine. The various forms of BIPAP are classified according to the respective proportions of mechanical ventilation and spontaneous breathing present in it. These classification include:

i. There is no spontaneous breathing → CMV − BIPAP.
ii. There is spontaneous breathing at the upper pressure level →APRV − BIPAP.
iii. There is spontaneous breathing at the lower pressure level → IMV − BIPAP.
iv. Continuous spontaneous breathing, both equal pressure levels → CPAP.
v. There is spontaneous breathing at both the pressure level → Genuine BIPAP.

On a ventilator, BIPAP is possible by administering PCV (a type of CMV) in conjugation with PEEP or PSV in conjugation with CPAP. For the BIPAP mode, two levels of pressure and inspiratory – expiratory time have to be set. BIPAP mode also

can be used by noninvasive ventilation via a facemask.

This BIPAP mode is said to have a number of advantages over conventional modes of ventialtion. Because as EPAP is applied during expiration, so it enhances alveolar recruitment, improves functional residual capacity and oxygenation. On the otherhand, IPAP improves hypoxaemia and/or hypercapnia by imrpoving tidal volume delivery by pressure support or pressure control ventilation. Other advantages of BIPAP include: it allows spontaneous breathing, require less sedation, need higher inspiratory drive and reduce atelectasis (Fig. 21.16).

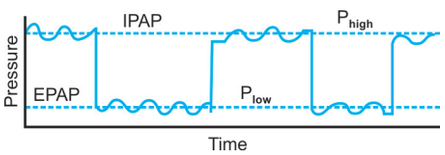


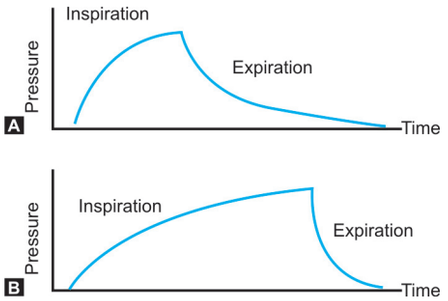
Fig. 21.16: Biphasic Positive Airway Pressure (BIPAP)

Inverse Ratio Ventilation (IRV)

During normal spontaneous respiration or in conventional mechanical ventilation, the inspiratory time is lesser than the expiratory time, i.e. I:E ratio is ≤ 1(1:1 to 1:4). But, IRV refers to a special type of mechanical ventilation in which the I:E ratio is set to greater than one (i.e I:R is ≥ 1 which varies between 1:1 to 4:1). By increasing this ratio to more than one, inspiratory time is made to prolonge and expiratory time is made to reduce. When IRV is used in conjunction with PCV or VCV, it is called as PC − IRV or VC − IRV (Figs 21.17A and B).

There are certain advantages after increasing the inspiratory time than expiratory. These advantages are:

i. Increase in inspiratory time causes increase in mean airway pressure (MAP), but without increasing the peak airway pressure, despite a constant tidal volume and PEEP level. This helps to open the collapsed alveoli. Within a certain range of increased MAP, there is a direct linear relationship between MAP and oxygenation.



Figs 21.17A and B: Inverse ratio ventilation (IRV).
A. Normal ins : exp ratio
B. Inverse ins : exp ratio

ii. In poorly compliant lungs such as ARDS, acute lung infections, etc. the alveoli are become of long 'time constant' (i.e. slow alveoli). It means they require longer inspiratory time for full inflation which is not possible by standard duration of inspiration during conventional ventilation. So, prolonged inspiratory time in such circumstances sustains the alveolar inflation and improves alveolar ventilation. This also decreases the dead space in diseased lung (V_D / V_T is reduced) and improves the oxygentation with better matching of ventilation – perfusion ratio.

The decrease in expiratory time also has certain effects. Due to the reduction of expiratory time, tidal volume cannot be expired completely, so intrinsic PEEP or auto – PEEP develops. This intrinsic PEEP also avoids the end-expiratory alveolar collapse of the slower lung compartments which give rise to an increase in FRC, increase in gas exchange area, and reduction of the intrapulmonary R to L shunt. Intrinsic or auto-PEEP has its own disadvantages, but here only the advantageous part is taken into account. It is important to say that IRV (or auto PEEP) is not a substitude for extrinsic – PEEP. The extrinsic PEEP is very important. It helps for the stability of those faster alveoli that empty completely under IRV. Also the effect of external PEEP is additive to the effect of internal PEEP and helps for a damaged lung compartment.

In PCV and VCV in conjunction with IRV (PC-IRV and VC-IRV), inspiratory time can be extended or modified by :

i. Applying an end – inspiratory pause,
ii. Decreasing the inspiratory flow rate,
iii. Changing from a constant to a decelerating flow pattern. The inspiratory flow during PCV is initially high. Then it decreases gradually as the alveolar pressure rises with lung inflation. This decelerating inspiratory flow pattern results in a better distribution of ventilation. It is also associated with increased MAP for any given tidal volume, inspiratory time and improved gas exchange.

Methods of setting IRV :

i. The IRV is likely to be most effective only during early period in the course of development of ARDS, when the recruitable lung units are still there.
ii. The decision of IRV is to be taken, only when the patient is unable to be properly oxygenated at acceptable levles of PEEP, FiO_2 and peak alveolar pressure on conventional PCV or VCV with CMV or ACMV mode of ventilation.
iii. The arrangement for extensive monitoring should be started including blood gas analysis, CVP, arterial line, etc.
iv. Deep sedation and neuromuscular paralysis should be added to prevent dys-synchronous breathing, to enhance comfort and to allow the measurement of MAP which reflect the lung distension.
v. If patient is already in VCV, then as a first step to change over to VC–IRV from VCV constant flow should be changed to decelerting flow. This will approximate the inspiratory flow pattern of PCV with its possible gas exchange advantages. In many ventilators, this will decrease the mean inspiratory flow rate, extend the inspiratory time and increase the MAP.

Airway Pressure Release Ventilation (APRV)

APRV is a new ventilatory mode and is not well understood till now. Presently only one ventilator (Drager Evita) can provide this APRV mode of ventilation. In this mode the patient is allowed to breath spontaneously during which high CPAP is applied. It is used on patients with decreased lung compliance such as ARDS, ALI (Acute Lung Injury), etc and on those patients who had decreased FRC. This is because in APRV mode air way pressure is much lower than conventional ventilatory mode if the conventional modes are applied in such pathological conditions of lungs. This mode should not be used on patients with high airway resistance (such as in bronchospasm), because success of this mode depends on rapid increase and decrease in airway pressure and rapid emptying of the lungs (Fig. 21.18).

Airway pressure release ventilation is nothing but a CPAP mode at high pressure level in which release valve is opened for a short time (1 to 2 second). When the release valve is opened for short time (automatically at a set pressure level), the high ventilatory CPAP pressure comes to a lower level (or zero) allowing lungs to exhale. Thus, the APRV breaths dance between the high and low CPAP levels. The gas delivery to the patient depends on the pressure gradient, patient's lung compliance and airway resistance.

The, APRV combines the features of CPAP and PCV mode. In this mode, the inspiratory flow valve is opened throughout the ventilatory cycle such that the patient is allowed to breathe spontaneously at any point during the high CPAP breathe. Through short pressure release, expiration and CO_2 elimination is ensured and again it return to the original CPAP levels which provides mechanical inspiration. If the patient is not breathing spontaneously, PC-IRV and APRV are indistinguishable.

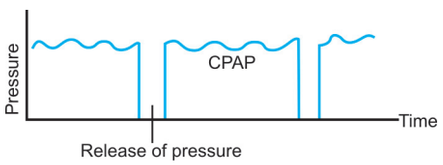


Fig. 21.18: Airway pressure release ventilation (APRV)

Apnoea Back-up Ventilation

This mode of ventilation provides mandatory breaths when the patient suddenly goes in apnoea due to any cause. So this mode of ventilation is also known as the safety mode, because it provides a mandatory ventilatory support during unpredicted apnoea. It is used in combination with all the modes and especially with SIMV and CPAP for spontaneously breathing patients. In completely controlled mode such as CMV, patient is automatically aponeic and thus this mode is not needed. So, apnoea back-up ventilation mode must be set for spontaneously breathing patients. The ventilators monitor the time period continuously during which the patient is taking the spontaneous breathing and/or there is sufficient inspiratory mandatory minute volume (MMV). When either of the criteria is violated, then the ventilator immediately starts delivering mandatory breaths to the patient. This will continue still the patient resumes spontaneous breathing and/or there is an increase in the inspiratory minute volume. In some ventilators this mode needs to be set, while in others it is automatically set.

Dual Control Mode (Dual Mode Ventilation)

It is one of the newer mode of ventilation and provides the advantages of both volume control and pressure control or pressure support ventilation. As it is a volume controlled, so ventilation guarantees the calculated volume delivery and also as it is pressure controlled ventilation, so also, it provides fine control over the distending pressure. It also provides more patient and ventilator flow synchrony for spontaneously breathing patient. Hence, combination of both the volume and pressure control can offer better ventilation solution to the patient. Even though it is called the dual control, still the ventilator actually controls either pressure or volume, but not both at the same time. In this mode, the target volume is set and the maximum pressure limit is also set. The ventilator automatically makes changes the pressure level breath by breath, but within a limit (set by the clinician) to achieve the target volume at the least possible pressure. It offers a full ventilatory support in the form of mandatory breaths, when needed and also it offers partial ventilatory support in the form of spontaneous breath. Actually the dual control mode is a volume target and pressure control (VTPC) mode (Dual Control = Volume Target + Pressure Control).

Dual control mode may be of three types:

i. Volume targeted pressure control and ACMV − Here breaths are patient or time triggered, time cycled, volume targeted and pressure control.
ii. Volume targeted pressure support − Here all the spontaneous breaths are supported by the ventilator. The breaths are patient triggered, volume targeted, pressure supported and flow or pressure or time cycled.
iii. Volume targeted pressure control and SIMV − Here the user sets a number of time or patient triggered mandatory breaths which are volume targeted and pressure control. In between the mandatory breath, there are also spontaneous breaths which are also volume targeted and pressure supported.

The advantages of dual control mode are :

i. Better ventilator and patient synchrony.
ii. Reduces the need for sedation.
iii. Keeping distending pressure under control this mode assures delivery of adequate tidal volume.

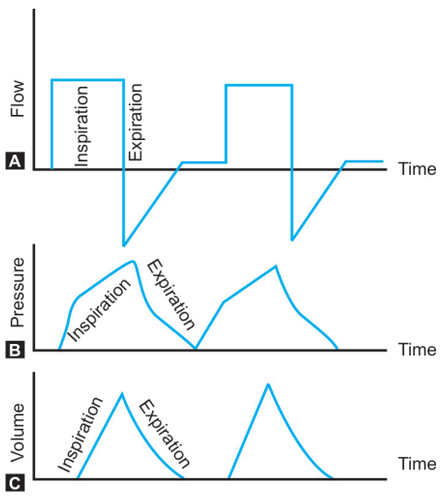
iv. Reduces work of breathing.
v. Helps quicker weaning.

WAVEFORM IN MECHANICAL VENTILATION

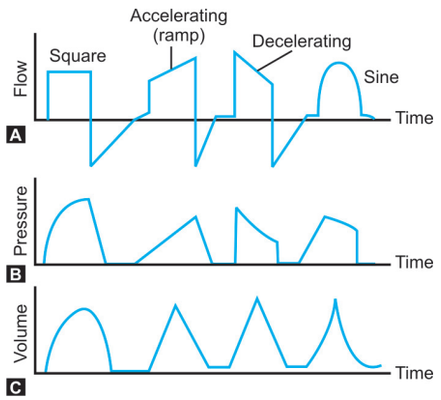
To optimise the mechanical ventilation, proper monitoring of four parameters of it is essential. These four parameters of ventilation are: Pressure, flow, volume and time. The real time graphic displays of these parameters as waveform and loop on the ventilator front panel offers the clinician to evaluate the adequacy of ventilator settings and to monitor the patient's response to ventilator therapy. So, the all newer mechanical ventilators are now equipped with a graphic package that displays many selected (by clinician) ventilator waveforms and loops, facilatating assessment of the patient's condition (Fig. 21.19A to C).

Any single variable parameter, displayed against time is known as the waveform graphic. When viewing the waveform graphics which is also called 'scalar', the time is conventionally shown on the horizontal (X) axis, whereas the the flow, volume and pressure are plotted on the vertical (Y) axis. Therefore, there are three main waveforms: Flow vs Time, Pressure vs Time and Volume vs Time and each waveform has its own characteristic which is shown in (Fig 21.19). Flow itself is again of four patterns: Square (constant), accelerating, decelerating and sine. Therefore, the pressure and volume waveforms also differ for each flow pattern which is also shown in figure (Figs 21.20A to C).

There are two graphic displays in loops: pressure–volume loop and flow-volume loop. Loops are the two dimensional graphic display of two parameters. When the pressure-volume loop is viewed, the horizontal (x) axis is used to indicate the pressure (in cm of H_2O) and volume (in ml) is displayed on the vertical (Y) axis. On the other hand, when viewing the flow-volume loop, then the horizontal (X) axis is used to indicate the volume, whereas the flow is displayed on the vertical (Y) axis. In vertical flow axis the inspiratory curve is plotted above the baseline and the expiratory curve is traced below the baseline. However, it is not unusual to see a completely reverse pattern where the inspiratory component is presented below the baseline (Figs 21.21 and 21.22).



Figs 21.19A to C: The typical flow-time, pressure-time and volume-time waveform. Among these only the flow-time waveform has negative deflection below the baseline and helps in proper interpretation of expiration. These waveforms also differ during mechanical and spontaneous ventilation, during volume controlled and pressure-controlled ventilation, and during different flow patterns



Figs 21.20A to C: Flow time, pressure-time, and volume-time waveform which corresponds with different flow patterns, during mechanical (not spontaneous) volume controlled, time cycled ventilation

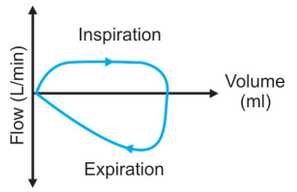


Fig. 21.21: Flow-volume loop

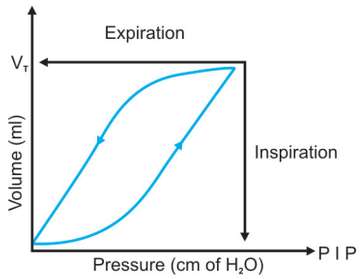


Fig. 21.22: Pressure-volume loop

Flow-Time Waveform

This waveform shows the gradual changes in flow during inspiration and expiration with time. In the graph, time is represented by the horizontal X-axis (in second) and the flow is represented by the vertical Y-axis (in litres per minute). The flow above the X-axis represents inspiratory flow and the flow below the X-axis represents the expiratory flow. Commonly, the two types of flows are used in clinical practice: constant or square flow and decelerating flow. The constant or square waveform of flow is the characteristic of volume controlled ventilation, whereas the decelerating waveform of flow is the characteristic of pressure controlled ventilation. However, most of the ventilator allow a clinician to select a specific flow pattern that is most suitable to the patient. Flow time waveform is similar for both mechanical and spontaneous breath. The flow time curve for a spontaneous breath resembles a sine waveflow pattern.

In the constant flow (a typical feature of classic volume-controlled ventilation), the flow rate during inspirations remains constant throughout the inspiratory phase. At the start of the inspiration, the flow quickly rises to the set value and then remains constant until the set tidal volume has been delivered (square area of the

curve). Then the flow rapidly falls to zero level at the begining of the pause time. At the end of the pause time, the expiratory flow begins, the course of which depends on the resistances in the ventilator system and on the parameters of lungs and airways (Fig. 21.23).

In decelerating flow (a typical feature of pressure controlled ventilation mode), the flow falls constantly after having reached an initial high value. This is because as the filling volume in the lungs increases, the pressure in the lungs also rises and flow starts to fall. Then at the end of inspiration the pressure in the lung is equal to the pressure in the breathing system, so there is no further flow.

In flow-time wave graphic, the tracing below the baseline, representing the expiratory flow is significant, because it shows the lung's characteristic and the airway resistance. Moreover, only the flow-time waveform demonstrates a significant tracing below the baseline. The other waveforms stay above the baseline except pressure-time waveform where a very small deflection occurs below the baseline when the patient initiates inspiration spontaneously.

Components of Flow-time Waveform

The square form of a flow time wave pattern will be used here throughout this discussion to identify the each component of graph during the inspiratory and expiratory phase of a mechanical volume controlled ventilation. Component 1 consists of initiation of flow at the beginning of inspiration. At this time, the exhalation valve is closed to permit a mechanical breath which deliver a preset volume to the patient's lungs. In second component, the peak inspiratory flow rate (PIFR) level is reached instantaneously by constant flow pattern. The flow remains at this constant peak level until the inspiration is terminated. The third component consists of the end of delivery of inspiratory flow and begining of expiration. This event occurs after the preset tidal volume is delivered. At this time the exhalation valve opens to allow for passive exhalation.

The expiration component of flow-time waveform, whether from mechanical or spontaneous breath, is generally a passive maneuver. After the end of inspiration expiratory flows reach their peak value instantaneously and then gradually return to the baseline. Usually, there is no gap between the end of inspiratory flow and the start of expiratory flow. In normal flow-time waveform, the transition from the inspiratory phase to the expiratory phase is smooth and there is no time interval. The components of expiratory flow are: Initiation of expiration, peak expiratory flow rate (PEFR) and duration of expiratory flow (or expiratory time T_E).

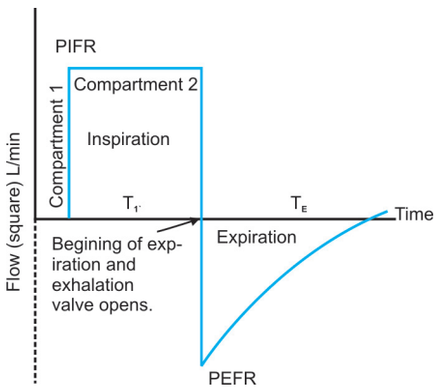


Fig. 21.23: Flow-time waveform (square pattern) in volume control ventilation. T_I = Inspiratory time, T_E = Expiratory time

Recognition of Common Abnormalities of Flow-time Waveform

The flow-time waveform helps in recognising of certain respiratory disorders. Different lung disorders show different flow time patterns. The common abnormalities are asynchrony between the ventilator and the patient, incorrect setting of inspiratory time, auto-PEEP and airway obstruction.

Asynchrony

If there is a dip in the inspiratory flow plateau, it suggests asynchrony. Asynchrony occurs when the patient's demand is more than the set ventilator's flow rate. This condition can be corrected by: increasing the inspiratory flow, adjusting ventilator's trigger sensitivity or changing the mode of ventilation according to the patient's demand (Fig. 21.24).

Incorrect inspiratory time setting

Incorrect inspiratory time setting is recognised by time interval between the end of inspiratory flow and the start of expiratory flow which is not present in the normal flow-time waveform, where the transition from inspiration to expiration is smooth. This can be corrected by: increasing the set inspiratory time and increasing the flow rate. If inspiratory time is set very short, then the inspiratory flow is suddenly stopped due to start of expiratory flow. Compare this with a smooth transition from inspiratory phase to expiratory phase in normal condition. This short inspiratory phase can be corrected by increasing the inspiratory time (Figs 21.25A and B).

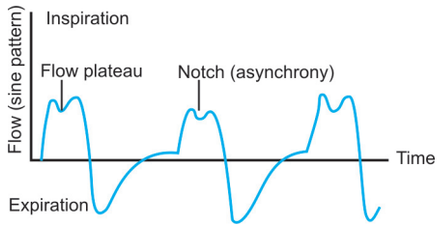
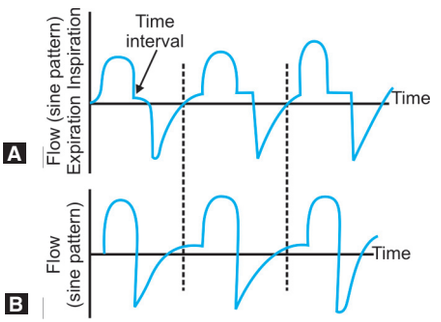


Fig. 21.24: Flow-time waveform (sine pattern) shows asynchrony between the ventilator and the patient. In normal flow-time waveform the flow plateau is smooth and no notch indicates adequate flow



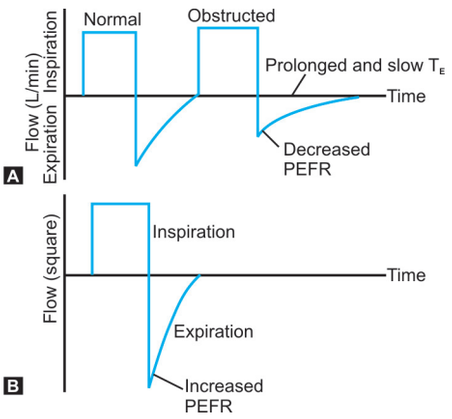
Figs 21.25A and B: A. Incorrect inspiratory time setting in flow-time waveform (sine pattern). B. Rectification has been done

Airway obstruction and active exhalation

Exhalation is normally passive. The expiratory flow pattern and PEFR depend upon the changes in patient's lung compliance, airway resistance, as well as patient's active efforts to exhale. Increased airway resistance due to bronchospasm or accumulation of secretions in the airway may result in decreased PEFR (peak expiratory flow rate) and a prolonged expiratory flow (T_E). If the patient begins to exhale actively using accessory expiratory muscles, this may result in an increase in PEFR and a shorter duration of expiratory flow. Flow waveform can also verify the clinically suspected bronchoconstriction. In such cases, the PEFR is reduced and the expiratory flow returns to the baseline very slowly. Administration of bronchodilator improves PEFR and allows for an expiratory flow to return to the baseline within normal time period (Figs 21.26A and B).

Airtrapping or auto-PEEP

Normally, the expiratory flow returns to baseline prior to the next breath. In the event, when the patient is unable to exhel completely leading to air trapping in alveoli, then the expiratory flow does not return to zero level or baseline and the subsequent inspiration begins below the baseline. It indicates insufficient expiration and the presence of auto-PEEP. The presence of auto-PEEP or airtrapping may result from: inadequate expiratory time, too high respiratory rate, long inspiratory time, and prolonged exhalation due to bronchoconstriction. Even though the auto-PEEP is best detected from the flow time waveform, but its magnitude is not directly measured from this graphic. A higher inspiratory flow rate (in volume cycled ventilators) or short T_I (in time-cycled ventilators) allows for a longer T_E and may eliminate auto-PEEP. Auto-PEEP can also be eliminated by increasing the PEEP level and bronchodilator therapy (Fig. 21.27).



Figs 21.26A and B: A. Flow-time waveform (square pattern) normal and obstructed, B. Response to bronchodilator, it has the same effect like active exhalation

Pressure-time Waveform

This waveform shows the gradual changes in airway pressure with time. In typical pressure-time waveform, the horizontal X-axis represents time in seconds and the vertical Y-axis represents the changes in pressure of airway in cm of H_2O. During mechanical ventilation, the inspiratory prssure rises in an upward direction above the baseline, while the expiratory pressure returns to baseline level. But, during spontaneous breathing, the inspiratory pressure moves in the downward direction below the baseline, while the expiratory pressure rises above the baseline at the start of expiration and then returns to baseline again. Thus, this pressure-time waveform during spontaneous ventilation is not same as that of controlled ventilation. Again in controlled ventilation pressure-time waveform differs in volume controlled and pressure controlled ventilation. In volume controlled ventilation, the pressure-time waveform again changes according to the flow of pattern, such as constant (square), declerating, accelerating and sine.

A typical pressure vs time waveform in volume controlled ventilation (with constant or square flow) is shown in figure. Here, the inspiration starts at point 1. At the begining of inspiration, the pressure between the points 1 and 2 increases instantly due to the resistances in system. The level of the pressure at point 2 is equivalent to the product of resistance and flow. After point 2, the pressure increases further gradually in straight line till the point 3 (Fig. 21.28) is reached (the peak pressure point). At point 3, the peak or maximum pressure is called the peak inspiratory pressure (PIP). The gradient of this curve is dependent on the inspiratory flow, airway resistance and the overall compliance of the lungs. Increased airway resistance (Raw) and/or decreased lung compliance result in an increased PIP. Up to point 3, the ventilator applies the set tidal volume and thereafter no further flow is delivered. So as there is no flow at this point (point 3), the pressure level quickly falls to the plateau pressure (point

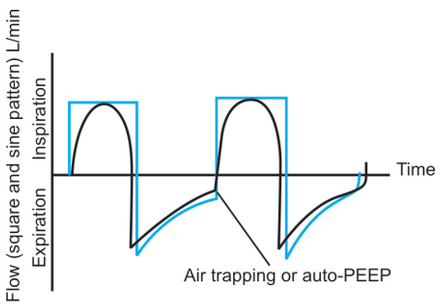


Fig. 21.27: Flow-time waveform (square pattern-red line and sine pattern - green line) showing air trapping

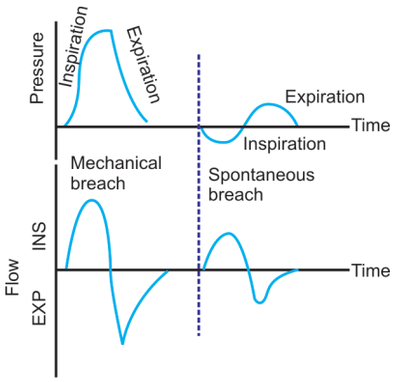


Fig. 21.28: Typical pressure - time waveform with corresponding flow - time waveform

4). This drop in pressure is equivalent to the rise in pressure, caused by the resistance at the beginning of inspiration and finally shows the compliance of lungs. After that there may be slight decrease in pressure between the points 4 and 5. The possible reasons for this drop is more and more recruitment of lungs and leaks in the system. The plateau pressure level is dependent on the compliance of lung and tidal volume. During the plateau time, no volume of air is supplied to the lung and the inspiratory flow comes to zero. At the point 4 passive expiration begins due to elastic recoil of thoracic wall and lungs. PEEP can be confirmed only by a pressure-time waveform and pressure volume loop. PEEP is present only when the baseline pressure remains above zero. The pressure-time waveform also varies with the triggering mechanism of the mechanical breath. If the breaths are initiated at the baseline at fixed intervals, the mode is definitely time tirggered and a control mode. In an assisted mode, the patient initiates the breath by generating a negative pressure. This event can be observed on the pressure-time waveform where a small negative deflection below the baseline precedes a mechanical breath. The ventilator sensor recognizes the patient's effort and delivers a mechanical breath (Fig. 21.29).

Although the dynamic mechanics of lungs can be observed from this pressure-time waveform, still the addition of an inspiratory pause provides some more information to calculate the static mechanics. For example the plateau pressure (P_{Plat}) or alveolar pressure is obtained by the activation of an inspiratory pause control knob which can produce a pause. During this manoeuvre the exhalation valve is kept in a closed position and the volume is held constant in the lungs for a moment. For clinical purposes, the plateau pressure is the same as the alveolar pressure at the end of inspiration. This measurement provides a means of measuring the static lung compliance. The transairway pressure which can be calculated by deducting the plateau pressure from the peak inspiratory pressure ($P_{TA} = PIP - P_{Plat}$) reflects the pressure required to overcome the airway resistance. In bronchospasm, the pressure required to overcome the recoiling force (lung compliance) can be determined. The static lung compliance can be obtained by dividing the volume of the lung by the plateau pressure minus (See Fig. 21.7) PEEP, if present (Fig. 21.30).

In pressure controlled ventilation, the pressure-time waveform has a different shape. Pressure increases rapidly from the lower pressure until it reaches the upper pressure level and then remain constant for the set inspiratory time. The drop in pressure during the expiratory phase follows the same curve as in volume controlled ventilation.

The pressure-time waveform is useful in :

i. Evaluating the peak inspiratory pressure (PIP),
ii. Determining the PEEP or CPAP level,
iii. Setting the ventilator trigger sensitivity levels,
iv. Indicating the changes in airway resistance and lung compliance.

Recognition of common abnormalities

From the diagnostic point of view some changes in the pressure-time curve have profound clinical significance. The common abnormalities which are found in the clinical practice in pressure time waveform during volume controlled ventilation are described below:

i. The large negative movement below the baseline of a pressure-time waveform in mechanical ventilation indicates excessive trigger work. It increases patient's work of breathing, because patient needs to do excessive work to trigger the ventilator to deliver a breath. This condition can be corrected by adjusting the trigger sensitivity setting in such a manner that the ventilator is made more sensitive to the patient's effort and thus reduces the work. But, during recovery the trigger sensitivity is reduced gradually to increase the work of breathing which helps in weaning (Fig. 21.31).
ii. In normal pressure-time waveform the peak pressure is achieved quickly and then a plateau pressure is maintained steadily. Failure to maintain a steady plateau pressure with a notch indicates a leak or an inability to deliver the required flow. This condition can be corrected by identifying and rectifying the leak in ET−tube or in ventilator circuit or by increasing the inspiratory flow (Fig. 21.32).
iii. The changes in the inspiratory airway resistance is also indicated in pressure-time curve by the increase or decrease

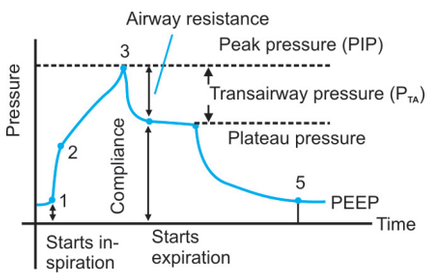


Fig. 21.29: A typical pressure - time waveform in volume controlled constant flow mechanical ventilation

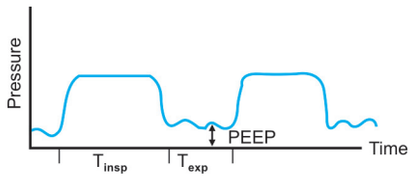


Fig. 21.30: Pressure-time waveform in pressure controlled ventilation

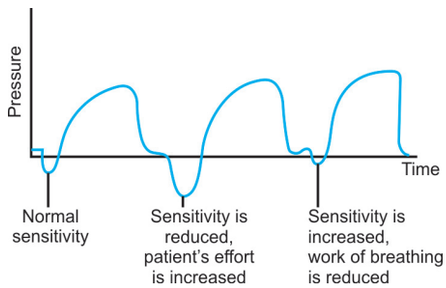


Fig. 21.31: Pressure-time waveform (when flow-time is sine pattern) shows different trigger sensitivity

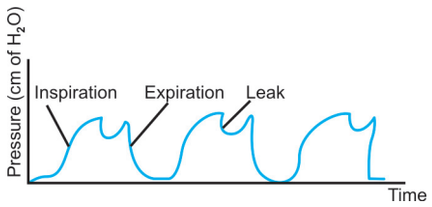


Fig. 21.32: Pressure-time waveform (with flow-time sine pattern) shows leak as peak inspiratory pressure level is not maintained

of peak pressure level, but without changes in the plateau pressure level. If the peak pressure increases with no change in the plateau pressure, then it indicates an increased airway resistance (R_{Aw}) and vice versa. The difference between the peak pressure and the plateau pressure indicates the pressure required to overcome the airway resistance (Fig. 21.33).

iv. The total pressure generated at the airway during mechanical ventilation is comprised of two components: (a) Pressure required to distend the respiratory system (lung) which is determined by the compliance and (b) The pressure required to overcome the airway resistance through natural and artificial airways. In peak pressure, gas is delivered to the alveoli and the lung is held inflated at that end inspiratory volume. Thus peak inspiratory pressure indicates the both airway resistance and compliance of lungs and thorax. Whereas the plateau pressure indicates the alveolar distending pressure only, i.e. the pressure required to distend the chest wall and lungs (compliance) (Fig. 21.34).

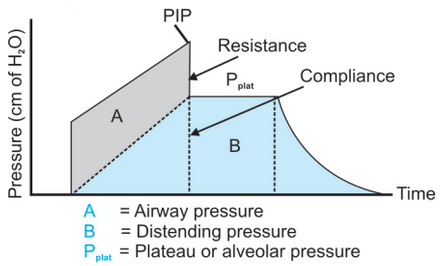


Fig. 21.33: This normal pressure - time waveform shows different components of inflation pressure

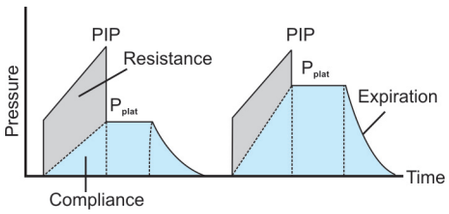


Fig. 21.34: Pressure-time waveform, increased resistance and decreased compliance

So, peak inspiratory pressure (PIP) = Resistance + Compliance and plateau Pressure = Compliance.

Thus, if the peak pressure and the plateau pressure both increase or decrease in same direction, then it reflects the changes in lung compliance. If both the pressure increase in a similar proportions simultaneously, then it indicates decrease in lung compliance and vice versa (in increased airway resistance only peak pressure increases).

v. When the pressure does not return to baseline before the next inspiration, then it indicates that expiratory time is inadequate (inspiration starts before completion of expiration) or PEEP is applied. If expiratory time is not adequate, then it can be corrected by increasing the expiratory time.

vi. During volume controlled ventilation, in the inspiration the rate of rise of pressure (slope) is related to the peak inspiratory flow settings and can be used to adjust the peak flow rates. Inadequate flow rate is indicated when the pressure rises (slope) very slowly, or sometimes is indicated when there is a depression in the inspiratory limb of the pressure contour (Fig. 21.35).

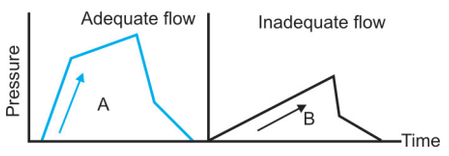


Fig. 21.35: Pressure-time waveform (volume controlled) with adequate (A) and inadequate inspiratory flow (B)

vii. High flow rate also can be determined by pressure-time waveform. It is indicated by shorter inspiratory time than normal.

Volume-time Waveform

This waveform shows the gradual changes in the volume, transferred to the lungs during the inspiratory and expiratory phase of respiration. In a mechanical ventilator the total inspiratory volume is derived from the integration of flow over time. In this waveform, the horizontal X-axis represents time in seconds and the vertical Y-axis represents volume in cubic centimetres (cc). During the phase of inspiratory flow, the volume increases continuously. Then during the pause it remains constant and next during expiration the transferred volume decreases as a result of passive (Fig. 21.36) exhalation. The volume-time waveform for mechanical and spontaneous breath are similar in pattern. Again the volume-time waveform in mechanical volume controlled and pressure controlled ventilation are more or less is same. Information obtained from this volume-time waveform includes: A visual representation of inspiratory time, tidal volume, inspiratory pause, expiratory phase and expiratory time (Figs 21.37A and B).

Interpretation

i. If the expiratory volume tracing does not return to the baseline at the end of expiration, then it indicates the leaks in endotracheal tube or at any place in the ventilator breathing circuit. By the graphic pattern the site of leak can be

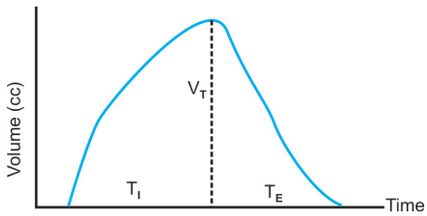
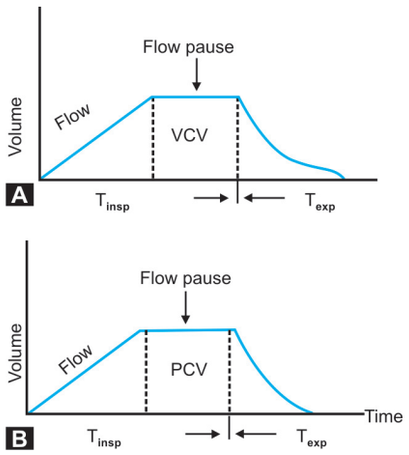


Fig. 21.36: Volume - time waveform without any inspiratory pause



Figs 21.37A and B: The volume - time waveform where there is gradual changes in the volume during inspiration and expiration in volume controlled and pressure controlled ventilation. Here an inspiratory pause is used.

located. The amount of leak also can be easily estimated by measuring the distance from the plateau to the end of the expiratory tracing (Fig. 21.38).

ii. If the expiratory volume tracing moves very slowly towards the baseline, then it indicates the slow movement of expiratory gases due to any obstruction. Hence it can lead to an auto-PEEP, since the exhalation is not completed. It can be corrected by administering the bronchodilators or increasing the expiratory time or decreasing the inspiratory time (Fig. 21.39).

iii. If the expiratory volume tracing goes downwards, touches the baseline and then further goes below the baseline,

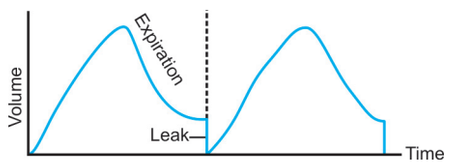


Fig. 21.38: Volume - time waveform showing leak.

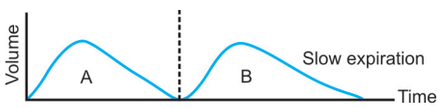


Fig. 21.39: Volume - time waveform A. Normal expiration, B Slow expiration

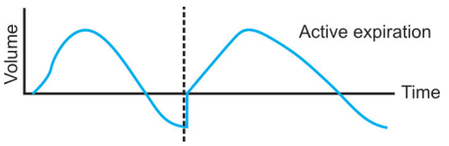


Fig. 21.40: Volume - time waveform showing active expiration due to cough, agitation or severe obstruction

then it indicates that the expired volume is more than the inspired volume and it is due to coughing, patient's agitation or auto-PEEP. It can also occur if the flow transducer is not properly calibrated (Fig. 21.40).

Pressure-Volume Loop (Fig. 21.41)

The pressure-volume loop indicates the changes in pressure and the corresponding changes in volume of lungs. Initially, inspiration begins from the FRC level which corresponds to the crossing of X and Y axis. Then, inspiration terminates when the preset volume or pressure (in VCV and PCV respectively) is achieved. After that expiration begins and the tracing returns to the FRC level at the end of exhalation. From this pressure volume loop, we can get PIP and tidal volume (V_T). Usually FRC level is situated at the junction of X and Y axis. But when PEEP is applied, then FRC level increases and shifts right wards along the X-axis from where inspiration begins (Fig. 21.42).

From the tracing of pressure-volume loop the type of breathing also can be recognised. For example, when the tracing is counter clockwise, then the delivered breath is mechanical one. On the other

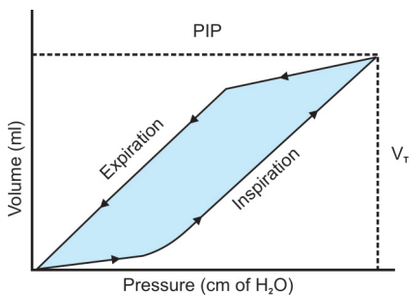


Fig. 20.41: Pressure-volume loop

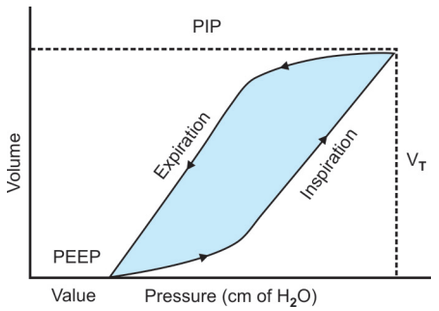


Fig. 21.42: Pressure-volume (P-V) loop with PEEP

hand, a clockwise tracing (Fig. 21.43) indicates a spontaneous breath. In an assisted mechanical breath the first part of tracing begins clockwise which indicate patient's spontaneous effort. Then, the last part of the tracing shows the counter clockwise direction which indicates mechanical breath (Fig. 21.44).

The major advantage of this loop is that it can provide a quick assessment of work of breathing. Because work of breathing is calculated from the product of pressure and volume (work of breathing = pressure × volume). Within this work of breathing,

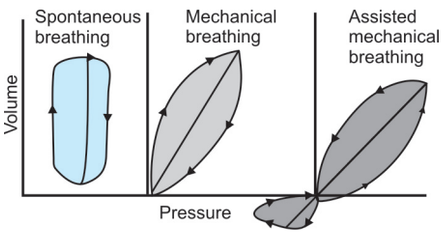


Fig. 21.43: Different types of breathing in P-V loop

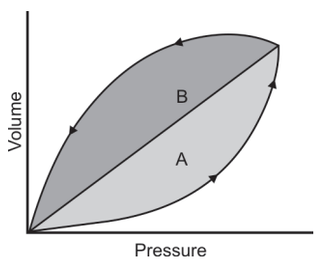


Fig. 21.44: Assessment of work of breathing by P - V loop. (A) Normal resistive work, (B) Normal elastic work

elastic and resistive part also can be classified. Both on the inspiratory and expiratory limb of pressure-volume tracing, there is a point where the slope is suddenly changed. This point is called the inflection point. It represents sudden changes in pressure responsible for opening and closing of alveoli. The lower inflection point means the opening pressure of alveoli and the upper inflection point means the closing pressure of alveoli. The higher opening pressure indicates the decreased compliance of lungs (stiffer lungs) and causes the loop moving laterally to the right along the pressure axis. During setting of PEEP, the lower inflection point is recommended to optimize the recruitment of alveoli and it will prevent the repeated opening and closing of alveoli (Figs 21.45 and 21.46).

A shift of loop to the right indicates decreased lung compliance and to the left indicates increased lung compliance. This can be judged by observing the pressure required to deliver the same tidal volume in three loops. This is applicable only in volume targeted ventilation. But in pressure targeted ventilation the tidal volume (V_T) is the changing variable, where peak inspiratory pressure (PIP) is constant.

An increased resistance of airway due to obstructive lung disease is responsible for abnormal widening of only the inspiratory part of tracing and exhibits a wide pressure volume loop. This abnormal widening of pressure – volume loop is known as the increased 'hysteresis'.

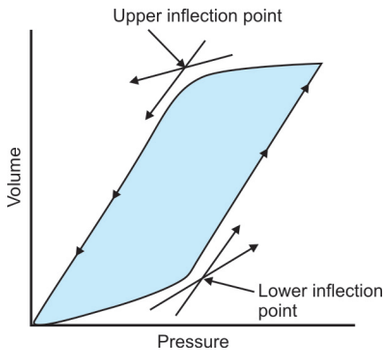


Fig. 21.45: Inflection points in P-V loop

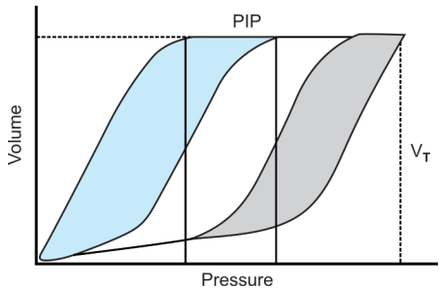


Fig. 21.46: Changes of lung compliance in P - V loop (Volume Controlled Ventilation). PIP is different but VT is same

Normally, the direction of a pressure-volume loop is counter clockwise and indicates mechanical breath. But a clockwise direction before mechanical breath indicates patient's effort for breathing. Adjusting the sensitivity of ventilator one can minimise or increase the effort of breathing and thus decrease or increase the work of breathing. In pressure-volume loop it is recognized by a significant clockwise deflection of a tracing below the baseline (Figs 21.47 and 21.48).

When the expiratory tracing of a pressure-volume loop does not return to zero level on the axis of volume, it suspects an airleak. On the other hand, an insufficient inspiratory flow is recognised by a scooped out pattern in the middle of inspiratory limb exhibiting a notch during mechanical breath (Figs 21.49 and 21.50).

Alveolar over distension is a common manifestation during ventilation of patient with ARDS by VCV mode and is detrimental to patients. This is classically seen in pressure-volume loop which is known as 'Beak effect' or 'Duckbill'. It is characterised by an increase in airway pressure without an appreciable increase in volume. In such circumstances, switch over to pressure targeted ventilation (PCV) with appropriate safe pressure level or reduction of tidal volume are indicated. (Figs 21.51 and 21.52).

Flow-Volume Loop

In this loop, there is no set convention in assigning the inspiratory and expiratory component around the volume or X-axis.

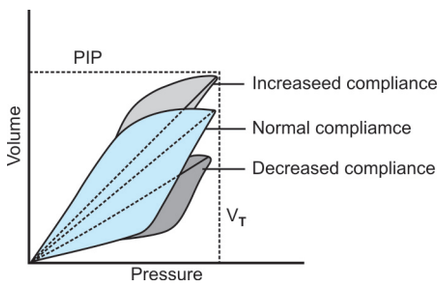


Fig. 20.47: Changes of lung compliance in P-V loop (Pressur 21.e Controlled Ventilation). PIP is same but VT is different

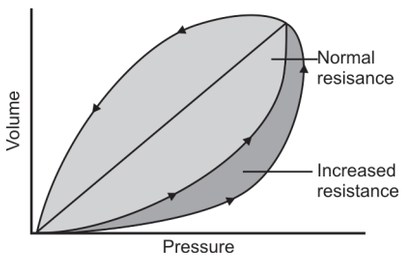


Fig. 21.48: Increased resistance shown in P-V loop

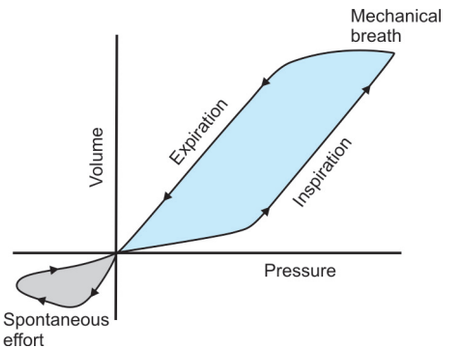


Fig. 21.49: P-V loop showing spontaneous breathing effort and mechanical breath

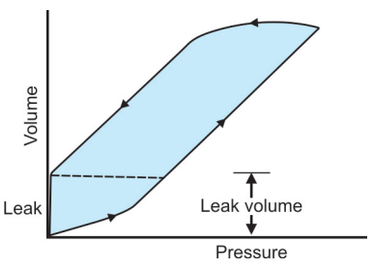


Fig. 21.50: Air leak in P-V loop

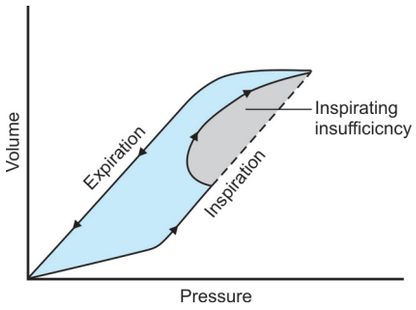


Fig. 21.51: P-V loop with inadequate inspiratory flow

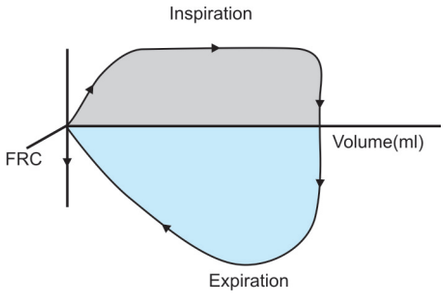


Fig. 21.53: A normal flow - volume (F - V) loop

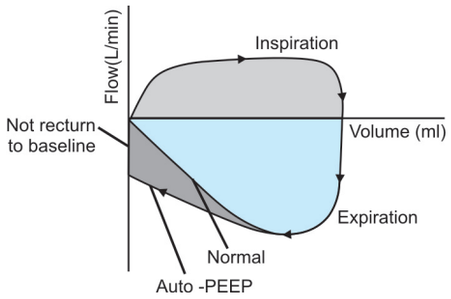


Fig. 21.55: Auto PEEP in F-V loop

Fig. 21.52: Duckbill effect of P-V loop

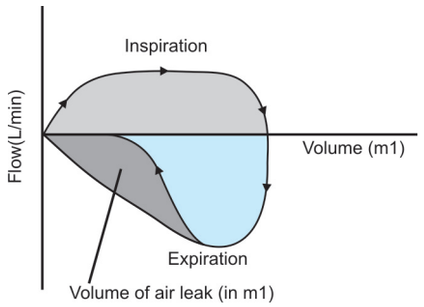


Fig. 21.54: Air leak in a F-V loop

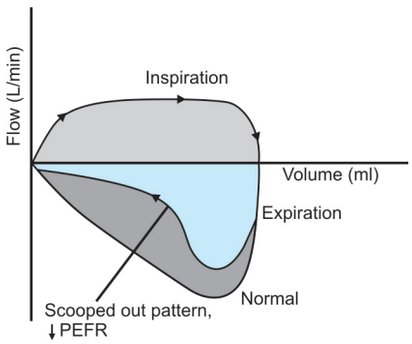


Fig. 21.56: Increased airway resistance in F-V loop

Some ventilators produce flow volume loop with inspiration on the upper half and expiration on the lower half. While in others it is reverse. A flow-volume loop provides information such as: tidal volume, beginning of inspiration and end of expiration, peak inspiratory flow rate (PIFR) and peak expiratory flow rate (PEFR) (Fig. 21.53).

Ideally, the inspired and expired volume should be equal. But with an airleak expired volume will be less than an inspired volume. This can be indientified from a flow-volume loop when the volume indicates the magnitude of airleak (Fig. 21.54).

In an air trapping or auto-PEEP condition the expiratory flow does not return to the zero level. But inspiration must begin from the zero flow level. So the expiratory tracing will jump abruptly from the trapped level to the zero level for the next inspiration (Fig. 21.55).

An increased airway resistance due to bronchospasm also can be diagnosed by a flow-volume loop. It is characterised by a scooped out pattern of the expiratory limb and decreased PEFR. Administration of bronchodilator may show an improvement in both the configuration of the expiratory tracing and PEFR. A continued scooped out configuration of the expiratory tracing and low PEFR suggest ineffectiveness of the bronchodilator therapy (Fig. 21.56).

22 Intraoperative Monitoring

INTRODUCTION

Monitoring of a patient is the key aspect of anaesthesiology. But, with the more and more development in the subject of anaesthesia, the range and complexity of the available monitors used in this discipline have also been increased rapidly. For example, the stethoscope, sphygmomanometer and electrocardiogram (ECG) are now supplemented by the pulse – oximeter, expired gas analyzer, processed electroencephalogram (EEG), evoked potential monitor, transesophageal echocardiography and a host of many others. While this has brought undoubted benefits, but their sophistication and complexity have also brought additional problems. The main problem is that they are very costly to use in every case and is not available in small hospitals and rural areas. So, till now there has been little progress towards an international consensus, regarding their use.

During the use of different monitors, high index of suspicion should always be kept in mind, regarding their accuracy. So this requires a constant comparison with clinical observation. Monitors may be tired by the end of the day. Calibration may slip and zero's may drift. So, they can not always provide a sleepless vigilance that we would like. Also, many problems in instrumental monitoring arise due to the patient machine interference at the site of contact. For this reason, repeated clinical examination and its corroboration with the instrument monitoring is still of primary importance.

But, the most primary equipment of clinical monitoring is the various special senses of the attending anaesthetist. The anaesthesiologist also develops a special sixth sense. This is a subconscious mental computation resulting from the observation, and previous experience which warns him of the impending wrong events and allows him to take a prompt action before hand to meet the need of a patient.

The basic clinical monitoring of patients during anaesthesia are:

i. Non-invasive blood pressure by sphygmomanometer,
ii. Pulse, by clinical palpation,
iii. Peripheral circulation,
iv. Degree of filling of the jugular vein,
v. Colour of the skin, mucous membrane and blood coming out of the surgical exposure,
vi. Temperature,
vii. Urine output (> 0.5 ml/kg/hour),
viii. Respiratory movement of chest and movement of anaesthetic bag,
ix. Depth of anaesthesia – by HR, BP, perspiration, lacrimation, movement of the body etc.
x. Muscle tone,
xi. Pupils.

As per definition, a 'monitor' is an instrument which is used continuously or at intervals to measure the condition or parameter of a patient that should be kept within prescribed limits and it reminds or gives us warnings when this condition or parameter goes beyond that limit. In a monitor, the mechanical energy within a physiological variable is converted into an electrical signal by a transducer. Then, it is processed and transmitted on the screen for display and to an automatic recording system for recording. In a monitor the physiological electrical signal, such as in ECG, is also amplified, processed and displayed on the screen. Accurate detailed recording of parameter is also a fundamental of monitoring.

Pen and paper are still the most reliable tools for anaesthetic records. Although automated recording is available nowadays, but the automated records are not regarded as infallible. The anaesthetist should initialise all the monitoring errors on any automated record sheet.

The manufacturers of early monitors generally paid little attention to the type of presentation. So, during that period the OT clinicians or anaesthesiologists were presented with a collection of boxes for monitoring of each parameter or physiological events of the body. In addition, an increase in the number of sensors attached to the patients for each parameter also led to a progressive increase in the number of boxes which cause predictably confusing results.

Recently, the tendency has changed with the development of a single central display unit, which allows a single monitor screen to provide a wide range of items for measurements. Also, addition and omission of information can easily be done by just changing the modules of a single multimonitor. In such central display unit faulty modules too, can be changed easily. While there are many benefits of this multimonitor approach in terms of clarity

and consistency, but the threat of information overload is still present. The current multimonitor may display up to six waveforms and digital values of different physiological parameters, with different colours and sizes which are alterable by the operator. In a stressful situation, there is limited ability for an operator to absorb all the information. So, a complex and crowded multimonitor is almost useless in acute crisis. Therefore, it is vital that the most important information is easily seen during crisis and not obscured by a mass of interesting, but nonessential life saving data.

Before taking steps for the treatment of a patient with the help of the results of a monitor, some points should always be kept in mind. These are:

i. Different companies use different methods to measure the same parameter in their instruments. So the results may not be the same in different instruments. Unfortunately, companies are usually reluctant to disclose the details of how their machine operates. They only do this to protect their market.
ii. During the measurement of some physiological variables such as the depth of anaesthesia, the electrical activity of brain is measured and is then transformed into mathematical data. This is then compared to a reference value, which is different for different companies. So, accuracy of result may vary.
iii. A monitor which functions well in an OT may give faulty results in an aircraft or ambulance, due to the noise or vibrations.
iv. Monitors may also provide additional hazards for a patient. Because, they are usually made of potentially magnetic material. When such a monitor is taken into the vicinity of a MRI machine, then its magnetism is likely to be accelerated by the huge magnetic field of MRI machine and may cause severe injuries to the patient or may even give inaccurate results. The strong magnetic field may also induce electrical current in the wires placed near the monitor, with the possibility of burning of patient due to heat. So, all the anaesthetic equipments used in radiology unit should, therefore, be made of non-magnetic material or moved outside the magnetic field with long cable to monitor the patient from outside of the radiology room. Several manufacturers now make specific MRI-compatible equipments.
v. Monitors should be checked, serviced and calibrated at regular intervals, set by the manufacturer. Because, many components used in the monitors may degrade with time and lead to suboptimal performance.
vi. Many equipments have been designed to be used for adults only. Their use in children, especially in neonates, may produce unreliable results.

NEUROMUSCULAR MONITORING

Introduction

Muscle power in an awake patient can easily be evaluated through some voluntary test. But, in an anaesthetised patient this is impossible. So, in an anaesthetised patient the muscle power is tested directly by nerve stimulation and indirectly by muscle tone, movement of anaesthetic bag, tidal volume, head lifting (for 5 sec), just after recovery by anticholinesterase, etc. The other indicators of adequate recovery of muscle strength include the ability to generate an inspiratory pressure of at least −25 cm of H_2O and a forceful hand grip. But, all these indirect methods are influenced by multiple factors other than the neuromuscular blockade by muscle relaxants. For example, twitch tension is reduced due to hypothermia of monitored muscle group by about 6°C. So, for accurate information about the status of neuromuscular function, a direct method by using a nerve stimulator is employed. This assesses the muscle power by the response of muscle to electrical nerve stimulation.

But, till now only a few anaesthesiologists use the nerve stimulator to assess the neuromuscular function or muscle power during anaesthesia. Instead, they use only clinical criteria for the evaluation of neuromuscular block, during and after anaesthesia. But, interest in monitoring the neuromuscular block by a nerve stimulator during anaesthesia has been growing over the past few years due to:

i. Increase in awareness, regarding the problems of postoperative residual neuromuscular blockade,
ii. Variations in patient sensitivity and also variations in sensitivity among some group of muscle to neuromuscular blocking agents,
iii. Use of long acting muscle relaxants,
iv. Use of continuous infusion of short acting muscle relaxants, etc.

There is no contraindication for the use of nerve stimulator for neuromuscular monitoring. But, certain sites may be excluded for the surgical procedure.

General Principles

The reaction of a single muscle fibre causing contraction to an electrical stimulus is an all-or-none phenomenon. But, the response of the whole muscle does not follow this all-or-none rule. Here, the response depends on the number of muscle fibres that are activated by the electrical stimulus or blocked by drugs and the amount or intensity of the stimulus. If a nerve is stimulated with sufficient or maximum electrical intensity, then all the muscle fibres supplied by that nerve will react. So, during neuromuscular monitoring all the stimuli should be of maximum strength or above. In practice, the electrical stimulus which is applied to a muscle is usually 20 to 25% above the maximum intensity to achieve the maximum response. This stimulus is called the supramaximal stimulus. To deliver a supramaximal stimulus, the peripheral nerve stimulator must be capable of generating at least 50 mA current with 100 ohm load.

But, one of the disadvantage of supramaximal stimulus is pain and discomfort. Though this drawback of supramaximal stimulus does not cause much problem during intraoperative period or anaesthesia, but it causes definite problem during recovery, as the patient may be awake enough to feel the pain. So, some researchers advocate electrical stimulus below the maximum level. This is called the submaximal stimulus. The disadvantage of this submaximal stimulus is its poor accuracy which is not very acceptable. So, the usual recommendation is to use a supramaximal stimulus, whenever possible.

The character of the stimulus should not only be supramaximal but will also be square wave, i.e. monophasic and rectangular. Biphasic stimulus will cause repetitive firing or burst of action potential and will increase the response to subsequent stimulation, leading to inaccurate results.

The standard optimal duration of stimulus (or pulse) should be 0.2 to 0.3 millisecond. Duration of stimulus exceeding 0.5 millisecond will cause direct stimulation of the muscle and give inaccurate results.

So, the electrical stimulus for monitoring of neuromuscular functional status should be a rectangular pulse of 0.2 to 0.3 millisecond and of supramaximal intensity (100 to 200 mV).

The Sites of Nerve Stimulation and Muscle Responsiveness

For stimulation of a nerve in neuromuscular monitoring, either silver chloride pads (used in ECG) or subcutaneous needles are used over the superficial peripheral motor nerve. Any superficially located peripheral motor nerve may be used for neuromuscular monitoring. But it must be remembered that different muscle groups supplied by a motor nerve have different sensitivities to neuromuscular blocking drugs. For neuromuscular monitoring, the evoked mechanical response (i.e. contraction) or electrical response (EMG) of the innervated muscle is observed. Direct stimulation of the muscle should be avoided. So, the electrodes should be placed over the course of the nerve, but not directly on the muscle itself. Ulnar nerve stimulation to see the response of adductor pollicis and facial nerve stimulation to see the response of orbicularis oculi are the most commonly monitored motor nerve and its supplying muscle respectively.

Among these, the ulnar nerve is the most popular nerve for neuromuscular monitoring and the elbow or the wrist are the most convenient sites. But the median, posterior tibial, common peroneal and facial nerves are also sometimes used. When the ulnar nerve at the site of the wrist is selected for neuromuscular monitoring by electrical stimulus, then the electrodes are placed over the volar side of the wrist. One electrode is placed 1 cm proximal to the point, where the proximal flexion creases of wrist crosses the tendon of flexor carpi ulnaris muscle. The second electrode is placed 2 to 3 cm proximal to the previous one. The stimulation of ulnar nerve at the wrist causes only flexion of the fingers and adduction of the thumb. When the ulnar nerve is selected at the elbow, then the second electrode is placed over the ulnar groove at the elbow.

While placing the electrodes, two things have to be kept in mind. These are : (i) avoid placing the stimulating electrode too close to the recording electrode, and (ii) avoid direct stimulation of the long flexors of the forearm. When the ulnar nerve stimulation is selected at elbow (this site is mainly chosen for paediatric patients), the active negative electrode should be placed at the wrist to ensure a maximal response. When the electrodes are placed close to each other at the wrist, then the polarity of electrodes are not important.

When the temporal branch of facial nerve is selected for neuromuscular monitoring, then the negative electrode is placed over the nerve directly and the positive electrode is placed anywhere over the forehead.

Regarding the muscle responsiveness, different groups of muscle have different sensitivity to neuromuscular blocking drugs, and the results obtained from one group of muscles cannot be extrapolated to other groups of muscles. For example the diaphragm is most resistant to neuromuscular blocking drugs than any other group of muscles of the body. In the second order, the muscles which will come in reference to resistance are the abdominal and respiratory muscles. This is followed by the laryngeal muscles and lastly the muscles of face. The most sensitive muscles to neuromuscular block are adductor policies, abdominal muscles, muscles of the limbs, the upper airway muscles and the masseter. So, keeping in mind the different sensitivities of different group of muscles, we can say that the neuromuscular functional status or intensity of block in adductor pollicis will not be the same as in the diaphragm. Thus, during anaesthesia and surgery the total elimination of response to a single twitch or TOF stimulation of the adductor pollicis does not exclude the possibility of the movement of diaphragm, causing cough, hiccup etc. On the other hand, if the most sensitive muscle such as adductor policies is chosen as the neuromuscular monitoring guide for the administration of muscle relaxants during surgery, then there will be less chance of an overdose of muscle relaxants. Again, the advantage of taking the most sensitive adductor pollicis muscle as a monitoring sample is that sufficient recovery of adductor pollicis (i.e. when TOF ratio exceeds 0.7) signify there is no residual block in the diaphragm.

Patterns of Electrical Stimulus

Five patterns of electrical stimulation for neuromuscular monitoring are used in clinical anaesthesia. These are:

i. Single-twitch stimulation,
ii Train-of-four (TOF) stimulation,
iii. Tetanic stimulation,

iv. Post-tetanic count (PTC) stimulation,
v. Double-burst stimulation.

(i) Single twitch stimulation

In a single twitch stimulation, a single supramaximal electrical stimulus of frequency 1 to 0.1 Hz (one stimulation after every 1 to 10 seconds) is generally used. After very intense or complete neuromuscular block (100%) by depolarising or non-depolarising muscle relaxants, there will be no initial response to any electrical stimulus (whatever may be the intensity) and this phase is called as the 'period of no response'. Then, when the block gradually dissipates from its 100% intensity or after incomplete paralysis by non-depolarising agents after its administration, the evoked contraction response to a single-twitch stimulation is small or even incomplete and there is successive fade in response during successive single-twitch stimuli. In contrast, during progress of block to no response phase after administration of depolarising muscle relaxing agent or during dissipation of depolarising block from its 100% intense block (i.e. from the phase of no response period), there is a well sustained response (no fade) to successive single-twitch stimulus.

(ii) Train-of-four (TOF) stimulation

In TOF stimulation, four successive single-twitch supramaximal stimuli of 0.02 millisecond (200 µs) duration are given at an interval of 0.5 second, i.e. at a frequency of 2 Hz (0.1 Hz = 1 impulse in 10 seconds, 1.0 Hz = 10 impulses in 10 seconds or one impulse every second, 2 Hz = 20 impulses in 10 seconds, i.e. one impulse every 0.5 second) and each stimulus causes the muscles to contract. In a normal condition before a muscle relaxant is administered, all the four evoked responses are ideally the same, i.e. the TOF ratio (dividing the amplitude of the fourth response by the amplitude of the first response provides the TOF ratio) is one. During intense or 100% complete neuromuscular block (both by depolarising and nondepolarising agents), there is no evoked muscular contraction response to TOF. This phase is called the 'period of no response' and indicates intense or near about 100% block. After administration of nondepolarising muscle relaxant when the intensity of block is gradually increased, then the TOF response shows the characteristic fade (i.e. the amplitude of response gradually decreases and the 4th response disappears) and is inversely proportional to the degree of block. Disappearance of the fourth response indicates > 75% block, the disappearance of third response indicates > 80% block and the disappearance of second response indicates > 90% block. When there is no response the even first stimulus, then the block is 100%. Surgical relaxation usually requires 70 to 90% neuromuscular block. Sometimes, it is difficult to estimate the train-of-four ratio. So, it is more convenient to visually observe the sequential disappearance of muscle responses or twitches, as this also correlates well with the degree of block.

After the administration of muscle relaxant in an intubating dose, intense neuromuscular blockade occurs initially. In this phase, the patient is intubated. In this intense phase of blockade (100%), there is no response to any stimulus of TOF or single-twitch stimulation or any other type of electrical stimulation. Duration of this no - response period depends on the type of muscle relaxant, the dose and the sensitivity of the patient to that drug. After this phase which lasts only for a few minutes, a single response appears first after TOF stimulation. Surgical relaxation phase begins now and surgery is started. Gradually 2nd, 3rd and 4th responses appear to TOF stimulation and a good correlation exists between the degree of neuromuscular blockade and the number of responses reappearing to TOF stimulation. When only one response appears against the four stimulus of TOF, then, the block is 90 to 95% and when all the four responses appear the block is 60 to 85%. The presence of one or two responses by TOF stimulus indicates sufficient relaxation for most surgical procedures. The reversal of neuromuscular block should not be attempted, when it is in intense or in no-response phase. Reversal should be tried when at least two or preferably three responses appear by TOF stimulation. Reversal in the intense phase will often be inadequate, regardless of the dose of reversal (Fig. 22.1).

The appearance of 4th response in TOF stimulation heralds the recovery phase. When the TOF ratio is more or less 0.4, the tidal volume is normal. But the vital capacity and inspiratory force are below the normal and the patient cannot raise his head or arm. When the TOF ratio is around 0.6, the patient can lift the head for 3 seconds, but vital capacity and inspiratory force are still below the normal. At a TOF ratio around 0.7, the patient can lift

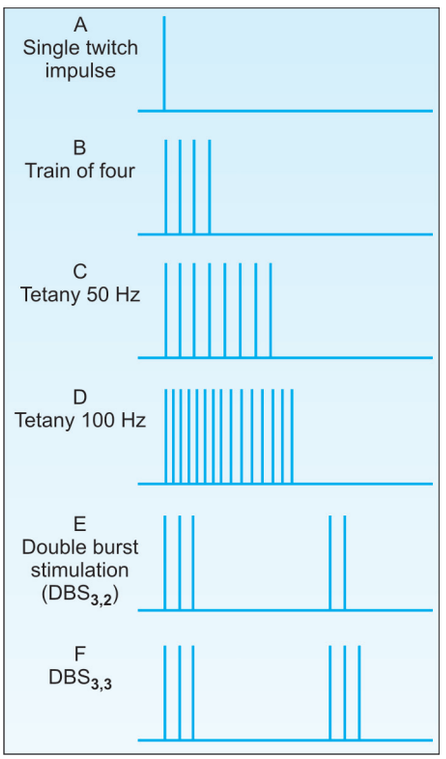


Fig. 22.1: Schematic diagram of the various patterns of electrical stimulus for monitoring of neuromuscular function

the head for 5 seconds, cough, protrude the tongue and open his eyes. Vital capacity and inspiratory force become normal at TOF ratio of 0.8. Adequate recovery from neuromuscular block in clinical anaesthesia is considered when TOF ratio varies between 0.5 to 0.7. TOF ratio of 0.8 indicates absence of residual neuromuscular block.

During a depolarising neuromuscular block (phase I) in the intense phase (100% block), there is no response to TOF stimulus like the nondepolarising muscle relaxant. Then, when the intense phase gradually dissipates, the response to TOF stimulus starts to appear, but does not show the characteristic fade, instead shows a sustained response, though of low intensity. In contrast, when some patients who have genetically determined abnormal plasma cholinesterase activity, are given the same dose of succinylcholine, then they show a non-depolarising like block, characterised by fade in the response to TOF stimulus. Such a block is called the phase II block. Also, when succinylcholine is given at repeated intervals, or by prolonged infusion, then phase II block also sometimes precipitates (Fig. 22.2).

Phase II block, due to prolonged infusion of succinylcholine in normal genotype, should be differentiated from phase II block due to abnormal genotype (with abnormal cholinesterase activity). Phase II block with normal genotype can be reversed by cholinesterase inhibitors. But the effect of cholinesterase inhibitors in phase II block with abnormal genotype is unpredictable and should not be used or used with extreme caution. This unpredictability can vary from re-potentiation of block to temporary improvement to full reversal. So, even if the neuromuscular function improves promptly, still patient's surveillance should continue for at least an hour.

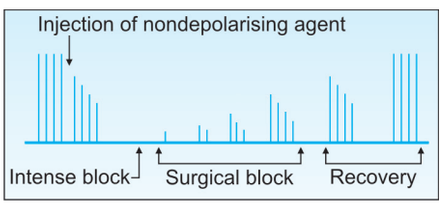


Fig. 22.2: Schematic diagram of changes in response to TOF stimulation during block, and recovery from nondepolarising muscle relaxants

The advantages of TOF stimulation in monitoring neuromuscular block is that the degree of block can be read directly from the TOF ratio, even though a preoperative value is lacking. It is less painful and does not affect the degree of block, like tetanic stimulation. It has a great advantage mainly during non-depolarising block.

(iii) Tetanic stimulation

The tetanic stimulation consists of multiple and very rapid single – twitch electrical stimulation given successively. It is commonly used at a frequency of 50 to 100 Hz for 5 seconds (1 Hz = 10 stimuli in 10 seconds. So 50 Hz = 500 stimuli in 10 seconds. So duration of every stimulus is 20 milliseconds). The effect or evoked response of tetanic stimulation on the normal muscle is a sustained contraction, without post-tetanic facilitation or fade. The effect of tetanic stimulation on a depolarising block is same as that of normal muscle, i.e sustained contraction but of low amplitude (according to the intensity of block, no response when block is 100%) and no post-tetanic facilitation or fade (when muscular response is found with <100% block). During nondepolarising and phase II block, when the block is intense, then obviously there is no response to tetanic stimulation like the single twitch and TOF stimulation (period of no response). When intensity of block progresses after the administration of the muscle relaxant, then the response to tetanic stimulation also shows the gradual fade and post-tetanic facilitation which ultimately shows no response with 100% block. Similarly, with the passage of time when the intense block gradually disappears after the no response phase, then the response to tetanic stimulation with fade and post-tetanic facilitation reappears. Thus, in nondepolarizing and phase II block the response to tetanic stimulation is not sustained but fade occurs and post-tetanic facilitation is seen (Fig. 22.3).

Probable mechanism of 'fade'

In normal circumstances when tetanic stimulation is given, then a large amount of ACh is released from the stored site. This causes depletion of the store of ACh and so its release gradually decreases. Thus, at the end of the process of tetanic stimulation an equilibrium is settled, when the release and synthesis of ACh becomes equal. At this stage of equilibrium, muscle response to tetanic stimulation is still sustained and does not show any fade. This is simply because the amount of ACh and the number of post-synaptic receptors where ACh acts is much greater than what is necessary to evoke a response. It means that there is a great margin of safety at the post-synaptic membrane. When this margin of safety is reduced by nondepolarising neuromuscular blocking agents, or phase II block, then the decrease in release of ACh during tetanic stimulation produces 'fade'.

Another explanation of fade is that it may be due to the prejunctional effect of nondepolarising agents. It reduces the amount of Ach available for release at the nerve terminals during stimulation. This is called blockade of ACh mobilisation. The absence of fade in case of nondepolarising neuromuscular block correlates well with clinical recovery. Fade is more obvious during double-burst or sustained tetanic stimulation, than following repeated single-twitch stimulation or TOF stimulus. So, the first two methods are more preferred to determine the adequacy of recovery.

The post-tetanic increase in twitch response is called the post-tetanic facilitation. This is due to the increase in synthesis and mobilization of ACh, caused by a tetanic stimulation which continues for

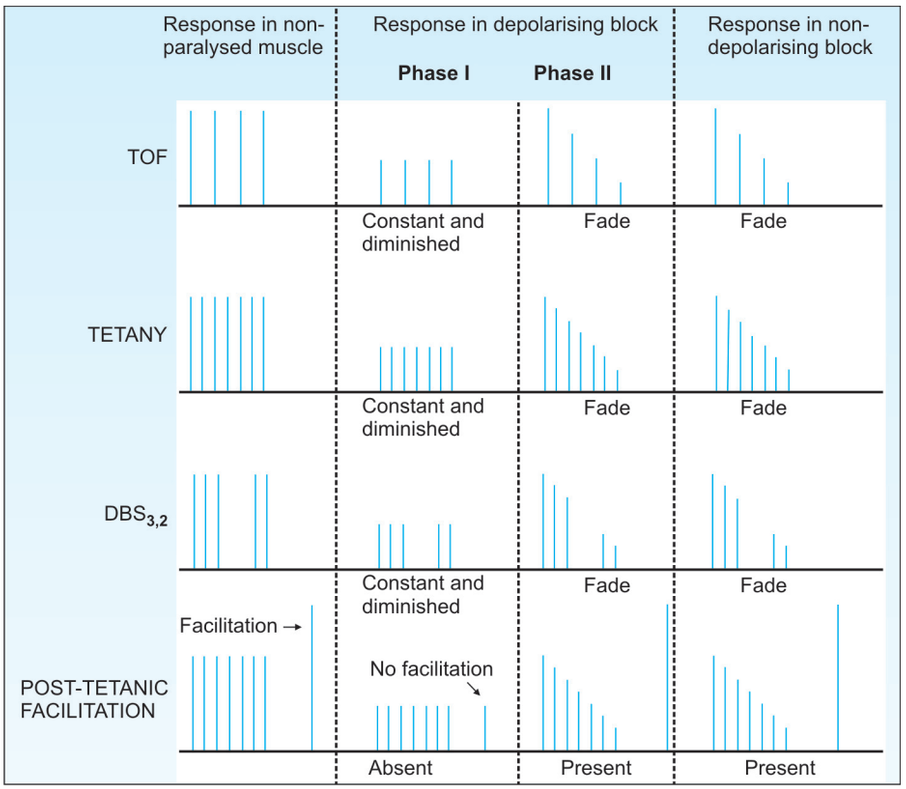


Fig. 22.3: This schematic diagram shows the different responses of muscle to different stimuli in nonparalysed state and both depolarising and nondepolarising blocks

sometime, even after discontinuation of the stimulus. The degree and duration of post-tetanic facilitation depends on the degree of neuromuscular block by nondepolarising agents. It is evident in partial depolarising block and disappears within 60 seconds of tetanic stimulation.

The disadvantages of tetanic stimulation is that it is very painful and cannot be used in an unanaesthetised patient. Tetanic stimulation has very little place in everyday clinical anaesthesia practise, because all the information can be easily obtained from TOF nerve stimulation response.

(iv) Post-tetanic count (PTC) stimulation

After administration of large intubating dose of a non-depolarising muscle relaxant during rapid sequence intubation, intense muscular block (100%) occurs in which single-twitch, TOF, tetanic stimulation or any type of stimulation does not create any response (no-response phase). So, to know the degree of block in this intense no response phase the post tetanic count stimulation method is used. However during very, very intense block, there is no response to post-tetanic stimulation also. As the intensity of block gradually dissipates and before the first response to TOF stimulation reappears, the response to single-twitch stimulation after a tetanic stimulation (so called post-tetanic stimulation) appears. Then, with the passing of time the number of responses to a single-twitch stimulus after a tetanic stimulus gradually increases and is counted. Increase in the number of count indicates the gradually waning of block, and the first single response to TOF stimulus will occur. As the block further wanes, the consecutive four responses to TOF stimulation arise. So, the post-tetanic count (PTC) stimulation is used to quantify the intensity of no response phase of neuromuscular block of the peripheral muscles, when the other types of stimuli (single twitch, TOF, tetanic) fail to respond in the 'no-response phase'. The PTC is used by applying tetanic stimulation (50 Hz for 5 secs), and then observing the post tetanic response to a single twitch stimulation, given at 1 Hz frequency and 3 seconds after the end of tetanic stimulation.

(v) Double-burst stimulation (DBS)

Without a recording instrument, muscular response to a stimulus (single-twitch, TOF or PTC) cannot be visualized or felt by any tactile means, which may help to evaluate or exclude the small degree of residual neuromuscular block. So, DBS was developed with the specific aim of allowing manual detection of small amounts of residual neuromuscular block, after recovery. With DBS, it is easier to feel 'fade' in the response.

DBS consists of two short bursts of high frequency tetanic stimulation at an interval of 780 milliseconds. It represents two variations. The $DBS_{3,3}$ pattern consists of three short (0.2 milliseconds or 200 µs duration) high frequency tetanic bursts, separated by an interval of 20 milliseconds (50 Hz), followed by another three bursts, 750 milliseconds later. $DBS_{3,2}$ consists of three 50 Hz impulses of 0.2 milliseconds duration, followed by two such impulses, 750 milliseconds later. The $DBS_{3,3}$ pattern is more in clinical use than the $DBS_{3,2}$ pattern. It is more sensitive than TOF stimulation for clinical (i.e. visual) evaluation of fade. In control study, the feel of two muscle contractions in response to DBS is equal. In a paralysed condition, the second response is weaker than the first (i.e. 'fade'), which can be felt easily. Thus, absence of fade in response to DBS usually means absence of clinically significant residual neuromuscular blockade. Measured mechanically, the TOF ratio correlates closely well with the DBS. The feeling and tactile evaluation of response to DBS, is superior to the tactile evaluation of response to TOF stimulation.

Recording of Evoked Response

By three methods we can record and measure the evoked muscular response to a stimulus.

i. Recording of evoked mechanical response of muscle (i.e. contraction) to stimulus (mechanomyography).
ii. Recording of evoked electrical response of muscle to stimulus (electromyography).
iii. Recording of evoked acceleration response of muscle to stimulus (accelero-myography).

(i) Mechanomyography (MG)

Here, the evoked contraction response developed by the muscle due to a stimulus is recorded and measured. This is most easily achieved in clinical anaesthesia by measuring the thumb movement due to electrical stimulation. When the ulnar nerve is stimulated by a nerve stimulator, the adductor policis muscle of thumb contracts and acts on a force displacement transducer which converts this mechanical force into an electrical signal. Then this signal is amplified, displayed and recorded.

(ii) Electromyography (EMG)

Here, the compound action potential of muscular contraction, produced by stimulation of a peripheral nerve is recorded. In clinical anaesthesia, the evoked electrical response from contraction of a muscle is most often obtained from the muscles of thenar and hypothenar eminences of hand innervated by the ulnar or the median nerve. Both the surface or needle electrodes can be used, but the needle electrodes have no extra advantage over the surface electrodes. In commercially available machines for evoked EMG, the results are displayed either as a percentage of control or as a TOF ratio and the results may also be given as 'twitch height' in the print-out.

Advantages of EMG over MG are:

i. Easier to set up,
ii. Response reflects only those factors which influence the neuromuscular transmission,
iii. Response can also be obtained from muscles which are not accessible to mechanical recording.

Disadvatages of EMG are:

i. EMG response is very sensitive to electrical interference, i.e. diathermy.
ii. Placement of electrodes is very critical and may cause false negative results with slightest variations.
iii. If the stimulating electrodes lie closer to the muscle than the nerve, then the muscle is stimulated directly and the recording electrode picks up the signal directly from the muscle even when neuromuscular transmission is completely blocked.

(iii) Acceleromyography (AMG)

It is a newer and simpler method of measuring and recording the neuromuscular function. It measures the acceleration of contraction of thumb muscles instead of force produced by contraction of muscle, after stimulation of a motor nerve. When the muscle mass of thumb is fixed, then the acceleration of contraction of thumb muscle is directly proportional to the force of contraction (Newton's second law) and this evoked acceleration of contraction, is measured. In clinical practice an accelerometer is fixed to thumb and the ulnar nerve is stimulated. Then the exposure of electrode of an accelerometer to the force of contraction of muscle generates an electrical voltage which is proportional to the acceleration of contraction of thumb muscles in response to nerve stimulation. This voltage signal is then analysed and displayed on a recording system.

It is a small handy instrument which fulfills most of the requirements of a neuromuscular monitoring unit and so, is used routinely during and after operation.

Stimulating Electrodes

The electrodes which transmit electrical impulses from a stimulator to a nerve are classified into surface electrodes and needle electrodes. Surface electrodes are most commonly used and are made up of rubber or disposable pregelled silver chloride like the ECG electrodes. The minimum conducting area of an electrode for monitoring of neuromuscular block should be 7 to 8 mm in diameter which is needed to transmit adequate current for the underlying nerve. Skin should be properly cleaned before using the electrodes and the old rubber electrodes should not be reused as it increases impedance.

Needle electrodes are used when the supramaximal responses cannot be obtained by surface electrodes. The needles should be placed subcutaneously and not within the nerve. If specially coated commercially made needle electrodes are not available, then the ordinary steel needles made for injection can also be used as electrodes.

MONITORING OF THE RESPIRATORY SYSTEM

Introduction

During anaesthesia, in addition to its normal function, i.e. O_2 uptake and CO_2 excretion, the respiratory system also transfers the inhalational anaesthetic agents into the circulation. So, the function of respiratory system can be monitored clinically by examination of patient and also instrumentally by measuring the different volumes and capacity of lungs during ventilation, the concentration of gases in inspiratory and expiratory gas mixture, and the tension of different gases in blood by blood gas analysis.

The measurement of total minute ventilation is simple. But, the more relevant portion of minute volume, i.e. alveolar ventilation is much more difficult to measure. The alveolar ventilation can be considered as a relatively fixed portion of minute volume. Because the physiological dead space, which is invariably increased during anaesthesia, remains a reasonably constant fraction of the tidal volume.

Over a wide range of tidal volume, the alveolar ventilation can be calculated from the equation which is written as:

$$V_A = V_E - V_D$$

V_A = Alveolar ventilation,
V_E = Respiratory minute volume (or minute ventilation),
V_D = Dead space ventilation.

The alveolar ventilation can also be calculated from PCO_2 of the exhaled gases, or alveolar PCO_2 (P_ACO_2) and arterial PCO_2 (P_aCO_2) from the following equation :

$P_ACO_2 = K (P_aCO_2 / V_A)$

So, if the PCO_2 of the exhaled gas (P_ACO_2) is known in relation to the arterial PCO_2 (P_aCO_2), then the alveolar ventilation can be calculated from the above equation.

The alveolar ventilation can also be calculated from another equation.

$P_ACO_2 = K (Vco_2/V_A)$, Vco_2 = CO_2 production

In this equation, P_ACO_2 is a function of only two variables. Since in clinical practice, the Vco_2 is relatively constant, therefore P_ACO_2 is only the determinant factor of alveolar ventilation (V_A), to which it is inversely proportional, i.e.

$P_ACO_2 \propto 1/V_A$

So, measurement of the end tidal CO_2 tension (P_tCO_2), which indicates P_ACO_2 is another way of monitoring the function of respiratory system.

Till now, the relationship between P_ACO_2 and ventilation has been discussed. Now, the relationship between P_aCO_2 and P_ACO_2 shall be discussed. If the CO_2 production remains constant, then the difference between P_ACO_2 and P_aCO_2 is dependent on the following factors, such as: (i) diffusion non equilibrium, (ii) ventilation / perfusion (V_A/Q) mismatching, and (iii) right to left shunting.

Diffusion non-equilibrium

It is the difference between the pulmonary capillary blood CO_2 tension and the P_ACO_2. This can occur under two conditions: (i) increased pulmonary blood flow to a level such that the blood lacks sufficient time in the alveoli, disabling gas tension to reach its equilibrium, and (ii) thickening of the alveolar capillary membrane, such that the rate of diffusion of gas from capillary to alveolus is slowed. In practice, there has never been any evidence of diffusion non-equilibrium for CO_2. Similarly, diffusion non-equilibrium of O_2 very rarely exists. It exists in patients with intestinal fibrosis or in patients with normal lung function, but undergo severe exercise.

V_A/Q mismatch

The CO_2 dissociation curve in blood is a monotonically increasing one. Therefore, it is possible for a lung unit with low P_ACO_2 to compensate for lung units with high P_ACO_2, producing a normal P_aCO_2 in the face of substantial V_A/Q mismatch. On the otherhand, unlike the CO_2 dissociation curve, the O_2 dissociation curve in blood has a plateau at the point at which Hb is fully saturated. Therefore, V_A/Q mismatch always results in arterial hypoxaemia, but not hypercarbia.

Right to left shunt

Discussed elsewhere.

Clinical Monitoring of Respiratory System

The continuous direct clinical observation of the colour of a patient (such as the mucous membrane, skin, lips, colour of blood, etc.), the respiratory rate of it, the movement of chest and breathing bag etc. help us to judge the adequacy of ventilation. The colour of mucus membrane of a patient can be used to assess the oxygenation. But anaemia, polycythemia, changes in the shape of O_2 dissociation curve, or poor lighting may lead to mistakes. Different anaesthetic agents, sedatives and opioid analgesics are potent depressants of respiration. Thus, hypoxic brain damage can occur in a few minutes if the respiratory system of a patient is not monitored properly and treated efficiently. So, in cases where the anaesthetised patient is breathing spontaneously, then a constant observation of patient by the anaesthetist is needed to detect any tracheal tug, paradoxical chest movement or failure of the reservoir bag to move adequately etc. Because, it indicates partial or complete airway obstruction.

Free passage of air through airways can also be confirmed clinically by hearing the sound of clear airflow through the nose or the mouth. It also can be confirmed by feeling the warmth of expired air at the back of the hand if it is placed by the anaesthetist himself. Snoring, rattles or complete silence indicates impending or complete airway obstruction. Maintaining a clear airway in an anaesthetised patient is a great skill. It requires much practice with constant vigilance to every detail and a pair of strong forearm muscles to push the mandible upwards and forwards towards floor in a nonintubated patient. Clinically, periodic auscultation of chest by a stethoscope also confirms the position of endotracheal tube and detects any accumulation of secretions, pneumothorax or bronchospasm, if present. Thus, we can ensure the monitoring of respiratory system clinically.

Monitoring of the Respiratory Function by Precordial and Oesophageal Stethoscope

Many anaesthetists still believe that during anaesthesia a patient's respiratory system should be monitored by a precordial or oesophageal stethoscope even in the presence of many electronic gadgets. But, though they (precordial stethoscope and oesophageal stethoscope) have many advantages, still they are being gradually replaced by modern pulse-oximetry and capnography for better bedside monitoring of the respiratory function. Oesophageal stethoscope is a very simple, cheap and much informative instrument for clinical monitoring of respiratory system. It has the advantage of ensuring that the anaesthetist stays in close contact with the patient. It is a small balloon-tipped probe that is inserted into the oesophagus through mouth and connected to

either a standard stethoscope head-piece or a moulded ear-piece. When the length of an oesophageal stethoscope has been adjusted so that the balloon is opposite to the heart, then it also provides a constant monitoring of heart rate and breath sounds together. It is especially very useful in children, because it may detect any air embolism by hearing the characteristic mill-wheel murmur. By a precordial or oesophageal stethoscope we can also detect the bronchospasm, moist sounds, or any other adventitious sound of the lungs early, before it is reflected through pulse-oximetry and capnography. ECG leads, pacemaker electrodes, temperature probe and/or ultrasound probe for continuous intraoperative oesophageal echocardiography can also be incorporated with the oesophageal stethoscope. The information provided by the precordial or oesophageal stethoscope are: confirmation of ventilation, quality of breath sound, confirmation of heart beat (even when there are multiple artefacts in cadiac monitors) and quality heart sound (a soft tone is associated with hypotension and low cardiac output). The main disadvantages of oesophageal stethoscope are that it can not confirm the bilateral equal breath sound after endotracheal intubation or cannot exclude the bronchial intubation. It should be avoided in patients with oesophageal varices or strictures.

Monitoring of the Respiratory System by Measuring the Respiratory Rate, Airway Pressure, Tidal Volume and Disconnection Alarm

Measurement of respiratory rate

It is usually measured clinically. It can also be obtained from the capnograph or continuous ECG monitor. When the ECG leads are used to monitor the respiratory rate, then a very high frequency electrical current is passed accross the thorax of patient from the chest electrodes and then the electrical impedance which changes cyclically with respiratory movement is measured. From this cyclical changes of electrical impedance, the respiratory rate is calculated and displayed.

Measurement of airway pressure

High airway pressure may cause damage to the alveoli, reduce the cardiac output and predispose to pneumothorax in all patients receiving positive pressure ventilation. So, the airway pressure should be measured continuously or intermittently. The airway pressure is usually measured by simple mechanical pressure gauges or electronic gadgets which are attached to the ventilators or even to the Boyel's machine. However, the narrow tracheal tube, long breathing system or high respiratory rate may not accurately reflect the correct airway pressure measured by the mechanical gauges.

Airway pressure is increased due to bronchospasm, pulmonary oedema, pneumothorax (↓lung compliance), head down position, reversal of neuromuscular block, laparoscopy (↓ thoracic compliance), plug of airway by sputum, or kinked tracheal tube (equipment problem) etc. On the otherhand, airway pressure is suddenly decreased due to disconnection of breathing system, any leak in the circuit or empty cylinder (Table 22.1).

Table 22.1: Causes of changes in airway pressure

A.	*Causes of increase in pressure*
	Bronchospasm
	Pneumothorax
	Pulmonary oedema
	ARDS
	Less surfactant
	Consolidation and collapse
	Reversal of neuromuscular paralysis
	Laparoscopy
	Head down tilt
	Kinking of breathing tube
	Plug of sputum
B.	*Causes of decrease in pressure*
	Sudden disconnection
	Low gas flow

Measurement of tidal volume

The measurement of tidal volume is an important way of monitoring the function of respiratory system. It confirms the ventilation of patient and optimises the ventilator settings. For the measurement of tidal volume by bedside method, spirometer has been used for many years. But, although this device is small and provides accurate result, still it has some disadvantages. The disadvantages are: (i) water vapour in expired air causes inaccuracies, (ii) weight of spirometer dictates its use at the machine end of breathing circuit, resulting in in accurate result (iii) its use is restricted mainly to the circle system when the volume of expired gas is measured as tidal volume, (iv) its tendency to under-read at low tidal volume and over-read at high tidal volume.

In modern tidal volume monitors there is a small connector which is attached to the ET tube. Two tubes lead from this connector to the pressor sensors which is situated in the body of main TV monitor. Measurement of small, differential pressure changes between the two tubes allows the calculation of airway pressure and inspired-expired tidal volume. The modern anaesthetic machines which have an integrated circuit and ventilator have hot-wire anemometer for measurement of tidal volume. It uses an electrically heated hot wire, placed across the flow of air. Airflow cools the wire and thus decreases its electrical resistance, from where the amount of airflow during each breath (tidal volume) can be calculated. These devices are simple and reliable. But, they are delicate enough and need great protection.

Most multi-monitors now have the facility to integrate the measurement of flow, pressure and time in order to produce the real-time measurement of compliance, flow-volume loops and pressure-volume

loops along with the tidal volumes and other parameters of lung volume. These displays are especially useful in patients whose lungs are difficult to ventilate. It is also helpful where there are rapid changes in compliance of lungs, such as during one-lung anaesthesia.

Disconnection alarm

Most breathing systems have a disconnection alarm, as they have multiple connections which are dislodged easily, causing failure of ventilation and harm to the patient. Disconnection alarm detects the cyclical changes in airway pressure and gives an alarm if there is any unexpected change (high or low) in pressure during ventilation. They are usually battery-powered and some need to have the alarm limits, set manually. But most, automatically detect the normal range, and then sets off an alarm if any significant change in respiratory rate, tidal volume or airway pressure occurs. They may also set off an alarm, if high airway pressure is sensed somewhere.

Monitoring of Respiratory System by the Measurement of Quantity of O_2 in Blood

One of the most important function of respiratory system is the delivery of O_2 from air to blood. So, the measurement of O_2 level in blood by measuring the oxygenation saturation, oxygen tension, total oxygen content, mixed venous O_2 tension, etc. are among the some methods of monitoring the respiratory function.

Measurement of oxygen saturation in blood

The O_2 saturation of blood is usually measured noninvasively by pulse oximeters which works on the principles of oximetry and plethysmography.

Oximetry

When light passes through a solute dissolved in solvent, then it is partly transmitted, partly absorbed and partly reflected back which depends on the concentration of solute. This principle of transmission, absorption and reflection of light is used in several monitoring devices to estimate the concentration of this dissolved solutes. In an oximeter, absorption of infrared light is used to estimate the concentration of oxy-Hb (as solute) which remains in plasma (solvent) by using Beer-Lambert's law.

The Beer's law dictates that the solvent (e.g plasma) is transparent to a particular frequency of light which is used for oximetry. Whereas, the solute (haemoglobin – reduced or oxy) absorbs this light and that absorption is directly proportional to the concentration of Hb.

On the other hand, the Lambert's law states that when a beam of light falls on a semitransparent, homogeneous substance, then due to absorption the intensity of transmitted light decreases exponentially, as the distance travelled through the solute increases and is proportional to the distance. So, the two laws (i.e. Beer and Lambert laws) can be combined and reproduced as:

$A = d\ c\ E$ ..... (1)

A = Absorbance of the light,

d = Distance,

c = Concentration of the solute,

E = Absorption coefficent of the solute, which is constant for a given molecular weight and specified wavelength of a light.

The absorption coefficients of the most common four types of Hb [oxyhaemoglobin (O_2 Hb), carboxyhaemoglobin (COHb), methaemoglobin (metHb) and reduced haemoglobin (HHb)] at the working range of wavelength of red and infrared light which are used for oximetry are obtained from a graph which is given next. So, for the four types of Hb, the equation will be:

$A = d\ (C_1E_1 + C_2E_2 + C_3E_3 + C_4E_4)$ ..... (2)

The normal blood contains nil or negligible amount of MetHb and COHb, and they do not take part in O_2 carrying. In a normal individual the blood contains mainly the reduced Hb and OxyHb which takes part in transport O_2. So, to measure the O_2 saturation we can shorten the equation (2) to equation (3) by measuring the absorption of light by the only two relevant haemoglobin such as oxy and reduced.

$A = d\ (C_1E_1 + C_2E_2)$ ..... (3)

So, if the MetHb and COHb were not present in the blood sample, then the concentration of O_2Hb and HHb, i.e. C_1 and C_2 could be determined by using the light of two wavelengths only instead of four wavelengths which is required to measure the concentration of 4 types of Hb.

From the figure, it is observed that at a wavelength of 800 nm of a light, the coefficent for O_2Hb and reduced Hb are the same. So, if an oximeter uses this wavelength of light and no MetHb or COHb were present, then the equation would be reduced to:

$A = d\ E_{800}\ (C_1 + C_2)$

Thus, the total sum of OxyHb and reduced Hb could be determined by using the light of a single wavelength only. Using lights of two wavelengths, the concentration of the two types of Hb can be determined separately and from there the percentage of individual Hb may be calculated easily.

So, the percentage of saturation of total Hb by the O_2 is:

$O_2Hb/\text{Total Hb}\ (O_2Hb + HHb) \times 100$

This is the value of SPO_2 in percentage, where S stands for saturation and P stands for pulsatile. Certain other abbreviations related to it are: SaO_2 = arterial O_2 saturation and SVO_2 = venous O_2 saturation. The abbreviation SPO_2 is used, because the oximeter can not differentiate an artery from a vein, but can only recognize the O_2 saturation of pulsatile tissues which is usually of the arterial system, i.e. capillary. So, practically the SPO_2 and SaO_2 are equivalent. This Beer-Lambert's law can also be applied to measure the concentration of other mixture of gases and vapour in blood.

If in any pathological condition, the concentration of MetHb and COHb increases, then the equation will be :

$SpO_2 = [O_2Hb / (O_2Hb + HHb + MetHb + COHb] \times 100\%$

Now, we are considering the equation (2). If absorbance is measured by a single light of a specific wavelength (h), and the coefficient for the four types of Hb at that wavelength is known from the graph, then the preceeding equation would contain four unknowns: C_1, C_2, C_3, C_4 (as E_1, E_2, E_3, E_4 are known from graph). So, to solve this problem of four unknowns the light of four different wavelengths are needed. Similarly, to know the two unknown such as C_1 and C_2 in equation (3) we need two lights of different wavelength, considering that CoHb and metHb is absent in blood. *In vitro,* the concentration of four or more types of Hb is measured by laboratory oximeters which use light of four or more wavelengths passing through a cuvette, filled with a solution of lysed red blood cells (Fig. 22.4).

Therefore, theoretically, an oximeter will require light of four different wavelengths to measure the fractional saturation of each type of haemoglobin, otherwise it may lead to erroneous results. But, this is not available clinically.

In clinical non-invasive oximetry the red and infrared lights of two separate wavelengths are transmitted through a tissue bed. There are many light absorbers, i.e. different types of tissues are present in the path of transmitted light. These are skin, soft tissues, muscles, bones, venous blood, etc. (nonpulsatile part), and the arterial or capillary blood (pulsatile part). But, the pulse oximetry does not take into account the effect of absorption of light by these non pulsatile tissue, because by some intelligent calculation it is deducted from pulsatile tissue, which is described later (Fig. 22.5).

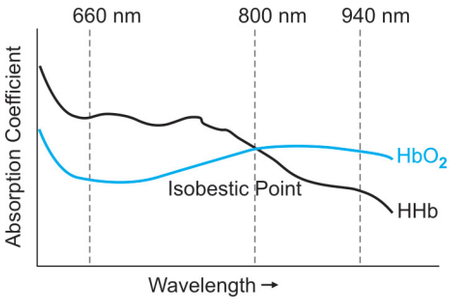


Fig. 22.5: Absorption spectra of oxy and reduced haemoglobin. For two types of Hb, two lights of different wavelengths (660 nm and 940 nm) are needed to get their absorption coefficient, respectively. By the light with a wavelength of 800 nm, we get a single coefficient, where the respective coefficients of HbO_2 and HHb are same and measures the total Hb

On one side of the probe which is used in pulse oximeter, there are two light emitting diodes (LED) which release red (660 nm) and infrared (940 nm) light respectively. On the other side of the probe there is a photo cell which detects the transmitted light after passing through the tissues and its absorption. The electrical output from the photodetector or cell consists of a steady signal (X), which results from the absorption of light by the non-pulsatile tissues, such as, bones, muscles, fat, venous blood, etc. On this steady nonpulsatile signal, a pulsatile signal (Y) is superimposed, resulting from the absorption of light by the pulsatile arterial or capillary blood, coming in the light-path. These two raw signals of which one is nonpulsatile and another pulsatile are then processed complexly by the microprocessor. The Y component is measured relative to the X component which is independent of the intensity of incident light. Then the ratio (R) of amplitude of the red and infrared pulsatile signal is determined, (using an algorithm), which is related to arterial O_2 saturation.

The pulsatile expansion of the capillary arterial bed increases the length of absorption path and thereby increases the absorption. As pulse-oximetry uses only two wavelengths of light – red light (660 nm) and infrared light (940 nm), so the pulse-oximeter first determines the Y component of absorption at each wave length, and then divides this value by the corresponding X component of absorption at each wavelength to obtain a 'pulse-added' absorption. The oximeter, then, calculates the ratio (R) of this 'pulse added' absorption which is emperically related to the percentage of arterial O_2 saturation (SaO_2).

$R = (Y_{660} / X_{660}) / (Y_{940} / X_{940})$

$= (Y_{660} / Y_{940}) \times (X_{940} / X_{660})$

Y_{660} / Y_{940} = Ratio of pulsatile components of absorption at 660 and 940 nm of wave-length.

X_{940}/X_{660} = Ratio of non-pulsatile components of absorption at 940 and 660 nm of wavelength (Fig. 22.6).

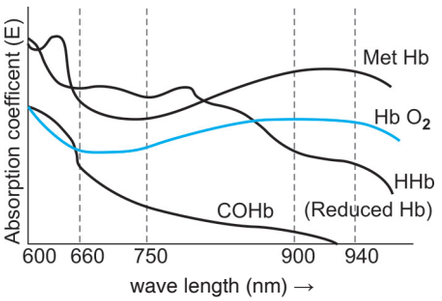


Fig. 22.4: Coefficients are plotted against the transmitted light absorption spectrum in the wavelength range, of the four species of Hb

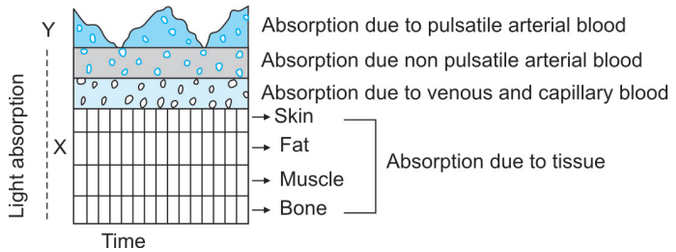


Fig. 22.6: Diagrammatic representation of the absorption of light by a living tissue. Arterial blood is the only pulsatile component of all the light absorbers in living tissues – Y components. The X component represents all the non pulsatile absorbers

The curves used in different commercial devices are prepared by different companies. These are based on the experimental studies, conducted by the companies on different group of human volunteers. Although, each curve is the property of this manufacturer, but the system being used is similar. So, the curves are very similar. For example, when the ratio of red to infrared absorbance is 1, the saturation of O_2 is 85% for all the machines.

For the best sensitivity, the difference between the ratio of absorption of red and infrared light by HbO_2 (oxy-haemoglobin) and HHb (reduced haemoglobin) at the two wavelengths should be maximised. At a wavelength of 660 nm the HbO_2 absorbs light 10 times less than reduced Hb and at a wavelength of 940 nm the absorption coefficient of HbO_2 is much greater than that of reduced haemoglobin (HHb).

Ear oximeter (which acts on the principle of simple oximetry, but not on pulse oximetry) has no ways of differentiating between the pulsatile arterial SO_2 of haemoglobin and nonpulsatile venous SO_2 of haemoglobin. So, it is applied on the ear with the idea that the earlobe contains predominantly arterial blood, and the reading shows the arterial SO_2. But, one cannot be sure that the earlobe contains only arterial blood. So, the other pulse oximetres, except the ear oximeter, are able to make this differentiation by assuming that the pulsatile portion of signal is entirely that of arterial blood. This is almost always true, except under unusual clinical conditions such as high venous pulsation in tricuspid regurgitation.

Pulse oximetre in practice

In practice, on one side of the probe of the pulse oximetre there is a light emitting diode (LED) which transmits two lights such as a red light at 660 nm of wavelength and an infrared light at 940 nm of wavelength from one side of the finger. It also has one photo diode, i.e. a sensing transducer on the opposite side of the finger. When the two LED are activated, it transmits two lights through the finger alternatively. Then, passing through the different tissues of finger the absorbed light on the opposite side is transduced into an electrical signal by the photo diode and is passed on to the computer. There, the ratio of absorption of these two lights by oxy- and reduced Hb is calculated electronically by a microprocessor, from where the SPO_2 is derived by an internally stored algorithm.

The measurement of SO_2 by light absorption technique was in existance for many years like ear oximeters, but it could not determine the pulsatile portion of the O_2 saturation. So, the development of pulse principle or plethysmography has increased substantially the reliability of such monitors and resulted in their extremely widespread use. However, the main drawback of this pulse oximetry is its insensitivity to the large changes in arterial PO_2 at the higher end of Hb-O_2 dissociation curve, i.e after reaching 100%, saturation it cannot be increased further with the increase in O_2 tension in blood.

In neonates when the repeated arterial puncture is not technically feasible to measure the arterial PO_2, then capillary PO_2 which is every close to arterial O_2 is measured by this pulse oximeter. But, capillary PO_2 is definitely lower than arterial PO_2. This difference can be reduced by taking capillary blood sample from prewarmed heel site, where there is abundance of local blood flow relative to the local tissue O_2 consumption. In contrast, in capillaries where PO_2 is significantly lower than arterial PO_2, but there the capillary SO_2 approximates arterial SO_2. This is because of the shallow slope of the lower part of the Hb-O_2 dissociation curve.

The other technical problems of pulse oximeter and their solutions are :

i. The LED in the probe do not emit light of a fixed wave length (monochromatic light), but usually emit light in a spectrum which should be narrow. But, certain companies use light in the range of wide spectrum. The central wavelength of this emission spectrum varies among the diodes of different manufacturers. But, this variation should not be more than 5 nm (e.g. 660 ± 5 nm). A shift in the centre of wavelength of light spectrium emitted by LED causes changes in the measured absorption coefficient and results in an error in the estimation of oxygen saturation. A light of narrow spectrum within acceptable range of wavelength increases the accuracy. If a light of wide range of wavelength for emission is used, then the pulse oximeter should be programmed accordingly to accept the centre wavelength of both the red and infrared light and also allow the device to correct internally and automatically the values for the different wave lengths. But, this will be a very costly affair.

ii. Another problem of pulse oximeter is that the photodiodes which are used opposite to the LED in the sensor probe, can not differentiate the light of different wavelengths, i.e. whether the light is coming from red, infrared or roomlight source. This problem is eliminated by alternating the red and infrared LED light sources on and off at a frequency of 100 times per second. After absorption through tissues, when the red light is on the photo diode detector, it produces a current in which roomlight also takes part. Then, similarly after absorption through tissues, when the infrared light is on the photo diode or detector, it also produces a current with the roomlight. Finally, when both the LED are turned off, then the photodiode detector produces the signal from roomlight only. Computer in the pulse oximeter eliminates all these common factors of light interference by calculating the ratio. This is a very clever design, but sometimes different sources of light

produces different artifacts which can be minimised by covering the sensor with an opaque shield.

iii. Another problem arises when the amplitude of signal ratio is very low. Usually, all the oximeters have devices to amplify their signals. But, with the amplification of signal, the noise is also amplified. So, to prevent this type of artefact a minimum value for signal to noise ratio is incorporated, below which level the device displays no value for SPO_2. Some oximeters display low-signal strength error message and some others display a plethysmographic wavelength for visual identification of noise.

iv. Patient's motion which is equivalent to high AC to DC signal ratio also produces artefacts. These artefacts are eliminated by increasing the signal averaging time (i.e., the device averages its measurements over a longer period of time). But, the longer averaging time also slows the response time to an acute change in SO_2. So, many pulse oximeters have a system to select one from several time-average modes. Some oximeters use sophisticated algorithms to identify and reject spurious signals.

Causes of errors in pulse oximetry

As clinically the pulse oximeter takes the help of two lights of two different wave lengths, so the presence of Hb species other than the reduced Hb and oxy-Hb may cause erroneous readings. In a research laboratory, the sophisticated pulse oximeter uses multiple lights of separate wave lengths and by this device this error can be reduced.

Carboxy-haemoglobin (COHb)

The carboxy-haemoglobin is formed during carbon monoxide (CO) poisoning. In the presence of COHb, there is falsely high pulse oximeter reading. When the concentration of COHb is 50%, then the pulse oximeter reading is about 95%. The probable explanation is that at 940 nm of wave length the COHb has no absorption and therefore does not contribute to total absorbance. At 660 nm of wave length, COHb has an absorbance close to that of O_2Hb. So, the O_2 saturation becomes falsely high.

Methaemoglobin (MetHb)

At 940 nm of wavelength the absorption of light by MetHb is highest among other species of Hb, and at 660 nm of wavelength the absorption of light by MetHb is very close to reduced Hb. Thus, the absorption ratio of 1:1 of methaemoglobin corresponds to O_2 saturation of 85%. Therefore, SPO_2 is falsely low when it is truely high (> 85%) and SPO_2 is falsely high when it is truely low (< 85%). Independent of actual arterial O_2 saturation, SPO_2 shows to be 85% in the presence of high MetHb concentration.

Structural Haemoglobinopathies

Absorption spectrum of HbF and HbA is more or less same. So, HbF has no major effects on pulse oximetry. There is also no significant effect of HbS on pulse oximetry. Only, it should be kept in mind that the sickle cell disease has a rightward shift of Hb-O_2 dissociation curve and, therefore, at any given P_aO_2 value, the SPO_2 will be lower than the expected.

Anaemia

Anaemia causes false negative pulse oximetry result. Polycythemia has no apparent effect on pulse oximetry.

Nail-polish

Blue nail-polish with an absorption spectrum near about 660 nm causes a false negative result. Nail polishes of other colours have minimum effects.

Jaundice

Bilirubin has no significant effect on pulse oximetry. But nonpulsatile oximetry may measure a falsely low value.

Skin

Very thick skin and deep pigmentation can result in reduced signals and cause slightly low false results. Otherwise, no significant effect is reported.

Movement

Movement, especially shivering, can falsely depress the SPO_2 reading.

Blood flow

Reduced amplitude of pulsation due to low tissue perfusion can cause difficulty in obtaining signals and thus gives a false low SPO_2 reading.

The causes of low tissue perfusion are low cardiac output, severe anaemia, hypothermia, increased systemic vascular resistance, etc. So, in addition to SPO_2 the pulse oximeter also provides an indication of tissue perfusion from pulse amplitude. Again, as SPO_2 is normally close to 100%, so only gross abnormalities are detected. Depending on a particular O_2-Hb dissociation curve in a patient, the 90% saturation reading in a pulse oximeter indicates the P_aO_2 of less than 65 mm of Hg. This compares with clinically detectable cyanosis, which requires 5 gm of reduced Hb and usually corresponds to an SPO_2 of less than 80%. In the absence of gross pulmonary diseases and low FiO_2, the bronchial intubation will usually go undetected by pulse oximeter.

Other causes

Other causes of artefacts of pulse oximetry are excessive ambient light, methylene blue dye, venous pulsation in a dependent limb, malpositioned sensor with leakage of light from LED to photodiode, bypassing arterial bed (optical shunting), etc.

Special uses of pulse oximeter

Other than the measurement of O_2 saturation in capillary blood the two special uses of pulse oximeter are: (i) measurement of mixed venous oxygen saturation (SVO_2), and (ii) non-invasive brain oximetry. SVO_2 continuously varies with the changes of

Hb concentration, cardiac output, arterial O_2 saturation and the whole body O_2 consumption. So, interpretation of SVO_2 is much informative but is very complex. It requires the placement of a PAC containing fibreoptic sensor in pulmonary artery that continuously measures the SVO_2 in a manner similar to a pulse oximeter.

A special type of noninvasive pulse oximetry can also measure the regional O_2 saturation (rSO_2) of haemoglobin in brain. Unlike ordinary pulse oximetry, it measures the venous, capillary and arterial blood O_2 saturation of brain tissue and represents an average reading. So, it is helpful to know the O_2 status or circulation of the brain during hypothermia, cerebral embolism, hypotension, hypoxia, etc,. where there is a dramatic decrease of rSO_2. In this type of special noninvasive pulse oximetry, a sensor is placed on the forehead which emits light of a specific wavelength and then measures the amount of reflected light after absorption by brain tissue. It works on the principal of infrared optical spectroscopy.

Measurement of O_2 Tension (PO_2) in Blood

Other than the measurement of saturation of O_2 in blood by noninvasive method, the most straightforward method of assessing the respiratory function is to measure directely the arterial O_2 tension (P_aO_2) from blood sample. This is done by the following methods.

(A) By oxygen electrode: the polarographic method

This is usually done by Clark polarographic O_2 electrode. The Clark's polarographic O_2 electrode consists of a platinum cathode and a silver anode. They are connected to a battery through a meter which measures the flow of current and this flow of current is proportional to the amount of O_2 present in solution.

As in any resistive circuit and according to the Ohm's law an increase in voltage increases the flow of current. However, this polarographhic electrochemical cell which measure the O_2 concentration or tension does not obey this Ohm's law ($E = I \times R$), but rather exhibits a plateau. That means with in certain range the increase in voltage does not increase the flow of current, but the increase in O_2 tension increases the flow of current. This is called polarogram. The platinum and silver electrodes are immersed in an electrolyte cell. A membrane, permeable to O_2 only but not to the electrolyte, covers one surface of the cell. A polarising voltage, ranging between 600 to 800 mV is applied in the circuit. O_2 diffuses through this membrane and reacts at the platinum cathode producing hydroxyl ions. For this reaction, electron is needed and it is supplied by the silver chloride anode. Thus, the reduction of O_2 which occurs at the platinum cathode corresponds with the oxidation which occurs at the silver chloride anode by the following reactions.

$$O_2 + 4\ e \rightarrow 2\ O_2^-$$
$$2\ O_2^- + 2\ H_2O \rightarrow 4\ OH^-$$
$$4\ Ag \rightarrow 4\ Ag^+ + 4\ e^-,$$
$$4\ Ag^+ + 4\ Cl^-$$

Thus multiple small cells are setup and tiny electrical circuits are generated which is dependent on the O_2 tension at the platinum cathode. The current meter measures the current produced by the consumed electrons in the reaction at the cathode and this consumption of electron is proportional to the local PO_2 (Fig. 22.7).

This polarographic method needs withdrawal of blood sample to measure PO_2. To obviate this need of drawing blood samples, intra-arterial PO_2 monitors have also been developed recently by using fibreoptic technique. This technique uses a particular property of O_2. This particular property of O_2 is to absorb energy from excited electrons of a fluorescent dye. To elevate the electrons in the dye to a higher energy state an incident light is used. These excited or highly energised electrons may then return to a lower energy level by emitting photons. Molecular O_2 by absorbing the energy inhibits this photon emission. This process of inhibition which is called fluorescent quenching is related to the concentration of O_2 and is used to measure the PO_2.

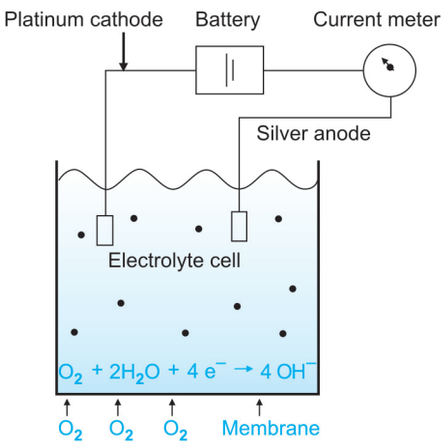


Fig. 22.7: Schematic diagram of the Clark polarographic O_2 electrometer. The circuit consists of a current meter which is connected to a platinum cathode, a silver anode, and a battery (voltage source). These electrodes are immersed in an electrolyte cell which have a membrane, permeable only to O_2 but not to the electrolytes. O_2 diffuses through the membrane and reacts with the platinum cathode. Here it receives electrons (e^-) and reacts with water and produces OH^- ion. This OH^- ion the reacts with the silver anode and gives up electrons. Thus small electrical circuit is generated. The current meter measures the current produced by these two electrodes and the concentration of O_2, which is responsible for this production of current

(B) By galvanic or fuel cell

A galvanic cell converts chemical energy (oxidation – reduction by O_2) into electrical energy and thus the generated potential is dependent on the O_2 concentration needed for the chemical reaction. At the cathode end (made by gold mesh) O_2 is reduced to hydroxyl ions by its reaction with electron and water and at the anode the lead is oxidised by removing electron. This chemical reaction produces a potential gradient and hence a flow of electrical current. This is measured and read out digitally on the screen of monitor with audible alarms. Unlike O_2

electrode in polarographic method, this fuel cell does not need any battery and is also cheap, portable and reliable. This also needs little maintenance. But, inaccurate response to calibration with O_2 and air suggests that the fuel cell is exhausted and should be replaced. The chemical reaction which takes place in fuel cell uses up the components of the cell. So, its life depends on the concentration of O_2 to which it is exposed and on the duration of exposure. Usually, a fuel cell lasts for 6 to 12 months.

(C) By transcutaneous electrodes

This is a non-invasive method of measuring PO_2 of blood. This device also consists of a small or miniaturized Clark O_2 electrode. The probe of this device is attached to the skin with an adhesive tape through a contact liquid to form an airtight seal and the area is also heated to 43°C by this probe. At this temperature the blood flow to the skin is increased and the capillary O_2 diffuses out of the skin. This allows the accurate measurement of PO_2 by the attached electrode. Actually, the measurement of PO_2 by this transcutaneous method ($PtcO_2$) reflects the capillary PO_2 which is lower than the P_aO_2. So, the skin is warmed to 43°C to increase the capillary blood flow and then $PtcO_2$ correlates well with P_aO_2. The main disadvantage of heating the probe electrically to improve the cutaneous circulation is burning of skin on prolonged use. Also, unlike the original electrode in blood-gas machine, this miniaturised probe contains only one drop of electrolyte. So, when the sensor is heated continuously to 43°C, then this elevated temperature causes the electrolyte to evaporate very quickly and reduces the life span of this device.

Peripheral vasoconstriction, thick adult skin and reduction of cardiac output causes a decrease in $PtcO_2$ level. This is because of cutaneous hypoxia due to hypoperfusion and may produce erroneous results. However, this technique is particularly useful in infants, in whom the local skin blood flow tends to be high and capillary PO_2 is as close as to the arterial PO_2 and in whom repeated drawing of arterial blood is technically difficult and may cause anaemia. Another disadvantage of transcutaneous O_2 electrodes is that the time constant of PO_2 measurement is nearly a minute. So, sudden decrease in P_aO_2 cannot be detected quickly enough to take any appropriate measure. Prolonged application may also cause skin burn. Problems also occur with surgical diathermy. Because, the heated circuit provides a return path for the cutting current which may overheat the transcutaneous electrode and cause burn.

Measurement of O_2 Content

The measurement of total O_2 content in blood is also a type of monitoring of the respiratory function. It can be measured from the value of O_2 saturation of the Hb, Hb concentration and the tension of O_2 in blood, using the formula below :

Oxygen content of blood (ml/dl) =
$[SO_2\ (\%) \times Hb(gm/dl) \times 1.34] + [0.0225 + PO_2\ (KPa)]$

The Oxygen content in blood can also be measured by Van Slyke technique, using chemical and volumetric analysis.

Measurement of Mixed Venous O_2 Saturation (SVO_2)

Mixed venous O_2 saturation is obtained from the equation

$SVO_2 = SaO_2 - [VO_2 / 13.9 \times Q \times (Hb)]$

Q = Cardiac output, [Hb] = Haemoglobin concentration,

VO_2 = Oxygen consumption.

Mixed venous O_2 saturation is decreased in circumstances where there is low SaO_2, low cardiac output, low [Hb], elevated VO_2, etc, Low SVO_2 is also found in all those conditions which produce impairment of O_2 delivery to the tissues. So, measurement of SVO_2 is very helpful in detecting any condition that may impair tissues oxygenation. The SVO_2 can be measured intermittently by taking blood sample from pulmonary artery catheter or continuously by a pulmonary artery catheter which is equipped with a fibre optic bundle and oximeter. Low level of SVO_2, usually less than 60%, may sensitively indicate an abnormality of any of the factors which are mentioned above.

Measurement of Tissue Oxygenation

Till now, the measurement of arterial oxygen level (saturation, tension or content) has been discussed which is an indicator of the status of respiratory function. But, adequate arterial oxygenation does not always indicate adequate tissue oxygenation, because there are many other factors which determine the tissue O_2 level, such as, local tissue blood flow, rate of O_2 consumption by tissues, acid base status, temperature, etc. So, for appropriate monitoring of the respiratory function of a patient, measurement of the level of O_2 in tissues or tissue-oxygenation is important.

Tissue oxygenation or O_2 level in tissues is measured by the tissue PO_2 measuring electrodes which has certain problems. These problems are :

i. Tissue destruction by electrodes,
ii. Since different tissues have different blood flow and different O_2 consumption levels. So different tissues have different PO_2 level, rather than a single standard value as in blood.
iii. Area within the same tissue, changes in oxygenation have been demonstrated under varying local conditions.

Recently, tissue oxygenation is being measured by using light whose wavelength falls within the near infrared band (wavelength 650 to 1100 nm) and which can penetrate the tissue reasonably well. Commercially, such an instrument is available which using this technique can measure the O_2 saturation of brain tissue. To measure the brain tissue O_2 level, the incident light is applied on the scalp from where it enters the brain. Then, a small proportion of light is scattered and returns back after

its absorption by brain tissues to the analyzer by a fibre optic bundle. The absorption and the intensity of this reflected light depends on the O_2 level of tissues and thus the machine measures the O_2 level of it. The measured O_2 saturation of brain includes arterial, capillary and venous blood. But, it is heavily weighted towards the values of venous blood. Whereas, pulse oximetry measures only the arterial O_2 saturation, as it only measures the pulsatile portion of the tissue. So, it indicates the amount of O_2 delivered to the tissues, but does not indicate the amount of O_2 diffused in it or the consumption and need of O_2 by it.

Recently, it has also become possible to measure the tension of oxygen at the intracellular level by mixing the light of different wavelengths. This is more likely to provide a better estimation of O_2 availability at the cellular level than the currently available clinical monitoring parameters. This technique has been used to monitor the intracellular changes of muscle and brain tissue during respiratory acidosis, hypoxia and cardio-pulmonary bypass.

Measurement of Inspired O_2 Concentration

An anaesthetic apparatus usually supplies the O_2 and anaesthetic gases to the patient. Thus, it regulates the arterial PO_2, and the uptake and elimination of inhalational anaesthetic agents by lungs. So, the knowledge of composition of the inspired gases, at least the concentration of O_2, is important for the routine monitoring of a patient.

Therefore, it is mandatory to analyse the inspired gas for O_2 concentration constantly during the all forms of anaesthesia. This will ensure that hypoxic mixtures are not used and will also confirm that the desired concentration of anaesthetic agents are being delivered. Thus, the delivery of an adequate amount of O_2 is so crucial for safe anaesthesia that multiple safety monitoring systems, including using of an oxygen analyser in the circuit are considered mandatory.

During low-flow closed circuit anaesthesia, the inspired concentration of O_2 cannot be calculated from the rotameter, if nitrous oxide is being used. So, measurement of inspired O_2 concentration becomes mandatory, as part of the intraoperative patient monitoring

The O_2 concentration in inspired gases can be measured by the following ways:

1. Paramagnetic O_2 analyser

Most of the monitors have a paramagnetic sensor. It uses the property of O_2 which is based on its weak attraction by a magnetic field. As most of the other anaesthtic gases are diamagnetic, so they are weakly repelled by a magnetic field. Two unpaired electrons, spinning at the same direction in the outer electron shell of O_2 atom make this molecules strongly paramagnetic, i.e. attracted towards a magnetic field.

In the chamber of a paramagnetic monitor there is a small sphere, filled with nitrogen. The sphere is suspended from a bar that is free to rotate by a strong magnetic field. In a normal condition, i.e. when exposed to air, the bar finds a position where the force exerted on the sphere by the magnetic field is balanced by the torsion of the suspending wire. If the O_2 concentration in the chamber increases, then the O_2 is attracted towards the magnetic field. This inward movement of O_2 displaces the sphere and causes the bar to rotate. This small twisting movement of the bar is measured and then amplified. Thus when calibrated, the O_2 concentration in the chamber may be calculated easily from the position of the bar. This instrument identifies and accurately measures the O_2 concentration in a mixture of gases over a wide range. It is reliable and a fast method. But, unfortunately, it cannot measure continuously the breath by breath changes of O_2 concentration and its sample volume is large.

2. Polarographic O_2 electrode and O_2 fuel cell

Some monitors use polarographic O_2 electrodes and some use O_2 fuel cell for the measurement of concentration of O_2 in the inspired gas. Although the response time for both of these instruments is long, but they are cheap, compact, portable and are of sufficient accuracy for clinical use, as a continuous monitor for inspired O_2 concentration. The fuel cell measures the partial pressure of O_2, instead of its concentration and its accuracy is usually around ± 2% with a response time < 10 sec. The long life (2000 hours when exposed to 100% O_2) and robustness of fuel cell lends it a valuable device for this role and it should be available with all the anaesthetic machines.

Before each use the analyser should be calibrated by exposure to air and 100% O_2.

Monitoring of Respiratory System by the Measurement of CO_2 in Blood

Measurement of CO_2 tension in blood

Like O_2 tension, measurement of CO_2 tension in the blood also reflects the status of respiratory function. So, monitoring of PCO_2 in blood is another way of monitoring the respiratory function of a patient. But except monitoring of respiratory function, measurement of PCO_2 of blood also monitors the acid-base status, cardiac function, function of the anaesthetic machine, etc. Blood PCO_2 can be measured directly or indirectly in different ways, some of which are described below.

1. Directly by CO_2 electrode

It is also called the Severinghaus CO_2 electrode and is used in the blood gas analyzer to measure the PCO_2 of blood.

This CO_2 electrode acts by measuring the changes of pH in blood. As a pH electrode, it is kept in contact with a thin layer of bicarbonate buffer solution which is separated from blood or plasma by a thin

teflon or silicone membrane. This membrane is only permeable to CO_2 but not to blood cells, plasma or charged ions. The whole unit is maintained at 37°C. The CO_2 diffuses from blood into the buffer solution through this membrane, and causes a change in H^+ concentration of solution which is reflected as the CO_2 tension on the screen of monitor. The electrode is calibrated by equilibrating the buffer solution with two known CO_2 concentrations which establish the relationship between pH and PCO_2.

2. Indirectly by transcutaneous measurement of PCO_2

Transcutaneous CO_2 electrode is nothing but a miniature modification of Severinghaus electrode which is used in the blood gas machine to measure the CO_2 tension of blood. Here, the CO_2 diffuses through a membrane into the cell, where it reacts with water and produces carbonic acid. The pH sensitive glass electrode, then, reacts to this change in concentration of hydrogen ions by producing a small electromotive force which can then be measured as the partial pressure of CO_2. After the introduction of Severinghaus CO_2 electrode in 1958, it was first used in a blood-gas analysing machine. Then, in 1970, this electrode was miniaturised and incorporated into a transcutaneous probe to measure the blood CO_2 tension through skin non-invasively (Fig. 22.8).

The advantages and disadvantages of this transcutaneous CO_2 probe is similar to that of transcutaneous Clark O_2 probe or an electrode which is used to measure the blood O_2 tension. Actually, transcutaneous CO_2 electrode measures the capillary PCO_2. So, to get the actual arterial PCO_2, the blood flow should be increased in the capillaries by warming the skin to 44°C through the probe. Again, heating of Severinghaus CO_2 electrode and applying it to the surface of skin increases the metabolic production of CO_2 in the tissue, resulting in a higher PCO_2 than the actual arterial

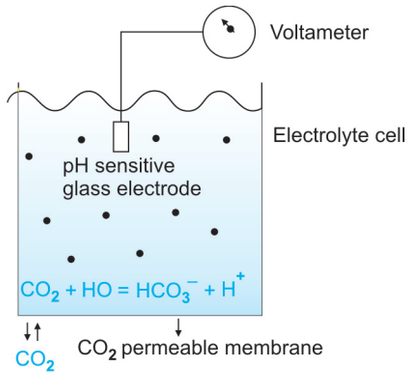


Fig. 22.8: Diagrammatic representation of a Severinghaus CO_2 electrode. This device consists of a pH sensitive glass electrode and an electrolyte cell, having a CO_2 permeable membrane covering on the surface. The gas electrode is immersed in the electrolyte cell. Through the permeable membrane, CO_2 diffuses into the cell. Then, it reacts with water producing carbonic acid and changes the pH. The pH electrode then detects the change in pH, which is directly proportional to the CO_2 concentration

PCO_2. Another disadvantage is that unlike the CO_2 electrode used in blood-gas machine in transcutaneous electrodes, the used electrolyte is only a few millimetre in amount. So, the continuous heating of probe to 44°C causes quick evaporation of water from the electrolyte, and hence results in a short life span of the transcutaneous probe. However, in the newer transcutaneous probes all these disadvantages are removed by incorporating some newer technologies and electronic calibration.

The main advantage of this transcutaneous CO_2 probe is that repeated withdrawal of blood to measure the blood PCO_2 is not required which is very helpful in children.

Measurement of end tidal CO_2 tension ($ETPCO_2$)—Capnography

The measurement of $ETPCO_2$ is another way of monitoring the respiratory function. The end tidal CO_2 tension ($ETPCO_2$) is used as an estimation of P_ACO_2 and hence P_aCO_2, because the level of P_ACO_2 and P_aCO_2 run parallel and very close to each other, except in some rare circumstances where the arterial and alveolar CO_2 tension difference is high. The normal gradient between P_ACO_2 and P_aCO_2 is 2 to 5 mm of Hg. It reflects the volume of alveolar dead space, i.e. the number of alveoli which are ventilated, but not perfused. Thus, any increase in the alveolar dead space by reduction in lung perfusion, such as, air embolism, ↓BP, ↓cardiac output, etc. decrease the expired CO_2 concentration and lessens the $ETCO_2$ tension and increases the $P_ACO_2 - P_aCO_2$ gradient. This gradient is also increased when there are other causes of impairment of lung perfusion and the end-tidal CO_2 level does not reach the arterial level. So, sometimes the $ETCO_2$ value should be checked with arterial blood samples, especially in more complex situations. These include: severe pulmonary diseases and situations where the accurate control of arterial CO_2 level is critical to save the life. So, the end tidal CO_2 ($ETCO_2$) analysis has achieved a high degree of popularity.

A variety of techniques can be used for the measurement of $ETCO_2$ concentration and its tension, such as, mass spectrometry, Raman's analysis, infrared absorption technique, etc. But, the last is used in majority of capnometers (Table 22.2).

Infrared radiation of 1 to 15 µm (1000 to 15000 nm) of wave length is absorbed by all the gases which have two or more dissimilar electrons at the outer orbit of their atoms. In the infrared absorption method, an infrared light beam is projected through the gas sample and then the intensity of this transmitted light is measured after its absorption while passing through it. However, this absorption of infrared light is different in degrees, depending on the concentration and the absorption spectrum of the gas to be analysed. CO_2 absorbs infrared light with a characteristic peak at the wavelength close to 4.3 µm (4300 nm). Several other molecules, such as, N_2O, CO, water vapour and O_2 can also absorb the light in this area of spectrum (absorption spectrum of N_2O and CO is 4.5 and 4.7 µm respectively). Thus, they may

Table 22.2: Conditions of end tidal CO_2 tension

A.	**Conditions of raised end tidal CO_2 tension**
	Hypoventilation
	Rebreathing
	Malignant hyperthermia
	Pyrexia
	Sepsis
	CO_2 inhalation
	Laparoscopy by CO_2
	After release of tourniquet
	Faulty equipment, exhausted sodalime
B.	**Conditions of low end tidal CO_2 tension**
	Hyperventilation
	Bronchial intubation
	Hypothermia
	Hypometabolism
	Hypoperfusion
	Pulmonary embolism
	Leak in breathing circuit
C.	**No tracing of graph of end tidal CO_2 tension**
	Oesophageal intubation
	Disconnection of breathing circuit
	Cardiac arrest

interfere with CO_2 measurement, especially if the composition of incident light includes wavelengths, other than those in a very narrow spectrum around the CO_2 absorption peak. But in practical use, the fixed geometry of this gas (CO_2) sampling cell, a narrow band infrared light source and a compensating electronic circuits of a computer can often automatically correct the interference by other gases. After absorption, a special photo cell detects and transduces the absorbed infrared radiation to a continuous electrical output. The modern CO_2 analyzers for clinical use are very stable, but it require calibration to its zero point routinely at a regular time interval.

To ensure the accuracy, most monitors modify the principles of infrared absorption technique by different methods to measure the CO_2 content accurately in several ways. Sometimes the beam is usually turned on and off upto 4000 times per minute to provide a zero light reference. Sometimes the infrared light from a single light source is usually split and passed through two indentical chambers : one contains the gas mixture to be analyzed and the other is empty. The absorption of CO_2 is then calculated by comparing the two beams. Lastly, each beam may be reflected through the chamber for several times by a series of mirrors to increase the amount of absorption and make it easier to measure.

Modern multimonitors for measurement of $ETPCO_2$ use infrared light of several wavelengths and are, therefore, able to automatically detect the concentration of various other gases which are present in the mixture. This method is also used to monitor different anaesthetic agents during inspiration and expiration. Estimation of the end-tidal O_2 tensions ($ETPO_2$) can also be used as a monitoring parameter for respiratory function, because $ETPO_2$ is equivalent to P_AO_2 and hence P_aO_2. But this is not always true, because of the variable alveolar and arterial oxygen tension gradient (A-a). In a normal individual, the gradient is less than 10 mm of Hg. But in a V_A/Q mismatch, this -a oxygen tension gradient will be very high, resulting in an arterial hypoxaemia which is not reflected by $ETPO_2$. But usually the V_A/Q mismatch has no effect on the relation between the $ETPCO_2$ and P_aCO_2. Futhermore, if a patient receives high inspired O_2 concentration, then the $ETPO_2$ will be falsely high and shall overestimate the P_aO_2. Even a dead patient may show high $ETPO_2$, if he is ventilated with 100% O_2.

A capnometer is usually of two types: (i) side stream capnometer, and (ii) main stream capnometer.

A. Side stream capnometer

In a side stream capnometer the main infrared analyser module is situated out of the anaesthetic circuit at a distance from the patient within the multimonitor. So, it constantly drains the gas sample of around 150 ml/min by a small pump via a fine gauge tubing. But the main analyser should be placed as close to the patient as possible. This will reduce the amount of gas drained out from the circuit. The infrared analyser module or sensor may be a separate unit or may be housed in the main multimonitor which measures the other parameters of the patient. The side stream capnometer is less reliable, but is less liable to accidental damage. The infrared measuring cell i.e. the core of the instrument should be protected from water vapour and other particulate matters, as they may cause erroneous readings due to their higher infrared absorption. Usually water vapour present in the expired air condenses at room temperature in the sampling tube and accumulates in a water trap which is then filtered out from the sampling gas before entering in the main analysing module. In critical-care settings or in very long cases, where inspired gases are warmed and humidified properly, then work load increases on the water-separating system of the capnometer as the inspired air has high water content.

The disadvantages of side stream capnometer are:

i. There is some delay in detection and measurement of PCO_2. This is further increased if the tubing, leading from the anaesthetic circuit is too long or too wide. This delay is called the 'CO_2 flight time'. It can be minimised and the sensitivity can be increased by using high gas flow rates (upto 250 ml/minute) for sampling and narrow short tubing (low dead space) assemble, compatible with the position of equipment with respect to the patient breathing circuit. On the otherhand, if the tidal volume is small such as in a paediatric patient, then this high rate of aspiration (gas sampling) may draw much fresh gas from the circuit and dilute the $ETCO_2$ reading. Low aspiration rates (less than 50 ml/minute) can also delay $ETCO_2$ measurement and underestimate it during rapid ventilation by drawing fresh gas from the circuit.

ii. Multiple connection sites in the assembly of side stream capnometer such as sampling gas pump, flow regulation, water-trap etc., may cause increased incidence of gas leakage or breakage and erroneous result.
iii. If the sampling flow exceeds the expired gas flow, then contamination from the fresh gas source may occur which may give inaccurate reading. The rate of gas sampling can be adjusted from 50 to 500 ml/minute, but the usual volume of the gas sample is maintained between 50 to 150 ml/minute.
iv. In certain circumstances such as during paediatric anaesthesia, the removal of 150 ml of gas from the circuit may affect ventilation. So, most monitors incorporate the facility to return the measured gas to the circuit through a second tube. Thus, this second tube also helps to prevent the OT pollution by anaesthetic gases coming out from capnometer.

B. Main stream capnometer

In a main stream capnometer there is no system of continuously drawing of sample gas by a pump. The sensor or the main infrared analyzing module of the mainstream capnometre is placed along the breathing circuit itself, resulting in a quick and accurate measurement of PCO_2 from expired gases. The analysis of end-tidal PCO_2 correlates well with the concentration of CO_2 in the alveoli and hence in the arterial blood. So, to get a correct result, mixing of expired gas with the fresh gas should by prevented. So, the instrument should be placed as close to the alveoli as possible. Hence, the measuring head is placed in close proximity to the ET tube (Table 22.3).

The advantages of main stream capnometer are:

i. No gas is subtracted from the breathing circuit, so does not effect the ventilation.
ii. No suction pump or other device is required for sampling which add complexities to the mechanical system.

Table 22.3: Indications of use of capnometer

1. Confirmation of tracheal intubation.
2. Confirmation of adequate ventilation.
3. Detection of hyperthermia (malignant or not).
4. Detection of rebreathing.
5. Detection of V_A/Q mismatch.
6. Detection of pulmonary embolism.
7. Detection of malfunctions of inspiratory and expiratory valve.
8. Confirmation of continued ventilation or detachment at any part of circuit.
9. Detection of cardiac activity during CPR.

iii. No uncertainty in gas sampling.
iv. Response time is faster.

The disadvantages of main stream capnometer are:

i. The measuring chamber is usually heated to about 40°C to prevent water condensation in the chamber window. So, the heated sensing head should be kept away from direct contact with the patient's skin.
ii. It is relatively heavy and must be supported to prevent ET tube kinking.
iii. Sensor's window must be kept clean of mucous and other particles to prevent false reading.
iv. Calibration is problematic.

Periodically the capnometer should be calibrated by using the gases of known concentration, guided by the respective companies. Mainstream capnometers are often equipped with calibration sample cells, sealed with a mixture of CO_2 and N_2 of known concentration. In some instruments, the room air is sampled in the mainstream cuvette for calibration and bring the CO_2 level automatically to zero.

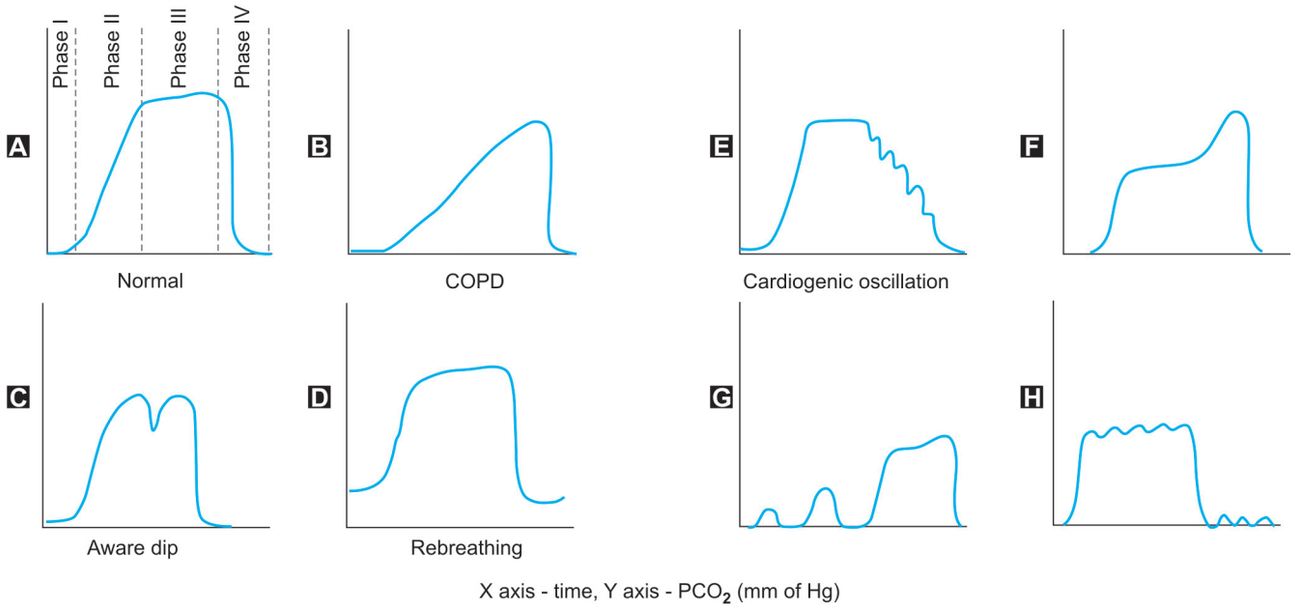
Capnographic wave form

In the capnographic wave form or tracing there are four phases Among these the phase I, II and III corraborates with expiration and phase IV corraborates with inspiration. In phase I the expired gas which comes out from the anatomical dead space such as the ET-tube and the large airways are devoid of CO_2. This is because they contain only the fresh gas and so in this phase there is no rise in PCO_2 in tracing which follows the base line. This phase I is followed by phase II. In short phase II as the expiration continues, so a rapid upstroke of PCO_2 level is recognised. This is called the 'rising front of CO_2'. This is because the anatomical dead space gases, mixed with the alveolar gases containing CO_2 now, starts to excrete and the concentration of CO_2 increases rapidly to a plateau level. Expiratory flow is highest in the beginning of expiration and then tapers off in an exponential fashion during the last third of the expiratory time. So, this phase II is followed by phase III which is called the alveolar plateau. This represents the constant slowly rising part of the graph and reaches a peak at the final phase of expiration. This represents final $ETCO_2$ tension value. The cause of this constant rising of PCO_2 in phase III is that gradually expired gases containing more and more CO_2 coming purely from the alveoli (not mixed with anatomical dead space gases) reaches the analyser. This is because CO_2 excretion from the pulmonary capillaries into the alveoli continues at a nearly constant rate during expiration and this CO_2 molecules are not diluted by the lung volume which becomes progressively smaller by the exhalation process. This gradual and relative increase in the concentration of CO_2 in the smaller lung volume is responsible for the constant slowly rising part of the graph or phase III. Slow exhalation as in the acute asthma patient induces a steeper alveolar plateau. Thus, the end of the phase III or alveolar plateau represents the final $ETCO_2$ tension. In a normal individual the $ETCO_2$ tension is 2 to 3 mm of Hg less than P_aCO_2. But, the chronic pulmonary diseases and acute V_A/Q mismatch wides this difference. At the end of phase III when expiration still continues and lung volume (FRC) goes below the closing capacity, then expired CO_2 concentration rise sharply at the end of phase III or the alveolar plateau. This is also

responsible for the peak of phase III. The phase III is followed by phase IV which is characterised by rapidly decreasing value of CO_2 tension towards the inspired value. This is caused by the inspired gas being sucked into the analysing site. The capnograph value during inspiration represents the CO_2 tension or concentration in the inspired air which depends on the type of the breathing circuit, fresh gas flow respiratory rate and the amount of rebreathing. Rebreathing of the expired gas containing CO_2 due to any reason causes an inspired level of CO_2 tension above the baseline. The probable causes of rebreathing are: improper circuit with increased dead space, low fresh gas flow, exhaustion of CO_2 absorber, high respiratory rate etc.

In a side stream capnometer the sampling flow rate has a greater impact on the capnograph value. So, it should be taken into account during interpretation. Sampling flow rate by suction pump in a capnometer can vary between 50 ml to 400 ml/min, but usually in an adult it is adjusted to 150 ml/min. When respiratory gas flow decreases below the sampling value, such as in paediatric anaesthesia or low-flow anaesthesia, then the capnometer contributes significantly to the bulk flow, in and out of the respiratory circuit (Fig. 22.9). In this situation, for sampling the monitor should aspirate gas alternatively from the trachea or the inspiratory limb, causing an oscillatory graph in phase III and IV which is known as 'cardiogenic oscillation'. It appears as a small, tooth like, regular wave at the end of expiratory phase.

Other probable explanations of cardiogenic oscillations are: (i) it is due to the contraction and relaxation of heart and the movement of intrathoracic great vessels of lungs which forces the air out of the lungs in oscillating fashion. So, this rate of oscillation matches with the heart rate.



Figs 22.9A to H: Schematic diagram for analysis of $ETCO_2$ tension waveform. Phase I represents the gas of anatomical dead space. So it does not contain CO_2 and seen as flat phase running along the base line. A raised phase I (See Fig. D) suggests rebreathing or malfunctioning of inspiratory and expiratory valve or an exhausted soda lime. Phase II represents the rapid rise of tracing after phase I. This is due to the exhaled gases coming first from anatomical dead space and then alveoli and so containing gradually more and more CO_2. This corresponds to begining of expiration. A slanted upstroke (See Fig. B) represent obstruction of airway during expiration. This obstruction may be due to asthma, COPD, kinking of airway, secretions, etc. No plateau is reached before next inspiration and the gradient between $P_{ET}CO_2$ and P_aCO_2 will increase. Phase III consists of a nearly horizontal plateau which corresponds with exhalation of gas coming entirely from alveoli. During expiration the gas leaving the alveoli comes from different parts of alveoli. Hence, this phase represents the average concentration of CO_2. The end of plateau represents the end tidal CO_2 concentration or tension when it attains fairly a constant level. In normal individual it is usually 3 to 5 mm of Hg lower than P_aCO_2. Measurement of slope of Phase III is a non-invasive method for estimating cardiac output, since mixed venous blood flow contributes to the generation of slope. Appearance of dips (See Fig. C) in this phase indicates spontaneous respiratory efforts in a paralysed patient or artefacts from the surgical manipulation in abdomen. Phase IV represents the beginning of inspiration which shows the rapid fall of CO_2 tension towards the base line. One may see (See Fig. E) some oscillation called 'cardiogenic oscillation' in this down stroke. They are believed to be due to the contraction and relaxation effect of heart and intrathoracic great vessels on the lungs, causing air to flow in and out. Fig. F indicates some leak in sampling line during IPPV. It results in a plateau of long duration and a brief upswing at the end of phase III. The plateau height is inversely proportional to the size of leak. The brief upswing is due to the next inspiration when positive pressure transiently pushes undiluted end-tidal gas through the sampling line. Fig. G shows return to spontaneous ventilation. The first breath is small. The subsequent breath increases in height with gradual resumption of normal waveform. Fig. H shows irregular plateau and/or base line. It may be due to displacement of ET-tube in the upper larynx or lower pharynx. It may also be due to pressure on the chest which causes small volume of gas to move in and out of the lungs

(ii) Negative intrathoracic pressure, low respiratory rate, reduction of vital capacity, increased heart size ratio, low tidal volume, low inspiratory and expiratory ratio, muscular relaxation, etc, may cause cardiogenic oscillations. But, in most of the cases it can be corrected by increasing the flow rate, respiratory rate, tidal volume or by applying PEEP. It is very common in the paediatric group of patients, because the size of infant's heart is relatively greater than the thorax. If the capnometer is less sophisticated or the wave of oscillations are large, then the instrument may count each wave as a breath and display an erroneously high respiratory rate.

The Inaccurate reading by a capnometer is also produced, if the sampling gas is diluted with the fresh gas from the circuit. This occurs :

i. If the fresh gas flow is too high,
ii. If the gas sampling site is far away from the patient,
iii. If there is high respiratory rate,
iv. If the tidal volume is small (particularly in neonates and infants) in comparison to the size of breathing system.

Normally, the end-tidal CO_2 tension ($ETPCO_2$) varies between 35 to 45 mm of Hg. The PCO_2 above 45 mm of Hg is called hypercapnia and below 35 mm of Hg is called hypocapnia.

Causes of hypercapnia:

i. Fever and malignant hyperpyrexia.
ii. Depression of the respiratory centre due to any cause with concomitant reduction of total ventilation and elevation of PCO_2.
iii. Reduction of ventilation, caused by partial paralysis of the respiratory muscles, neuromuscular transmission disorders, high spinal anaesthesia etc.
iv. Acute respiratory distress including acute asthma, pulmonary oedema, acute exacerbation of COPD, respiratory failure etc.
v. Inadequate ventilation in a controlled ventilated patient.
vi. Insufflation of CO_2 in the peritoneal cavity, during laparoscopy.
vii. Defects in mechanical ventilation setting.
viii. IV administration of bicarbonate.
ix. Inadequate fresh gas flow.

Causes of hypocapnia:

i. Hyperventilation
ii. Increased dead space in presence of normal P_aCO_2. In some alveoli where there in no blood flow, there is no transfer of CO_2 from blood to alveoli. Thus the gas emanating from such alveoli containing no CO_2, dilutes the exhaled gas with CO_2 coming from other region of the lungs and $ETCO_2$ tension decreases.
iii. High sampling rate in presence of an elevated fresh gas flow rate for side stream capnometre.
iv. In atelectasis, where alveoli are perfused but are ventilated, then there is a shunting of mixed venous blood and no diffusion of CO_2 from blood to alveoli.

In atelectasis there is high P_aCO_2, and normal or low $ETCO_2$ tension. This causes high arterial and alveolar end-tidal CO_2 tension difference (P_aCO_2-$ETPCO_2$), which ensures one of the indications of delivery of PEEP ventilation. This low $ETCO_2$ tension in atelectasis is due to the impairment of diffusion of CO_2 from the blood in to alveoli. Excessive PEEP again causes over distension of the alveoli which hamper perfusion and CO_2 exchange, causing high P_aCO_2 and $ETPCO_2$ difference. So, optimum PEEP should be maintained.

Sometimes, a sudden dip in the alveolar plateau phase or phase III during controlled ventilation indicates initiation of spontaneous respiration. This is due to the passing of a small bolus of fresh inspired gas in the sampling site by a sudden onset of spontaneous inspiration. This dip can be interpreted as (i) recovery from anaesthesia, (ii) activation of respiration, induced by sudden stimulation from the surgical site, (iii) inadequate inspiratory power during switching over from mechanical to spontaneous ventilation and (iv) first sign for the need of reversal of neuromuscular blockade.

Monitoring of Anaesthetic Gases

For three reasons each component of a mixture of anaesthetic gases or vapours are analysed and measured in practice, both during inspiration and expiration. These reasons are :

i. To establish the identity and concentration of individual anaesthetic agent which is required for better control and delivery of anaesthesia to patient, including the judgement of depth of anaesthesia and also the stability of haemodynamic system.
ii. To detect and reduce the atmospheric pollution.
iii. To assess the metabolic or cardio-respiratory function by measuring cardiac output, either by analysing the respired gases (O_2, CO_2 and N_2) or by using inert tracer gases, such as helium, argon, etc.

The concentration of different anaesthetic gases or agents such as nitrous oxide, halothane, isoflurance, sevoflurane, etc., used during anaesthesia (including O_2 and CO_2 also) are measured by the following various methods.

(i) Mass spectrometry

The mass spectrometer, which once upon a time was a special laboratory tool for research purposes only, has now become a common operating room instrument for measuring the concentration of anaesthetic gases. It measures the concentration of individual gases in a mixture, largely depending on the basis of their molecular weight. The basic principle on which the mass spectrometer works is based on the ratio between the quantity of charge of a molecule after its ionisation (q) to its mass (m), i.e. (q/m) (Fig. 22.10).

Gas samples are passed through an electron beam (ionizer) which strips from the individual gas molecule one or more electrons and gives them a positive charge. Then, after ionisation the ions of individual

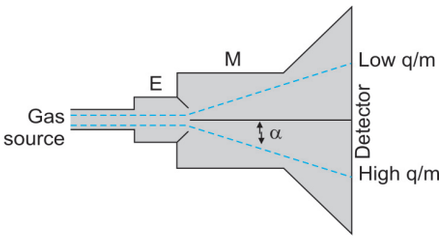


Fig. 22.10: Schematic diagram of a mass spectrometer. Gas molecules at low pressure are ionised and accelerated by an electrical field (E). The ions are then passed through a perpendicular magnetic field (M) that deflects their path through an angle α. This deflection angle is determined by the ratio of charge to mass (q/m) of the ions and is used to identify the species of the gas

gas molecules are passed through a magnetic field, oriented perpendicular to their direction of motion. The side ways magnetic force deflects each ion by an angle 'α', and falls on the photodetectors. The deflecting force (i.e. the path of the ion becomes curved) is proportional to the charge 'q', and the sideways acceleration from this force is inversely proportional to the mass 'm' of the molecule. Therefore, the angle of deflection 'α' is the function of q/m. Thus, photodetectors which are placed at specific locations measure the individual gas concentration, which is proportional to the count of molecules deflected per minute.

During measurement the gas samples are drawn from the anaesthetic circuit into an evacuated ionising chamber, where they are bombard by electron beams. Then, the positively charged ions are passed through a slit from the ionising chamber to the next chamber. In the next chamber these ions are accelerated by a plate to which negative voltage is applied. The magnetic field from the plate deflects the ions according to their charge and mass-ratio (q/m). Then, the number of ions that strike on the detector is proportional to the partial pressure of the gas sample. Thus the streams of ions of different gases are detected by varying the accelerating and focusing voltage. Hence, thus, a mass spectrum is produced by relating the detector output on the Y-axis (calibrated to the concentration of gas) and by accelerating the voltage on the X-axis (calibrated to the molecular weight).

The ability of a mass spectrometer to measure the concentration of different individual gases depends upon the charge/mass ratio. Since, most of the ions created by the ionisation are singly charged due to the missing of a single electron, so the most important variable is, therefore, the molecular weight. Hence, the two different gases of same molecular weight such as N_2O and CO_2 are not distinguishable ordinarily by a mass spectrometer, using the principles outlined above.

During ionisation, some molecules also lose two electrons, instead of one and become doubly charged. So, they behave like ions, with half of their mass. Also, during ionisation some molecules become fragmented causing a secondary peak, rather than a single peak for each gas molecule, such as during the identification and quantification of CO_2 and N_2O. Both the CO_2 and N_2O produce a parent peak at 44 Da but also produce a secondary peak at 12 Da and 30 Da, respectively.

Mass spectrometer is a bulky and expensive instrument, but has a very short response time which is approximately 100 to 200 milliseconds. So, the original implementation of its use in anaesthesia has placed it in a remote-central location. Hence samples are conveyed by a tubing from multiple operation theatres to the remote-centrally located spectrometer for analysis of gases used in anaesthesia on a time-sharing basis. This time-sharing basis increases the delay time and because of the greater length of the tubing necessary to convey the sample gases from the patient to the machine. Recently, a number of small spectometer instruments are available for use in individual operating rooms. These instruments typically can measure the O_2, CO_2, N_2O, N_2, halothane, enflurane, isoflurane, etc., simultaneously.

(ii) Raman scattering analyser

When a photon from a light source collides with a molecule of any gas, then there is some absorption of kinetic energy from the photon. After that this photon is scattered sideways having a lower energy level and longer wave length. This phenomenon is called the 'Raman scattering'. In this phenomenon, the degree of absorption of energy by a gas molecule from the falling photon and the wavelength of the scattered photon or light depends upon the molecular weight and the structure of the gas molecule. Spectral analysis of that scattered light may, therefore, be used to measure the concentrations of individual gas in the mixture. As a photon source the light which is usually used is argon laser with the wavelength of 488 nm. This type of gas analyser is fast, accurate and relatively compact for measurement of CO_2, N_2, O_2 and other anaesthetic gases.

(iii) Infrared absorption technique

This technique is used in most of the modern monitors with the same principle as for the measurement of CO_2 in a capnometer and with the same problems. The advantages of this technique are rapid and an accurate analysis with identification of each gas present in the mixture. In this method, the infrared light beam is first projected through the gas sample and then the intensity of the transmitted light after absorption is measured. Gases, whose molecules contain two dissimilar atoms or more than two electrons in their outer orbit absorb infrared radiation in the same region of spectrum.

The CO_2 absorbs light with a characteristic peak at the wavelength close to 4.3 μm (4300 nm). Several other molecules of anaesthetic gases such as N_2O, O_2, CO and water vapour also absorb light in this area of the spectrum. Thus, CO_2 measurement is disturbed especially if the composition of incident light includes wavelength, other than those of a very narrow spectrum around the CO_2 absorption peak (Fig. 22.11).

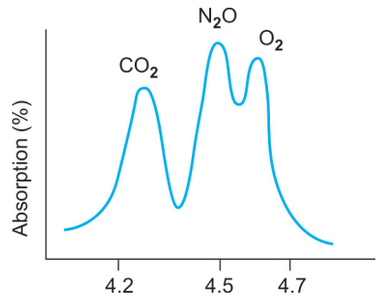


Fig. 22.11: Infrared analyser is an instrument which gives a continuous recording of the concentration or tension of CO_2. It is also used to measure the other volatile anaesthetic agents by careful selection of the infrared wavelength which depends on the potential components of the gas mixture. Use of a specific infrared wavelength of 4.2 μm for the analysis of CO_2 should avoid interference from the presence of N_2O and O_2. The infrared radiation is emitted from a hot wire and a particular wavelength is obtained by passing it through an interference filter. There may be a rotating disc which permits passing of infrared light of different specific wavelengths and simultaneous analysis of various types of gases. Basically, the amount of absorption of radiation is proportional to the concentration of CO_2 and other gases present in the analysing chamber. After passing through the sample analysing chamber and absorption, the radiation is focussed on the photo detector situated on the opposite site. Greater the absorption of infrared radiation by the gas sample, lesser the radiation monitored by the detector. Consequently, it is possible to process the detector output electronically to indicate the concentration of the gas present. Most of the newer instruments use a second beam, which passes through the reference chamber. Any changes in output which are not due to changes in CO_2 concentration in the sample cell, also appear at a reference detector and is subtracted from the output of the sample detector. Such an analyser is called a double beam instrument

As discussed above, the infrared absorption technique is used to analyse the molecules having only a diapole atom, therefore, it can not be used to identify O_2 and nitrogen.

(iv) Gas-liquid chromatography

Chromatography was originally introduced in 1906 by a Polish botanist, named Tswett, for separation of different colour pigments, present in a plant extract. It is of four different types such as : (i) paper chromatography, (ii) thin layer chromatography, (iii) column chromatography, and (iv) gas-liquid chromatography. The gas-liquid chromatography is a very helpful instrument to analyze and separate the components of gases in a mixture. Not only that, in addition, it may be used to analyse the blood samples containing different solute such as the volatile, intravenous, local anaesthetic and anticonvulsant agents etc. In combination with the mass spectrometer, it is also an important analytic tool, because the mass spectrometer identifies the molecular fragments present in any concentration which are eluded from chromatography.

Measurement of Central Respiratory Drive for Monitoring of Respiratory Function

The main causes of respiratory failure are: depressed central ventilatory drive, abnormalities of pulmonary mechanics, and impairment of respiratory gas exchange. Among these, the depressed central ventilatory drive is the commonest cause of respiratory failure. So, the measurement of ventilatory drive is very important for the assessment of function of respiratory system, particularly in anaesthesia where most of the anaesthetic agents are respiratory depressants and also in the process of weaning of patients from mechanical ventilators. Ventilatory drive is measured directly by minute ventilation (V_E) and indirectly by P_aCO_2 level. But clinically the measurement of V_E and P_aCO_2 is very difficult. So, various measures for the assessment of neural respiratory central drive have been sought.

These are:

i. Divisioning and examining the respiratory waveform into inspiratory and expiratory components.
ii. By measuring the inspiratory flow rate (tidal volume/inspiratory time). The draw back in this method is that many patients have high ventilatory drive, but is not able to translate this drive into a respiratory output, because of their impaired ventilatory mechanics.
iii. Measurement of the rate of respiration is also a method of monitoring the respiratory drive. But, the main disadvantage is that respiratory depression does not always indicate reduction of the respiratory rate. In narcotic-induced respiratory depression, tidal volume is mainly depressed with a little change in the respiratory rate.
iv. Measurement of P_{100} is another sophisticated method for assessing the respiratory drive. The P_{100} is defined as the maximum negative inspiratory airway pressure, which is obtained 100 milliseconds after a temporary occlusion of the airway in a spontaneously breathing patient. It is an useful index of the respiratory drive without being affected by any volumentary effort and changes in respiratory mechanics. The normal value of P_{100} is 1 to 2 cm of H_2O and is not appreciably noticed by a patient during its measurement. Possibly, one could also use P_{100} as a guide to the discontinuation of mechanical ventilation, after general anaestheisa.

Monitoring of Pulmonary Mechanics

Till now, we were monitoring the function of respiratory system by measuring the concentration of O_2, CO_2 and other anaesthetic agents in blood, inspiratory and expiratory air. Also, we have tried to monitor the function of respiratory system by measuring the ventilatory drive which are described just before. But, now we will discuss the monitoring of the functions of respiratory system by measuring the respiratory mechanics.

There are four principal determinants for the measurement of pulmonary mechanics. These are: flow, pressure, volume and time. From them we can monitor the respiratory mechanics by measuring the compliance and resistance and by drawing the different loops such as flow-volume loop, pressure-volume loop, etc. But, it should be kept in mind that all these parameters are interrelated.

A. Flow

The measurement of flow of gases (both inspiratory and expiratory) is useful for two reasons: (i) measurement of resistance and compliance requires measurement of both flow and pressure, and (ii) from the measurement of flow the most ventilators calculate the different lung volumes, such as: tidal volume, minute volume, etc. by multiplying it with time. Again from volume, the computers of modern ventilators can also calculate the volume-pressure curve, the flow-volume curve, compliance, resistance, etc. So, before the measurement of any parameter, measurement of flow and pressure is most important. The flow is measured by the following methods.

Rotameter

It is a variable orifice (constant pressure change) type of flow meter. Another type of variable orifice type of flow meter is a peak flowmeter. Rotameter consists of a vertical glass tube, inside of which a metal alloy-made bobbin rotates. At the bottom of the rotameter there is fine flow control valve which controls the flow of gas. When this bottom valve is opened, then the pressure of the gas forces the bobbin up in the tube and gas starts to flow. The inner wall of the rotameter tube is cone shaped. This causes the pressure to remain constant throughout the range of flow. The tube is calibrated according to the amount of gas flow, keeping the pressure of constant and so the bobbin rotates freely. Each rotameter and its calibration is specific for a specific gas. The laminar flow in a rotameter is found at low-flow rates and depends on the viscosity of that gas. But, turbulent flow predominates at a higher flow rate and it depends on the density of that gas. It is the commonest type of flow meter which is used in all the anaesthesia machines to measure the flow of gas.

Peak flow meter

This instrument can measure a peak flow rate upto 1000 litre/minute and is very useful clinically. In this instrument there is a vane, which rotates during the flow of air through it or a piston which moves against a constant force, produced by a light spring. The maximum position, adopted by the vane or piston, depends on the peak expiratory flow rate and this position is held by a ratchet. Then, the reading is obtained from a mechanical pointer which is attached to the vane or the piston. Serial measurement of peak expiratory flow rate is useful to assess the prognosis in asthmatic patients. This measurement may be performed using a hand-held Wright's peak flow meter.

Bourdon gauge flowmeter

It is already said that the two above mentioned flow meters are of variable-orifice, but pressure-change is constant. But, this Bourdon gauge flow meter and pneumotachograph (discussed next) are of variable pressure-change but fixed-orifice flow meter. This gauge is calibrated to the gas flow rate according to the pressure changes across a fixed orifice. However, these rugged flow meters are useful for measuring the flow of gas from cylinders at high pressure.

Pneumotachograph

When patients are being ventilated mechanically, then the respiratory parameters are easily measured. It is also relatively easy to make such measurements continuous by a pneumotachograph. The pneumotachograph measures the flow rate by sensing the pressure changes across a small but fixed orifice. Usually the tidal volume is measured by observing the displacement of inflating bellows, or by passing the respired (inspired + expired) gas through a respirometer. But in some machines the gas flow are also measured by pneumotachographs. In a pneumotachograph, a differential pressure transducer records any tiny pressure change across a slight obstruction to the flow of gas. Then, the pressure-transducer transduces it into a continuous electrical output, which is integrated to give the amount of flow and volume digitally. The obstruction produced in pneumotachograph may be in the form of a gauge screen (screen type – pneumotachograph), or a bundle of small tubes aligned along the airway (Fleisch pneumotachograph). The pressure change against the obstruction in pneumotachograph is related to the flow rate and from this pressure change the flow is measured in a pneumotachograph. Pneumotachographs are not accurate over a very wide range of gas flow rate and are also affected by humidity, temperature, gas composition, etc. So, it requires frequent calibration, correction and compensation. In some ventilators, the measured minute volume is compared with the selected or set volume and an alarm is sounded off, whenever there is a discrepancy. A vortex – type pneumotachograph which is also frequently used in modern mechanical ventilators works by measuring the interruptions of an ultrasonic beam, placed across a tube which disrupts the laminar flow, resulting in vortices.

Ultrasonic flowmeter

This instrument works by measuring the speed of ultrasonic waves, propagated parallel to the direction of flow.

Hot-wire anemometers

It consists of an electrically heated wire, placed across the flow of a gas stream. The flow of gas tends to cool the wire and changes the electrical conductivity, thus sending changes in electrical signal. The changing electrical signal reads the amount of gas flow.

Flow is also measured by the amount of additional electrical current, necessary to maintain the wire at a constant temperature during flow of gases, because when gases flow over a wire, it cools down. This method is highly sensitive for measurement of gas flow, but is highly dependent on gas temperature and contamination of gas with water droplets.

B. Volume

Different lung volumes are measured by the following ways.

Dragger volumeter

This is a very simple and accurate device which measurer the volume of dry gas. But, it is affected by moisture. Here, the volume of gas that flows through this volumeter is measured by measuring the rotation of two light, interlocking, dumb-bell shaped rotors which is directly proportional to the flow of gas.

Wright spirometer

This device contains a light mica vane which rotates within a small cylinder. Then, the inflowing air volume which is to be measured is directed to it by a tangential slits. Thus, during the flow of air through a wright spirometer the rotation of vane drives a gear chain with a pointer on a dial, from where the flow rate can be measured. From the flow rate the machine calculates the volume of air or gases that flow through it. Thus, the minute volume can be read directly and then the tidal volume can be calculated from this reading and the respiratory rate.

It has dead space of only 25 ml and is of low resistance which is self rectifying. Although, the response in this spirometer is nonlinear, still it is reasonably accurate in the relevant range of minute volume (4 to 15 litres/min). But, the Wright spiro meter seriously over-reads at a high minute volume (>15 lit/min) and under reads at a low minute volume (<4 lit/min). This is due to the inertia of moving parts of machine. As with many other devices, its accuracy also deteriorates when it becomes wet. It is also clinically a very useful and convenient instrument for co-operative and unanaesthetised patients. But for more accurate measurement of lung volumes in a cooperative patient, dry gas meters and other sophisticated pulmonary function analysers may be employed. However, these instruments are not in common use in the ITU.

Alternatively, a bellows-type of dry gas spirometer (e.g. the vitalograph) can be brought to the bed side to measure the peak expiratory flow rate, vital capacity and times expiratory volume (e.g. FEV_1).

Integration from flow signal

Volume is also measured indirectly from the flow rate. The flow signal from different flow meters is integrated electronically over the time to measure the volume.

Indirect method to measure volume

In an unintubated anaesthetised patient the volume of ventilation can also be measured by monitoring the changes in external dimensions of thorax and abdomen, either clinically by direct observation or by using one of the techniques mentioned below.

In an unintubated, anaesthetised patient the volume of thorax is measured from the movement of thorax and abdomen by a magnetometer. This works by measuring the anterio-posterior and lateral thoracic and abdominal dimensions and is called pneumography. Here, some nonelastic tapes are placed around the chest and abdomen. The ends of the tapes are connected to the displacement sensors and the volume is measured. Another method of measurement of volume is from the movement of the thorax and the abdomen by using coils of wire, sewn into an elasticated strap that encircles the thorax and the abdomen. The expansion of the chest and the abdomen increases the space between the coils. So, it alters the inductance, generated by a high frequency AC current and converts it into electrical signal. This method is called the 'Respiratory Inductance Plethysmography'. The self inductance of the coils which changes in proportion to the changes of the encircled areas can be calibrated to provide continuous monitoring of the volume of ventilation. As the result of this method is sensitive to the changes in posture and position of the body, so it cannot be used during surgery on thorax and abdomen.

In an intubated patient, measurement of the tidal volume, respiratory rate and from these the measurement of minute ventilation is easy. Now, these parameters are routinely measured by modern mechanical ventilators.

Measurement of the ventilatory volume in a conscious patient has been discussed before, during the discussion of flow and volume measurement (by spirometer, vitalograph, etc.)

C. Pressure

Methods of measurement of pressure has been discussed before (See the measurement of airway pressure).

Pulmonary Compliance

During the process of expiration when the lung volume reaches at the level of functional residual capacity (FRC), then the pressure at the level of mouth and alveoli is same and atmospheric, So, of position there is no tendency of gas to flow in and out of the lungs. In such position, the tendency of the lungs to collapse (due to the elastic tissue of lungs and chest wall and the surface tension of alveoli all of which constitute the elastic resistance) is exactly counter balanced by the outward pull of chest wall. After that during the process of inspiration gas may, now, be made to flow into the lungs by (i) reducing the pressure in alveoli by primary expansion of chest wall due to spontaneous breathing caused by the contraction of inspiratory muscles which constitutes the work of breathing, or (ii) by increasing the pressure at the mouth (IPPV).

So, each method of inspiration causes a development of pressure gradient between the mouth and alveoli, resulting in flow of gas into the lungs and thus causing volume changes in it. Hence, the relationship between the change in volume (Δv) of lungs and thorax, and the pressure gradient (Δp) is known as compliance (c). At the end of inspiration, gas flow stops and the pressure in all the alveoli again becomes

same as that of the mouth and atmosphere. The force acting to impede this flow of gas during inspiration into the lungs are: (i) the elastic resistance of the lung parenchyma and soft tissue of chest wall (ii) the nonelastic resistance of chest wall comprising the movements of bones at joints (iii) the nonelastic frictional resistance due to the flow of gas through air passage. So, for air to flow into the lungs, a pressure gradient has to develop to overcome all this elastic and nonelastic resistance of the lungs and the chest wall.

Thus from the point of view of inspiration and to produce tidal airflow the lungs are passive organs and rely solely on the work done actively by the diaphragm and the intercostal muscles. Under normal resting conditions all the work is done actively during inspiration, while expiration is passive. During IPPV the work is done by the breathing machine and again this is also usually done during inspiration, while the expiration is generally passive.

Hence, during inspiration expansion of both the lungs and chest wall requires a distending force which is expressed as volume change (ml) per unit change of distending pressure (cm of H_2O), and this is called as the compliance (c).

Therefore, Compliance (c) = Increase of Volume (Δv) in ml/Pressure gradient (Δp) in cm of H_2O

$C = \Delta v / \Delta p$

For air to flow into the lungs and to make a volume change, a pressure gradient (a negative or positive i.e. Negative in normal spontaneous breathing, and positive in IPPV) should be developed to overcome the elastic and nonelastic resistance and frictional resistance. So, the relationship between compliance (c) and resistance (E) is reciprocal, i.e.

$C = 1/E$ or $C = \Delta p / \Delta v$.

The total resistance include both the elastic and nonelastic resistance of the lungs and the chest wall, and also the frictional resistance. Total compliance (CT) is the sum of the compliance of the lungs (C_L) and the compliance of the chest wall (C_{CW}). The relationship between the total compliance (C_T) and the individual compliance of lungs (C_L) and chest wall (C_{CW}) is

$1/C_T = 1/C_L + 1/C_{CW}$ or

$C_T = (C_L\ C_{CW})\ (C_L + C_W)$

The individual compliance of the lungs and the chest wall in a normal healthy person is approximately same and it is about 0.2 litres/cm of H_2O (200 ml/cm of H_2O). Thus the final and total change in volume of chestwall with lungs (i.e. thorax) is 0.2 litre and this is obtained by pressure gradient of 1 cm of H_2O, exerted both by the chestwall and lungs each. So, the total pressure gradient exerted together by the chestwall and lungs is 2 cm of H_2O. Thus, the total thoracic compliance is 0.1 litres/cm of H_2O or 100 ml/cm of H_2O. However, the normal average value is 50 to 100 ml/cm of H_2O.

To detect only lung compliance (C_L), volume change (Δv) and trans pulmonary pressure gradient (which is $P_A - P_{PLU} = \Delta P$) should be measured. To detect only the compliance of the chest wall (C_{cw}), volume change Δv and transmural pressure gradient ($\Delta p = P_{PLU} - P_{ENVIORNMENT}$) should be measured. Thus, to determine the total compliance (C_T), the volume changes (Δv) and the transthoracic pressure gradient ΔP ($\Delta p = P_A - P_{ENVIORNMENT}$) should be measured. In clinical practice, individual C_L and C_W are not measured but only C_T is measured.

The compliance is approximately linear over most of the ranges. But, it is lower when the volume of lung is very small i.e almost fully deflated or when the volume of lung is very high i.e almost fully inflated.. The former is due to the added force needed to expand the collapsed areas of the lung, and also to overcome the surface tension effects. The latter is due to the elastic fibres of the lung reaching their maximum limit.

The lung exhibits hysteresis, i.e the compliance differs both during inflation and deflation. If the compliance is measured when the flow of air has ceased as during breath holding or apnoea in anaesthesia, then it is known as the static compliance. But, when the volume changes of the lung and the thorax in relation to pressure changes is measured during the process of respiration, then it is known as the dynamic compliance. For example, during inspiration the work is done to expand the lungs and the thorax from their resting position at FRC. In a healthy supine, paralysed patient, a sustained inflation pressure of 1kpa (10 cm of H_2O) will increase the lung volume to about 0.85 litres. So, static compliance is 0.85 lit/pka or 85 ml/cm of H_2O, or 0.085 L/cm of H_2O. However, during an inflation if it is necessary to consider the dynamic compliance, then it is nearly about 70% of the static compliance.

Measurement of compliance

We can measure both the static (C_{STAT}) and dynamic compliances (C_{DYN}). It is measured by the pressure-volume relationship, through curves or loops. In this curves and loops the changes in lung volume are displayed on the vertical axis against the inspiratory or expiratory pressure changes which is displayed on the horizontal axis. It is important to know that the pressure used to calculate the total compliance may be that of at the end of inspiration or plateau pressure (P_{PLAT}). This is for determination of static compliance. However, during the period of inspiratory gas flow the peak airway inspiratory pressure (P_{PK}) is necessary for determination of dynamic compliance. For calculation of compliance always the end expiratory pressure (PEEP) must be subtracted from the peak pressure or plateau pressure. The PEEP value is usually obtained from the airway pressure monitor at the end of expiration.

So, $C_{DYN} = V_T / (P_{PK} — PEEP)$

$C_{STAT} = V_T / (P_{PLAT} — PEEP)$

V_T is the tidal volume, which is fixed in volume-cycled ventilators. When there is a development of auto-PEEP, then it should

be considered in the place of PEEP in the above mentioned equation. Otherwise, the measurement of compliance shall be affected. Auto-PEEP is developed when there is insufficient expiratory time. This is because it prevents complete emptying of the lungs and elevates the end expiratory alveolar pressure. This is not detected directly by the airway pressure monitor. Auto-PEEP causes ↓cardiac output, ↓BP and even EMD (electromechanical dissociation), when the patient is on a ventilator. The auto-PEEP is most likely to be present, when there is an increase in airway resistance or compliance causing prolongation of (Fig. 22.12) the expiratory time. It also occurs when high ventilation rates are required. The measurement of auto-PEEP is accomplished by obstructing the exhalation port of the ventilator, while waiting for the onset of next ventilator breath. Alveolar pressure will then become equal to that of the ventilator circuit and auto-PEEP can be measured on the airway pressure monitor. During the measurement of auto-PEEP, it is important to prevent fresh gas flow from entering the circuit, which shall falsely elevate the auto-PEEP.

The total static compliance can also be measured in an intubated patient by occluding the tube and measuring the pressure in the system. After that the tube is unclamped and the volume of air or gas expired is collected and measured in a spirometer. From this, a pressure – volume curve can be plotted and the total static compliance can be measured. For the measurement of only static compliance of lung, the pressure gradient between the airway and the pleural space has to be measured. The direct measurement of intrapleural pressure by placing the tip of a sampling catheter within the pleural space is not possible practically. So, the oesophageal pressure, which closely parallels the intrapleural pressure is measured. Since this measurement is a static one, so it is made with the patient holding his breath, after having inspired a known volume of air from the spirometer. The procedure is then repeated a number of times with different volumes, so that a pressure volume curve can be constructed. This is usually linear and gives an average value of the static lung compliance. Compliance of the chest wall is obtained by subtraction of the lung compliance from the total thoracic compliance. During measurement of the compliance, compliance of the anaesthetic circuit, including humidifier and the gas warming system (which may be as high as 10 ml/cm of H_2O) must be accounted too, for an accurate result.

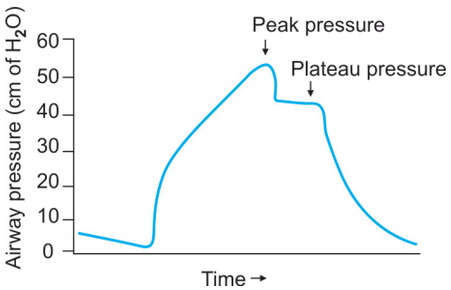


Fig. 22.12: Airway pressure waveform against time. Decrease in the static compliance causes increase in the plateau pressure. Whereas the decrease in the dynamic compliance results in an increase of peak airway pressure. Peak airway pressure is related to both the airway resistance and the thoracic compliance, whereas plateau pressure is only related to compliance

Values of the measured compliance should always be read in relation to the predicted normal value of a person of the same sex, age, height, weight, lung volume and FRC. Any change in FRC, such as, a simple change in posture can produce a change in compliance. Total static compliance is decreased during atelectasis, pulmonary oedema, pneumothorax, emphysema, mitral stenosis, external compression on the chest, ↑intra-abdominal pressure by any cause, ↑pressure on the rib cage, ↑intrathoracic pressure (pleural effusion), etc. Total dynamic compliance is decreased by an elevated airway resistance, such as, due to bronchospasm, mucous plug, kinking of airway or tubes, induction of anaesthesia, etc. It has been known for many years that the induction of anaesthesia itself causes a decrease in compliance, which is due to the increased elastic recoil property of the lungs after induction. A typical value of the static compliance of the lungs and chest wall in an anaesthetised, paralysed patient is 85 ml/cm of H_2O. Whereas in the supine, conscious patient it is 120 ml/cm of H_2O.

Decreased thoracic compliance to less than 25 ml/cm of H_2O is unlikely to result in a successful weaning off from the mechanical ventilation. During anaesthesia many factors operate at the same time, affecting the compliance and the situation changes so often that it is frequently impossible to relate any change in compliance to a specific single agent or procedure. For example, drugs may affect the muscles of the thorax and change the compliance. The secretions in the respiratory tract, alterations in the cardiac output, constriction of the bronchioles or dilatation of the pulmonary vessels, etc. – also alter the compliance.

Resistance

For air to flow in and out of the lungs, a pressure gradient has to be developed at the cost of energy. Work of breathing supplies this energy which is responsible for this propulsion of air. But, the flow of air in and out of the lungs is opposed by some factors or force which is called the resistance (R). So, the function of the work of breathing is to supply energy which will overcome this resistance by creating a pressure gradient, and thus helps the air to flow. Hence, the relationship between the pressure gradient (Δp) and the flow or the rate of change of volume (Δ) is influenced by the resistance. So, the resistance (R) is defined as the change in pressure per unit change in volume, or

$R = \Delta p/\Delta v$

This equation of resistance is equal to the equation of elasticity, but is reciprocal to compliance. The normal value of total resistance in respiratory system is 1.5 cm of H_2O/lit. But, under anaesthesia it may rises as high as 9 cm of H_2O/lit.

There are three essential components of resistance. These are:

i. Elastic resistance due to lung parenchyma itself and soft tissue of thoracic wall.
ii. Nonelastic resistance due to the movement of the structure of chest wall.
iii. Frictional resistance in airway due to the movement of air.

(i) Elastic resistance of the lungs

During inflation the changes in the lung volume occur as a result of the expansion forces applied to the lungs, which is expressed as pressure. This is the concept of compliance. Whereas the concept of elastance or elastic resistance is opposite to the compliance which prevents this change in volume.

Thus, to summarise, the compliance which is the change in volume per unit change of pressure works against the resistance, which is change in pressure per unit change in volume.

The elastic resistance of lungs is also the force which tends to return the lungs to its original size after stretching or inflation and is responsible for the air exit. It should not be thought of as the force required to expand the lungs. One of the principal factors causing the elastic recoil of the lung is the presence of elastic fibres within the pulmonary tissue. Another important factor contributing to the elastic resistance is the surface tension of the fluid, lining the alveolar walls. At larger lung volumes, connective or elastic tissue elements predominate in the elastic resistance. Whereas, at lower lung volumes the effects of the surface tension predominate in elastic resistance. The important role of surface tension of the fluid, lininig the alveolar walls, is to draw the opposing walls closer together, so that the alveoli collapse. If this fluid is only water, it would exert a considerable elastic pull of about 70 dynes/cm. But, fortunately, the presence of surfactant (detergent like agent which reduces surface tension) in the alveolar wall reduces this collapsing pull to as little as 2 to 8 dynes/cm.

The alveolar wall is always lined with a thin layer of fluid and the curved surface of the lining fluid on the alveolar wall creates a tension. This tends to make the surface area of the alveoli which is exposed to the air as little as possible, and hence the alveoli collapse. Thus this collapsing force or tension in alveoli is called the surface tension. It follows the Laplace rule i.e.

$P = 2T / R$ or $T = ½PR$

where, P is the alveolar pressure, T is the surface tension and R is the alveolar radius.

From the above equation it is clear that radius is directly proportional to the surface tension. If the radius of the alveoli decreases, i.e. when the alveolar size reduces during expiration, then the surface tension tending to collapse will increase and a vicious cycle is established. It can be explained simply by the fact that liquid molecules are crowded much closer together on the curved lining surface when the alveoli decreases in size and thus gradually increases the collapsing pulling surface tension force (elastic resistance).

But, in fact this does not happen. as alveoli are coated with a detergent like chemical, called surfactant, which reduces the surface tension or elastic recoiling property of the alveoli. As the alveoli deflate and the size decreases, the amount of surfactant per unit area of alveolar membrane increases, and so the surface tension is more and more reduced, which is proportional to the increase of surfactant due to the reduction of alveolar radius. In this way, the action of surfactant becomes more efficient, when the alveoli decrease in size. Therefore, contrary to what would be predicted on the basis of Laplace's law, the elastic recoiling resistance of the smaller alveoli is lesser than the larger alveoli, and hence smaller alveoli can be inflated more easily than the larger ones.

(ii) Non-elastic structural resistance

Nonelastic structural resistance is composed of the thoracic wall, the diaphragm and the abdominal contents and is due to the movement of these structures among them.

(iii) Airway frictional resistance (Non-elastic)

Airway resistance is important because it is dependent on the length and size of the lumen of the bronchial tree. Airway resistance also depends on the type of flow. The flow of air through the bronchial tree may be turbulent or laminar. Laminar flow occurs at low flow rates and in the smaller bronchi. Laminar flow rate (V) is related to the driving pressure (δp) by Poiseuille's law or equation, i.e.

$V = \delta p \pi r^4 / 8nL$

where, r is the radius of the tube, L is the length of the tube and n is the viscosity of gas.

Radius of the tube is critical. Halving of the tube diameter reduces the flow by a factor of 16, for the same driving pressure (δp). This has a very important implication in paediatric practice. Because, to maintain the same flow in a tube which is reduced half in diameter, the driving force should be increased by 16 times.

Laminar flow occurs when the gas passes down the tube, less than a certain critical velocity. When flow exceeds the critical velocity, it becomes turbulent. Airway resistance in turbulent flow can be lowered by density. This explains why low density gases, such as helium, diminshes the resistance to flow, in severe upper airway obstruction.

The total cross-sectional area of the airway increases as branching occurs. Therefore, velocity of airflow decreases. Laminar flow is therefore chiefly confined to the airways, below the main bronchi. The flow in the trachea is turbulent during most of the respiratory cycle. Airway resistance is estimated indirectly by monitoring the flow-time or volume-time relationship, in a passive exhalation after manual inflation of the lungs.

MONITORING OF THE DEPTH OF ANAESTHESIA

Introduction

Conceptualisation of the depth of anaesthesia is very complex. It ranges from in-depth scientific discussion of MAC (Minimum Alveolar Concentration of the anaesthetic) to the clinical assessment of light, moderate and deep anaesthesia.

Horace Wells failed to demonstrate the anaesthetic properties of N_2O in 1845, when the patient screamed out of pain during dental extraction, even though he later could not recall the sensation of pain (loss of memory, but no loss of pain sensation). One year later, WTG Morton succeeded in anaesthetising a patient named Gilbert with ether. Gilbert later reported that he had been aware of the surgery, but had experienced no pain (loss of pain sensation, but no loss of memory). Thus, it seems that Well's patient was aware of pain, but had no post-operative recall. While Morton's patient had some post operative recall, but there was no awareness of pain. After that, 158 years have passed. But, still the assessment and monitoring of the depth of anaesthesia which includes both the depth of analgesia and the depth of loss of memory remains evasive. Even now, despite the fact that awareness under anaesthesia is terrifying both to the patients and also to the anaesthesiologists, still the general notion regarding the awareness under anaesthesia remains cloudy.

History

A greek philosopher in 100 BC had first described the analgesic and amnesic properties of Mandogra. The word 'Anaesthesia' was also first used by him. Then, after a long gap in 1721 the word 'Anaesthesia' first appeared in Bailey's English Dictionary. There it was described as 'the loss of sensation, but not the loss of consciousness'. After that in 1771, in Encyclopedia Britanica the word anaesthesia was defined as 'the privation of senses'. Now, anaesthesia is defined as the triad of analgesia, hypnosis and skeletal muscle relaxation, with recent addition of the depression of autonomic nervous system.

For long time immobility in response to a noxious stimulus has been used as the measure of the depth of anaesthesia. But, it was before the appearance of muscle relaxants. So, after the routine use of muscle relaxants in practice of anaesthesia, there appears many problems regarding the assessment of depth of anaesthesia, as the movement part is removed by the paralysis of muscles. So, to circumvent these vexing problems, the anaesthetists have turned towards the more easily quantifiable EEG changes, as a measurement of the depth of anaesthesia.

In 1847, after the introduction of ether in 1846, Plomley had first defined the depth of anaesthesia by describing it in different stages, starting from the onset of anaesthesia to the surgical end-point. These stages, described by Plomely were: intoxication, excitement and the deeper levels. In the same year a Paris physiologist, named Marie Flourens concluded that ether with the deepening of anaesthesia, causes the depression of CNS gradually in order of the higher cerebral centres, the cerebellum, the spinal cord and finally the medulla oblongata, where the respiratory and cardiovascular centres are located. Then, in 1847, John Snow who became very interested on ether soon after its introduction, described five stages of etherisation as a concept of depth of anaesthesia in his publication. Among these five stages, the first three were of light anaesthesia. The fourth comprised of what we would regard as surgical anaesthesia and in the fifth, respiration became progressively impaired. In the same year two deaths were reported from ether anaesthesia. So, the early 1900's saw the introduction of premedication, different sedatives and opioids and more other rapid acting anaesthetics such as N_2O, ethylene etc., as the anaesthetic excitement phase could be traversed more rapidly by them. So, the attempt to measure the depth of anaesthesia by only the degrees of etherisation soon became blunted.

Then, in 1911 the concept of a balanced anaesthesia had come, when George Washington taught that psychic stimuli could be obliterated by light general anaesthesia, while noxious impulses due to surgery could be blocked by local analgesia. After that in 1926, John S. Lundy of Mayo clinic first introduced the term 'Balanced Anaesthesia' by combining different methods such as premedication, regional analgesia and general anaesthesia, so that pain relief was obtained by judicious mixing of agents and techniques.

Then, in 1937, Guedel's book named 'In halational Anaesthesia' was published. In this publication he described the depth of anaesthesia in four stages in a case of unpremedicated ether anaesthesia, with four planes of stage III. Then in 1954, Artusio expanded Guedel's stage I, describing it more into three planes:

- In plane I, the patient had no amnesia oranalgesia,
- In plane 2, the patient had total amnesia, but partial analgesia,
- In plane 3, the patient had complete analgesia and amnesia.

After that, for a long time the clinical signs to measure the depth of anaesthesia, defined by Guedel and Artusio, had significant practical utility during the administration of ether and chloroform.

Memory and Awareness

Before the introduction of ether, in 1846, any surgical operation was like a dream to the physician and a nightmare to the patient. So, there are many stories of torture and suffering by the victims of surgical operation, performed before the introduction of ether. But, even with the passage of time and dramatic improvement of medical science with the introduction of many potent drugs, equipments and methods, till now the vivid descriptions

of pain and recall during surgery have not been eliminated completely.

Two degrees of inadequate depth of anaesthesia has been described by Vickers. The first degree involves the retention of memory of an event that occurred while under anaesthesia. This retention of memory or awareness is termed as the 'recall' and represents a conscious or explicit memory. This conscious memory involves spontaneous recall without the aid of any clue. This positive information may help in enhanced patient recovery. The second degree of inadequate depth of anaesthesia involves patients with no memory of events, i.e. no recall, but have the responsiveness to the auditory input or verbal command, which is called the 'wakefulness'. This 'wakefulness' has been described as the response of a patient to a verbal command during and after surgery without recall. This detection of meaningful auditory input under anaesthesia has also been termed as the unconsciousness or implicit memory. This implicit memory or memory in an unconscious state may alter the behaviour or performance of a patient. This negative information could have deleterious psychological effects postoperatively.

Although, lot of literature exists regarding the intraoperative recall and wakefulness, but much of it is anecdotal. As a result, our understanding of the factors relevant to a patient's recall or wakefulness is limited.

The incidence of memory (explicit or implicit) during anaesthesia is probably underestimated. This is because very often only the conscious recall is taken as an evidence but implicit memory or memory in unconscious state cannot be taken into account. The incidence of intraoperative awareness or wakefulness has been reported to be about 0.2 to 2%, but it may be as high as 40% in high risk situations like trauma, caesarean section, etc. where narcotics and sedatives are used less judiciously. The incidence of intraoperative memory or recall is similar to both the volatile agents and the TIVA technique. The incidence of recall is high in patients who are given anaesthesia with only N_2O, O_2 and muscle relaxants than with potent inhaled anaesthetics. However, the use of potent inhaled anaesthetics does not guarantee the lack of recall. The intra operative awareness or recall can also occur with high dose of opioid anaesthesia, though it was not thought so previously.

There are many ways of rendering adequate depth of anaesthesia. But what is 'adequate' is difficult to define. We don't have definite end points to measure the adequacy, unlike analgesia. The only reliable end point for consciousness is absence of response to a voice command, but this does not distinguish light sleep from a deeper one. However, most patients end up with more hypnotic effect than necessary during intraoperative period and probably is the cause of postoperative drowsiness and delay in discharge from the hospital. At the same time, when large doses of opioids and muscle relaxants are used to suppress the somatic and autonomic responses, then hypnosis is usually inadequate. It has been shown that even maximum doses of opioids fail to suppress the conscious awareness or memory formation. In a recent study, even at Bispectral Index (BIS) values of 60 to 70 which correspond to adequate hypnosis, 2/3rd of the patients respond to voice commands, though fortunately only 1/4th of the patients recall episodes of awareness.

Unfortunately, there is no 'gold standard' to compare the different states of anaesthesia. So, some argue that the 'depth' is a wrong term. It is better to know whether the patient is adequately anaesthetised or not. So, to divide these states into various levels seems practically inappropriate.

Grades of awareness:

i. Explicit memory with recall.
ii. Expicit memory without recall.
iii. Implicit memory.
iv. Not aware.

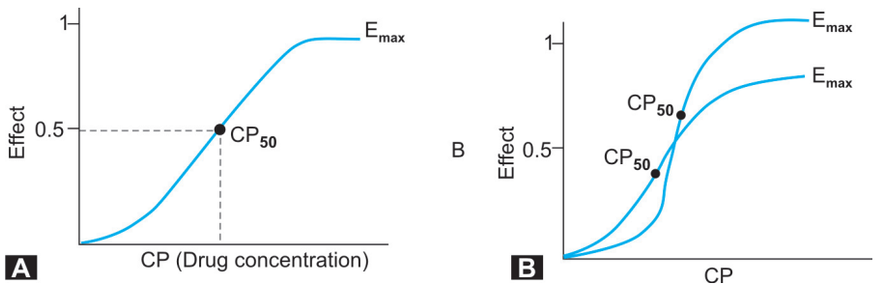
The last stage is only obtained in deep anaesthesia with no sign of awareness or recall at all.

The memory may be explicit (needs effort to recall) or implicit (effortless). An explicit memory system is more sensitive to the effects of GA. With increasing anaesthetic concentration, there is little effect on conscious awareness, but explicit memory is lost. Further increase of anaesthetic concentration abolishes awareness, but implicit memory may be present leading to post-operative psychosomatic dysfunctions.

Pharmacodynamics and Depth of Anaesthesia

Actually, the process of anaesthesia and its depth is nothing but the pharmacological responses (or pharmacodynamics) of an anaesthetic agent. The pharmacodynamics of anaesthetic agents again depend on pharmacokinetic of them. So, before discussing the clinical and electrophysiological methods of measuring the depth of anaesthesia, we must try to understand the pharmacological concepts of it, i.e. pharmacokinetics and pharmacodynamics of the anaesthetic agent which is related to the depth of anaesthesia. Actually, anaesthesia is the pharmacological response of an anaesthetic drug (pharmacodynamics) and its depth, i.e. the intensity of action depends on the administered dose, the concentration of it in blood and the elimination of that drug (pharmacokinetics) from the body. So, measurement of the depth of anaesthesia is governed by the pharmacokinetics of that agent and is nothing but the pharmacodynamic measurement of it (Fig. 22.13).

Though, a continuous measurement of the depth of anaesthesia is actually a continuous measurement of the pharmacodynamics of the anaesthetic agent being used, but we indirectly measure it by measuring the blood concentration of the drug (pharmacokinetic factor) and plotting the concentration versus effect relationship on



Figs 22.13A and B: A. The relationship between the plasma concentration of a drug (CP) and its effect is a sigmoidal curve, where: E_{max} = maximal drug effect, CP_{50} = the plasma concentration of the drug that produces 50% of maximal effect. Slope of the curve = rate of change.
B. Two anaesthetic agents have different concentration - response curves, with different maximal effects. CP_{50} values are also different

a graph. Actually, the concentration and effect (kinetic-dynamic) relationship of a drug is a sigmoid-shaped curve. The lower minimal or baseline effect and the upper maximal effect of an anaesthetic agent are the extremes of drug response. However, the mid-point between the baseline and the maximal effect is commonly referred to as the CP_{50}. This indicates the plasma concentration of a drug that results in 50 percent of its maximal effect. This parameter indicates the potency of the drug and the sensitivity of the individual to that drug. Although, CP_{50} can be measured and the concentration-versus-effect curve of a drug can be generated, but there are some limitations of this methodology. Because the concentrations-effect curves of two drugs have two different curves, and if the maximal effects differ, then the CP_{50} values cannot be used to compare the drug potency or the individual sensitivity to it. There are also some other limitations, such as the type of stimulus given to measure the response of a drug (Table 22.4).

The MAC Concept for Measurement of Depth of Anaesthesia for Volatile Anaesthetic Agent

At equilibrium the partial pressure of inhaled anaesthetic agents should be similar in all the body tissues e.g. alveolus, blood and brain. Thus, the measurement of end tidal concentration of an anaesthetic agent which is representative of the alveolar concentration is nothing but an indirect measurement of the concentration of this agent in brain which is again parallel to the depth of anaesthesia. This is because cerebral perfusion is very large and most of the volatile anaesthetic agents are highly lipid soluble. So, it is possible to achieve easily an equilibrium between the end tidal alveolar, arterial and brain concentration (or partial pressure) within 15 minutes of exposure to a constant alveolar anaesthetic concentration.

So, MAC is defined as the minimum alveolar concentration of inhaled anaesthetic agent, which is required to prevent 50 percent of the subjects from responding to a painful stimulus with gross powerful movement. In this definition, there are two things which are not properly explained: (i) the nature of the stimulus and (ii) the extent of the response. Therefore, for determination of MAC in human beings initially surgical skin incision is taken as the standard noxious stimulus, because skin incision represents a reproducible form of supramaximal surgical stimulation. Again, respone to stimulation must entail a positive, gross, purposeful muscular movement, usually of the head or extremities, and this is taken as the standard response.

Regarding the type of stimulus and the type of response to the stimulus, there is some controversy in MAC concept for measuring the depth of anaesthesia. For responses, twisting and jerking of head is also considered as positive, but twitching or grimacing is not. Coughing, swallowing, chewing response are not considered as positive movement for responses. Similarly, there are also other stimuli which are stronger than the initial skin incision. These are intraoperative profound surgical manipulation, peritoneal traction, endotracheal intubation, etc.

Thus, MAC concept has been expanded by using different noxious stimuli and observing their different clinical response. These are MAC-awake, MAC-intubation, MAC-skin incision, MAC-BAR etc.

MAC-awake

'MAC-awake' is the minimum alveolar concentration of an inhaled anaesthetic agent that would allow opening of the eyes on verbal command. This type of stimulus and response is used during emergence from anaesthesia. Thus, stimulation is less intense than surgical skin incision, and response occurs at lower concentrations of anaesthetics than movement to skin incision.

MAC-intubation

'MAC-intubation' is the minimum alveolar concentration of an inhaled anaesthetic

Table 22.4: Pharmacokinetic and pharmacodynamic components of the dose-response relationship

Dose of a drug → Concentration in blood → Response in tissue	
↑	↑
PHARMACOKINETICS	PHARMACODYNAMICS
Initial volume of distribution	Concentration or response relationship
Distributional clearance	Threshold effect
Steady state level	Maximal effect
Metabolic clearance	Slope factor
Terminal elimination	Equilibrium delay or hysteresis

agent that would inhibit the movement and coughing during endotracheal intubation. Here, the stimulation is more intense and the response is inhibited by minimum alveolar concentration of the anaesthetic agent which is necessary for that strong stimulus.

MAC-BAR

'MAC-BAR' is the minimum alveolar concentration of an anaesthetic agent which is necessary to prevent the adrenergic response to skin incision and is measured by the concentration of catecholamines in the venous blood.

All the MAC values are nothing but the representation of concentration or dose effect relationship curves (i.e. pharmacokinetic-pharmacodynamic relationship) of that inhaled agent. But the difference of it depends on the type of the noxious stimuli, used to elicit the different types of responses. However, for measuring the depth of anaesthesia, the MAC concepts have other limitations also (which cannot be discussed fully here).

Methods of Measuring and/or Monitoring the Depth of Anaesthesia

The depth of anaesthesia is measured and/or monitored by the followind methods:

A. Clinical or conventional methods of monitoring , and
B. Brain electrical activity monitoring.

A. Clinical or conventional methods of monitoring

This is performed by (i) some clinical techniques or signs, (ii) isolated forearm technique, (iii) lower oesophageal contractility technique, (iv) heart rate variability technique, etc.

Clinical signs

Among the clinical signs that are used to assess the depth of anaesthesia are: checking for any movement, any response to commands, eyelash reflex, pupillary response, perspiration, tearing, etc. Conventional monitoring also includes ASA standard monitoring. For measurement of the depth of anaesthesia by clinical signs the most commonly used scoring system is the Evan's score (or PRST system). This scoring system assesses the autonomic activity, related to the changes in systolic pressure (P), heart rate (R), sweating (S) and tear (T). It is a very simple system and does not require any sophisticated instrument. But, the parameters are not specific for the type of anaesthesia or the anaesthetic agent and the results can vary widely among the individuals. The score ranges from 0 to 8. But, the mid point seldom exceeds which reflects the inadequacy of the scoring system. This can be explained by the fact that tachycardia secondary to anticholinergic drugs such as atropine makes the heart rate uninterpretable. This is also applicable to β-blockers, opiates, etc. which obtund the sympathetic system activity producing bradycardia and stops response to pain.

Isolated forearm technique

This technique of detecting awareness was used previously in clinical practice and in some experiments during research. Here, a tourniquet is applied on the upper arm and inflated above the systolic blood pressure, before administration of the muscle relaxant. Movement of the hand either to command or spontaneously or after skin incision indicates awareness. But the absence of movement does not indicate the absence of wakefulness. Because, some argue that a response to command intraoperatively is a late sign of attempting to prevent awareness. However, not all responding patients have a recall. One limitation of this technique is the available fixed time due to the tourniquet-induced ischaemia, before patients are unable to move their hands.

Lower oesophageal contractility (LOC)

After full skeletal muscle relaxation by a neuromuscular blocking agent, the smooth muscles of the lower half of the oesophagus still retain their potential contractile activity. This activity is related to the CNS depression and so is used to measure the depth of anaesthesia. Two types of smooth muscle activity in the lower oesophagus are detected: one is the spontaneous lower oesophageal contractions (SLOC) and another is the provoked lower oesophageal contraction (PLOC). SLOC is under the control of higher centres and can be induced spontaneously by emotion and stress in an awake individual. It arises spontaneously and is not affected by muscle relaxants. It can be detected only by a pressure transducer. On the otherhand, PLOC is induced by a provoked stimulation by inflating the balloon in the lower oesophagus and the interpretation is similar to SLOC.

Both SLOC and PLOC are reduced in latency and amplitude during general anaesthesia. But, the published data about its use in the monitoring of depth of anaesthesia is limited. One way of improving the available information is by combining the measurement of SLOC frequency with PLOC amplitude which leads to the derivation of the oesophageal contractility index (OCI). The OCI is easy to interpret and can be used in the presence of muscle relaxants. However, the general opinion is against this method and it is now considered unreliable in measuring the depth of anaesthesia.

Heart rate variability (HRV)

It is postulated that the anaesthetic agents first acts directly or indirectly on the brain stem. Then, it inhibits the cerebal cortex through the ascending efferent projections from the midbrain. Therefore, the measurement of one of the important brain stem mediated autonomic activity, such as, heart rate, which is not affected by any factor other than the anaesthetic agent is a good method to monitor the depth of anaesthesia. The special analysis of the heart rate variability reveals three components: (i) circadian low frequency fluctuation,

(ii) baroreceptor attributed medium frequency fluctuation, (iii) respiration induced high frequency fluctuation. The last component is also called the respiratory sinus arrhythmia (RSA), which is manifested by an increased heart rate during inspiration and a decreased heart rate during expiration. This is mediated by a parasympathetic reflex, connecting the stretch receptors in the lungs to the vagal motor neurons, innervating the heart. RSA is easily recognised by the ECG monitor, which is time locked to R-wave peak. Using an on-line analysis of RSA, it is found that RSA is reduced during anaesthsia and is increased during recovery, while it is also related to the depth of anaesthesia.

Though RSA is useful for monitoring the depth of anaesthesia, but needs a healthy myocardial conducting system and an intact autonomic nervous system. Any factor which affects these two systems, such as, β-blocker, conduction block, autonomic neuropathy, etc., may interfere with the result.

B. Electrophysiological approaches to monitor the depth of anaesthesia

The realisation that anaesthetic drugs affect the EEG dates back to the discovery of electrical activity in brain. The electrical activity of brain in animals was first noted by Richard Caton of Liverpool, in 1875. But, he was unable to record it. Then, in 1920, development of electronic amplifiers allowed the recording of low voltage electrical activity of brain. Berger, in 1929, recorded the changes in electrical potential by placing electrodes on the scalp of human beings. In 1930, Berger also measured the influence of chloroform on EEG. Then in 1931, he described the alpha rhythm. In 1934, Adrian and Matthews developed the clinical use of electroencephalogram (EEG). Then, Gibbs postulated that EEG might be used to measure the depth of anaesthesia and also reported in 1937 that anaesthetic agents change EEG activity from a high frequency-low voltage to a low frequency – high voltage character. In 1952, Faulconer demonstrated the relationship between the concentration of ether in blood and the pattern of EEG with the increased depth of anaesthesia.

EEG represents the cortical electrical activity, derived from the summated excitatory and inhibitory post-synaptic potentials of the large and symmetrically arranged pyramidal cells in the cortical layer III and IV of which are again controlled by subcortical thalamic nuclei. Originally, it was thought that EEG waves were the summated action potential of the cortical cells, discharging in a volume conductor. But, this concept has changed and now it is thought to be due to the current flowing in the fluctuating dipoles which are formed by the dendrites of cortical cells or cell bodies. Cortical dendrites are the forests of dense units placed in the superficial layers of cerebral cortex. Dendrites are the sites of local non-propagated hypopolarisising and hyperpolarising potential changes, induced by the excitatory and inhibitory axo-dendritic synapses. Dendrites are not the processes for conduction and do not propagate action potential. Action potentials are propagated through the axonic terminals. When the excitatory axo-dendritic synapses are activated, then current flows in and out of the cell body and the axo-dendritic endings, causing a wave like potential fluctuation in the volume conductor. Thus, EEG is the potential fluctuation in volume conductor, but not the actual action potential and is conducted through the axon only. Thus the dipole, formed in between the dendrites and the cell bodies, fluctuates constantly due to the excitatory and inhibitory axo-dendritic synapses.

The electrical activity of the cerebral cortex is mainly of two types: spontaneous and evoked. The spontaneous EEG which is used to measure the depth of anaesthesia is again classified into raw and processed.

Raw EEG

The record of spontaneous electrical activity of the brain is known as the electroencephalogram (EEG). Whereas the process of recording of changes in electrical potential in various areas of the brain by means of electrodes placed on the scalp is known as electroencephalography, and the instrument used in recording is known as electroencephalograph. An EEG record may be bipolar or unipolar and consists of different types of rhythmic waves. Bipolar EEG is the record of fluctuations of potential between the two cortical electrodes. Whereas the unipolar EEG is the record of potential difference between a cortical electrode and an indifferent electrode placed on any part of the body. EEG is a more complex signal with very low amplitude of 50 to 200 μv and with frequency that is classified conventionally into four categories: delta waves (0 to 4 Hz), theta waves (4 to 8 Hz), alpha waves (8 to 13 Hz) and beta waves (>13 Hz).

The EEG is more or less a non-invasive indicator of the cerebral function. When the patient is unresponsive or unconscious, then EEG helps to assess the cerebral physiology. But, recording of the electrical activity of brain with acceptable low level of artefacts and interferences is very difficult. This is because EEG signals are very small and easily masked by extraneous activities, such as, muscular contractions. So, it requires careful, secure and correct placement of electrodes for correct recording and interpretation. Then, they have to be amplified and filtered for frequencies which are outside of the optimal range. Again, multiple channels are required and the interpretation can be tedious and time consuming.

All the anaesthetic agents can cause changes in the cortical neural activity, reflected by the EEG. However, frequency changes are never accurate diagnostic tools and they have to be interpreted with a particular relevant context. For example:

i. Induction of anaesthesia – increases the β-activity with decrease in the α-rhythm.
ii. Deepening of anaesthesia – 'θ' or 'δ' activity predominates.
iii. Further deepening of anaesthesia – results in a burst suppression (Fig. 22.14).

Processed EEG

Actually, the unprocessed raw EEG is not a practical tool for monitoring the depth of anaesthesia. Hence, many techniques are developed to process and analyse this raw EEG. So, gradually sophisticated and automated analysis of various processed EEG components have generated several potentials for measuring the depth of anaesthesia. But, still there are two generic problems with these processed EEGs.

These are: (i) Dissimilar anaesthetic agents generate different EEG patterns, and (ii) Various pathophysiological events other than anaesthesia also affect the EEG such as hypotension, hypoxia, hypercarbia, etc. Such events may also modify both the patient's level of consciousness and the expected EEG pattern, which can be generated by any given anaesthetic agent and thus confuse the interpretation.

The recording of raw EEG involves accumulation of large amount of information on the EEG paper. But, newer computer analysis techniques can distill and summarise the raw EEG into a condensed (data reduction), descriptive format which is called the 'processed EEG'. In a processed EEG after distillation or filtration and amplification the analog signal is converted to a digital signal. Then, various signal processing algorithms are applied to the frequency, amplitude and latency of the signal to derive a phase-relationship data which generates a single number. This single number system is often referred to as 'index' which is typically scaled between 0 and 100. This index represents the progression of clinical states of consciousness such as awake, sedated, light anaesthesia, deep anaesthesia, etc. Artefact recognition algorithm which is used to avoid contamination and spurious index is an important component of the software in most monitors. Although EMG activity from the scalp muscles (as electrodes are placed on it) is considered as an artefact from the view point of pure EEG analysis, but it may be a very important source of clinically relevant information. Because, sudden appearance of the frontal EMG activity suggests somatic responses to noxious stimuli, resulting from inadequate analgesia and may give a warning of impending arousal. For these reasons, some monitors separately provide information on the level of EMG activity.

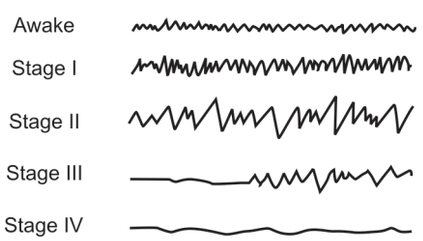


Fig. 22.14: Increasing plasma concentration of thiopentone, produces a characteristic progress of changes on EEG
Stage I: Frequency and amplitude of waveforms increase
Stage II: Decrease in frequency and an increase in amplitude is observed
Stage III: Thiopentone produces burst suppression pattern
Stage IV: It shows an isoelectric EEG

For the processed EEG two methods of data reduction such as: (i) Fast Fourier Analysis and (ii) Aperiodic Analysis are used. The Fast Fourier Analysis method measures the power of EEG and is used to derive the spectral edge. So, this power spectral analysis by fast fourier the depth of anaesthesia is performed on the blocks of EEG and the result is displayed either as a spectral array or as a power in a series of frequency bands. The characteristic of anaesthesia is a shift to a lower value of the dominant frequency power. The median power frequency (Median Power Frequency – MPF) with 50% of power above or below its value; or the spectral edge frequency (Spectral Edge Frequency – SEF) with 95% of power below its value, both have been used routinely to measure the anaesthetic depth. For example, MPF of less than 4.8 Hz predicts loss of consciousness and is the basis of its use in closed-loop delivery of drugs in TIVA. Most of the newer anaesthetic monitors used to measure the depth of anaesthesia include a module for monitoring EEG and its processed forms like SEF, MPF etc. Then periodic analysis is performed by serially examining each wave, recording its wavelength and its peak to peak amplitude. Another method of data reduction, such as bispectral analysis has been used to predict the movement in response to surgical stimulation, i.e. depth of anaesthesia.

Therefore, the combined power and spectral analysis modules provides the following measurements: two channels of raw real-time EEG wave, continuous spectral analysis of each channel of EEG, total power, percentage of total power in each frequency band, spectral edge frequency, mean dominant frequency, peak power frequency and a continuous impedance for each electrode.

Other Processed EEG's

Other than Median Power Frequency (MPF) and Spectral Edge Frequency (SEF), which have been already discussed, the other processed EEGs are: Bispectral EEG, Narcotrend, Patient State Analyser, Evoked Potential Monitor etc.

(i) Bispectral EEG (BIS) monitors

The characteristics of this Bispectral (BIS) EEG monitoring system include:
i. It is a more advanced EEG signal processing approach than the traditional Fast Fourier methodology.
ii. It has a greater correlation among the huge collection of clinical data (patient's movement, haemodynamics, drug concentrations), EEG data and advanced multivariate statistical data to create a BIS parameter.
iii. BIS analysis specially measures or is more sensitive to the hypnotic

component of the anaesthetic agent. But it does not measure or is less sensitive to the analgesic components of an anaesthetic agent.

iv. BIS in EEG monitoring definitely improves the quality of anaesthetic regime.

Before BIS in EEG monitoring the signals were processed only by time domain, i.e. only by the frequencies. Frequency analysis involves the amplitude (power), frequency (rate) and phase angle. Actually in the traditional power (Fourier) spectral analysis, only the frequency and amplitude (power) estimation were used and information on the phase angle was ignored. This is because power spectral analysis assumes that the frequency component is independent and does not interact. However, this is not always true. So this disadvantage is overcome by Bispectral (BIS) analysis which is nothing but a higher order statistical approach. This approach involves taking EEG, removing artefacts and then performing spectral calculations by both Fourier and Bispectral methods. This method analyses both the linear and non-linear components of EEG and quantitates them. After that a set of EEG features are combined, like power frequency, beta-activation and burst suppression to give a statistical valid prediction of sedation and hypnosis. Thus, to compute the BIS several variables which are derived from the time domain (burst supression analysis) and frequency domain of EEG (power spectrum, bispectrum, interfrequency-phase relationship) are combined into a single index of hypnotic level. Additional clinical data (such as movement or no movement to skin incision, along with equilibrated anaesthetic concentration data) and statistical data are also used to identify the components of EEG that appear to correlate best with the clinical and pharmacological end point.

Thus, BIS is a complex parameter composed of a combination of time domain, frequency domain and also higher spectral subparameters which are derived from the various clinical data. The BIS module and the software which are present in the depth of anaesthetsia monitoring machine uses EEG signal upto 47 Hz, and computes it to a dimensionless number in a numerical scale of 0 to 100, where 0 is the isoelectric or cortical electrical silence and 100 is the awake. Response to voice command is unlikely when BIS is below 70. BIS less than 60 indicates deep sedation. No subject is responsive to any stimulus when BIS is less than 57.

BIS has been validated for many commonly used anaesthetic drugs. It shows a good correlation with the end tidal sevoflurane concentration as well as measured blood propofol concentration. Studies have shown that the use of BIS can decrease the consumption of anaesthetic agents. So it also helps in speed of awakening and in a faster discharge. The utility of BIS is maximal when the anaesthetic regimen is a combination of low doses of opiate analgesis with high doses of hypnotic drugs which is titrated to the bispectral response. For the BIS to reflect maximally, higher doses of hypnotic drugs with lower doses of opiates should be used. The higher doses of opiates result in a significant synergistic interaction with the hypnotic drugs. Also, the reduced amount of hypnotic drugs result in less profound hypnotic EEG effects on CNS and therefore a less sensitive BIS response. It appears that the synergistic interaction of opiates and hypnotics to reach the clinical end point does not correlate well with the EEG effects of hypnotics. The pharmacodynamic relationship of BIS to hypnotic drug concentration is unchanged (i.e. lowering of BIS with increasing hypnotic drugs) if opiate concentration increases.

The clinical use of BIS monitoring involves separating the hypnotic and analgesic components of an anaesthetic regimen. During routine anaesthesia with small to moderate doses of analgesic drugs, an adequate dose of hypnotic agents are used and it keeps the BIS level at the range of 50 to 60. During intense surgical manipulation if BIS increases and patient exhibits movement or haemodynamic responses, then it should be corrected by increasing the dose of hypnotic agent and and thus lowering the BIS value to 50 to 60 range. On the contrary, if BIS remains lower, but the movement and haemodynamic responses continue, then incremental doses of opiates should be added to increase the analgesic component of anaesthetic regimen, until the movement and haemodynamic responses are controlled.

BIS demonstrates the dose-response relationship of hypnotic effects of intravenous and inhalation anaesthetic agents, such as propofol, midazolam, halothane, etc. and correlates well with the clinical assessment of the level of anaesthesia. It is the first processed EEG technique to be used for correlation between the behavioural assessment and the level of consciousness. Ketamine and sometimes N_2O, however, cause EEG activation, complicating the BIS interpretation. Baseline BIS value is not decreased by N_2O at an inspired concentration upto 50%. However, during surgery, the antinociceptive effect of N_2O may be responsible for the observed decrease in value of BIS. As the paediatric EEG only approaches the adult pattern by about 5 years of age, so it cannot automatically be extrapolated to young children. But still, healthy adult EEG data are used to authenticate the BIS algorithm of children, because early investigation suggests that BIS may be valid in children, older than 1 year of age. Comparison of BIS values at various clinical end points between the adults and children suggests that BIS performs similarly in adults and children in respect to dose-response relationship of anaesthetic agents. Its use is also rapidly expanding, especially during care of a critically ill patient admitted in the ICU.

BIS has also been used in cardiopulmonary bypass, vegetative states, CPR,

hypoglycemic coma, etc. But here an increase or decrease in BIS may not always reflect adequate awareness or lack of it. Recently, it has been seen that when BIS is used along with ECT, then values fall to 26 to 28. This is due to the post-tictal EEG depression after ECT. Hence, in such circumstances correlation of BIS with the awakening is affected. It may be unreliable in conditions like dementia. Also, electro magnetic operating systems used in surgeries might affect the BIS monitoring.

Like an EEG signal, BIS is also subject to interference and artefacts, particulaly from EMG activity which can artificially elevate the BIS value. So, some monitors also show a display of signal quality index and an indicator of EMG interference. As there is no 'gold standard' monitor against which BIS can be compared, so studies have used predictive probability that is likely to occur in various clinically relevant end-points such as the loss of consciousness, recovery, recall, etc, at different BIS values. The probability of post-operative recall is very low when BIS is kept < 60 intra-operatively (Table 22.5).

(ii) Narcotrend monitor

This EEG derived monitor used for assessment of depth of anaesthesia performs automatic computer analysis of raw EEG during anaesthesia. In this system two electrodes are placed on the forehead of patient and a third electrode serves as a reference. It uses a 6 letter classification with 14 subclassifications. The letters are A to F, where A represents an awake patient and F denotes burst suppression. In between these the the B and C represent the sedated and light anaesthesia of patient, respectively. With this system the stages D and E are aimed (D = general anaesthesia, E = general anaesthesia with deep hypnosis) at steady-state anaesthesia. During practice, B and C should be avoided and F is considered unnecessarily deep.

Table 22.5: Comparison between BIS and Narcotrend

1. BIS ≈ 100 to 85 = A and B levels of Narcotrend system (A = Awake, B = Sedated)
2. BIS ≈ 85 to 65 = C levels of Narcotrend system (C = Light anaesthesia)
3. BIS ≈ 65 to 40 = D and E levels of Narcotrend system
4. BIS ≈ < 40 = F (burst suppression)

(iii) Patient state analyser

The patient state analyser is also an EEG derived colour-coded patient safety index (PSI) which is recorded on a scale between 0 to 100. Green colour indicates the hypnotic state and comes in the 25 to 50 PSI range. Yellow indicates deep hypnosis and involves an index below 25. Blue indicates burst suppression. Whereas white indicates artifacts which the analyser machine identifies and discards. The main advantage claimed with this system is that there is little interference with cautery, electromagnetic operating system or noise pollution (Table 22.6).

(iv) Cerebral state monitor

It is a handheld device that analyzes a single channel EEG and presents a cerebral state index (CSI) which is also scaled between 0 to 100. In addition, it also provides EEG suppression percentage and measurement of EMG activity. The monitor is also on-line and evaluates the amount of instantaneous burst suppression (BS) during each 30 seconds period. The CSI is a unitless scale from 0 to 100, where 0 indicates a flat EEG and 100 indicates EEG activity corresponding to awake state. The range of adequate anaesthesia is defined to be between 40 and 60.

Evoked potential

The evoked response or activity in the cerebral cortex is elicited directly by stimulating the cortical surface (Direct Cortical Evoked Response) or indirectly by stimulating the peripheral sense organs like: the retina − by photostimulation (Visual Evoked Potential – VEP), the ear − by auditory click (Auditory Evoked Potential – AEP) or the peripheral sensory nerve endings (Somato Sensory Evoked Potential – SSEP). The type of stimulation may be sensory, electrical, magnetic or even cognitive in nature. The two major types of evoked potentials are sensory (SEP) and motor (MEP), which assess the functional integrity of sensory and motor pathways respectively and is greatly influenced by the effect of narcotics, drugs, and physiological conditions, like sleep, etc. The most commonly used evoked potential for assessing the depth of anaesthesia is SEP. Here, the stimulus is applied at the peripheral nerves and the resulting response is recorded centrally at the cerebral or cortical level. The evoked waves consists of some positive, followed by a few small negative and then by many larger and more prolonged positive deflection. The first positive-negative wave sequence is called as the primary evoked response, while the second one is called as the diffuse secondary response. This evoked response can be separated by means of a special computer from the underlying spontaneous EEG.

Table 22.6: Colour-coding of PSI

Green (25 - 50)	:	Hypnotic state
Yellow (< 25)	:	Deep hypnosis
Blue	:	Burst suppression
White (artifacts)	:	Discarded

The computer techniques which process the EEG signals, first extract the evoked potential from the underlying spontaneous cortical electrical activity after the respective stimulus. Thus, evoked response represents a time versus voltage relationship that can be quantified by measuring the post-stimulus latency and inter-peak amplitude in the waveform.

The evoked responses are used primarily (i) to monitor the functional integrity of neural structures, (ii) to identify the anatomical integrity of neural structures and (iii) to diagnose the neurophysiological conditions. As evoked response is sensitive to anaesthetic drugs, so they have been used to measure the effect of

anaesthetic drugs on brain and also the depth of anaesthesia.

There are several advantages and disadvantages of using evoked potentials for monitoring the effects of anaesthetic drugs and the depth of anaesthesia.

Advantages:

i. Body's response to some form of stimulation forms the pivot for assessing the depth of anaesthesia.
ii. Measuring the evoked potential is a noninvasive and continuous method of measuring the body's response to appropriate stimuli.

Disadvantages :

i. Though all the anaesthetic agents cause changes in evoked response, but there is no standard to measure the drug effect that enables one to identify or characterise this drug effect or the depth of anaesthesia.
ii. There is no known parameter to measure the evoked response.
iii. There are also technical, clinical and practical complexities of recording the evoked responses, like stimulus characteristics (intensity, duration etc.), electrode placement, recording equipment, recording technique etc.

Auditory evoked response or potential (AEP)

Among all the evoked response, AEP is the most important. So, it is only discussed here. Sense of hearing is the last to be lost and first to be recovered during induction of anaesthesia and return of consciousness respectively. This is the basis of using the auditory evoked response for measuring the consciouness and depth of anaesthesia. The applied auditory impulses hit the cochlea of the ear, then it travels via the eighth nerve and reach the brain stem. The auditory stimuli are given as clicks from ear phones. Normally, 1024 clicks at the rate of 6 per second are given, depending on the background noise. Any disturbance in hearing could affect the ability of AEP to reflect the depth of anaesthesia.

The auditory evoked response is again divided into (i) the brain – stem response, (ii) the early cortical response and (iii) the late cortical response.

Brain-stem responses

This is also termed as Brainstem Auditory Evoked Potential (BAEP). These occur within the first 10 milliseconds and consists mainly of six waves, labelled as I to VI. The BAEP is presented as a smooth curve, therefore, typically only the wave V can be detected. They are preserved with all the volatile anaesthetic agents and change very little with anaesthesia. So, they are not so useful to us.

Early cortical responses

This is also termed as Middle Latency Auditory Evoked Potential (MLAEP). These occur within 10 to 80 milliseconds and are designed as PoNo, PaNa, PbNb, etc. These responses, especially Nb shows graded changes with the effect of anaesthetic agents and are so useful to grade the depth of anaesthesia. Nb with a frequency of 47 secs is 100% sensitive and specific for explicit memory during isoflurane anaesthesia. All the volatile anaesthetic agents suppress the early cortical response component of AEP to a similar extent at equipotent MAC. All the volatile anaesthetics increase the latency and decrease the amplitude in a reversible dose-concentration related manner. N_2O decreases it in a progressive dose related manner, due to an increase in the auditory threshold. Intravenous anaesthetic agents also change the evoked potential similar to the inhaled anaesthetics, except benzodiazepines. Ketamine does not affect the early cortical response. Opioids produce only the partial suppression, even in high doses. High doses of opioids do not suppress the consciousness or sensory function. Thus, benzodiazepines, ketamine, opioids and MAC 0.5 volatile agents preserve the early cortical response and so cannot be used to prevent the intra-operative awareness.

Reversible headphones or earphones deliver the active auditory stimulus. Cost effective disposable surface electrodes are used to measure the AEP and the subsequent result enables to measure the patient's level of consciousness. From the mathematical analysis of the AEP waveform, the device generates an AEP index that provides a correlation of depth of anaesthesia with the anaesthetic drug concentration. The AEP index is scaled from 0 to 100. In contrast to other EEG indices, the AEP corresponds with low probability of consciousness at less than 25, rather than the higher numeric threshold associated with the other monitors. More recently AEP index is scaled from 0 to 60. When using this 0 to 60 range, fewer oscillations are observed, while the patient is awake. When asleep, the graphical resolution of the lower index value is higher. It is recommended to use the AEP index in 0 to 60 range. AEP index is very specific and sensitive. When compared to SEF, MPF and BIS, then AEP index is most sensitive in distinguishing transition from consciousness to unconsciousness.

Late cortical responses

This is also termed as Long Latency Auditory Evoked Potential (LLAEP). These occur after 80 milliseconds and are designated as P_1N_1, P_2N_2 etc. These evoked responses are very less sensitive to anaesthetic drugs and volatile agents. Hence, they are of no practical use. The disappearance of P_1N_1 indicates transition from consciousness to unconciousness. Other single derivative derived from the late cortical response like second differential, first differential, coherent frequency, ARX index, etc. are all being evaluated, but are not so promising.

Other Monitors

The other equipments which are used to monitor the depth of anaesthesia are :

i. Positron Emission Tomography (PET)

ii. Super Conductive Quantum Interference Device (SQUID)
iii. Ocular Microtremor Monitoring (OMT)

(i) PET

PET scanning is an invasive method and cannot be used in routine cases.

(ii) SQUID

It is non-invasive, measuring the functional activity of the brain, but is very expensive.

(iii) Oculomicrotremor (OMT) monitoring

Oculomicrotremor is a high frequency physiological tremor of the eye, present in all the subjects and is related to the toxic activity in the brainstem oculomotor neurons. It has been shown that OMT correlates well with the level of consciousness. OMT is suppressed by thiopentone, propofol and sevoflurane. It is measured by a piezo-electric strain gauge technique where probe is placed on the conjunctiva or closed eye. Earlier, the probe was placed on the anaesthetised sclera. But nowadays it can be placed on the closed eyelid. End tidal sevoflurane concentration of 1 to 2% does not decrease OMT, nor decrease BIS, though it shows a falling trend. When compared to BIS, OMT may exclude an aware patient more accurately than BIS, though the graded measure of emergence is better seen with BIS. OMT remains depressed until just before the first response to verbal command appear. Hence, it is more useful as an awareness monitor, than the depth of hypnosis monitor.

MONITORING OF THE CARDIOVASCULAR SYSTEM

Introduction

The cardiovascular system is responsible for the transport of different substrates, products of their metabolism, and adequate oxygen to tissues and CO_2 to lungs, in order to support their continued normal function. Thus, the adequate organ function reflects the adequacy of performance of the cardiovascular system. So, clinically sometimes we measure the urine output, skin colour, body temperature, mental status, sensory or motor functions (cerebral indices), etc. for monitoring of the adequacy of function of cardiovascular system. But, it is not always true or possible due to the presence of some intrinsic end organ dysfunction. Because this kind of clinical monitoring requires the absence of intrinsic end organ dysfunction. So, direct monitoring of different facets of CVS by instruments is more practical and reliable than the only clinical monitoring of the function of end organs. But, both the complexity and diversity of monitoring (both noninvasive and invasive) of CVS by instruments depends on many variables, such as the nature of surgical procedure, fragility of the patient's cardiovascular system, considerations of the risks and costs of various monitoring techniques, etc. So, the ultimate and final decision regarding the extent of the monitoring of CVS by instruments depends on the judgement of anaesthetist, who choose a particular technique for monitoring will provide sufficient information with minimum risks and cost to optimise the management of a particular patient.

History

It was the 28th January of 1848, when the first death due to anaesthesia was reported and it was an excision of an ingrowing toenail during administration of choloroform. This was just 2 years after the first public demonstration of anaesthesia by ether and the patient was only 15 years old, named Hannah Greener. However, before that another two deaths were also reported unofficially in March 1847. The first was a young woman at Yrantham, named Lincs and the second was a 52 years old man at Essex.

So, nearly a century and a half later this incident still reminds us that even a rudimentary awareness and a minimum monitoring of patient's cardiovascular system can avert many of the mishaps. Also, the development of newer and far less toxic anaesthetic drugs than choloroform emphasises that the necessity of adequate and careful monitoring of CVS is still not less important today or in future, than it was thought previously at the time of invention of anaesthesia. At that time, the assessment of patient's cardiac performance was entirely subjective, i.e. without any equipment. Then, the remainder of 19th century saw little or no advancement in the development of objective monitoring with equipments during anaesthesia.

In 1860, Joseph Clover had first initiated the monitoring of a patient by keeping his fingers on patient's pulse, while administering choloroform. Then the end of that century, a feather was added to the vulcanite face-piece to monitor the respiration by observing its movement. Then in 1894, Earnest. A. Codman, a surgeon of Harvard, developed a system of intraoperative monitoring and a record-keeping system at the Massachusset's General Hospital. After that, in 1903, a routine and a new form of cardiac monitoring protocol was first placed in anaesthesia practice in USA. This had included the measurement of systolic blood pressure by Riva-Rocci's sphygmomanometer, measurement of heart rate, measurement of respiratory rate, etc. The mercury manometer was first used to measure the blood pressure by Poiseuille in 1828. Then, in 1834 Herrison developed a crude instrument which was placed directly over an artery to measure the blood pressure. Vierordt was the first to estimate the amount of counter pressure which is just necessary to obliterate the arterial pulse. After that Jules Marey and Von Basch had become the pioneer in clinical sphygmomanometry (sphygmo means pulse, manometer means measurement of pressure of liquid and gas in a container). Riva Rocci first introduced the blood pressure cuff in 1896, although

the breadth of cuff he used was only 5 cm. Then Von Recklinghausen drew attention to the importance of the width of cuff to get better results.

Then in 1905, Korotkoff, a Russian physician, described the sphygmomanometric sounds using stethoscope from large peripheral artery during deflation of the cuff. This was called the Korotkoff sounds and still remains the standard technique for blood pressure measurement manually in all the spheres of medical care. After that in 1911, Mckesson added the measurement of respiratory rate and the measurement of inspired O_2 concentration to the monitoring armamentarium of anaesthesia. The oximetry was first performed as early as in 1913. Then, there was a steady development in the sphere of monitoring during anaesthesia with the Einthoven's discovery of ECG. This was the early 1960 and was done by using a cathode ray oscilloscope which eventually led to its gradual introduction into the anaesthetic practice.

The oscillotonometer principle which was first developed in 1931 by Von Recklinghausen by using a cuff to sense the changes in arterial pulsations has now become the corner stone of methodology for most of the today's automated noninvasive blood pressure measuring devices. Originally, Von Recklinghausen used the oscillations of a needle to indicate the systolic and diastolic pressure. Later in 1970, automatic oscillotonometers were developed by various equipment companies. Here the changes in pressure of the cuff is detected by the transducer of the monitor which is analysed and presented digitally as systolic, diastolic and computed mean arterial pressure.

Though the intra-arterial BP was first measured invasively by Stephen Hales, in 1733, by direct cannulation of an artery of an animal, but it was not in practice till 1949 when Peterson and Dripps developed a safe, percutaneous arterial cannulation method. However, in the next decade the developement of transducer technology and arterial catheters made the invasive BP monitoring a standard and widely accepted method in all the areas of critical care.

Venous pressure was also first measured by Stephen Hales in 1733 on a mare. But, then after a long interval it was first measured on man by Fray in 1902 and was first used clinically in 1910. Then in 1929, Forssman's pioneering work on human cardiac catheterisation which was first done on himself, stimulated the progress of this chapter. This landmark achievement and also the development of many better materials for manufacturing of catheter allowed the subsequent completion of many important cardiac investigations which have formed the basis of understanding of our current use of central venous pressure monitoring. The first plastic (polythene) intravenous catheter was used in 1945, and the plastic central venous catheter was developed rapidly after this.

Lagerlof and Werko had first reported the value of pulmonary capillary wedge pressure (PCWP) as a reflection of the left vetricular filling pressure. Finally in 1970, the development of flexible, ballon tipped and flow directed Swan-Ganz catheter by Swan had made the pulmonary artery catheterisation possible routinely. After that, Seldinger developed a guide wire directed deep vascular cannulation technique which added a great safety and ease to this type of cardiac monitoring. Now, the modern pulmonary artery catheters provide a variety of additional diagnostic and therapeutic tools such as determination of cardiac output by thermodilutional technique, determination of mixed venous oxygen saturation by oximetry, atrial or ventricular pacing and many others. Thus, gradually it became the hallmark of a 'full' invasive cardiac monitoring system in anaesthesia and critical care unit.

Blood – gas analysis was first started by Pflunger as early as in 1872. Then, Leland Clark developed polarographic oxygen electrode in 1956, which forms the basis of modern oxygen electrode. At the same time, the polio epidemic in Copenhagen had stimulated the search for different methods of measuring the arterial PCO_2. At first, Astrup had measured the pH of blood with different CO_2 concentration to determine its PCO_2. But later, the development of CO_2 electrode greatly facilitated this measurement and a full acid-base picture could be derived from the Siggard – Anderson nomogram. However, today these calculations are performed by a microprocessor. Capnography was first used clinically in 1960, although the infrared analyser was first employed as early as in 1865.

However, the most unique addition in the armamentarium of intraoperative cardiac monitoring system took place in 1954 with the first use of ultrasound in cardiology by Edler and Hertz. But their one dimensional motion (M-mode) analysis has rapidly given way to the two dimensional (2-D) echocardiography. It displays different cardiac anatomy in various planes, even in real time. The development and use of transoesophageal transducer was first established in 1980 by Hisanaga. Then, gradually TEE has gained significant popularity in anaesthesiology and has built a stable platform for continuous, noninvasive, high quality intraoperative monitoring of the cardiac functions. Moreover the addition of doppler technology and colour-flow imaging have further established TEE as an important tool in modern anaesthesia practice.

Clinical Monitoring

The priciple aim of function of cardiovascular system (CVS) is to ensure adequate supply of O_2 to tissues. The supply of adequate amount of O_2 to tissues (or O_2 content) is the product of cardiac output (CO), haemoglobin concentration and haemoglobin by saturation of O_2. Clinically, the haemoglobin concentration and saturation

may be estimated by looking at the mucous membrane and the skin. The CO may be estimated clinically by the pulse volume, urine output and warmth of extremities. Therefore, observation of a good pulse, pink skin and warm extremities, especially when combined with urine output of > 0.5 ml/kg/hr implies that there is unlikely to be any cardiovascular problem, provided there is no peripheral vascular disease.

In children, the observation of capillary circulation by capillary refill time provides a valuable indication of a stable cardiac status, as peripheral vascular diseases are rare in children. The capillary refill time is the time taken by capillaries to be refilled, after the digit has been exanguinated by firm pressure. When a finger has been kept under pressure for 3 seconds, then a capillary refill time of less than 1.5 seconds is considered normal. But a time greater than 5 seconds is indicative of impaired circulation or shock. While the patients presented with complex cardiovascular problems may require more sophisticated monitors, but still the value of direct observation of patient and the examiner's fingers on the patient's pulse, can never be underestimated. But in practice, sometimes dimmed theatre light and surgical drapes may cause difficulties for direct observation of patient and clinical monitoring. So, in such situation electronic monitors become essential. But still direct observation of patient should always be maintained as far as possible and should be taken as supplementary to the instrumental monitoring. Therefore, for many healthy patients who are undergoing minor procedures, the above mentioned physical signs and clinical monitoring may provide a considerable important portion of the total cardiovascular monitoring. But, when the operation becomes more complex or the patient presents with more advanced unstable CVS, then the extent of supplementary electronic monitoring grows accordingly. However, still the careful clinical assessment of patient helps the clinician to confirm or refute the information, derived from the important monitoring systems.

Monitoring by Stethoscope

In 1818, Lacnnce had first introduced the stethoscope in general medical practice. After that 100 years have passed, when in 1908, Harvey Cushing first proposed that stethoscope could be used for continuous routine monitoring of CVS during surgery.

Two types of stethoscopes are used for continuous cardiovascular monitoring during surgery. These are the precordial stethoscope and the oesophageal stethoscope. They provide simple breath sounds and heart sounds continuously throughout the operation. In a precordial stethoscope the metal bell is strapped on the precordium. Then both the heart sounds and breath sounds are heard through a long tube and a custom moulded monoaural plastic ear piece. Electronically amplified stethoscopes also have been designed in an attempt to improve the quantity and clarity of the heart rounds and breath sounds. Stethoscope with wireless system using radio transmitted signals have also been developed. Wireless stethoscopes also allow continuous monitoring of CVS, while the anaesthetist pays attention to the other monitors instead of sitting by the side of patient. An oesophageal stethoscope is minimally invasive, but provides clear breath sounds and distinct heart sounds when the tip is positioned at 28 to 30 cm from the incisors. By this core body temperature can also be measured via a thermistor which is incorporated in the tip of the oesophageal stethoscope. Specially configured oesophageal stethoscopes also permit recording of transoesophageal ECG which sometimes may be come useful in diagnosing atrial arrhythmias, right ventricular ischaemia or posterior left ventricular ischaemia. Transoesophageal atrial pacing also can be accomplished by these transoesophageal stethoscopes, which is equipped with bipolar pacing electrodes on its outer surface.

But the routine use of the pulse oximeter, capnometer and other electronic monitors, driven by their ubiquitous usefulness and imposed law, has diminished recently the wide spread application of precordial and oesophageal stethoscopes in clinical practice, despite their immense utility in basic patient monitoring. Currently, the precordial and oesophageal stethoscopes are used intraoperatively in institutions where there are no electronic monitors. Then, their role in diagnosing important respiratory problems, such as bronchospasm, crepts etc., probably exceed their value as continuous monitors for the circulatory system.

Failure of these stethoscopes to detect untoward events is more frequent than the electronic monitors and it is due to the difficulty to concentrate continuously or to listen to both the heart and breath sounds simultaneously.

Heart Rate Monitoring

It is the most simplest and non-invasive (or rather least invasive) form of monitoring CVS. It acts as an important guide in determining the influence of anaesthetic agents on CVS, reaction of CVS to surgical stimuli and any underlying cardiovascular pathology. The monitoring of the heart rate (pulse rate) by keeping 'fingers on pulse' is ubiquitous and is fundamental of all the monitoring. But practically, it is not always possible due to other engagements of an anaesthesiologist. However, fortunately most of the monitors (invasive or noninvasive) used during anaesthesia practice provide a continuous audio and numerical display of the heart rate.

In ECG monitors the heart rate is displayed by measuring the QRS interval by recognising the peak of R wave on a beat-to-beat basis. The electrocardiographic measurement of heart rate begins with an accurate detection of R-wave and measurement of R-R interval, which is displayed and updated by every 5 to 15 seconds. The automatic noninvasive blood pressure

devices also usually display the heart rate by counting the cuff oscillation. The invasive blood pressure monitoring system derives the heart rate from the arterial and as well as from the pulmonary artery waveform. Pulse oximeter computes and displays the heart rate from capillary pulsation.

All the heart rate monitors, like other monitors, are also subjected to errors from artefacts, pathological states or other therapies (Table 22.7).

Pulse Rate Monitoring

The electrical depolarisation and the systolic contraction of heart per minute is called the heart rate. It generates a palpable peripheral arterial pulsation and its rate per minute is called the pulse rate. Pulse deficit is the difference between this heart rate and the pulse rate. So, the monitoring of pulse rate is more important than the heart rate and is very helpful to make an idea of the peripheral organ perfusion. This is because all the cardiac systoles (which produce the heart rate) do not produce sufficient cardiac output which is responsible to produce a palpable pulse and peripheral circulation. The typical example of pulse deficit is AF in which the short R-R intervals compromise cardiac filling during diastole and results in a reduced stroke volume with an imperceptible peripheral arterial pulse. Thus, all the cardiac systoles do not end in palpable peripheral pulses and there is a deficit between the heart rate and the pulse rate in AF. The other extreme example of difference between the heart rate and the pulse rate is EMD (electro mechanical dissociation). This is actually a condition where the electrical activity and contraction of heart is present, but there is no or minimal stroke volume. Therefore, there is presence of heart rate, but absence of pulse rate. This is usually seen in patients with cardiac tamponade, extreme hypovolaemia, extreme peripheral vasodilatation, anaphylactic shock, etc.

Table 22.7: Some common errors in heart rate monitors

1. ECG monitors often count pacemaker artefacts (especially atrial) - resulting, the faulty heart rate.
2. When the T-waves are exceptionally tall, ECG monitor counts these T-waves in addition to QRS complexes, causing an apparent doubling of the actual heart rate. Intra-aortic balloon pump counter pulsation also can cause the same doubling error in blood pressure (from arterial form) - derived heart rate.
3. Presence of pulsus paradoxus apparently reduces the actual heart rate to half.
4. Electrocautery invariably interferes the counting of heart rate by ECG monitor.

On the monitor's screen we get the heart rate from ECG tracing and the pulse rate from different pulse sources. For example, pulse oximeter uses the capillary pulsation where an optical transducer measures the capillary volume changes (plethysmograph) and provides the pulse rate for most patients, except in patients with severe arterial occlusive diseases or marked peripheral vasoconstriction. Pulse rate is also obtained by electromechanical transducers in NIBP devices which determine the pulse rate by counting the oscillations in the pressure cuff. When during direct and invasive arterial pressure measurement a catheter is in place in side the arterial lumen, then the arterial pressure waveform also provides a reliable pulse rate. The peizo-electric devices of Doppler probes are also used for pulse rate monitoring. The output of these monitors is displayed upon an oscilloscope. Qualitative index of the pulse volume and flow may be obtained from this oscilloscope.

Pulse rate counting using intra-arterial pressure tracings may sometimes be misleading, when the non-systolic arterial pulsations are detected by the monitor and are counted separately. For example, when a patient is treated with an intra-aortic balloon pump, then the pressure pulse resulting from the balloon inflation during diastole may be detected, producing a fictitiously high pulse rate. When the morphology of pulse becomes double-peaked, (which is called bisferiens pulse), such as those arising in patients with aortic valve regurgitation, then it may also produce a similarly increased (doubled) pulse rate. In contrast, patients with pulsus alternans may have an inappropriately low pulse rate (half), due to the diminished magnitude of every alternate arterial pulsation. In such cases, counting of pulse rate from the pulmonary artery pressure wave-form can provide a reliable pulse rate.

Monitoring of the CVS by ECG

Electrocardiography during monitoring of CVS warns us about the changes in heart rate, its rhythm and the development of any ischemia which may precede to the bad haemodynamic changes. The disturbances in potasssium and calcium levels of blood may also be recognisable from ECG during monitoring of CVS. However, a major limitation of ECG in cardiovascular monitoring in cardiovascular monitoring is that there is no indication of cardiac output, which may fall to be zero inspite of a normal ECG tracing. The quality and ease with which the electrical signals of heart may be obtained is due to the improvement in electronics and electrode design. Thus, the 'mat' electrode has greatly reduced the time required to establish a good interface. With many systems, however, the signal is interfered following the use of electrosurgical diathermy. But, recently many commercially available ECG monitors are capable of rejecting the diathermy interference (Fig. 22.15).

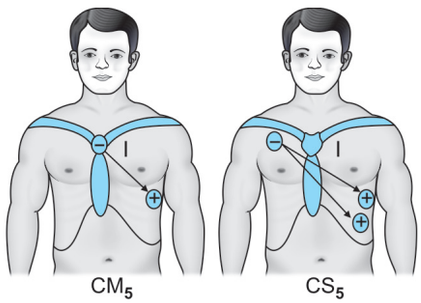


Fig. 22.15: Monitoring of the CVS by ECG

The standard lead II is the commonly used lead configuration for monitoring, which allows the excellent detection of any intraoperative arrhythmias. But, it does not always show the ischaemic changes, which may only be visible in lead V_5. So, the unusual bipolar lead named CM_5 (central manubrium to the fifth intercostal space in the left anterior axillary line) allows an excellent detection of both the ischaemia and arrhythmias. Therefore, it is always recommended for continuous intraoperative ECG monitoring.

Another lead, named CS_5 (central subclavicular) is also very important for intraoperative ECG monitoring. Here, the right arm (RA) electrode is placed under the right clavicle, the left arm (LA) electrode is placed in the V_5 position and the left leg (LL) electrode is placed in its usual position. In this CS_5 lead arrangement, the lead I is selected for the detection of anterior myocardial wall ischaemia and the lead II is selected for the detection of inferior wall ischaemia or arrhythmia. If a unipolar precordial V_5 lead is not available, then this CS_5 bipolar lead is the best and easiest alternative for monitoring of myocardial ischaemia and arrhythmia (Table 22.8).

Arterial Blood Pressure Monitoring

Measurement of blood pressure is one of the most fundamental parameters for monitoring of cardiovascular function. It represents the force of contraction of heart that drives the blood to flow from centre to periphery (systolic pressure) and also represents the load against which heart has to work (diastolic pressure). The peak pressure generated within the vessels during systolic contraction of ventricle is called the systolic blood pressure and the continuous pressure within the blood vessels during diastolic relaxation of ventricle is called the diastolic blood pressure. The pulse pressure is the difference between these two pressures. The average arterial pressure over a period of full cardiac cycle is termed as the mean arterial pressure. It is a time-weighted average pressure, which prevails throughout the whole cardiac cycle. So the mean blood pressure is approximately equal to the diastolic pressure plus one-third of the pulse pressure, i.e,

Mean BP =DP + 1/3(SP – DP)

The monitoring of the function of cardiovascular system is aimed at to assess the amount of cardiac output, which is required to maintain the oxygen-flux. So, the most important parameter for monitoring of CVS is the cardiac output or flow. But, it is very difficult to measure the cardiac output clinically and it has been discussed in the last part of this chapter. So, to monitor the perfusion of organs which is the most important function of CVS, we measure HR and BP. But, fortunately the more easily monitored parameter such as HR and BP bear some constant relationship with CO, by the following equations :

Pulse rate = CO ÷ Stroke Volume

Blood pressure = Cardiac Output × SVR

Arterial blood pressure is generally affected by the site where it is measured. This is because the pulse wave moves peripherally along the wall of the arterial tree. So, this pulse wave may distort the pressure waveform which moves along the column of the blood, leading to an exaggeration of the systolic and pulse pressure. The level of the measuring site of BP relative to the level of heart also affects the value. This is because of gravity. In patients with severe peripheral vascular disease there may be a significant difference in the value of measured blood pressure between the right and left arm and between the arms and legs. However in such circumstances the higher value should be taken for these patients.

The easily measured parameters of cardiovascular function such as BP and pulse rate are less reliable than the CO and SVR, which are more reliable but difficult to measure. For example, if the SVR is high, then the BP will also be high but the cardiac output will be low which cannot be understood by the level of the blood pressure only. Thus, the arterial pressure should be viewed as an indicator, but not always as a measurement of organ perfusion. All types of anaesthesia, no matter how 'trivial', is an indication for the measurement of BP. But its frequency and technique of measurement depend on the gravity of surgery, the condition of patient and the experience of anaesthetist. Generally, the measurement of BP which in based on noninvasive oscillometric principle and is measured after every 3 to 5 minutes interval is adequate in most cases.

Blood pressure is measured mainly by two techniques: indirect (non-invasive) and direct (invasive). The noninvasive method of measurement of BP is based on the technique of palpation, Doppler,

Table 22.8: Some effects of electrolyte and other disturbances on the ECG

Hyperkalaemia	Appearance of tall and tented T wave, appearance of wide bizarre QRS merging with the T wave. Disappearance of P wave, ventricular extrasystole, fibrillation or asystole.
Hypokalaemia	Flattening or inversion of T-wave, increase of PR interval, depression of ST segment, appearance of U-wave, apparent longation of QT interval, atrial, ventricular extra systole, ventricular tachycardia.
Hypercalcaemia	Reduction of QT_C interval, blending of T with QRS.
Hypocalcaemia	Prolongation of QT_C interval.
Hypomagnesaemia	Prolongation of QT_C interval.
Venous air embolism	Right heart strain pattern, atrial and ventricular extra systole.

The QT interval varies with the heart rate. So, when it is corrected to a heart rate of 60 beats per minute, then it is signified as 'QT_C' ($QT_{Corrected}$)

auscultation, oscillometry and plethysmography (Fig. 22.16).

1. Indirect or non-invasive methods

The most indirect methods for measurement of BP are based on the principle of Riva-Rocci sphygmomanometer. The use of this method consists of inflation of a pneumatic cuff, occlusion of blood flow of a large artery and then sensing the sequence of physical changes that occur in and around the just opened artery as the pressure is released and blood flow begins. Originally, Riva-Rocci described the measurement of systolic blood pressure by the disappearance of the radial pulse when the cuff was inflated (cuff-inflation technique). But nowadays a variation of this Riva-Rocci method is employed where both systolic and/or diastolic pressures are measured during the deflation of cuff and when pulse reappears (cuff-deflation or return-to-flow technique). The reappearance of pulse which helps in detection of systolic and diastolic blood pressure is detected by palpation, doppler, auscultation or oscillometry method. This indirect methods of BP measurement may be intermittent or continuous.

(i) Non-invasive intermittent techniques

BP can be measured intermittently and non-invasively either manually or by an automatic machine.

Manual method

This is the most simplest way of measurement of BP and is based on auscultation of the Korotkoff sounds. Using a Riva-Rocci sphygmomanometer cuff, Korotkoff an another scientist, applied a stethoscope on the artery, directly below the cuff to auscultate the sound which is generated as the cuff was slowly deflated and the blood starts to flow through the just opened arteries. This sound is created by a complex series of audible frequencies, produced by the (i) turbulent flow of blood, (ii) vibration of unstable arterial wall and (iii) shock wave formation as the external occluding pressure on a major artery is reduced. When the pressure cuff is deflated gradually after its inflation, then the pressure level where the completely occluded artery just opened and blood starts to flow through a narrow opening of arterial lumen first producing sound (Phase I) by the above mentioned mechanism is considered as the systolic pressure. Then, gradually the character of the sound changes (phase II and III). Finally, the sound becomes muffled (phase IV) and becomes absent (phase V). The pressure where the sound becomes muffled or absent (phase IV and V) is taken as the diastolic pressure. In certain pathological conditions such as inaortic incompetence the phase V may not occur and phase IV is continuous.

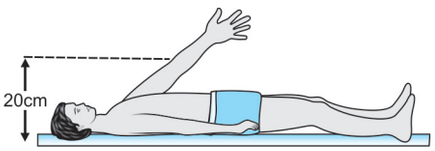


Fig. 22.16: Difference of arterial BP (mm of Hg) at different sites of measurement. This difference is equal to the height of an interposed column of water (cm of H_2O). This is obtained by multiplying the numerical value of the water column by this conversion factor (1 cm of H_2O = 0.74 mm of Hg)

The accuracy of BP, measured by this manual method, depends on the width of cuff and the rate of the release of pressure. The width of cuff should be at least 20 to 30% of the circumference of the limb and the pneumatic bladder should cover at least half of the circumference of arm. A cuff of 14 cm wide and 30 cm long is considered satisfactory for accurate measurement of BP in adult. An excessively narrow cuff produces a falsely high value and an excessively wide cuff shows a falsely low value. Similarly, the optimal rate of the release of pressure for accurate result is 3 mm of Hg/sec. The rapid release of pressure causes falsely low value. If we calculate the rate of deflation of cuff with the HR, then the deflation of pressure of 2 mm of Hg per beat will further increase the accuracy. As the generation of Korotkoff sounds depends on the blood flow, so the pathological or iatrogenic causes which decrease the blood flow, such as cardiogenic shock or use of vasopressor agents, etc, can result in a falsely low blood pressure reading. Aneuroid manometer needs frequent calibration for correct results. During shivering, the pneumatic cuff may need a high occluding pressure due to low compliance of the underlying tissues. So, it may result in pseudohypertension.

Sometimes, only the systolic pressure is estimated by inflating the cuff around the upper arm to a high pressure above the systolic level and then detecting the return of radial pulse when the cuff is deflated (palpation method). When the cuff pressure in gradually decreased, then the pressure level at which the pulse is first palpated is taken as the systolic pressure. Despite its crudeness, this method is very helpful in situations where other monitoring devices are not available and where a patient has suddenly deteriorated, necessitating only systolic pressure measurement as life-saving.

Automatic method

The standard ausculatory method which is used manually to measure the blood pressure often fails, when the arterial blood pressure is less than 60 mm of Hg. This is because the Korotkoff sounds are of too low-pitch to be audible at that pressure. In that situation, BP can be measured intermittently by automatic noninvasive methods based on the oscillotonometric principle or ultrasound technology (doppler principle and arteriosonade). This automatic non-invasive blood pressure (ANIBP) measurement devices provide consistent and reliable data. Again, many of these machines can compute an accurate mean arterial pressure (MAP) from the systolic and diastolic pressure which is a very valuable haemodynamic parameter (Table 22.9).

Table 22.9: Disadvantages of oscillometry

1. Inaccurate, if systolic BP is < 60 mm of Hg.
2. Inaccurate, if arrhythmia is present.
3. Inaccurate in the presence of a wrong-sized cuff.
4. Inaccurate during movement of limbs.
5. Discomfort in an awake patient.
6. Does not provide continuous or beat-to-beat result.
7. If the interval between the two measurements is too short, there is chance of skin and nerve damage.
8. Back flow of blood into the IV cannula, if it is in the same arm.
9. Delay in drug reaching the circulation.
10. Malfunctioning of the pulse oximeter, if it is used on the same limb.

In the oscillotonometric principle the variations or oscillation of pressure within the cuff which is transmitted from the arterial pulsation during deflation are sensed by the electronic monitor and are used to determine the values of arterial blood pressure. Originally, in Von Recklinghausen's BP measuring device (sphygmomanometer) this principle of oscillotonometer was used which sense the arterial wall motion and displays this as an oscillation of a pointer on a scale. The systolic blood pressure is that at which small oscillations of needle suddenly increase in amplitude when the cuff pressure is reduced and blood starts to flow. Unfortunately, at that time interpretation of the diastolic point was controversial and subjective. Later the second cuff which was originally used in Von Recklinghausen's device is replaced by stethoscope with hearing the sound first by Korotkoff (Korotkoff's sound). But now this technique has become even more accurate than the conventional sphygmomanometry, and has been improved by electronic devices. Arterial pulsations make small oscillations in the completely sealed air of the cuff. These oscillations are absent or very small if the cuff is inflated above the systolic pressure and the artery is completely occluded with no flow of blood through it. Mercury or aneuroid manometer provides an unreliable and gross measurement of these small oscillations. But, when the intracuff pressure is decreased to the systolic blood pressure after its initial inflation to a higher pressure, then the oscillations are markedly increased. Maximum oscillation occurs at MAP after which it again decreases. The electronic devices measure the pressure at which the amplitude of oscillation changes. Then from these changes, a microprocessor calculates the systolic, mean and diastolic blood pressure, using an algorithm. Thus, oscillometric principle needs identical consecutive pulse waves for its measurement. So, it is unreliable during arrhythmias.

The ultrasound technology for measurement of (Fig. 22.17) ANIBP uses the doppler principle to determine the blood flow distal to the cuff or the arterial wall motion. In arteriosonade principle the motion of the arterial wall is sensed by ultrasound when blood starts to flow through large arteries during deflation of cuff after its initial occlusion by inflation of cuff above the systolic blood pressure. The main drawback of this ultrasound technology is that it requires an extreme attention to the placement and securing of ultrasound transducer directly over the artery. Because, dislodgement of the transducer from just over the arterial site leads to sudden loss of information and disturbs the attention of anaesthetist who has to quickly decide whether the cause of failure is with the machine or with the patient. The ultrasound technique is not suitable for measurement of diastolic BP but has the added advantage of using the probe as a pulse monitor.

What is Doppler effect ?

It is the shifting of frequency of the reflected ultrasound wave, when the reflecting source moves relative to the point from where the ultrasound is originating. It can be explained in this way that the pitch of a moving vehicle increases or decreases as it approaches or departs. Similarly, the frequency of the reflected ultrasound wave will increase or decrease from a moving object, causing a shift in frequency. A Doppler probe transmits an ultrasonic signal, which is reflected from the underlying moving tissue which may be the blood flow. Then, the shift of reflected frequency is detected by the detector incorporated within the same probe. Thus, the difference between the transmitted and received frequency causes the characteristic changes of sound, which indicates the nature of blood flow.

(ii) Non-invasive continuous technique

In this technique, the BP is measured continuously and non-invasively from the finger by using a microprocessor and

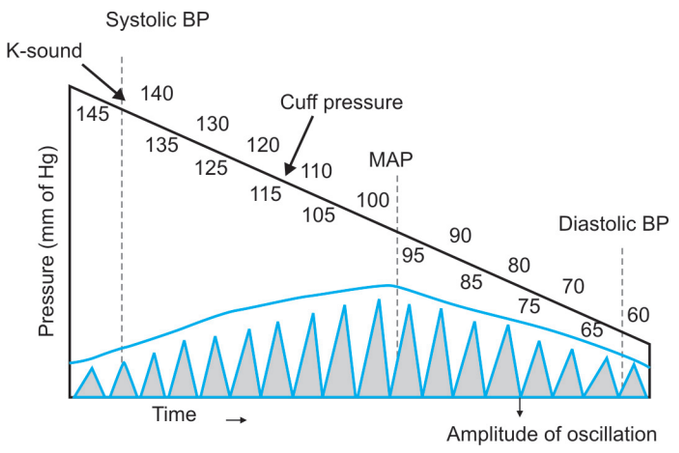


Fig. 22.17: The principle of oscillometric method for determination of arterial BP

servo-technology (arterial-volume-clamp method). This is better known as the servo-plethysmomanometer. In this device there is a cuff within which there is an infrared photoelectric probe that produces a photoplethysmograph and continuously measures the size (diameter) of digital arteries by transillumination. The cuff pressure and the photoplethysmograph interact through a sophisticated servocontrolled mechanism and tracks the arterial pressure throughout the cardiac cycle which is displayed on the monitor screen as a numerical value and a continuous waveform.

Recently, the BP is also measured noninvasively and continuously by devices which use the changes in arterial (Fig. 22.18) wall elasticity by arterial tonometry. Arterial tonometry actually is a version of 'applanation tonometry'. Here, a superficial artery (usually radial) is compressed and partially flattened against the underlying bone. Then this flattened arterial surface serves as a transducer for intravascular pressures, acting perpendicularly against the vessel wall. An array of piezoelectric crystals, positioned on the skin overlying this flattened portion of artery senses this perpendicular arterial pressure changes and translates them into a continuous arterial pressure waveform. Previously, it was thought that this arterial tonometry is better than other forms of continuous noninvasive pressure monitoring. But, unfortunately the more recent clinical studies have identified limitations of this device in paediatric patients and in patients receiving vasodilating drugs.

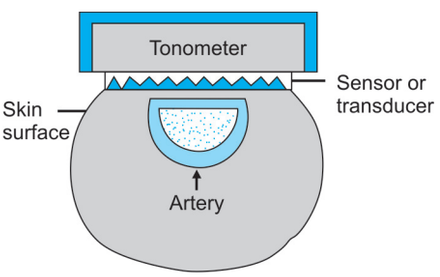


Fig. 22.18: Schematic diagram of a tonometer for continuous beat-to-beat measurement of the arterial BP non invasively

So, now in terms of absolute accuracy of blood pressure measurement, the intermittent oscillometry appears to be superior than the radial artery tonometry.

The role of these newer, continuous and noninvasive BP monitors is still unclear. This is because there is still some doubt about the accuracy of their result (compared with the invasive method). Again, though it is still controversial whether these devices can actually supplement the continuous invasive monitoring or not, but there certainly will be a population of patients in whom these techniques shall find a niche and become an important part in their monitoring armamentarium.

2. Direct or invasive method

This requires an intraarterial cannula of 20 to 22 G in diameter (a Teflon catheter causes less thrombosis than a catheter made of polypropylene) to be inserted into an artery for direct measurement of blood pressure. The radial artery is usually first chosen in an adult for direct invasive intra arterial BP monitoring and the femoral artery is used more often in children. The radial artery is commonly chosen, because of its superficial location and collateral flow. The collateral circulation is very important to prevent distal ischaemia and necrosis due to arterial injury by unsuccessful attempt. Only 5% of total individuals have incomplete palmar arches and inadequate collateral flow to radial artery. Ulnar artery cannulation is more difficult, because of its deeper position and more tortuous in nature. If a patient's radial artery is punctured but cannulation is unsuccessful, then the ipsilateral ulnar artery should never be tried for fear of compromised blood flow to the portion of hand distal to it. The anaesthetists are also very fond of brachial artery cannulation, for invasive measurement of blood pressure because: (i) it is easily identified in the antecubital fossa and (ii) its proximity to the aorta provides less waveform distortion (the more peripheral is the position of artery, the more is the waveform distortion). But, as it is nearer to the elbow, so it is more predisposed to kinking during flexion of the forehand. On the otherhand, the femoral artery provides an excellent access to intraarterial cannulation for continuous invasive BP monitoring. But it is more prone to pseudoaneurysms, sepsis, thrombosis and atheroma. As the dorsalis pedis and posterial tibial artery are far away from the aorta, so they have the most distorted waveforms and are not chosen for invasive intraarterial BP monitoring. The another chosen site for intraarterial BP monitoring is the axillary artery. But the axillary artery is surrounded by the nerves of brachial plexus. So, any unsuccessful cannulation can produce haematoma and nerve damage.

After insertion into the artery, the cannula is attached to a transducer (fluid filled electromechanical strain gauge) by a narrow-bore, low-compliance pressure tubing. Then the entire system is attached to a flushing system through a stopcock for flushing the catheter and to prevent thrombus formation. Many systems incorporate an automatic flushing device with a continuous slow (1 to 3 ml/hour) infusion of heparinised saline (1 unit/ml), or a spring controlled valve that allows a peroidic high pressure flushing for clearing the arterial line after a blood sample is taken. The practice of using heparinised saline may unnecessarily expose the patient to heparin and hence increase the risk of immune-mediated thrombocytopenia. The stopcock in the system provides a site for blood sampling and allows the transducer to be exposed to atmospheric pressure which establishes a zero reference value. But, the newer systems include a needleless sampling port and an in-line aspiration system. These permit blood sampling without the use of sharp needles and allow the aspirated waste blood to be returned to the patient within a closed system.

The pressure transducer is set at the level of patient's left ventricle and is opened to

air to obtain a reference pressure which is taken as zero. When the pressure is zeroed, then the transducer converts the pressure changes directly into the changes of electrical resistance which are measured by the monitor. Thus, the transducer is calibrated and on this zero level the arterial pressure is superimposed and measured. A real-time arterial pressure waveform is usually displayed in addition to digital values of the pulse rate and the systolic, diastolic and mean arterial pressure on the screen of monitor. In a few patients, there is marked discrepancy between the arterial pressure measured invasively and non-invasively.

Though the invasive pressure is more likely to be accurate, but it is more complex, expensive, and not without any fear of major complication. So, a patient's arterial pressure is mostly measured non-invasively in less critical patients.

Prior to initiating pressure monitoring, the pressure transducer should be zeroed, calibrated and positioned to an appropriate level of the patient. Because the accuracy of invasive BP monitoring depends on correct calibration and zeroing procedure of transducer. The stopcock at the level of desired point of measurement is opened, which is usually at the mid-axillary line. This activates the zero trigger in the monitor. Then, if the patient's height is altered by lowering or raising the OT table, then the transducer should also be moved accordingly, or should be zeroed to the new level of midaxillary line. The zero reference point of the transducer should be checked regularly to eliminate the drift. In a sitting position of the patient, the arterial pressure in the brain differs significantly from that of the left venticle. In such a position, the arterial pressure of brain is determined by setting the transducer to zero at the level of the ear.

The damping effect during invasive BP monitoring is caused by some part of the measuring system. It may be caused by (i) the bubbles of air in the tubing, (ii) too long or too elastic tubes, (iii) a kinked cannula or arterial spasm. The damping produces a graph, which reduces the amplitude of measurement of systolic and diastolic pressure, tending towards the mean pressure.

The direct or invasive arterial pressure measurement has become a standard monitoring procedure for any high risk patient during anaesthesia or in patients with severe circulatory instability caused by an underlying medical condition, or when the planned operative procedure causes large and sudden cardiovascular changes. The other indications for intraarterial cannulation for invasive BP measurement include: induced hypotension, end-organ diseases necessitating precise beat-to-beat pressure measurement, and the need for repeated blood-gas analysis. It is also commonly used for the patients in intensive care unit and in high dependency areas. Extensive experience with this technique over the years has demonstrated its value and safety, so that current indications for its use have become numerous. Also, the threshold for applying it has been lowered to encompass its use in nearly all seriously ill patients, or complicated surgical procedures. (Few indications for arterial cannulation are listed later).

Limiting the blood flow in vessels and thus causing ischaemia distally is the chief complications of intra-arterial cannulation and measurement of BP invasively. This usually does not happen due to the presence of a collateral blood supply. So, before a radial intra-arterial cannulation, it is advisable to check the efficiency of collateral circulation (for radial and ulnar artery it is done) by Allen's test or Weber's test. Allen's test is simple, but not so reliable. In this test, the patient first makes a tight fist and exanguinates his hand. Then the operator occludes the radial and the ulnar arteries by his finger. After that the operator releases only the ulnar artery and the collateral flow through the radial artery and the palmar arterial arch is confirmed by flushing of thumb within 7 seconds. Delayed return of colour of the thumb in between 7 to 15 seconds indicates an equivocal test. If the delay is greater than 15 seconds then insufficient collateral circulation is confirmed. Alternatively, collateral circulation distal to the radial artery occlusion can be diagnosed by a Doppler probe, plethysmography or pulse oximetry.

The advantages of direct arterial pressure measurement are:

i. Accuracy.
ii. Beat to beat observation or continuous real time monitoring of changes in blood pressure.
iii. Very essential when there is a very rapid swing of blood pressure.
iv. Also accurate even at very low pressure level, where cuff based measurement techniques may prove impossible.
v. Helpful in some morbidly obese patients or those with burned extremities.
vi. Arterial cannulation also helps to obtain blood samples frequently. New devices allow continuous monitoring of the arterial blood-gas values using fibre-optic sensors placed directly into the artery through the vascular catheter.
vii. Intentional pharmacological or mechanical cardiovascular manipulation, such as intra-aortic balloon counter pulsation, deliberate induced hypotension and administration of vasoactive drug infusions are possible.

Various physiological and pathological states can produce a generalised arterial pressure gradients, i.e. different levels of pressure at different sites of body. Thus, the difference in BP at different heights of measurement can be equalised by the addition or subtraction of height of an interposed column of water (cm of H_2O) multiplied by a conversion factor (1 cm of H_2O = 0.74 mm of Hg). Larger differences are seen between the peripheral and the central arterial pressures in patients with shock. For example, the femoral artery systolic pressure may exceed the radial artery systolic pressure by more

than 40 mm of Hg in septic shock, patients receiving norepinephrine infusions, etc. This difference has significant therapeutic implications during the management of critically-ill patients. Other vasoactive drugs, neuroaxial block, different patient's position and changes in the patient's temperature also produce gradients that alter the relation between the central and the peripheral arterial pressure measurements. Hypothermia and thermoregulatory vasoconstriction also causes the radial arterial systolic pressure to exceed the femoral artery systolic pressure. (Table 22.10).

The complications of direct arterial cannulation are:

i. Bleeding,
ii. Thrombosis and arterial damage,
iii. Ischaemia of tissues distal to artery,
iv. Embolisation,
v. Sepsis,
vi. Needs high skill to insert,
vii. Expensive.

The intraarterial blood pressure monitoring is a gold standard as it provides a continuous beat-to-beat accurate pressure measurement. So, the quality of waveform which depends on the dynamic characteristics of intra-arterial catheter-tubing and the transducer system is very important. Because a false reading leads to inappropriate therapeutic intervention and diaster (Table 22.11).

Table 22.10: Indications of arterial catheterisation for continuous beat to beat measurement of BP

1. Anticipated CVS instability such as severe cardiovascular disease, major trauma, massive transfusion, major surgery etc.
2. Direct manipulation of CVS such as during cardiac surgery, major vascular surgery, induced hypotension, etc.
3. Surgery with severe cardiovascular diseases such as valvular diseases, history of MI, severe angina, etc.
4. Massive obesity where indirect measurement of BP is not possible or inaccurate.
5. When frequent blood sampling is required such as for blood gas analysis, severe acid-base disturbance, severe electrolyte imbalance, severe sepsis, coagulopathies, etc.

An arterial pressure waveform is an expression of summation of simple sine and cosine of waves (Fourier analysis). So, for accurate results the catheter-tube-transducer system must respond adequately to the high test frequency of arterial waveform, or the frequency of measuring system must exceed that of the arterial wave form (average 16 to 24 Hz). The frequency of modern measuring system is > 200 Hz and so if gives very accurate results. The damping coefficient of transducer and other parts of measuring system should be optimum which ranges between 0.6 to 0.7. Because underdamping is a serious problem and may lead to overshooting with a falsely high BP. The dynamism of the catheter-tube–transducer system can be improved and damping can be reduced by: eliminating the unnecessary stop cocks, minimising the tube length, using the low compliance tubes and removing any air bubble from the system.

What is a pressure transducer?

The transducer is a device where the mechanical energy of pressure wave is converted into an electrical signal. It contains a diaphragm which is distorted by an arterial or venous pressure wave. Most of the transducers are of the resistance-type and work on the strain-gauge principle. Here, the diaphragm is made of multiple silicone crystals which are arranged as a Wheatstone bridge circuit. The stretching or pressure on the silicone crystals causes change in resistance and change in voltage output, which is proportional to the pressure applied to the diaphragm.

Table 22.11: Pressure at different sites of cardiovascular system

Site		Range (mm of Hg)	
svc		0 - 5	4
ra	Systolic	4 - 8	6
	Diastolic	0 - 5	4
RV	Systolic	15 - 30	20
	Daistolic	0 - 10	5
PA	Systolic	15 - 30	25
	Diastolic	5 - 15	10
PCWP	Mean	5 - 15	10
LA	Systolic	10 - 15	10
	Diastolic	5 - 0	5
LV	Systolic	80 - 120	110
	Diastolic	5 - 10	8

SVC = Superior venacava, RA = Right atrium, RV = Right ventricle, PA = Pulmonary artery, LA = Left atrium, LV = Left ventricle

Central Venous Pressure (CVP) Monitoring

The overall cardiac performance depends on the filling of heart during diastole, i.e. the end diastolic filling volume and pressure of right atrium for right ventricular function and the end diastolic filling volume and pressure of left atrium for left ventricular function. So, the monitoring of CVP at the junction of SVC and right atrium reflects the filling and function of the right side of the heart directly and also the filling and performance of the left side of the heart, indirectly. Whereas, the measurement of PCWP from the pulmonary capillary which is connected to the left atrium without any valve reflects more or less indirectly the pressure of the left atrium and the function of the left side of the heart. This is because the Sterling's law relates the stroke volume or cardiac function with the end diastolic filling volume and pressure. Again, the relationship of these parameters, i.e. filling pressure and stroke volume depend on the state of the intrinsic myocardial performance, i.e. contractility of heart and the status of pulmonary vasculature (Table 22.12).

Although the CVP or right heart filling pressure is the indicative of circulatory volume or right heart function, but it is often possible with appropriate assumption to use CVP for monitoring and management of the left heart function. For example, the low left ventricular output or low systemic BP due to blood or fluid loss

Table 22.12: Complications during central venous cannulation

1.	Injury to vital structures such as carotid artery, trachea, oesophagus, other large blood vessels.
2.	Injury to lung and pneumothorax.
3.	Bleeding, Haematoma (Haemothorax, hemomedia-stinum).
4.	Unable to stop bleeding by pressure.
5.	Arrhythmias, heart block.
6.	Sepsis, bactaerimia, endocarditis.
7.	Thrombosis, embolism.
8.	Cardiac puncture.

or due to any condition causing reduction of preload can be diagnosed by measuring the CVP. However, the measurement of pulmonary capillary wedge pressure has drawn attention to the inadequacy of CVP as a measurement of left heart function, because there are major differences between the two pressure systems. Such discrepancies are particularly common during pump failure due to endotoxaemia, myocardial infarction, etc. Here, CVP is highly elevated, but cardiac output is very low due to the intrinsic failure of myocardial contractility or performance. Rapid infusion of small amount of fluid may also be a useful clinical test for the determination of cause of failure, i.e. whether due to reduction of preload or intrinsic pump failure. The measurement of CVP by catheterisation of SVC not only helps to measure directly the pressure of the right side of the heart or indirectly the pressure of the left side of the heart, but also has some other functions such as:

i. Rapid infusions of fluid to correct severe hypovolaemia and shock.
ii. To administer some vasoactive drugs that might irritate and injure smaller peripheral veins.
iii. For hyperalimentation.
iv. For aspiration of air from air emboli during craniotomy in sitting position.
v. For comprehensive cardiac monitoring during major vascular surgery, and during all cardiac surgery for placement of pulmonary artery catheter (PAC).
vi. For insertion of transcutaneous pacing leads.

In a normal individual the average value of CVP varies between 0 to 5 cm of H_2O. It depends on the intravascular volume status, the intrinsic tone of the musculature of the vessels and the functional integrity of the right side of the heart. It reflects the filling pressure or volume and subsequently the stroke volume of the right ventricle. As the tip of the CVP catheter is located at the junction of SVC and RA, so it is exposed to the changes in intrathoracic pressure. Hence, inspiration will increase or decrease the CVP, depending on whether the ventilation is controlled or spontaneous. But, whatever may be the pressure, it should be measured at the end of expiration.

It is reduced in hypovolaemia due to any cause but is increased during heart failure, pulmonary embolism, IPPV, cardiac tamponade and fluid overload etc. Ideally for measurement of CVP, the tip of the catheter should be placed just above the right atrium or at the junction of right atrium and SVC. Advancing the catheter too far may cause arrhythmias and even damage to the myocardium. If monitoring of the pulmonary arterial pressure and the left atrial pressure is planned, only then the pulmonary artery catheter (PAC) should be advanced beyond the right atrium and the right ventricle into the pulmonary artery. Because of the large swings in the pleural pressure which may accompany the mechanical ventilation, it is preferable that all the measurements of central venous pressure should be made with the ventilator disconnected.

There are usually three techniques which are a adapted by anaesthetists for central verous cannulation to monitor CVP.

These are:

i. A catheter over a needle technique. This is similar to simple peripheral venous catheterisation.
ii. A catheter through a needle technique, which requires a large-bore needle stick
iii. A catheter over guidewire techinque, which is commonly known as Seldinger's method.

The central venous cannulation for measurement of CVP is also usually done by any of the three routes.

(i) Long catheter through the brachial or femoral vein

The more peripheral veins such as the brachial veins in the antecubital fossa or femoral vein in the femoral triangle are also chosen for central venous cannulation using a long catheter. Sometimes, the cephalic or basilic vein on the outer upper arm may also be used. But, here success is less likely due to the long tortuous route of these veins. Otherwise, this method is relatively easy and has a very low incidence of acute and serious complications. But, unfortunately, the tip of the cannula commonly fails to reach the central vein, if these peripheral superficial veins are used. Infection and thrombophlebitis are common, if the catheters left in-situ for more than 48 hours in any route.

(ii) Subclavian vein

As the subclavian is a large vein and quite close to SVC, so a short central venous catheter can be inserted easily through the skin into this vein. For subdavian cannulation either supra or infraclavicular approach in adopted. But, the infraclavicular approach to this vein for central venous cannulation is most commonly accepted. During cannulation, the angle of the needle should be low and tangential to the ribs, in order to avoid the perforation of the pleura. The subclavian artery is posterior to the vein in this line of approach. So, its puncture may result in significant haemomediastinum and haemothorax. In this approach the overlying clavicle affords easy fixation of catheter to the skin and this is comfortable for the patients too. But, unfortunately as the needle, wire and the catheter are not inserted under direct vision, so accidental perforation of the adjacent subclavian

artery or pleura is common. Importantly, if arterial bleeding occurs, it may not be evident and cannot be controlled by external pressure because of the position of the clavicle. Damage may also be caused to the brachial plexus, which runs along the main vessels. Because of the higher incidence of these major complications, subclavian cannulation is generally used only where specific advantages are evident.

(iii) Internal jugular veins (IJV)

This route is the safest and most reliable for central venous cannulation because:

i. The vein is close to the skin
ii. The consistent predictable anatomic location of IJV within a palpable land mark
iii. The short, straight (right IJV) and valveless course of IJV to the SVC and right atrium
iv. Bleeding if occurs can be controlled by direct external pressure
v. Success rate is more than 90% in both adults and children.

However, due to the proximity of internal jugular vein to the carotid artery, cervical spine, major nerves and pleura, the life threatening complications are still relatively common during central venous cannulation through this route.

Whatever is the route, the central venous catheter should be inserted only when a clear indication for measurement of central venous pressure is present. For central venous cannulation always the safest route should be chosen and catheter should be removed at the earliest opportunity. Careful technique and adequate observation of the patient is mandatory, including a mandatory chest X-ray after insertion of catheter. During the central venous cannulation the ECG should be continuously monitored in order to observe any dysarrhythmias which can occur if the tip of catheter crosses the SVC and right atrial junction, or when the catheter is more advanced into the right ventricle and PA to monitor the other filling pressures. If the direct pulmonary arterial pressure monitoring is planned, then it should be established prior to the central venous cannulation.

The complications of central venous catheterization are (i) Immediate → arrhythmias, bleeding, pneumothorax, damage to the thoracic duct, oesophagus and other vital structures, carotid artery injury, cardiac puncture, catheter embolisation, etc. (ii) Delayed → sepsis, thrombosis, kinking, displacement of catheter, etc.

The central venous pressure measurement can be made either by a simple water filled manometer, connected to a running fluid line via a stopcock or by an electronic transducer and digital display. The measurement of CVP by water manometer is simplest, least expensive and sufficient in many cases for general assessment of intravascular volume status. When CVP is measured by water manometer, then the right atrium of patient's heart and the zero point of the manometer scale should be kept at the same level. As the normal value of CVP varies between 0 to 5 cm of H_2O due to low pressure system, so a small change in the relative height of reference, e.g. when an operating table is moved up and down may lead to an appreciable error. In practice, a single measurement of CVP is unreliable as the value is altered in an unpredictable manner by several factors, such as positive pressor ventilation, patient's position, etc. The response of CVP to a fluid challenge is more valuable. In hypovolaemic patients the initial change in CVP is small with a rapid infusion of fluid. But, with continued infusion the CVP increases more quickly as normovolaemia is achieved. Contrary, in patients who are overloaded with fluid or have a heart failure, even a small amount of intravenous fluid causes a marked increase in CVP at initial phase. Sudden increase in CVP may also be caused by events such as pulmonary embolism, myocardial infarction, pneumothorax, etc.

The CVP monitoring during anaesthesia and surgery are very useful in determining the overall fluid volume status of patient, the effect of fluid or blood loss and in guiding the replacement therapy. The responses of CVP to fluid replacement therapy can also provide information regarding the venous compliance and the functional efficiency of the right side of the heart.

When a pressure transducer is used for monitoring of CVP, then the device displays the pressure unit in millimetre of Hg, but not in centimetres of H_2O as in a water manometer (1.36 cm of H_2O = 1 mm of Hg). It is also important to understand that during monitoring of this low pressure system the transducer should be placed and zeroed at correct level, i.e. the right atrial level. The zero reference at the level of right atrium or the manubriosternal joint and the manometer scale or the transducer must bear a constant relationship. The waveform of CVP which is displayed on the screen of the electronic device is actually a wealth of information. The venous pressor waves reflect the normal sequences of the mechanical events of cardiac cycle. The first large positive deflection 'A' wave is caused by atrial contraction, which is quickly followed by a small positive 'C' wave due to the bulging of tricuspid valve in the atrium with the onset of ventricular systole. Then, this 'C'wave is followed by 'X' descent due to the atrial relaxation which is again followed by a late positive deflection 'V' wave due to the gradual accumulation of blood in the venacava and the right atrium. Finally, the 'Y' descent is caused by the opening of tricuspid valve and rapid right ventricular filling. In atrial fibrillation the 'A' wave is absent, as there is no effective atrial contraction. However, sometimes large 'A' waves (canon waves) also occur in some arrhythmias, such as heart block, nodal rhythm, etc. when atrium contracts against a closed tricuspid valve. The tricuspid regurgitation, ventricular overfilling or heart failure etc. cause distortion and an increased size of the 'V' wave (Fig. 22.19).

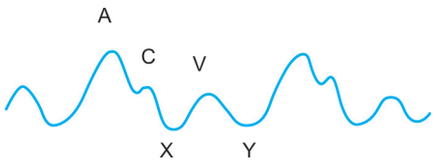


Fig. 22.19: Central venous pressure wave

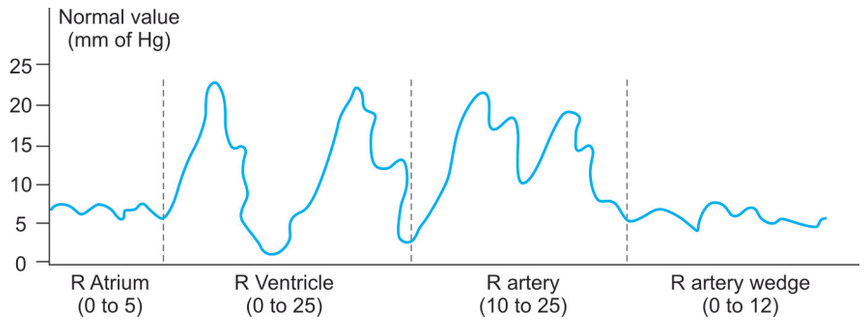


Fig. 22.20: This is a diagrammatic representation of the pressure wave form which is seen on the monitor, while the tip of the pulmonary artery catheter is advanced through the right atrium and right ventricle and ultimately to lie in the pulmonary artery. The right atrial pressure wave is characterised by low systolic and low diastolic value. The right ventricular pressure wave is characterised by high systolic and low diastolic value. The main pulmonary artery pressure wave is characterised by high systolic and high diastolic value. Pulmonary artery wedge wave is characterised by low systolic but high diastolic value. When the balloon is inflated with the tip of the catheter wedged in a branch of a pulmonary artery, immediately the pulmonary artery wedge pressure wave form is seen on the monitor. The pressure values, shown here, represent in a normal spontaneously breathing patient.

Pulmonary Arterial Pressure Monitoring

Starling first demonstrated that the left ventricular flow or cardiac output is directly proportional to the LVED fibre length, which is again proportional to the LVEDV. LVEDV is again directly proportional to LVEDP which we try to measure indirectly by pulmonary artery pressure (PAP). Thus, one of the main determinants of CO and hence O_2 delivery to the tissues is the left ventricular end diastolic volume (LVEDV), which assumes the amount of blood ready to be pumped out during left ventricular systole. But it cannot be measured directly. So, if left ventricular compliance is normal, then the left ventricular end diastolic pressure (LVEDP) can be used as an indicator of LVEDV. Thus, the measurement of LVEDP is very vital for determination or assessment of left ventricular performance and CO.

Again, unless an abnormal pressor gradient exists across the mitral valve, then the left atrial pressure (LAP) and pulmonary venous pressure (PVP) reflect LVEDP. On the otherhand, the measurement of pressure in the small pulmonary artery reflects the PVP which ultimately reflect (Fig. 22.20) the LAP, LVEDP and CO. So, the measurement of pressure in a small pulmonary artery by wedging the tip of a pulmonary artery catheter which is known as PCWP gives us a vital clue of CO. The entry and wedging (by inflation of a balloon) of the tip of a pulmonary artery catheter into small pulmonary artery (capillary) ceases the phasic and pulsatile blood flow distal to the wedging portion of this small pulmonary artery. Thus, it leaves a static column of blood between the catheter tip and the pulmonary veins and left atrium. Now, the pressure detected at the small pulmonary artery where the tip of the catheter is wedged is called the pulmonary capillary wedge pressure (PCWP) and approximates subsequently with the PVP, diastolic LAP, LVEDP and LVEDV. Thus PCWP which is also termed as PAOP (pulmonary artery occlusion pressure) provides an indirect nearly accurate estimation of the preload or diastolic filling of the left side of the heart under most circumstances. But, when diastolic LAP exceeds 15 mm of Hg due to mitral stenosis or other causes, then PCWP may be a poor detector of LAP and subsequently LVEDV or LVEDP. Sometimes, in the absence of PCWP pressure the pulmonary artery pressure is also taken indirectly as the left ventricular filling pressure. This inference is based on :

CVP $\propto$ PA $\propto$ PCWP $\propto$ PV $\propto$ LAP $\propto$ LVEDP $\propto$ LVEDV (Fig. 22.21).

But in ill patients, particularly in those with right ventricular failure, pulmonary oedema, mitral valve diseases, and those receiving positive pressure ventilation,

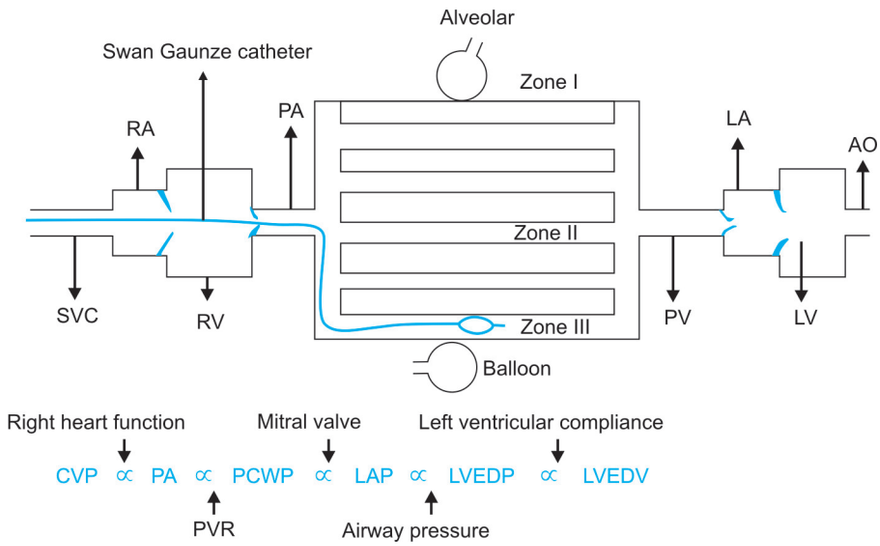


Fig. 22.21: Relationship between various determinants of cardiac output

etc; the relation between the pulmonary artery pressure (or pressure of the right side of the heart) and LAP or PVP (pressure of the left side of the heart) is uncertain. Unfortunately, as it is not possible to cannulate the left atrium easily, so we try to estimate or measure indirectly the LVEDP (proportional to LVEDV – which is again the main determinant of CO) by measuring the pressure of the right side of the heart by measuring the PCWP, PAP, RVP, CVP, etc.

On the basis of relationship between the PA pressure, PV pressure and alveolar pressure (P_{ALV}), the lung is divided into three zones (I, II and III). For the measurement of PAP and PCWP the tip of the pulmonary artery catheter (PAC) should be in zone III, where PVP exceeds alveolar pressure and the capillary conduit is completely opened being capable of directly transmitting the pressure of blood from left side of heart to the right side. In the supine position, as a large portion of lung remains in zone III, so it is assumed that the tip of PAC always remains in zone III. When the patient is ventilated with high positive pressure or PEEP, then most of the zone III will be converted to zone II or I. In this situation, the relationship between PCWP and LAP is lost. The maximum limit of PEEP is 10 cm of H_2O, below which the relationship is maintained.

In an average the pulmonary artery diastolic pressure (PADP) which is about 10 mm of Hg is often used as a good indicator of PCWP which is about 9 mm of Hg . But in some situations, where the pulmonary artery diastolic pressure increases such as in pulmonary hypertension (or ↑ PVR) due to hypoxia, hypercarbia, chronic obstructive lung diseases or vasoactive drugs, etc., then PADP does not correlate well with PCWP or pressure of the left side of heart. Therefore, to summarise, it can be stated that in conditions where the left heart function correlates well with the right heart function and there is no condition suggesting grossly abnormal PVR, then CVP can be trusted as sole indicator of the overall left sided cardiac filling pressure and cardiac output.

The pulmonary artery catheter (PAC) usually have three lumens and a thermistor near at the tip. The most distal lumen opens at the tip and is connected proximally to a pressure transducer which displays the pressure waveform on the monitor screen. Proximal to the tip, there is another lumen which is used to inflate the balloon. There is another proximal lumen, which is used for the measurement of CO. In addition to the measurement of CO, the PAC is also used for sampling of mixed venous blood. However modern PAC have five lumens with provisions for CVP monitoring port, extra-venous infusion ports, a fibre-optic bundle for blood O_2 saturation measurement, and a lumen for the passage of wire for ECG recording and atrial or ventricular pacing.

Insertion of PAC first requires the insertion of a central venous cannula at any site. Then, PAC can be placed successfully through any of the central venous cannulation sites. But, the right IJV is preferred by most of the clinicians. External jugular vein may also be used. But the success rate is less than IJV. If neck veins are not available, then left subclavian vein is next preferred to the right subclavian vein. Because, the left subclavian vein courses to SVC in a smooth gradual turn than its right counterpart. Prior to insertion of every PAC, it should be checked by inflating and deflating the balloon and irrigating all the three or five intracatheter lumens with heparinised saline. The distal lumen is connected to an electronic pressure transducer which is zeroed at the mid-axillary line. After the introduction of the PAC through the valved port of the introducer used for central venous cannulation, the distal port of PAC is connected to the pressure transducer. When the catheter is first placed into the SVC and a central venous waveform is seen on the monitor, then the balloon is inflated. If the central venous waveform varies with respiration, then it confirms the intrathoracic position of the tip of the catheter, but either in the superior venacava or RA. At approximately 15 cm distance from the insertion point the distal tip should enter the RA. The balloon is inflated with air, the volume of which is according to the manufacturer's recommendation (usually 1.5 ml). It protects the myocardium and endocardium from injury by the tip of the catheter. It also allows the flow of blood or the right ventricular output to direct the catheter forward from chamber to chamber and from chamber to main artery. On the otherhand, the balloon is always deflated during withdrawal or for any manipulation.

After its introduction the pulmonary artery catheter is first advanced towards the RA and then towards the tricuspid valve from SVC. From this point onwards ECG monitoring for detection of any dysrhythmias is very important. This is because premature ventricular contractions (PVC) are often seen during PAC insertion and its passage through the different chambers of heart which may require intervention. As the PAC advances, then the ballooned tip of the catheter tends to move towards the pulmonary artery from the right ventricle by the direction of the flow of blood. Although some manipulation may be required, but it usually advances easily through the right atrium and the right ventricle into the pulmonary artery. However the corresponding changes in the measured pressure can be observed over the screen as the catheter advances. The location of the tip of the PAC is also determined by identifying the characteristics of the pressure waves of that cardiac chambers and vessels which are encountered during its passage. The advancement of catheter tip from chamber to chamber is facilitated by the different phases of cardiac cycle and also by the flow of blood as PAC is

a flow-directed catheter. For example, the catheter tip with balloon passes from the SVC into the right atrium and then to the right ventricle during diastole. But, the catheter passes from the right ventricle to the pulmonary artery during systole.

The location of catheter tip in the right ventricle is characterised by a sudden increase in systolic pressure and a wide pulse pressure. Then from the right ventricle to the pulmonary artery (PA), the catheter passes on during the systole, and the location of the tip of the PAC at PA is characterised by a sudden increase in diastolic pressure and a narrow pulse pressure. The entry of the tip of the catheter into the PA normally occurs by 35 to 45 cm distance from the entry site. The catheter further advances through the pulmonary artery, until it eventually fills the lumen of a small pulmonary artery to become wedged and to lose much of its pulsatile character as seen in the small PA. In this position, the tip of the catheter is isolated from the proximal part of this small PA by the balloon. The transducer then measures the pressure of the pulmonary capillaries which are in continuity with the pulmonary veins and hence the left atrium in front. This is then taken as the measurement of the left atrial pressure at diastole. If the balloon is deflated at this wedged position, then the pulmonary artery wave form is restored again and at the end of each measurement of left atrial pressure the balloon must be deflated to avoid pulmonary infarction. During passage of catheter through the right atrium, right ventricle and pulmonary artery, there is chance of knotting. So, to prevent knotting the balloon should be deflated and the catheter is withdrawn, till the pressure changes do not occur at the expected distance. In very difficult cases, such as, in low cardiac output, pulmonary hypertension, congenital heart diseases, etc, the catheter advancement by flotation of the balloon can be enhanced: (i) by the deep breaths of patient, (ii) by positioning of patient in a right lateral or head-up position, (iii) by increasing the cardiac output, (iv) by administering a small dose of inotropic agent, etc.

If the wedging of catheter occurs before the maximum inflation of balloon, then it signals its overwedged position. In such condition the catheter should be withdrawn slightly, because there is a chance of pulmonary artery rupture which may carry 50 to 70% mortality rate. So, the PAP should continuously be monitored to detect any overwedged position which is an indication of catheter migration. The correct position of catheter is also confirmed by the lateral chest X-ray. Usually, most catheter migrate caudally (basal portion of lungs) and to the right side (right lung). But, sometimes it wedges anterior to the venacava, where the true pulmonary capillary pressure is less than the alveolar pressure. This results in a spuriously elevated pressure measurement during IPPV.

The relative contraindication of pulmonary artery catheterization are: complete LBBB which may lead to complete heart block, W-P-W syndrome and Ebstein malformation which may lead to severe arrhythmias. The risk of complications increase with the duration of catheterisation. So, it should not be kept for more than 72 hours.

Though, the PAC can provide invaluable information for the care of critically ill patients, but still there are several pitfalls in the procedure of measurement and interpretation of these data. So, it sometimes make the PAC a counter-productive and even hazardous tool. For example, the balloon of the catheter is inflated blindly only by the observing the PA pressure tracing, which guides the balloon's position. But, unfortunately the PA pressure waveform can be distorted by artefacts and can misguide the actual position of the catheter balloon, whether it is properly wedged or not. This confusion may result in an erroneous and dangerous over-inflation of balloon, causing severe complications. So, the routine use of PAC should not be performed, till the benefits over balance the risks. Thus, the decision of monitoring with a PAC depends on the clinical judgement of the anaesthetist who must weigh all the pros and cons of this process in the background of the status of the particular patient, the proposed surgical procedure and the particular process setting.

The complications of pulmonary artery catheterisation are: tachydysrhythmias (such as PVC, VT, VF etc.), heart block (RBBB, LBBB or complete AV block in patients with prior LBBB), endocarditis, pulmonary embolism, pulmonary infarction, pulmonary artery rupture, sepsis (positive catheter tip culture), tricuspid and/or pulmonary regurgitation, etc. (Table 22.13).

Monitoring of the Left Atrial Pressure (LAP) Directly

Directly the LAP is measured only during open cardiac surgeries. This parameter affords a more definite data of the left ventricular filling pressure. Thus, it provides a definite direct assessment of the left ventricular filling volume and performance of the left side of the heart. The LAP monitoring also directly helps in the diagnosis of malfunctions of the mitral value prosthesis. Direct LAP monitoring is usually

Table 22.13: Complications of pulmonary artery catheterisation with reported incidence (%)

Bleeding	5 -10 %
Mural thrombus	25 - 60 %
Thrombophlebitis	6 - 10 %
Arterial puncture	1 - 3 %
Pneumothorax	0.3 - 4 %
Air embolism	0.5 - 1 %
Minor arrhythmia	4 - 68 %
Severe arrhythmia (VT, VF)	0.5 - 60 %
RBBB	0.1 - 4 %
LBBB	0.1 - 8 %
Pulmonary artery rupture	0 - 1 %
Pulmonary infarction	0.1 - 5 %
Positive culture at catheter tip	1 - 34 %
Endocarditis	2 - 9 %
Catheter knotting	1 - 2 %

performed by putting a thin catheter into the left atrium through a purse-string suture in the right superior pulmonary vein. The catheter is then brought out of a wound through the infraxiphoid portion of the chest wall and is connected to a pressure transducer.

Monitoring of Cardiac Performance

The principal function of CVS is to supply the oxygenated blood to the tissues. So, the principal aim of monitoring of cardiovascular system should be the monitoring of the efficiency of performance of the heart as a pump. Efficiency of the performance of the heart as a pump is only assessed by measuring the following parameters such as cardiac output, mixed venous O_2 saturation (SVO_2) and SVR.

(i) Cardiac Output Measurement

The measurement of CO is a straight forward method for the assessment of efficiency of cardiac function, because CO is the revealing indicator of the entire functional efficiency of CVS. The importance of knowing the CO can also be explained from the fact that a patient with normal BP and PCWP may have poor vital organ perfusion if there is high SVR, causing low CO and SVR can not be measured easily. So, the knowing of cardiac output is very vital, and is measured by the following methods: invasive and noninvasive.

1. Invasive methods

A. Fick's principle

It was shown by Fick that the amount of O_2 consumed per minute (VO_2) by an individual is equal to the difference between the arterial and venous O_2 content ($CaO_2 - C_VO_2$) multiplied by the cardiac output (CO).

Therefore, $VO_2 = (CaO_2 - C_VO_2) \times CO$

$$CO = (VO_2) / (CaO_2 - C_VO_2)$$

The O_2 consumption can be calculated from the difference between the O_2 content in the inspired air and the expired air. Again, from the arterial line we can measure the arterial O_2 content and from PAC the venous O_2 content. Alternatively, Instead of O_2 cardiac output can also be measured by the Fick's principle using CO_2. The steps are as follows:

i. CO_2 output per minute is determined with Douglas bag,
ii. Alveolar air is collected and its CO_2 tension is determined which is identical to that of the arterial blood,
iii. Alveolar air is again collected after holding of the breath for 5 seconds, which is identical to that of the venous blood.

Therefore, CO = CO_2 output in minute / $(P_aCO_2 - P_VCO_2)$

Cardiac output can also be measured invasively by the indicator-dilution technique and the thermodilution technique. But, the variations of Fick's principle are the basis of these indicators dilution and thermodilution method for the measurement of CO.

B. Indicator dilution method

This method is not used in clinical practice, so is not discussed here.

C. Thermodilution method

This is a gold standard invasive method for the measument of CO. In this method a bolus of cold water is injected through the proximal lumen of PAC in the right atrium. Then when the cold water passes from the right atrium through the right ventricle to the pulmonary artery, then a thermistor at the tip of the PAC measures the difference in temperature of blood in the pulmonary artery, before and after the injection of cold water. Now, we know that the degree of changes in temperature is inversely proportional to the output of the right ventricle which is equal to the cardiac output of the left ventricle, and it is determined from this change in temperature. The temperature change is high, if the flow or cardiac output is high and the temperature change is low when the flow or cardiac output is low. Thus, a plotting of changes of temperature against time produces a thermodilution curve. Computer in the device computes the CO from this temperature difference data.

Though, it is the gold standard method, but it has some drawbacks. These are :

i. The Injection of bolus cold water may be too slow or too fast.
ii. There are possibilities of poor mixing of cold water within the blood.
iii. there are chances Ectopic heart beats, causing variation of CO.
iv. Variability of CO with each breath.
v. Time consuming.
vi. All the drawbacks of pulmonary artery catheterisation.

Practically, several measurements are taken. But the most extreme results are discarded and the average of three closely paced results are taken.

Recently, through PAC small filament or coil is used at the tip which is electronically heated periodically and provides small pulses of heat into the blood, proximal to the pulmonary valve instead of bolus cold water. It also contains a thermistor that measures the change in temperature blood of pulmonary artery. Then, the computer in monitor device determines the CO by cross-correlating the heat production and the change in temperature. Thus these monitors provide a continuous measurement of CO and also gives us the record of changes of CO with time graphically.

Though, this method has multiple benefits, still PAC is an invasive technique and has all the complications similar to pulmonary artery catheterisation (listed above) which leads to a search for a more safer and easier method.

2. Non-invasive methods

A. Doppler – ultrasound technology

Measurement of CO by Fick's Principle is invasive and an expensive one. The popular and gold standard thermodilution technique for measurement of CO also use the Fick principle and needs PA catheterisation

with all its risks. So, these limitations led to the exploration and development of newer non-invasive method for determination of CO by ultrasound. The doppler ultrasound technology measures the blood velocity by using the principal that frequency of a wave changes if it is reflected off from a moving object. Thus, doppler ultrasound technology measures the velocity of blood in the ascending or descending aorta (according to the route and position of the probe) over a period of ejection time (T_{EJ}), and determine an average velocity value (V_{AVG}) for each heart beat. It also measures the cross-section of aorta (ascending or descending) – $Area_{AO}$. Then, the device calculates the CO by multiplying V_{AVG}, $Area_{AO}$, T_{EJ} and HR.

Thus, $CO = V_{AVG} \times Area_{AO} \times T_{EJ} \times HR$

The ultrasound probes are placed on the suprasternal notch or in the oesophagus, or in the trachea with ET-tube. The probe emits an ultrasonic sound wave that is then reflected off the red cells in aorta. The machine, then, measures the velocity of blood, the cross sectional area of the aorta and various patterns of flow to calculate the CO. The Estimation of stroke volume and cardiac contractility are also possible by this method. If the descending aorta is used, then the proportion of CO directed to the upper arms, head and neck must be assumed and the calculated flow through the descending aorta should be adjusted accordingly to determine the CO. When the probe is placed on the suprasternal notch, it measures the velocity of blood at the aortic valve. It can also emit continuous waves (CW) and pulse waves (PW) for continuous and intermittent measurement of the CO. Through transoesophageal route the probe is attached to the tip of the standard oesophageal stethoscope and determines the velocity of the blood flow in the descending or thoracic aorta. The transtracheal device uses a special type of ET tube with a PW doppler ultrasound transducer incorporated in its tip and measures the velocity of blood flow in ascending aorta.

The great advantage of this ultrasound device is that it is noninvasive, easy to use and provides an almost instantaneous measurement of CO with a very low incidence of complications. But the disadvantage is that, unfortunately, the probe usually has a very narrow angle of detection, and the calculated velocity is much dependent on the angle between the direction of sound waves and direction of the red cells in which they travel. (Since the cosine of this angle Q is a part of the doppler formula for velocity measurement). So, a constant alignment between the probe and the blood flow through aorta is necessary. Small movements of probe, therefore, changes the calculated CO markedly.

The recent clinical trials have shown that these doppler ultrasound monitors are unable to determine an absolute value of CO reliably. So this technique has been dismissed as inaccurate and impractical for routine use. They are used more now to provide a trend with time. They are, therefore, very useful in guiding perioperative fluid management, but have a limited scope in the intensive care unit.

B. Transthoracic impedance plethysmography technology

This technique was first reported by Kubicek and his colleagues. They used the principle that, as the amount of blood in the thoracic wall varies with each heart beat, it causes a corresponding change in the electrical conductance or impedance of the thorax. From these changes of impedance of the thorax, an impedance plethysmograph is developed, from which CO is determined (using an algorithm and the computer). Due to its high noninvasiveness and more or less accurate results, it has an increased acceptibility in the intraoperative and critical care cases. In practice, the main disadvantage of this method is interference from other electrical equipments and changes in electrode conductance, which may produce unreliable results.

(ii) Measurement of mixed venous O_2 saturation (SVO_2)

SVO_2 is possibly a more comprehensive measurement of the cardiac performance, than the CO itself. This is because it also reflects whether the CO is adequate enough to meet tissue metabolic needs or not. SVO_2 is a function of:

i. level of arterial O_2 saturation, SaO_2,
ii. the rate of O_2 consumption, VO_2 and
iii. the concentration of Haemoglobin Hb.

So, $SVO_2 = (SaO_2 - VO_2) / (CO \times 1.34\ Hb)$

An advantage of this method is its ability to provide a continuous assessment of the cardiac performance. The disadvantage is that SVO_2 depends on multiple variable parameters (as the above equation says). So, when any of these variables change significantly, one cannot assume that a change in venous O_2 saturation results solely from a change in CO or cardiac performance.

(iii) Measurement of SVR

Cardiac performance also can be assessed indirectly by the measurement of systemic vascular resistance (SVR). It is measured from the formula:

$SVR = (MAP - CVP) / CO \times 80$

MAP = Mean Arterial Pressure (mm of Hg)
CVP = Central Venous Pressure (mm of Hg)
CO = Cardiac Output (L/min)
[×80] = Factor to convert Wood units (mm Hg/L/min) to (dynes/s/cm^5)

The normal value of SVR is 15 Wood units (range 10 to 20 Wood units) or 1200 dynes/s/cm^5 (range 800 to 1600 dynes/s/cm^5).

23 Peripheral Nerve Block

INTRODUCTION AND HISTORY

Two American surgeons, named Halsted and Hall, had first injected cocaine at the peripheral sites near ulnar, musculocutaneous, supratrochlear and infratrochlear nerve and produced nerve block for minor surgical procedures in 1880. Then, James Leonard Corning used Esmarch bandage in 1885 with peripheral nerve block and had tried to prolong the duration of action of local anaesthetic agent by arresting the circulation and reducing the absorption of it from the tissues. This idea was further advanced by Barun using epinephrine mixed with LA agent as chemical tourniquet in 1903.

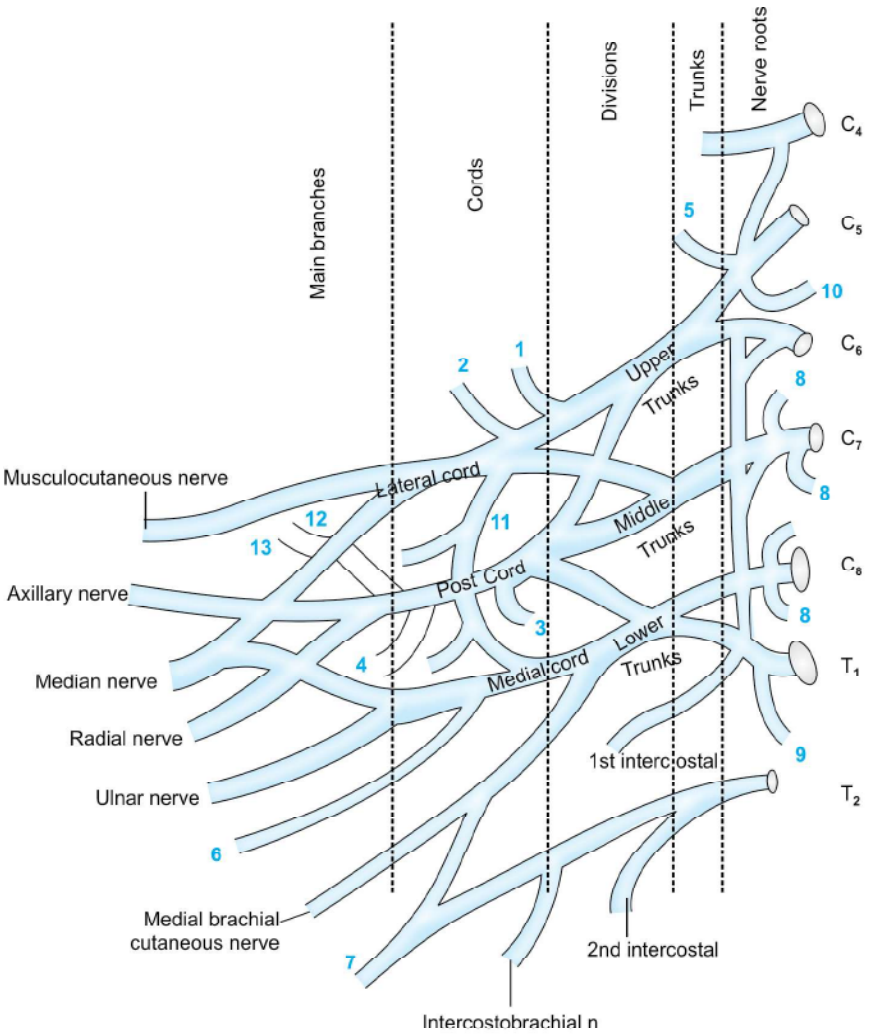
At the beginning of civilization, though the surgeons were the pioneer, regarding the early discoveries of regional anaesthesia but the developing speciality of anaesthesiology had gradually dominated over it. So, after that the role of regional anaesthesia or peripheral nerve block has expanded from the operating room to the arena of postoperative recovery and pain management clinic by holding the hand of anaesthetist. Previously, the peripheral nerve block was applied only on the adult and selected group of patients. But later it was proved that with the appropriate selection of patients and with the help of sedation the regional techniques of peripheral nerve block can also be used for all the age group of patients. There are different techniques of RA for extrimities. But, the duration of surgery influences both the type of regional technique selected and the choice of local anaesthetic agent used. The plans for postoperative pain relief also influence the approach to the peripheral nerve block or technique of RA.

Any anaesthesiologist does not under estimate the role of sedation during surgery under RA or peripheral nerve block. For example, many perfect brachial plexus block has been undone due to the inadequate management of sedation. Regional blockade on the extremities or peripheral nerve block has wide application by not only providing the surgical anaesthesia and analgesia, but as well as treating the chronic pain syndromes involving the extremities. RA on extremity (upper or lower) or others regional anaesthesia on trunk, including sympathetic ganglion blockade, have also several other advantages during the postoperative period, compared with general anaesthesia. These include: decreased requirement of sedation, decreased nausea and vomiting, minimum stay in hospital, early discharge and a smooth transition from parenteral to oral analgesic or other drugs as the block or anaesthetic effects dissipate gradually. During peripheral nerve block continuous infusion of local anaesthetic agents near a peripheral plexus of nerve via a percutaneous catheter has also become an increasingly common form of regional anaesthesia, if surgery is prolonged or post operative analgesia is needed.

UPPER EXTREMITY BLOCK OR BRACHIAL PLEXUS BLOCK

Applied Anatomy

The brachial plexus provides the complete motor and nearly the total sensory innervation to the upper limb. It is formed by the anterior primary rami (or ventral rami) of C_5, C_6, C_7, C_8 and T_1 spinal nerve with variable contribution from the anterior primary rami of C_4 and or T_2 spinal nerve. These anterior primary rami (or ventral rami) are called the roots (Fig. 23.1) of brachial plexus. The after exit from their respective intervertebral foramen, these spinal nerves first cross the transverse process of corresponding cervical vertebra at the same level and lie between the anterior and middle scalene muscle. The anterior scalene muscle arises from the ant.tubercle of transverse process of seven cervical vertebrae (C_1 to C_7) and take insertion on the scalene tubercle of first rib in front of the subclavian artery. The middle scalene muscle also arises from the posterior tubercle of the transverse process of seven cervical vertebra (C_1 to C_7) and takes insertion on the 1st rib behind the subclavian artery. The prevertebral fascia which arises from the ant and posterior tubercle of the transverse processes of seven cervical vertebrae, after first investing both the scalene, fuse laterally and enclose the brachial plexus in a fascial sheath. This is called the brachial plexus sheath. Thus, the brachial plexus sheath is continuous from its origin at the level of seven transverse processes of cervical vertebrae in the neck to its distal insertion at the level of the origin of coracobrachialis muscle. Hydrostatically this brachial plexus sheath is intact throughout its course. So, filling of this sheath with LA agent at various levels is the basis of brachial plexus block



1. Nerve to subclavian muscle
2. Suprascapular nerve
3. Subscapular nerve
4. Thoracodorsal nerve (or nerve to latissimus dorsi)
5. To phrenic nerve
6. Medial antebrachial cutaneous nerve
7. Medial brachial cutaneous nerve
8. To longus cervicis and scalene muscles
9. Long thoracic nerve (or nerve to serratus anterior)
10. Dorsal scapular nerve
11. Anterior thoracic nerve
12,13. Upper and lower subscapular nerve

Fig. 23.1: The brachial plexus

for conducting different type of regional anaesthesia (RA) of upper extrimity. As the roots of the brachial plexus emerge through the groove between the anterior and posterior tubercles of the transverse process of the seven cervical vertebrae, therefore it also emerges through the groove between the scalene anterior and scalene medius muscle, because they take origin from the anterior and posterior tubercle respectively. So, they lie in a fibrofatty tissue space which is situated between the two sheaths of fibrous tissue (brachial plexus sheath) investing these two muscles. Laterally, this sheath also extends into the axilla as a coveing membrane around the brachial plexus as it emerges into the axilla.

Between the scalene muscles (anterior and middle) the nerve roots of the brachial plexus, i.e anterior primary rami of C_{5-8} and T_1 spinal nerve unite and first form the three trunks of brachial plexus. There they lie cephaloposterior to the subclavian artery as it courses along the upper surface of the first rib. The superior trunk is formed by the union of the anterior primary rami of C_5, C_6 and sometimes C_4 nerve root. The middle trunk is formed by the anterior primary rami of the C_7 nerve root alone. The inferior trunk is formed by the anterior primary rami of the C_8 and T_1 nerve root and sometimes from T_2 nerve root. After their formation these three trunks of brachial plexus converge towards the apex of axilla to meet the anatomical needs of neck, which requires hypermobility in all directions. This convergence of nerve trunks is maximally tightest just medial to the first rib, which is about 4 cm lateral to the tranverse processes of C_6 vertebra. At this point, the brachial plexus assumes its most compact arrangements and block of it at this level cause rapid and complete surgical anaesthesia and analgesia of the upper limb. The trunks of brachial plexus in the neck lie in the posterior triangle and is also invested by the sheath of prevertebral fascia. In the posterior triangle the trunks of brachial plexus are superficially placed and covered only by skin, platysma and deep fascia. In such position they are also crossed by a number of structures such as the inferior belly of omohyoid, external jugular vein, tranverse cervical artery and supraclavicular nerves. Within the posterior triangle of neck, in a thin subject, the trunks of brachial plexus can also easily be palpated by the fingers. The upper and middle trunks of brachial plexus lie above the subclavian artery as the artery crosses the 1st rib. But the lower tunk lies behind the artery and it may make a groove on the rib immediately posterior to the subclavian artery (Fig. 23.2).

At the lateral border of 1st rib each trunk of brachial plexus divides into anterior and

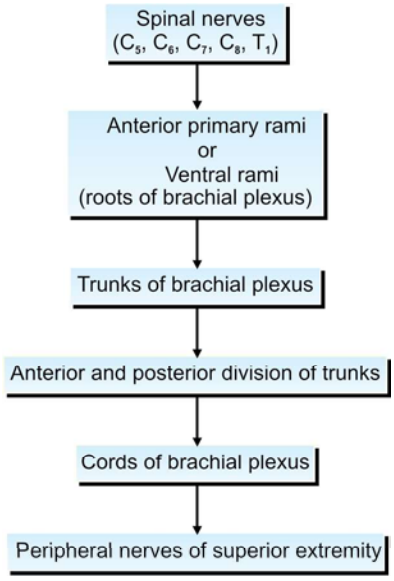


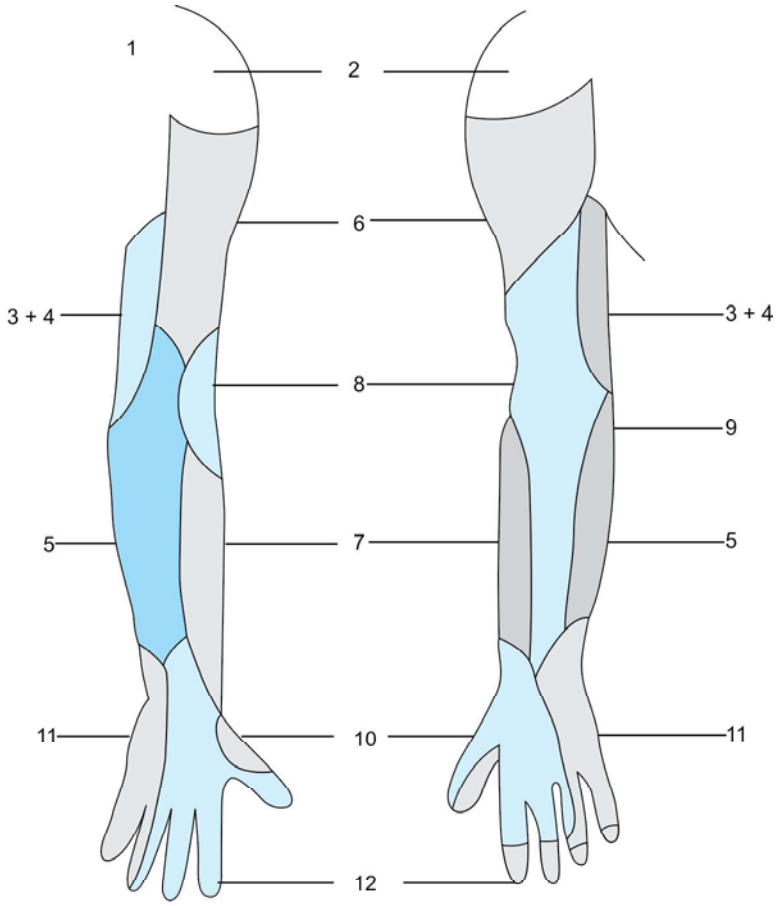
Fig. 23.2: Formation of brachial plexus

posterior divisions that passes posterior to the middle 1/3 of the clavicle. Then, the different combinations of joining of the anterior and posterior division of the three trunks form the cords of brachial plexus just when they enter into the axilla. Within the axilla these cords are named as lateral, posterior and medial according to their relationship with the 2nd part of the axillary artery which is situated within the same brachial sheath. The superior (or anterior) divisions of the superior and middle trunk joins to form the lateral cord. The inferior (or posterior) divisions from all these trunks join to form the posterior cord. The anterior division of inferior trunk continues as medial cord. Within the axilla at the lateral border of pectoralis minor muscle these cords again divide into peripheral nerves supplying the upper extremity.

Among the peripheral nerves of upper extremity, the musculocutaneous nerve which arises from the lateral cord of brachial plexus is the most proximal branch. So, the proximity of this nerve explains why it is the most commonly spared nerve during the axillary approach of brachial plexus block. The next highest or proximal branch of the brachial plexus, after musculocutaneous nerve, is the axillary nerve and it arises from the posterior cord. Its position also explains why surgical procedures, requiring wide spread total upper extrimity motor block are conducted most often by the technique or approach which is more proximal than the axillary approach of the brachial plexus block. After the axillary nerve, the median nerve arises from the lateral and medial cord. The radial nerve arises from the posterior cord and the ulnar nerve arises from the medial cord respectively.

Beside the terminal branches or peripheral nerves which arise from the cords, several branches also arise from the roots of brachial plexus providing motor intervation to the rhomboid muscle (C_5), subclavian muscle (C_5, C_6), serratus anterior muscle (C_5, C_6, C_7), etc. Suprascapular nerve arises from the C_5, C_6 nerve root and supply the muscles of the doral aspect of scapula and sensory to the shoulder joint. So, to block these nerves higher approaches for brachial plexus block such as the interscalene approach is necessary (Fig. 23.3).

For brachial plexus block four sites or approaches for injection of local anaesthetic agents are chosen such as: interscalene, supraclavicular, infraclavicular and



1. Supraclavicular nerve
2. Upper lateral cutaneous nerve of arm
3. Medial cutaneous nerve of arm
4. Intercostobrachial nerve
5. Medial cutaneous nerve of forearm
6. Lower lateral cutaneous nerve of arm
7. Lateral cutaneous nerve of forearm
8. Posterior cutaneous nerve of arm
9. Posterior cutaneous nerve of forearm
10. Radial nerve
11. Ulnar nerve
12. Median nerve

Fig. 23.3: The cutaneous distribution of peripheral nerves over upper extremity

axillary. The indications, results, technique and complications of brachial plexus block are specific for each site or approach. The site should be selected according to the surgical requirement, potential complication and anaesthesiologist's ability or skill. The proximal branches of brachial plaxus arising from the roots at cervical region are usually blocked only by the interscalene approach of brachial plexus block. The axillary approach of brachial plexus block takes places at the site of origin of the terminal branches of the plexus. At this level the terminal branches have a constant relationship to the axillary artery. For example the median nerve is lateral to the artery, the ulnar nerve is medial to the artery and the radial nerve is posterior to the artery. This constant relationship of these nerves helps in easy identification and complete block of these nerves through axillary route.

The composition of the brachial plexus can be summarized as follows:

1. Five roots

These roots are made by anterior primary rami of C_5 to T_1 spinal nerves and situated between anterior and medial scalene muscles. These roots receive grey rami communication carrying only post ganglionic sympathetic fibres from the cervical sympathetic chain. For example : C_5 and C_6 roots receive post-ganglionic sympathetic fibre from the middle cervical sympathetic ganglion. C_7 and C_8 roots receive post ganglionic sympathetic fibre from the inferior cervical sympathetic ganglion. T_1 root receives pos tganglionic sympathetic fibre from T_1 sympathetic ganglion.

The roots of brachial plexus give branches to:

i. longus cervicis muscle (C_{5-8})
ii. scalenes muscle (C_{5-8})
iii. serratus anterior (C_{5-7}) (long thoracic nerve)
iv. subclavian muscle (C_5, C_6)
v. rhomboidus muscle (C_5) (dorsal scapular nerve)
vi. phrenic nerve (C_5)

2. Three trunks (in the posterior triangle of neck)

There are three trunks (a) Upper (C_{5-6}), (b) middle (C_7 alone), and (c) lower (C_{8-1}). These trunks give branches : nerve to subclavian muscle and suprascapular nerve.

3. Six divisions (behind the clavicle)

Each trunk divides into an anterior and posterior divisions. These divisions do not give any nerve branch.

4. Three cords (within the axilla)

a. Lateral cord – It is formed by the union of anterior divisions of upper and middle trunks. It gives the following branches: lateral pectoral nerve, musculocutaneous nerve and lateral head of medium nerve.
b. Medial cord – It is the continuation of anterior division of lower trunk. It gives the following branches: medial pectoral nerve, medial cutaneous nerve of arm, medial cutaneous nerve of forearm, medial head of medium nerve, ulnar nerve.
c. Posterior cord – It is formed by the union of post divisions of all the three trunks. It gives the following branches: upper subscapular nerve, nerve to lattissimus dorsi (thoracodorsal nerve), lower subscapular nerve, axillary nerve and radial nerve.

The branches arising from the roots and trunks of the brachial plexus is situated in the neck above the clavicle and so these are called the supraclavicular branches. But, the major distribution of the brachial plexus is derived from its cords and are situated below the clavicle. Therefore, they are called the infraclavicular branches.

Interscalene Approach of Brachial Plexus Block

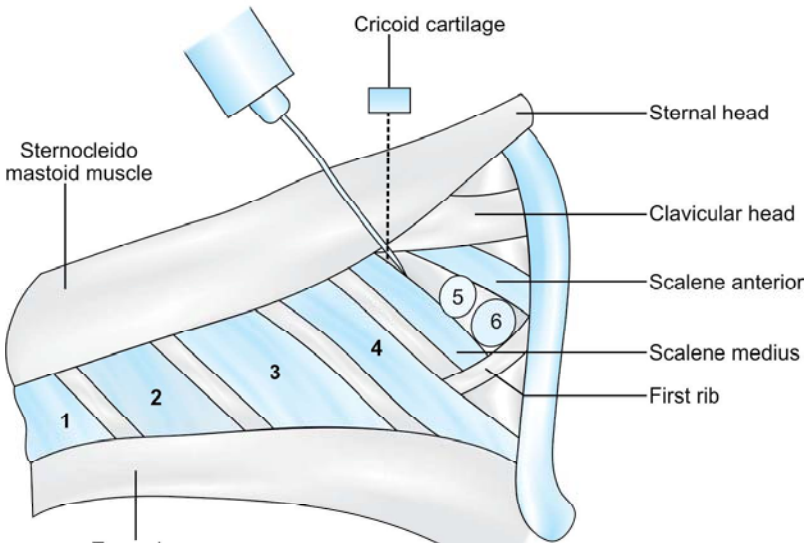
Among all the approaches of brachial plexus block, it is the most proximal and cephalad approach. So, all the complications related to this approach of brachial plexus block are due to its proximality to the vital structures in neck. It is performed at the level of the roots and trunks of brachial plexus and most often at the level of superior trunk over the transverse process of C_6 vertebra

Indication

The principal indication for interscalene approach of brachial plexus block is the surgeries over the proximal part of upper extremity, e.g shoulder and upper arm. This is because surgery over shoulder requires partial cervical plexus block with the full brachial plexus block and this is only achieved by interscalene approach. On the other hand, for forearm and hand surgery this approach can also be used (Fig. 23.4).

But the block of inferior trunk of brachial plexus which supply mainly the forearm and hand (C_8, T_1) is often incomplete and frequently require supplementation by isolated ulnar N bock for adequate surgical anaesthesia along their distribution. The nerves responsible for thoracic innervation from brachial plexus enters the thorax through axilla, but they remain outside the brachial plexus sheath. So, if the surgical incision for surgeries on upper extrimity involves the medial side of the upper part of thorax and axilla as in the transdeltoid approach for surgeries on upper extrimity, then these areas might remain unblocked by the interscalene approach of brachial plexus block. Similarly, if the skin surface which are innervated by the nerves arising from C_2 to C_4 segment of spinal cord is involved in surgery it may not be blocked by this approach of brachial plexus block and may requires supplementation by paravertebral injection. An inferior axillary surgical approach for the operation on shoulder joint may also require too large, skin area, so this approach of brachial plexus block is of no help.

The brachial plexus block may still be used with light GA for extended pain relief of upper extrimity. Scarring developed from the previous surgery could be



1 = Semispinalis capitis, 2 = Splenius capitis, 3 = Levator scapulae, 4 = Scalene posterior, 5 = Brachial plexus, 6 = Subclavian artery

Fig. 23.4: The site of interscalene approach of brachial plexus block

another obstacle to the use of pure regional anaesthesia (brachial plexus block) for the repeated shoulder surgery. This is due to the isolation of some nerve structure from the action of LA agent by the developed fibrosis. So, the use of nerve stimulator and elicitation of paresthesias is recommended with this technique, in order to place the needle accurately near the nerve. In the posterior triangle the brachial plexus sheath is very thin and so the feeling of piercing the sheath by needle is very difficult during interscalene approach of brachial plexus block.

Technique

The anatomical background for the correct interscalene approach for the brachial plexus block is the exact identification of location of brachial plexus in the groove which is formed by the overlapping of anterior and middle scalene muscles at the level of cricoid cartilage. This overlap occurs over the transverse process of C_6 vertebra. The entire brachial plexus is accessible at this point from outside, because the complete sheath of brachial plexus is formed here. Any injection within the sheath at this level of nerve trunk will have access to the entire brachial plexus including the roots and cords. By the use of nerve locator and motor evoked response or paresthesia felt in the arm, the origin of specific nerve is also identified which helps in specific nerve block. But, injection of drug outside the sheath will not result in block. So, the knowledge of the branches of nerves of brachial plexus which lie outside the brachial plexus sheath will prevent these potential failure of block. Examples of such instances are the suprascapular N, axillary N, long throcic N, etc, which leave the sheath at this level. So, the paresthesia to the anterior chest (pectoral area) or the area of the scapula or the acromion region which is due to the stimulation of these nerves, lying outside the plexus sheath should not be mistaken as a confirmatory sign of brachial plexus entry of needle at this level.

For the interscalene approach of brachial plexus block, patient should lie in supine position with head turned away from the side of the block. The posterior border of sternocle domastoid muscle is palpated first by asking the patient to lift the head. Then, the interscalene groove (where middle and ant. Scalene muscle cross each other) can be palpated by rolling the finger laterally from the post border of the sternocledomastoid muscle over the belly of the anterior scalene muscle. Then a line is drawn laterally from the cricoid cartilage to intersect the interscalene groove which indicates the level of transverse process of C_6 vertebra. After proper sterile preparation, a 4 cm short beveled needle is inserted perpendicularly to the skin, with 45° caudal and slightly posterior angulation. Needle is then advanced in that direction until the paresthesia is felt. This usually occurs at very superficial level. A click may be detected, if blunt needle is used when it goes through the prevertebral fascia. If bone is encountered within 2 cm of skin, it is likely to be the transverse process of C_6 vertebra. Nerve stimulator may be helpful to identify the individual nerve of brachial plexus or the plexus itself. The perceived feeling anywhere in the arm is a reliable indicator of the superior trunk of brachial plexus. Appreciation of paresthesia over the region of scapula, acromion or pectoral area indicates the suprascapular, axillary or long thoracic N, respectively which are not located within the sheath of brachial plexus and there is chance of failure. After getting paresthesia over the arm (which indicates that the tip of the needle within the sheath) the needle should be fixed at that position and it can be helped by using a flexible extension tubing. After negative aspiration, 10 to 40 ml of LA drug is injected incrementally, depending on the desired extent of block. There is a definite relationship between the volume of LA agent and the extent, depth and duration of regional anaesthesia. For example, 40 ml of LA solution is associated with complete cervical and brachial plexus block for prolonged period.

Complications

Ipsilateral phrenic nerve block with diaphragmatic paralysis occurs in all most all the patients during interscalene approach of brachial plexus block. It causes 25% reduction in pulmonary function. This is due to the anterior spread of LA solution

over the anterior scalene muscle blocking the phrenic nerve. This may cause dyspnoea in respiratory compromised patient. Therefore, sedation required for these patient to tolerate these symptoms also have negative impact. On the other hand, the ipsilateral involvemant of vagus, recurrent laryngeal nerve and stellate ganglion with the concomitant block of brachial plexus through interscalene approach has little or no significance, but related symptoms may require assurance or sedation. For postoperative pain relief after the total shoulder replacement surgery under GA the interscalene approach of brachial plexus block can be adopted, but only after confirming that there is no nerve damage during surgery. Otherwise, later this block should be blamed for nerve injury what was done during surgery under general anaesthesia. If the needle is long enough and the direction is caudal, then any of the epidural or subarachnoid block can be precipitated during the interscalene approach of brachial plexus block. This is due to the close proximity of dural sleeve over the spinal nerves and the site of interscalene approach for brachial plexus block. As several important vascular structures are also in close proximity to the site of injection, so during interscalene approach of brachial plexus block repeated aspiration and incremental dose of LA agent should be given which guard against the inadvertent intravascular injection of drug. In this approach of brachial plexus block the nerve damage or neuritis can also occur like any other peripheral N block.

Supraclavicular Approach for Brachial Plexus Block

The advantage of this approach for brachial plexus block over the interscalene approach is that a small volume of LA drug can be delivered directly near the three trunks where they are compactly arranged, resulting in rapid onset and reliable dense brachial plexus block. But the rate of complication may restrict this approach. During the application of this technique the incidence of complication (risk) should be balanced with the benefit (rapid and dense block) achieved by it. Distal to the transverse processes of cervical vertebrae the prevertebral fascia invests the nerve of brachial plexus, forming the brachial plexus sheath. When the nerves of brachial plexus passes over the first rib, then this sheath of it becomes complete and formed a neurovascular bundle which lies posterior and inferior to the clavicle at about its midpoint. For this approach of brachial plexus block striking the 1st rib with needle is the land mark. Then, walking of needle in the correct plane on the surface of the rib will lead to the identification of brachial plexus. Another landmark for this approach of brachial plexus block is the apex of palpable subclavian artery which can be traced cephalad to identify the interscalene muscular interval. Lateral to the subclavian pulse at the level of the clavicle the supraclavicular part of brachial plexus can be found. During interscalene block if the crossing of anterior and middle interscalene muscle is traced distally toward the clavicle then the brachial plexus also can be approached at the supraclavicular level (Fig. 23.5).

Indication

Three anatomical points are important for the performance of supraclavicular approach of brachial plexus block. These are:

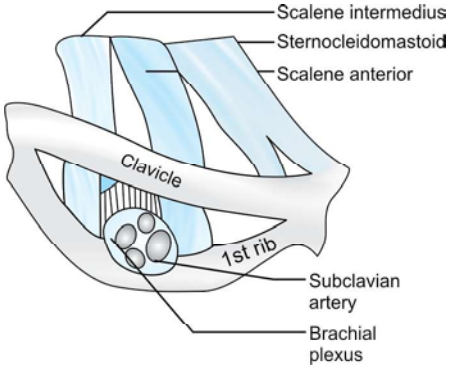


Fig. 23.5: The brachial plexus with subclavian artery on 1st rib

i. The three trunks of brachial plexus are clustered vertically over the first rib and liecephaloposterior to the subclavian artery which often can be palpated in a thin patient.
ii. The neurovascular bundle lies posterior to the clavicle at about its midpoint.
iii. The first rib acts as a barrier for the needle piercing the pleural dome.

This approach is applicable for any surgical procedures of upper extremity, where the brachial plexus block can be used theoretically. But due to the sparing of most proximal part of brachial plexus by this approach and thus not blocking the nerves which arise from the roots and supply over the shoulder somebody would recommend the interscalene approach when the surgical procedure is performed on the shoulder. However, practically supraclavicular approach for brachial plexus block with adequate amount of LA drug usually provide adequate anaesthesia for any surgical procedure on shoulder with reasonably high success rate. This is because large amount of LA drugs, placed at this site can easily spread cephalad and block the roots of brachial plexus.

Technique

The patient is first placed in supine position with head turned to the opposite site. Then at the midpoint of clavicle, the pulse of subclavian artery is felt, and the point just lateral to the pulse is the site of injection. If pulse is not palpable, then midpoint of clavicle is also the landmark for the site of injection of LA agent for this approach of brachial plexus block. Proper aseptic measure is taken. Then, for this block a 22 to 25 G and 1″ long blunt beveled needle is selected. It is advanced through the skin wheal in a caudal, but slightly medial and posterior direction toward the subclavian pulse, until the paresthesia is encountered. If no paresthesia is elicited, then the needle is advanced more until the 1st rib is encountered by the tip of the needle. If artery is encountered, needle

is withdrawn till blood is no longer aspirated. After encounterment with the 1st rib, the needle is walked on the rib, first lateral and then medial direction, until the paresthesia is elicited. When paresthesia is encountered then 20 to 30 ml of LA drug is injected. The caudal direction of needle must be avoided which increases the (Fig. 23.6) incidence of the entry of the tip of the needle into the pleural cavity and the lung parenchyma at their apex and development of pneumothorax. Advancing the needle deeper than the reasonable length to encounter the 1st rib must be avoided for fear of also pneumothorax. If any air is aspirated, then chest X-ray is mandatory. Air aspiration does not preclude complicating the block, because fine needle usually prevents significant air leak from the lung producing pneumothorax. So, it is unwise to discharge an outpatient without overnight observation after brachial plexus block through supraclavicular approach, particularly if there is an increased chance of pneumothorax.

The modified plumb-bol's technique for this approach of brachial plexus block needs the same patient position.The needle entry site is at the point where the lateral border of sternocleidomastoid muscle inserts on the clavicle. After aseptic preparation, 22G and 4 cm a long short bevel needle is inserted through the skin, while mimicking a plumb bob suspended over needle entry site. Often paresthesia is encountered prior to contacting the 1st rib or subclavian artery. If no paresthesia is elicited, needle is directed cephalad. If still no paresthesia is elicited then the needle tip is directed caudal until the 1st rib is contacted.

Complication

The incidence of pneumothorax after supraclavicular approach of brachial plexus block is 0.5 to 0.6 % and is most common in this approach. The incidence of pneumothorax, even in experienced hands, is more if routine diagnosis is sought by X-ray than clinical findings. Subclinical pneumothorax is more common than symptomatic pneumothorax. The onset of symptoms is sometimes delayed and may take 24 hour. Therefore, routine X-ray just after the block is not justified. Injury of subclavian artery and subclavian vein are also possible in this approach, like injury to the thoracic duct (on left side). Injury to the nerves of brachial plexus may also happen from direct traumatic needle insertion within the nerve or intra-aneural injection of LA agent. Other complications of this approach of brachial plexus block include: phrenic nerve block (40 to 60%), Horner's syndrome, neuropathy and cervical sympathetic block which only requires reassurance.

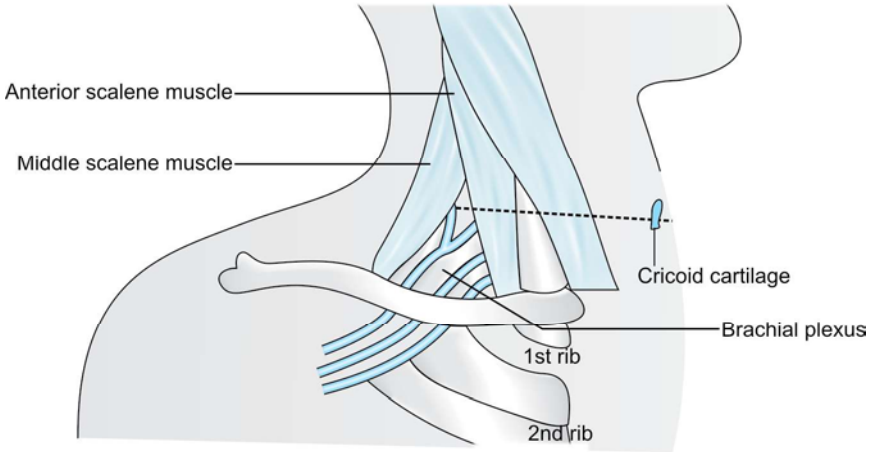


Fig. 23.6: The site of interscalene block, supraclavicular block and infraclavicular block

Infraclavicular Approach for Brachial Plexus Block

This approach of brachial plexus block is only described for historical reasons. Infraclavicular approach offers same advantages as supraclavicular approach. But high complication rate due to (i) the long distance crossed by the needle, (ii) very closeness of the needle to the parenchyma of lungs and great vessel and (iii) the scarcity of experienced anaesthetist to teach this technique has made its application limited (Fig. 23.7). So, the excessive high rate of complication for potential pneuomothorax, trend to limited hospitalization time, quick discharge of patient and increasing the number of outpatient extremity procedures under the regional anaesthesia have made this approach now obsolete. As the divisions of brachial plexus pass over the 1st rib and move towards the posterior surface of the clavicle, their tight and vertical disposition is still maintained.Then the plexus (cords) passes under the clavicle and move towards to the axilla, passing just inferior to the coracoid process. At this point, the brachial plexus is still directly over the first rib in the horizontal plane and this rib theoretically prevents any needle approaching the plexus at this site from entering the thorax. The infraclavicular part of brachial plexus is also tightly arranged within its sheath and any access of plexus at this level will result in rapid exposure of the entire plexus to LA agent. The disadvantage of approach for brachial plexus at this site is that it lies two to three inches deep to the surface, making it more difficult to approach.

Indication

Like supraclavicular, in this approach there is also high failure rate in blocking the branches, arising from the proximal part of brachial plexus which is only possible by inerscalene method. So, the

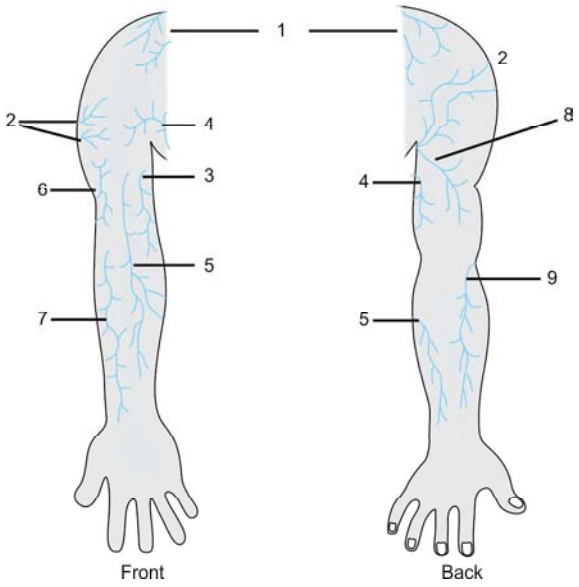


Fig. 23.7:

1. Lateral supraclavicular nerve ($C_{3,4}$)
   It arises from cervical plexus - divides into three - medial, intermediate, and lateral - pierces the deep fascia of neck and descends over clavicle - supplies skin over deltoid, pectoralis major as far down as the level of a horizontal line drawn from 2nd costal cartilage.
2. Upper lateral cutaneous nerve of the arm ($C_{5,6}$)
   It is a branch of axillary nerve - supplies skin over the lower half of deltoid muscle.
3. Medial cutaneous nerve of the arm ($T_{1,2}$)
   It arises from the medial cord of brachial plexus - supplies skin on the medial side of the arm.
4. Intercostobrachial nerve (T_2)
   It arises from 2nd intercostal nerve - crosses axilla - pierces deep fascia of upper arm - supplies the floor of axilla and medial side of upper arm.
5. Medial cutaneous nerve of forearm (C_8, T_1)
   It arises from the medial cord of brachial plexus - pierces deep fascia at middle of the arm - supplies skin over the front of upper arm between basilic and cephalin vein - also supplies the medial half of forearm.
6. Lower lateral cutaneous nerve of the arm ($C_{5,6}$)
   It is a branch of radial nerve - arises from radial nerve before it leaves the radial groove of humerous - pierces the deep fascia 2 to 3 cm below deltoid tuberosity - supplies skin of the front, lateral and posterior side of upper arm.
7. Lateral cutaneous nerve of the forearm ($C_{5,6}$)
   It is the continuation of musculocutaneous nerve - pierces deep fascia lateral to biceps muscle, 2 cm above elbow - supplies the skin of both the front and back of lateral side of forearm - also supplies the skin over the ball of thumb.
8. Posterior cutaneous nerve of the arm (C_5)
   It arises from the radial nerve in axilla - pierces the deep fascia a little below the posterior fold of axilla - supplies a wide area of skin on the back of arm from the level of deltoid tuberosity to the elbow.
9. Posterior cutaneous nerve of the forearm (C_{6-8})
   It arises from the radial nerve - pierces the deep fascia 2 to 3 cm above the elbow - passes downwards behind the lateral epicondyle - descends on the back of forearm upto the wrist - supplies skin of the back of forearm from elbow to wrist

block of brachial plexus through this route is not the choice for shoulder surgery which need the block of brachial plexus more proximally. Because the most proximal approach only such as interscalene approach can block the nerves or branches of brachial plexus arising from root which supply the shoulder. But, in contrast to interscalene approach the high success rate is anticipated of ulnar nerve block in this approach. This approach is also relatively contraindicated for out patient, because of its potential risk for subclinical pneumothorax like supraclavicular approach which may be manifested after the patient has left the hospital. Like supraclavicular brachial plexus block, the distinct advantage of this approach is that rapid high density block can be achieved without requiring movement of hand prior to the onset of anaesthesia. This is unlike the axillary approach where hand is moved before the block which causes pain due to injury for which surgery is advised or due to presence of any contracture which prevents abduction and circumduction of axilla.

Technique

The patient is positioned supine and the head is turned towards the opposite direction. After proper aseptic measure, a skin wheal is raised on the inferior border at the midpoint of clavicle. Then a 22G and 3" long needle is advanced at 45° angle towards the humeral head through this skin wheal. The insertion point of needle should be just lateral to the subclavian pulse if it can be identified. Always the needle should be advanced away from the chest wall to reduce the chances of entry of the needle into the apex of lung producing pneumothorax. The right position of needle can be identified by ilicitation of paresthesia. If bone (coracoid) is encountered by the needle, then it should be withdrawn and advanced again with slightly different direction. During aspiration test by a fluid filled syringe if air is aspirated, then chest X-ray is must. If a long insulated needle is available, then the nerve stimulator can also be used to elicit motor-evoked response for better identification of brachial plexus (Fig. 23.8).

Complication

The most common complication of this approach of brachial plexus block is pneumothorax and hemothorax which may not be detected at the time of block, but can be serious later on. Thoracic duct injury, on the left side, would be an insidious occurance. The injury of other great vessels and nerves of chest are also common.

Axillary Approach for Brachial Plexus Block

It is the most common approach of brachial plexus block for surgery on upper extremity.

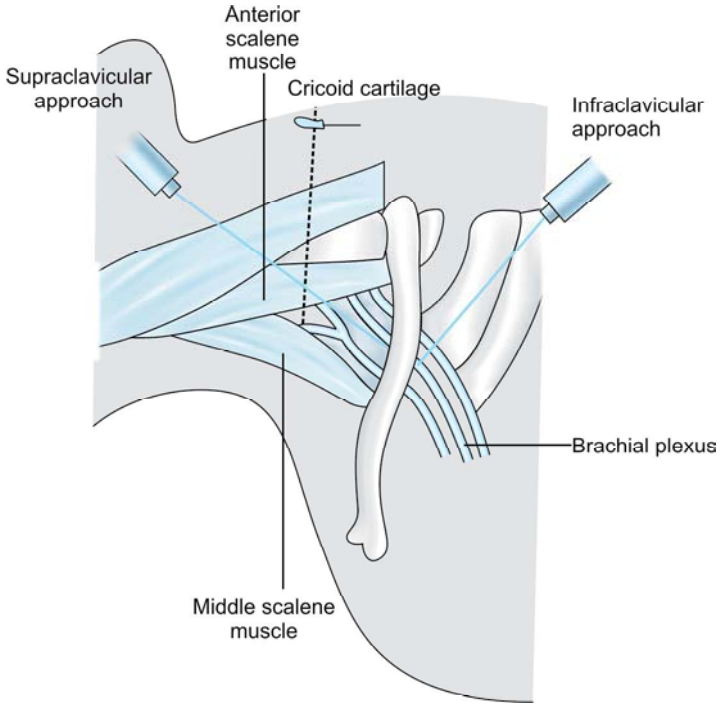


Fig. 23.8: Using nerve stimulator to elicit motor-evoked response for identifying brachial plexus

This is because of easy performance, reliability for hand and forearm anaesthesia, widespread familiarity of this approach, and low complication rate. This block is ideally suited for out patients and can also easily be adopted for pediatric group. The axillary approach for brachial plexus block is unsuitable for upper arm and shoulder surgery. Because musculocutaneous and other nerves arising from the proximal part of brachial plexus is often spared by this approach and should be supplemented separately at axilla or elbow. Patient who can not abduct his hand due to injury or other causes should not be selected for this approach of brachial plexus block.

Applied Anatomy

In axilla, the axillary artery lying within the sheath of brachial plexus along with the nerves, forms an important landmark. The brachial plexus is represented in axilla as cords and peripheral nerves. Cords are named as medial, lateral and posterior, according to their relationship with the axillary artery. The lateral cord is branched out terminally into the musculocutaneous nerve and contributes to the formation of median nerve. The posterior cord creates axillary and radial nerves. The medial cord gives rise to ulnar nerve and contributes to the formation of median nerve with the contribution from lateral cord. These terminal branches of brachial plexus also maintain the same relationship with the axillary artery like their primary contributors. Thus, the radial nerve remains posterior to the artery, ulner nerve remains medial to the artery and median nerve remains lateral to the artery. When the brachial plexus block is performed most proximally (interscalene approach) then the distal nerve such as usually the ulnar nerve is spared frequently and when the brachial plexus block is performed distally (axillary approach) then the proximal branches such as the musculocutaneous nerve is spared frequently. The medial part of the upper arms get sensory innervation from the branches of T_1 and T_2 spinal nerves which lies outside the brachial plexus and comes from thoracic wall. These nerves are called the medial brachial cutaneous and intercostobrachialis nerve and are found in the subcutaneous tissues of axilla. These nerves cannot be blocked by the axillary approach of brachial plexus block. These can be blocked by a separate subcutaneous field block at the medial site of upper arm. For this a vertical line, created by the skin wheal is infiltrated upward to the deltoid prominence and downward to the edge of the triceps. Then about 5 ml of local anaesthetic agent is deposited at this straight line in the subcutaneous tissue. A 25 G spinal needle can be a convenient tool for this injection (Fig. 23.9).

The neurovascular bundle in axilla around the brachial plexus is a multicompartmental structure. It make no complete, but partial barrier for diffusion of drug among the compartments. So, due to this multicompartmental structure, some recommend multiple injection site for axillary block to produce better results. But, some practitioners are reluctant to reenter the sheath of brachial plexus for second time after a bolus LA agent has already been injected. Because they fear that if nerve is pierced during the entry of sheath by needle in 2nd time will, leave the patient unaware (due to 1st time block) of pain and will cause potential severe nerve damage. So, controversy surrounds between the single versus multiple injection technique and still it remains unresolved. The elicitation of parasthesia for successful axillary block is also controversial, because of reportedly higher risk of nerve damage. Although actual data are limited, but motor evoked response by nerve locator is very helpful for success of axillary block.

Technique

There are four different techniques for axillary approach of brachial plexus block, depending on the different method of placement of needle tip within the sheath of brachial plexus. These are: transarterial technique, 'sheath-pop' technique, elecitation of paresthesia technique, and nerve stimulator technique.

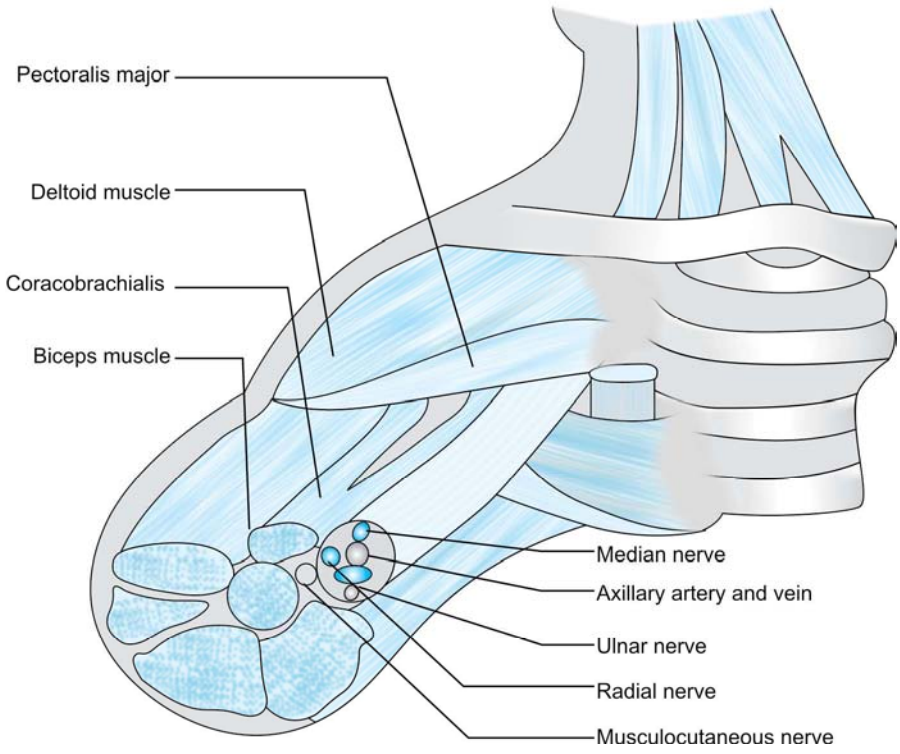


Fig. 23.9: The brachial plexus in axilla

The patient should be first placed in supine position. Then the arm is positioned at right angle to the body and elbow is flexed to 90°. The dorsum of the hand should rest on the bed or pillow. This is called the neutral position of the arm. Any further dorsal or ventral displacement of arm from this neutral position will distort the palpation of axillary artery. The more dorsal displacement of arm may accentuates the prominence of the underlying head of humerus and flattens the contents of the overlying sheath of brachial plexus which may make the palpation of axillary artery difficult.

The axillary artery is first palpated in axilla and then it is fixed against the head of the humerus. After that a skin wheal is raised directly over the artery by LA agent. Whenever possible, the most proximal area of pulse appreciation is selected. This is because the sheath begins to loss distally from this point. The best proximal site of injection of LA agent for brachial plexus block in axilla is the site of skin fold, formed by the crossing of the pectoralis complex arsing from the thorax with the arm.

After injection of LA agent arm should be returned to the patient's side. This will allow the head of the humerous to move further from the sheath and ensure the maximum proximal spread of the LA agent. This is because filling of the sheath as far proximally as possible with the anaesthetic agent from the site of injection results in better regional block. After a time span of 2 to 3 minutes, arm can be repositioned and any supplemental blocks (for medial brachial cutaneous nerve, inter costobrachiales nerve and musculocutaneous nerve) if indicated can be performed.

Methods of Identifying the Brachial Plexus Sheath

As previously described, there are four different techniques or methods for identifying the brachial plexus sheath. But all these techniques that have in common in them is the positioning of arm which allow the best palpation of axillary artery and maximize the anatomical information from the palpation of this surface anatomy.

A. Transarterial technique

In this technique a skin wheal is raised first by the LA agent at the most proximal site, where the pulsation of axillary artery is appreciated best. The anaesthetist's nondominant hand is positioned at this site in such a way that it can identify the pulse best, but will not occlude the arterial flow. For easy operation of this technique, the needle is usually connected first to an extention tubing and then to the syringe. It will help for the maximum needle control and fixation of it, if needed. In this transarterial technique the needle will pierce the artery and blood is to be aspirated during the passage of its tip through the arterial lumen. The needle will advance gently through the palpable pulse, perpendicular to the plane of artery, while a constant gentle aspiration by syringe is applied by the assistant. When aspiration of blood ceases, then it implies a sign that the tip of the needle is just beyond the arterial wall at its posterior surface. Now, 40 ml solution of LA agent is injected posterior to the artery. Alternatively half of the LA solution is injected posterior and half anterior to the artery. But, a great care must be taken to avoid intravascular injection of LA agent by using test dose or using epinephrine as marker in it. Some investigators report nearly 100% success of axillary brachial plexus block with this transarterial technique. But, some practioner avoid this transarterial technique in the belief that it is unnecessarily traumatic (Fig. 23.10).

B. 'Sheath pop' technique

This axillary approach for brachial plexus block is developed by identifying the brachial plexus sheath, without piercing the axillary artery or eliciting paresthesia, i.e not injuring the vessels and nerves. This

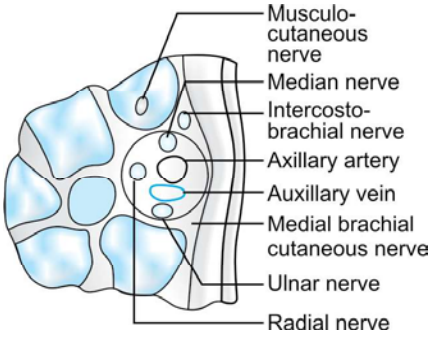


Fig. 23.10: Auxillary block

technique is facilitated due to the development of new blunt short beveled regional needles. This small, blunt, short beveled regional needle maximizes the tactile information during its insertion through the brachial plexus sheath. Due to the superficial nature of the artery, the short length of the needle is selected. After the appropriate positioning and creation of a sterile field, the needle is directed towards a position next to the underlying pulse. Usually the sheath is approached lateral to the pulse. The blunt-bevel needle is advanced through the skin until the axillary sheath is entered by the side of the axillary artery, as evidenced by a 'fasical click' (sheath-pop). Then, the needle is advanced 1 mm further into the sheath from distal to proximal where upto 40 ml drug is injected after negative aspiration. By this technique the success rate is very high, but it is most difficult to teach. Benefits of this technique is elimination of persistent paresthesia or compressive hematoma of axillary artery which is occurred due to directly prick of the nerve and artery.

C. Elicitation of paresthesia

It is one of the most oldest method for identification of nerve or its plexus for conduction block. Elicitation of paresthesia also can be applied easily for brachial plexus block, like other nerves and the result can be improved by anatomical approach, based on the dermatomes involved in the proposed surgical procedure. So, the knowledge of the proper location of nerves of brachial plexus in axilla is essential. The success of block for a given terminal nerve of plexus is further improved by injection only at that site from where the paresthesia is elecited. The axillary artery is the correct constant landmark creating a fixed relationship with these nerves. Again correct identification of paresthesia requires extensive knowledge of the terminal sensory components of these nerves. For example, the elecited paresthesia in the hand must easily be identified by its origin. If it is located in the dorsal aspect of thumb, then the radial nerve is implicated. If the paresthesia is located in the midpalm, especially on the palmar surface, then the median nerve is implicated.

Selection of the needle used to elicit paresthesia is controversial. Some thought that large blunt needle push the nerve away causing less chance of piercing it. Whereas fine needle may more likely enter the substance of nerve and can cause more injury to the nerve. But, some thought that fine needle will cause less nerve injury if nerve substance is inadvertently entered at all than the blunt needle.

During the initial injection, paresthesia perhaps is slightly increased due to the pressure, caused by the LA agent on nerve. This pressure initially induces the activation of nerve fibres (i.e. action potential of nerve fibres) and increases the conduction through it, before the Na^+ channels are blocked. Thus it increases the paresthesia initially. The advantage of this technique is that it relatively increases the success rate of block in selected dermatomes. But, the potential complication rate may increase due to the intentional elicitation of paresthesia by piercing the nerve. Whether this techniques of elicitation of paresthesia would influence the rate of persistant paresthesia postoperatively is unknown.

D. Nerve stimulator technique

With the minimum required frequency and voltage, it is possible to stimulate and elicit the motor activity of a nerve with little or no painful sensation. Thus, it helps to verify the placement of the tip of a needle very close to the nerve. Again, the use of variable voltage nerve stimulator, combined with insulated needle also increases the success rate. Because this combination gurantees that current can be delivered only to the tissues near to the desired nerve, adjacent to the injecting port of the needle. But, it is difficult to prick the blunt insulated needle through the dermis. So, after raising a skin wheal the passage of insulated needle through the dermis is facilitated by the passage of similar gauge sharp needle before and thereby avoiding the bending of regional insulated needle or folding of the insulating layer over the needle. Nerve stimulator unit is turned on after the skin is penetrated by the needle and during search for the nerve. The current is kept at 1 mAmp or less and at 2 Hz frequency to avoid the recruitment of nociceptive fibres, when the nerves are searched for. If pain occurs stimultaneously with the motor evoked response, patient may move his limbs involuntarily and may displace the needle. Gentle muscle movement elicited from an appropriate nerve muscle unit confirm the correct needle placement. Then decrease of voltage to 0.5 mAmp or less and still elecitation of muscle movement indicate very closeness of needle tip to the nerve and high probability of successful block. The further confirmation of the correct placement of needle is also possible if the equipment allows the injection of LA agent during the delivery of current. If injection is given during the stimulation of nerve, initially there is an increase in the magnitude of motor evoked response analogous to pressure paresthesia. This increase of motor evoked response should be followed quickly by decrease and gradual abolition of the movements of muscles as injection proceeds.

If the nerve stimulator technique is employed without the use of an insulated

needle, then the current density flowing along the entire shaft of the needle must be considered and a large area will be stimulated. There is also another technique to increase the probability that the injecting port of needle will be close to the part of the nerve, eliciting motor evoked response. For that, the needle is advanced gradually till the response occurs, then withdrawn until it just disappears and again moves forward in the same track until the response barely occurs again.

The complications of nerve stimulator technique are same as others. Insulated or noninsulated needle may encounter the artery, vein or nerve and may be the potential for injury.

Continuous Brachial Plexus Block with Catheter

Since 1940s, the continuous brachial plexus block has been described. It is usually obtained by placing and securing a catheter in the vicinity of the nerves of brachial plexus.This can be performed by technique using both the catheter 'over' and 'through' the needle methods. Catheter 'through' and 'over' the needle method means it can be passed through the needle after it pierces the skin or needle can be threaded through the catheter before piercing the skin. Longer catheter is helpful for better fixation and provide superior blockade, if the tip of the catheter lies more proximal to the plexus. However, stimulating electrode with catheter is not available still now for continuous brachial plexus block.

The advantages of this technique are:

i. Potential prolongation of surgical anaesthesia if needed,
ii. Decreased risk of toxicity of LA agent as small incremental doses are used,
iii. Postoperative pain relief,
iv. Sympathectomy.

Disadvantages are:

i. Increased incidence of inadequate surgical anaesthesia, as repeated small does are given
ii. Infection,
iii. Difficulty in securing catheter causing kinking, migration, etc.

Indications for continuous brachial plexus block with catheter are:

i. Upper extremity or digit replantation,
ii. Total elbow arthroplasty,
iii. Reflex sympathetic dystrophies for which prolonged pain relief by sympathectomy are advantageous.

SUPPLEMENTAL BRACHIAL PLEXUS BLOCKS—MEDIAL BRACHIAL CUTANEOUS AND INTERCOSTOBRACHIALIS NERVE BLOCK (FIG. 23.11)

Brachial plexus block alone cannot anaesthetize some area over the medial upper part of the arm which is supplied by the T_1 and T_2 segments of spinal cord through the medial brachial cutaneous and intercostobrachialis nerve. They remain outside the brachial plexus sheath. So, sometimes to make the brachial plexus block complete supplemental peripheral block of these nerves are sometimes necessary. The medial brachial cutaneous nerve and the inter-costobrachialis nerve are found in the subcutaneous tissue over the medial part of the upper arm. So, they can only be blocked by subcutaneous tissue field block over the medial part of the upper arm. For this field block a skin wheal is created along a transverse line which extends anteriorly upto the deltoid prominence and posteriorly upto the edge of triceps. Then, about 5 to 10 ml of LA agent is deposited at this straight line in subcutaneous tissue to block the medial brachial cutaneous and the intercostobrachialis nerve.

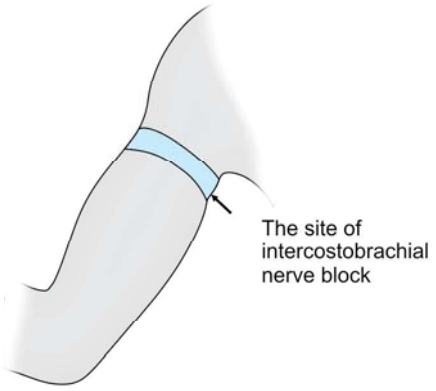


Fig. 23.11: Medial brachial cutaneous and intercostobrachial nerve block

DISTAL UPPER EXTREMITY CONDUCTION BLOCK OF INDIVIDUAL NERVE

This can be performed as sole anaesthetic technique with limited dermonates or as supplemental for partial brachial plexus block. Each of the peripheral nerve (musculocutaneous N, Radial N, Median N and Ulnar N) is identified and can be blocked at the level of elbow or wrist according to the need. Intravenous upper extremity regional anaesthesia is also a type of peripheral upper extremity block (Fig. 23.12).

Musculocutaneous Nerve

The individual conduction block of this nerve is frequently used to supplement the primary brachial plexus block, because there is high incidence of sparing this nerve when axillary route is approached. It is specially useful in surgical procedure where complete motor block of the upper arm is required by brachial plexus block through axillary route. It is also equally effective in blocking this nerve on the radial and dorsal surface of the foreman and hand where the terminal sensory supply of this nerve is located (Fig. 23.13).

Anatomy

This nerve is the continuation of the lateral cord of brachial plexus. It lies external to the brachial plexus sheath

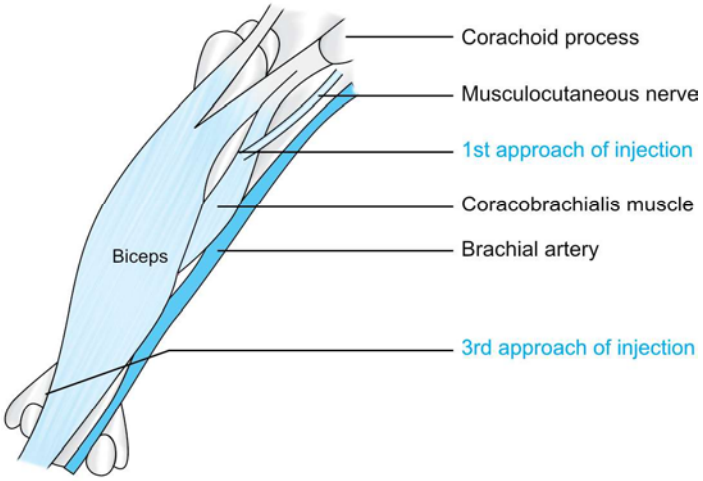


Fig. 23.12: Musculocutaneous nerve block (right side)

and passes through the substance of coracobrachialis muscle, lying posterior to the artery. It leaves the axilla by piercing the coracobrachialis muscle. This is the 1st site for block of this nerve, when it lies within the coracobrachialis muscle. Then, the nerve follows the axillary artery towards the arm where it gives of numerous motor branches supplying the coracobrachialis, both heads of biceps and the medial part of brachialis muscle. The nerve then exit the coracobrachilis muscle and runs downward and laterally between the biceps and brachialis muscles to reach the lateral side of arm (2nd approach of block). It then extends upto the elbow. At the elbow it pierces the deep fascia on the lateral side of the tendon of the biceps and continued as the lateral cutaneous nerve of forearm (3rd approach of block) and supplies the skin on the radial side of the anterior surface of forearm. Block of this nerve at the first approach causes complete motor loss of biceps and coracobrachialis muscle, weakness (partial motor loss) of brachialis muscle and sensory loss over the lateral half of the forearm (Fig. 23.14).

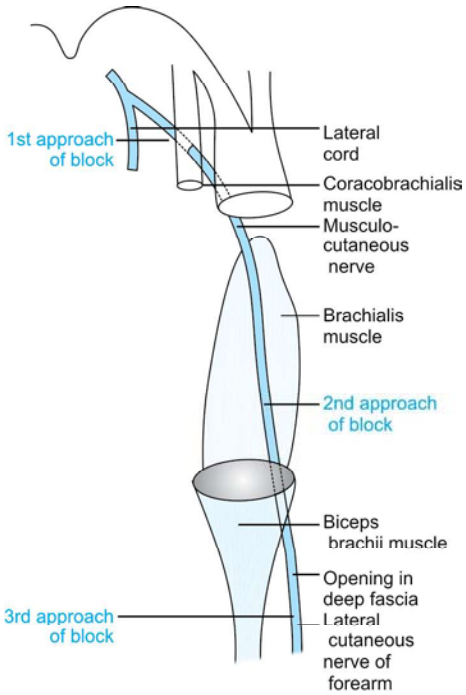


Fig. 23.13: The course of left musculocutaneous nerve

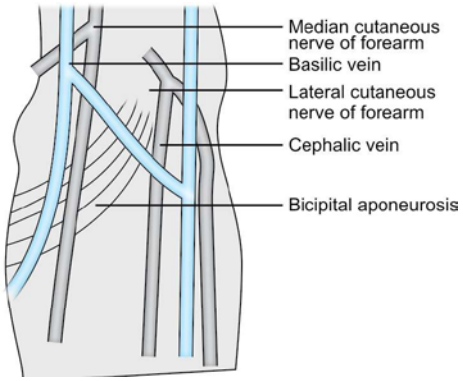


Fig. 23.14: Structure over the roof of cubital fossa

For the 1st approach of block, the substance of coracobrachialis muscle is palpated and pulled upward first. Then, a 22 G blunt, short beveled needle is inserted into the substance of the muscle and 5 ml of local anaesthetic agent is injected locally. For the 2nd approach of block, biceps is found between the skin and the nerve. So, the biceps muscle is pulled upwards by fingers and the nerve is left behind over the brachialis muscle and humerous (Fig. 23.15).

Then, the needle is inserted perpendicular to the surface of the skin down to the humerous. After contact with the bone by the needle, 5ml of drug is injected. For the 3rd approach of block the lateral cutaneous nerve of forearm which is the continuation of musculocutaneous nerve can be blocked at 1cm proximal to the intercondylar line, immediately lateral to the biceps tendon. Infiltration of 5 ml of LA solution subcutaneously at this site provides an excellent block of this nerve (Table 23.1).

Table 23.1: Musculocutaneous nerve

A. Branches:

1. *Muscular*
   - To the coracobrachialis
   - To the both heads of biceps brachii
   - To the medial part of brachialis (lateral part of brachialis is supplied by radial nerve)
2. *Atricular*
   - To the elbow joint
   - *Sensory*

Lateral cutaneous nerve of forearm

B. Effect of block:

1. *Motor loss*

Biceps and coracobrachialis are paralysed. The brachialis is weakened because a part of it is also supplied by the radial nerve. So, due to paralysis of these muscles flexion of the elbow joint becomes weak. But still it is possible by the unaffected part of the brachialis and superficial flexors of elbow joint in supine position of hand.

2. *Sensory loss*

It is present only over the lateral half of forearm. But clinically this area of sensory loss is less due to the overlapping of the adjacent cutaneous nerve which are not affected.

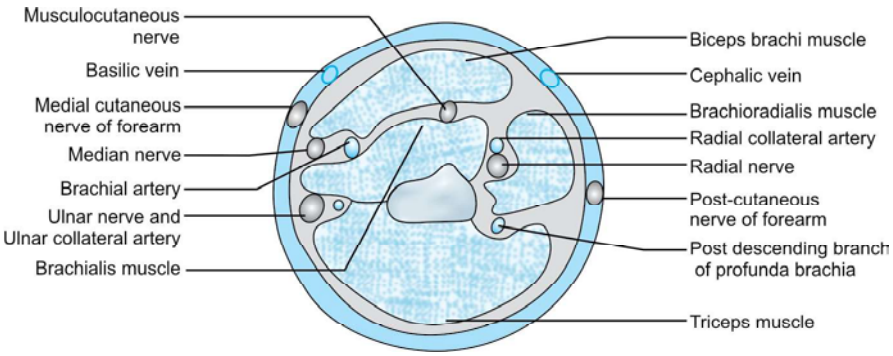


Fig. 23.15: Transverse section passing through the lower one third of the arm

Radial Nerve

The radial nerve can be blocked proximally at the level of arm and also distally at the level of elbow and (Fig. 23.16) wrist. It depends on the purpose of the supplementation of brachial plexus block or individual block of this nerve. Above the elbow, the nerve is a mixed one and contains both the motor and sensory component. But at the wrist, the block of radial nerve is purely sensory.

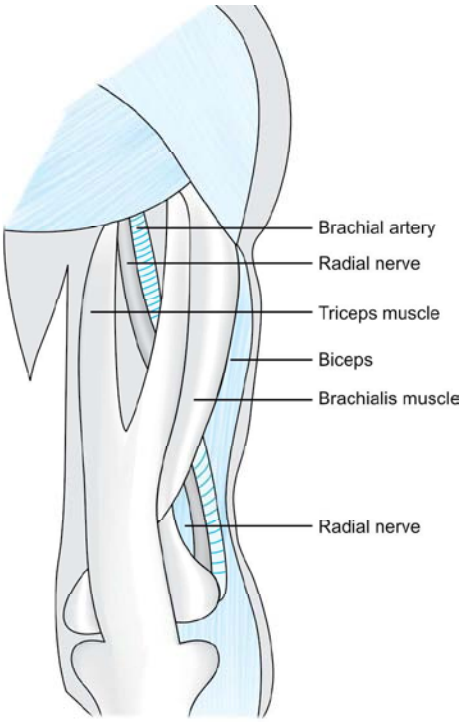


Fig. 23.16: Radial nerve block under triceps muscle and at the proximal site of elbow (posterior surface of nerve)

Anatomy (Fig. 23.17)

Radial nerve is the continuation of the posterior cord of brachial plexus. After exit from the axilla the nerve enter the spiral groove on the post surface of the humerus in between the long and medial head of triceps (1st approach of block of this nerve). At the spiral groove, it gives off branches as the lower lateral cutaneous nerve of arm and postcutaneous nerve of forearm. Then, after running through the spiral groove with arteria profunda brachialis the radial nerve pierces the later intermuscular septum and enters the anterior compartment of arm, 4 to 6 cm above the elbow. In the anterior compartment of arm, the radial nerve reaches in front of the lateral epicondyl where it passes between the epicondyl and the head of the radius (2nd approach of block at the elbow). Here, the nerve divides into deep motor branch (posterior interosseous nerve) and superficial sensory branch. The superficial sensory branch descends with the radial artery along the lateral side of the forearm (Fig. 23.18).

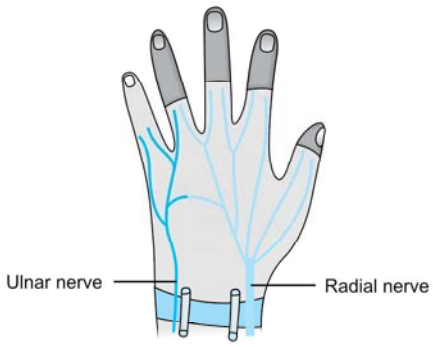


Fig. 23.17: Showing ulnar and radial nerve

Then, 7 cm above the wrist joint or the styloid process of radius the nerve winds round the lateral border of the forearm deep to the tendon of brachioradialis muscle and passes to the back on the dosal surface of the forearm. Then, going to the base of the forearm, it pierces the deep fascia and passes superficial to the extensor reticulum, medial to the cephalic vein (3rd approaches of block at wrist). Finally, it reaches on the back of the hand where it divides into five digital branches, supplying fingers. The motor posterior interosseous nerve descends on the back of the forearm by passing between the superficial and deep fibres of supinator muscle. Then the nerve passes on the abductor policies longus and extensor policis brevis. After that it passes deep to the extensor policis longus and extensor retinaculum to end as pseudoganglia.

The most proximal approach (1st approach) of radial nerve block is selected when the complete motor paralysis of elbow is essential, because at this level the radial nerve supplies all the muscles which are responsible for the movement of elbow joint. For the 1st approach of radial nerve block the lateral edge of the triceps muscle and the musculospiral groove of the humerus are palpated first. Then a blunt needle is introduced between the two heads of the triceps muscle towards the humerous and 5 to 8 ml of LA drug is injected after contact of needle with

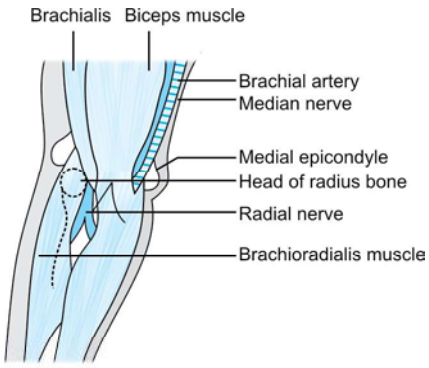


Fig. 23.18: Radial nerve block at antecubital fossa

the bone on the spiral groove is felt. Like other field blocks, the needle is withdrawn and again advanced forward with different directions for one or more injections close to the humerous at different locations (Fig. 23.19).

For the 2nd approach, the radial nerve can be blocked at the elbow as it passes over the anterior aspect of the lateral epicondyle. A 22 G, 4 cm needle is inserted at the intercondylar line, 2 cm lateral to the biceps tendon and is advanced till the bone in encountered. Then the area between the lateral epicondyl of humerous and the head of radius is infiltrated by local anaesthetic agent as a field block. To avoid nerve injury, elicitation of paresthesia should be avoided. If paresthesia is elicited, the needle should be relocated prior to any injection.

The terminal part of the radial nerve is purely sensory and is subcutaneous in the distal forearm. At the distal part of the forearm it first runs overs the radius, then sweeps from the ventral to the dorsal surface of the wrist and supply the area shown in figure. At the wrist level the nerve can be blocked at the site where it is subcutaneous and palpable. For the 3rd approach of radial nerve block (at wrist) the extensor pollicis longus tendon is identified first when the patient extends his thumb. Then needle is inserted subcutaneously over the tendon at the base of the 1st metacarpal bone. The injection should be subcutaneous and superficial to the tendon. 2 ml of LA agent is injected proximally along the tendon and 1 ml is injected as the needle passes at right angle across the 'anatomic snuff box' (Table 23.2).

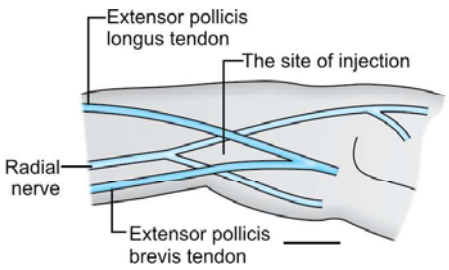


Fig. 23.19: Radial nerve block at the left wrist.

Table 23.2: Fact file of naval nerve

A. Branches

1. *Motor*
   - To the long and medial head of triceps
   - To the lateral part of brachialis
   - To the brachioradialis
   - To the extensor carpi radialis longus and brevis
   - To the supinator
   - All the extensor group of muscle of forearm
2. *Sensory*
   - Posterior cutaneous nerve of arm
   - Lower lateral cutaneous nerve of arm (upper lateral cutaneous nerve of arm is the branch of axillary nerve)
   - Posterior cutaneous nerve of forearm
   - Dorsal digital branches supplying lateral and medial side of thumb, lateral side of index finger upto middle phalanx, adjacent sides of index and middle finger up to middle phalanx and adjacent sides of middle and ring finger upto middle phalanx

B. Effect of block

At the wrist

Only sensory loss of digits supplied by this nerve

At the elbow

- Sensory loss as the wrist
- Motor loss—all the extensor of wrist causing wrist drop. When an attempt is made to extend the fingers, the proximal phalanx remains flexed. But the middle and distal phalangs will be extended by the unaffected interossei and lumbricals.

At the spiral groove

- Sensory loss as wrist
- Motor loss as elbow plus muscles of back of arm.

Ulnar Nerve

Among all the peripheral nerve blocks of the upper extremity, the ulnar enrve block at the level of elbow is most easily performed. But, it is most likely to cause nerve injury from the incorrect technique. It can also easily be accomplished in Guyton's canal at the wrist, in much the same way as the median nerve block in the carpal tunnel. The block of ulnar nerve is usually performed for anaesthesia of the hypothenar region, the fifth finger and the ulnar half of the fourth finger, which is shown in the Figure 23.20.

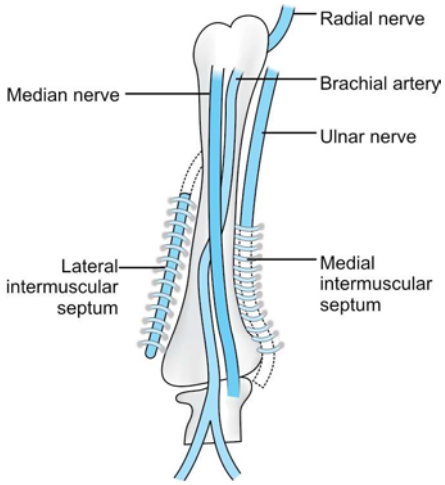


Fig. 23.20: The course of different nerves in right arm (anterior aspect)

Anatomy

After exit from axilla, the ulnar nerve first runs along the medial side of the brachial artery which is a continuation of axillary artery. Then, at the middle of the arm the nerve pierces the medial intermuscular septum from anterior to posterior and runs down on the back of the medial epicondyl of the humerous (site of block at elbow) where it is covered by the arcuate ligament. Ulnar nerve, then, enters the (Fig. 23.21) front side of forearm by running between the 2 heads of the flexor carpi ulnaris and descends downwards on the flexor digitorum profunds muscle. Here, it is overlapped by flexor carpi ulnaries muscle in the upper part, and by the skin and deep fascia in the lower part. The nerve then enters the hand along with the ulnar

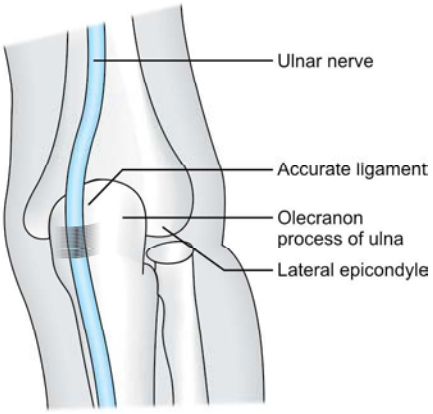


Fig. 23.21: Ulnar nerve block at elbow

artery running in front of the flexor retinaculum, but lateral to the pisiform bone (site of block at wrist). Here, the ulnar nerve is located in the interval between the ulnar artery and the flexor carpi ulnaris tendon (Fig. 23.22).

On entering the hand, it divides into terminal muscular and sensory branches. The muscular terminal branches supply the palmaris brevis, all hypothenar muscles, adductor pollicis, all dorsal interossei, and 3rd and 4th lumbricles. The sensory branches supply the palmar medial side of the little finger and the adjacent palmar sides of the ring and little finger. At the middle of the forearm, the ulnar nerve gives a cutaneous branch which pierces the deep fascia and descends in front of the flexor retinaculum and supply the skin of the medial side of the palm. Another dorsal cutaneous branch arises from the ulnar nerve, 5 cm above the wrist which supplies the medial side of dorsum of hand, medial dorsal side of little finger and adjacent dorsal sides of little and ring finger. The block of ulnar nerve at this side provides only the sensory loss along the ulnar side of the hand, little finger and the ulnar half of ring finger. The ulnar nerve can most easily be blocked at its subcutaneous position which is situated posterior to the medial epicondyl of elbow (block at elbow). But, block at this site is associated with high incidence of neuritis. So, use of very fine needle, avoidance of intraneural injection and small amount of drug reduces this

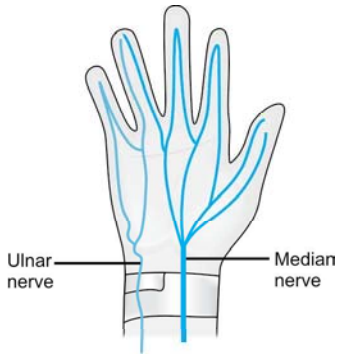


Fig. 23.22: Location ulnar and median nerve

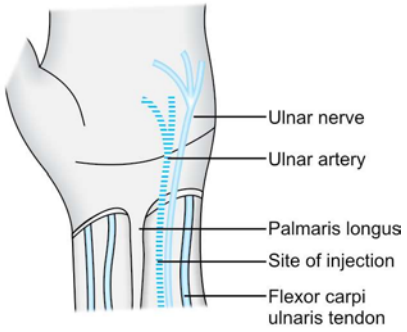


Fig. 23.23: Ulnar nerve block at wrist

incidence. At elbow the LA agent should be injected in a fanwise fashion without elicitation of paresthesia (Fig. 23.23).

At the wrist, the nerve is located in between the ulnar artery and flexus carpi ulnaris tendon, which can easily be defined by forced flexion of wrist. Then, needle is inserted perpendicular to the skin upto the depth of artery and 3 to 5 ml of drug is injected in a fanwise fashion (Table 23.3).

Table 23.3: Fact file of ulnar nerve

A. Branches:

1. *Muscular*
   To the flexor carpi ulnaris, medial part of flexor digitorum profundus, hypothenar muscles, all dorsal interossei, 3rd and 4th lumbricals, adductor policis.
2. *Sensory*
   Palmar and dorsal surface of hand, little finger, medial side of ring finger.

B. Effect of block:

At the wrist

Motor loss: All the intrinsic muscles of hand except those supplied by median nerve, i.e. all interossei, 3rd and 4th lumbricals, hypothenar muscle. Thus it produces claw hand, loss of power of abduction of 2nd to 5th digits, loss of power of adduction of thumb.

Sensory loss: Loss of sensation of little finger and medial side of ring finger.

At the elbow

Motor loss: Same as block at wrist plus paralysis of the medial part of flexor digitorum profunds going to the little and ring finger. So, the distal phalanges of these fingers are not acutely flexed as in claw hand.

Sensory loss: Same as loss at wrist plus medial side of dorsal and palmar aspect of forehand.

Median Nerve

The median nerve can easily be blocked in the antecubital space at the level of elbow or in the carpal tunnel at the level of wrist. The anatomical land marks for the median nerve are constant and are readily accessible for conduction block. The median nerve block is performed for anaesthesia over the median dermatomes of the hand which is shown in Figure 23.24.

Anatomy

The median nerve is formed by the union of medial head coming from the medial cord and lateral head coming from the lateral cord of brachial plexus. In the axilla, this nerve first runs along the lateral side of the axillary artery. Then it exits the axilla and descends on the brachialis muscle still lying at the lateral side of the artery. At the insertion of coracobrachialis muscle, the nerve crosses in front of the artery and then further descends down on the brachialis muscle to reach the cubital fossa where it is covered only by bicipital aponeurosis (Fig. 23.25).

After that, the median nerve enters the forearm between the two heads of pronator teres. Then, it runs downwards in forearm on the flexor digitorum profundus muscle, but deep to the flexor digitorum superficialis muscle. About 5cm above the flexor retinaculum, it becomes more superficial lying only deep to the deep fascia. Now, the nerve enters the palm deep to the flexor retinaculum and through

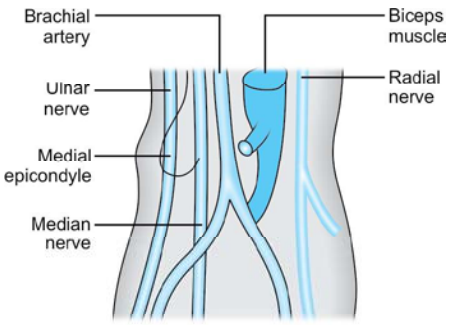


Fig. 23.24: Acute cubital fossa and its contents (left arm)

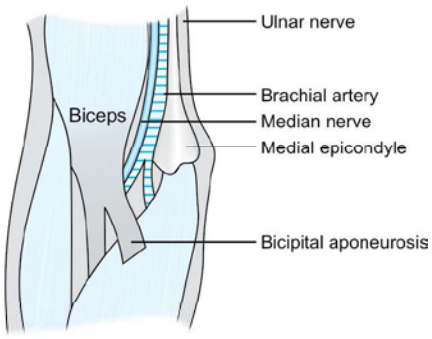


Fig. 23.25: Median nerve block at elbow

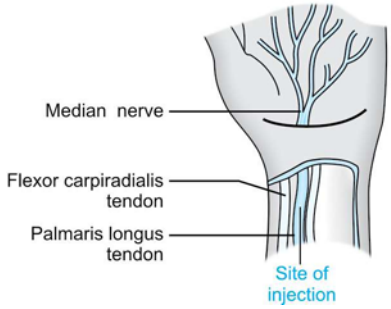


Fig. 23.26: Median nerve block at wrist

the carpal tunnel, i.e. the space between the flexor retinaculum and carpal bones. On entering the palm the nerve supplies the muscles of thenar eminence, 1st and 2nd lumbricals and sensory to the palmar aspect of thumbs, index finger, middle finger and lateral side of ring finger. In the lower part of the forearm a cutaneous branch arises from the median nerve. It pierces the deep fascia and enters the palm superficial to the flexor retina culum to supply the skin of lateral aspect of palm. Block of the median nerve provides only the sensory loss over the palmar aspects of the thumb, index finger, middle finger, radial half of ring finger and nail beds of the same digits. The median nerve can be blocked at elbow in the antecubital fossa or at the wrist. At the cubital fossa where the nerve is only covered by bicipital aponeurosis, the relation of the nerve with the vessels from lateral to medial is biceps tendon, brachial artery and median nerve. This is the major landmark for the median nerve block in the antecubital fossa at the intercondylar line elbow. For the median nerve block in antecubital fossa the brachial artery is palpated first and then 3 to 5 ml of drug is injected medial to the artery (Fig. 23.26).

At the wrist the median nerve is located in between the palmaris longus and flexor carpi radialis tendon and can be blocked by injecting 2 to 3 ml ofv LA agent in between these two tendons, proximal to the wrist crease. For this block the patient is asked to flex the wrist against resistance which help these tendons to be prominent. As the nerve passes deep to the retinaculum, through the carpel tunnel, needle should be passed through the retinaculum with the feeling of loss of resistance and then the drug is injected. A superficial palmar branch of the median nerve, supplying the skin of thenar eminence does not pass below the retinaculum. This branch should also be blocked separately by injecting 0.5 to 1 ml of LA solutions, subcutaneously above the retinaculum (Table 23.4).

Table 23.4: Fact file of median nerve

A. Branches

1. *Muscular*
   To the pronator teres, flexor carpi radialis, palmaris longus, flexor digitorum superficialis, flexor policis longus, lateral part of flexor digitorum profundus, pronator quadratus.
2. *Sensory*
   Skin over the thenar eminence, later half of palm and palmar aspect of fingers including the nailbed of thumb, index, middle; and lateral half of ring finger.

B. Effect of block

1. *At the wrist*
   Motor loss : Thenar muscles and 1st and 2nd lumbricals are paralysed. Thus it causes wasting of thenar prominance and inability to oppose the thumb.
   Sensory loss : Loss of sensation of digits supplied by this nerve. Carpal tunnel syndrome affect this nerve producing wasting of thenar muscles and pain in digits supplied by this nerve.
2. *At the elbow*
   Motor loss: All the muscles of palm supplied by this nerve, all the flexors of wrist, pronator teres and quadratus. Thus it causes loss of flexion of wrist, loss of pronation.
   Sensory loss: Same as loss at wrist.

INTRAVENOUS REGIONAL ANAESTHESIA OF EXTREMITY

This technique was first described by a German surgeon, named August Bier, in 1908. So, it is also called as the Bier's block. During that period, after its introduction, it was very much popular in clinical practice. But, it had gradually lost its popularity due to the evaluation of other less risky procedures of conduction block such as brachial plexus block and other individual nerve block which the help of nerve stimulator.

General Consideration

The Bier's block is an excellent technique of regional anaesthesia for short surgical procedures (<90 minutes) over the extremities, mainly the superior extremity. When the peripheral venous system of extremity is filled with LA agents, then backward diffusion of the LA agents into the tissues provides dense motor and sensory block. The duration of this type of anaesthesia is mainly limited by the length of time that the pneumatic tourniquet can be inflated without any ischaemic injury of limbs which is usually about 60 to 90 minutes. In Bier's block patient's safety depends on the integrity of the pneumatic tourniquet, which must be inflated to a pressure which is high enough to prevent the reaching of LA agent in the systemic circulation and this pressure is maintained until a safe time interval between the inflation and deflation is reached, regardless of the duration of surgery during which period the drug is completely diffused into the tissue. It is because though a very low concentration of local anaesthetic agent is used, still a bolus high volume is injected into the venous circulatory system directly after the tourniquet is inflated. This technique or type of regional anaesthesia can be applied to any surgical procedure distal to the elbow or knee, provided its expected duration is one hour or less and it allows a site for placing a small intravenous

catheter in the distal dorsum of the hand or foot. Due to any surgical reasons when an anaesthetist becomes reluctant to deflate the tourniquet even after exceeding an hour from the time of inflation, then pain elicited by the tourniquet which is usually a normal phenomenon after a specific time interval, can result in failure of this type of RA, even though the sensory anaesthesia at the surgical site is still in effect. On the other hand, very short surgical procedures (under 10 to 15 minutes) should be taken into account and the pneumatic tourniquet should not be deflated within 45 minutes after injection of LA agent, even though the surgery has been completed long before. In orthopedic procedures where vigorous manipulations are required, then attention must also be given to the potentiality of disrupting the integrity of tourniquet and distribution of drug in the systemic circulation after its absorption from the affected limb causing CVS and CNS toxicity. Bupivacaine is not recommended for this Bier's procedure due to the high incidence of its systemic toxicity and death. Other rare complication of Bier's block are compartmental syndrome and loss of limb.

Advantages of Bier's Block

i. Easy administration.
ii. Rapid onset.
iii Rapid recovery.
iv. Complete muscular relaxation.
v. No special skill.
vi. Controllable extent of anaesthesia.

Disadvantages of Bier's Block

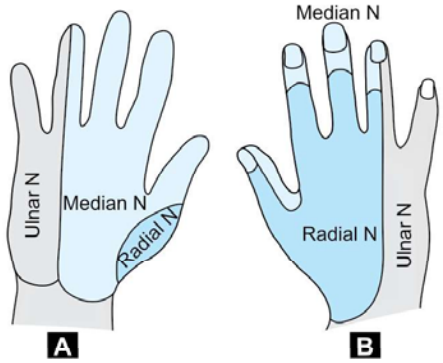
i. Tourniquet discomfort.
ii. Rapidity of recovery leading to post operative pain.
iii. Difficulty in providing blood less field.
iv. Difficulty in exanguination for painful hand.
v. Sudden, accidental or early deflation of tourniquet may lead to toxic reaction.

Technique

As a first step in this technique, an intravenous cannula is placed as distally as possible, for giving LA agent on the upper or lower extremity which is to be blocked. Another intravenous cannula is also placed on the opposite limb for giving drugs in emergency. Double tourniquet is applied on the operated side proximal to the surgical field. After exsanguination of limb by elastic esmarch bandage, the proximal pneumatic cuff is inflated first to approximately 50 to 100 mm Hg higher than the systolic pressure of this patient. Then, calculated total dose of local anaesthetic agent (4 to 6 mg/kg of 0.5% lignocaine without epinephrine and preservative) is injected IV slowly through the canula. Then onset of the effect of regional anaesthesia starts within 5 minutes. If the patient complains of tourniquet pain, then the distal tourniquet which overlies the anaesthezed skin is inflated, and the previous proximal tourniquet which is situated on the non anaesthetized skin is released or deflated. The use of single wide cuff pneumatic tourniquet during intravenous regional anaesthesia allows the lower inflation pressure which causes less incidence of neurological complications in contrast to high inflation pressure with narrow double pneumatic cuffs. Somebody inflates and deflates the proximal and distal cuffs alternately to increase the patient's tolerance. At the end of the completion of surgical procedure, care must also be taken in deflating the tourniquet, so that patient is not suddenly exposed to the bolus dose of local anaesthetic agent which is absorbed from the affected limb causing CVS and CNS toxicity. The tourniquet can safely be released minimum after 25 minutes from its application. It may also be deflated for one or two seconds and reinflated again. Thus, this maneuvers are repeated several times with certain pause between each step to reduce the systematic LA toxicity. If minor CNS or CVS sign appear at any time between the consecutive deflations, then the interval between the deflation of cuff is increased.

DIGITAL BLOCK

The digital branches of the radial, ulnar and median nerve first run in the intermetacarpal interval or space. Then they divide and enter the base of each digit from the four corners, close to the palmar and dorsal surfaces of each digit. The duplication of dorsal and palmar digital nerves demands that the injection technique for digital block must takes into account this duplication of nerves. In addition, these nerves are small and only sensory and would be very intolerant to the intraneural injection of LA agent or hydrostatic pressure produced from outside on the nerve due to increased volume of the drug. A 25 G (or more fine) blunt bevel needle is selected for digital block with a length of 1 inch or less. The injection usually starts with the entrance of needle on the dorsal surface, proximal to the web space. Then the needle is directed to the palmar side, close to the perioteum of the metacarpal head. Elicitation of paresthesia is avoided and if it occurs, the needle is redirected. Then 2 to 3 ml of LA agent is injected as the needle is withdrawn. A good digital block is assured by gentle massage of the web space after injecting the drug and withdraw of the needle (Figs 23.27A and B). Local anaesthetic agent with vasoconstrictors should not be used for the digital block due to the fear of ischaemia and necrosis of fingers. The maximum volume of drug which is usually 2 to 3 ml on each side should not exceed. The excessive volume of drug can cause vascular insufficiency and gangrene as a result of digital artery occlusion by the mechanical pressure effect. Digital nerve block is commonly used and is very effective method for wide varieties of minor outpatient surgical procedures on the digits.



Figs 23.27A and B: Sensory innervation of radial, ulnar and median nerve of the hand. A. Palmar surface, B. Dorsal surface

WRIST BLOCK

Wrist block is a very superficial and easy to perform technique for regional anaesthesia. It is devoid of any systemic complications. So, it should be in the armamentarium of every anaesthesiologist. Actually wrist block is nothing but the ulnar, medial and radial nerve block at the same sitting at the level of wrist. The wrist block is commonly performed for any hand surgery where tourniquet is not required or as a supplementation for incomplete brachial plexus block.

At the wrist, the median nerve is located between the tendons of palmaris longus (medially) and flexor carpi radialis (laterally).The palmaris longus tendon is often made most prominent among all the tendons at the wrist and the median nerve passes immediately lateral to it. At the wrist this nerve can be blocked by inserting a needle at that position (by the lateral side of palmaris tendon) until it pierces the deep fascia or retinaculum when the fascial 'click' is appreciated. If the 'click' is not felt, then the needle is further inserted until it contacts the bone. After contact with bone, the needle is slightly withdrawn for 2 to 3 mm and the local anaesthetic agent is injected.

At the wrist the ulnar nerve is situated between the ulnar artery (pulsation may be felt) and the tendon of flexor carpi ulnaris at the level of the ulnar styloid process. At this level, the ulnar nerve is blocked by inserting a needle under the tendon of flexor carpi ulnaris muscle, close to its styloid attachment. The needle is then advanced further for 5 to 10 mm and 3 to 5 ml of local anaesthetic agent is injected at that site.

At the wrist the radial nerve (superficial branch) runs along the medial aspect of the brachioradialis muscle and lateral to the radial artery. It quits the artery about 7 cm above the styloid process of the radius. At that level, the nerve winds round the lateral border of the forearm between the tendon of brachioradialis and the radius, and then passes to the back of the forearm. Going to the back of the forearm, it pierces the deep fascia and descends superficial to the extensor retinaculum, medial to the cephalic vein. Above the styloid process, it gives off the digital branches for the skin of the dorsal aspect of thumb, index finger, middle finger and lateral half of the ring finger. Several of its branches pass superficially over the anatomical 'snuff box'. The radial nerve block requires a more extensive infiltration because of its less predictable anatomical location and divides into multiple smaller cutaneous branches. A subcutaneous infiltration of 5 ml of local anaesthetic agent, just above the radial styloid process is done aiming medially. The infiltraton is then extended further laterally using another 5 ml of local anaesthetic agent.

LOWER EXTREMITY BLOCKS

Like upper extremity, the lower extremity blocks are less popular. This is because:

i. There is widespread acceptance and safety of spinal and epidural anaesthesia for lower extrimity.
ii. Like brachial plexus, nerves supplying the lower limbs are not anatomically clustered at one place where they can easily be blocked
iii. With anatomical consideration these blocks are technically more difficult and require more training
iv. Persistent block of any major nerve of lower extremity makes the patient unambulatory and causes an unacceptible side effect for outpatients (Fig. 23.28).

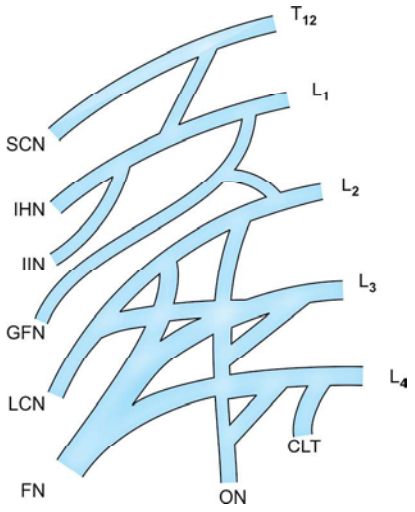
But, still there are some advantages of lower extremity block. These are:

i. Postoperative pain relief,
ii. Lack of complete sympathectomy (as is occurred in central neuroaxial block) which make it ideal for very ill patients.

Nerves supplying the lower extremity are sciatic, femoral, lateral femoral cutaneous and obturator nerve. These nerves can be blocked as proximal as at the lumbosacral plexus or as distal as at the toes, depending on the surgical procedure and the postoperative plan for analgesia.

Anatomy

The nerves supplying the lower extremity is derived either from lumber plexus and/or sacral plexus. The lumbar plexus is formed by the anterior or ventral rami of upper four lumbar spinal nerves (L_1, L_2, L_3, L_4). The 1st lumbar spinal nerve receives a contribution from T_{12} spinal



SCN = Subcostal nerve, IHN = Iliohypogastric nerve, IIN = Ilioinguinal nerve, GFN = Genitofemoral nerve, LCN = Lateral cutaneous nerve of thigh, FN = Femoral nerve, ON = Obturator nerve, CLT = Contribution to lumbosacral trunk

Fig. 23.28: Formation of lumbar plexus

(subcostal) nerve. And the anterior rami of the 4th lumbar spinal nerve gives a contribution to the L_5 spinal nerve forming the lumbo sacral trunk which take part in the formation of sacral plexus. The lumbar plexus lies in the space situated between the psoas major (infront) and quadratus lumborum (behind) muscle. This space is called the psoas compartment. So, the lumbar plexus block at this level is also called the 'psoas compartment block'.

The branches of lumbar plexus emerges from the lateral border of the psoas muscle. These branches are:

i. Iliohypogastric N. (L_1),
ii. Ilioinguinal N. (L_1),
iii. Genitofemoral N. (L_1, L_2),
iv. Lateral femoral cutaneous nerve of thigh (L_2 L_3 dorsal division),
v. Femoral N. ($L_{2,3,4}$ dorsal division),
vi. Obturator N. ($L_{2,3,4}$ ventral division).

The sciatic nerve is not the only branch of lumbar plexus, but it arises from both the lumbar and sacral plexus. It is formed by the combination of two major nerve trunks: tibal nerve (ventral branches of L_4 L_5 S_1 S_2 S_3) and common peroneal nerve (dorsal branches of L_4 L_5 S_1 S_2 S_3). The posterior cutaneous nerve of thigh (dorsal division of S_1 S_2 and ventral division of S_2 S_3) is a branch of sacral plexus.

LUMBAR PLEXUS BLOCK

The lumbar plexus block is usually indicated for knee surgery, any surgery on thigh (only antero lateral aspect), saphenous vein stripping, for chronic pain management of lower extremity, etc. It eliminates the need for individual nerve block such as the femoral nerve, lateral femoral cutaneous nerve of thigh and obturator nerves. When combined with sciatic nerve block, this lumbar plexus block can be used for any surgery on lower extremity.

The lumbar plexus can be blocked by two technique: (i) psoas compartmental technique or block and (ii) '3-in-1' technique or perivascular block.

Psoas Compartment Technique

In this technique needle is placed into the space between the psoas major and the quadratus lumborum muscle and a large volume of LA drug is injected into this space to block the iliohypogastric, ilioingninal, genitofemoral, femoral, obturator and lateral femoral cutaneons nerve of thigh causing surgical anaesthesia of groin, hip and anterolateral portion of thigh. This technique must be combined with the sciatic nerve block for regional anaesthesia of the entire lower extremity (Fig. 23.29).

Technique

The patient is first placed in the lateral position with the hips are flexed and operated side is up. Then the intercrestal line is identified which corresponds to the 4th lumbar spine or L_3 – L_4 intervertebral space. From 4th lumbar spine, a point which is situated 3 cm caudal and 5 cm lateral is marked. This is the site for injection for psoas compartmental block. Then after proper antiseptic skin preparation a 22 G and 15 cm long needle is advanced perpendicular to the skin from the site of injection till it contacts with the 5th lumbar transverse process. After that the needle is slightly withdrawn and redirected in cephalad direction till it slips off the tranverse process of 5th lumbar vertebra. Now, it is sure that the needle is within the substance of the psoas muscle. At this position, high resistance should be felt if a glass syringe filled with air or saline is connected with the needle and piston is pushed. Now, the needle which is already attached with the 20 ml air or saline filled syringe is slowly advanced till the loss of resistance is detected as like epidural technique. Nerve stimulator offers further confirmation of this point by motor evoked response from the femoral or obturator nerve. The needle is manipulated until the twitches of quadriceps muscle are seen or felt at 0.5 mA or less voltage. Thus, following successful identification of the lumbar plexus in psoas compartment, 30 to 40 ml of local anaesthetic agent of choice is injected with intermittent aspiration to rule out any intravascular injections (Fig. 23.30).

The complication of psoas compartment block are: Increased risk of possible epidural block, subarachnoid block (the dural sleeve over the nerve root containing subarachnoid space is no more than 2 to 4 cm from the site of injection), intravascular injection; peripheral nerve damage, sympathetic block secondary to extravasation of local anaesthetic agent, etc. Though unilateral sympathetic block has little significance, still one of the advantage of psoas compartment block over the spinal or epidermal anaesthesia is that the incidence of hypotension is less if this occurs. The proximity of the pelvis and pelvic viscera to the psoas compartment makes the infection a potential issue of this type of block especially, if the needle makes undetected contact with the lumen of these

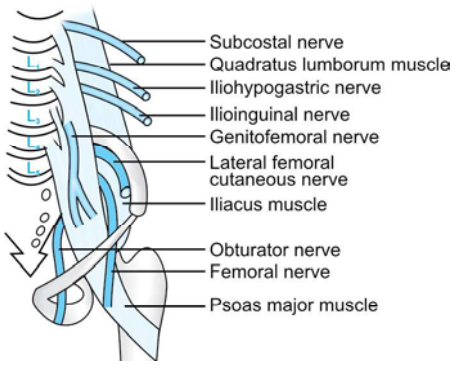


Fig. 23.29: Nerves arising from lumbar plexus

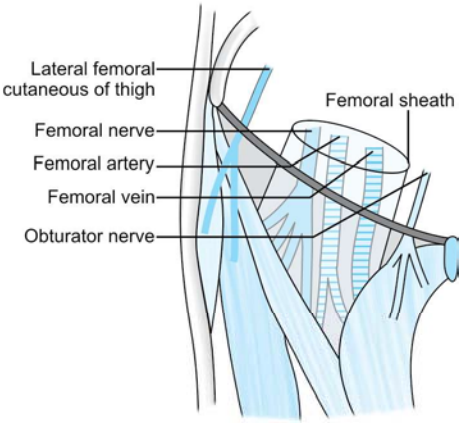


Fig. 23.30: The site of femoral nerve block

visceras. This psoas compartment block requires adequate sedation and analgesia as these are very deep invasive procedure and the needle traverses the multiple muscular planes. The success rate of this block is dependent on the volume of LA agent. A volume of less than 30 ml in an adult patient of 70 kg weight are less reliable in achieving anaesthesia of the entire lumbar plexus. When surgery requires the use of tourniquet or anaesthesia is required on the posterior aspect of the leg, then the sciatic nerve block must should accompany the psoas compartment block. This can easily be achieved in the same patient with the same position as psoas compartment block.

Perivascular Approach (3-in-1 Femoral Block)

Technique

This technique is the modification of the classic approach of single femoral nerve block in the femoral triangle. The idea of this modified technique is that a sheath surrounding the nerve roots while arising from lumbar plexus extends downwards as the femoral sheath in the femoral triangle. So, it acts as an enclosed conduit around the femoral nerve, artery and vein for the spread of local anaesthetic agent proximally, if it is injected within the femoral sheath below the inguinal ligament at the femoral triangle, maintaining a distal pressure. Thus, it results in proximal spread of LA solution into the psoas compartment-from femoral triangle. The femoral sheath is confluent all the way proximally upto the origin of the nerves from the lumbar plexus in the prevertebral area of the lumbosacral region. At the same proximal location, the lateral femoral cutaneous nerve and the obturator nerves are also formed and are situated within this sheath. So if local anaesthetic drugs tracks proximally, it will also bathe these three nerves at their origin; resulting in '3-in-1' blocks (femoral nerve, lateral femoral cutaneous nerve and obturator nerves).

The modification of the technique which converts the only femoral nerve block into the '3-in-1' block mainly involves the pressure, applied distal to the injection site in the femoral triangle and the increased volume of local anaesthetic agent (20 versus 40 ml). This method also requires selecting the site of injection as close to the inguinal ligament as possible. The sheath covering the femoral nerve, artery and vein becomes incomplete distally at a variable distance just below the inguinal ligament. So, beyond this point any attempt to fill the sheath and try to induce proximal spread of LA agent will be unsuccessful. Placement of pressure distal to the injection site in the femoral triangle must be as complete as possible, but without disrupting the needle placement within the femoral sheath. Confirmation of needle placement within the sheath is not different from that of the classical approach of individual femoral nerve block.

A continuous '3-in-1' femoral block can also be accomplished with insertion of a catheter within the femoral sheath of femoral triangle. If the femoral sheath is catheterized correctly and the catheter is advanced for upto 5 to 8 cm proximally, then the injected LA solution will be very close to the lumbosacral plexus and the complete block of all the nerves of the plexus becomes a high probability.

The inguinal ligament is marked as a line, connecting the pubic tubercle and the anterior superior iliac spine. Then, the femoral artery is marked by its pulsation-just below the injurinal ligament. After that a short beveled, 22 G and 5 cm long needle is advanced lateral to the artery in cephalad direction after piercing the skin, subcutaneous tissue and femoral sheath. Then 20 to 40 ml of drug is injected incrementally after the negative aspiration test while applying pressure by fingers distally on the femoral sheath. By 20 ml drug femoral and lateral femoral cutaneous nerve block can be predicted. But obturator nerve block may require minimum 30 ml of drug.

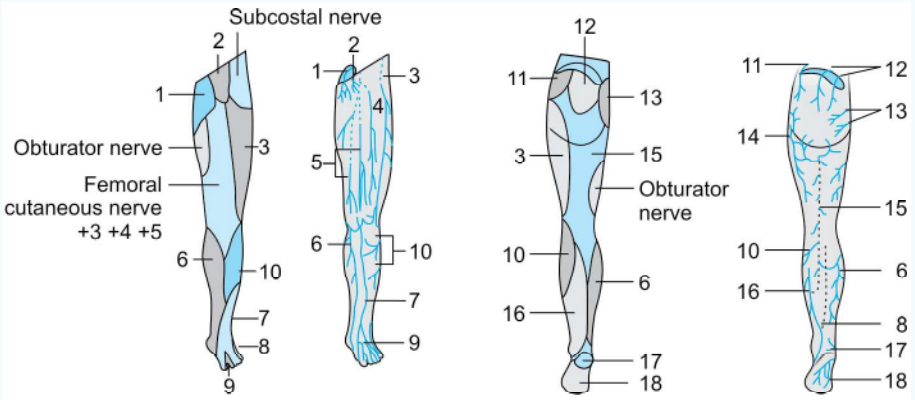
INDIVIDUAL NERVE BLOCK OF LOWER EXTREMITY

Femoral Nerve Block (Fig. 23.31)

After formation with in the substance of psoas major muscle, the femoral nerve emerges from the lateral border of it. Then the femoral nerve descends downward lying in the groove between the iliacus and psoas muscle. Here, the nerve innervates both the psoas and the iliacus muscles. Then, it enters the thigh passing beneath the inguinal ligamant lateral to the femoral artery. Here, the nerve also lies in the groove between the iliacus and the psoas muscle. At this point femoral nerve divides into anterior and posterior divisions which then subsequently break into multiple branches and supply the motors to the quadriceps group of muscles and the sartorious muscles and sensory over the skin of anterior thigh from inguinal ligament to knee and as saphenons nerve (sensory) on the medial side of leg from knee to the big toe and supplies articular branches to hip and knee joint. Beyond the inguinal ligament, the femoral nerve does not represent as a discreet structure, but has split into a bundle of spaghetti strands.

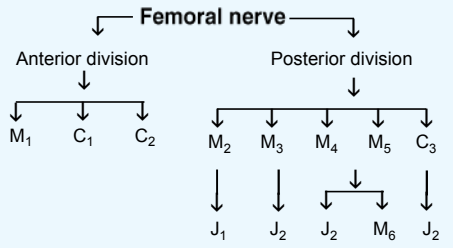
Practical Application

The only femoral nerve is blocked for virtually some minor specific surgical procedures on the upper part of thigh and for any lower extremity procedure where immobility of the knee joint is necesary or the use of pneumatic tourniquet are essential. Practically the isolated femoral nerve block is primarily used in combination with other peripheral nerve block. It can be used alone for: (i) small surgical procedures limited only on the anterior thigh, for example muscle biopsy, skin grafting, etc. (ii) knee arthroscopy and any operation on patella, (iii) surgical repair of the midfemoral shaft fracture, e.g. acute pain relief, reduction and traction placement in the setting of an acute fracture of shaft of femur, (iv) postoperative pain



1. **Ilioinguinal nerve (L_1):** It escapes through the lateral part of superficial inguinal ring—most of its branches go to scrotum or libia majora—some of its branches supply skin over the medial adjacent part of thigh.
2. Femoral branch of genitofemoral nerve ($L_{1,2}$): It pierces the deep fascia 2cm below the inguinal ligament and slightly lateral to the saphenous opening—supplies an area of skin, about size of the palm of hand, immediately below the inguinal ligament.
3. Lateral (femoral) cutaneous nerve of thigh ($L_{2,3}$): Discussed in the text.
4. Intermediate femoral cutaneous nerve ($L_{2,3}$): It is a branch of femoral nerve-pierces the deep fascia in the midline of thigh—extends up to the knee.
5. Medial femoral cutaneous nerve ($L_{2,3}$): It is a branch of femoral nerve—pierces the deep fascia on the medial side of thigh—divides into two—anterior and posterior branch—extends upto the knee.
6. Saphenous nerve ($L_{3,4}$): Discussed in the text.
7. Superficial peroneal nerve ($L_{4,5}$ S_1): Discussed in the text.
8. Sural nerve: It supplies the lateral part of the dorsum of the foot.
9. Deep peroneal nerve: It supplies the adjacent sides of 1st and 2nd toes.
10. Lateral cutaneous nerve of calf: It arises from the common peroneal nerve on the lateral head of gastrocnemius—pierces the deep fascia almost at once and descends to supply the skin over the lateral and anterior surface of upper part of leg.
11. Lateral cutaneous branch of subcostal and iliohypogastric nerve: They supply the upper and lateral gluteal region of thigh.
12. Lumbar nerves: They are the branches of dorsal rami of L_{1-3} lumbar spinal nerves and supply the upper medial region of thigh.
13. Sacral nerves: They are the branches of dorsal rami of S_{1-3} sacral spinal nerves and supply the upper medial region of thigh.
14. Lateral (femoral) cutaneous nerve of thigh: (it is the same nerve numbered in figure as 3). It supplies the lower lateral region of thigh.
15. Posterior cutaneous nerve of thigh ($S_{1,2,3}$): It arises from sacral plexus—comes out of pelvis through greater sciatic foramen under coverage of gluteus maximus muscle—lies on the medial border of sciatic nerve—leaving the gluteal region it enters the back of thigh—runs downwards under the deep fascia—pierces the deep fascia at the back of knee—terminal branches descend downwards upto halfway of the back of leg—supplies gluteal region, perineal region, back of thigh and upper part of the back of the leg.
16. Peroneal (sural) communicating branch: It arises from common peroneal nerve in popliteal fossa together with lateral cutaneous nerve of calf-pierces deep fascia—passes downwards to join sural nerve—supplies skin over proximal 2/3 of the back of the leg with sural nerve.
17. **Medial calcaneal branch:** It arises from tibial nerve at ankle-pierces the flexor retinaculum-supplies the skin of the posterior and lateral surfaces of the heel.
18. **Medial and lateral plantar nerves:** They are the terminal branches of posterior tibial nerve-supply the whole sole and planter surface of digits.

Fig. 23.31: The cutaneous nerves of lower extremity



M_1 = Sartorius, M_2 = Rectus femoris, M_3 = Vastus lateralis, M_4 = Vastus intermedius, M_5 = Vastus medialis, M_6 = Articularis genu, C_1 = Intermediate cutaneous nerve of thigh, C_2 = Medial cutaneous nerve of thigh, C_3 = Saphenous nerve, J_1 = Hip joint, J_2 = Knee joint

Fig. 23.32: Division of femoral nerve

relief for surgical procedures on leg or knee (Fig. 23.32).

Technique

For the classical individual femoral nerve block the important anatomical landmark is the point which is situated below the inguinal ligament and immediately lateral to the pulsation of the femoral artery. After a proper antiseptic skin preparation a skin wheal is created by LA agent just 1 to 2 cm lateral to the femoral pulse, at the level of femoral crease. It is to be noted that the femoral crease is located 2 to 4 cm below the inguinal ligament. For 'single shot femoral block', a short (< 1 inch) blunt-bevel needle is usually used and it will allow the good appreciation of needle's entry into the femoral sheath. The needle is first inserted lateral to the femoral artery and is then directed parallel to the artery in a cephalad and posterior direction, within the sheath at an angle of 45° to the skin. The proximity of the needle to the nerve can be confirmed by the feeling of entry of needle into the sheath. An alternative to this technique is the field block by injection of LA agent at multiple sites.

The confirmation of the proximity of nerve to the needle is also done by the elicitation of paresthesia or by the use of nerve stimulator by eliciting the motor-evoked response in the quadriceps group of muscles. The ultimate goal is to obtain twitches in quadriceps muscle or patella at the minimal voltage of 0.4 mA or less. Success

with nerve stimulator technique requires differentiation between the evoked motor response and the direct stimulation of muscles due to the immediate vicinity of the tip of the needle from where the current is discharged directly to the muscle. When the sartorius twitches are obtained first as motor evoked response, then the needle should be redirected which subsequently and promptly results in the stimulation of quadriceps muscle. Injection of local anaesthetic agent only after stimulation of the sartorius muscle may result in failure to achieve the femoral block. For isolated femoral nerve block, 10 to 20 ml of local anaesthetic drug within the femoral sheath at the femoral triangle will accomplish the complete block, whereas larger of LA agent volume with technique modification results in '3-in-1' block (Fig. 23.33). The advantages of performing the isolated femoral nerve block at the level of femoral skin crease over performing the block at the level of inguinal ligaments are: (i) more superficial position of the femoral artery and nerve, (ii) greater width of the femoral nerve, (iii) more consistent femoral nerve-artery relationship and (iv) more consistent results of block. The isolated femoral nerve block is a superficial one and does not result in significant patient discomfort. Thus, light premedication is usually sufficient.

Because of the proximity of femoral artery and vein, the most likely complication of attempted femoral nerve block would be haematoma due to the puncture of vessels. Intravascular injection is also very likely. Intraneural injection is also possible, but unlikely because of the extensive branching of the nerve at the site of the attempted block. Poor site preparation or poor care of the continuous catheter (if it is used) would make the infection of injection site common and it is due to its proximity to the groin.

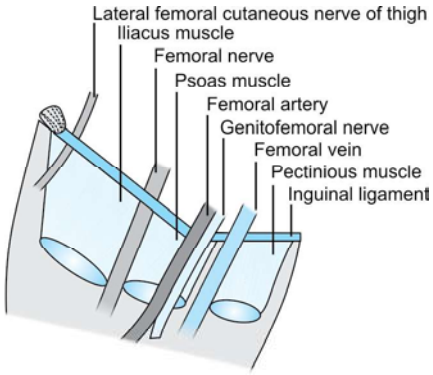


Fig. 23.33: Anterior aspect of high showing different site for injection of different nerve block

The femoral nerve is fully enclosed in a sheath which is extended downwards up to orjust below the inguinal ligament. This is an ideal site for catheter placement within the sheath for continuous femoral blockade. The most common technical approach to this procedure is the Seldinger technique. In this method, a smaller pliable, non-traumatic catheter is inserted through a larger, non-permanent catheter. Proper intra sheath placement of catheter is most commonly confirmed by motor evoked response using a nerve stimulator. However, ideal confirmation of placement is accomplished with injection of LA agent through the catheter, while the stimulation is still performed where augmentation followed by extinction of muscular contraction is observed.

The continuous femoral nerve block by catheter has an unique place for long-term postoperative pain relief after surgery. Low concentration local anaesthetics can provide pain relief without motor block. Bupivacaine of 0.125% concentration is ideally suited for only pain relief with minimal resultant toxicity or motor block. Due to close proximity to groin. The site of insertion of needle and catheter for femoral nerve block mandates sterile procedure and proper dressing to avoid infection. Like other catheter technique, nerve trauma and catheter breakage are also potential complications here.

Lateral (Femoral) Cutaneous Nerve Block

Lateral (femoral) cutaneous nerve of thigh (L2 L3) is a pure sensory nerve and originates from the dorsal branches of ventral rami of 2nd and 3rd lumbar spinal nerve. It provides only sensory innervation to the lateral side of the thigh above the knee. After its origin, it moves ventrally and laterally through the psoas compartment between the psoas and iliacus muscle, immediately caudal to the ilioinguinal nerve. Then after emerging from the lateral border of the psoas muscle it descends over the iliacus muscle but under the iliac fascia. Then it enter the thigh deep to the inguinal ligament, 1 to 2 cm medial to the anterior superior iliac spine. Distal to the inguinal ligament, the nerve divides into anterior and posterior branches in the thigh. The anterior branch becomes superficial after piercing the deep fascia about 10 cm distal to the anterior superior iliac spine and supply the skin over the anterior and lateral side of the thigh as far as upto the knee. The posterior branch pierces the fascia lata at higher position than the anterior branch and directly supply the skin over the lateral surface of thigh extending from the greater trochenter to about the mid thigh. This nerve has no motor supply, so stimulation of this nerve by stimulator does not produce any motor evoked response and is not helpful (Fig. 23.34).

The site of injection for the block of this nerve is 2 cm medial and 2 cm caudal to the anterior superior iliac spine. After proper antiseptic skin preparation, for the block of this nerve a 22 G and 4 cm long needle is inserted perpendicular to the skin until a sudden loss of resistance is felt which indicates the passage of needle through the fascia lata. Then the needle is gently advanced just slightly beyond this resistance and a volume of 10 to 15 ml of LA solution is injected fanwise below and above the fascia. This procedure is again repeated for second time with a slightly different direction of the needle. Multiple injection sites make this field block technique successful. This nerve block is indicated only for the superficial minor surgical procedures which require sensory

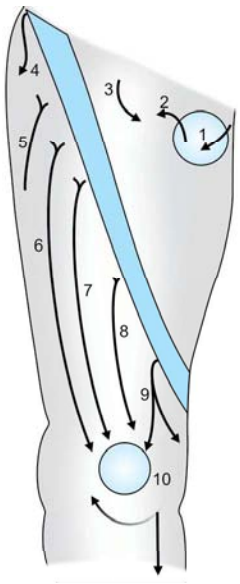


Fig. 23.34:
1. Femoral branch of genitofemoral nerve
2. Branch of illioinguinal nerve
3. Branch of medial femoral cutaneous nerve,
4. Branch of subcostal nerve

5 and 6. Posterior and anterior division of lateral cutaneous nerve of thigh (not the branch of femoral nerve)

7 and 8. Lateral and medial division of intermediate femoral cutaneous nerve (branch of femoral nerve)

9. Anterior and posterior divisions of the medial femoral cutaneous nerve (branch of femoral nerve)
10. Saphenous nerve (branch of femoral nerve)

but no motor block of the lateral side of the thigh, for example simple muscle biopsy from vastus lateralis, skin graft harvesting from upper part of lateral thigh, meralgia paresthetica, etc.

Obturator Nerve Block

The obturator and the genitofemoral nerves are rather large branches of the lumbar plexus. They provide sensory innervation over the inguinal area, femoral triangle, medial part of the thigh, knee joint, hip joint and as well as the motor fibres to the adductors of thigh such as adductor longus, adductor brevis, adductor magnus, obturator, internus, obturator externus, etc. This relatively large area of sensory and motor coverage by this nerve has proved the potentiality or wide applications of block of this nerve in surgical anaesthesia, postoperative analgesia and chronic pain management over this area (Fig. 23.35).

Anatomy

The obturator nerve arises from the ventral division of anterior rami of L_2, L_3, L_4 spinal nerves. It descends first through the substances of psoas major muscle upto the sacroiliac joint where it pierces out the medial border of this muscle and passes down behind the bifurcation of common iliac vessel. It then descends over the fascia covering the obturator internus muscle and subsequently runs on the periosteum of ischium bone. Then, it descents through the pelvis, along its lateral wall and in close proximity to the inferolateral wall of bladder, bladder neck and lateral wall of prostetic part of the urethra. Here, it accompanies the obturator artery and vein. Finally, it reaches the obturator canal through the obturator foramen and exits into the thigh from pelvis after dividing into anterior and posterior divisions.

The anterior branch of obturator nerve provides: (i) sensory supply to the skin over the inner part of the thigh, hip joint, (ii) cutaneous branch to the subsartorial plexus and (iii) several motor branches to the adductors of the thigh (pectineus, adductor longus and the adductor brevis). The posterior branch supplies the motor to the posterior group of adductors of thigh (adductor brevis, adductor magnus and obturator externus) and an articular branch to the knee joint.

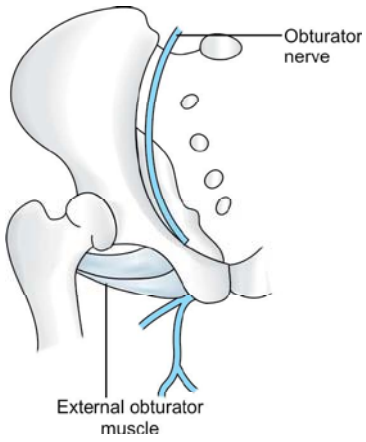


Fig. 23.35: The site of obturator nerve block

Clinical application

The obturator nerve can most easily be blocked with other nerves by using the same approach for the block of lumbosacral plexus. But it can also separately be blocked the for following procedures such as:

i. for superficial surguries over the medial part of the thigh,
ii. to relief spasm of adductors of the hip joint which causes relaxation of the medial thigh,
iii. to relieve intractable hip pain due to osteoarthritis,
iv. as a diagnostic aid for pain syndromes in the hip joint, inguinal area, or lumbar spine,
v. muscle biopsy and tendon transfer or release from medial thigh,
vi. any lower extremity procedure requiring the prolonged use of a pneumatic tourniquet.

The individual block of obturator nerve is very difficult for any anaesthesiologist and very uncomfortable for the patient, even under ideal conditions. Usually the obturator nerve block is combined with other nerve block in the following conditions such as: (i) superficial surgery of thigh (combined with femoral and lateral femoral cutaneous block), (ii) knee surgery (combined with femoral, lateral femoral cutaneous and / or sciatic nerve block).

Technique

The patient is placed in the supine position and the anaesthesiologist should stand at the patient's side which is to be blocked. The leg should be flexed at the knee joint and should be slightly abducted to make the adductor longus tendon prominent, close to its attachment to the pubic bone i.e pubic tubercle. The site of injection or the needle's entry point is 2 cm lateral and 2 cm caudal to this pubic tubercle. At this point the needle will enter medial to the

femoral artery and above the tendon of the adductor longus, but midway between the pubic tubercle and femoral artery and 2 to 3 cm below the inguinal ligament.

To avoid patient discomfort, a skin wheal should be created which is followed by injection of local anaesthetic agent at deeper level. Once the tissues have been prepared, the needle used for the block is first directed from the skin surface toward the inferior pubic ramus until contact is made with the bone. When the contact with bone is made, then the needle should be 'walked off' the inferior ramus in a dorsal and distal direction until it begins to slip into the obturator canal. Then the proximity of the needle tip to the nerve can be confirmed by three ways : (i) creating field block with relatively more volume of drug and repositioning the needle, (ii) eliciting paresthesia on the medial part of the thigh and (iii) using a nerve stimulator to elicit the movement of adductor group of muscles. Any of these strategies requires 10 to 20 ml of drug.

The complications of obturator nerve block are same as that of others such as nerve damage, intravascular injection, haematoma, sepsis, etc. The most common complication of attempting this block is excessive patient discomfort. The failure rate for successful block of this obtutator nerve is also and high this is because of the location of it. Higher infection rate may also be a concern with this nerve block than with others.

Sciatic Nerve Block

Combined with other nerves, the sciatic nerve block is also required for most of the surgeries over the lower extremity and for all the procedures requiring application of pneumatic tourniquet. The nerve can be blocked at the hip both from the anterior and posterior approach and this is known as the sciatic block. The terminal branches of the sciatic nerve also can be blocked isolatedly at the knee and below of it. At the knee, the block of the component of the sciatic nerve is called the popliteal block. Individual peripheral branches of the sciatic nerve also can be approached such as the common peroneal nerve near the fibular head and the other branches at the ankle as a component of ankle block (Fig. 23.36).

Anatomy

The sciatic nerve is the thickest and the largest nerve in our body, with root value of L_4, L_5, $S_{1,2,3}$. Its width is 2 cm. It leaves the pelvis with the posterior femoral cutaneous nerve of thigh (a branch of sacral plexus) through the greater sciatic foramen below the pyriformis muscle but within the sciatic notch. Then, it descends between the greater trochanter of the femur and the ischial tuberosity and passes distally under the gluteal muscles in the sciatic groove, running just over the lesser trochanter of the femur. Then, it becomes superficial at the lower border of the gluteus maximus muscle and descends downwards along the posterior aspect of the thigh lying on the adductor magnus muscle up to the popliteal fossa. At the popliteal fossa, the common trunk of the sciatic nerve splits into two distinct entities—the tibial and the common peroneal nerve, although they run together within a fibrous sheath until just above the knee.

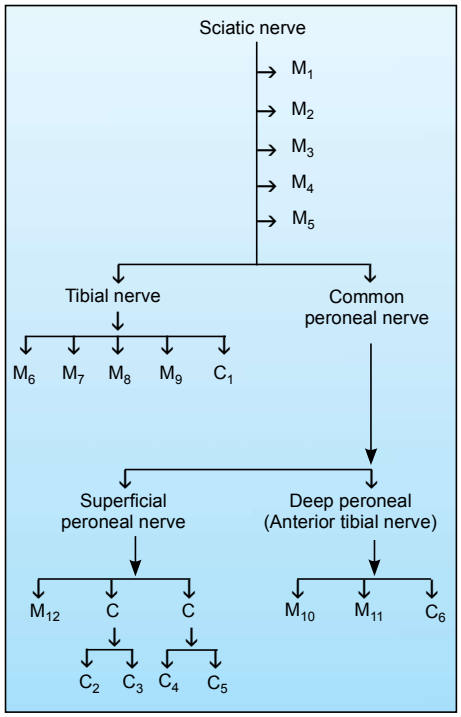


Fig. 23.36: M_1 = Semi-membranosus, M_2 = Ischial fibres of adductor magnus, M_3 = Semi-tendinosus, M_4 = Long head of biceps femoris, M_5 = Short head of biceps femoris, M_6 = Both heads of gastrocnemius, M_7= Plantaris, M_8 = Soleus, M_9 = Popliteus, M_{10}= Tibialis anterior, M_{11} = Extensor digitorum longus and brevis, Extensor hallucis longus, 1st and 2nd interossei, M_{12} = Peroneus longus and brevis, C_1 = Sural nerve, C_2 = Adjacent sides of 3rd and 4th toes, C_3 = adjacent sides of 4th and 5th toes, C_4 = Medial side of great toe, C_5 = Adjacent sides of 2nd and 3rd toes, C_6 = Adjacent sides of great toe and 2nd toe

The sciatic nerve block provides paralysis to the hamstring group of muscles, sensory anaesthesia over the posterior aspect of the thigh and sensory anaesthesia of the entire leg below the knee except a medial strip of skin which is innervated by the saphenus nerve, a branch of the femoral nerve. Since the branches to the hamstring muscles depart the sciatic nerve significantly below the level of the blockade, therefore the twitches of these muscles can be accepted as a sign of reliable localization of the sciatic nerve by the nerve stimulator.

Clinical Application

Sciatic nerve block together with the femoral or saphenons nerve block can be used for any surgery below the knee that does not require toruniquet. Toruniquet can not be applied in this type of combination of block because sensory supply of thigh remains intact. This type of combination of peripheral nerve block avoids sympathectomy and its complication which are common consequences of central neuraxial block So, this type of combination of sciafic, femoral, and raphenous nerve block can be taken as alternative to central neuraxial block. Therefore, its use may be advantageous in cases in which any shift in haemodynamics may be deleterious, such as patient with significant aortic stenosis. Sciatic nerve can be blocked by two

approaches; posterior approach and anterior approach.

Technique

Posterior approach

The patient is positioned laterally with the leg to be blocked should be up and both the hip and knee is flexed. At first a line is drawn connecting the posterior superior iliac spine to the greater trochanter of femur (line A). Then, a perpendicular line (line B) is drawn bisecting the line A. After that another line is drawn from the greater trochanter to the sacral hiatus (line C). Thus intersection of line B and line C is the point of needle entry. After proper antiseptic skin preparation a 22 G and 12 cm long needle is introduced perpendicularly through the skin, till the paresthesia is elicited or bone is contacted. If bone is encountered, then the needle is redirected in lateral or medial direction. Nerve stimulator may also be useful in locating the nerve (Fig. 23.37).

For nerve stimulator, a 100 mm long insulated needle which is connected to a stimulator (initial current 1.5 mA, 2 Hz) is gradually inserted perpendicularly to the skin at the site of injection which is described above. As the needle is gradually advanced to the deeper plane, then a twitch of the gluteus muscles are observed first. This is due to the direct stimulation of muscle by current. Once the twitching of gluteus muscle disappear with the further needle advancement, then the stimulation of sciatic nerve is obtained. The stimulation of sciatic nerve is recognised by the contraction of hamstring group of muscles supplied by the tibial and common peroneal nerve. Typically, the twitching of hamstrings group of muscles are observed first. Then, with the minimal further advancement of needle the twitches of foot are also readily observed. When this maneuver fails to localize the sciatic nerve, the needle is withdrawn up to the skin and is again redirected. The sciatic nerve is typically located at the depth of 5 to 8 cm from skin in an average size adult patient. Once the stimulation of foot is obtained by 0.2 to 0.4 mA or less amount of current then it is thought that the needle is in correct position and 20 to 30 ml of local anaesthetic agent is injected. The sciatic nerve block is of very deep in nature. So, adequate analgesia and sedation is necessary during this procedure to ensure the patient's satisfaction and comfort.

Anterior approach

This approach is applicable when the patient cannot be positioned laterally due to pain or lack of cooperation. The another advantage of anterior approach for sciatic nerve block is that this approach is very convenient and also allows the performance of femoral nerve block in the same position which subsequently shortens the time required to complete the block of both the nerves. With patient in supine position, a line is drawn over the inguinal ligament from the anterior superior iliac spine to the public tubercle (line A). Then, a second line is drawn parallel to the previous line begining at the tuberosity of greater trochanter (line B). After that a third line is drawn perpendicular to line A at the juncture of lateral 2/3 and medial 1/3 (line C). Then, intersection of line B and line C is the point of needle entry for the block of sciatic nerve through anterior approach. After proper antiseptic skin preparation a 22 G and 12 cm long needle is advanced perpendicular to the skin till it contacts with the bone which is lesser trochanter. Needle is then redirected medially passing the femur and paresthesia is sought. At that position, 20 ml of LA drug is injected incrementally after the negative aspiration test (Fig. 23.38).

If nerve stimulator is used, then the proper position of needle is recognised by stimulation of the sciatic nerve which results in rhythmic movements of the foot (simultaneous plantar or dorsi flexion).

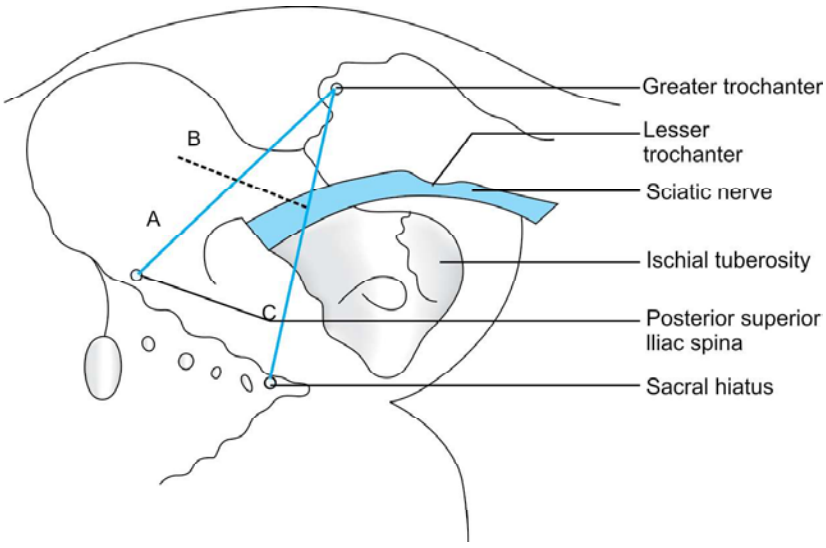


Fig. 23.37: Sciatic nerve block. Posterior approach

NERVE BLOCK AROUND KNEE

Just as the terminal branches of the nerves of brachial plexus can be blocked distally around the elbow and wrist joint, similarly

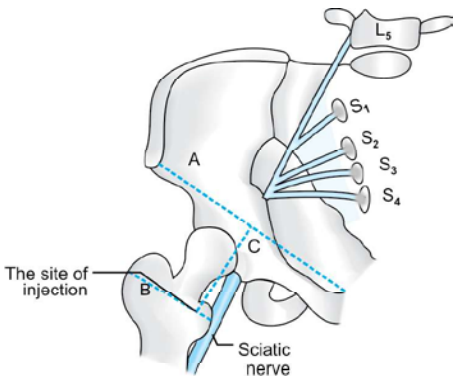


Fig. 23.38: Sciatic nerve block, anterior approach

the individual terminal branches of the nerves of lower extrimity arising from the lumbosacral plexus can be blocked around the knee, ankle and foot depending on the objective.

Popliteal Block

By this technique the components of the sciatic nerve such as the tibial and the common peroneal nerve can be blocked together in popliteal fossa behind the knee. With the saphenous nerve block this popliteal block can also be used for (Fig. 23.39) any surgery at any site on leg, ankle and foot. The popliteal fossa is formed above by the semi tendinosus and semi- membranosus tendon medially and biceps tendon laterally and below by the two heads of gastrocnemious. Within the fossa, from medial to lateral are situated popliteal vein, popliteal artery and sciatic nerve. Proximal to the flexion crease of knee, the terminal branches of sciatic nerve, i.e. the tibial and common personal nerves are bundled together and this is the site for the injection of LA agent for popliteal block. This posterior approach of popliteal block is performed with the patient in prone position and the leg is fully extended. Two inches proximal to the flexion crease of knee the pulsation of popliteal artery is identified first. Then the site 1 cm lateral to this pulsation is the needle entry point for popliteal block. After proper antiseptic skin preparation a 22 G and 4 cm long blunt bevelled needle is inserted perpendicular to the skin first and then it is advanced till the paresthesia or motor evoked response (if nerve stimulator is used) is elecited which is plantar flexion or dorsiflexion of foot. Then, 10 to 20 ml of local anaesthetic drug is deposited.

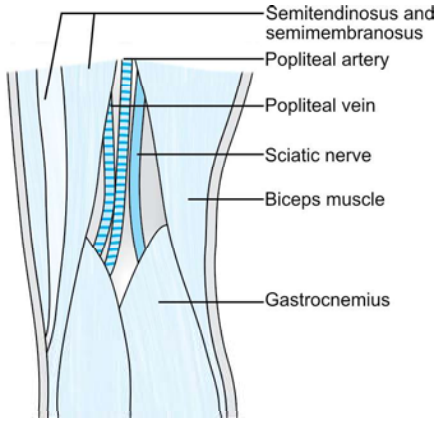


Fig. 23.39: The popliteal block (right leg)

Tibial Nerve Block

It is one of the two terminal divisions of the sciatic nerve (another division is common peroneal nerve) and comes out of it at the level of junction of the upper 2/3 and lower 1/3 on the back of the thigh. But they (the two terminal division of sciatic nerve) lie side by side in a common fibrous sheath. After that it descends on the popliteal fossa along the lateral side of the popliteal vein. Then it crosses superficial to the vein and artery at the back of the knee and descends on the fascia covering the popliteus muscle lying medial to the popliteal vein and artery. It then continues downwards finally as the posterior tibial nerve (PTN) from the lower border of the popliteus muscle on the back of the leg, with the posterior tibial artery within the posterior compartment of the leg. At the ankle, it reaches the midpoint between the medial malleolus and calcaneus under the flexor retinaculum and divides into lateral and medial plantar nerves. The posterial tibial nerve (continuation of tibial nerve) innervates all the muscles of the posterior compartment of the leg and supplies sensory to the ankle joint, and skin over the heel. The medial and the lateral plantar nerves which are the terminal branches of PTN innervate all the intrinsic muscles of the sole and supply sensory to the entire sole and many of the tarsal and metatarsal joints.

Common Peroneal Nerve Block

It is one of the two terminal divisions of the sciatic nerve. It runs downwards and laterally on the popliteal fossa along the medial margin of the biceps femoris muscle. It then comes in direct contact with the lateral surface of the neck of the fibula between the two heads of the origin of peroneus longus muscle. Here it divides into superficial peroneal (or musculocutaneous) and deep peroneal (or anterior tibial) nerves.

The superficial peroneal nerve is the nerve of the lateral (peroneal) compartment of leg. It supplies the peroneus group of muscles and the skin over the lower part of the leg. After supplying the peroneal group of muscles, it pierces the deep fascia at the junction of the medial and lateral third of the lateral surface of the leg and becomes a superficial sensory nerve. Then, it passes to the front of the leg and divides into medial and lateral cutaneous branches. Both of these divisions then reach the dorsum of the foot in front of the superior and inferior extensor retinaculum and then is distributed as follows. The medial division sends two digital nerves: (i) one goes to the medial side of the great toe upto its tip, (ii) the other divides to supply the adjacent sides of the 2nd and 3rd toes. Nailbed of any toe is not supplied by the digital branches of the nerves of the dorsum. Nailbeds are supplied by the plantar digital nerves. The lateral divisions again divides into two dorsal digital nerves. One divides to supply the adjacent sides of the 3rd and 4th toes. Other divides to supply the adjacent sides of the 4th and 5th toes (Fig. 23.40).

The deep peroneal or anterior tibial nerve is one of the branches of the common

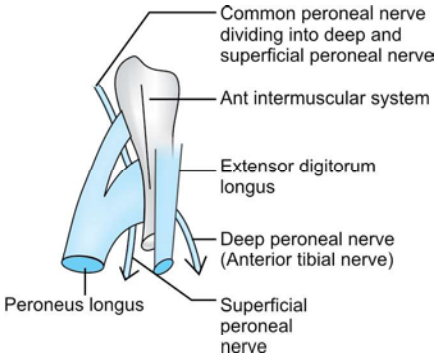


Fig. 23.40: Block at the level of fibular head

peroneal nerve and originates at the lateral surface of the neck of the fibula. It first enters the anterior compartment of the leg and then descends on the interosseons membrane. It innervates all the muscles of the anterior compartment of the leg. On reaching the front of the ankle, it divides into lateral and medial branches. The lateral branch supplies the tarsal joints, metatarsophalangeal joints and interossei muscles. The medial branch runs along the lateral side of the arteria dorsalis pedis and supply motor to the 1st dorsal interosseous muscle and sensory to the adjacent sides of the great toe and 2nd toe.

The block of this common peroneal nerve is appropriate only for surgery on the lateral side of the foot, when popliteal block is difficult. The site of injection or block is just distal to the head of the fibula below knee, where this nerve crosses the head of the fibula from posterior compartment to lateral compartment of leg. The nerve can be blocked by field block technique or with the help of nerve stimulator. Relatively a small volume of 5 to 10 ml of drug is required for this block.

Saphenous Nerve Block

It is one of the branch of the posterior division of the femoral nerve and purely sensory. It descends through the femoral triangle lateral to the femoral artery and then enters the adductor canal. Here, it superficially crosses the femoral artery from lateral to medial side and pierces the aponeurotic roof of the adductor canal. It then descends along the medial side of the knee where it pierces the deep fascia between the sartorius and gracilis tendon. It now descends over the deep fascia along the medial surface of the tibia with the great saphenous vein, but in front of it. At lower 1/3 of the leg, it divides into two branches: one descends along the medial border of the tibia to end over the skin of the ankle. The other enters the foot in front of the medial malleolus and then runs along the medial border of the foot up to the ball of the great toes. Thus, the saphenous nerve is the terminal sensory continuation of femoral nerve in the leg and foot. It can be blocked by infiltration of subcutaneous tissue with local anaesthetic agent in a straight line, perpendicular to the course of the nerve at any one of the several easily identified sites such as: (i) at the medial side of the knee joint, over the femoral condyle by a transverse skin infiltraton with 5 to 10 ml of local anaesthetic agent, which can be confirmed by testing by pinprick between the first and second toes on the dorsal surface of the foot, (ii) over the medial prominence of tibia just distal to the knee joint, and (iii) as a routine part of full block around the ankle.

NERVES BLOCK AROUND THE ANKLE

The complete anaesthesia of foot (both motor and sensory) requires the blockade of five nerves supplying it around the ankle. These are: posterior tibial and sural nerve (branch of the tibial nerve), superficial and deep peroneal nerve (branch of the common peroneal nerve), and saphenous nerve (branch of the femoral nerve). Depending on the site of surgical procedure, it may also be possible to block less than five nerves with accurate knowledge of their sensory and motor supply.

Ankle block is selected especially in patients who are too sick for central neuroaxial block, or unable to handle higher volume of local anaesthetic agent required for the other regional anaesthetic techniques for the block of lower extremity, but need surgery on the foot distal to the malleoli (Fig. 23.41).

Posterior Tibial Nerve Block

At the ankle, behind the medial malleolus, posterior tibial artery pulsation is the landmark for the block of this nerve. Here, the nerve lies lateral (behind) to the artery. After a proper antiseptic skin preparation a 22 G and 3 cm long blunt bevelled needle is inserted perpendicular to the skin but posterior to artery at the level of medial malleolus. Paresthesia may be encountered, but should not be sought. The tip of the needle must be under the covered edge of medial malleous and drug is administered like field block technique and 5 ml drug will accomplish the block. Then, the needle is withdrawn back from the posterior aspect of tibia. The blockade of posterior tibial nerve provides anaesthesia of the heel, plantar aspect of the toes, the medial aspect of sole (lateral aspect of sole is supplied by the sural nerve) and as well as some motor block supplied by it.

Sural Nerve Block

It is the cutaneous branch of tibial nerve and arises from it in the popliteal fossa. It is also joined by a sural communicating branch coming from the common peroneal nerve. The sural nerve pierces the deep fascia at the level of lower 1/3 on the back of the leg. Then, it passes behind the lateral malleolus along with the small saphenous vein and goes along the lateral border of the foot upto the tip of the little toe. At the level of the ankle, it is located superficially between the lateral malleolous and

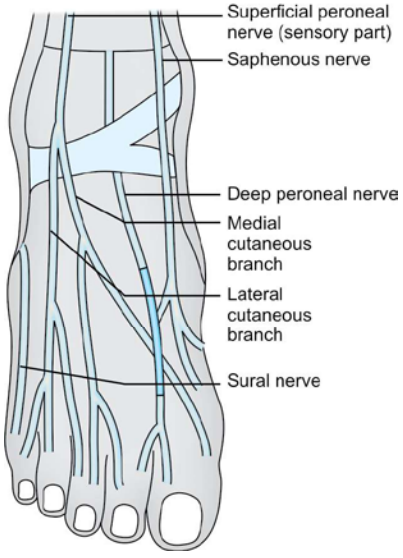


Fig. 23.41: Ankle block

the Achilles tendon. After proper antiseptic skin preparation a 25 G and 3 cm long needle is inserted lateral to the tendon directing towards the lateral malleolus and then 5 ml of LA solution is injected subcutaneously. This block provides anaesthesia of the lateral aspect of the foot and the lateral aspect of the proximal part of the sole.

Deep Peroneal, Superfacial Peroneal and Saphenous Nerve Block

These three nerves can be blocked through a single needle entry point at the inter malleolar line (between medial and lateral malleolus) in front of the ankle. At the intermalleolar line, the tendon of extensor hallucis longus is identified first by asking the patient to dosiflex his big toe. At this intermalleolar line, the tendon of extensor digitorum longus can also be palpated easily on the lateral side of the extensor hallucis longus tendon. Between this two tendons the anterior tibial artery is situated and is palpable at this level. The needle is inserted perpendicular to the skin on the intermalleolar line by the side of the anterior tibial artery between these two tendons and 5 ml of LA drug is deposited under the extensor retinaculum. This will block the deep peroneal nerve and anaesthetize the skin between the first and second toes.

During withdrawal of the needle, it is again directed laterally along the intermalleolar line through the same entry site of skin and 5 ml of LA drug is deposited subcutaneously blocking the superficial peroneal nerve resulting in anaesthesia of the dorsum of foot, excluding the fist interdigital cleft which is already anaesthetized by the block of deep peroneal nerve. The same maneuver can now be performed in the medial direction along the intermalleolar line anaesthetizing the saphenous nerve, supplying a strip of skin along the medial aspect of the foot.

ILIOHYPOGASTRIC, ILIOINGUINAL AND GENITOFEMORAL NERVE BLOCK

Indications

Iliohypogastric (L_1), ilioinguinal (L_1) and genitofemoral (L_1L_2) nerves are the branches of lumbar plexus and lies in the muscular layers of abdominal wall. They mainly supply the groin and the genital areas. So, blockade of these nerves is used for surgical procedures on inguinal and genital areas, such as herniorrhaphy, orchidopexy, chronic pain, postoperative pain relief over this area, etc. The block of these three nerves is also done along with femoral nerve block for long saphenous vein stripping. The block of these nerves has also been used to diagnose and treat pain due to nerve entrapments, neuralgias, neuromas, etc. on their site of sensory supply (Fig. 23.42).

Anatomy

The ventral ramus of the first lumbar spinal nerve (L_1) after receiving a twig from ventral ramus of T_{12} spinal nerve divides into two branches, the upper and the lower. The upper branch again divides into two branches. These are : ilihypogastric and ilioinguinal nerve. The lower branch unites with a branch from the second lumbar ventral ramus (L_2) and form the genitofemoral nerve.

After formation, the iliohypogastric nerve first emerges from the lateral border of the psoas major muscle by piercing it. Then, it runs downwards and laterally in front of the quadratous lumborum and transversus abdominis muscle, but behind the kidney. Here the nerve is embeded in the fascia covering the quadratus lumborum. Now the nerve pierces the transversus abdominis muscle and runs obliquely forwards between it and the internal oblique muscle of the anterior abdominal wall. Here, it supplies both the muscles. Then, the nerve divides into lateral and anterior cutaneous branches. The lateral cutaneous branch pierces the internal and external oblique muscles above the iliac crest and supplies the posterolateral area of the gluteal skin. On the otherhand, the anterior cutaneous branch runs further forward between the transversus abdominis and internal oblique muscles, and pierces the internal oblique muscle 2 cm medial to the anterior superior iliac spine and runs between it and the external oblique aponeurosis towards the inguinal region. Then, it pierces the external oblique aponeurosis 3 cm above the superficial inguinal ring and supplies the skin over the suprapubic region.

The ilioinguinal nerve after its formation also runs like iliohypogastric nerve but below it. It is smaller in size (Fig. 23.43) than the previous one and pierces the internal oblique muscle close to the anterior superior iliac spine. Then, the nerve runs medially on the internal oblique muscle and enters the inguinal canal from

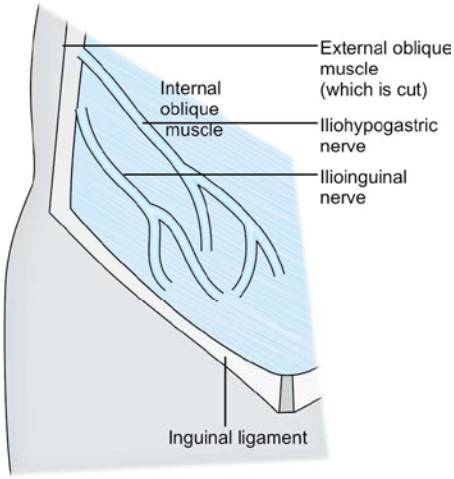


Fig. 23.42: Iliohypogastric and ilioinguinal nerve block

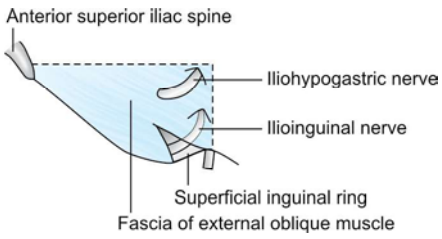


Fig. 23.43: Iliohypogastric and ilioinguinal nerve

above. This nerve is the only content of the canal which does not pass through the deep inguinal ring. It then traverses along the medial part of the canal to come out through the superficial inguinal ring and supplies: (i) the skin over the symphysis pubis, (ii) the skin over the root of the scrotum and penis in male or libia majora in female, and (iii) the skin over the superomedial angle of the femoral region.

After its formation the genitofemoral nerve pierces the psoas major muscle and emerges from its abdominal surface at its medial border, opposite to the body of L_3 or L_4 vertebra. It then descends subperitoneally on the psoas major muscle behind the ureter. Here it devides into genital and femoral branches above the inguinal ligament at variable distance. Then, the genital branch enters the inguinal canal through the deep inguinal ring and becomes the content of spermatic cord. In the spermatic cord it is also known as the nerve to cremaster, supplying the cremaster muscle and scrotal skin (in male). In female, the genital branch in the inguinal canal accompanies the round ligament and supplies the skin of labia major and mons pubis. The femoral branch of the genitofemoral nerve descends lateral to the external iliac artery. It then passes behind the ingiunal ligament and enters the femoral triangle lateral to the femoral artery, but within its sheath. It supplies the skin of the upper part of femoral triangle, but below the inguinal ligament.

Technique

Iliohypogastric and ilioinguinal nerve block

For the block of these two nerves the patient is first positioned in supine and then the anterior superior iliac spine is identified. After that an imaginary line is drawn from it to the umbilicus. From this line a point is marked which is 2 cm medial and 2 cm cephalad to the anterior superior iliac spine. This is the entry point of needle to block the above mentioned nerves. After proper skin preparations, a 22 to 25G needle which is 3.5 inch long is inserted perpendicular to the skin until it just pierces and cross the external oblique aponeurosis below which these nerves lie. Then, 8 to 10 ml of local anaesthetic agent is injected fanwise at that site to block both the iliohypogastric and ilioinguinal nerves.

Genitofemoral nerve block

For the block of this nerve the patient is first positioned supine and then hips are extended. The genital branch of genitofemoral nerve is first blocked by infiltrating 3 to 5 ml of local anaesthetic agent just lateral to the pubic tubercle below the inguinal ligament. Similarly, the femoral branch of genitofemoral nerve is blocked by injecting 3 to 5 ml of local anaesthetic agent subcutaneously just below the inguinal ligament at the lateral border of the femoral artery, after a negative aspiration test.

These three nerves also can be blocked together by a new transpsoas approach or technique, described by Hartrick. But, there is no scope to discuss it here.

Contraindications

The absolute contraindications of block of these nerves are: Sepsis, local infection, coagulopathy, lack of consent, etc. If there is coagulopathy but presence of strong indication, then the procedure can be executed very cautiously using a 27 G fine spinal needle.

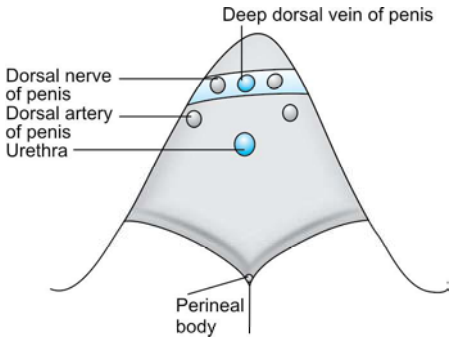


Fig. 23.44: Perineal membrane (in male)

PENILE BLOCK (FIG. 23.44)

The penile block is performed for any surgical procedure over the penis or for postoperative pain relief after any surgery over the penis under general anaesthesia. Penis is actually innervated by the dorsal nerve of penis or clitoris. It is the branch of pudendal nerve and gives this branch while it runs in the pudendal canal. Then the dorsal nerve of penis enter into the penis deep to its Buck's fascia under the symphysis pubis and divides into dorsal and ventral branches. The genital branch of the genitofemoral nerve and the terminal branches of the ilioinguinal nerve also supply the skin over the root of the penis near symphysis pubis (Fig. 23.45).

Bilaterally, the dorsal nerve of penis is blocked by injecting 2 to 3 ml of local anaestheitc agent under the Buck's fascia at 10 and 2 o'clock position using 25 G needle which is one inch long. The whole penis also can be anaesthetized by giving

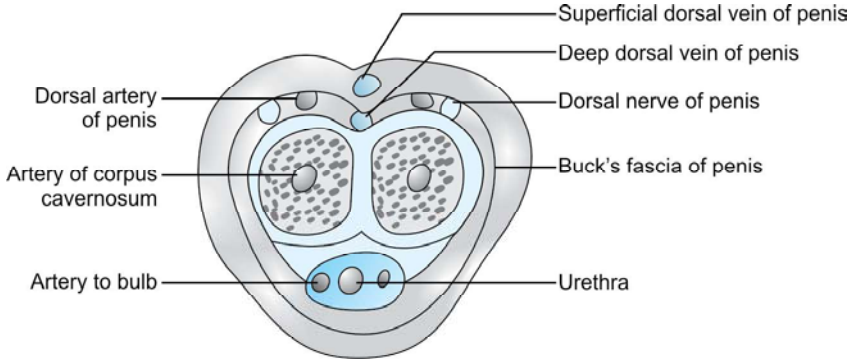


Fig. 23.45: Transverse section through the body of penis

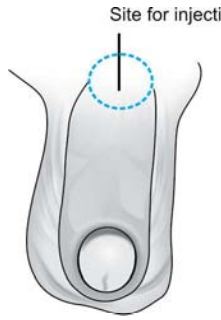


Fig. 23.46: Penile field block

a fan shaped (triangular or rounded) field block around the root of the penis with 10 ml local anaesthetic agent. For penile block epinephrine or any other vasoconstricting agents mixed with the local anaesthetic solution always should have to avoid to prevent the end artery spasm, leading to ischaemic injury of penis (Fig. 23.46).

As the penis is a very vascular structure, so careful aspiration before every injection is mandatory to avoid any inadvertant intravascular administration of LA agent.

INTERCOSTAL NERVE BLOCK

Indication

The intercostal nerve block is very useful in many circumstances, though it has some disadvantages. The bilateral blockade of 6th to 12th intercostal nerves provides motor block and sensory anaesthesia of anterior abdominal wall extending from xiphoid process to symphysis pubis. Bilateral blockade of intercostal nerve is necessary, because there is some overlap of innervation over the midline from each side. Anterior abdominal muscles are relaxed, but there is no anaethesia of visceral peritoneum. So, light general anaesthesia or supplemental bilateral celiac plexus block is necessary if any intra-abdominal procedures is attempted by only intercostal nerve block. This combined technique (bilateral intercostal block plus celiac plexus block) is ideally suited for upper abdominal surgery such as cholecystectomy, gastrectomy, splenectomy, etc. But for mid-abdominal surgery this intercostal block and celiac plexus block is further supplemented by paravertebral block of the first and second spinal nerve roots. In a similar fashion, intrathoracic surgery also can be performed by combination of upper intercostal nerve block and stellate ganglion block, with or without light general anaesthesia. However,though these are not generally used, but very useful for severe debilitated patients. Thus, intercostal nerve block with plexus or ganglionic block provides an alternative approach to spinal and epidural anaesthesia for intra-abdominal or intrathoracic surgical procedures, if the central neuroaxial blocks are contraindicated. On the otherhand, only intercostal nerve block without plexus or ganglion block also can replace the spinal or epidural anaesthesia for surgical procedures performed only on the abdominal or chest wall without the price of sympathectomy, which is associated with central neuroaxial block (Fig. 23.47).

The unilateral intercostal nerve block of three or more ribs at a time provides an excellent pain relief for fractured ribs, herpe zoster, pleurisy, chest tube insertion or replacement, percutaneous biliary drainage, etc. This technique is also useful to relieve the acute post-thoracotomy pain, midline abdominal surgical incision pain, subcostal incisional pain, etc. It improves ventilatory function and reduces the narcotic requirements. But, intercostal nerve block does not provide analgesia as effective as continuous epidural infusions. On the otherhand, it needs frequent and repeated injection to relief the pain.

Anatomy

Each intercostal nerve is the continuation of the ventral ramus of a thoracic spinal nerve. They are twelve in number on each side. Among these the 3rd to 6th intercostal nerves are accounted as the typical intercostal nerves. Because they are only confined to the thoracic wall. The major portion of the first (Fig. 23.48) thoracic spinal nerve (first intercostal nerve) joins with the C_8 spinal nerve and forms the lower trunk of brachial plexus. The lateral cutaneous branch of the second intercostal nerve remains undivided. Rather, it becomes the intercostobrachial nerve and supply the medial side

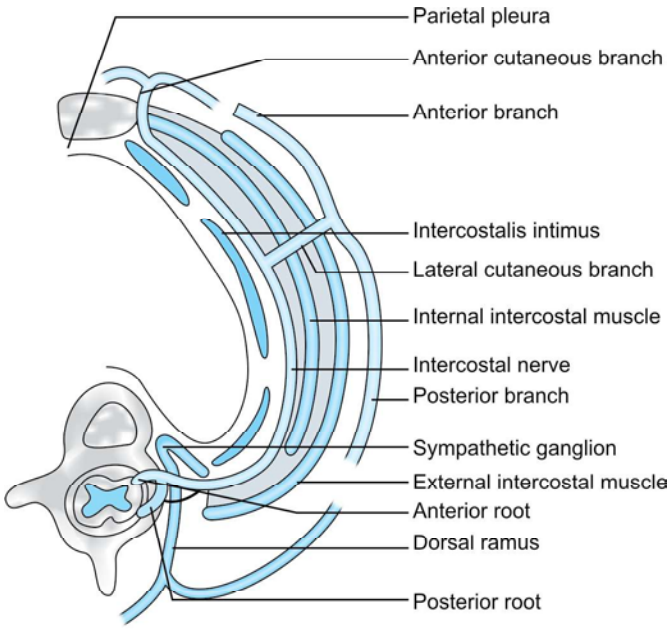


Fig. 23.47: The intercostal nerve—its origin and branches

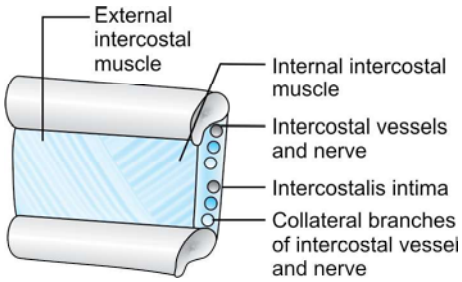


Fig. 23.48: Contents of intercostal space

of the upper arm and arm pit. The 7th to 11th intercostal nerves pass to the anterior abdominal wall. They enter the intercostal space through the digitation between the costal origin of the diaphragm and the transversus abdominis muscle.

After its origin in the vertebral canal each intercostal nerve comes out though the respective intervertebral foramen and appears in the posterior part of the intercostal space. It then runs upwards and laterally behind the sympathetic trunk to reach the undersurface of the respective ribs. Here, it lies inbetween the costal pleura and the posterior intercostal membrane (which is the posterior membranous part of internal intercostal muscle). Then, each nerve runs in the costal groove along the inferior edge of each rib which provides a channel for the nerve and its companion artery and vein. The overhanging outer external edge of the lower border of each rib protects these fellow travelers from direct external assault. In the costal groove the arrangement of these travelers from above down wards are vein, artery and nerve (VAN). When these neurovascular structures run under the lower edge of respective rib in the costal groove, then it runs between the external intercostal and internal intercostal muscle lying externally, and intercostalis intima muscle and parietal pleura lying internally. On reaching the angle of respective rib, each nerve gives off a lateral cutaneous branch. Then the main trunk of the nerve passes forwards along the costal groove between the internal intercostal muscle and intercostalis intimus. Near the midaxillary line the costal grove becomes less well defined and the nerve migrates away from the rib. Because of these two factors, reliable block of intercostal nerve is more difficult beyond the anterior axillary line (Fig. 23.49).

In the anterior part of the intercostal space, the nerve passes in front of the sternocostalis muscle and crosses the internal thoracic artery. Then, it pierces the intercostalis internus, anterior intercostal membrane (membranous part of intercostalis externus), pectoralis major and comes out as the anterior cutaneous nerve to supply the skin of the anterior chest (T_2-T_6) and abdomen (T_7-T_{12}) wall.

The ventral ramus of the first thoracic spinal nerve is not entirely the intercostal nerve. It divides into upper and lower branches. The large upper branch crosses the neck of first rib and joins with C_8 nerve to form the lower trunk of brachial plexus. The smaller lower branch is continued as the first intercostal nerve.

The 12th intercostal or subcostal nerve is unique in that it is not closely associated with its corresponding rib. The branches of it depart early and join with L_1 spinal nerve to form the iliohypogastric and ilioinguinal nerve. So, the standard subcostal injection technique is less likely to produce anaesthesia of this nerve.

The lateral cutaneous branch of each intercostal nerve arises near the angle of each rib and pierces the muscle in the midaxillary line. After being cutaneous, this branch again divides into two branches–anterior and posterior. The anterior branch runs anteriorly and unites by the side of the sternum with the terminal anterior cutaneous branch of each main intercostal nerve. Posterior branch runs posteriorly and unites with the cutaneous branch of the dorsal ramus of the same thoracic nerve which also supply the paravertebral muscles and the skin over it. Both these branches supply the skin over the corresponding area. A collateral branch also arises from the each intercostal nerve near the angle of each corresponding rib. It also passes forwards in the same intermuscular plane like the main nerve, but along the upper border of the next lower rib. Anteriorly, it terminates as additional anterior cutaneous nerve by piercing the muscle like the terminal part of main nerve.

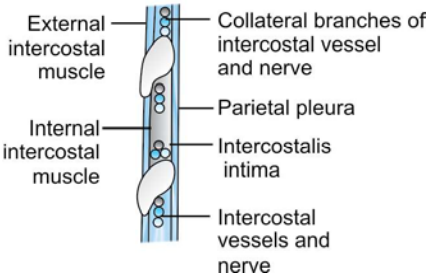


Fig. 23.49: Vertical section through an intercostal space

Each intercostal nerve is connected with the corresponding sympathetic ganglion of the sympathetic chain by white and grey rami communicantes. White ramus carries the preganglionic sympathetic fibres. While the grey ramus carries the postganglionic sympathetic fibres from the ganglion.

Technique

The anatomy of ribs may themselves vary. Posteriorly by the side of the midline all the ribs are well protected by paravertebral group of muscles. The lower six ribs are broad, flat and more superficial than the upper six ribs. So, they are easily palpated lateral to these paravertebral muscles. The upper ribs are narrower, deeper and more protected by scapula and paravertebral muscles. So, they are not easily palpated and technically more difficult to reach by the needle. As the upper ribs are protected laterally by the scapula, so paravertebral approach is more practical in this region.

The intercostal nerves can readily be blocked at the angle of the rib, just lateral to the sacrospinalis group of muscles. The patient may be placed in the lateral, sitting, supine or prone position. But, prone position is more practical and technically easy to block the intercostal nerve. In prone position a pillow is placed under the

abdomen to provide slight flexion of the thoracic spine. The arms will hang over the edge of the operating table, so that scapulla falls away laterally from the angle of the rib. First a line is drawn along the thoracic vertebral spines. Then, the ribs are identified along the line of their most extreme posterior angulation. For the 12th rib, this is usually 7 cm from the midline. Whereas for the 6th rib, this is usually 5 cm from the midline. Thus, a line is drawn connecting the posterior angles of these two ribs which will run upwards lying 3 to 5 cm away from the midline and is angled medially at the upper level. The posterior angles of the rest of the rib will come on this line and inferior border of each rib is marked on this line.

Then, after appropriate skin preparation, sedation and analgesia, a 22 G and 4 cm long needle is inserted perpendicular to skin until it rests on the rib. Then, the needle is walked in a caudal direction until it pass below the inferior border of the rib, where 3 to 5 ml of local anaesthetic agent in injected. This process is repeated at each rib, starting with the lower most and moving gradually upward.

The six or seven designated ribs on each side are blocked in this process. The ribs on the opposite side also can be blocked in a similar manner. Alternatively, intercostal block can also be performed on a supine patient at the midaxially line. In practical situation, the lateral cutaneous branch of intercostal nerve is not targeted for block. Because, in reality, CT studies show that injected solution spread several centimeters along the costal groove and block this lateral cutaneous branch.

If intercostal nerve block are to be supplemented by somatic paravertebral nerve blockade and sympathetic celiac plexus blockade, then these should be performed at the completion of intercostal anaesthesia. But care should be taken to adjust the total dose of the LA drug, so that the maximum recommended doses does not exceed.

COMPLICATIONS

The probable complications are: pneumo thorax (most common), respiratory inadequacy, systemic toxicity, hypotension, etc.

24 Spinal, Epidural and Caudal Anaesthesia or Central Neuroaxial Block

HISTORY

It was 1855, when Friedrich Gaedcke (FG) of Germany had first isolated cocaine (alkaloid) from coca plant (Erythroxylon coca), which usually grew as bush in Bolivia and Peru. Before that discovery, the plant was well-known to the local Indians as an euphoriant and stimulant. But, the modern local or regional anaesthesia began with the introduction of cocaine into the medical practice in September 1884 by Karl Koller (Fig. 24.1) after its isolation from plant by FG. Karl Koller was then a 27 years old trainee ophthalmologist in Vienna. He was also the first medical man who used and publicised the analgesic and local anaesthetic properties of cocaine by applying it as topical drop in ophthalmic surgery.

Before the discovery of analgesic and local anaesthetic property of cocaine Karl Koller was working under professor, named Carl Ferdinand who was then considerably dissatisfied with the standard and condition of general anaesthesia for ophthalmic surgery during that period. Karl Koller also soon began to share the same dissatisfaction with his professor, regarding the restlessness, coughing, vomiting, etc. during operative and postoperative period after general anaesthesia. So he began to realise that this problem would only be solved, if any local anaesthetic agent could be invented which when instilled into the conjunctional sac would abolish pain. With this aim, Koller also tried with morphine and other sedatives, by instillating them in the conjunctival sac. But, he was unsuccessful and turbulent ophthalmic operating conditions under general anaesthesia continued.

Sigmund Freud, a friend and contemporary of Karl Koller was also working as his junior colleague in the neurology department of the same hospital. He later achieved world fame as the originator of psychoanalysis. In a fine summer in 1884, Freud was working with cocaine what was then a fairly new drug and had reached Europe from South America in and around 1860. As cocaine produced euphoria and CNS stimulation, so it led Freud to believe that cocaine might be a remedy for morphine addiction and as well as can be used as a tonic for his psychoneurotic patients. He also knew that cocaine deadened mucous membrane. But, Sigmund Freud never thought that it was due to the local anaesthetic property of cocaine. He was also not clear about the effects of cocaine on muscular contraction. Then, once Freud went on a holiday, asking Koller to do some experiments on cocaine and to elucidate the problem.

Fig. 24.1: Karl Koller

Thus when Freud was on holiday, Koller had started same experiments by applying cocaine on his own tongue. But he was astonished by cocaine's strange power to deaden all the sensation of tongue. In a flash, he realised that this might be that agent, he had been looking for long period to act as a local anaesthetic in his eye operations. Then, he started serial experiments to investigate the analgesic and local anaesthetic properties of cocaine in his experimental laboratory on animals. Later, Koller used cocaine on his friends and lastly on his patients. He was extremely satisfied with his work and had lost no time in making his discovery public. Then, he wrote a short preliminary report and asked his friend, Dr Josef Brettaver, to read it for him at the forthcoming meeting of German Ophthalmological Society which is to be held in Heidelberg where Koller himself was not be able to attend it. In 15th September 1884, Brettaver's paper made a sensation. After that Koller had given many lectures on the local anaesthetic property of cocaine. He also gave many clinical demonstrations on the local anaesthetic property of 2% cocaine solution in the outpatient clinic. In the following months, Koller read two full papers on the local anaesthetic property of cocaine before the Imperial Medical Society. But Freud, whose interest in surgical anaesthesia was minimal, made no claim to this discovery by Koller.

However before Koller's work, in 1849 Simpson had also recorded some history of local anaesthesia and some experiments of his own. But between 1849 to 1884 and before Koller's discovery, ether spray was used for local anaesthesia and it acts by freezing the skin. Later ethylchloride spray was also used for the same purpose in 1880 by Rothenstein.

After Koller's work in 1884 and in the early part of 1890, Reclus in Paris and Karl Ludwig in Berlin had first popularised the infiltration anaesthesia using cocaine. But, the first direct nerve block with cocaine had been employed by WS Halsted and RJ hall and the mandibular nerve was their first nerve. Then, Halsted extended his work on this concept by blocking other nerves. Subsequently, he was the first surgeon to block the nerves of face, brachial plexus, internal pudendal nerve and posterior tibidal nerve using cocaine. He also first showed that the reduction of circulation in any part of a body by an Esmarch bandage would prolong the effects of local anaesthetic agent. Then, when the use of cocaine was popularised, gradually its toxicity became evident due to the use of its higher doses. These were: CNS stimulation, addiction among the general surgical patients, and clouding of cornea when used as topical anaesthesia in ophthalmic surgery.

So, subsequently the relatively less toxic substitutes for the highly toxic cocaine as local anaesthetic agent was searched for. Hence in 1890, in dentistry, oil of cloves (eugenol) was first used as a local analgesic and anaesthetic agent in stead of cocaine. Then, gradually Giesel's tropococaine appeared in 1891 and subsequently Fourneau's stovocaine was marketed in 1904. Einhorn's novocaine (procaine) was described in 1899, but was first used clinically in 1904. Then, it was popularised by H Braun in 1905. Subsequently, Miescher and Uhlmann introduced nupercaine (cinchocaine) in 1929. Amethocaine was first described in 1931. Then first important milestone about local anaesthetic agent came when Lofgren and Lundqvist first synthesised lignocaine in 1943. But Gordh was the first to use it clinically in Stockholm in 1948. Then the local anaesthetic agents which were appeared chronologically are: Chlorprocaine in 1952, mepivacaine in 1956, prilocaine in 1959, bupivacaine in 1963, etidocaine in 1972 and ropivacaine in 1993.

H Braun first introduced adrenaline in 1902 (which was first isolated in pure form in 1897) with cocaine to retard the absorption and to prolong its effect. The term 'block' was first used in 1897 by Crile and the term 'regional anaesthesia' was first used by Cushing in 1901.

The cerebrospinal fluid (CSF) was first discovered by Domenico Cotugno in 1764. But, its circulation was first described by F Magendie in 1825, who gave its name as CSF. In 1885, when J L Corning was experimenting with cocaine on the spinal nerve of his dog, he accidentally pierced the dura and gave first spinal anaesthesia. Later, he deliberately had repeated the intradural injection and called it as spinal anaesthesia. Then, he suggested that this type of anaesthesia might be used in surgery. After that this lumbar dural puncture was standardised as clinical procedure by HI Quincke in Germany in 1891 (Fig. 24.2).

The first planned spinal anaesthesia on human for surgery was performed by August Bier on 16th August in 1898. The patient was a 34-year-old parturient and Bier courageously injected 3 ml of 5% cocaine solution in CSF through the lumbar spinal route. However, this experiment became a great success. Then, subsequently Mr Bier had used spinal anaesthesia on 6 patients. After that, to prove his faith on his method Bier and his assistant each injected 2 ml of 1% cocaine into each other's subarachnoid space. The name of assistant was Hildebrandt. The procedure was actually first attempted on Bier by his assistant. However, after successfully locating the subarachnoid space of Bier, Hildebrandt was unable to attach the syringe to the needle and a considerable amount of CSF was lost on the floor. So, in order to salvage the experiment, Hildebrandt volunteered himself as the research subject to Bier. This time the intrathecal injection of cocaine was successfully completed by Bier. Then, Bier and Hildebrandt celebrated their achievement with wine and cigars. Unfortunately, on the next day Bier complained of severe headache which resolved only after nine

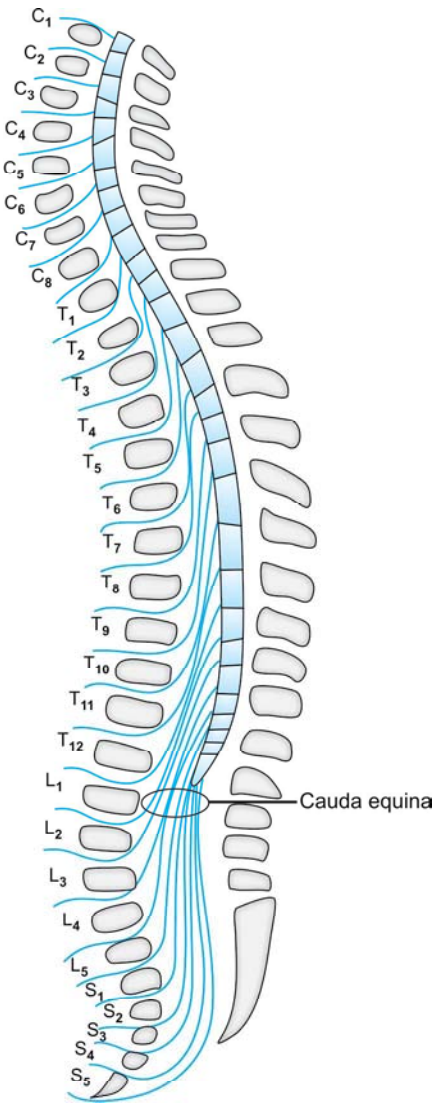


Fig. 24.2: The longitudinal section of vertebral column

days. However, Hildebrandt had also suffered from headache significantly more. While anaesthetised, their degree of analgesia and anaesthesia had been tested and monitored by being kicked on their shin bone and pinched with instruments. As a result, they not only developed a postdural puncture headache, but also suffered from severe bruises over their legs due to the repeated assessment of their sensory block. Then this work was published in April 1899 under the title 'Research on the cocainisation of the spinal cord' and the popularity of spinal anaesthesia had quickly spread. August Bier had also described in this book that his own post spinal headache is due to the excessive leakage of CSF. Bier also advised spinal anaesthesia for operation on legs. But, later he gave it up, owing to the toxicity of cocaine.

Soon after that, Tuffier and Sicard of Paris extended the scope of spinal anaesthesia in the field of surgeries, including the external genitalias and the lower abdomen. In 1903, adrenaline was introduced with local anaesthetics to increase the duration and to reduce the toxicity of cocaine used in spinal anaesthesia. Due to the toxicity of cocaine, stovocaine was first used in spinal anaesthesia in 1904 and novocaine (procaine) in 1905, soon after their discovery. In 1907, A E Barker, a surgeon of London, was the first to realise the importance of the curves of vertebral column and the use of gravity in controlling the level of spinal anaesthesia. He first introduced 'heavy' or hyperbaric solution of stovocaine in 5% glucose. Contrary Babcock of Philadelphia was the first to use the hypobaric solution. His hypobaric formula was stovaine containing alcohol, lactic acid, etc.

G Labat, in 1921 first used novocaine crystals which was dissolved in CSF for barbatose technique. In the mean time, during 1923 ephedrine was introduced in the practice of medicine and spinal anaesthesia had also gained popularity. So, ephedrine was first used to control the hypotension and to maintain the blood pressure in spinal anaesthesia in 1927.

For surgery on the head, neck and thorax spinal anaesthesia was also first used in 1909. After discovery of nupercaine in 1929, it was used as hyperbaric solution by McLelland of New York in 1930 with great success. It was partly due to the longer duration of action of it. At that time nupercaine was also used as hypobaric solution. Then gradually amethocaine (tetracaine), lignocaine and bupivacaine was used in spinal anaesthesia, shortly after their discovery.

In UK, spinal anaesthesia was under cloud for many years though it was used rampantly worldwide during that period. It was partly because of the tendency for litigation, if complication occurred. A burning example of this was the Wolley and Roe case, in early 1950, in which paraplegia had occurred followed by spinal anaesthesia in two patients, operated upon the same day. At that time, it was thought that this complication was due to the contamination of anaesthetic solution by phenol which entered the ampoles through a minute crack in the glass. But after prolonged investigation, a much more likely explanation was that the used needle and its accessories was sterilised by boiling in a steriliser which had been contaminated with acid substances, used to prevent scale formation.

In 1901, F Cathelin and A Sicard in Paris were the first to use sacral approach for the epidural space independently. This was some years before the lumbar route for the epidural space came into use. Sacral block was then employed in Germany in 1909 and was popularised by G Labat, in 1923 by his book. The use of sacral analgesia in infants was first described by Campbell in 1933. The method of continuous caudal analgesia by catheter was developed by Hingson in 1943.

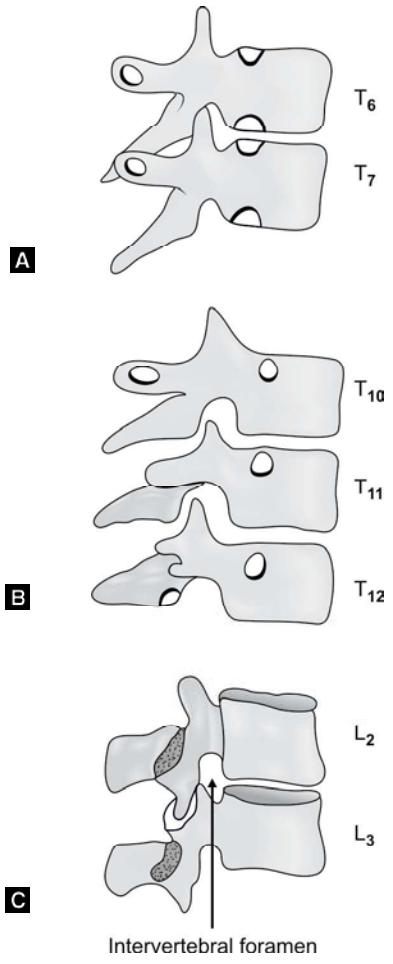
The history of lumbar epidural block is somewhat cloudy. It was not certain, whether Corning had deposited cocaine into the intradural or extradural space, in 1885. Although the interspinous approach for the epidural space has also been demonstrated at the beginning of the century, but Pages of Madrid in 1921 was the first to describe the practical application of lumbar epidural anaesthesia. Later, in 1931, Dogliotti of Italy had popularised this lumbar epidural technique. This is followed by other clinical exponents such as Hess (1934), Odom (1936), Harger and his associates (1941). Curbelo of Cuba was the first to insert a ureteric catheter into the epidural space to introduce the continuous epidural block, using the Tuohy needle. This needle was first designed for intrathecal use and later was adapted to allow the passage of smaller bore catheter. The first report of the injection of opiates into the epidural space came from Jerusalem in 1979.

INTRODUCTION

The central neuroaxial block (spinal or epidural anaesthesia) results in chemical sympathetomy, sensory block, and motor paralysis. The spinal anaesthesia is devoid of any systemic pharmacological effect of the anaesthetic drug due to its small volume. On the other hand, epidural block is not always devoid of the systemic effect of used local anaesthetic agent as it needs large volume. Both the individual spinal and epidural or continuous epidural block have their own advantages and disadvantages. But the combined spinal and epidural (CSE) anaesthesia blurs the difference between the two, covering the disadvantages of each other and added flexibility to the wide range for clinical use.

Cocaine was the first drug used in spinal anaesthesia. But Gorton had first promoted the high spinal anaesthesia for head and neck surgery. However, Koster first used total spinal block for intrathoracic and intracranial procedures (Figs 24.3A to C).

In previous days, spinal block was also used for medical therapy, e.g. pulmonary



Figs 24.3A to C: A. Lateral view of 6th and 7th thoracic vertebrae, B. - Lateral view of 10th, 11th and 12th thoracic vertebrae, C - Lateral view of 2nd, 3rd lumbar vertebrae

oedema due to its hypotensive effect. During that period anaesthesiologists continued to face the confusion regarding the balance between the risks and benefits of spinal anaesthesia, especially those involving continuous spinal anaesthesia or the use of 5% xylocaine. In USA, the FDA withdrew the very fine spinal catheter and 5% xylocaine due to the perceived association between them and cauda equina syndrome. It seems likely that more spinal and epidural block have failed due to inadequate IV sedation and anxiolysis, rather than due to the technically flawed blocks. The continuous epidural block for the postoperative analgesia decreases the length of hospital stay and allows the more efficient use of ever increasingly stretched health care service. There is a common believe that in epidural block there is less reduction of BP and is slower in onset. But, this is not always correct. Ephedrine which is used to check the hypotension due to regional anaesthesia is a mixed adrenergic agonist and is preferred than a pure adrenergic agonist. Gradually the days are coming, when the infusion of large amount of crystalloid solution as preload to minimise the spinal or epidural hypotension should be rethinked. Sometimes, during epidural anaesthesia due to large amount of drug, the level of anaesthetic agent in blood may reach a concentration (toxic level) which is sufficient enough to produce the systemic effects.

ANATOMY

In the vertebral column multiple vertebrae are arranged in a column. So, it is thus named. The vertebral column consists of 23 fibrocartilaginous discs and 33 vertebrae of which 7 are cervical, 12 are thoracic, 5 are lumbar, 5 are sacral and 4 are coccygeal. The cervical, thoracic and lumbar vertebrae are called the free vertebrae and each of them presents regional characteristics. On the otherhand, the next sacral and coccygeal vertebrae are called the fixed vertebrae. This is because the five sacral vertebrae are fused to form the sacrum and the four rudimentary coccygeal vertebrae are united to form the coccyx (Fig. 24.4).

Functions of the vertebral column are:

i. Support of trunk.
ii. Transmission of body weight.
iii. Protection of spinal cord, spinal nerves, and its menings.
iv. Attachment of muscles and ligaments for various movements of the trunk.

There is very slight movement between the two adjacent vertebrae. But a very wide range of movements of vertebral column are possible when the entire column and the small movement between the two vertebrae are considered as a whole.

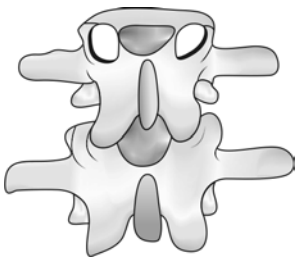


Fig. 24.4: Lumbar vertebrae and its posterior view

The Parts of Vertebra

1. Body

The body of a vertebra transmits body weight and is connected to the bodies of adjacent upper and lower vertebrae by the intervertebral discs, forming the secondary cartilaginous joints. The body of a vertebra is enclosed by a shell of compact bone, except at the upper and lower surfaces, where it is composed of spongy bone and is covered by a plate of a hyaline cartilage. The front and sides of the body of a vertebrae are somewhat concave in shape and pierced by blood vessels. The posterior surface of the body of a vertebra presents one or more centrally placed basivertebral formina, through which the basivertebral vein and some nutrient arteries pass. Along the entire mobile part of the vertebral column, the anterior and the posterior surfaces of the body of each vertebra are connected respectively by the continuous flow of anterior and posterior longitudinal ligaments of which the anterior ligament is stronger than the posterior (Fig. 24.5).

2. Vertebral arch

It is situated behind the body of each vertebra and is composed of 2 pedicles and 2 laminas. This predicle and lamina of each side of a vertebra joins together posteriorly at the midline to form a vertebral arch which forms the boundary of vertebral foramen laterally and posteriorly. This vertebral foramen is also bounded anteriorly by the posterior surface of the

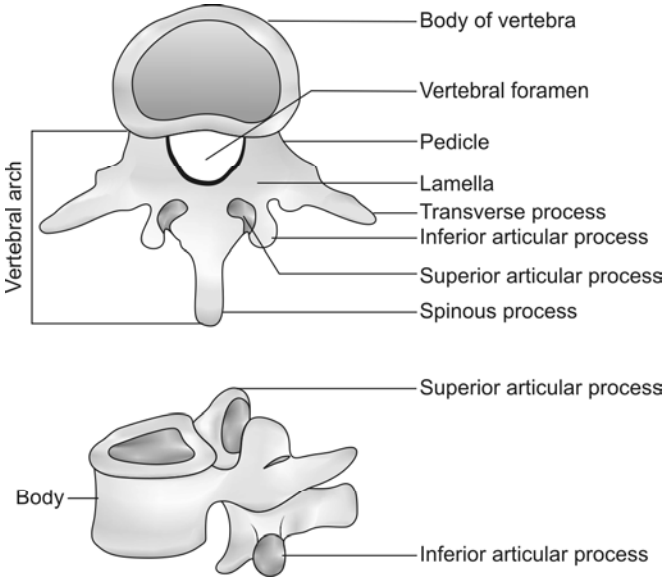


Fig. 24.5: Typical lumbar vertebra

body of respective vertebra. Thus, both the body and vertebral arch complete a vertebral foramen. The vertebral forminas of the adjacent upper and lower vertebrae join continuously to form a vertebral canal for the lodgement and protection of spinal cord, spinal nerve, its meninges and CSF. In the cervical region, the vertebral canal is triangular in shape and more roomy for the accommodation of cervical enlargement of spinal cord. However, in the thoracic region, the vertebral canal is comparatively smaller and circular. In the lumbar region this vertebral canal is again some how more larger and triangular in shape to accommodate the lumbar enlargement of the spinal cord. In adults the spinal cord ends usually at the level of the lower border of L_1 vertebra and the subdural and the subarachnoid spaces (containing CSF) end at the level of S_2 vertebra. After the end of the spinal cord the vertebral canal contains a bunch of spinal nerves called the cauda equina and a non-nervous pial thread known as the filum terminale interna. This pial thread (filum terminale interna) is nothing but the continuation of the pial membrane as a thread after the end of the spinal cord.

An area called the epidural space (or extradural space) intervenes between the periosteum of vertebral canal and the dura mater, covering the spinal cord. This epidural space extends from the foramen magnum above to the sacral hiatus below and contain loose fibro fatty tissue with valveless internal vertebral venous plexus. This epidural space is also traversed by the roots of spinal nerves with their covering meningeal sheaths after coming out from the spinal cord and crossing over the subarachnoid space. Two deficiencies are present at the lateral and posterior walls of the vertebral column. The former is being the inter vertebral foramen and the later is being the interlaminar foramen.

3. Pedicle

Each pedicle springs from the posterolateral surface of the vertebral body, and is situated at somewhat midway between its upper and lower surfaces. It projects backward with slight lateral inclination. Each pedicle is grooved above and below and is called as the superior and inferior vertebral groove or notch, respectively. Inferior groove is more deeper than the superior. Each groove together with the groove of the pedicle of the vertebra above and below form the intervertebral foramen. Thus, each intervertebral foramen is bounded above and below by the pedicles of the adjacent vertebrae, behind by the interarticular joint, and in front by the lower part of the body of upper vertebra and the intervertebral disc. The intervertebral foramina are smallest in the cervical and upper thoracic regions. It gradually increases in size and becomes largest in relation to the 5th lumbar vertebra. Along with the gradual increase in size of the intervertebral foramina, the thickness of the spinal nerves are also increased in craniocaudal direction. So, the lower lumbar nerves are more vulnerable to compression within the intervertebral foramina (Fig. 24.6).

The intervertebral foramen contains (a) both the ends of the anterior and posterior nerve root with dorsal root ganglia, (b) the beginning of mixed spinal nerve, (c) the beginning of two rami of spinal nerve – anterior and posterior, (d) a spinal artery, and (e) an intervertebral vein. In cervical region the superior vertebral notches transmit the numerically corresponding cervical nerves and the inferior notches transmit the immediately succeeding cervical nerves. But in rest of the vertebral column, however, the superior notches transmit the immediately precceding spinal nerves and the inferior notches are occupied by the numerically corresponding spinal nerves.

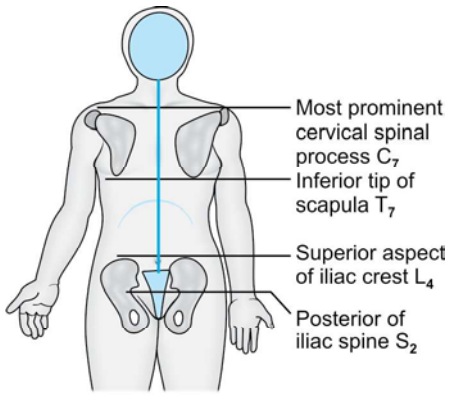


Fig. 24.6: The surface landmarks for identifying the spinal vertebral levels

This is because cervical vertebrae are seven in number, whereas the cervical spinal nerves are arranged in eight pairs.

4. Lamina

The each lamina arises from the dorsal or posterior end of the each pedicle. Then, it passes medially and backwards and fuses with the fellow of the opposite site at midline. From the fused laminae an elongated spinous process projects backward with a slight downward inclination. The laminae of the adjacent vertebrae are connected by a series of fibroelastic membrane called the ligamentum flavum. In the mid thoracic region the laminae partially overlap with one another. The space between the laminae of two adjacent vertebrae and the interarticular joint is called the interlaminar foramen. So, the interlaminar foramen is bounded above and below by the adjacent laminae and at the sides by the inner aspect of articular process of the vertebra of above and below. During the extension of vertebral column it is small, but during flexion it enlarges and provides an access to the spinal or epidural needle (Fig. 24.7).

5. Processes

They are 7 in numbar, such as 2 transverse, 1 spinous and 4 articular arising from each vertebra. The transverse and spinous processes give attachment to the different ligaments and muscles acting on the vertebral column.

Transverse process

The transverse process project laterlly from each side of the vertebral body at the junction of pedicle and lamina. In cervical vertebrae the transverse processes present a foramen, called the foramen transversarium which transmits: the 2nd part of vertebral artery (except in the seventh cervical vertebra), a plexus of vertebral veins and a plexus of sympathetic nerves. In thoracic vertebrae the transverse processes present a costal facet (except the last two thoracic vertebrae) on its anterior surface close to the tip for articulation with the tubercle of numerically corresponding rib, forming costotransverse joint. In lumbar vertebrae the transverse processes are relatively slender. The transverse processes of all the free vertebrae are connected to one another by inter transversus muscles. In some regions these transverse processes give attachment to erector spinae and paravertebral group of muscles which help in flexion, extension and rotation of the trunk.

Spinous process

The unpaired spinous process of each vertebra projects generally backwards in the midline from the fused laminae of both sides. In the cervical region these spines are horizontal, short and present a bifid tip, except the 2nd and 7th cervical spine which are elongated and prominent. The 7th cervical spine is called the cervical prominence. The tip of the spinous process of cervical vertebrae are connected to

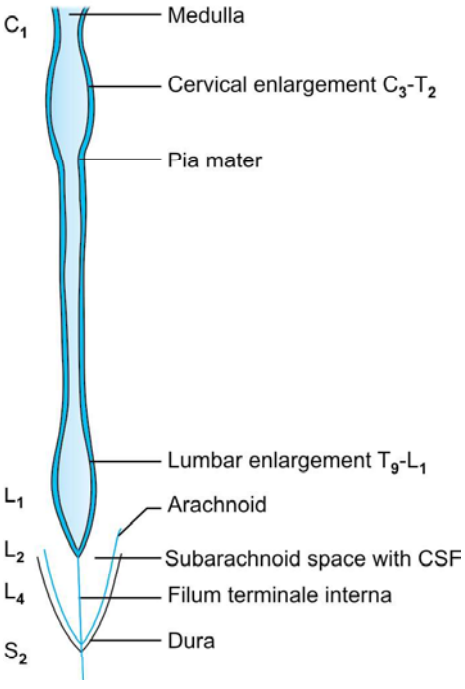


Fig. 24.7: Important vertebral levels in relation to the spinal cord. Blue covering is the pia mater, black covering is the arachnoid mater and red covering is the dura mater

one another and to the external occipital crest (with its protuberance) by a fibrous band, called the ligamentum nuchae. This ligamentum nuchae at its lower end is attached to the C_7 spinous process. The the thoracic spines are more elongated with pointed tips and is inclined backwards and downwards. The first four thoracic spines slope obliquely downwards but does not overlap on one another. While the fifth to eighth thoracic spines overlap on one another. The lower four thoracic spines from eighth to twelveth are almost horizontal. The lumbar spine are broad, quadrilateral and horizontal in direction. All the thoracic and lumbar spines are connected to one another by the interspinous ligament along their shaft and supraspinous ligament along their tip. They also provide attachments to the posterior layer of thoracolumbar fascia and extensor muscles of the trunk. Since, considerable spaces are available in the interval between the horizontally directed lumbar spines, so the spinal or epidural anaesthesia is often made through the lumbar puncture. This lumbar subarachnoid puncture is usually performed distal to the caudal end of spinal cord (below L_1) to avoid its injury.

Articular process

There are 4 articular processes arising from each vertebra. Among these each pair of superior and inferior articular processes project respectively above and below from the junctions of pedicles and laminae. These articular process are meant for articulation with the vertebra immediately above and of a particular vertebra of a particular vertebra. When viewed from behind, it is shown that the vertebral spines occupy the median plane and the two vertebral grooves, each lie lateral to the spines. Bilateral vertebral grooves are occupied by the deep extensor muscles of the back. In the cervical and the lumbar regions the grooves are shallow and formed by the laminae. In the thoracic region they are deep, wide and formed by the laminae and transverse processes also.

Some landmarks of vertebral column are:

i. T_3 spine corresponds with the level of scapular spine.
ii. T_7 spine coprresponds with the inferior angle of scapula.
iii. L_4 spine corresponds with the summits of iliac crest (useful for lumbar puncture).
iv. S_2 spine corresponds with the posterior superior iliac spine (end of the spinal subarachnoid space).
v. The upper end of the natal cleft between the two buttocks corresponds with sacral hiatus useful for sacral epidural anaesthesia.

Ligaments

The vertebrae are hold together by a series of overlapping ligaments. These ligaments not only bind the vertebrae together, but also assist in protecting the spinal cord. These ligaments are:

(i) Anterior and post longitudinal ligaments

It runs in front and behind of the bodies of vertebra, extending from the axis or second cervical vertebra to the sacrum.

(ii) Ligamentum flavum

As this name says, it is made up of yellow elastic fibres. Above, it is attached above to the anterior and inferior aspect of the lamina of the upper vertebrae and below it is attached to the superior and posterior aspect of the lamina of the lower vertebrae. It blends medially and posteriorly with the interspinous ligaments and the ligamentum flavum of the opposite side. Laterally and anteriorly it blends with the capsule of interarticular joint of that side.. It is thinnest at the cervical region and thickest at the lumbar region. These ligaments are muscle sparers and assist in straightening of the vertebral column after bending forward. It also helps in maintaining the erect posture of body. It comprises half of the total length of the posterior wall of vertebral column (Table 24.1).

Table 24.1: Characteristics of ligamentum flavum at different level of vertebral column

Site of vertebral column	*Distance from skin to ligament (cm)*	*Thickness of ligament (mm)*
Cervical	2 - 3	2 - 3
Thoracic	3 - 5	3 - 5
Lumbar	3 - 8	5 - 6

(iii) Interspinous ligaments

It extends forwards from the tip of spinous process where it fuses with supraspinous ligaments to the point where the two laminae of opposite sides fuses in the midline. Here it blends with the ligamentum flavum. Above it is attached to the inferior border of spine of the upper vertebra and below is attached to the superior border of spine of the lower vertebra. In the lumbar region it is most wide and dense.

(iv) Supraspinous ligament

It extends from the tip of the 7th cervical spine to the sacrum joining the tip of all the thoracic and lumbar spinous processes. From 7th cervical spine and above it is continuous with the ligamentum nuchae. It is thickest and widest in lumbar region.

Curvature of Vertebral Column

There are 4 curvatures in the vertebral column – two concave ventrally one at thoracic and one at sacrococcygeal regions, and two concave dorsally one at cervical and one at lumbar regions. Thoracic and sacral curvatures are the remnants of flexion attitude of the foetus in uterus. So, they are called the primary curvature. Whereas the cervical curvature appears after birth when the child lifts his head and lumbar curvature appears at the end of 1st year when the child learns to stand. So, they are called the secondary curvatures. The cervical and the lumbar curvatures (secondary curvature) are caused by the inequal thickness of the intervertebral discs (thicker anteriorly) and the primary curvatures are caused by the bony configuration. The accentuated pathological ventral concavity of vertebral column at the thoracic region is called the Kyphosis and the accentuated dorsal concavity at the lumbar region is called the lordosis. Scoliosis is the exaggerated form of lateral curvature of the vertebral column. The cervical curvature extends from the atlas to the 2nd thoracic vertebra. The thoracic curvature extends from the second to the twelfth thoracic vertebrae. The lumbar curvature extends from the L_1 to L_5 vertebra and the pelvic curve or the sacrococcygeal curvature extends from the lumbosacral joint to the tip of the coccyx and faces downwards and forwards.

Intervertebral Disc

The intervertebral discs connect the upper and lower surfaces of the adjacent vertebral bodies and is present from axis (2nd cervical vertebra) to sacrum. They actually intervene between the plates of hyaline cartilages which cover the upper and lower surfaces of the adjacent vertebral bodies. Each intervertebral disc is made up of a central gelatinous part, called the nucleus pulposus and a peripheral fibrocortilaginous part, called the annulus fibrosus. It accounts for 1/4 to 1/5th of total length of the vertebral column. It is thicker at cervical and lumbar region where the vertebral column needs more mobility and is thinner at thoracic region where the vertebral column needs less mobility. In cervical and lumbar regions it is more thickened anteriorly than posteriorly. So it also gives rise to the ventral convexity of vertebral column. It also functions as a shock absorber when placed between the two vertebral bodies and connects the vertebrae strongly. The intervertebral disc also provides resiliency to the vertebral column and ensure even distribution of compressive forces on the upper and lower surfaces of the bodies. If during spinal block, the needle hits the annular fibrosus, then the nucleus pulposus may prolapse through it and may cause sciatica (Fig. 24.8).

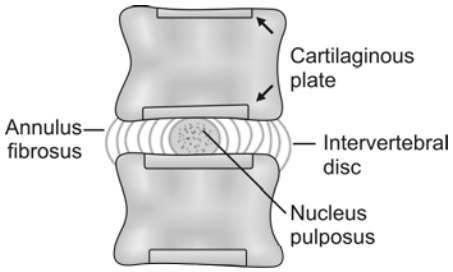


Fig. 24.8: Intervertebral disc

The annulus fibrosus is composed of a series of concentric laminae of fibres. These fibres in each lamina of annulus fibrosus are arranged in parallel to each other, but run obliquely between the body of two adjacent vertebrae. The posterior fibres of the laminae are predominantly vertical which predisposes to herniation of nucleus pulposus. The peripheral fibres of the annulus fibrosus consists of collagenous tissue and the inner fibres are made of fibrocartilages which blend with the nucleus pulposus without any demarcation. At the front and behind of the vertebral bodies the annulus fibrosus blends with the anterior and posterior longitudinal ligaments respectively. Some fibres sink deeply into the bone and the others are attached to the epiphyseal ring of the vertebral bodies.

The nucleus pulposus is a gelatinous mucoidal mass containing abundant water, cartilage cells and a few multinucleated notochordal cells in children. In young persons the water content of the nucleus pulposus is about 90%. This produces great turgor or fullness of the disc. In healthy young adults, the intervertebral discs are so strong that the vertebrae may break before the discs are ruptured during a fall. By the end of the first decade, the notochordal cells disappear and the mucoidal materials are replaced by fibrocartilage. The water content of the discs also diminishes with the advancement of age.

The contents of vertebral canal from outwards to inwards are:

i. Epidural space (or extradural space),
ii. Spinal dura mater,
iii Subdural potential capillary space,
iv. Arachnoid mater,
iv. Subarachnoid space with (CSF),
v. Pia mater (arachnoid and pia together from leptomenings),
vii. Spinal cord, spinal nerves and cauda equina.

Epidural Space (Extradural Space)

It is a space between the spinal dura mater and the periosteum of vertebral bone which is also called the periosteal dura. Therefore, it is bounded on one side by the spinal dura mater and on another side by the bodies of vertebrae with posterior longitudinal ligament (anteriorly), pedicles and intervertebral foramen (laterally), lamina and ligamentum flavum (posteriorly). Superiorly, it is closed by the fusion of the spinal dura mater with the periosteum of the skull and the vertebral bone (periosteal dura) at the foramen magnum. The periosteum of the vertebral canal is nomenclatured as the periosteal dura and the true dura mater of spinal cord is known as the spinal dura. As the spinal dura mater extends only up to the S_1 level inferiorly, so the subarachnoid space extends up to that level, but the epidural space is extended beyond that up to the sacral hiatus where it is closed by sacrococcygeal ligament (Fig. 24.9).

Through the intervertebral foramen epidural space communicates with the paravertebral space outside the vertebral canal. The fibrous strands, anchoring the spinal dura mater posteriorly with the periosteum partly divide the epidural space into two half in the midline. Actually in undisturbed

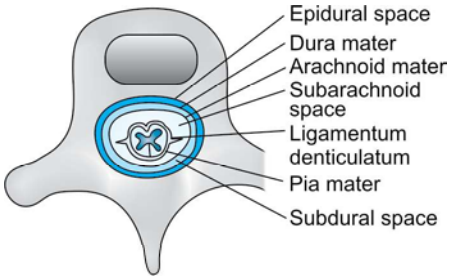


Fig. 24.9: Relationship of spinal cord to the meninges and vertebra

state the epidural space is a potential one with some loose areolar tissue in the midline and the epidural venous plexus by the side of the midline. The spinal dura or the investing layer of dura is in contact with the ligamentum flavum (where periosteum is absent) or with periosteum (where bone is present) but is not adhere to it. After an inflammatory disease, the spinal dura is adhered to the periosteum (periosteal dura) of vertebral bone and the epidural space is oblitered. When an epidural needle passes through the ligamentum flavum the blunt edge of the needle can contact with spinal dura and push it away. Thus, pushing away the spinal dura from the periosteum or periosteal dura creates a negative pressure which can be used to verify the placement of the needle in the epidural space. It also creates a space which can accept the local anaesthetic agent or a catheter. The epidural space at each vertebral level must be filled with local anaesthetic agent to ensure a complete anaesthesia while the general rule is that 1 ml of anaesthetic agent is required for each vertebral segment. But the range for a normal human being is wide which may vary from 0.8 to 2 ml for each segment while a catheter with a titrated dose is most commonly used.

The contents of epidural space are:

i. Loose areolar tissue,
ii. Liquid fat,
iii. 31 pairs of spinal nerve with their dural cuff on their way to intervertebral foramen,
iv. Sacral and coccygeal nerves,
v. Spinal arteries, arising from different sources at different levels enter the epidural space through the intervertebral foramen and supply the spinal cord, spinal nerves, meninges, periosteum and ligaments.
vi. Vertebral venous plexus: It forms a network of veins running vertically in epidural space. It can be divided into the anterior venous plexuses and

the post venous plexus. The anterior venous plexus lies anteriorly on the other side of midline and basivertebral veins empty into it. The posterior venous plexus lie posteriorly on other side of the midline. These venous plexuses communicate above with the intracranial venous sinuses and below with the pelvic, portal and caval system of veins. They also connect with the intervertebral veins which pass out through the intervertebral foramina and so communicate with the vertebral ascending cervical, deep cervical, intercostals, iliolumbar and lateral sacral veins. These venous plexuses have no valves. So, these epidural veins become distended during coughing, straining, pregnancy, etc. when the venous pressure rises. Through the valve less veins blood also can flow in opposite direction during increased intrathoracic and intra-abdominal pressure.

Meninges

The brain and the spinal cord are enveloped by three connective tissue membranes which are called meninges. These are named from outside inwards as dura mater, arachnoid mater and pia mater. The space outside this dura mater is called the epidural space. It is bounded between periosteum where bone (lamina) is present and ligamentum flavum where bone is not present on one side and and the dura mater on another side. A potential subdural space which is filled with a capillary layer of fluid, intervenes between the dura mater and the arachnoid mater. A subarachnoid space appears between the arachnoid mater and the pia maters and is filled with the CSF. In some parts of the brain and spinal cord, the subarachnoid space is significantly enlarges forming the cisterns. These three meninges primarily support and protect the soft tissues of the brain and spinal cord. Hence, they are surnamed by the word 'mater' which means mother for protection (Fig. 24.10).

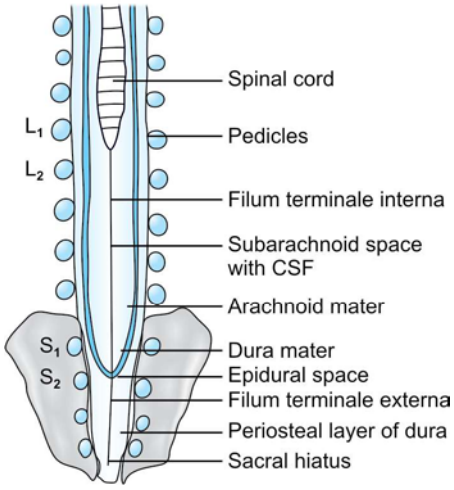


Fig. 24.10: Diagrammatic longitudinal section through the lower end of the vertebral column

Dura mater

It is a thick, fibrous and non-elastic membrane. In the cranial cavity the dura mater is arranged in two layers called the periosteal and the investing layer. Here, the periosteal layer of the dura mater represent the inner periosteum layer of the skull bones and adhere firmly with the investing layer of the dura mater, except where they split to enclose the venous sinuses of cranium. So, in the cranial cavity there is no epidural space (as the periosteal and investing layer adhere firmly). In the vertebral column, this periosteal layer of dura mater represent the inner periosteum layer of the bony part of the vertebral canal and the investing layer represent the dura mater of the spinal cord or spinal dura mater and the space between them is called the epidural space. The investing layer of dura is continued from the cranium into the vertebral canal as spinal dura, but is firmly adhered at the margins of the foramen magnum with the periosteal layer. Hence, the epidural space of the vertebral column is closed above at the level of the foramen magnum and local anaesthetic solution deposited in epidural space of vertebral canal can never enter into the cranial cavity. Below, the investing layer of dura or spinal dura mater ends with the arachnoid mater as a tube at the level of the 1st or 2nd sacral vertebra, so that CSF is not found below this level. At S_2 level the investing layer of dura or spinal dura mater ends with arachnoid mater by giving an covering layer to the filum terminale interna. This filum terminale interna is now known as the filum terminale externa with the coverings of dura and arachnoid mater and goes down to blend with the periosteum on the back of coccyx. The anterior and the posterior nerve roots, issuing from the spinal cord pierce the dura and carry a tubular prolongation of dural sheath (dural cuffs) which blends ultimately with the perineurium of mixed spinal nerve. In the vertebral canal the spinal dura is loosely attached anteriorly by fibrous stands to the posterior longitudinal ligaments and thus anchors its place anteriorly. Similarly, it is loosely attached posteriorly by fibrous strands to the vertebral arch and thus anchors its place posteriorly.

Arachnoid mater

The word arachnoid mater owes its name from the Greek word 'arachnes' which means a spider. In the cranial cavity and vertebral canal this meningeal layer is so named, because the numerous spider like trabeculae extend between the arachnoid and the pia mater. It does not follow the pia mater so intimately to line the every indentation of the brain and spinal cord which the pia mater does. The arachnoid mater is a thin, delicate and transparent structure. It constitute the middle of the three investing membranes (dura, arachnoid and pia), covering the brain and spinal cord. Spinal arachnoid mater is the continuation of the cerebral arachnoid mater and closely applied (but not yet attached) to the dura. The subdural space (between dura and arachnoid) is a potential capillary interface, containing little serous fluid, but not the CSF and possibly such a thin film of fluid exerts a negative force of traction which prevents the arachnoid mater from projecting inwards. The space between

the arachnoid mater and the pia mater is called the subarachnoid space and contain CSF. It is divided by an incomplete mid-line septum along the dorsal surface of the cord. The arachnoid mater is adhered (but not applied) to the dura only where some structures pierce both the membranes and where the ligamentum denticulata is attached to the dura.

Pia mater

It is made of two layers: (a) the outer epi-pia layer containing large blood vessels, and (b) the inner pia – intima layer (or pia-glia) lying in close contact with the nervous tissue. The blood vessels run between these two layers of pia mater. The epi-pia layer is lined by the flattened mesothelial cells and is connected to the overlying arachnoid mater by a number of trabeculae. The blood vessels extend through these trabeculae from the arachnoid mater to the pia mater and ramify between the epi-pia and pia-glia layer. The intercommunicating space around the arachnoid trabeculae (i.e. subarachnoid space) contains the CSF. The pia intima or pia-glia layer covers intimately the surfaces of the brain tissue and spinal cord. It consists of mesothelial cells held in a mesh work of reticular, elastic and collagen fibres and rests on a basement membrane which is lined internally by the foot plates of the astrocytes. Posteriorly the pia mater is adherent to the posterior median septum of the spinal cord and is also connected to the arachnoid mater by a fenestrated subarachnoid septum. Anteriorly the pia mater is folded into the anterior median fissure of the spinal cord. On each side, between the ventral and dorsal root of spinal nerve, the pia mater form a narrow vertical ridge with tooth like processes, projecting from its lateral free border. This is called the ligamentum denticulatum and attached through the arachnoid to the dura mater between the two roots of spinal nerves. These processes help to suspend the spinal cord in the middle of the subarachnoid space. The blood vessels going to the brain and spinal cord lie in the subarachnoid space before piercing the pia. They carry with them a sleeve of pia mater in the brain tissue and spinal cord.

Filum terminale (FT)

It starts as a thread like structure at the level of L_1 or L_2 vertebra from the terminal end of spinal cord (conus medullaris) and is named as FT interna. Filum terminale interna is composed of only pia mater and its length is of 15 cm. It then end by piercing the dura and arachnoid at the level of S_2 vertebra and continues below as the filum terminale externa, which ends eventually by blending with periosteum at the back of coccyx. FT externa is 5 cm in length and is composed of dura, arachnoid and pia mater.

SUBARACHNOID SPACE

It is a CSF filled wide space lying between the pia and arachnoid mater and surrounds the entire CNS like water bath. The spinal subarachnoid space is wider than its cerebral counter part. In spinal canal it is widest below the L_1 vertebra where spinal cord ends and continues as cauda equina (Fig. 24.11).

Cerebrospinal Fluid (CSF)

CSF is a clear, colourless liquid with pH of 7.4. Average volume of CSF in adult is near about 135 ml, of which 35 ml is in the ventricule, 25 ml is in the cerebral subarachnoid space and 75 ml is in the spinal subarachnoid space. Choroid plexus in the ventricles secrets CSF at a rate of 0.3 to 0.4 ml/minute. The normal glucose content of CSF is 2.5 to 4.4 mmol/litre (45 to 80 mg/dl) and protein content is 20 mg/dl. The normal albumin and globulin ratio in CSF is 1:1. After spinal anaesthesia the albumin level in CSF rises and becomes double of the normal value on the 18th day. The normal CSF pressure varies from 70 to 180 mm of H_2O in lateral position to 375 to 550 mm of H_2O in vertical posture. During epidural anaesthesia the increased pressure in the epidural space is transmitted to the subarachnoid space and hence the sensation of dizziness is felt by the patient. The specific gravity of CSF at body temperature, compared to water is 1.007. Whereas the specific gravity of 10% dextrose which is commonly used to make the anaesthetic solution hyperbaric is 1.034.

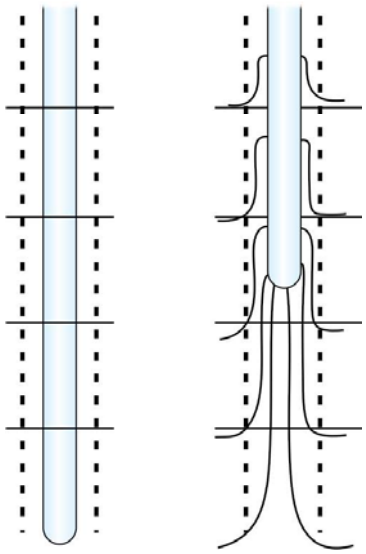


Fig. 24.11: The effect of recession of the spinal cord, during development, on the course of the spinal nerves

SPINAL CORD

The spinal cord as a part of CNS is a continuation of brain. It is an elongated and cylindrical neural structure and is contained within the upper two-third of the vertebral canal. Although cylindrical, it is some what flattened ventrodorsally. It retains actually the primitive form of CNS which is present in all the animals. The spinal cord is mainly concerned with the reception of different modalities of sensory impulse, integration and association of these information, and production of reflex response of basic characters. It is the direct continuation of medulla oblongata of brain. Spinal cord

begins at the upper border of atlas and ends, in adult, as a conical structure named conus medullaris at the level of the lower border of L_1 vertebra or upper border of L_2 vertebra. The apex of conus meduladris is continued down as filum terminale interna.

The length of a spinal cord is 42 to 45 cm in an adult. Sometimes, it extends up to the second or even, more rarely, up to 3rd lumbar vertebra. In newborn the spinal cord extends up to the 3rd lumbar vertebra and in foetal life the cord extends the entire length of the vertebral canal. At the third month of foetal life, the length of the spinal cord is as long as the vertebral canal and each spinal nerve arises from the cord at the level of the corresponding intervertebral foramen. During subsequent development the spinal cord does not grow as fast as the vertebral column. Therefore, the lower end of the spinal cord gradually ascends to reach the level of the third lumbar vertebra at the time of birth, and the lower border of the first lumbar vertebra in the adult. As a result of this relative upward migration of the spinal cord, the roots of the spinal nerves have to follow an oblique and downward course to reach the appropriate intervertebral foramen. This obliquity is most marked in the lumbar spinal nerves and many of these roots occupy the vertebral canal below the level of the spinal cord. So, below the 1st lumbar vertebra the vertebral canal is occupied by the leash of lumbar, sacral and coccygeal spinal nerve roots, termed the cauda equina. Another result of this upward recession of the spinal cord is that the spinal segments do not lie opposite to the corresponding vertebrae. In estimating the position of spinal segment in relation to the surface of the body and spine of vertebra, it is found that the later is always lower than the corresponding spinal segment. As a rough guide, it may be stated that in the cervical region there is a difference of one segment (e.g. the 5th cervical spine overlies the 6th cervical spinal segment), in the upper thoracic region there is a difference of two segments (e.g. the 4th thoracic spine overlies the 6th thoracic spinal segment), in the lower thoracic region there is a difference of three segments (e.g. the 9th thoracic spine lies opposite the 12th thoracic spinal segment). The spinal cord has two enlargements cervical and lumbar, corresponding to the increased nerve supply to the upper and lower limbs. The cervical enlargements extends from C_3 to T_2 spinal segment and the lumbar enlargement extends from T_9 to L_1 spinal segment.

Blood Supply (Fig. 24.12)

The spinal cord is mainly supplied by two posterior and one anterior spinal arteries. The posterior spinal artery, one on each side of the midline, arises from the posterior inferior cerebellar arteries at the base of the skull. It supplies the posterior horn and the posterior columns and is reinforced by the numerous posterior radicular arteries arising from the ascending cervical artery, deep cervical artery, intercostal artery and the lumbar artery. The single anterior spinal artery arises by the union of two small branch each of which arise from each vertebral artery at the level of the foramen magnum (Fig. 24.13).

The reinforcement of anterior spinal artery is few and irregular. But, one radicular artery, reinforcing the anterior spinal artery at the level of T_{11} segment,

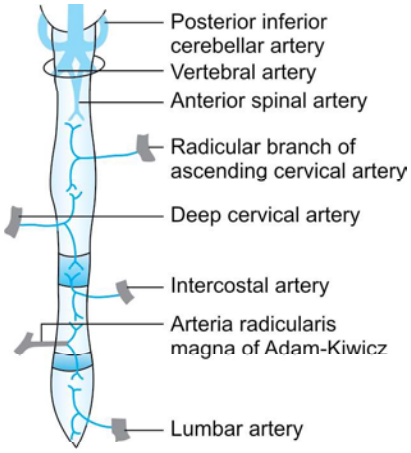


Fig. 24.12: Anterior arterial trunk of the spinal cord

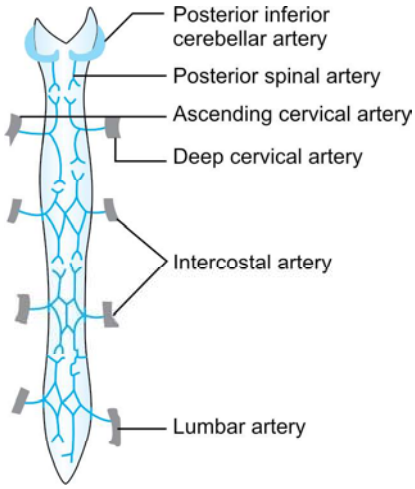


Fig. 24.13: Posterior arterial trunk of the spinal cord

supply the lumbar enlargement of the cord and is constant. This is called the radicular magna or artery of Adam-Kiewiez. Anterior spinal artery supplies the anterior and the lateral columns of white matter and most of the grey matter. The anterior and posterior spinal arteries do not anastomose with each other and thus creates three distinct vascular areas of the cord, with no anastomoses between them. Hence, this arrangement make the cord more prone to the damage by hypotension, thrombosis, vasoconstriction, aortic clamping, etc. (Fig. 24.14).

Anterior spinal artery syndrome

It is due to the thrombosis of anterior spinal artery and is manifested as paraplegia, but the retention of sensation of post column

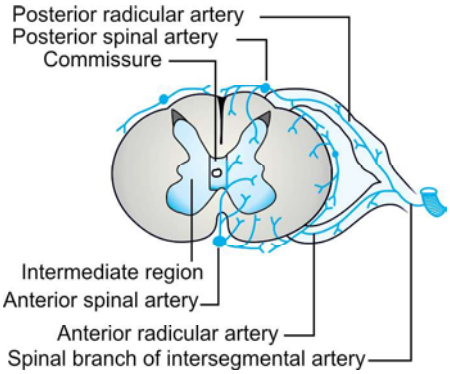


Fig. 24.14: Arterial supply of the spinal cord

which includes joint position, vibration, pain, touch, etc.

Venous drainage of spinal cord

It is done by anterior and post venous plexuses which again drain through the intervertebral foramina into the vertebral, azygos and lumbar veins. The normal intraspinal capillary pressure is 30 mm of Hg. Deprivation of blood supply for 2 minutes may result in infarction of cord.

SPINAL NERVES

The spinal cord gives attachment on either side of it to a series of 31 pairs of spinal nerves. These are 8 cervicals, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal. Each spinal nerve arises from spinal cord by two roots—anterior (or ventral) and posterior (or dorsal). Again each nerve root is formed by the aggregation of a number of rootlets that arise from the cord over a certain length. The length of the spinal cord, giving origin to the rootlets for one spinal nerve constitutes one spinal segment. So, the spinal cord is made up of thirty one such segments: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and one coccygeal. The anterior or ventral roots contain motor fibres (both intrafusal and extrafusal) to the skeletal muscles of trunk and limbs and in some places preganglionic autonomic sympathetic (motor) fibres to the glands, smooth muscles of internal organs and blood vessels. The dorsal or posterior or sensory roots convey the sensory fibres from the peripheral general exteroceptive receptors of the internal organs, skin and subcutaneous tissues carrying sensation of pain, temperature, touch, pressure, etc. and general proprioceptive sensations from the muscles, bones and joints. Some fibres convey, in addition, general visceral sensations including visceral pain from internal organs and blood vessels (Fig. 24.15).

Both the roots of spinal nerve receive a tubular prolongations from the spinal menings and enter the corresponding

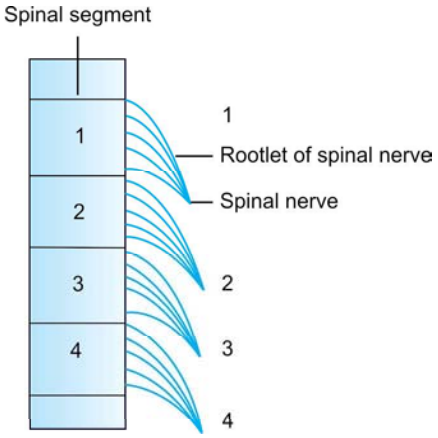


Fig. 24.15: Scheme to illustrate the concept of spinal segment and spinal nerve

intervertebral foramen. There they unite to form the mixed spinal nerve trunk. Just before joining with the ventral root, the dorsal root presents a spinal ganglion (dorsal root ganglion) which usually lodges in the corresponding intervertebral foramen. After coming out of the spinal cord and piercing the pia mater within the vertebral canal, the spinal nerve roots run in the subarachnoid space and carry a sleeve of CSF within the tubular prolongation of meninges (arachnoid mater and dura mater) up to the intervertebral foramen where they pierce the arachnoid and dura mater. After piercing the arachnoid and dura mater in the intervertebral foramen, when the spinal nerves come out, then the arachnoid covering blends with the perineurium and the dura mater with the epineurium of the spinal nerves. Each spinal ganglion which is present on the dorsal root contains 50,000 to 1,00,000 unipolar neurones. The axon of each neurone of the spinal ganglion sends a peripheral process into the mixed spinal nerve which carry the sensory impulses from the periphery and a central process into the dorsal horn of spinal cord through the dorsal root. It is roughly estimated that the number of sensory fibres in a dorsal nerve root is about 50,000 to 1,00,000 whereas the motor fibres in the ventral nerve root is about 5000. In more than half of the population, the first cervical and the coccygeal spinal nerve present no dorsal root.

The upper seven cervical spinal nerves leave the intervertebral foramina above the pedicles of the respective vertebrae. The eighth cervical nerve emerges below the pedicles of the 7th cervical vertebra. Then, eventually all the thoracic, lumbar and sacral spinal nerves emerge below the pedicles of the corresponding vertebrae. Due to the cranial shift of spinal cord during development with increased age, the spinal nerve roots become progressively oblique from above downwards. In the lumbosacral regions, the roots of the spinal nerve descends almost vertically and form a bunch of nerves, known as the cauda equina. It is so named because it resembles to the tail of a horse. This cauda equina is formed around the non-nervous pial filament called the filum terminale interna by the roots of five pairs (below L_1 or L_2) of lumbar, five pairs of sacral and one pair of coccygeal spinal nerves.

After emerging from the intervertebral foramen each mixed spinal nerve divides immediately into the dorsal and ventral primary rami. Each ramus receives fibres from both the roots, i.e. each ramus has both the sensory and motor fibres. Immediately after division, the dorsal primary ramus passes backwards and supplies the muscles and the skin of the back. It is to be noted that the C_1 nerve has no cutaneous branch and the dorsal rami of C_7, C_8, L_4 and L_5 nerves do not supply the skin. In the neck the dorsal ramus supplies the splenius muscle and the other muscles deep to it. After piercing and supplying the muscles, the dorsal ramus again divides into medial and lateral branches to supply the skin segmentally. In general, the extensor muscles of the vertebral column (motor), the scalp and the varying extent of skin over these muscles (sensory) are supplied by the dorsal ramus.

The ventral ramus supplies the prevertebral flexor group of muscles of the neck and trunk, the muscles of the thorax and

abdominal wall, the muscles of the upper and lower extremities (motor) and the skin of the sides and the front of the neck and trunk and extremities (sensory). The prevertebral flexor group of muscles include the longus capitis, longus colli, scalene, psoas, quadratus lumborum, etc. and piriformis. In the trunk the ventral ramus of 12 thoracic and first lumbar spinal nerves supply the intercostal muscles and the overlaying skin segmentally. The ventral rami of upper eleven thoracic spinal nerves form the intercostal nerves and that of the twelve thoracic spinal nerve form the subcostal nerve. The ventral ramus of first lumbar spinal nerve is distributed via the iliohypogastric and ilioinguinal nerve. Each intercostal nerve supplies the muscles of intercostal space. But the lower six intercostal nerves pass beyond the costal margin to supply the flat muscles of anterior abdomen and rectus abdominis. Moreover, the ventral rami of spinal nerves (which are also called the roots of plexus) form the cervical, brachial, lumbar and sacral plexuses at their respective places. The skin and the muscles of the upper limbs are supplied from the brachial plexuses and those of the lower limbs are supplied from the lumbosacral plexuses.

Out of the 31 pairs, only 14 pairs (12 thoracic and 2 lumbar) of spinal nerve have connection by the white rami communicans with the sympathetic chain. While all the spinal nerves are connected with the sympathetic chain by grey rami communicantes containing postganglionic fibres. The white rami communicantes contains the preganglionic sympathetic fibres, arising from the lateral horn cells of spinal cord extending between T_1 and L_2 segment of it. After arising from the lateral horn cells of spinal cord the preganglionic sympathetic fibres reach the sympathetic chain by the white rami communicantes and make connection with the postganglionic fibres at the corresponding ganglion in the sympathetic chain or passes uninterruptedly to the upper or lower ganglion of the sympathetic chain where they make synapses with the postganglionic fibres. Thus, the postganglionic fibres arise from all the sympathetic ganglion situated on the sympathetic chain and is then carried by the grey rami communicantes to all the spinal nerves. Thus, the sympathetic chains get its inflow from only the 14 pairs of white rami communicantes from 14 pairs of spinal nerves ($T_1 – L_2$), but have 31 pairs of grey rami communicantes for outflow to all the spinal nerves. Hence, each of the 31 pairs of spinal nerves receive the grey rami communicantes from the sympathetic trunk and conveys the postganglionic sympathetic fibres (non-myelinated) to supply throughout the whole body, except the abdominal and thoracic visceras and the structures head and neck supplied by cranial nerves. The thoracic visceras get their sympathetic supply through pulmonary and cardiac plexus and abdominal visceras get their sympathetic supply through splanchnic nerves. Thus, the sympathetic system innervates the entire body wall and all the four limbs through 31 pairs of spinal nerves.

DERMATOMES

The area of the skin supplied by a single segment of spinal cord through its ventral and dorsal nerve root is called the dermatome. As because the dorsal root of 1st cervical nerve (C_1) conveys only the proprioceptive fibres, so it does not present any dermatome. The front and the sides of the neck is represented by the C_2, C_3 and C_4 dermatomes. This is because the C_2 to C_4 spinal nerves supply this area of skin through the branches of cervical plexus such as great auricular (C_2, C_3), lesser occipital (C_2), transverse cervical cutaneous (C_2, C_3), and supraclavicular nerves (C_3, C_4). The upper limit of cervical dermatome involves the skin overlaying the angle of mandible, most of the auricle and occipital region of the scalp. Above that limit, the cervical dermatome meets with the sensory area supplied by the vth cranial nerve (trigeminal N). Below, the cervical dermatome extends up to the sternal angle in front, and over the rounded shoulder laterally (Fig. 24.16).

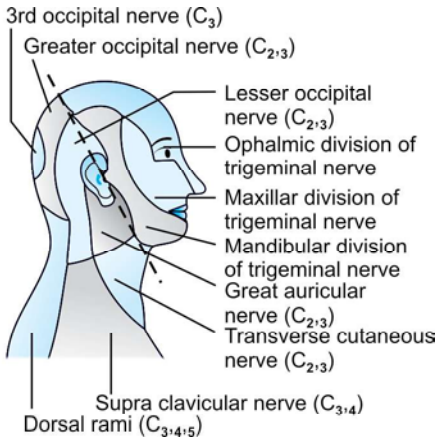


Fig. 24.16: The segmental innervation of scalp, neck and face. One side of the dashed line is supplied by cranial trigeminal nerve and another side is by spinal nerves

The dermatomes of trunk are represented by T_2 to L_1 spinal nerves and are arranged in regular series like strips. On the body the adjacent dermatomes overlap on each other considerably. So, the interruption of a single dermatome does not produce any effect on regional anaesthesia. At the level of sternal angle, the C_4 and T_2 dermatomes meet. This is because the missing of C_5, C_6, C_7, C_8 and T_1 dermatomes are carried over by the branches of brachial plexus to supply the upper limb which develops as a lateral outgrowth from the body wall.

The upper limb is supplied by the nerves of brachial plexus which is formed by the spinal nerves arising from the cervical enlargement of the spinal cord. The brachial plexus is formed by the ventral rami (which form the root or starting point of plexus) of C_5, C_6, C_7, C_8 and T_1 spinal nerves. The brachial plexus consists of roots (ventral ramus of the spinal nerve), trunks and cords. The five roots which extend from C_5 to T_1 emerge through the interval between the scalenus anterior and scalenus medius muscles.

The anterior division of brachial plexus supply the flexor compartment and the posterior division supply the extensor compartment of muscles. The flexor group of muscles possess richer innervation than the extensor group of muscles, because their actions are more powerful and precise. This explains why the most caudal root of the brachial plexus which is derived from T_1, is distributed entirely to the muscles of flexor compartment. This same principle is also applicable to lumbosacral plexus where S_3 root supplies only the muslces of the flexor compartment (Fig. 24.17).

The extreme peripheral end of the upper limb is supplied by the central dermatomes. Thus, the radial side of the arm is supplied by C_5, the radial side of the forearm is supplied by C_6, the middle three fingers with their adjacent palmar and dorsal surfaces is supplied by C_7, the little finger with the ulnar side of forearm is supplied by C_8 and the ulnar side of the arm is supplied by T_1 segments. The dermatomes overlaying the deltoid and bottom of the axilla are borrowed from the neck and trunk and are supplied respectively by the C_4 and T_2 spinal segments.

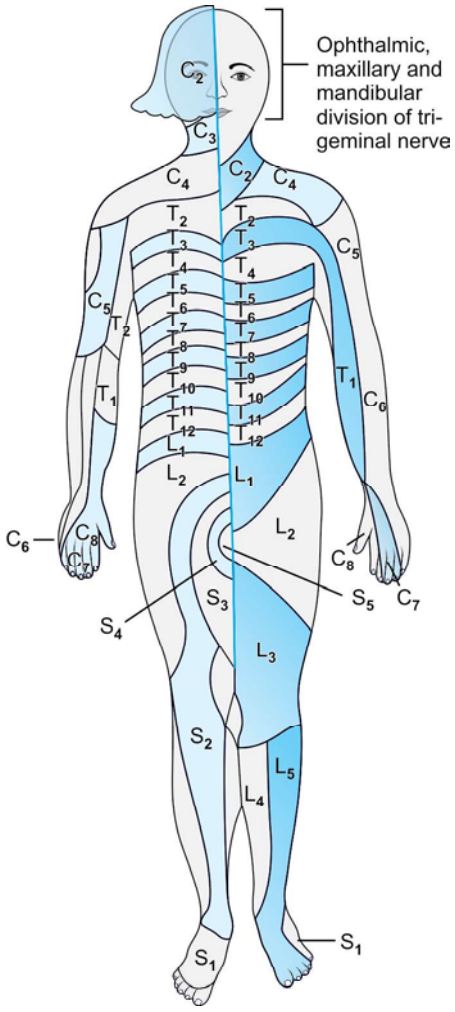


Fig. 24.17: The illustration of dermatomes

Each lower limb is supplied by the lumbar and sacral plexus which is formed by the spinal nerves arising from the lumbar enlargement of the spinal cord. The lumbar plexus is formed by the ventral rami of the upper three lumbar spinal nerves and the larger upper part of the ventral ramus of the 4th lumbar spinal nerve (L_1 to L_4). These are called the roots of the lumbar plexus. The smaller lower part of the ventral ramus of fourth lumbar spinal nerve joins with the ventral ramus of the 5th lumbar spinal nerve to form the lumbosacral trunk. Then, this trunk enters in the formation of sacral plexus. So, as the L_4 nerve makes connecting link between the two plexuses, it is called the nervous furcalis. Thus, the lumbar plexus is formed by the anterior rami of 1st, 2nd, 3rd and ascending part of 4th lumbar spinal nerve, assisted by a twig from the anterior rami of T_{12} nerve ($T_{12,}$ $L_{1,\ 2,\ 3,\ 4}$). On the otherhand, the sacral plexus is formed by the ventral rami of the 4th and 5th lumbar (lumbosacral trunk) spinal nerve and upper three sacral spinal nerves ($L_{4,\ 5}$ $S_{1,\ 2,\ 3}$) with a contribution from the upper part of 4th sacral spinal nerve.

Since, the lower limb buds grow as the lateral outgrowth from the body wall, opposite to the lower four lumbar and upper three sacral segments of spinal cord (at the level of junction of the ventral one third and dorsal two-third of genital labiosacrotal swelling), so the overlaying skin of each lower limb is supplied by $L_{2,\ 3,\ 4,\ 5,}$ $S_{1,\ 2,\ 3}$ spinal nerves through the lumbosacral plexus.

The consecutive dermatomes, involving the front of thigh (in front of the anterior axial line) are arranged in the following sequence from above downwards L_1, L_2 and L_3. In front of the leg, L_4 dermatomes lies on the tibial side and L_5 area on the fibular side. S_1 dermatomes lies along the lateral side of the dorsum and sole of the foot. The S_2 segment forms a narrow strip which extends up between the anterior and posterior axial lines along the middle of the calf and back of the thigh. The S_3 segment involves a wide semicircular area around the anus and between the axial lines. The S_4 segment supplies the adjacent perianal skin.

MICROSCOPIC STRUCTURE OF THE SPINAL CORD

On cross-section the spinal cord presents a white matter at the periphery and a butterfly like grey matter in the centre.

Grey Matter

The grey matter consists of nerve cells, neuroglia and blood vessels. In the centre of the spinal cord they are arranged in H-shaped manner. So, it is butterfly in shape. All the nerve cells in this area is non-myelinated, so it is grey in colour. Grey matter presents a pair of ventral horns, a pair of dorsal horns, an intermediate region which intervenes between the ventral and dorsal horns, and a commissure which connects the symmetrical halves of grey matter of each side across the midline. The ventral horns are broad than the dorsal horns and are more broad in the cervical and lumbar region than the thoracic region to accommodate numerous motor neurones, suppling the muscles of the upper and lower limbs. The dorsal horn consists of apex, head, neck and base. The base is continuous with the intermediate region of grey matter. The apex of dorsal horn is caped with a translucent mass of nerve tissue, called the substantia gelatinosa of Rolando which allows the entry

of sensory impulses through the dorsal nerve roots. The intermediate region of grey matter intervenes between the bases of ventral and dorsal horns and lies lateral to the commissure. In thoracic and lumbar regions, this intermediate region forms a lateral projection, called the lateral horn which is the centre of sympathetic output (Fig. 24.18).

The grey commissure is longitudinally transversed by a central canal, containing CSF. It is lined by ependymal cells and is continuous above with the cavity of the fourth ventricle, through the central canal of medulla oblongata. Within the conus medullaris of spinal cord the central canal is dilated to form the terminal ventricle. It may also extend for a distance of about 4 to 5 mm into the proximal part of the filum terminale interna. The central canal is surround by neuroglial tissue, called the substantia gelatinosa centralis.

The anterior or ventral horn of grey matter contains motor neurones and interneurones (internuncial or connector neurones). Motor neurones send axon fibres to the muscles. Interneurones or internuncial neurones possess small cell bodies and their processes are confined within the grey matter. They connect between the axons of sensory neurones in the dorsal horns and the cell body of motor neurones in the ventral horn, and is responsible for reflex activities. Their reflex activities may be intrasegmental or inter segmental, and ipsilateral or contralateral. Sometimes, the axons of sensory neurones in the dorsal horn make the direct connection with motor neuron of the ventral horn, without intervention of internuncial neurones. This is called the monosynaptic relays. The interneurone or internuncial neurones may be excitatory or inhibitory. But a particular interneurone cannot act in both ways. The Renshaw cell is classical example of inhibitory interneurone. The neurochemical transmitter substance of inhibitory synapses within the spinal cord is usually glycine. While the inhibitory neurotransmitter substance in the brain in GABA.

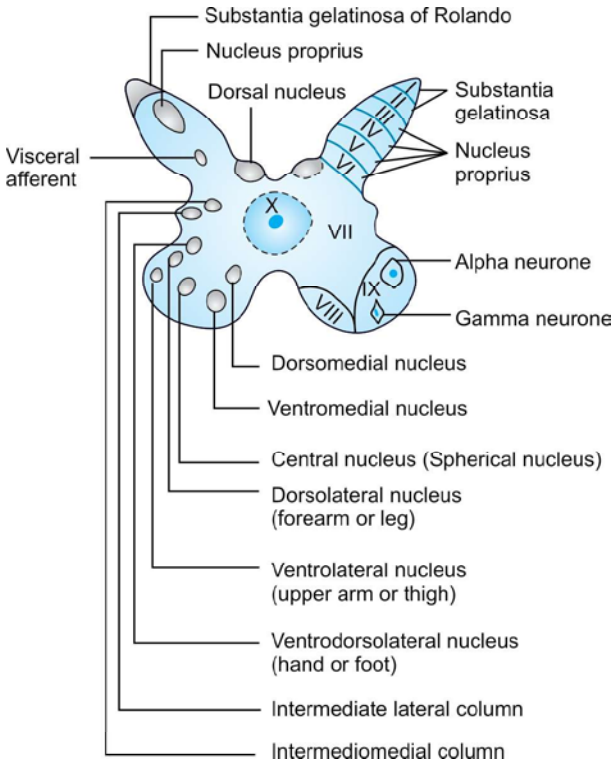


Fig. 24.18: Schematic representation of grey matter

The motor neurones in the anterior horn of grey matter is of three types—α, β and γ. Axons of these motor neurones leave the spinal cord through the ventral roots of mixed spinal nerve and then reach the effector striated muscles through the ventral and dorsal ramus which are the branches of this mixed spinal nerve. The cell bodies of α-neuron is large and their axons are thickly myelinated, conducting at a velocity of about 15 to 120 metres per second. These axons end on striated muscles by forming motor end plate over the individual muscle fibre (extrafusal fibre). The number of muscle fibres or muscle cells supplied by a single α (alpha) neuron is known as the motor unit, which may be large or small. The larger motor unit includes 100 to 200 muscle fibres or more (supplied by one motor neurone) and is concerned with gross movements. The smaller motor unit is comprised of 5 to 10 muscle fibres and appears in skillful movements, such as movements of the fingers of hand and eyeballs. On the otherhand, a single α-neurone may receive one thousand or more synaptic connections from the interneurones or from the fibres of dorsal roots with cells lying at the dorsal root ganglia or from the descending fibres of upper motor neurones. These synapses may be excitatory or inhibitory. The α-motor neurones also receive connections from the muscle spindles, corticospinal tract and vestibulospinal tract. Sometimes, the axons of α-neurones provide collateral branches which make synapses with the cell body of Renshaw cell type of interneurones situated in the anterior grey column or (ventral horn). In turn, the axons of Renshaw cells send impulse to inhibit the corresponding α-neurones and prevent excessive alpha firing. On occasions the Renshaw cells also inhibit the adjacent α-neurones and suppress the action of antagonistic muscles at the same time (Fig. 24.19).

The γ (gamma) neurones are small in size and their axons are thinly myelinated, conducting at velocity of 10 to 45 metres

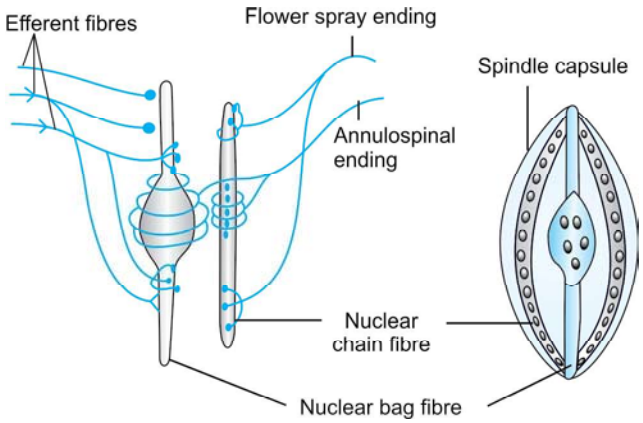


Fig. 24.19: Neuromuscular spindle

per second. The simple act of picking up a pencil from table not only employs the α-motor pathways, but also engage some afferent pathways which reach the spinal cord from the sensory endings of the skin, joints and the muscles spindle of hand and the fingers muscle to control the total muscle movement of hand and to pick up the pencil. In fact, the muscles spindles are the sensory end-organ of the skeletal muscles and are responsible for signaling the degree of shortening or lengthening of the whole muscle. In this way, they can provide information, so that only the exact amount of muscle activity which is required for the task is used. Histologically, the muscle spindle is an elongated and encapsulated structure which lies in parallel with the skeletal muscle fibres and shares its attachment. This latter point is of particular importance, as its principle function is to signal the exact length of the skeletal muscle fibre. Within the capsule of muscle spindle, small specialised intrafusal fibres can be recognised as the nuclear bag fibre and the nuclear chain fibre. γ-neurone (motor) supplies to the contractile polar regions of both the nuclear bag and nuclear chain type of intrafusal fibres of muscle spindle. The non-contractile equatorial region of intrafusal fibres are supplied by the general sensory nerve endings which act as stretch receptors and convey the sensory impulses when the polar regions contract, subsequent to the excitation of gamma neuron or when the entire muscle is passively stretched. The cell bodies of both the sets of afferent fibres are located in the dorsal root ganglia of posterior root and their central process reach the spinal cord through the dorsal nerve root and make monosynaptic connection directly or through internuncial neurones with the α-neurones which supply the extrafusal fibres of the corresponding muscle. Therefore, the α-neurones are excited and the whole muscle is thrown into contraction, until it shortens to equal with the degree of contraction of muscle spindle controlled by the γ-neurone. This method of control of contraction of a voluntary muscle by the gamma reflex loop maintains its residual length, even in resting condition and without any influence from the higher centre. The gamma loop acts as a servo mechanism and forms the basis of the reflex control of the residual muscle tone. The function of the intrafusal fibres is to inform the central nervous system through the gamma loop about the length and the rate of change in length of the extrafusal fibres. Whereas the α-neurones, on stimulation produce the final shortening of the muscles without limit, but the gamma neurones cause the muscle to contract to a predetermined length. The activities of gamma neurones are controlled by both the pyramidal and extrapyramidal fibres which may be excitatory or inhibitory. Considerable control of these motor neurone is exerted directly by the reticular system and indirectly by the cerebellum and basal ganglia.

The cell body and the axon of β-neurone is intermediate in size and diameter. Their axons supply both the extrafusal muscle fibres and the intrafusal fibres of the muscle spindle (Fig. 24.20).

There are four sets of neuronal column in the dorsal horn of grey matter. From apex to base they are named as follows: Substantia gelatinosa of Rolando, nucleus proprius, Clarke's column (nucleus dorsalis) and visceral afferent nucleus. The substantia gelatinosa (SG) is composed of cell body of sensory neurones and the small and medium sized cell body of interneurones. It extends along the entire length of

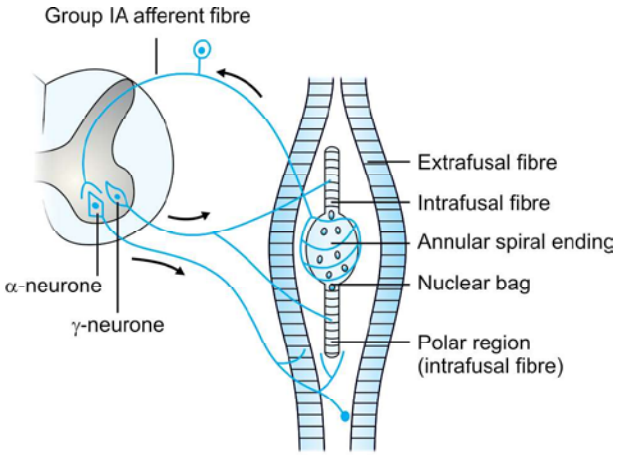


Fig. 24. 20: Pathways of active stretch reflex

the spinal cord. Traced above, it is continuous with the nucleus of the spinal tract of trigeminal nerve. The SG is traversed by the fibres of the dorsal nerve roots which are the axons of neurones situated in the dorsal root ganglia and carry the peripheral sensation. Some of these fibres make synapses with the SG cells, while others pass more deeply to the cells of nucleus proprius. The nucleus proprius (NP) lies deep to the SG and constitutes the head and neck of the dorsal horn of grey matter. It extends along the entire length of the spinal cord and is composed of the cell body of interneurones and tract cells. The axons of tract cells contribute to form the ascending tracts of the anterolateral white funiculi. The sensory fibres of the dorsal root which passes through SG and does not make synapses there, make synapses in NP or make tract. The nucleus dorsalis (Clarke's column) occupies the base of the dorsal horn and extends from C_8 to L_2 segments of the spinal cord. The nucleus dorsalis is also consist of interneurone and tract cells. The SG and NP is responsible for pain and temperature sensation, whereas the Clarke's column or nucleus dorsalis receives the proprioceptive afferent (i.e. muscle (Fig. 24.21) and joint sensation), touch and pressure sensation. Axon's of cell body of dorsal nucleus or Clarke's column pass ipsilaterally and form the posterior spinocerebellar tracts. The visceral afferent nucleus is situated at the base of the dorsal horn and extends from T_1 to L_2 and S_2 to S_4 segments of spinal cord. The cell bodies situated within this visceral afferent nucleus (VAN) receives visceral afferents fibres from the dorsal nerve roots and projects fibres to the preganglionic visceral efferent nuclei of the autonomic system which are located in the lateral horn of the corresponding segments of the spinal cord.

The lateral horn of the intermediate region of grey matter extends from T_1 to L_2 segments of the spinal cord. It is composed of intermediolateral and intermedio medial columns of cells and act as preganglionic motor neurones of sympathetic system (thoracolumbar outflow). The preganglionic fibres arising from these sympathetic motor neurones are thinly myelinated and pass successively through the ventral roots, mixed spinal nerve trunk and reach the corresponding ganglia of sympathetic chain via the white rami communicate. So, T_1 to L_2 spinal nerves have white rami communicantes in addition to grey rami communicantes which is present in all the spinal nerves, carrying the postganglionic sympathetic fibres which arises from the sympathetic chain. The intermedio medial group of cells reappears in the sacral region without any lateral projection. It extends from S_2 to S_4 segments of the spinal cord. These cells also act as the preganglionic motor neurones for the sacral outflow of parasympathetic system. Their axons pass through the ventral roots of corresponding mixed spinal nerves and then they leave the spinal nerves to form the pelvic splanchnic nerves (parasympathetic) (Fig. 24.22).

Recently, the entire spinal grey matter is mapped out by Rexed into ten laminae, according to the cytoarchitecture and packing density of neurones. Laminae I to VI are confined in the dorsal horns. Among these lamina I and II corresponds with the substantia gelatinosa (SG) and lamina III to VI corresponds with the nucleus proprius. Lamina VII occupies the intermediate region of grey matter. It includes nucleus dorsalis, intermediomedial and intermediolateral nucleus of autonomic system. Lamina VIII is located in the medial part of the ventral grey column in the cervical and lumbosacral enlargements of the spinal cord. In the other segments of the spinal cord, lamina VIII is located at the base of the ventral horn. Lamina IX is located in the lateral part of ventral horn at the enlarged segment of spinal cord for the limbs. Whereas in the rest of the segments of spinal cord (except the enlarge segment of spinal cord for limbs – such as cervical and lumbar segment), it occupies the head of the ventral horn. Lamina X occupies the area around the central canal which consists mostly of neuroglial cells (Fig. 24.23).

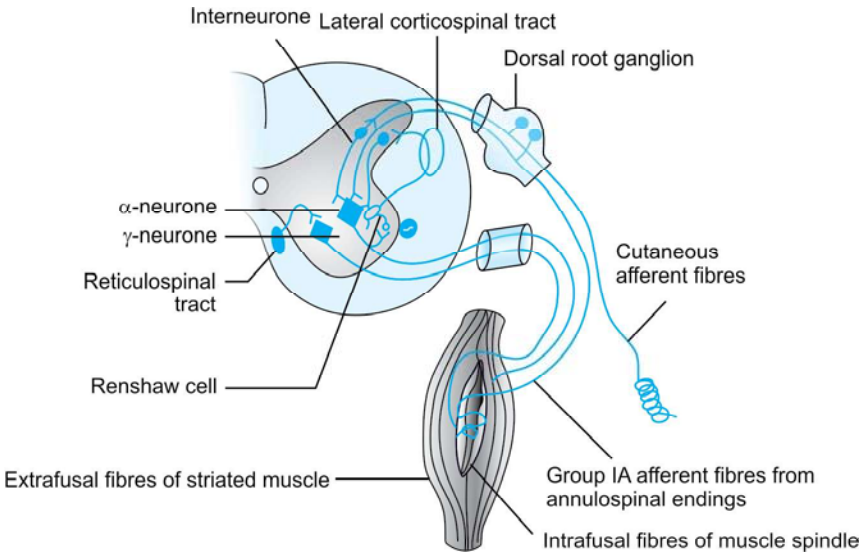


Fig. 24.21: Neurones of the anterior grey column and their functional role

White Matter

The white matter of spinal cord consists of nerve fibres (but not the nerve cell bodies), neuroglial cells and blood vessels. It is white due to the myelination

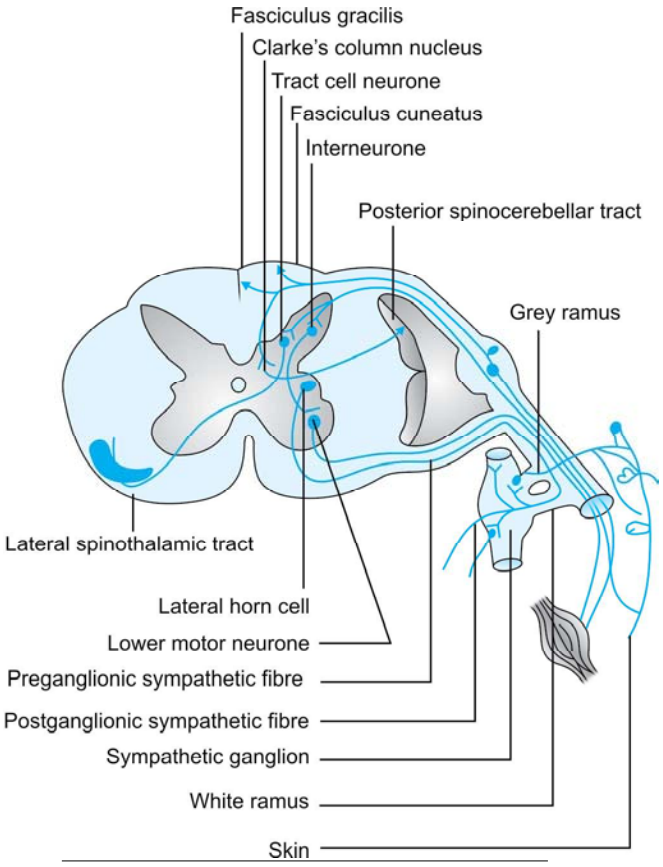


Fig. 24.22: Neurones of the posterior grey column and lateral horn cells with their functional role

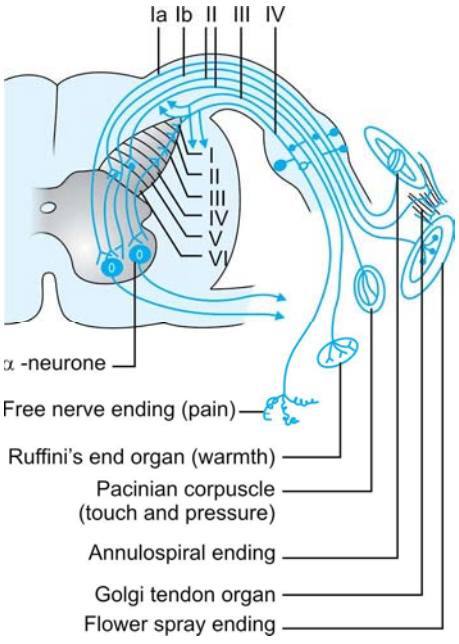


Fig. 24.23: Arrangements of sensory fibres at the root entry zone and their immediate termination

of nerve fibres. In the spinal cord the white matter occupies the periphery of the butterfly shaped central grey matter and is arranged into three pairs of funiculi—anterior, lateral and posterior. Usually all white funiculi are essentially composed of longitudinal nerve fibres which are grouped into different functional tracts and runs upwards or downwards on the same side of the spinal cord. But, some fibres of the white matter dicussate horizontally or obliquely across the grey matter and white commissure and pass to the opposite side of the spinal cord.

Fibres of Dorsal Nerve Roots and their Termination

All types of sensation such as exteroceptic, proprioceptive, and interoceptive, reach the spinal cord through the dorsal nerve root. Each dorsal nerve root has a ganglion near the intervertebral foramen and each ganglion contains 'T' shaped bipolar neurones with peripheral and central processes. Distal to the ganglion, dorsal root (sensory) meets with the ventral root (motor) to form the mixed spinal nerve which then comes out through the respective intervertebral foramen. The peripheral processes of the T-shaped ganglion cells which are situated in the dorsal root ganglion reach (i) the exteroceptive sensory receptor organs in the skin, (ii) proprioceptive receptors in the muscles, bones and joints, and (iii) interoceptive or visceroceptive receptors in the blood vessels and viscera. The central process of these T-shaped ganglionic cells form the dorsal nerve root and fans out centrally into six or eight root lets and reach the spinal cord. At the entry zone of root each rootlet presents medial and lateral divisions or bundles.

The medial divisions consist of thickly myelinated group I and group II fibres. Group I fibres are again subdivided into Ia and Ib. Ia fibres convey primary afferents from the muscle spindle. Ib fibres carry afferents from Golgi tendon organs, touch and pressure. Group II fibres convey secondary afferents from the muscle spindle, touch and pressure receptors and vibratory receptors (Pacinian corpuscles). All the fibres of the medial division enter into the posterior fasiculi and joint with the ascending tracts.

The lateral divisions consist of thinly myelinated group III and unmyelinated goup IV fibres. Group III fibres conduct fast and discriminative pain and temperature sensation. Group IV fibres are concerned with slow (aching) pain and visceral sensation. On reaching the spinal cord, the fibres of lateral division divide into short ascending and descending branches in the dorsolateral tract of Lissaur. Then, it extends one or two segments cranially and/or caudally and provide collateral and terminal branches which enter into the dorsal horn of grey matter.

BLOOD-CSF AND BLOOD-BRAIN BARRIER

The projection of vascular pial fringes into the ventricles of brain such as lateral, third and fourth ventricle is called the choroidal plexus. Ependyma is the simple layer of ciliated columnar cells. This lines the ventricles of brain including the choroidal plexus and the central canal of spinal cord. The ependyma, lining the choroidal plexuses of ventricles, helps actively in the formation of CSF. Actually, it also presents the blood − CSF barrier. The choroidal plexus presents numerous villi like projection on the ventricular aspect of the ependyma. Each villus contains capillary plexus. It is formed by afferent and efferent vessels, a small amount of connective tissue stroma derived from pia mater, and few nerve fibres. This aforesaid structure of the choroidal villi are enveloped by the ependymal cells which are simple ciliated columnar resting on the basement membrane and are connected to one another by tight junction (Fig. 24.24).

Thus, the blood - CSF barrier consists of the following:

i. Fenestrated endothelium of choroid capillaries resting on a basement membrane,
ii. A tissue space intervening between the vascular endothelium and the pial membrane,
iii. A continuous layer of ependymal cells connected by tight junctions.

The ependymal cells are actually the cells which is derived from the germinal layer of primitive neural tube and give rise to the development of neuroblasts and spongioblast. The spongioblast differentiates into astrocyte and oligodendrocytes.

The arterial blood of choroidal plexus is derived from the anterior and posterior choroidal arteries. The former are the branch of internal carotid artery. The latter are usually three or four in number and are derived from the posterior cerebral artery. The venous blood from the choroid plexus is assembled on each side to form a single choroid vein. The choroid veins join with the thalamostriate veins and ultimately drain into the straight sinus through the internal cerebral and great cerebral veins. The mechanism of the control of circulation of blood through the choroidal plexuses is not yet established.

The ependymal cells on ventricular surface exhibits microvilli. The structures of ependymal cells suggest that they are concerned with the transcellular and bi-directional transport of solvents and solutes between the choroidal capillaries and the ventricular cerebrospinal fluid. The total surface area of choroidal plexuses ranges from 150 to 300 sq cm. The active transport through the ependymal cells provides higher concentrations of Na and Cl ions and lower concentrations of other substances in the CSF than that of the plasma.

It is important to mention at this stage about the existence of two more brain barrier. These are CSF-brain barrier and blood-brain barrier. The CSF brain barrier intervenes between the CSF and the extracellular (neurone or glial cells) space. It includes extrachoroidal ependymal cells of the ventricles which have gap junctions between them, basement membrane and subependymal glial cell membrane. The blood-brain barrier includes the tissues that intervenes between the blood in the capillaries and the neurones.

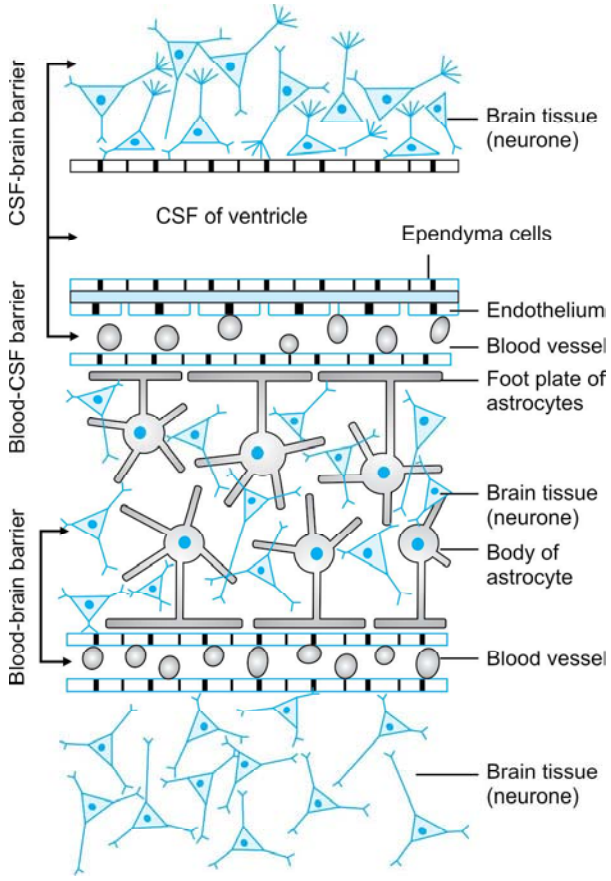


Fig. 24.24: The blood-CSF, CSF-brain, and blood-brain barrier

The blood-brain barrier consists of the following:

i. Nonfenestrated endothelium of the capillaries connected by tight junctions,
ii. A basement membrane for vascular endothelium,
iii. Perivascular feet and cell bodies of the astrocytes,
iv. A network of intercellular spaces between the astrocytes and the neurones, having an

interval of about 200A wide. The blood-brain barrier permits the entry of water, O_2, CO_2, some drugs like sulphadiazine and erythromycin, etc. readily into the brain. But proteins, bile salt, catecholamines and drugs like penicillin, etc. cross the barrier to a limited extend.

The CSF-brain barrier is weaker than the blood-brain barrier. This is because vital dyes and isotopes injected into the CSF gain quick access into neurones and neuroglia. In general, substances possessing high lipid solubility, such as CO_2, volatile anaesthetics and barbiturates, etc. pass from the blood to the brain and ultimately to the CSF. On the otherhand substances with limited lipid solubility, such as electrolytes, sugar and amino acids, etc. pass from the blood to the CSF and ultimately to the brain.

SELECTION OF THE PATIENT FOR REGIONAL ANAESTHESIA (RA)

Psychological Factors

During the training period many anaesthetists have the experience of successfully placing the block, but the effect of regional anaesthesia fails. In such circumstances, one of the most common reason for this unfortunate event is that the regional technique selected was not suitable for that patient. These patients are easy to identify. So, it is a mistake from the side of an anaesthetist to try to coerce with such patients to accept the regional anaesthesia without heavy sedation or GA. Because it is likely to be very difficult to manage these patients in the OT room, only with regional anaesthesia. So, regional anaesthesia without heavy sedation or GA is impossible or rarely provided to children. The patients of adolescent age group can be difficult to evaluate. Patients with psychiatric diseases, e.g. schizophrenia, manic depression, claustrophobia, Alzheimer's, dementia, etc. are not suited for regional anaesthesia.

Some orthopedic surgeries require special position during operation. This does not cause problems for short surgeries. But this can become extremely uncomfortable over long period of time, specially for patients who are suffering from body arthritic changes. Then, the gradual movement of patient that result from the restlessness during lengthy procedures can require excessive sedation and spoil the advantage of RA. Some procedures, e.g. shoulder surgery, surgery over head and neck area, etc. requires the patient to be drapped over the head for considerable period of time. But some patients may not be able to tolerate this situation and RA is not suitable for these group of patients. Another problem of RA is if the patient does not understand the principal language which is used in the OT by stuffs and the anaesthetists is not fluent with the language of the patient. Sometimes, RA without supplement of sedation or GA is also probably not wise. Some surgeons prefer to work with RA and modify his surgical techniques to accommodate it. So, to make RA successful, he also explains to the patient about the benefits of RA over GA, before the patient meets the anaesthetists. Contrary, some surgeons are uncomfortable to work with RA. So, he becomes reluctant to convey to the patient regarding the benefit of RA. Then, the preparation for RA may become more complicated or even impossible by anaesthetist.

Physical Factors

i. Regional anaesthesia should not be attempted when patient has any signs of systemic infection. So, general sepsis should be considered as absolute contraindication.
ii. Psoriasis and hidradenitis are two conditions in which although the skin is not infected, but this area must be avoided for needle prick. So, another site for regional technique should be selected, otherwise general anaesthesia is preferred.
iii. Herpes, found at preoperative examination, may pose problems. Secondary and subsequent recurrence of this disease is not contraindicated for RA. But, primary herpes is often associated with viraemia and so is a contraindication for RA.
iv. Chronic osteomyelities does not show any evidence of bacteraemia and so RA is not contraindicated. However, presence of bacteraemia in acute case is a contraindication for RA and should be avoided.
v. Pelvic infection presents controversy when RA is considered. The confluence of lymphatic drainage from the pelvis and the epidural space make placing of a needle (a potential nidus for infection) in vertebral canal during such infective condition controversial.
vi. For regional anaesthesia to be considered – no systemic signs of sepsis or clinical signs of pyelonephritis should be present.
vii. Many of HIV positive patients are severely ill, and might be considered ideally suited for RA due to severe illness. However, invasion of CNS by the HIV virus is of particular concern for RA. This is because the virus has property to cause demyelination. So, it is now generally agreed that any disease state which cause demyelination is an absolute contraindication for RA, since local anaesthetic agent too accelerates this demyelination. Here, the risk benefit ratio must be calculated.

Neurological Diseases

i. For diseases with central demyelination, such as, amyotrophic lateral sclerosis, Guillain-Barrè syndrome, etc. the RA is an unwise choice.
ii. The diabetic peripheral neuropathy is an area, where there is less consensus between RA and GA. Patient with this type of peripheral neuropathy often have other endorgan diseases which make them ideal for RA. But, however

due to medicolegal issues for postoperative changes in the extent of neuropathy due to diabetes (but not due to anaesthesia) some anaesthetists are reluctant to use regional anaesthesia in such cases. So, though mechanism of diabetic neuropathy is unknown and unaffected by action of local anaesthetics, still proper preoperative evaluation for any neurological deficit of such patient by thorough physical examination and risk/benefit analysis of the situation should be clarified before taking the decision for RA.

iii. An history of old stroke, especially an old embolic event, is not a contraindication for RA. The patient requiring urgent surgery in the period immediately after a haemorrhagic stroke, RA is strongly contraindicated. It is also contraindicated for any patient with a potential for increased intracranial pressure. The grey zone is the time interval between an acute condition and a chronic one. So, risk/benefit analysis and complete documentation of patient status is mandatory.

Coagulopathy

The actual incidence of neurological dysfunction associated with central neuroaxial block, resulting from cord compression by haemorrhagic complications such as haematoma paraplegia, abscess, etc. is unknown. But, the incidence which is cited in different literature vary from 1 in 1,50,000 in epidural to less than 1 in 2,20,000 in spinal anaesthesia. Among these complications the epidural haematomas is most common and, 68% patients have the history of coagulation abnormality due to intravenous heparin, antiplatelet medication, oral anticoagulants intake, dextran 70, administration, etc. Like the introduction of needle and/or catheter, the epidural haematoma also can occur immediately after the removal of the epidural catheter. These suggest that catheter removal is not entirely atraumatic. So, determination of patient's coagulation status at the time of catheter removal is perhaps as critical as that at the time of catheter placement. Neurological outcome is good only in 38% of the patients who underwent laminectomy within 8 hours of diagnosis of epidural haematoma. But, routine screening for coagulation profile in healthy patients, who are not taking any medicine that influences the coagulation cascade, is no longer advised before RA. But, practitioner of RA must take proper history of symptoms and signs of any coagulation defect. History of taking any anticoagulants, antiplatelets (aspirin, NSAIDs), a prior history of surgical bleeding diathesis, etc. should not be excluded from indication of RA, but should be evaluated carefully. The most valuable tools to detect potential bleeding problems during RA are bleeding time (BT), prothrombin time (PT) and partial thromboplastin time (PTT) which are the gold standard indicators of the integrity of an intrinsic and extrinsic pathways of coagulation. Salicylation of platelet by antiplatelet aggregating factors such as aspirin is irreversible and effect is not resolved till new generation of platelets are synthesised. Thus, two weeks withholding of aspirin and NSAID makes preoperative choice easier. However, not every patient could be prepared in this manner. Coagulopathy from this medication should be considered unusual. Prophylaxis of deep vein thrombosis (DVT) may involve low dose heparin/warfarin / coumarin, etc. and should be titrated against a defined prolongation of PT/PTT ratio. In such cases of prophylaxis, coagulation cascade is usually not altered, keeping in mind that a small percentage of patient will always have abnormal coagulation test. So, laboratory testing should be minimal for preoperative preparation of anesthesia. Withholding the medication for a period and documenting their normal coagulation tests after withdrawal is best choice. Preparing a risk / benefit ratio for these patients is mandatory. For a patient with clinically documented embolism and in need of urgent surgery of stopping the anticoagulant must be a joint decision by surgeon and anaesthesia team. Rarely, an indication for RA is so strong that active reversal of anticoagulation is executed with blood component therapy (fresh frozen plasma, cryoprecipitate, vit K) to allow anaesthetists to use RA technique. Resumption of heparin is decided by surgeon when surgical bleeding is stable in postoperative period.

Regional anaesthetic management of the patients who are on oral anticoagulants (warfarin)

The anaesthetic management of patients who are orally anticoagulated preoperatively with warfarin is dependent on the dosage and timing of initiation of therapy. The PT and INR valve (normal value of PT − 9.6 to 11.1 S which correspons to an INR value of 1.4) of patients on chronic oral anticoagulation will require at least 3 to 5 days to become normal after discontinuation of the anticoagulant therapy. Therefore, except in extraordinary circumstances, the spinal or epidural needle or catheter placement and removal of it should not be performed in dully anticoagulated patients. It is, therefore, recommended that documentation of the patient's normal coagulation status should be achieved prior to the implimentation of neuroaxial block.

Patients who are getting warfarin as thromboprophylaxis preoperatively have significantly higher PTs and complication rate. On the otherhand, many orthopaedic surgeons administer the first dose of warfarin on the night before surgery. For these patients, the PT and INR have should be checked prior to the neuroaxial block, if the first dose was given more than 24 hours earlier or a second dose of oral anticoagulant has been administered.

Patient receiving low dose of warfarin therapy for long period should have their PT and INR monitoring during

central neuroaxial block on a daily basis and checked before the removal of catheter specially if initial dose of warfarin is more than 36 hours before hand. There is a large variability in patient's response to warfarin. For example, usually the mean PT, by low dose (5 mg) of warfarin given postoperatively, does not increase beyond the normal range until 48 hours is passed. Again average therapeutic value is not achieved until the seventh postoperative day have passed. But few patients have PT value greater than 12.8 S after a single dose of warfarin. Higher dose of warfarin may require more intensive monitoring of the coagulation status. Reduced doses of warfarin should be given to patients who are likely to have an enhanced response to the drug. An INR > 3 should prompt the physician to withhold or reduce the dose of warfarin in patients with indwelling neuroaxial catheters. There is no definitive recommendation for removal of neuroaxial catheters in patients with therapeutic levels of anticoagulation status during a neuroaxial catheter infusion. But caution must be exercised in taking decision about the removing and maintaining these catheters.

Regional anaesthetic management of the patients who are receiving heparin

The safety of central neuroaxial block with intraoperative heparinization is well documented, provided no other coagulopathies are present. But the concurrent use of other medications that affect the coagulation status may increase the risk of bleeding complications for patients receiving standard heparin.

Intravenous heparin administration should be delayed for at least 1 hour after needle placement. Indwelling catheter should be removed 1 hour before a subsequent heparin administration or 2 to 4 hours after the last heparin dose. Evaluation of the coagulation status may be appropriate or mandatory prior to the placement of catheter or removal of it in patients who have demonstrated enhanced response to anticoagulants or are on higher doses of heparin. Although the occurrence of a bloody or difficult needle placement may increase the risk, but there are no data to support the mandatory cancellation of a schedule dose. If the decision is made to procede for central neuroaxial block in a patient who is receiving heparin, then a full discussion with the surgeon and careful postoperative monitoring are warranted.

There is no contraindication to use of spinal or epidural block after administration of subcutaneous standard dose of heparin provided coagulation parameters remain within recommended level and close monitoring is performed.

Regional anaesthetic management of the patients who are receiving LMWH (Low molecular weight heparin)

The patients on preoperative LMWH should be assessed to have altered coagulation profile at the time of spinal or epidural needle or catheter placement. A single short spinal anaesthesia may be the safest neuroaxial block in patients receiving preoperative LMWH. In these patients, needle placement should occur at least 10 to 12 hours after the last LMWH dose. Patients receiving higher doses of LMWH will require longer delays (24 hours). Neuroaxial block should be avoided in patients where a dose of LMWH is administered two hours preoperatively. This is because needle placement coincides with the peak anticoagulant activity of LMWH. Antiplatelet, oral anticoagulant, standard heparin or dextran administered in combination with LMWH may increase the risk of spinal haematoma.

Patients who are not receiving any anticoagulant, heparin or LMWH at present, but with proposed postoperative initiation of LMWH for thromboprophylaxis may safely undergo single dose and continuous catheter techniques. But the first dose of LMWH should not be administered earlier than 24 hours postoperatively. In addition, it is recommended that the indwelling catheter should be removed at least 24 hours after last dose of LMWH.

The decision to implement LMWH therapy in the presence of an indwelling catheter must be made with care. Extreme vigilance of the patient's neurological status is warranted. A minimum dose of opioid or very dilute local anaesthetic solution which does not block the motor is recommended in these patients in order to allow frequent monitoring of the neurological function. If epidural analgesia is anticipated to continue for more than 24 hours, LMWH administration may be delayed or an alternate method of thromboprophylaxis may be selected based on the risk profile for the individual patient. These decisions should be made preoperatively to allow optional management of both postoperative analgesia and thromboprophylaxis.

Regional anaesthetic management of the patients who are receiving antiplatelet medication

The antiplatelet medications are seldom used as primary agents for thromboprophylaxis. The only antiplatelet drugs, by themselves, appear to represent no added significant risk for the development of spinal haematoma in patients having epidural or spinal anaesthesia. Several large studies have demonstrated the relative safety of neuroaxial blockade in both obstetric and surgical patients receiving these medications. However, the concurrent use of medications that affect the other components of clotting mechanisms, such as oral anticoagulants, standard heparin and LMWH, may increase the risk of bleeding complications for patients receiving antiplatelet agents. Assessment of platelet function prior to performance of neuroaxial block is not recommended.

Ticlopidine and clopidogrel are also used as platelet aggregation inhibitors. These agents interfere with the platelet

fibrinogen binding and subsequent platelet – platelet interactions. The effect is irreversible for the whole lifespan of the platelet. Ticlopidine and clopidogrel have no effect on platelet cyclo-oxygenase and act independently of aspirin. The risk of spinal haematoma in patients receiving ticlopidine and clopidogrel in unknown.

EQUIPMENT REQUIRED FOR REGIONAL ANAESTHESIA

A failure of an anaesthetist to provide basic resuscitation, immediately after development of any complication due to toxicity of LA agent from any regional block, may accentuates this LA toxicity. This is because the toxicity of LA agent is magnified by hypoxia, hypotension and acidosis and a vicious cycle may set up. The LA agent induced grandmal seizure should also be promptly identified and treated by securing the patients airway, and giving a dose of thiopental intravenously. It is followed by a intubating dose of succinylcholine and subsequent intubation and ventilation. This prevents hypoxia and meet the excessive demand of O_2 for skeletal muscles due to seizure. By the time, the action of drugs used for induction wear off, the seizure precipitated by local anaesthetic agent used for RA will also be resolved.

So, the minimum requirements for a safe performance of regional anaesthesia (both peripheral nerve block and central neuroaxial block) are:

i. Emergency resuscitation drugs,
ii. Appropriate needles, syringes, IV cannulas, etc.
iii. Access to circulation and IV fluids,
iv. Thiopental, succinylcholine, atropine, adrenaline and other emergency drugs,
v. Oxygen and device for assisted positive pressure ventilation,
vi. Suction, laryngoscope and tracheal tubes,
vii. Monitoring devices,
viii. All facilities for general anaesthesia,
ix. Trained assistance.

Many anaesthetists do not routinely wear the sterile gown or face mask for regional techniques. But, it is mandatory to wear gown and mask for central neuroaxial blockade and introduction of catheter. However, this may not be mandatory for other regional blockade such as plexus block or field block. There is some controversy regarding the routine monitoring during the injection of any regional block. But, this is mandatory during central neural blockade.

INDICATIONS AND CONTRAINDICATIONS OF CENTRAL NEUROAXIAL BLOCK (CNB)

As a general rule, the central neuroaxial block is only indicated for the surgical procedures which can be accomplished on the awake patient with the sensory and motor block that is appropriate for this surgical procedure and the level of block does not produce adverse patient's outcome. Therefore, low spinal or epidural anaesthesia (block up to T_{10} spinal level or below it) carries different implication than the high (block up to T_5 spinal level or below it) spinal or epidural anaesthesia. Neuroaxial blocks may be used alone usually for the procedures on the lower half of body or in conjunction with GA usually for the procedures on the upper half of the body (upper abdomen, thorax and neck). Indeed in some European centres, cardiac surgery has also been routinely performed under thoracic epidural anaesthesia, typically with light GA.

Indications

Spinal anaesthesia may be an especially good choice than any other regional anaesthetic procedure. This is because the total dose of local anaesthetic drug to achieve up to the level of T_{10} block is quite small and will not push the total dose, as given during the epidural anaesthesia or different plexus blocks, close to the toxic level. The central neuroaxial block as a primary anaesthetic procedure is most commonly used to provide surgical anaesthesia for all procedures, carried out on the lower half of the body. Hence, the usual indications for CNB include surgeries on the lower limb, pelvis, genitals, perineum, obstetrics and most urological procedures. Regional anaesthesia in the form of central neuroaxial block (CNB) is also used for upper abdominal surgery, but in combination with GA or sedation. It is less commonly used as a sole anaesthetic procedure for upper abdominal surgeries. Recently, the RA technique has found in favour of analgesia in obstetric practise and provide anaesthesia for both elective and emergency obstetric procedures. Patients with respiratory diseases may definitely get benefit from regional anaesthesia by avoiding GA but only if the block does not extent beyond the level of T_{10} spinal segment. So, caution should be exercised in patients with severe respiratory and cardiac diseases if the level of block extends high up above the T_{10} level. Because, in acute respiratory disease the motor block of accessory respiratory muscles may impaired the pulmonary mechanics and aggravate the impairment of ventilation. Except lumbar approach, other approaches for spinal block such as thoracic and cervical approach are not used for the fear of damage to the spinal cord. So, the dural puncture for spinal block is usually performed below the level of first lumbar vertebra to prevent the damage of spinal cord which terminates at this level. But this is not true for epidural anaesthesia which can be approached through any route such as cervical, thoracic, lumbar and sacral. A relatively uncommon, but useful indication for spinal anaesthesia is elective surgical procedures over spine, especially lumbar such as laminectomy, spinal stenosis revision, lumbar fusion, etc. Usually majority of these cases are performed under GA, but there have been a number of reports of successful application of spinal anaesthesia for the above mentioned surgical procedures on spine. The reluctance to use spinal anaesthesia for lumbar spine surgery is based on several factors which

are discussed later. Many surgeons are unaccustomed to perform spine surgery on an awake patient. Occasionally, patient's movement and change in pattern of ventilation of an awake patient can be very disturbing. Many anaesthetists are also reluctant to employ any regional technique on a prone patient. This is because if GA is needed intraoperatively, then intubation of such patient in the prone position is difficult and potentially very dangerous. So, some anaestheologists prefer to have control over patient's airway under GA before the patient is placed in the prone position. On the otherhand, surgery on lumbar spine requires sensory block up to T_{12} segment. And an awake patient with block up to T_{12} level is capable of safely positioning their upper part of body with head and neck and can maintain his or her own airway unless oversedated or sensory level of spinal block is too high. If the duration of operation is too prolonged and the effect of original spinal anaesthesia receeds, then the dura will be in view and an enthusiastic surgeon can perform another second subarachnoid injection of LA agent. But except periosteum, rest of the spinal tissue where surgery is going on is insensitive. So, the need for supplementation of anaesthesia is confined to infiltration of skin only for wound closure.

Contraindications

The contraindication for spinal and epidural anaesthesia are grouped under two headings – absolute and relative. But at some point the demarcation between these two groups is blurred.

Absolute contraindications

i. Patient's refusal and proved allergy to local anaesthetic agent.
ii. Patient's inability to maintain stillness due to any medical causes.
iii. Lack of co-operation and understanding from patient's side.
iv. Intracranial lesion due to any cause resulting ↑ICP. It is a very important contraindication for spinal anaesthesia, because it may result in brain stem herniation due to excessive lea age of CSF. Epidural is also contraindicated (relative) in such patient because inadvertent intrathecal puncture during the procedure of epidural anaesthesia may result in a sudden fall in CSF pressure with herniation of brainstem through the foramen magnum.
v. Coagulopathy and untreated clotting defect.
vi. Skin infection at prick point of needle.
vii. Severe spinal and neurological abnormality, causing it technically impossible.
viii. Fixed cardiac output states, e.g. severe MS, MI, AS, etc. with very low left ventricular ejection fraction.
ix. Absence of resuscitation equipment and no intravenous access to meet emergency.

Relative contraindications

i. Coagulopathy – Intrinsic or idiopathic. In a patient taking anticoagulant, the risk must be weighed against the benefit. Well controlled anticoagulant treatment is not always a contraindication for spinal or epidural anaesthesia.
ii. Fever − General sepsis is an absolute contraindication for spinal or epidural anaesthesia, because infection may become settled at the point of injection, if there is any haematoma. But simple fever without any general sepsis is not an absolute contraindication.
iii. Severe hypovolaemia or continuing rapid blood loss.
iv. Lack of anaesthetists experience.
v. The potential for major blood loss during surgery.
vi. Previous laminectomy is not an absolute contraindication for spinal or epidural anaesthesia. It may be relative contraindication.

Heparin for deep vain thrombosis (DVT): APTT ratio up to 2 and in case of coumarin, INR up to 2 is safe ground for epidural or spinal anaesthesia.

Spinal or Epidural

The choice between the spinal and epidural anaesthesia for a patient depends on the following multiple factors:

a. Predictability of the length of surgery – epidural with catheter is preferred for prolonged surgery.
   Spinal anaesthesia is preferred where the duration of surgery is highly predictable.
b. Need for prolonged postoperative analgesia, epidural (with or without catheter) is preferred.
c. Where both spinal or epidural is applicable – chances of post spinal headache should be considered.
d. If patient is discharged immediately – single shot epidural without catheter is preferred.
e. For short surgical procedures waiting for epidural to take effect makes spinal more practical.
f. For more sick patient epidural block with catheter is preferred than spinal, because it avoids the sudden physiological changes which occurred during spinal anaesthesia.
g. For obstetric analgesia (not anaesthesia) subarachnoid block has no role.

PHYSIOLOGICAL EFFECTS OF CENTRAL NEUROAXIAL BLOCK (SPINAL AND EPIDURAL)

The central neuroaxial block is associated with certain physiological changes in the body and these are described below. When these physiological changes in our body cross their limits, then complications occur. For example, the physiological effects of neuroaxial block such as hypotension is not a complication. It becomes a complication when the hypotension is severe and produces damage, because complications imply damage to the patient.

Cardiovascular Effects

The central neuroaxial block, i.e. spinal or epidural anaesthesia produces pharmacological sympathectomy. The effect of this pharmacological sympathectomy due to spinal or epidural anaesthesia is similar to that of the α and β adrenergic blocking agent. However, the level of this sympathectomy and its effects depends on the height of block. In spinal anaesthesia the level of sympathectomy is 2 to 4 dermatomes above the level of the sensory block and in epidural anaesthesia it is at the same level of sensory block. Sympathetic block, i.e. sympathectomy causes both venous and arterial dilatation. But the venodilatation effect predominates as 75% of total blood volume is on the venous side. In general, the dilatation of arteries and resistance vessels cause reduction of the after load and increase in CO (if preload is maintained). Whereas, the dilation of venous capacitance vessel cause reduction of preload and decrease in CO. But the resultant effect of this arterial (resistance vessels) dilatation against venous dilatation in spinal or epidural block is decrease in CO and hypotension. This is due to the prepondarance of venodilatation. The decrease in myocardial contractility and heart rate also lead to decrease in CO and hypotension in a high spinal or epidural block. This happens when the block extends above the level of T_1 spinal segment and there is blockade of the cardioaccelerator sympathetic fibers which arises from the T_1 to T_4 segment of spinal cord (sympathetic outflow is from T_1-L_2). This causes decrease in compensatory outflow from the cardiac spinal sympathetic centre in response to the afferent impulses from the intrinsic chronotropic stretch receptor of the right atrium and great veins which in turn decreases the chronotropic and inotropic drive of heart, leading to further reduction of CO and hypotension. Thus, a vicious cycle starts.

There is also decrease in the coronary blood flow. This is because the coronary blood flow parallels with the mean arterial pressure. The myocardial O_2 consumption rate also varies. When there is fall of systemic vascular resistance and mean arterial pressure without tachycardia, then there is also reduction of after load and subsequent reduction of O_2 consumption rate by heart. But when there is compensatory tachycardia, O_2 consumption tremendously increases. Usually, there is no change in blood flow in organs, when sensory block extends only up to T_{10} level. This is because reduction of preload due to venodilatation causing decrease in CO and simultaneously reduction of afterload due to arterial dilatation causing increase in CO balance each other. But, when the block extends above the T_{10} level, then the balance tilts towards hypotension and the blood flow in different organs are impaired. Till up to 20% fall of mean arterial pressure (MAP) cerebral blood flow does not fall. But untill now it is still controversial and unanswered that up to which level the decrease of mean arterial blood pressure is acceptable. However, the reduction of blood pressure below 30% of mean arterial pressure is not advisable.

In summary, the sympathetic outflow to the capacitance vessels of the whole body originates from the T_1-L_2 segments of spinal cord. Among these the sympathetic cardioaccelerator fibres arise from the T_1-T_4 segment of spinal cord. The degree of compensatory sympathetic response to the central neuroaxial block is proportional to the number of segments blocked. In spinal and epidural block due to pharmacological sympathectomy the decrease in venous return decreases cardiac preload and hence cardiac output. In response to this change there is a compensatory increase in the heart rate (provided the cardioaccelerator fibres are not blocked) which tries to maintain the cardiac output and BP. This is mediated by the sinoaortic baroreceptors. On the otherhand, the decreased afterload due to dilatation of arteriolar resistance vessels due to pharmacological sympathectomy in spinal or epidural block may improve the performance of LV (provided preload is maintained by fluid) CO, BP and visceral perfusion. But the ultimate result regarding the CO, BP and organ perfusion depends on the severity of the reduction of preload and afterload which again depend on the extent of block of sympathetic outflow. Coronary flow increases as long as CO and pressure head in aorta is maintained. If CO and pressure head is not increased, then vasopressor agents are required to maintain BP, tissue perfusion and patient's well-being by constricting the capacitance vessels and the arteriolar resistance vessels. Compensatory increase in heart rate to maintain CO and BP requires intactness of the sympathetic efferent fibres to the heart which originate from the T_1 to T_4 segment of spinal cord. If sympathetic block extends above this height, then the compensatory increase in heart rate and myocardial contractility will not occur and this will result in severe hypotension. It is also possible in such situation that increased unopposed dominance of vagal tone to heart may drive the heart rate slow causing bradycardia and hypotension. So, to counteract this increased vagal tone anticholinergic agents (atropine) are also needed.

Respiratory Effect

The spinal or epidural anaesthesia with sensory block up to a certain level, i.e. more or less around T_{10} level have little clinical significance on the mechanics of respiratory system. Up to this level of block tidal volume remains unchanged. But, vital capacity may decrease due to the reduction in inspiratory and expiratory reserve volume. This is again due to the paralysis of some accessory respiratory muscles of abdomen. Rarely, respiratory arrest occurs and if it occurs it is due to the hypoperfusion and hypoxia of respiratory centre in brainstem due to severe hypotension. This occurs when the block extends up to a very higher level or due

to total spinal block. Hence, central neuroaxial block should be used catiously in comprised (respiratory system) patient because unintentional extension of block to the higher level causes paralysis of accessory respiratory muscles and further deterioration of pulmonary function even respiratory arrest due to hypoperfusion and hypoxia of central respiratory centre.

As the level of block rises an increasing proportion of the muscle, involved in respiration, are affected. The principal muscle of respiration, i.e. the diaphragm, usually remains unaffected, except in extreme cases of high spinal anaesthesia extending to cervical region or total spinal block. As the block ascends, gradually more and more intercostal muscles become paralysed after the paralysis of abdominal muscles. But most healthy patients should be able to maintain normal ventilation by the remaining unaffected muscles. Although the subjective feeling of immobility of chest wall and suffocation may be alarming, if they are not informed in advance. In such situation mild sedation may be needed to increase the tolerance of the patient. But the subjective distress may be early and greatly magnified in patients suffering from respiratory disease and if heavy sedation is used. So, the panicky sense of suffocation may sometimes make the central neuroaxial blockade a poor choice of anaesthesia for some patients. The degree of sedation necessary for the patient to tolerate anxiety could cause further respiratory depression in a patient who has limited respiratory reserve. In order to achieve the goal of avoiding instrumentation of the airway (i.e. intubation) by using spinal or epidural anaesthesia, the general rule is to keep the sensory level of blockade below T_7. If higher block is necessary for surgical procedure, then the selection of general anaesthesia with controlled airway should be considered, with or without combination of central neuroaxial block.

Gastrointestinal Effect

The sympathetic supply to GI tract originates from the T_5-L_1 segment of spinal cord. So, when the spinal anaesthesia extending up to T_5 segment results in sympathectomy, then vagal tone over the GI tract dominates and sympathetic tone disappears. This results in hyperperistalsis and early emptying of GI tract. So, gastric emptying is facilitated. Nausea and vomiting also results due to the hyperperistalsis of gut and vagal stimulation. Hence, atropine is effective in treatment of this type of nausea and vomiting by blocking the vagus. The spinal or epidural anaesthesia provides excellent surgical condition of GI tract due to contracted gut. Hepatic blood flow decreases in proportion to decrease in MAP. But its function remains unaffected and there is no hepatic ischaemia. Hepatic function is less impaired in central neuroaxial block than GA. In postoperative stage of epidural analgesia and anaesthesia, intramucosal pH of stomach remains high and provides a protective effects from gastric ulceration.

Renal Effects

Due to wide physiological reserve, the decrease of renal blood flow for reduction of BP following central neuroaxial block, have little physiological importance. But neurological block is a frequent cause of urinary retention, causing delayed patient discharge from the hospital and frequent catheterisation. Urine production is unaffected by the spinal or epidural block, as long as the mean arterial pressure is not significantly reduced. During regression from spinal or epidural block, it starts from the higher level and the thick nerve fibres are freed first. Hence, as the centre of bladder innervation is situated at $S_{2\text{-}4}$ spinal segment and some of the nerve fiber involved in urination are thin and easily blocked, so they may be the last to regress. Therefore, the passing of urine may be one of the last effects of regression of spinal or epidural anaesthesia.

Neurological Effects

Preoperative anxiety before surgery leads to sympathetic stimulation and increased release of catecholamine that results in gluconeogenesis amd myocardial stress. Sympathetic stimulation also causes increased heart rate and increased myocardial oxygen demand. But, sympathectomy resulting from spinal anaesthesia interrupts this catecholamine release and causes reduction of its level. The plasma level of ACTH varies from unknown to decrease, in the presence of sympathetic block.

PREOPERATIVE PREPARATION, PREMEDICATION AND INTRAOPERATIVE MANAGEMENT OF PATIENT FOR REGIONAL ANAESTHESIA

The patients scheduled for regional anaesthesia should also be prepared like general anaesthesia. Because all the regional techniques have a certain failure rate, (though small) and patients may require GA at any moment. Therefore, all the protocols regarding history, fasting, premedication, preoperative investigation, etc. are the same for regional and general anaesthesia. Reassurance is the corner stone of the successful outcome of a regional anaesthetic technique. Many patients prefer to go to sleep during operation. These patients should be reassured that sedation will be available, if required. Some patients have the fears of development of backache or neurological complications, particularly paralysis in future following spinal and epidural anaesthesia. These patients should also be reassured regarding the safety of this technique.

The risks and benefits of the proposed regional anaesthetic technique should also be discussed in advance with the patient. This discussion and written consent should be recorded in the patient's chart. There is always considerable anxiety in patients regarding the outcome of proposed surgery and the procedure of spinal or epidural

anaesthesia. Hence, mild anxiolytic premedication is very essential. If the patients have previous back pain, it increases when the patient is positioned for spinal or epidural anaesthesia. So, this pain can be relieved by any narcotics given in small doses. This will help in better positioning of patient and facilitate anaesthetist to give spinal or epidural block easily. But whatever may be given, it has to keep in mind that over-premedication does not allow the patient to maintain the needed position for extradural or dural puncture, particularly if sitting position is selected. Anxiolysis to the point of disinhibition should also be avoided, because it can lead to sudden untowards movements and agitation of patient, resulting difficulty for RA. The site of injection or block must be cleaned with an appropriate antiseptic agent according to the local hospital or institution policy. The anaesthetists must wear sterile gown and face mask especially during the central neuroaxial block. If the patient is awake the procedure can be made more tolerable by subcutaneous infiltration of small amount of local anaesthetic agent by a very fine 30 G needle or by applying eutectic local anaesthetic mixtures on the skin, before pricking by needle. Care must be taken to avoid inadvertent intravenous injection of local anaesthetic agent. So, prior to injection, aspiration must be performed to detect any blood in the syringe. Aspiration should also be repeated when large volume of drug is used in epidural technique. At the end, the whole procedure should be appropriately documented.

Aspects, other than the regional block, must be carefully considered to ensure that the overall experience of the patient regarding regional anaesthesia should be as much pleasant as possible. Most patients, except those undergoing minor surgical procedure, expect to be sleepy or unconscious. So, attention must be paid to the patient's overall comfort and warmth feeling while lying on a hard table and the provision of a relaxed enviornment. The patient should be protected from viewing the operation by the use of screens and towels, if needed. In some operations the position of the patient may itself give rise to some discomfort and embarrassment due to exposure. So, adequate sedation may make such procedures more tolerable.

Supplementation of Regional Anaesthetic Technique may be Done by the Following Methods

(i) By distraction of mind

The diversion of patient's attention from surgery is the major adjunct of regional anaesthesia. This can be performed by the use of personal stereos. Alternatively, a member of the operating room staff may engage the patient's mind by continuous chating.

(ii) By use of sedation

Properly titrated sedation can be used to supplement the regional anaesthesia. The provision of amnesia and hypnosis for the events in the operating room can be an advantage for many patients. But, the extensive use of sedation in conjunction with regional anaesthesia is illogical at best, and dangerous at worst. In such situation, anaesthesiologist must justify the use of excessive sedative drugs. Theoretically, the choice of sedative drugs during RA appears to be wide. But, in practice only a few drugs are used. Among all the sedatives, benzodiazepine is the first choice. Midazolam, the water soluble benzodiazepine, offers considerable advantages over its predecessor diazepam. It may be administered by intravenous bolus (0.15 to 0.17 mg/kg) or by continuous infusion (0.25 mg/kg/hour) technique. There is wide variation of dose – response relation with midazolam. The above mentioned dose is for guidance only. So, care and caution are required during the use of midazolam.

The newer anaesthetic agent propofol can also be used in place of midazolam. Continuous infusion of propofol is probably the best method of administration of sedation with RA throughout the whole surgical procedure. An infusion of propofol at the rate of 2 to 4 mg/kg/hour will provide sedation with rapid recovery. Now, some newer methods of administration of propofol are also of interest. For this a software algorithms is attached within the infusion pump with the aim to maintain the blood levels of propofol at the selected level (target controlled infusion). By this technique precise degree of sedation may be maintained. Another method of administration of propofol is to allow the patient to self-administer it in anxiolytic doses. This is called the patient controlled sedation and is analogous to the patient controlled analgesia (PCA). The advantages of propofol over midazolam are that the drug is easier to titrate. Over sedation is probably less common and recovery is more rapid, though the amnestic effect of propofol is not as powerful as that provided by midazolam. Care and caution with regard to cardiorespiratory system should be maintained like midazolam.

Small doses of short-acting opioids such as fentanyl (1 to 2 µg/kg) or sufentanyl (0.2 to 0.6 µg/kg) also can be used for analgesia in addition to or instead of sedative drugs. Supplementary analgesia have synergestic action with sedatives and may help to relief the discomfort. During the use of sedatives and analgesics, it is mandatory to monitor the saturation of oxyhaemoglobin and to administer oxygen, whenever necessary.

(iii) By use of general anaesthesia

It may seem unlogistic to render deliberately a patient insensible, when the central neuroaxial block (CNB) is providing perfect operating condition. But, sometimes the anxiety or doubt concerning the efficacy of block provided, or inadequate block may force the anaesthetist to apply general anaesthesia in addition to CNB. In such circumstances very light plane of general anaesthesia is needed. The combination of GA with CNB will give excellent

operating condition, as well as prolonged postoperative analgesia. But while combining GA with CNB, an anaesthetis must keep in his mind that this combination may sometimes produce a potential problem in which sudden onset of sympathetic block from CNB and cardiac depression effect of GA together can cause considerable haemodynamic compromise.

Awake versus Asleep

There has been recent controversy regarding the performance of central neuroaxial blockade in the awake, sedated or anaesthetised patient. The reason of controversy evolves from the fact that awake patient will tell and warn the anaesthetist when neural tissue is deemed to be damaged by a needle or catheter or injecting solution. But, there is no clear cut evidence that always CNB or any other plexus and peripheral nerve block should be performed with the patient awake. Because, there are multiple reports when neural damage has occurred in an awake patient and the patient did not complain at the time of institution of regional block. On the otherhand, there is no doubt that warning signs such as paraesthesia and pain, associated with nerve damage will be masked by sedation or anaesthesia. Again, it is easier to perform regional anaesthesia on a patient who is asleep or anaesthetised, particularly in children. Thoracic epidural blockade with or without catheter is the most difficult situation to resolve. The technique of thoracic epidural anaesthesia is very challenging and success is more likely when the patient is asleep. So, the careful use of nerve stimulators (when a nerve with motor function is to be blocked) is imperative during regional anaesthesia in the anaesthetised patient. But, this cannot be performed when the nerve to be blocked is purely sensory. So, at the conclusion, it can be said that the question regarding the use of spinal, epidural or any regional block in awake and sedated patient is still remain unresolved. But always we will have to keep in mind that if any damage occurs in sedated or anaesthetised patient, then it may be very difficult to defend in the court, though it is widely used all over the world.

Position of Patient

Usually, three positions of patient are used for spinal or epidural anaesthesia. These are lateral, sitting, and prone. Before positioning, to lateral or prone it is mandatory to secure an intravenous line with a large bore indwelling cannula and monitoring devices are connected. The preintervention administration of 0.5 to 1 litre of intravenous crystalloid or colloid solution as bolus to limit the hypotension, induced by central neuroaxial block is considered as standard practice. But, care may be required for those patients with severe pulmonary disease, heart disease, renal disease, etc. Treatment with vasoactive drugs is an alternative approach to IV fluid loading. But, controversy surrounds this topic (Fig. 24.25).

Lateral position

It is the most common position which is practised now for CNB and does not need any well trained assistant. It is useful for more sedated patient also. Patient should be positioned with head slightly tilted down or up, so that the spread of hypo, iso or hyperbaric anaesthetic solution to operative site is optimised. The spinal column has two ventral concavity – thoracic and sacral. So, when the patient is placed in supine after lateral position, the movement of hyperbaric local anaesthetic solution within the spinal subarachnoid space is not always towards the dependent part, if the injection is given at the mid lumbar region. This is because the thoracolumbar kyphosis, moves cephalad from the maximum lumbar prominence situated at the level of L_2-L_3 vertebra towards the most dependent part of the thoracic curvature in supine position, situated at about T_4 or T_5 vertebra level.

If the dural puncture is performed in lateral position and this position is maintained for few minutes, then there is a slight tendency for the dependent limb to be more influenced or paralysed by unilateral manner, although due to CSF mechanics both sides are ultimately affected equally. Leaving the patient on lateral position for 5 to 10 minutes after the injection of hyperbaric solution, there is more likely to produce a unilateral denser block on the dependent side, but not the complete unilateral block. Only at the higher spinal segmental level there is preferential unilateral blockade. With regard to cephalad and caudal spread the lateral position functions in the same way as the supine position. In any position, lateral, sitting or prone few moments should always be spent for careful identification of the most appropriate interspinous space for the dural puncture or EA which may save much time, increases the chances of successful block and will ensure that the procedure is as speedy and comfortable as possible for the patient.

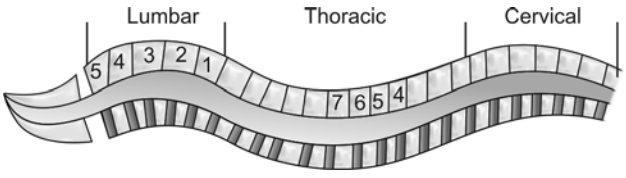


Fig. 24.25: The most prominent part of the lumbar lordosis and the most dependent part of the thoracic curvature in supine position

Sitting position

It is chosen only when the lower lumbar and sacral levels of anaesthesia are required or is adequate for surgical procedure such as perineal, lower urinary tract, vaginal, etc. Sometimes obesity and

scoliosis make identification of spinous process and interspinous spaces at midline more difficult in lateral position. So, if for only obesity and scoliosis, sitting posture is chosen but higher sensory anaesthesia is needed, then the patient should be made supine immediately after the procedure in sitting position. Some anaesthetists also prefer the sitting position than lateral position for routine spinal anaesthesia. This is because the sitting position has the advantages that generally the vertebra column remain in a straight line in such position and the identification of the interspinous spaces and so the technique of block is easier to perform. On the otherhand, some patients may find it is difficult to sit for the lumbar puncture (e.g. fractured neck of femur) and in such situation the lateral position will be more appropriate. Care may be required if premedication has been administered and there should be an assistant for positioning of the patient. After giving block at L_{2-3} interspinous space, if sitting position is maintained for 5 to 10 minutes, then it blocks the lower lumbar (below the puncture site) all sacral (S_{1-4}) and coccygeal spinal nerves, i.e. cauda equina only, which is called the saddle block. It also depends on the lumbar level where dura is punctured. If dura is punctured at higher thoracic level and sitting position is maintained for 5 minutes then more higher spinal segments will be blocked.

Prone position

This position is chosen only when the patient is to be maintained in that position during surgical procedure. Paramedian approach is more indicated and helpful in that position. For confirmation of subarachnoid block, we have to aspirate CSF, because CSF pressure is minimum in that position. In some circumstances the spinal or epidural anaesthesia is given in lateral position and then patient is make prone. In such situation. If the patient is placed in prone position before fixation of drug, then the movement of drug in CSF is determined by the same factors such as change the compliance of the subarachnoid space, tilting of vertebral column and as well as the gravity of the drug. As the thoracolumbar kyphosis is reversed when the patient is prone and the degree of flexion – extension achieved by prone position influences the location of the most dependent site as well as the movement of drugs, so the placement of patient into prone position with the downward direction of head before the onset of a gravity dependent spinal anaesthesia could result in dangerously high cephalad spread.

SPINAL ANAESTHESIA

Technique of Intrathecal Anaesthesia Through Lumbar Puncture Route

Worldwide, the intrathecal (spinal or subarachnoid) anaesthesia is the most commonly performed regional anaesthetic technique. Whereas extradural (or epidural) blockade is used to provide the labour analgesia and postoperative analgesia, in addition to any surgical anaesthesia. For intrathecal anaesthesia thoracic or cervical route are not used for fear of spinal cord injury, except when the dura is inadvertently punctured during the thoracic or cervical extradural analgesia/or anaesthesia. So, for intrathecal or spinal anaesthesia only the lumbar puncture is conducted under strict aseptic technique with all the required equipment for resuscitation.

Once, the anaesthetist is happy with the patients positions, then the skin of the back should be cleaned with an antiseptic solution or spray, guided by the protocol of that institution and allowed to dry. Then the patient should be drapped properly. After that the skin and the deeper structures over the lumbar spines can be infiltrated with local anaesthetic agent prior to the insertion of spinal needle but this will depend on the anaesthetist's choice. Some anaesthetists do not infiltrate the skin by LA agent prior to the main technique. Now the anaesthetists has choice for several types of needle for lumbar puncture, i.e. from the traditional cutting (Quincke) to the more recently introduced pencil tip (Whitcare and Sprotte) needles. However, the pencil tip needles are now the first choice of many anaesthetists for intrathecal anaesthesia, as it is associated with reduced incidence of PDPH.

Most anaesthetists perform intrathecal lumbar puncture in the midline and the space is selected between the spine of L_3 and L_4 or L_2 and L_3 vertebrae. First the vertebral spinous processes is selected and identified. Then, the spinal needle is inserted through the area of an anaesthetised skin, making an angle cranially to compensate for the (Fig. 24.26) angle of the spinous process. The needle will pass gradually through the skin, subcutaneous tissue, supraspinous ligament, interspinous ligament, ligamentum flavum and finally through the epidural space, dura mater and arachnoid mater before entering the subarachnoid space. There is often a characteristic 'give', when the tip of the needle passes through the dura and arachnoid layer. The successful intrathecal puncture of needle is confirmed, when the removal of the stylet is followed by the appearance of CSF at the hub of the needle. The appearance of CSF may be delayed if a very fine needle such as 27G is used. Again if there is any doubt regarding the authenticity of the fluid, then the use of a bedside glucose testing strip may be helpful. If a cutting tip spinal needle is used, then it is recommended that the needle should be inserted with the bevel parallel to the fibres of the ligamentum flavum and dura mater, so that the fibres are parted away rather than cut by the needle tip, as it is advanced. Inserting the needle in this fashion also reduces the chances of postdural puncture headache (PDPH). The lateral or paramedian approach to the subarachnoid space is also

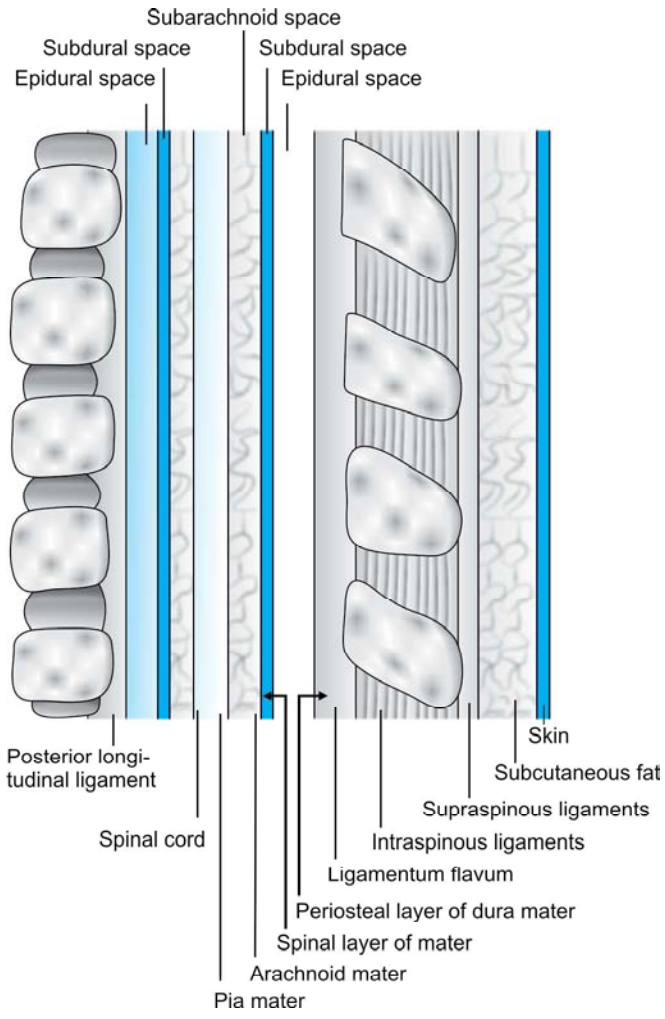


Fig. 24.26: The sagittal section through lumbar vertebrae

useful when the midline approach is difficult due to some scar tissue or arthritic changes. Once, the tip of the needle is confirmed to be lying in the subarachnoid space, then the local anaesthetic solution is injected. It is a good practise to confirm that the tip of the needle has not moved during aspiration of CSF or at some point during the injection of LA agent. Once the block has been established, then the upper level of anaesthesia should be identified with the loss of sensation to pin prick (a common measurement), although some would suggest that the touch is a more reliable method for the assessment of the level of block.

Choice of Local Anaesthetic Agent for Spinal Anaesthesia

In spinal or subarachnoid anaesthesia various drugs with different volumes, concentration, doses, baricity, sites, and position of patient are used to meet the aim. There are multiple studies regarding all these variables. Comparison of these multiple studies is also very difficult as different parameters for the measurements of neural block (both sensory and motor) have been used. The most important factor for the choice of local anaesthetic drug in spinal block is its duration of action which also varies according to the concentration, volume and total dose (in mg) of drug and the, site of injection and the position of patient. Among these the most important factor for duration of action is the drug itself. Till now, many different drugs have been used, but only a few drugs remain in current practise. In the recent years the choice of drug, available to anaesthesiologist, has been reduced only to the most commonly used 0.5% bupivacaine in 8% dextrose. Other drugs that are available in other countries (not in India) include procaine, lignocaine, mepivacaine and tetracaine. The duration of action of these drugs varies, (the reason of which is described above) but in general, procaine has a short duration of action, lignocaine and mepivacaine have a moderate duration of action and tetracaine, bupivacaine have a longer duration of action. The action of hypobaric solution persists for longer period than that of the isobaric solutions which in turn have a more prolonged action than that of the hyperbaric solutions. Sometimes, the epinephrine is added to the local anaesthetic agents to extend the duration of action. It doubles the length of duration of action of LA agents. The epinephrine may also have a direct antinociceptive effect on the spinal cord by the direct activation of descending inhibitory systems that modulate the dorsal horn neural activity. If patient plans to go home after outpatient surgical procedure, then the short acting LA drug is preferred.

Three drugs are commonly used for spinal or epidural anaesthesia. These are lignocaine, tetracaine and bupivacaine (Table 24.2).

Lignocaine

It has wide application in regional anaesthesia, mainly in spinal anaesthesia as hyperbaric or isobaric solution and provides a short to intermediate duration of action. It is chosen for the procedures that can be completed within 1 hour or less. The commonly used concentration of lignocaine in spinal block is 5% solution in 7.5% dextrose (hyperbaric). For the standard spinal anaesthesia 50 to 100 mg of lignocaine is used at L_2-L_3

Table 24.2: Specific gravities of some spinal anaesthetic agents

Agent	*Specific gravity*
1. Bupivacaine	
0.5% plain	0.99 - 1
0.5% in 8.25% dextrose	1.02 - 1.03
2. Lignocaine	
2% plain	1
5% in 7.5% dextrose	1.02 - 1.03
3. Tetracaine	
0.5% in water	0.99
0.5% in dextrose	1.01 - 1.02
4. Procaine	
10% plain	1.01
2.5% in water	0.99

interspinous space to achieve block up to mid thoracic level for a duration of 60 to 90 minutes. The onset of action of hyperbaric lignocaine is vary rapid and the upper level of block can be pushed higher by different physical intervention within 5 minutes after administration of LA drug or within 10 minutes, if epinephrine is added. The hyperbaric lignocaine solution is also an excellent preparation for the saddle block in sitting position. And in these cases dose can be reduced if the patient can be kept sitting for 5 minutes after injection. In such situation the dense motor and sensory block below the level of dural puncture is expected. If the patient is placed supine rapidly from sitting position after injection, then it will be not a saddle block and higher sympathetic, motor, and sensory block is anticipated due to the cephalad spread of LA agent. It was found in different studies that there is higher incidence of transient radicular irritation with the use of 5% lignocaine in subarachnoid space. But the relation between 5% lignocaine and transient radicular irritation is controversial. So, the reduction of concentration of lignocaine in hyperbaric spinal preparation is under trial.

Till now, there is also some controversy regarding the use of vasoconstrictor with different local anaesthetic drugs, like lignocaine, tetracaine and bupivacaine during spinal anaesthesia. The addition of 0.1 to 0.2 mg epinephrine or 5 mg phenyl ephedrine prolonges the duration of lignocaine and its efficacy, during the central neuroaxial block. Here two segment regression is the measurement of duration of neuroaxial block. But the addition of adrenaline in spinal drug to increase the duration of action of it may increase the risk of anterior spinal artery syndrome and cord ischaemia, particularly if associated with hypotension.

The subarachnoid block by isobaric solution is also possible by using 2% plain solution of lignocaine without added preservative. But the standard dose of isobaric lignocaine solution in subarachnoid block is 3 cc to 4 cc with or without 0.2 mg epinephrine. It provides anaesthesia up to T_{10} level for 60 to 90 minutes if drug is administered at L_3-L_4 space in supine horizontal position. However, the level of anaesthesia by isobaric lignocaine solution does not depend on the physical position of the patient after injection. But the level of anaesthesia in isobaric solution depends only on the volume, total dose, direction of needle-bevel and the speed of injection of local anaesthetic drug. Mixed with sterile water, preservative free 2% lignocaine also can be used as hypobaric solution for subarachnoid (SA) block.

The allergy caused by LA agent is commonly due to PABA (para-aminobenzoic acid) which is the breakdown product of ester linked LA agents such as procaine by plasma enzymatic cleavage. It is thought to trigger an allergic reaction in certain individual. This is because that patient may have previous immunological sensitisation to PABA as it is a common ingredient in many fragrances and cosmetics. Thus, I_gG or I_gM mediated anaphylaxis is a possibility of some ester linked LA agent. True allergy to amide local anaesthetic agent is uncommon, except in multiple-use preparations that have methylparaben as preservative. Methylparaben is a common allergen and is related to PABA. Even skin testing conducted under optimum circumstances to identify allergy of LA agent does not totally eliminate this concern. So, reasonable caution is mandatory.

The dose, concentration and volume of lignocaine used in epidural anaesthesia is discussed in separate section.

Bupivacaine

Like lignocaine it is also very commonly used LA agent for spinal anaesthesia and in some country it is the only available drug for subarachnoid block. Commonly used hyperbaric concentration of bupivacaine for subarachnoid block is 0.75% and 0.5% in 8.25% dextrose. The 2 cc of these hyperbaric bupivacaine solution, injected at L_3-L_4 interspinous space in supine horizontal position can block sensory level up to T_4 or T_6 spinal segment. However, lower dose is used in some extreme age group of patient due to the reduced compliance of subarachnoid space. The expected duration of action of 2 cc hyperbaric bupivacaine in subarachnoid space is average 2 hours. This duration of action can be reduced if the drug is made to spread over a wide area and diluted with CSF by the change of physical position of patient. However, as the spread of LA agent reduces the duration of action, but it increases the level of block of spinal segment. Isobaric form, i.e. 0.5% and 0.75% bupivacaine in plain aqueous solution are also used in spinal anaesthesia. Different studies indicate that there is no difference in the duration of action over a wide range of concentration from 0.25 to 0.75% as long as the total dose (in mg) of isobaric bupivacaine is kept constant. Below 0.25% the intensity and the duration of motor block is decreased. With isobaric solutions the onset of action of bupivacaine is also slow, with full sensory and motor block evolving only after 10 minutes. As with other isobaric techniques, the level of block is typically up to T_{12} segment and the haemodynamic alterations are minimal due to the lower level and slow onset of

anaesthesia which allows adequate time for endogenous compensation. When the isobaric form of bupivacaine is used, then the injected total dose of drug (i.e. total dose in mg) is more important in determining the height of block than the volume of drug and position of the patient. The action of bupivacaine lasts for 2 to 2.5 hours. The typical subarachnoid dose of bupivacaine is 15 to 20 mg. Addition of epinephrine with bupivacaine for spinal anaesthesia has minimal clinical significance.

(Epidural dose of bupivacaine is further discussed in separate chapter).

Tetracaine (Amethocaine)

It is available in package as both crystal (20 mg) and 1% solution (20 mg) which can be drawn in sterile water (hypobaric), dextrose solution (hyperbaric), or in CSF (isobaric). Thus, an anaesthetist will prepare their own solution (baricity) of tetracaine according to their need. The onset of action of tetracaine is 5 to 10 minutes and the duration of action is 2 to 3 hours with epinephrine. It may persist for 5 hours in lower extremity. It is the most commonly used agent for spinal anaesthesia in USA. In some country premade tetracaine with different baricity is also available. Premade tetracaine spinal kits contain 1% tetracaine solution in 2 cc ampoule which is mixed with 10% dextrose for hyperbaric solution. Some anaesthesiologists do not prefer premade preparation. Instead, they constitute the solution themselves immediately before their use. Because as tetracaine is an ester local anaesthetic, it loses its potency in premixed solution after exposure to heat, which explains occasional failure of block after the use of premade tetracaine. The usual dose of hyperbaric tetracaine is 6 to 20 mg, depending on the patient's height, weight, age and other factors that decrease the compliance of subarachnoid space. The level of sensory and motor block usually extends up to the level of T_4-T_6 spinal segment after lumbar spinal of 20 mg tetracaine at L_2-L_3 interspinous space in supine position. The onset of action of tetracaine is relatively rapid than bupivacaine, but some what slower than lignocaine. The addition of 0.2 mg epinephrine with tetracaine increase the duration of action by 20 to 50%. The classic isobaric tetracaine solution can be prepared by mixing its crystal with CSF, drawn from patient after dural puncture. Like other isobaric solutions the speed of injection, total dose, orientation of the bevel of spinal needle, etc. influences the level of block, but not the patient's position or posture (physical condition).

The dose of isobaric tetracaine solution is same as in hyperbaric.

Choice of Needle for Spinal Anaesthesia

1. The first question about the choice of spinal needle is if it should be disposable or reusable. But, the most anaesthetists accept the disposable tray, though there is no indication that the disposable set shifts the risk-benefit equation in patient's favour.
2. The second question regarding the choice of needle is cutting or noncutting pencil tipped. Cutting tipped needle like Quincke or Babcock, cut the dural fibre during their introduction causing more leakage of CSF and more incidence of post spinal headache. Whereas, the noncutting conical pencil tipped needle like Greene / Whitacre / Sprotte, etc. do not cut the dural fibres and are associated with decreased incidence of PDPH, when the needle sizes are compared.
3. The third question regarding the choice of needle is if it should be fine or thick. Fine needles such as 25-gauge or above are preferred for less incidence of post spinal headache. But, the introduction of these fine needles is technically difficult and the incidence of failure rate is high. Very fine needles may be inserted through an introducer or a 20 G needle. The introducer aids the passage of fine spinal needle through the tough ligamentous structure of the vertebral column. In older patients in whom the ligamentous structure of the vertebral column become calcified, it may be impossible to insert a fine tip pencil point needle in the subarachnoid space without the use of an introducer. The introducer has an additional advantage that spinal needle does not touch the skin and so also reduces the chance of infection.
4. The fourth question regarding the choice of needle is if it should be long or short bevelled and sharp or blunt pointed. The standard sharp pointed long bevelled needles are suitable for many blocks and may permit smooth passage of needle through the tissues. This enables fine control of the needle tip, but less recognition of the tissue plane. Whereas, the short bevelled blunt needle (e.g. Sportte needle) may enable tissue planes to be identified more easily, but the passage of needle through the tissues is not so smooth. The nerve damage caused by the type of needle is controversial. It is assumed that the standard sharp long bevelled needles cause less nerve damage if it is pierced accidentally but there is more chance to pierce the nerve by this type of needle. On the other hand, the blunt short bevelled needle has less chance to pierce the nerve, but if happens cause more damage. The less nerve damage by the sharp long bevelled needle is due to the fibres being separated rather than torn.

Needle

The standard hypodermic needle has a sharp pointed tip with bevel less than 20°. This is called the 'A' bevel type of needle. But a needle which is used for nerve block in regional anaesthesia is designed to be less traumatic to the nerve tissue. So, it is made slightly blunt with the bevel greater than 45° and is called the 'B' bevel type of needle. Depending on the purpose of

needle the bevel can be either sharp, polished or dull. The usual site for exit of drug from the needle is at the tip of it. But for some special applications the exit site is sometimes kept not exactly at the tip of the needle, but slightly proximal to the tip of the needle. Some other needle's modifications may also improve the dexterity of the operator. These are wings that can be attached to the hub of the needle. This allows the two handed better grip of the needle and enable the operator to feel the tissues better during its passage through it. Some needles have alternating polished and dull surface along the shaft of it for better tissue feeling. The shape, sharpness, bevel and hole at the tip of the needle are all variable that can be manipulated to suit the special needs. The Touhy and Huested modification are such examples of altering the tip of needle for special task such as epidural anaesthesia. The 2 to 4 mm area at the tip of Touhy needle is gently curved, which is designed to pass it through the soft tissue smoothly and make contact with dura without penetrating it (Fig. 24.27).

The spinal needles are also classified (i) according to the size of the needle, and (ii) according to the shape of the needle tip. According to the size, the type of spinal needle extends from 20 to 30 G. Thicker needle helps to feel the tissue structures better during its passage through it and after piercing the dura the flow of CSF through wide bore needle is faster. So, it helps in easy recognition of proper placement of needle in subarachnoid space. Another advantage of thicker needle is less failure rate in compare to finer needle. But PDPH incidence is high in case of thicker needles due to the large dural hole and significant CSF leak. On the otherhand, these advantages of thick needle becomes the disadvantages of fine needle. So, in fine thin needle there is less feeling of tissue structure during its passage through it and the flow of CSF through needle is not easy. So recognition of placement of it in subarachnoid space is difficult, and failure rate is high. But one distinct advantage of fine needle is less incidence of PDPH. Sometimes very fine spinal needles (25 to 30 G) need introducer (18 to 20 G) to facilitate their insertion through skin, ligaments and other structures. The introducer also prevent needle deflection, bending or breaking while passing through the tissues. The introducer also helps to keep the spinal needle sterile as it does not come in contact with skin and other structures.

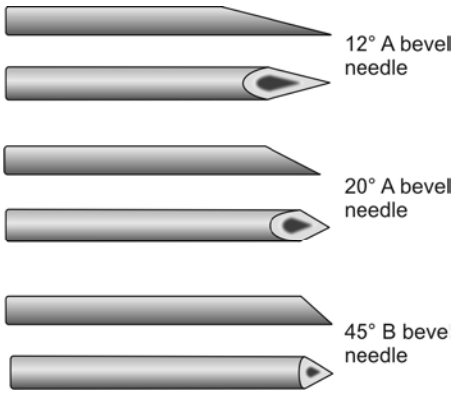
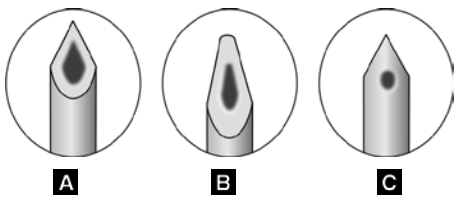


Fig. 24.27: The different types of A and B needle used for regional block

According to the shape of the tip of spinal needle, it is again subclassified into: (a) cutting tip spinal needle, and (b) noncutting pencil tip spinal needle (Figs 24.28A to C).

(a) Cutting tip spinal needle are

i. Pitkin needle – It has short, cutting bevel, and eccentric sharp pointed tip.
ii. Howard Jones – It is metallic spinal needle with cutting tip, available in size ranging between 20 to 24 G.
iii. Quincke-Babcock – It is the most widely used spinal needle with a cutting tip and long sharp bevel. It has exit point at the tip and available from 16 to 30 G.



Figs 24.28A to C: Spinal needle. A. Quincke, B. Sprotte, C. Whitcare

iv. Atrucan – It is cutting tip needle with double bevel.

(b) Noncutting pencil tip spinal needles:

i. Green needle – Long sharp bevel and rounded tip with orifice at end.
ii. Whitcare needle – Solid pencil tip with small lateral orifice, 2 mm proximal to the tip – proximal injecting needle.
iii. Sprotte needle – Solid pencil tip with large lateral orifice whose diameter is equal to the internal diameter of the needle with proximal injecting point.

Factors Affecting the Height of and Duration of Block in Spinal Anaesthesia

1. Density

The density of any solution is the weight of solute in gram per 1 ml of solvent. Concentration is nothing but density, but concentration in w/v means weight of solute in gram per 100 ml of solvent. Increased concentration of any local anaesthetic solution in CSF increases the duration and the height of block. It influences the duration more than baricity. But baricity influences the height of block more than the concentration.

2. Specific Gravity

It is the ratio of density of a solution compared to the density of water. It also influences the duration and the height of block like the baricity of solution of a LA drug by influencing the spread.

3. Baricity

Baricity is the ratio of comparing the specific gravity of one solutions to another. Baricity of LA solution is classified as hyperbaric, isobaric and hypobaric in reference to the specific gravity of CSF which varies between 1.003 and 1.005. The plain LA solutions such as 2% lignocaine and 0.5% bupivacaine which is available commercially for local infiltration are prepared

at a specific gravity nearly identical to CSF (isobaric) at room temperature and hence they are isobaric. When they are warmed to body temperature before injection, then they become slightly hypobaric. The classic isobaric LA injection can also be prepared from crystal of local anaesthetic agent such as tetracaine after mixing it in patient's CSF. Hypobaric solutions are also can be made by mixing the crystal of local anaesthetic agent in preservative free sterile water. Hyperbaric solution are created by mixing the LA agent with 7.5 to 10% dextrose (in order to achieve a gravity of 1.02 or above) (Table 24.3).

Hyperbaric Solution

The hyperbaric solution of LA agents are made by adding 5 to 10% dextrose with it. They move downward in CSF and block the roots of nerve below the puncture level. In sitting position and if it is maintained for 5 to 10 minutes after the administration, of LA agent, then the LA agent moves caudally and blocks the coccygeal, sacral and lumbar spinal nerves (below the puncture site) only. This is called the saddle block. The hyperbaric solution of LA agent also moves to the dependant side in lateral position and cephalad up to the midpoint of thoracic curvature in supine position if the site of dural puncture is at the height of the lumbar lordosis and the patient is in slightly Trendelenburg position. Otherwise, (if the patient is in anti-Trendelenburg position and the site of dural puncture in at the height of the lumbar lordosis) the drug will accumulates caudally in the sacral hollow and will produce inadequate height of block. In supine position the hyperbaric solution causes more higher block than the isobaric or hypobaric solution. In lithotomy position baricity have little effect on the height of the block. The hyperbaric solution acts in a more predictable manner than the hypobaric or isobaric plain solution of LA agent. The peripheral nerve toxicity of local anaesthetic agents is increased in the presence of dextrose. But it is uncertain, whether this is a direct effect of dextrose on nerve or whether the presence of dextrose enhances the toxic effect of local anaesthetic agent.

Table 24.3: Factors affecting the level of spinal anaesthesia (arranged according to their importance from more to less)

i.	Site of injection
ii.	Baricity of anaesthetic solution
iii.	Position of patient
	– During injection
	– Immediately after injection
iv.	Drug dose
v.	Drug volume
vi.	Patient height
vii.	Curvature of spine
viii.	Pregnancy
ix.	Needle direction
x.	Age
xi.	Intra-abdominal pressure

Isobaric Solution

They are the simplest solutions of LA agent. They are commonly marketed for infiltration anaesthesia such as 2% xylocaine and 0.5% bupivacaine in vial with preservative and are also used in epidural block. The spread and consequently the height of block by isobaric local anaesthetic solution in spinal anaesthesia does not depend on the position or the posture of the patient. So, the effects are somewhat unpredictable. Tetracaine (amethocaine) isobaric formulation is made by diluting the tetracaine crystal (20 mg) in CSF. The distribution of isobaric local anaesthetic solution and consequently the height of block produced by it mainly depends on the volume of drug, the temperature and the direction of injection (Table 24.4).

Hypobaric Solution

They are usually used and most useful in prone positions for anorectal procedures or in lateral positions for hip surgery. Theoretically, 2% lignocaine has been investigated as a 'clinically' hypobaric spinal drug. But, practically physiochemical properties of 2% lignocaine is more isobaric than hypobaric. Still some anaesthesiologists find it more useful in situations reserved for hypobaric techniques.

Table 24.4: Factors that probably do not affect the height of spinal block

- Rate of injection
- Addition of vasoconstrictor
- Barbotage technique
- Cough or any strain, like bearing down during labour
- Bevel of needle
- Weight of patient
- Gender

4. Lipid and Water Solubility of Drug

More lipid soluble anaesthetic agent such as fentanyl spreads less than the less lipid soluble anaesthetic agent such as morphin in spinal anaesthesia. This is because when an agent becomes more and more lipid soluble, then it is absorbed more and more quickly by the lipid rich nervous system impairing the spread it.

5. Volume of Anaesthetic Solutions

Like baricity, position of patient and site of injection, the volume and the total dose of drug (in mg), has same effect on the height of spinal anaesthesia. But increased dose in mg certainly prolongs the duration of block. On the otherhand, the greater spread of a large volume of local anaesthetic agent may briefs its duration of effect due to quick absorption by the blood vessels of large area. So the spread increased by baricity, posture or other means curtailed the duration of effect of LA agent.

6. Barbotage

This term is derived from the French word named 'barboter' which means to paddle or mix. Repeated aspiration of CSF (Table 24.5) by syringe and injection of LA in the subarachnoid space cause mixing and dispersing of the original dose of local anaesthetic agent in it. Thus, the spread of a given dose of local anaesthetic drug and

Table 24.5: Dosages and duration of action of commonly used spinal anaesthetic drugs

Drug	Preparation	(Doses in mg)			(Duration in minute)	
		Perineum and lower limbs	Lower abdomen (up to T_{10})	Upper abdomen (up to T_4)	Plain	With adrenaline (0.1 to 0.2 mg)
Lignocaine	5% in 7.5% dextrose	20 - 50	50 - 70	70 - 100	60 - 90	90 - 120
Bupivacaine	0.5% in 8.25% dextrose	5 - 10	10 - 15	15 - 20	90 - 120	120 - 150
Ropivacaine	02 - 1% solution	6 - 12	12 - 16	16 - 18	90 - 120	90 - 120
Tetracaine	1% in 10% dextrose	5 - 10	10 - 15	15 - 20	90 - 120	120 - 150

subsequently the height of anaesthesia can be increased by barbotage, which is now hardly used.

7. Site of Injection

Any site (or interspinous space) for injection can be chosen for the administration of local anaesthetic agent for spinal or epidural anaesthesia. But, obviously the higher will be the site of injection, the higher will be the height of block. This is applicable to both the spinal and epidural anaesthesia. But in spinal anaesthesia the higher will be the site of injection, the higher will be the chance of cord injury and severe hypotension. The L_{3-4} / L_{4-5} is the safer intervertebral space to restrict the dural puncture for spinal block, in order to avoid the possible damage of spinal cord. But, epidural block can be given at any site such as cervical, thoracic, lumbar, and sacral.

8. Position of Patient during and Immediately after Injection

Like the above mentioned factors, the position of patient during and immediately after injection in subarachnoid or epidural space is also very important in determining the height of block. But the Baricity of LA solution, concentration and volume of drug, position of the patient and the site of injection are all interrelated and can be modulated according to the necessity of the height of block. After placement in subarachnoid space the local anaesthetic agent is very rapidly taken up by the nerve tissues of spinal cord and disappears from CSF. So, the first 5 minutes after administration of drug are very crucial for the local anaesthetic agent for tissue fixation. In lateral position, the vertebral column is more or less horizontal. However in lateral position in some women, the vertebral column is inclined towards the head and it is due to increased width of pelvis relative to the shoulder. In some men the vertebral column is inclined towards the coccyx because of the increased width of shoulder relative to the pelvis. So, the operating table should be inclined during CNB in lateral position according to the necessity, keeping all the factors in mind.

For anorectal, perineal, genital and bladder neck surgeries, 1 ml hyperbaric solution in sitting position (maintained for 5 minutes) at L_{4-5} space is useful which blocks only the sacral, coccygeal and L_{4-5} spinal nerve with little or no fall of blood pressure. This is known as the saddle block. Increasing the volume and concentration of LA agent the duration of this type of block can be increased according to the duration of surgery. But for lower abdominal surgery 1.5 to 2 ml drug (hyperbaric) at L_{3-4} space is injected in lateral position and the patient is turned immediately in supine position. This is sufficient for 45 minutes to 1 hour surgery in lower abdomen. L_{3-4} interspace forms the apex of the lumbar curvature. So, administration of heavy drug in that space in supine position spreads up to the mid thoracic segment as T_5 is the most dependent part of the thoracic (Fig. 24.29) curvature in supine position. Sometimes, after injection drugs may fall in the hollow of the sacrum, leading to block of only sacral and coccygeal spinal nerve roots. For upper abdominal operations block up to T_4 or T_5 spinal segment is required. This is obtained when 2 to 3 ml of hyperbaric LA drug is injected at L_{2-3} interspace with slight head-down position. For upper abdominal surgery the level of anaesthesia is needed up to T_4 segment, along with the greater splanchnic nerve ($T_{4, 5, 6, 7, 8}$) block supplying the omentum and mesentry. So, intraoperative paraoesophageal vagus block is also given by surgeon for upper abdominal surgery, along with the spinal or epidural anaesthesia.

Some landmarks of segmental supply which is very useful for spinal anaesthesia are: perineum – S_{2-4}, groin – L_{1-2}, umbilicus–T_{10}, xiphoid – T_7, nipple – T_{4-5}, 2nd intercostals space – T_2, clavicle – $C_3 - C_4$, subcostal arch – T_{6-8}. Factors that decrease the size of subarachnoid space also cause the compression and the decrease of the compliance of subarachnoid space. For example, increased intra-abdominal pressure transmitted via intervertebral foramen to epidural space cause compression and reduction of subarachnoid space. Thus pregnancy, obesity, ascities, huge ovarian tumour or any other factors that increase

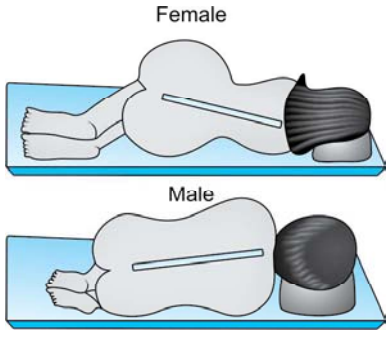


Fig. 24.29: The natural tendency of inclination of vertebral column in lateral position of male and female patient

the intra-abdominal pressure cause reduction of the volume of subarachnoid space and increase in the height of block with the same volume of drug. Age decreases the compliance of subarachnoid space and increases the height of block also. The decrease of compliance of subarachnoid space with increase of age is due to the increase of stiffness and decrease of the size of subarachnoid space.

9. Pregnancy

Pressure over inferior vena cava by gravid uterus causes dilatation of the epidural veins which in turn decreases the volume of the epidural space and increases the epidural pressure. Thus compession of subarachnoid space from increased epidural pressure causes lower volume of it and higher spread of LA solution. Progesteron also potentiate LA action, which is also responsible for the increase in spread of action of local anaesthetic agent in pregnancy.

10. Ascites

It has also the same effect as gravid uterus on inferior vena cava and in turn on epidural vessels and space. Also increased intra-abdominal pressure from ascities is transmitted directly into the epidural space through the intervertebral foramen and thus increases the epidural pressure which in turn decreases the size of subarachnoid space and increases the spread and action of local anaesthetic agent in spinal anaesthesia.

11. Obesity

Obese patients also have decreased subarachnoid compliance, particularly when the patient is in supine position, where the weight of abdominal pannus acts much in the same way as a gravid uterus or ascitis.

12. Spinal Stenosis

For the same reasons, decreased compliance of subarachnoid space in spinal stenosis causes wider spread and increased action of local anaesthetic agent (LA) in spinal anaesthesia.

13. Age

The age influences the conduct and outcome of subarachnoid anaesthesia to some extent. Geriatric patients have the decreased compliance of subarachnoid space and reduced CSF volume which causes greater spread and increased extent of the level of spinal anaesthesia with same volume of drug. This is applicable to hyperbaric, as well as to isobaric and hypobaric anaesthetic solutions.

Geriatric patients rarely develop PDPH. So, the use of fine, noncutting spinal needle to minimise this complication is not necessary. On the otherhand, the thick and cutting sharp spinal needle have advantage for geriatric patients, since these patients have difficult dural puncture due to the calcification of the ligaments such as supraspinous, interspinous, etc. and may offer greater dexterity. The low incidence of spinal headache in geriatric patient is probably related to the advanced degenerative arthritis which is common in the geriatric spine and makes the continued leak of CSF unlikely due to inflammation that induces sealing of the dural puncture.

14. Temperature

It also acts for movement of the drug.

Height of block necessary for few common operations

Prostate, bladder, thigh – block up to T_{10}
Inguinal hernia – block up to T_{10}
Umbilical operation – block up to T_{6-7}
Lower abdominal operation – block up to T_7
Upper abdominal surgery (cholecystectomy gastrectomy, transverse colectomy) – block up to T_4

For gut surgery, some afferent stimuli pass through the vagus nerve. So, such type of surgeries require para oesophageal block of vagus nerve or GA along with spinal or epidural block. Here the central neuroaxial block helps by producing an ischaemic field, gut retraction, good relaxation, reduction of stress and postoperative analgesia.

Fate of Local Anaesthetic Agent in CSF

Anatomically, it is likely that the exposure of spinal cord and its nerve roots to local anaesthetic agent which is injected in the CSF, results in blockade of conduction of impulses through them, before they exit through the intervertebral foramen. However, though there is also exposure of spinal cord to local anaesthetic agent, but the conventionally used concentration and doses of LA drug make penetration of it into the deeper parts of intact spinal cord unlikely. Termination of action of LA agent after spinal anaesthesia is likely to occur by dissociation of drug into the spinal fluid from the cord and its roots first and later by absorption of it into the vascular space. The principal site of action of epidural block is also the spinal nerve roots while they are passing the epidural space. The direct injection of local anaesthetic agent into CSF for spinal anaesthesia allows a relatively small dose and volume of local anaesthetic agent to spread over an wide area and to achieve dense sensory and motor blockade. In contrast, the same concentration but much higher volumes of local anaesthetic agent is injected in epidural space as there is no influence of spread of drug by CSF. Moreover, the injection site (level) for epidural anaesthesia must generally be close to the nerve roots that must be anaesthetised. The termination of action of LA agent after epidural block is likely to occur by the absorption of drug by epidural venous plexuses and partly by passing of the drug into the subarachnoid space.

First very quick, then gradual fall of concentration of local anaesthetic drug in CSF is seen in spinal block. The first steep fall in concentration of local anaesthetic agent in CSF is due to the mixing of drug with CSF and then rapid intake of drug by the nerve root and spinal cord. The second

gradual decrease of drug concentration is due to the vascular absorption of drug from CSF and nervous tissue. The CSF flow into venous sinuses via arachnoid villi may also contribute to some extent in the clearance of local anaesthetic agent. The lymphatic drainage has also contribution in the clearance of drug. Local anaesthetic acts both on the spinal cord and nerve roots, but opioids act only in the substance of the cord.

ORDER OF BLOCKING OR SENSITIVITY OF DIFFERENT NERVE FIBRES TO LOCAL ANAESTHETIC AGENTS

All types of fibres within a nerve are affected by local anaesthetic agents during spinal or epidural anaesthesia. But, within one mixed nerve there is a tendency for the smaller (thin) and slow conducting fibres (sensory) to be more readily blocked than the larger (thick) and fast conducting fibres (motor), though always this rule does not hold good. Because it is well established that myelinated autonomic preganglionic sympathetic B fibres which are larger and have a faster conduction time are about three times more sensitive to local anaesthetic agent than the thiner and slower conducting non-myelinated postganglionic C fibres (Fig. 24.30).

The preganglionic autonomic B fibres are the most sensitive of all the nerve fibres, causing early vasodilation and consequent hypotension which is a well recognised early sequel to epidural, spinal or paravertebral block. Large (or thick), rapid conducting, motor A fibres are the most resistant to local anaesthetic agents. It is probable that A-δ fibres, responsible for pain and temperature sensation are more sensitive than the C pain fibres, although it is larger and more rapid conducting than C fibres. This explains why sometimes the pathological pains, such as impending uterine rupture or placental separation, conducted by C fibres, may break through an epidural block which is relieving the physiological labour pain conducting through A-δ fibres. This is called the 'epidural sieve'. Sensory (proprioceptive) A-α fibres appear to be more sensitive to blockade than motor A-α fibres, although both have the same conduction velocity. This is because sensory fibres conduct at a higher frequency (Fig. 24.31).

All the local anaesthetic agent block the small and slow conducting sensory fibres more rapidly than motor fibres. The varying ability of different LA agents to produce the sensory and motor block would appear to be related largely to their epidural use. Thus, bupivacaine, the most selective for sensory fibres on epidural use, produces profound motor block on peripheral and intrathecal use. In summary, starting from the most sensitive, the order of sensitivity of nerve fibres to blockade is like that: preganglionic, pain and temperature, touch, proprioception and motor fibres.

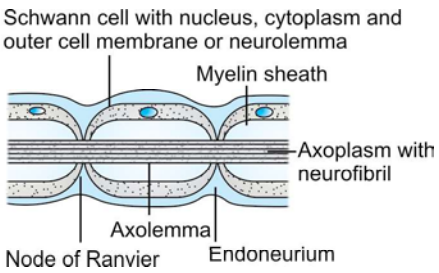


Fig. 24.30: Longitudinal section of myelinated peripheral nerve

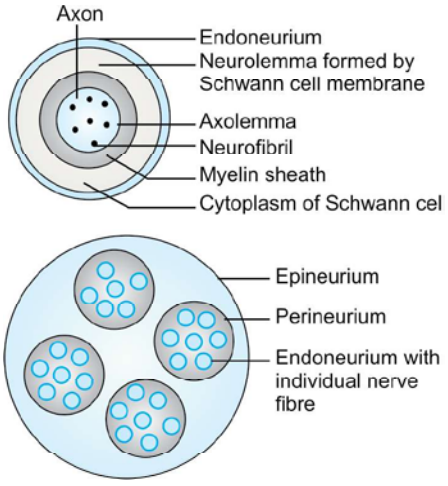


Fig. 24.31: Organisation of a trunk of peripheral nerve

Explanation of feeling of some pain or failure of RA after technically correct procedure

The probable explanation of failure after a technically good spinal or epidural block are:

i. A given concentration of local anaesthetic solution may block the fine fibres carrying the ordinary or sharp pain sensation, but may not be adequate to block some large fibres, responsible for carrying pressure and dull pain sensation. Increasing the concentration of local anaesthetic agent will solve this problem.
ii. Some pain fibres pass via sympathetic nerve and then via sympathetic chain to reach the spinal cord at higher level than the site of injection and may be the cause of failure.
iii. Dura can be punctured in the midline as well as laterally and even possibly at the dural investment of nerve root resulting in false feeling of placement of needle tip in the subarachnoid space.
iv. The tip of the needle may be moved further during pushing of injection after proper placement of it in the subarachnoid space and the local anaesthetic agent has not been deposited into the proper CSF.
v. Rarely, fluid-filled cyst in the subarachnoid space where the needle tip is entered may be responsible for failure. The membrane of the cyst limits the spread of the local anaesthetic agent.
vi. A problem with the potency of local anaesthetic solution may be responsible and possible (Table 24.6).

Sometimes, the local anaesthetic agent accumulates in the sacral hollow from the highest injecting point at the lumbar lordosis during dural puncture in supine position through lumbar route due to antiTrendelenberg position of the patient. In such

Table 24.6: Characteristic features of various nerve fibres

Fibre type	Diameter (μm)	Conduction velocity (m/sec)	Function	
			Sensory	Motor
A-α	13-20	70-120	Proprioception	Somatic
A-β	5-12	30-70	Touch, pressure	–
A-γ	4-11	15-30	–	Muscle spindle
A-δ	1-4	12-30	Pain, temperature	–
B	1-4	3-15	–	Preganglionic sympathetic
C	0.5-1	0.5-2.5	Pain, reflex	Postganglionic sympathetic

situation, inadequate level of anaesthesia up to the groin results.

The partial failure is a more common problem than the complete failure and is mainly due to insufficient dose and improper position of patient rather than individual variation. In partial or complete failure, the block can be repeated. But often general anaesthesia is more appropriate.

During spinal anaesthesia before injecting drug. It is wise to verify that the spinal needle is surely located in the subarachnoid space and is freely communicating with CSF. To confirm this the needle should be rotated 360°, with observation of free flow of CSF in all quadrants. If dural puncture is oblique or at the dural sleeve, there may be one or more quadrant where free flow of CSF does not occur. This may signal inadequate or partial dural puncture and needle should be removed and placed again correctly. Failure to replace the needle correctly results in two adverse outcomes. In an oblique puncture, an inadequate level of spinal anaesthesia may result. If injection is into the dural sleeve, hydrostatic injury to the nerve root may occur. Intense searing paresthesia at the time of CSF withdrawal during test may signal the nerve root damage and is early enough to avoid morbidity.

CONTINUOUS SPINAL ANAESTHESIA (CSA)

Continuous spinal anaesthesia (CSA) is a comparatively newer concept of regional anaesthesia and is performed by the introduction of microcatheter into the spinal subarachnoid space. But, it is always remained in controversy due to many neurological complications. The history of CSA can be dated back to 1907 when Dean, a British surgeon, first used this technique to prolong the duration of spinal anaesthesia. He performed CSA by the repeated injection of local anaesthetics into the subarachnoid space through a lumbar puncture needle which was left *in situ* after its successful entry. But, the needle breakage and spinal cord trauma were some of the ominous complications of this procedure. Then, in 1940, Lemmon introduced malleable needle and split mattress technology for this procedure. After that in 1944, Edward Touhy used a malleable spinal catheter, i.e. a No. 4 ureteral catheter for CSA and had popularised this technique. But during that period PDPH due to large needle and thick catheter was very rampant in CSA, which led to the introduction of microcatheters in 1990. Then, different sizes of microcatheters, varying from 27 to 32 gauges were made available and could be introduced into the subarachnoid space via 22 to 27 gauges spinal needle for CSA. But surprisingly, this did not reduce the incidence of PDPH. On the contrary, it causes increased neurological complications, termed the cauda equina syndrome. Hence, in 1992, FDA in USA banned CSA with spinal catheters, thinner than 24 gauge.

Before discussing more about CSA, let us first innumerate its various advantages and disadvantages.

Advantages of CSA

i. Reduced failure rate as CSF flowed into the catheter can be visualized.
ii. Prolonged anaesthesia which further can be extended even in the postoperative period for adequate analgesia.
iii. Requires low doses of local anaesthetic agent, especially when compared to CEA (continuous epidural anaesthesia).
iv. Extreme haemodynamic and cardiovascular stability due to the use of low and gradual incremental dosage of local anaesthetic agent.
v. May be used for prolonged pain relief, as in cancer patients by allowing subarachnoid narcotic administration for long duration.

Disadvantages of CSA

i. Increased incidence of PDPH.
ii. Increased incidence of nerve injury causing sensory loss, or motor loss or both.
iii. Increased chances of infection and haemorrahage.
iv. Increased incidence of cauda equina syndrome.
v. Very fine spinal needles (27 G and 29 G) and very fine catheters (30 G and 32 G) have made the technique possible without the risk of severe PDPH. But, these sizes of needles and catheters make the successful lumbar puncture more difficult.

Haemodynamic Stability in CSA

Perhaps the most undisputable indication for CSA is very elderly or critically ill patients who are put up for surgeries on lower abdomen or inferior extremities. Elderly patients generally have some cardiovascular compromise due to hypertension, ischaemic heart disease, heart failure, etc. or respiratory compromise due to low respiratory reserves or both. Critically ill patients are also similarly compromised. Hence, they require very good haemodynamic stability during anaesthesia, which is offered best only by CSA. The CSA offers a very good haemodynamic stability because very low dose of local anaesthetic agent is given at a time which prevents very rapid

and wide spread of drug and thus causes slower onset of action. This helps in gradual slow sympathetic block and easy gradual cardiovascular adaptability. It also gives enough time to an anaesthetist for adequate fluid infusion and vasopressor therapy if required. The low incidence of hypotension, low requirement of vasopressors, low failure rate are some of the indications of haemodynamic stability in CSA.

Postdural Punctural Headache in CSA

Though it was first thought that the incidence of PDPH was low with microcatheters in CSA, yet now the topic is still very controversial. The various studies at various times have proved that the microcatheters not always lower the incidence-PDPH. In fact, one study also showed that severity of PDPH was more in microcatheters and maximum patients required epidural blood patch for treatment of it. Also PDPH was observed to be more in younger age group of patients. Hence, it was inferred that PDPH was more frequently seen in lower age group patients (especially parturients) with microcatheters and with longer duration (especially for postoperative analgesia by microcatheter).

Cauda Equina Syndrome

Microcatheters for CSA was initially introduced for decreasing the incidence of PDPH. But, in reality it hardly did so. On the contrary, it more commonly causes neurological deficit, termed as the 'cauda equina syndrome'. A local anaesthetic agent, when introduced into the CSF through a conventionally used spinal needle, then it causes a turbulance which helps in mixing of the drug in CSF. But, when microcatheters are used, then lack of this turbulance causes improper mixing of drug in CSF. Hence if there is no turbulance and proper mixing, then the hyperbaric local anaesthetic agents thus will settle at the bottom of the spinal theca depending on the position of the patient. Hence, higher concentration of local anaesthetic agent is found near the caudal portion of the spinal cord, exposing the nerves of cauda equina long enough to the high concentration of these drugs which sometimes become toxic to the nerve fibres. This causes serious neurological defects, known as the cauda equina syndrome.

Failure of CSA

One of the causes of the failure of CSA is its technical difficulty during the introduction of catheter in the subarachnoid space through the needle successfully. Inability to inject local anaesthetic agent, knotting of the catheters inside the spinal canal, broken catheters, etc. are the other major causes of frequent inability of producing adequate anaesthesia by CSA. Therefore, very thin microcatheters, like 32 G, are also supplied by a steel wire stylet to help in threading it through 25 to 27 G spinal needle. These catheters would bend very easily during their introduction in the spinal canal. Then straightening or even removing of them, would often pose a problem. Sometimes, threading of the catheter becomes difficult even though the spinal needle is in place. This is due to the dura which may cover the opening of the spinal needle or needle touches the lateral or anterior wall of the spinal cord. In such cases, little withdrawal of the needle may help in threading of microcatheter through it into the CSF. The spinal microcatheters should not be introduced more than 2 to 3 cm inside the dural sac. More than 4 cm insertion often changes the direction of the microcatheter caudally, causing frequent cauda equina syndrome. 22 G Sprotte spinal needle prevents caudal migration of 28 G spinal microcatheters. Often the spinal catheter may also get entangled in the nerve roots or may even enter the intervertebral foramen with the nerve roots causing low backpain, radicular pain or even transient paraesthesia during the procedure. This may result in transient or permanent neurological damage.

During any failure or difficulty in threading catheter through the fine spinal needle, the procedure should be reassessed or abandoned. In such situation general anaesthesia is better option than facing the grave neurological defects in postoperative periods.

Present Status of CSA

For very elderly or compromised patients with severe systemic complication, CSA may still be the best and safest opted technique. It gives a stable haemodynamic platform, and thus decreases both morbidity and mortality of patient. As small, slow and gradual incremental doses of LA agents are given in CSF, so haemodynamic status remains almost unaltered. Hence, high risk patients with chronic bronchitis, emphysema, hypertension, coronary artery diseases, myocardial ischaemia, myocardial infarction, congestive cardiac disease, etc. tolerate this method of CSA much better. PDPH is the main disadvantage of CSA with an incidence of 6 to 9% with 20 G catheters. But, it is more common in younger age group of patients and incidence becomes almost nil after 60 years of age. Neurological injuries are more common with microcatheters. But by abandoning the technique, whenever there is some techical difficulty during insertion (as discussed before), the possibility of neurological trauma can be avoided.

Thus, it can be concluded that CSA is the choice of anaesthesia in elderly and very high risk patients with many systemic complications, or a severly compromised state. It is best avoided in young and obstetric age group of patients where continuous epidural anaesthesia (CEA) is still the choice. The ultra thin microcatheters need not be used as they have no added advantages. The anaesthetist should be well prepared to abandon the technique and goes for a general anaesthesia, whenever there is some problem in insertion and threading of a microcatheter through the fine spinal needle, especially if patient complains of radial pain or paraesthesia.

This shall avoid neurological damage and postoperative neurological deficits.

EPIDURAL ANAESTHESIA

Though epidural anaesthesia and analgesia had lead its journey from a small arena like labour ward and/or the obstetric operating room but now it has spread a strong foot hold over a wide area and become a common practice in surgical patients including neck, thoracic, abdominal and cardiothoracic surgeries. Recently, it has also made its strong presence in the pain clinic. However, at present epidural analgesia and anaesthesia for obstetric surgery has been superseded by spinal anaesthetic technique in some underdeveloped countries. But, painless labour by walking epidural anagesia and subsequent obstetric surgery (if needed) by epidural anaesthesia is still the routine practice in many developed countries. On the other hand, the postoperative epidural analgesia following major surgery is now the best means of analgesia in the modern postoperative care.

Epidural anaesthesia is provided by the effect of local anaesthetic agent on the spinal nerve roots as they pass from the spinal cord to the intervertebral foramen through the extradural or epidural space. Some part of the local anaesthetic agent which is deposited in the epidural space also (Table 24.7) penetrates the dura and arachnoid mater and passes into the CSF to act directly on spinal cord and the spinal nerve roots, bathed by CSF. Epidural analgesia provided by low concentration of LA agent also acts by the same mechanism as epidural anaesthesia. But, the addition of other drugs such as opioids, clonidine, benzodiazepine, etc. acts only through the receptors on the spinal cord which proves that the drug placed in the epidural space diffuses through the CSF.

The indications and contraindications for epidural anaesthesia and analgesia are similar to those of intrathecal anaesthesia. But, the commonest indication for epidural technique is where the duration of surgery is prolonged, the patient is very ill and high quality postoperative analgesia is needed which can be provided only by intermittent bolus injections or by continuous infusion of LA agent or narcotics using an epidural catheter.

Table 24.7: Indications of epidural block

A. *Surgical, obstetric, diagnostic, prognostic*
- Surgical anaesthesia and analgesia
- Obstetric anaesthesia and analgesia
- Differential neural blockade to evaluate pain
- Prognostic indicator before destruction of nerve

B. *Acute pain*
- Palliation of acute pain in any emergency
- Patients with multiple fractured ribs by thoracic epidural
- Management of pain due to acute pancreatitis
- In cervical epidural
  - To evaluate head, neck, face, shoulder and upper extremity pain
- In lumbar epidural
  - To evaluate lower abdominal, back, groin, pelvic, bladder, perineal, genital, rectal, anal and lower extremity pain
- Postoperative pain
- Pain due to acute herpes zoster
- Pain due to vascular insufficiency of the extremities

C. *Prophylactic and pre-emptive pain*
- Before amputation of ischaemic limbs

D. *Chronic benign pain*
- Radiculopathy
- Spinal stenosis
- spondylosis
- Vertebral compression fracture
- Diabetic polyneuropathy
- Postherpetic neuralgia
- Reflex sympathetic dystrophy
- Phantom limb syndrome
- Peripheral neuropathy

E. *Cancer related pain*
- Pain secondary to malignancies
- Pain due to bony metastases
- Chemotherapy-related peripheral neuropathy

Some Important Characteristics of Epidural Anaesthesia and Analgesia

i. It needs more skill.

ii. Sitting position is only preferred when it is absolutely necessary. Otherwise, increased pressure of CSF in sitting position increases the risk of dural puncture, leading to spinal anaesthesia.

iii. Absolute stillness of the patient's posture during the procedure is very necessary.

iv. Movement, cough, cry etc; cause increased CSF pressure and enhance the chances of dural puncture.

v. The intervertebral space like L_{2-3}, L_{3-4}, L_{4-5} is preferred for epidural anaesthesia and analgesia, though any interspinous space can be chosen. The choice of site for the introduction of Touhy needle or any epidural needle is determined by the surgical incision site. The insertion of needle should be at the level of the middle of the dermatomes that innervate the area of the skin in which the incision will lie. During difficulty, the best interspinous space may be one vertebra above or below the ideal level. The anaesthetist should balance the practical problems of a potentially difficult space against the benefit of a successful first time identification of the epidural space which is one or two vertebra below or above. In difficulty of flexing spine or lumbar lordoris, upper spaces can be chosen. Thoracic approach for epidural block is generally used by skilled person for upper abdomen and thoracic surgery and / or postoperative analgesia.

vi. Prior application of eutectic LA mixture or skin infiltration by local anaesthetic agent is very important for the use of thick 16 to 18 G Tuohy needle or any epidural needle in awake patient.

vii. In lumbar approach of epidural anaesthesia the depth of ligamentum flabum from the skin for most of the patient is 3.5 to 6 cm (average 4 cm). On the other hand, ligamentum flabum is itself 5 to 6 mm thick in midline.

viii. Patient with the history of previous spinal surgery at the site of planned epidural anaesthesia have more chance of failure or partial block. It is either due to technical difficulty in identifying the

space or an anatomical distortion of the space by scaring, haematoma, adhesion, etc. which prevents the spread of local anaesthetic agent in the epidural space. Even in patient without previous spine surgery or disease, repeated epidural anaesthesia at the same site becomes less effective with each application. Explanation of this failure is that repeated entry of needle and injection of local anaesthetic agent into the same small epidural space cause anatomical changes (due to bleeding, haematoma, inflammation and scar formation) and obliterate some parts of epidural space.

ix. One of the probable causes of one-sided epidural anaesthesia is migration of catheter into the dural sleeve or moving out of the epidural space with outgoing nerve root through the intervertebral foramen.

x. Another important characteristic of the epidural anaesthesia and analgesia is that there is relatively large absorption of LA agent from this space due to large absorption area, dense epidural venous plexus, and large volume of drug (Fig. 24.32).

Needle of Epidural Anaesthesia

Most commonly the Tuohy needle is used for epidural anaesthesia and analgesia. The important feature of this needle is the rounded Huber point tip which is curved and blunt. The curvature of this tip directs the passage of the catheter and bluntness of the tip reduces the risk of dural puncture. The large caliber of the Tuohy needle helps in easy detection of the epidural space, particularly by the loss of resistance. The Tuohy needle is graduated in centimeter and so it can also help to assess the depth of epidural space. For single shot epidural technique where catheter is not used, Crawford epidural needle is also very much appropriate. It is a modification of Tuohy needle with a small sharp area at the tip.

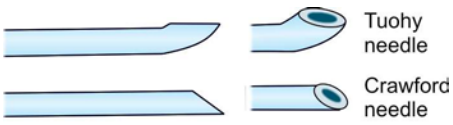


Fig. 24.32: Epidural needle

Approach for Epidural Space

Our approach for epidural space may be in the midline or from the lateral side (paramedian). In midline approach, once the tip of the needle is in supraspinous ligament after crossing the skin and subcutaneous tissue, then considerable resistance during the advancement of needle and injection of fluid is felt. This resistance is due to the advancement of needle through the interspinous ligament and ligamentum flavum. After that as soon as the tip of the needle enters the epidural space, then there is feeling of sudden loss of resistance. The advancement of the needle just under and parallel to the spinous process of the vertebra above will yield easiest entry of it into the epidural space in the midline. Contact with bone close to the skin usually suggests obstruction due to spinous process, whereas contact with bone at deeper level suggests obstruction due to lamina or pedicle and signals the possibility that needle has perhaps strayed from the midline or is angled too cephalad or caudal.

During lateral or paramedian approach of epidural space the sacrospinal and other paravertebral group of muscles are encountered first after the skin and subcutaneous tissue and offer a doughy feeling, as supraspinous and interspinous ligaments are bypassed. Strong resistance only felt when the paravertebral group of muscles are crossed and the tip of the needle hits the ligamentum flavum. The key to successful insertion of needle in epidural space in this approach is the change from doughy soft feeling to tough gritty feeling, due to the change from the muscle to ligamentum flavum. Too abrupt advancement of the needle in any approach may result in accidental dural puncture and subdural block. The chances of traumatic damage to the nerve roots and epidural vein is more during epidural anaesthesia in lateral approach because the two posterior epidural venous plexus lie by the side of the midline. Like spinal anaesthesia, lateral approach for epidural block is also applicable only when the interspinous space is narrow and there is difficulty to approach the epidural space through midline due to any cause.

Methods of Identifying Epidural Space

The epidural space can be identified by different methods. These are as follows:

1. By feeling the loss of resistance

The feeling of loss of resistance when the tip of the epidural needle enters the epidural space can be tested by two ways, either by fluid-filled syringe or by air-filled syringe with epidural needle.

(i) Advantage/disadvantage of fluid-filled syringe (glass or plastic) for detection of epidural space

The question between the glass or plastic syringe for detection of epidural space by the feeling of loss of resistance depends on the individual anaesthetist's choice and experience. The loss of resistance is less clear by plastic syringe, because there is more friction between the plunger and the barrel. But glass syringe is always of low friction syringe. On the other hand, plastic syringe is more consistent in its behaviour than the glass syringe. The advantage of fluid-filled syringe over an air filled syringe for the detection of epidural space by the feeling of loss of resistance is that the needle can be advanced by (Fig. 24.33) pressing on the plunger and not by pushing the barrel. When the epidural space is entered, the movement of the needle and barrel is halted automatically and the plunger moves forward injecting the fluid in the epidural space, and pushing the dura away from the tip of the needle and creating an actual space. This also reduces the chances of dural puncture. The advancement of the needle must be at the right

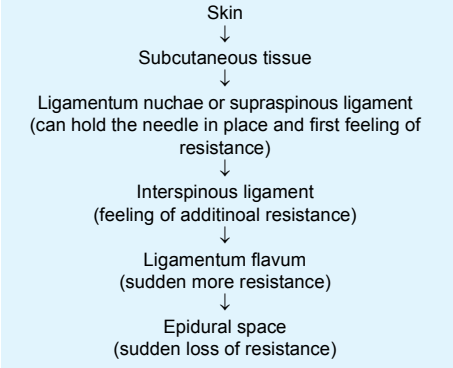


Fig. 24.33: Resistance offered to the needle during passage to epidural space

angle to the hip and shoulder. However, being parallel to the floor has no importance. The hole at the needle tip pointing cephalad will minimise the angle at which the needle tip encroaches the epidural space and thus will reduce the chances of dural puncture. The advancement of needle should be smooth and continuous. The disadvantage of fluid-filled syringe is that sometimes a few drops of fluid drips back from the needle hub after proper entry in the epidural space and can create confusion for CSF as dural puncture occurs.

(ii) Advantage/disadvantage of air filled syringe for detection of epidural space

Here, the epidural needle cannot be advanced by giving pressure on the plunger alone. But, the needle must be advanced step by step by holding the needle shaft or the barrel of the syringe, rather than in a continuous fashion like fluid-filled syringe, described before. Thus, the use of air-filled syringe needs the elicitation of the bounce of plunger with every millimetre of advancement of needle to feel the loss of resistance for detection of epidural space. It is a more slower process and there is more chance of dural puncture, because like fluid the air does not automatically remove the dura from the tip of the needle when it enters the epidural space. But, as no fluid drips back from the needle hub after entry of the tip of the needle in epidural space, no confusion is created for dural puncture. However, here is the more chances of emphysema and air embolism (if the needle enters into a vein). There are other many mechanical helps to feel the sign of loss of resistance by air-filled syringe. These are Macintosh's needle with spring-loaded stilette, Ilke's spring loaded syringe, Macintosh's ballon, etc. In spring-loaded stilette or syringe, the stilette or plunger is automatically pushed in due to the loss of resistance when the needle tip enters the epidural space. In Macintosh's balloon, it is automatically deflated when the tip of the epidural needle enters the epidural space. But they are usually not used now, because they are more complicated, produce more false negative and false positive result, and cause more distractions.

After entering the epidural space, the air or fluid-filled syringe is disconnected. If a small amount of fluid (in case of air-filled syringe) leaks back, it may raise concern about the partial dural puncture. But it can be resolved by two ways. If the fluid is of room temperature and flow is self-limiting, it is surely fluid of epidural space. Whereas, CSF would feel warm, if it is allowed to drop on the forearm of anaesthesiologist as it is coming from the core of the patient's body and flow is not self-limiting. The use of teststicks for glucose would also make the distinction between the CSF and other fluids, since CSF would contain some glucose, whereas other fluid such as fluid of the epidural space, saline or local anaesthetic agents would not.

2. By negative pressure sign

A negative pressure is detected in 50 to 80% of cases in the epidural space. There are three explanations which have been put forward to account for this negative pressure in epidural space.

i. The first theory is that the negative pressure which is normally present in the pleural cavity is transmitted from this cavity via the thoracic paravertebral spaces and through the intervertebral foramen to the epidural spaces.
ii. The second theory is that negative pressure is created by expanding the volume of vertebral canal and consequently that of the epidural space by the flexion of the spine.
iii. The third theory is that the negative pressure is simply created by indenting the dura with the tip of the needle. This is the most probable explanation of negative pressure in epidural space. The negative pressure is obliterated once the fluid is injected and then the epidural pressure may rise to as high as 30 cm of water during an epidural injection. Clinically the negative pressure in the epidural space has been demonstrated in a number of ways.

Hanging drop method

While the needle is progressing towards the epidural space a drop of fluid (saline or LA agent) is deposited at the hub of the needle, until the drop is hanging. Then, as soon as the tip of the needle reaches the epidural space, then due to the negative pressure created by pushing the dura away, fluid is sucked in the hub. However, this technique should be limited to the experienced hands, because heavy skill is required to interpret the feel of tissue during very slow approach to the epidural space and to see the drop movement simultaneously. This technique is further limited by the possibility of tiny bit of tissue or blood clot at the needle tip which may prevent the passive transmission of negative pressure from the epidural space to the hub of the needle. Very slow approach and the increased feel of tissue is mandatory, when the epidural anaesthesia is applied in thoracic or cervical spine.

Odom's indicator

A drop of fluid being contained in a small glass capillary tube is attached with the epidural needle. As the epidural space is entered by the tip of the needle, then the fluid moves inward to the negative pressure of the space. This is Odom's indicator. This

negative pressure sign has also the distinct advantage in lateral approach.

Technique of Epidural Anaesthesia

Usually EA is applied by two methods catheter single shot or continuous epidural by catheter.

Single shot epidural anaesthesia

The single shot epidural anaesthesia is rarely used nowadays, except for fewoutdoor or day-case surgery. It is unjustified if the epidural anaesthesia is used for any surgery, but the patient is not allowed to enjoy a good postoperative analgesia by repeated doses or by continuous infusion of local anaesthetic or narcotic agents in the epidural space through the epidural catheter later on.

Continuous epidural anaesthesia by catheter

The ability to insert a catheter safely into the epidural space allows slow injection of local anaesthetic agents and / or narcotics, intermittently as bolus or continuously as infusion to control the rate of neural blockade, to decrease the haemodynamic side effects and to reinject the drug when necessary and thus maintaining anaesthesia and / or analgesia indefinitely. There are multiple positive points about the epidural anaesthesia using catheter. The safe access to the epidural space in the thoracic and cervical regions also will create the possibility of selective block in limited dermatomes and thus will accomplish the only analgesic objective (pain control), minimizing the side effects of wide-spread motor block and wide-spread pharmacological sympathectomy. For orthopaedic anaesthesia the control of postoperative pain is valuable, especially where the orthopaedic surgical indication requires the excellent postoperative pain control for continuous passive or active motion of limbs (physiotherapy) after fracture repair, joint replacement, release of frozen joint, etc.

The obstetric analgesia and postoperative pain control, are the ideal conditions for continuous epidural analgesia. Here the surgical anaesthesia is not sought for as it will hamper the objective of obstetric analgesia by hindering the vaginal delivery. The ideal situation would be only analgesia in the restricted dermotomes of surgical site with no or minimal motor block. When used alone or in conjunction with a low concentration of local anaesthesic agent (e.g. 0.25% bupivacine) and a lipophilic narcotic (e.g. fentanyl, etc.) this catheter technique should make possible near total relief of postoperative and labour pain. It does not interfere with pulmonary mechanics (in COPD) and allows a patient of enough motor strength to take self-care. In instances, where complete motor function is essential, the use of only narcotic drug without local anaesthetic agent can achieve analgesia without even slight degree of motor block.

Epidural Catheter

The size of epidural catheter varies from 19 G wide bore to 30 G microbore. The wide bore large catheters are used for adult patients and fine microcatheters are used for the paediatric patients. The objective regarding the epidural catheter is to pass largest possible catheter through a given needle, since the tensile strength of a catheter decreases with the higher number (or fine bore). Impregnating the walls of catheter with a special substance or chemical which increases the tensile strength of it is an another approach to use the fine catheters, without decreasing the tensile strength. The goal is to minimize the risk of catheter loss under the skin or long-term follow-up for evaluation, if a part of a catheter is lost. The material selected for construction of catheter is determined by many factors. When catheter is made up of Teflon, then the advantages are : increased-firmness cause easy insertion, greatest possible resistance to kinking during continuous use, linear shear strength is maximal and does not soften when it reaches the body temperature. The disadvantage of Teflon catheter is increased rigidity and absence of increased flexibility at body temperature which increases the risk of trauma to nerves and blood vessels.

Spinal nerve roots are usually located in tight epidural compartment with minimal mobility. Thus, a rigid catheter which is inserted in this tight epidural space can lacerate or penetrate the surface of these rigid nerve roots. In that situation, if a catheter is left in place when the patient is mobile or in anticoagulant, the gradual softening of a catheter, made of polyvinylchloride (PVC) would be a distinct advantage. Teflon lacks this softening property. So, PVC catheters are thinked better for softness and flexibility during insertion and use. But, this material causes decreased resistance to breakage and increased kinking. The chance of breakage is even more for a catheter which has multiple exit ports at their tip and this is because of their inherent weakness at the ports.

The catheters with a single orifice at the most distal end are selected for accurate delivery of anaesthetic solutions at the exact site of placement of it. But, there is more chance of occlusion of this type of catheter with single distal orifice by blood clot or tissues. Whereas, the multiorificed catheter cannot deliver the injecting anaesthetic solution accurately at the site of its placement, but minimise the potential for occlusion of it by blood clot or tissues that can occur with single port catheter. The size of port around the diameter of the catheter also theoretically increases the area of spread of the solution at the site of injection, but at the cost of decreased shear strength of catheter. Some epidural catheters are designed with fine metal stylet inside it which makes them quite rigid, and helps to guide the catheter easily. In such situation besides potential nerve injury, there is higher risk of dural

puncture with stylet catheter, even after the successful placement of needle. This risk can be decreased by withdrawing the stylet so that the 1 to 2 cm tip of the catheter is free of stylet and is not rigid any more. But still the stylet gives the necessary rigidity to the catheter within the hub of epidural needle, during initial entry into the epidural space and helps its insertion. Epidural catheter increases the versatility and duration of the central neuroaxial block. Catheter tip emerges from the tip of the needle, if the 10 cm mark on the catheter disappear at the hub. Resistance may be felt at this point. If resistance during the passage of catheter is felt beyond this point, then it should never be withdrawn without needle, neither should it be forced onwards. Withdrawal of the catheter alone without the needle, once it has emerged from the tip, may cause the end of the catheter to be sheared off by the tip of the needle and remain in the epidural space. If a piece of an epidural catheter is accidentally left behind in the epidural space, then there has been some debate over whether the patient should be informed or not. It is probably best to be honest. So it should be explained what has happened. But the patient will be very anxious after this explanation. Hence, Patient should be reassured that the chances of adverse long term sequelae are remote.

The obstruction during passage of catheter through the epidural needle may be due to:

i. catheter tip hits against nerve root,
ii. catheter tip hits against blood vessel,
iii. it hits against the dura,
iv. the needle or the catheter tip is not in the epidural space at all.

Catheter tip should not be passed more than 15 cm from the needle hub. Once catheter enters into the epidural space in the midline, it will generally pass freely. If resistance is encountered well before this, the needle may be carefully rotated through 90 degree. If this still does not enable the catheter to pass, then increasing spinal flexion of the patient may be helpful. Sometimes catheter may run a short distance in the epidural space and then is curled back or pass out through the intervertebral foramen. The tendency for a catheter to pass in one side of the epidural space increases the likelihood of an asymmetrical or unilateral block which, if resistant to treatment, may necessitate removal and reinsertion of the catheter. If blood is aspirated, the catheter is slightly withdrawn. If flow of blood still persists, then another space is tried. As aspiration of blood or CSF does not give one hundred percent guarantee that if catheter is in blood vessels or in subarachnoid space or not, so a test dose is mandatory before giving the full clinical dose. Epidural catheter should be inserted only 2 to 3 cm in the epidural space from the tip of the needle. There is no advantages in passing the catheter for more than 4 or 5 cm from the tip of the needle into the epidural space. Migration of catheter in the ant. epidural space is the commonest misposition of it. The use of multi or uniport catheter depends on the anaesthetist's choice. Multiport catheter has less chances of unilateral and unblocked spinal segments than the single port catheter.

Epidural Test Dose

The epidural test dose procedure has in common the objective of decreasing the incidence of inadvertantly injecting a large volume of anaesthetic agent, scheduled for epidural anaesthesia into the intravascular or subarachnoid spaces. A variety of agents and strategies have been described for this test dose procedure, but the ultimate choice depends on the experience of the anaesthetist. Any evidence of epidural anaesthesia even partial signals an extremely low probability that the needle or catheter is fully within the subarachnoid space or within the lumen of a blood vessel. On the contrary, extended anaesthesia than expected by the test dose signals the probability that the needle or catheter is in the subarachnoid space. The 2 to 3 ml of local anaesthetic drug (a dose insufficient for epidural blockade, but sufficient for spinal effect and expected to occur within 2 minutes) is used as test dose, before giving the total dose scheduled for epidural anaesthesia. However, the correct period of timing between the test dose and the next principal injection is very important and is determined by the type of LA agent used. There is no reliability in this procedure, if correct time interval (2 to 3 minutes for lignocaine's onset of action) is not maintained prior to the next main injection. If bupivacaine is selected as the epidural agent, then the time interval between the test dose and the principal anaesthetic doses would need to be longer or initial test dose would have to be performed with another agent, e.g lignocaine. During continuous epidural anaesthesia and analgesia each subsequent epidural injection should also be preceded by aspiration and epidural test dose, because catheter migration into vessel or subarachnoid space does occur at any time.

The intravascular injection of LA agent during the administration of test dose or principal dose is identified by the systemic signs, based on the occurrence of cranial nerve paraesthesia and this is due to the disinhibition of limbic system of brain curved by LA agent. Thus, intravascular injection of LA agent can be identified by general ill feeling, unexplained fear, perioral paraesthesia, lingual paresthesia (metal taste), ocular paraesthesia (scotoma), aural events (roaring in the ear), etc. These symptoms are very obvious with 2-chloroprocaine, but less obvious with lignocaine and absent with bupivacaine, because of its very high protein- binding property. The CNS toxicity as signs of intravascular injection are reported being unreliable, following small doses of LA agent alone. So, vasoactive substances are often injected with LA agent as indicators or markers and their systemic effects are used as signs of intravascular injection of LA agent. The

classical choice of vasoactive substance as marker is epinephrine. The commonest test dose is 3 ml of LA agent with 15 µgm of epinephrine (adrenaline). This dose of epinephrine will produce 20 to 30% increase in patient's heart rate within 20 to 30 seconds of injection. It will last for a brief period (1 to 2 minutes) and is unlikely to harm patient. To detect the increase in heart rate caused by epinephrine which is used as test dose, ECG monitoring is mandatory and mere symptom like palpitation is unreliable. The use of epinephrine as test dose is contraindicated in cardiac patients and parturients (potential risk of uterine artery vasoconstriction).

At last, in conclusion it can further be told that a false sense of security does not develop, if a test dose has no adverse effects. Although it is rare, still it is not uncommon for epidural catheters to migrate into blood vessels or into the subarachnoid space after satisfactory test doses. Therefore, the anaesthetist must be vigilant at all times.

Drugs and Doses for Epidural Block

Lignocaine

For epidural anaesthesia initial 15 to 18 ml of 1.2 to 2% (commonly 1.5%) lignocaine hydrochloride is used with or without adrenaline in the dose of 5 µmg/ml. The action of this dose lasts for 1 to 1.5 hours. If adrenaline is used with LA agent, then some prolongation of local anaesthetic action occurs. Subsequent repeated doses of lignocaine cause tachyphylaxis and so it is impossible to maintain continuous analgesia and anaesthesia by lignocaine by infusion or repeated bolus doses, without ultimately producing any serious systemic toxicity of it. The 0.5% solution of lignocaine gives sensory block without affecting the motor and 1.5% solution of it gives both sensory and good motor block, while 2% solution causes intense motor and sensory block (Table 24.8). So, for epidural anaesthesia and analgesia the dose of lignocaine varies according to the volume, concentration, site of injection, and the desired effect.

Bupivacaine

The 0.5 to 0.75% solution of bupivacaine HCl is usually used in a dose of 2 mg/kg or 0.4 ml/kg for epidural anaesthesia. The action of surgical anaesthesia of this dose and concentration of bupivacaine lasts for 4 hours. However, the only analgesic or sensory action may last for 8 hours. A concentration of 0.125 to 0.25% bupivacaine is used only for postoperative analgesia, avoiding motor block and the analgesic action of this concentration lasts only for 4 hours. A concentration of 0.25% solution of bupivacaine is usually satisfactory only for sensory block, but the duration and reliability of 0.125% solution are not usually acceptable. On the other hand, in 0.25% solution of bupivacaine there may, however, be minor degrees of motor block and some risk of haemodynamic instability. So, such a concentration of bupivacaine would be unsuitable for upper abdominal or thoracic analgesia which may produce a high incidence of hypotension. Again in general, lower concentration (0.125%) of bupivacaine does not cause motor block by any degree, but necessiate larger volume of drugs and consequently increases the spread which may result in higher incidence of hypotension. Unlike lignocaine the epidural dose of bupivacaine can be repeated for indefinite period without producing tachyphylaxis and any risk of systemic toxicity. The 0.75% bupivacaine is not recommended in USA.

The dose of continuous epidural infusion by bupivcaine is 0.125 to 0.375% solution at the rate of 10 to 20 ml/hr. Levobupivacaine may be used in place of bupivacaine.

Table 24.8: Onset and duration of action of local anaesthetic agents administered epidurally in 20 to 30 ml of volumes

Drug	*Concentration (%)*	*Onset (min)*	*Duration of action*	
			Plain (min)	*Adrenaline 1:2,00,000 (min)*
Lignocaine	2	10-20	60-90	90-180
Bupivacaine	0.5	15-25	160-240	160-240
Chloroprocaine	3	10-15	45-60	60-90

Chloroprocaine

Preservative free 2 to 3% chloroprocaine is also used both for spinal and epidural block. But duration of action of chloroprocaine is very short and only 45 minutes. So, combining of chloroprocaine with catheter technique allows a good matching of surgical procedure with minimal recovery time. It is mainly used in USA. However, it antagonises the action of fentanyl.

Ropivacaine HCl

Ropivacaine has less CNS and CVS toxicity than bupivacaine, but more or less has same onset and duration of action like it. It causes better differential block, i.e. at lower concentration ropivacaine profoundly blocks only sensory, but completely preserve the motor. So, 0.05 to 0.1% solution of ropivacaine is used for only sensory block, but 0.3% for profound sensory and slightly motor block and 1% for both profound sensory and motor block. Therefore, it is best suited for obstetric anaesthesia and analgesia and postoperative pain by infusion technique.

Method of Injection of Anaesthetic Agent through Epidural Catheter

There are many methods or sequences for the injection of anaesthetic agent during continuous epidural anaesthesia using

catheter. Among these the first choice is after an appropriate test dose. The calculated first schedule dose of local anaesthetic agent is injected through the needle prior to the catheter placement. The advantage of this method is allowing the time for the onset of anaesthesia while the catheter is being placed and when the catheter placement is complete, then there is already enough anaesthesia to begin the surgical procedure without wasting any time. Also the bolus first dose of local anaesthetic agent, injected through the needle, will expand the epidural space and make the catheter placement much easier and successful.

But disadvantages of this method are found in those cases where even the correct placement of needle and injection of anaesthetic agent through this needle will not allow the subsequent successful insertion of catheter. In such cases, replacement of needle in another space is much riskier as local anaesthetic has already filled the epidural space, which may confuse the detection of epidural and subarachnoid space and once epidural anaestheisa has been set up, absence of paraesthesia does not indicate needle contact with neural tissue and cannot prevent the trauma of nerves.

The second choice is after the test dose through needle (which expands the epidural space) the catheter is inserted first. Then after positioning the patient, the first bolus dose of local anaesthetic agent is injected through the catheter, followed by subsequent doses or continuous infusion. Another choice is that some anaesthesiologists prefer to give the first dose of local anaesthetic agent through epidural needle before the catheter placement with patient in sitting position. This approach offers maximum bathing of large nerve roots (L_5-S_1) by gravitating down the anaesthetic agent for those cases where the dermatomes supplied by these nerve roots are a major part of surgery. Due to the downward movement of LA agent, subsequent insertion of catheter does not produce confusion like 1st technique. Although uncommon, it is also possible to thread a catheter caudally by directing the tip of the needle caudally. This is because the needle may be rotated caudally after entry into the epidural space. But, this entails more risk because the needle is directed against the dura and rotating the needle would cause a cork-screw like effect in which case the needle would advance either partially or completely from epidural space into the subdural or subarachnoid space.

Mechanism of Action and Fate of Local Anaesthetic Agent in Epidural Space

Till now this discussion is full of a controversy and unclear, but some postulated hypothesis exist. The principal site of action of LA agent in epidural anaesthesia is the portion of nerve roots which are present in the epidural space. Local anaesthetic agents injected in the epidural space also can pass out of the intervertebral foramina and act on the mixed spinal nerve in the foramina. As these foramina are generally occluded by spinal nerves and accompanying vessels, so with the increased age these foramina become narrower and thus confine the anaesthetic solution more in the epidural space and cause much higher block by increased spread with same volume of drug. Also the substantial amount of drug diffuses in the subarachnoid area from the epidural space for its action. But, the two modes of block, i.e. in the epidural space and in the subarachnoid space is different. This is explained by the fact that epidural block works segmentally, nearest to the injection site which would be impossible if intrathecal route of distribution was the only factor for mechanism of action of epidural anaesthesia. Local anaesthetic agent in epidural anaesthesia also penetrates the dural cuff to block the nerve roots and transmit centrally along the nerve to block the conduction in the spinal cord. Whatever may be the destination of the epidurally administered local anaesthetic agent, they must ultimately be absorbed into the bloodstream. Absorption of local anaesthetics into the circulation takes place more rapidly from the epidural than from the subarachnoid space. The speed with which they are absorbed depends upon the local vascularity, which may again be influenced by the injected adrenaline and by the characteristics of drug itself.

Epidural Anaesthesia using Catheter and CVS/RS

Epidural anaesthesia has unique effect on CVS. If the patient is properly prepared with volume expander and the level of anaesthesia is properly titrated by catheter, then the influence of epidural anaesthesia on LV performance is favourable, even in patients with cardiac disease with decreased cardiac output and decreased LVEF. Experimental work demonstrates the reversal of myocardial ischaemia with segmental thoracic epidural analgesia. This is because EA allows suitable placement of catheter and then proper titration of anaesthetic drug with the level of block which results in controlled rate and degree of sympathetic block, allowing adequate time for compensation for decreased venous return and reduced cardiac output by activating cardiac acceleration fibres.

Continuous epidural anaesthesia (EA) by catheter controls the respiratory mechanics more easily than the subarachnoid block. The decrease of pulmonary function is proportionate to the height of the motor block achieved. Even the lowest level of lumbar EA causes abdominal muscular paralysis which is only involved in active expiration. Impairment of active expiration has no clinical significance on respiration in the absence of COPD. As the level of motor block ascends, it effects the increasing amount of muscles involved in quiet respiration. Intercostal muscles act by stabilising and expanding bony thorax and thus help in respiration by creating

negative intrathoracic pressure. As more and more intercostal muscles are blocked then respiration becomes more dependant on diaphragm alone. Block of high sensory level in EA, blunts normal endocrine response to surgical stress and also the respiratory response to increased level of arterial PCO_2.

Factors Controlling the Spread of Epidural Block

The factors controlling the spread of epidural block are:

1. Volume and concentration of local anaesthetic agent

The volume and concentration of LA agent influence the epidural anaesthesia as spinal anaesthesia which has been discussed earlier.

2. Posture

Though 0.5% bupivacaine and 2% lignocaine is isobaric, still it tends to spread in epidural space according to the gravity, but not so reliably as hyperbaric solutions given intrathecally. As the fat has a lower specific gravity than the aqueous local anaesthetic solutions, but the very thin film of it in the epidural space is unlikely to be sufficient to account for such positive geotropism. Gravity is more effective for epidural spread in obese than in normal subject. This is because of more presence of fat in epidural space in obese than in a normal individual. The height of block is not so clinically predictable by position and posture changes in epidural anaesthesia, because gravity and baricity are not so intimately related to the spread of block in epidural anaesthesia. Still, it is apparent that tilting can determine the caudal and cephalad spread in epidural anaesthesia. Thus, lateral position produces a block which is significantly higher on the dependent side. In most subjects, it is possible to induce only sacral spread of local anaesthetic solution in epidural anaesthesia with the aid of sitting position. But it may be necessary to use a low space and / or a large volume.

3. Site of injection

Epidural anaesthesia mainly work segmentally at the roots, nearest to the injection site. So, the site of injection is very important for the level of anaesthesia in epidural procedure. As for example, during upper abdominal surgery where the dermatomes are supplied by thoracic spinal nerves, very large volume of drug (which may reach toxic level) is necessary to reach the thoracic segments, if epidural is given by lumbar route. So, in such cases higher interspinal space is preferable and idealy throcic epidural approach greatly reduces the dose requirement and unnecessary lumbar anaesthesia. For leg and perineal block, lower lumbar interspaces are preferred. For obstetric analgesia, a lower lumbar approach than L 2/3 interspinal space causes standard volume of solution to be ineffective and has too much effect on the legs.

4. Age

The total dose requirement of local anaesthetic agent during epidural anaesthesia is inversely related to the age. Age-related arteriosclerosis and osteoarthritis changes cause gradual closure of the intervertebral foramen and thus prevents the leak of anaesthetic solutions in the paravertebral space from epidural area through the intervertebral foramen, causing increased spread of it along the vertebral column and higher level of block with same volume of LA agent.

5. Pregnancy or intra abdominal tumours

Increased pressure on inferior vena cava by gravid uterus or any other intra-abdominal tumours or ascitis leads to the diversion of venous return from the lower part of the body through the vertebral and epidural venous plexuses. Therefore, distension of these venous plexuses causes reduction of epidural space and so higher spread by the same volume of LA drug results higher level of block and more hypotension. But some schools do not believe in it. They believe that pregnant patients are more sensitive to hypotensive effect of LA agents (by vasodilation) due to high level of progesterone. Thus, for pain relief in labour a small volume of drug is adequate (where very few segments have to be blocked) than obstetric anaesthesia.

6. Height and weight of patient

Obesity reduces and height of patient increases the dose requirement of local anaesthetic agent.

7. Nerve root size

S_1 nerve root is thickest of all the spinal nerves and is notoriously resistant to epidural block. So, S_1 dermatome has a very long latency and shorter duration of block.

INDIVIDUAL EPIDURAL BLOCK

Thoracic Epidural

The thoracic epidural space extends from the lower margin of C_7 vertebra to the upper margin of L_1 vertebra. The vertebral column in the thoracic area normally has a kyphotic curvature (concave ventrally) with its apex at the approximately T_6 level in supine position. The inclination of the spinous processes of thoracic vertebrae is different at different levels. The spines from T_1-T_4 vertebrae have very little inclination, whereas those of T_5-T_8 vertebrae tilt significantly downward, making a midline approach to the epidural space practically impossible in that area. The T_9-T_{12} spines direct dorsally without any significant inclination. So, the midline approach for epidural space is possible in that T_9-T_{12} spaces. The ligamentum flavum in the thoracic region is not as thick as in lumbar region. So, in the thoracic region the epidural space can be entered

without encountering much resistance. In thoracic area, the epidural space is only 3 to 4 mm wide and like other space contains loose areolar tisue, fat and vertebral venous plexuses. The lumbar enlargement of the spinal cord is situated within the thoracic vertebra between T_9-T_{12} segment. The pressure in the thoracic epidural space is approximately −15 cm of H_2O and is very close to that of the negative intrapleural pressure. It is more pronounced in the sitting position. However, the negative pressure in the epidural space is also considered to be secondary to the tenting of the dura by the blunt epidural needle during procedure. In 12% of cases, the pressure in the epidural space is not negative.

The cardiovascular effect of thoracic epidural anaesthesia depends on the level of block. The preganglionic sympathetic fibres as white rami communicans are present in all the thoracic spinal nerve. Sympathetic block up to T_{10} level, extending from L_2 produce minimal cardiovascular changes. The degree of hypotension due to sympathetic block up to that level will depend on the existing blood volume. The hypotension if occur usually will be partly compensated by vasoconstriction of the upper extremities and partly compensated by cardiac stimulation by tachycardia and increased myocardial contraction as T_1-T_4 cardiac (Fig. 24.34) sympathetic fibres are not blocked. If the block extends up to the segment T_6 from L_2 then hypotension will not be compensated and it will be revealed. This hypotension is primarily due to venodilatation, pooling of blood in venous side, and subsequently decreased right heart filling and decreased cardiac output. Blocking of the sympathetic fibres to the abdominal viscera, including those to the adrenal medulla, also can reduce the response to stress during the lower abdominal and pelvic surgical procedures. If the block extends up to the T_1 segment, the sympathetic fibres innervating the heart will also be affected. Therefore, the cardioaccelerator fibres, coming out of the

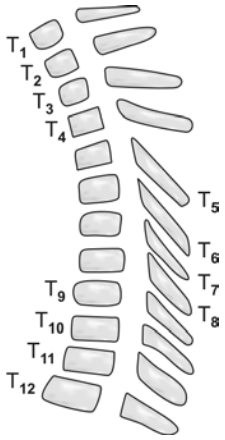


Fig. 24.34 : The inclination of spine of different thoracic vertebrae

T_1-T_4 segment will be blocked producing severe bradycardia and hypotension due to nonavailability of cardiac compensatory mechanism and also due to the unopposed action of the parasympathetic fibres derived from the vagus nerve. Sometimes, it results in cardiac standstill. So the response is manifested primarily by the combined effects of degree of sympathetic denervation and unopposed vagal nerve dominence. Sympathetic denervation produces arterial and more important, arteriolar dilatation. But this arterial or arteriolar dilatation is not complete, however, because vascular smooth muscle on the arterial side maintains a significant degree of autonomous tone which is not dependent on sympathetic system. The venous system has very little smooth muscle present within its walls and maintains no significant residual tone due to complete sympathetomy. Thus, venodilatation and severely reduced preload result in a reduction in cardiac output with severe hypotension, but without any compensation as the cardioaccelaratory fibres are blocked. Bradycardia or cardiac standstill also can occur after blockade of the cardioaccelaratory fibres arising from T_1-T_4 segment or failure of activation of the great vein and right artrial cardiac receptors which usually occurs due to the decreased venous return, and reflexly increase the heart rate (Bainbridge reflex). During sympathetic block below the T_4 level, the baroreceptors in the carotid sinus and aortic arch normally respond to a fall in blood pressure by producing a compensatory tachycardia (Marey's law), through vagal afferent and efferent pathways.

Bainbridge reflex

The venous engorgement of the right atrium and the great veins reflexly increase the heart rate. The afferent fibres, arising from the roots of the great veins and right atria pass along the trunk of the vagus to the cardiac centre. Engorgement of these parts stimulates the nerve endings and reflexly inhibit the vagal tone and also stimulates the sympathetic to some extent. Thus, the heart rate rises and cardiac output increases. This reflex is called the Bainbridge reflex or more appropriately the venous reflex.

Cardioinhibitory reflex (Sinoaortic or Marey's reflex)

There are the stretch receptors in the carotid sinus and aortic arch. When the blood pressure rises, these nerve endings become stimulated due to stretching, and cause sensory impulses to pass up through the sinoaortic nerves and increase the vagal tone. So that heart rate falls. When blood pressure falls, no inhibiting impulse passes up and heart rate rises. Thus the heart rate and blood pressure have an inverse relation. This is known as the Marey's law.

Paralysis of the intercostal muscles by thoracic epidural block can affect the respiratory volumes. When this block affects all the intercostal muscles, then normal ventilation and P_aCO_2 can still be maintained by the activity of the diaphragm only, since the phrenic nerve is not affected. But, patient suffers from a severe feeling of suffocation. So, sedation is very much needed which again reduces the central ventilatory drive. On the other hand, secondary to intercostal muscle paralysis increased diaphragmatic shortening improves the tidal volume. But, the

inspiratory reserve volume and functional reserve capacity are significantly decreased with the decrease of vital capacity.

Thoracic epidural with Tuohy needle and catheter can be performed by the patient sitting, lateral or prone position. Sitting position provides better alignment of the spine and facilitates better identification of landmarks. But a patient who is anxious may have a strong vasovagal and hypotensive reaction. So, for them lateral decubitus is preferred. Flexion of the patient contributes very little by expanding the interlaminar space in the thoracic region (Fig. 24.35).

Thoracic epidural space also can be approached from three directions—midline, paramedian and laminar. The midline approach is applicable in the upper part of the thoracic spine between C_7 and T_5 and in the lower part of the thoracic spine between T_9–T_{12}. Because in these areas the spinous processes are more or less horizontal and project directly to the posterior without inclination. In these segments, the level of the spinous process corresponds to the same level of vertebra.

The paramedian or lateral approach can be used at any level of the thoracic spine. In paramedian or lateral approach the epidural needle is advanced at a 45 to 55 degree angle towards the cephalad and at 15 to 30 degree angle toward the midline. Contacting the lamina with the epidural needle significantly increases the safety of this approach, because the epidural space can be entered by just walking off the superior margin of the lamina. Extreme angles can result in the needle passing between the spinous processes into the paraspinal muscles of paravertebral space of the opposite side. For laminar approach, the starting point is 1 to 2 cm lateral to the superior margin of the spinous process (like paramedian approach), but the needle is not angled toward the midline. It runs parallel to the spinous process and enters the interlaminar foramen medial to the interarticular process. Here, only the lateral portion of the epidural space is entered (Fig. 24.36).

The complications of the thoracic epidural technique or approach are similar to those of the lumbar epidural.

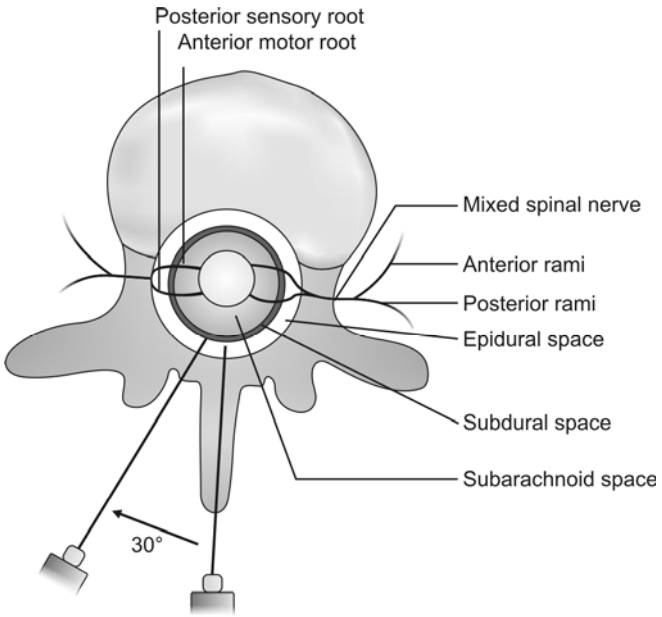


Fig. 24.35: Cross-section of median and paramedian approach to the lumbar epidural space. The red colour circle indicates the dura mater and the green colour circle indicates the arachnoid mater

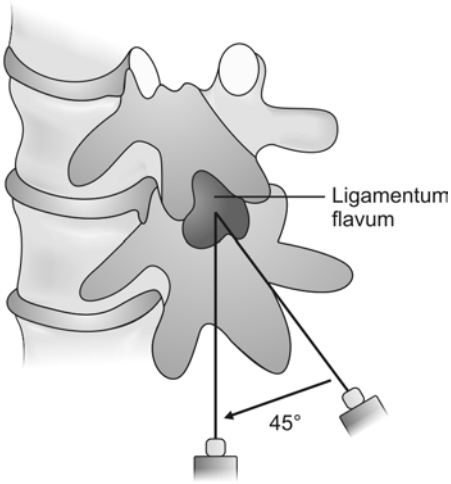


Fig. 24.36: The median and paramedian approach to the lumbar epidural space

There are many indications for thoracic epidural block. Among them a few are stated below. Thoracic epidural catheters are increasingly utilised for providing intraoperative and especially postoperative analgesia for thoracic and upper abdominal surgical procedures, such as mastectomy, cholecystectomy, gastrectomy, repair of diaphragmatic hernia, etc. It has also been utilized for thoracotomy and cardiac surgery in conjunction with light general anaesthesia. Patients with multiple fractured ribs get excellent analgesia by thoracic epidural with catheter at selected segments. Local anaesthetic, such as 0.125% bupivacaine and / or an opioid can be used without any motor block and hypotension. Catheters placed in the thoracic epidural space can also be used to provide only long-term analgesia using opioids, local anaesthetics, phenol or alcohol in alone or with combination for chronic pain due to many causes or acute pain in nonoperable malignancy. The catheter should be placed in the area of the involved nerve roots. If alcohol is used it should be injected through the catheter in 0.5 ml incremental doses to a maximum of 5 ml. The injection has to be repeated daily for at least 3 days. Phenol is used in concentration of 5% with dextrose or with normal saline.

Cervical Epidural

The cervical epidural space is bounded above by the fusion of the investing layer of drug (vertebral periosteum) and the spinal layers of dura at the foramen magnum and below it is continuous with the thoracic epidural space at the level of the T_1 vertebra. The cervical epidural space is bounded anteriorly by the posterior surface of the body of cervical vertebra with posterior longitudinal ligament and posteriorly by the vertebral laminae and ligamentum flavum. The ligamentum flavum is thin in the cervical region and gradually becomes thicker caudally. It is thickest at the lumbar region. This fact has direct clinical implication, because the loss of resistance felt during cervical epidural block is more subtle than it is in the lumbar and lower thoracic region. The vertebral pedicles and intervertebral foramina form the lateral boundary of cervical epidural space. The degenerative changes and narrowing of these intervertebral foramina associated with aging may be marked in the cervical region. Such changes reduce the leakage of local anaesthetic solution out of the foramina and account for the reduced anaesthetic dose requirement in elderly patients undergoing cervical epidural block. At the level of C_7, the distance between the ligamentum flavum and the dura is only about 1.5 to 2 mm. It is due to the presence of cervical enlargement of spinal cord, serving the upper extremities. Whereas, the distance between ligamentum flavum and the dura is greatest at the L_2 interspace, measuring about 5 to 6 mm in adults. It should also be noted that flexion of the neck moves this cervical enlargement more cephalad, resulting in widening of the epidural space to 3 to 4 mm at the C_7-T_1 interspace. This fact has important clinical implications for cervical epidural block.

Like other epidural space, cervical epidural space also contains loose areolar tissue, fat, epidural veins, arteries and lymphatics. Fat in the epidural space serves as a shock absorber for other contents of the space and as a depot for injected drugs. The amount of epidural fat varies in direct proportion to the amount of fat, stored elsewhere in the body. The epidural fat is relatively vascular and appears to change to a denser consistency with aging. This change in consistency may account for the significant variations in required dose of a drug in adults, especially with the cervical approach to the epidural space. The valveless epidural veins are concentrated principaly at the anterolateral portion of the epidural space and transmit both the intrathoracic and intra-abdominal pressures. When pressure in either of these body cavities increases such as during Valsalva's manoeuvre or compression of the inferior vena cava in the abdomen by a gravid uterus ascitis or a tumour mass, etc. then the cervical epidural veins distend and reduce the volume of this epidural space. This decrease in volume of the cervical epidural space can directly affect how much drug is needed to obtain a given level of neural blockade. Most of the epidural arteries with significant anastomoses lie in the lateral portions of the cervical epidural space. The arteries enter the epidural space via two routes: through the intervertebral foramina and via direct anastomoses from the intracranial portion of the vertebral arteries. Trauma to these epidural arteries can result in the formation of epidural haematoma and compromise the blood supply to the spinal cord itself.

Cervical epidural block can be carried out with the patient in the sitting, lateral or prone position and each position has its advantages and disadvantages.

1. The sitting position for cervical epidural block is most preferred, because (i) it enhances the operator's ability to identify the midline, (ii) it also ensures that the cervical spine is flexed which widens the lower cervical epidural space, (iii) the sitting positis avoids the rotation of the spine which is inherent in the lateral position and makes identification of the cervical epidural space difficult. But, sitting position is not always an option for patients with acute vertebral compression fracture or with the history of vasovagal syncope or sedated, where lateral position is preferred. For the patient's comfort lateral decubitus or position is more suitable and also for those who cannot assume the sitting position. If lateral position is selected, then care must be taken to ensure that there is no rotation of the patient's spine because it will make the cervical epidural block extremely difficult or impossible or produce complications. During cervical epidural it will have to-kept in mind that flexion of the cervical spine is mandatory to maximise the width of the epidural space. Another important point for cervical epidural anaesthesia is that the needle entry site should be exactly in the midline. Failure to accurately identify the midline is the most common cause of difficulty in performing the cervical epidural block. Prone position is selected in special cases, such as during placement of epidural catheters with spinal stimulation electrodes. However, prone position should be avoided if sedation is required, because access to the airway is limited.

For the purposes of diagnostic and/or prognostic cervical epidural block, 1% preservative-free lignocaine is most suitable as local anaesthetic agent. For therapeutic purpose, 0.25% preservative-free bupivacaine in combination with 80 mg of depot methylprednisolone is injected. Subsequent doses of methylprednisolone is 40 mg daily with or without local anaesthetic agent to treat the acute painful conditions. Chronic painful conditions such as cervical radiculopathy, diabetic neuropathy, etc. are treated by daily or every alternate day or once in a week injection through the catheter as the clinical situation dictates. Other indications for cervical epidural block are intractable pain, thyroidectomy, carotid end arterectomy, etc. During cervical epidural analgesia differential block is used to avoid

motor block of phrenic nerve. For this purpose drugs used are bupivacaine 0.125% or lignocaine 0.5%.

Like thoracic and lumbar epidural block, cervical epidural block can also be employed by Hustead or Tuohy needle which is advanced slowly at an angle of 30 degree cephalad. Catheter is advanced approximately 2 to 3 cm beyond the needle tip. The needle is then carefully withdrawn over the catheter. Under no circumstances only catheter should be withdrawn back through the needle, because it will cause shearing of the catheter at the needle tip and lost in the epidural space. If significant pain occurs during placement of the epidural needle or catheter or during injection of drug, then the physician should immediately stop the procedure and ascertain the cause of pain to avoid the possibility of neural trauma. So, intravenous sedation or GA before initiation of cervical or other epidural nerve block renders the patient unable to provide accurate verbal feedback, if the needle is misplaced. Like other central neuroaxial block, during cervical epidural block if an epidural needle or catheter is accidentally placed in the subarachnoid space and the problem goes unrecognised, then injection of a fraction of epidural doses of local anaesthetics solution will cause immediate total spinal anaesthesia and its consequences. So, implication of test dose in cervical epidural anaesthesia is not as helpful as thoracic and lumbar epidural anaesthesia.

The administration of opioids and local anaesthetic agents into the cervical epidural space may be associated with a greater incidence of urinary retention. This side effect is more common in elderly male and multiporous females whose bladders are prolapsed. Overflow incontinence may occur when such patients are unable to void or bladder catheterisation is not done. So, all patients must empty their bladder before their discharge from the pain clinic, if they get cervical epidural anaesthesia or analgesia.

Caudal (or Sacral) Epidural Anaesthesia

Anatomy of sacrum, sacral canal and hiatus

The sacrum represents the fusion of 5 sacral vertebrae. However, many variations of this fusion are common and have an important bearing on the incidence of failure rate of caudal epidural anaesthesia. The sacrum is triangular in shape. The apex of this triangle is directed below and is formed by the 5th sacral vertebra which articulates with the coccyx. The base of the triangle is formed by the first sacral vertebra and articulates with the body of 5th lumbar vertebra. The anterior surface of the sacrum is concave and is characterised by four anterior sacral foramina on both sides of the midline (4 pairs) through which the anterior primary rami of four sacral spinal nerves pass out. The posterior surface of the sacrum which has a greater interest for anaesthetist is convex. A bony ridge with three or four rudimentary spinous processes runs in the midline and is called the median sacral crest. On the both sides of this median sacral crest, there are 4 posterior sacral foramina, (total 4 pairs) corresponding with the anterior one, through which posterior primary rami of the four spinal sacral nerves pass out. The local anaesthetic solutions injected into the sacral epidural space or sacral canal can pass freely through these foramina and this is an important factor for the unpredictability of the height to which caudal anaesthesia may extend. The canal in the sacrum is called the sacral canal. It is also triangular in shape and continuous above with the lumbar portion of vertebral canal and terminate below at the sacral hiatus (Fig. 24.37).

The sacral canal contains:

i. the epidural space with venous plexus and fibrofatty tissue. This sacral epidural space is continuous above with the lumbar epidural space,

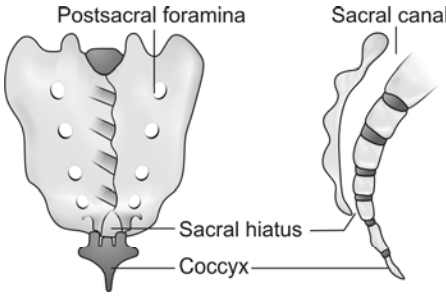


Fig. 24.37: The posterior and sagittal view of sacrum and coccyx

ii. the dural sac made of spinal dura mater and arachnoid mater contains CSF and ends between S_1 and S_3 vertebrae (usually at the lower border of S_2),
iii. the five sacral nerve roots,
iv. coccygeal nerve,
v. filum terminal externa.

The epidural venous plexus in sacral canal generally ends at S_4 level, but may also continue caudally. Most of these vessels are concentrated in the anterior portion of the canal. Both the dural sac and the epidural vessels are susceptible to trauma during the excessive cephalad advancement of the epidural needles and catheters used for caudal block through the sacral canal. The remainder of the sacral canal is filled with fibrofatty tissue which is subjected to age-related increase in density.

The sacral hiatus is actually a deficiency on the posterior wall at the lower end of the sacrum. It results from the failure of the fusion of laminae of 5th sacral vertebrae. It is triangular in shape. The apex of the hiatus is formed by the spine of 4th sacral vertebrae. The lateral margin of hiatus bears prominence called the sacral cornu which represents the articular process of 5th sacral vertebrae. Base of the hiatus is formed by the superior surface of coccyx and is covered by posterior sacrococcygeal mambrane. In surface marking, the sacral hiatus forms an equilateral triangle with the two posterior superior iliac spines. There may be multiple anatomical variations of sacral hiatus. Some of which are described below. The apex of hiatus may be formed by the spine of 2nd or 3rd sacral vertebrae due to the absence

of laminae of 3rd and 4th sacral vertebrae, respectively. Occasionally, the whole bony post wall of the sacrum remains deficient. On the other hand, when the lamina of 5th sacral vertebra is present, then hiatus may become very small with the diameter as narrow as 2 mm and makes the introduction of needle for caudal epidural anaesthesia almost impossible. There are many fibrous bands in the sacral canal which divide the sacral epidural space into multiple loculi, causing incomplete spread of local anaesthetic agents in the sacral canal and incomplete anaesthesia. Now a days caudal epidural anaesthesia is often combined with GA for paediatric patients to decrease the amount of intraoperative anaesthetic agents and/ or to provide postoperative analgesia for the surgeries on inguinal region, perineal region, lower extremities and sometimes lower abdomen.

Technique

It is better to see and practice than to read the technique of caudal epidural anaesthesia. Usually the needle, selected for caudal anaesthesia, should be malleable enough to adapt itself with the curvature of the sacral canal and will not break. A wide bore needle gives a better feel of the structures as it passes through the hiatus and canal, while a short bevel at the tip minimises the risk of puncturing the dura. However, nowadays many operators use an ordinary disposable hypodermic needle for caudal epidural block. The ideal position of patient for caudal block is prone or lateral. The sacral hiatus is identified first by sacral cornu. The needle then pierces the skin and sacrococcygeal ligament at right angle. After that needle should be depressed in the intergluteal fold and is advanced cranially in the sacral canal, maximum up to the line joining the two posterior superior iliac spine, where the dural sac (with the subarachnoid space) ends. Aspiration for blood or CSF is done. Blood through needle indicates puncture of epidural vein and in that case needle should be withdrawn for a few millimetre. If CSF comes through needle, then procedure should be abandoned or converted it to spinal block. For test dose (test for confirmation whether the tip of the needle has enter the dural sac or remains outside the dural sac in the epidural space), 2 ml of local anaesthetic drug is used first. If patient can move his toes then it is sure that the tip of the needle is in epidural space and not in subarachnoid area. Then rest of the drug is injected.

Problems

The needle may miss the sacrococcygeal ligament and may pass dorsal to the sacrum under the skin or may pass under the periosteum of the posterior surface of sacrum. This can be tested by injecting a few ml of air and palpating the crepitus under the skin. The needle may slip under the base of the coccyx and can pierce the rectum or foetal head (in pregnancy). The needle may run beneath the periosteum of the sacral canal causing marked resistance to injection and complain of severe backache. Any feeling of resistance during injection of LA agent indicate needles is not properly placed.

Doses

The level of block by caudal epidural anaesthesia depends on the volume of local anaesthetic solution, and the position of the patient. With the patient in horizontal position 20 to 30 ml of local anaesthetic drug is required to block up to $L_{4\text{-}5}$ level. It is used for operation on anus, perineum and vagina. 40 ml drug is needed for analgesia and anaesthesia up to the umbilical level. But, with the patient in horizontal position such a large dose may risk the systemic toxic reaction. However, Trendelenburg position helps in upward extension of the drug and reduces the dose.

Indications

The main indication of epidural anaesthesia through this caudal route is the production of conduction block of only the lower lumbar and sacral spinal nerve roots for procedures such as urinary bladder operation, anal-vulva-vaginal operation, operation on inguinal region, circumcision, etc. without affecting blood pressure and much systemic conditions. In some conditions where caudal-epidural is highly indicated due to severe illness of the patient, but sacral approach is technically very difficult, then it may be easier to perform lumbar epidural block in sitting position. Postoperative analgesia by caudal epidural block in conjunction with GA is a good choice, particularly in children and obstetric analgesia.

Continuous caudal epidural anaesthesia using catheters

An epidural catheter may be placed into the sacral canal in a manner, analogous to that of continuous lumbar, thoracic or cervical epidural anaesthesia, through an epidural needle placed in sacral canal though sacral hiatus. The epidural catheter is advanced through the needle approximately 2 to 3 cm beyond the tip and then the needle is carefully withdrawn over the catheter. But, under no circumstances, the catheter is withdrawn back through the needle to avoid the shearing of catheter tip. A test dose of 3 to 4 ml of local anaesthetic agent is then given via the catheter and the patient is observed for any sign of local anaesthetic toxicity due to intravascular injection or inadvertent subarachnoid injection. If no sign of side effects or toxicity of LA agent are noted, then intermittent boluses or continuous infusion of local anaesthetic agent with or without opioids are administered through the catheter. Because of proximity to the anus, the risk of infection limits the long-term use of caudal epidural catheters.

Paediatric caudal block

Though placement of an epidural catheter allows for continuous infusion of local anaeshtetic agent with or without opioid or opioid alone for continuous caudal block

for various reasons, till the single injection caudal or sacral block is one of the most popular paediatric regional anaesthetic techniques for intra and postoperative analgesia. A combination of caudal block, supplemented with light general anaesthesia allows for a quicker recovery due to lesser need of volatile and other general anaesthetic agent.

Technically, the caudal blocks are much easier to perform in children than adults. This is because in children:

i. landmarks defining the sacral hiatus are easy to palpate,
ii. limited amount of gluteal pad of fat,
iii. less subcutaneous fat over hiatus,
iv. gluteal musculature are poorly developed,
v. there is less fusion and less distortion of sacral hiatus,
vi. the sacrococcygeal ligament is not calcified.

In children dural sac ends in between the 2nd and 3rd sacral vertebrae which is generally much lower than that of adult and sacrum is smaller in proportion to the overall size of the body. So, there is much higher possibilities to pierce the dura during caudal block in children.

It is previously stated that when the caudal block is combined with GA, then it provides excellent perioperative analgesia. So, the common indication of paediatric caudal epidural block are: (i) sacral segment surgeries – circumcision, rectal operation, club foot repair, etc. (ii) groin surgeries – herniorrhaphy, orchidopexy and hydrocele, etc. (iii) urologic procedures, (iv) lower extremity orthopaedic procedures. By increasing the volume of drug, the level of caudal block can be increased high by which the different lower abdominal surgeries can also be performed.

For caudal epidural, 0.25% bupivacaine is the commonly used drug which provides minimal motor blockade with adequate sensory blockade. But the total dose of bupivacaine should not exceed 3 mg/Kg. An easy calculation of volume of 0.25% bupivacaine is: 0.5 ml/kg for only sacral blockade, 0.75 ml/kg for the blockade of lumbar segments and 1.25 ml/kg for the blockade of thoracic segments. Test dose is unreliable in children, so close observation, frequent aspiration, and fractionated injection of drug is the best safeguard against undetected subarachnoid and intravascular injection.

COMPLICATIONS OF SPINAL AND EPIDURAL BLOCK

As some complications are common for both the spinal and epidural anaesthesia, so they are discussed together.

Hypotension

Vasodilation and hypotension is a predictable and desirable feature of central neuroaxial blockade when the nerve roots above the L_2 levels are affected from where the preganglionic sympathetic fibres originate. Severe hypotension is more likely in the older patients, and in patients with higher level of block (T_5 and above). The definition of hypotension during CNB varies, but a systolic blood pressure of less than 90 mm of Hg is challengeable. It is more appropriate to consider a fall in BP of 25 to 30% from its preoperative mean arterial pressure (MAP) level as a practical guide to dictate the treatment. The incidence of hypotension following CNB has been reported to be 92% in an untreated control group undergoing caesarean section with spinal anaesthesia. It is a very serious problem in spinal anaesthesia and is due to its rapid onset and giving no time for adequate cardiovascular compensation. More quick acting anaesthetic drugs cause more fall of blood pressure. In continuous epidural, this incidence of hypotension can be reduced by giving the full dose of LA agent in multiple small incremental doses, when a extensive epidural block is needed and thus giving CVS the time for compensation. This complication can be managed by intravenous preloading with crystalloid (1 to 2 litres) or colloid solution. Colloid solutions are more effective in reducing the hypotension at lower volumes than the crystalloid solution. But, the colloids are more expensive and carry a slightly increased risk of allergic reaction. So, crystalloids are generally preferred for IV preloading as routine prophylaxis against hypotension. However, caution is required for the patients with cardiac disease where smaller volumes of IV fluids plus earlier use vasopressors is advisable. The administration of large volumes of IV fluid as the only treatment of persistent hypotension, produced by central neuroaxial blockade is potentially dangerous and is not recommended. Pressure-rising drugs like ephedrine or methoxamine are used where preloading fails to maintain MAP. Combination of preloading and vasoconstrictor had maximum effect and is the best in preventing spinal hypotension. This is followed by the sole use of vasoconstrictor which is the second choice. Preloading alone offers least protection against spinal hypotension.

The optimal treatment of hypotension induced by central neural blockade remains still unresolved. A correction of the fall of the systemic vascular resistance generally includes the treatment with α-adrenergic agonist such as methoxamine. Whereas the impaired venous pooling is corrected by IV fluids and β-adrenergic agonists. A slight head down tilt and elevation of legs encourage venous return. Methoxamine, as an α-adrenergic agonist, increases the peripheral vascular resistance and restores pressure, but perhaps at the expense of organ blood flow. This drug may produce or extend bradycardia and is preferable to ephedrine when tachycardia is present. So caution should be exercised when (Table 24.9) there is a normal or lower than normal heart rate, as more reflex bradycardia due to increase of vascular resistance may follow the administration of methoxamine. The initial intravenous bolus dose of methoxamine should be 2 mg. Ephedrine is a predominantly β-adrenergic agonist

Table 24.9: Complications of central neuroaxial block (CNB)

A.	**Related to needle and/or catheter introduction**
i.	*Trauma*
	Nerve root damage
	Spinal cord damage
	Cauda equina syndrome
	Dural puncture leak causing PDPH, tinnitus, diplophia, etc.
	Cranial nerve injury
	Backache
ii.	*Bleeding*
	Intraspinal haemorrhage
	Epidural haematoma
iii.	*Infection*
	Meningitis
	Epidural abscess
iv.	*Displacement of needle or catheter*
	Inadvertent intravascular injection
	Inadvertment subarachnoid block or total spinal (epidural block)
	Inadequate block
	No effect
	Shearing and retention of catheter
B.	**Exaggerated physiological responses**
	Total spinal anaesthesia (in case of epidural block)
	Higher block than expected
	Respiratory arrest, cardiac arrest
	Urinary retention
	Anterior spinal artery syndrome
	Horner's syndrome
C.	**Toxicity of drugs**
	Systemic toxicity
	Transient neurological symptoms
	Cauda equina syndrome

and has little direct effect on peripheral resistance. It mainly acts on heart. Thus, it maintains the blood pressure by increasing the heart rate with some effect on the venous pooling. Ephedrine is also advantageous over methoxamine in pregnancy, because here the preservation of uterine blood flow in the presence of hypotension is more important. It is administered in a bolus dose of 3 to 6 mg intravenously.

Sometimes, the simple treatment of bradycardia by atropine may restore the blood pressure to an acceptable level. Raising of legs to increase the venous drainage and thus to reduce the chance of hypotension may encourage further cranial spread of the local anaesthetic block, if this is under taken in the early stages of anaesthesia, and may cause more hypotension.

Postdural Puncture Headache (PDPH)

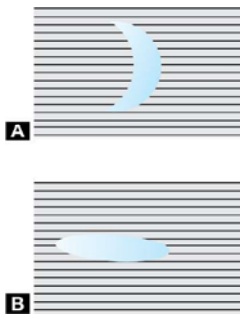
It is the complication of spinal block only and in epidural anaesthesia when the needle inadvertently punctures the dura. The principal cause of PDPH in spinal anaesthesia is low CSF pressure and it is due to its continuous seepage through the punctured hole on dura or aseptic meningeal irritation. It also may herald the onset of infective meningitis. The rate of leakage of CSF from subarachnoid space to epidural space, causing PDPH should be above 10 ml/hour. The loss of CSF up to 10 ml/hour has no symptom or headache. The healing of dural puncture usually takes 3 weeks. So, PDPH usually lasts for 1 to 2 weeks. But it may last for days, weeks or even months. In traumatic leakage the choroid plexus can form CSF maximum at the rate of 500 ml/day.

The mechanism of PDPH is when the rate of leakage of CSF exceeds its rate of formation then it leads to some change in hydrodynamics of CSF. This causes the loss of cushioning effect of brain and produce traction on vessels, basal dura, tentorium and other sensitive brain structure. Attachment of these structures to the cranium on one hand and meninges on the other hand leads to the stretching of meninges and blood vessels, causing pain. The PDPH is mainly posturally mediated and is being worse in upright position. This is due to the increase in downward traction of brain tissue by the gravity. Typical PDPH starts 6 to 12 hours after the puncture of dura and lasts for weeks. It is worse in sitting up position and disappears after lying down. The pain is typical and different from any other previously experienced headache. Usually the pain is experienced at the frontal region or behind the eye ball. Nausea and vomiting may accompany this pain. Tinnitus and deafness may also accompany the PDPH and is due to the low CSF pressure, resulting in fall of intra-labyrinthine pressure. The normal CSF pressure is 150 mm of water. When PDPH precipitates it drops to 50 mm of water. It is most common in obstetric patient, because during contraction of uterus and bearing down there is more leakage of CSF. The PDPH is also more commonly associated with young female patient, large bore spinal needle, cutting tip, passing of the bevel of needle tip at right angle to dural fibres etc. Other factors that increase the rate of PDPH are those that increase CSF pressure, e.g. obesity, ascites and pregnancy (Figs 24.38A and B).

Classification of postdural puncture headache (PDPH)

PDPH is classified into mild, moderate and severe form.

i. *Mild PDPH:* Here PDPH is slight and does not restrict daily activities. The patient is not bed ridden at any time during the day. There are no other associated symptoms like nausea, vomiting, etc. with PDPH.
ii. *Moderate PDPH:* Here PDPH is significant and restricts daily activities. The patient is bedridden for some part of the day. Associated symptoms may or may not be present.



Figs 24.38A and B: A. The apperture of hole in dura made by the bevel of spinal needle which is perpendicular to the direction of dural fibre. B. The apperture of hole in dura made by bevel of spinal needle which is parallel to the direction of dural fibre

iii. *Severe PDPH:* Here PDPH is very intense and forced the patient to stay in bed throughout the whole day. Associated symptoms are always present.

In one study, it is found that 86% of patients who developed PDPH have associated symptoms such as nausea (60%), vomiting (24%), stiffness of neck (43%), ocular (13%) and auditive symptoms (12%). Other symptoms associated with PDPH are:

Vestibular symptoms − nausea, vomiting, vertigo, dizziness, etc.

Cochlear symptoms − hearing loss, hyperacusis, tinnitus, etc.

Occular symptoms − photophobia, diplopia, difficulty in accomodation, etc.

Musculoskeletal symptoms − stiffness of neck, scapular pain, etc.

Prophylaxis and management of PDPH

Prophylaxis and mangement of PDPH are:

i. Use of more and more finer and pencil tipped needle.
ii. Bevel of the needle tip should be parallel to the dural fibre during its puncture.
iii. Lateral position of the patient during procedure is associated with less incidence of PDPH.
iv. Postoperative monitoring should be done in lying down position, at least for 24 hours in bed. In case of the use of wide bore needle postoperative rest in bed should be atleast for 72 hours. This rest will help in repair of hole of dural puncture and will reduce the incidence of PDPH.
v. Avoiding all types of straining activities and trying to lie down in prone position.
vi. Analgesics, adequate oral intake of water which ensure maximum production of CSF, use of DDAVP – 4 mg/day, etc. are other methods by which the incidence of PDPH can be reduced. Another conservative method for the management of PDPH is use of IV caffeine and sodium benzoate. Caffeine is a potent vasoconstrictor and may relieve the symptoms of PDPH by preventing the traction on blood vessel of brainstem. Rapid administration of 500 mg caffeine mixed in one litre of crystalloid solution has the dual effect of caffeine in bolus and aggressive hydration. Caffeine may be an adrenergic stimulant for some patients also.
vii. In most cases by the above simple measures PDPH can be avoided or treated. But, still when the headache persists with the above measure, an epidural blood patch by 10 to 20 ml of autologus blood is considered. Success rate of autologus blood patch is 90%. With the possible accumulation of CSF under ligamentum flavum, successful epidural placement of needle during the placement of blood patch may yield small amount of clear or straw coloured liquid and confuse. However, it may frequently produce mild headache, neckache and paraesthesiae. Also the introduction of infection by such a means would be disastrous. So, this procedure should be reserved only for the severe refractory cases of PDPH.

Sometimes excessive leakage of CSF can cause death due to herniation of uncus against the tentorium cerebellae. This is due to high ICP for any cerebral lesion which was present before dural puncture.

D/D of PDPH

Other causes of postoperative headache not related to dural puncture should be differentiated from PDPH. These are: migraine, meningitis, dehydration, hyponatraemia, neck muscle spasm due to stiffness of operating room table, withdrawal from caffeine, etc.

Cranial Nerve Paralysis

Any cranial nerve can be affected by central neuroaxial block. This is possibly due to the result of excessive spread of local anaesthetic agent in the brain, causing direct neural toxicity or as a result of downward traction of brain along with cranial nerves due to low CSF pressure from leakage. Among all the cranial nerves sixth cranial nerve is more prone to injury and it is due to its long and tortuous course. Due to the low CSF pressure from leakage, there is descent of medulla and pons which causes stretching of this nerve and injury between its origin at pons and anchoring site at cavernous sinus, over the apex of petrous temporal bone. Sixth cranial nerve injury causes photophobia and diplopia due to lateral rectus muscle paralysis.

Accidental Total Spinal Block

Total spinal block results when the full epidural dose of local anaesthetic solution is inadvertently placed in the subarachnoid space, during an attempted epidural anaesthesia. In total spinal the large doses of local anaesthetic solution, scheduled for epidural anaesthesia, spread all over the spinal and cranial CSF and blocks all the nerve roots including the cranial nerves, vital centres on the 4th ventricle and all the sympathetic outflows, causing complete cardiopulmonary shut down. Effects of these are severe hypotension, severe bradycardia, apnoea, aphonia, unconsciousness, dilatation of pupil and even cardiac arrest. Appearance of patient resembles like death even if cardiac arrest does not occur. Usually, it comes soon after the injection of drug in the wrongly diagnosed epidural space, but it may be delayed for 30 to 45 minutes.

The corner stone of management of this total spinal block is quick diagnosis, intubation, ventilation with 100% O_2, aggressive management of hypotension by pressure rising drugs, correction of bradycardia, IV fluids, etc. Patients usually recover completely after LA drug is withdrawn from the cranial CSF which usually occurs within 1 to 2 hours. Then surgery can also be carried out when the patient's condition becomes stable. Hypotension should not be allowed to persist for long time. Due to hypotension and ischaemia of neural tissue, or due to irritant effect caused by the large volume of drug in intrathecal space

(which is in direct contact with nerve tissue) prolonged neurological disturbances may occur.

Epidural analgesia for labour pain (obstetrics analgesia) can be made safely via adjacent interspinous space after an inadvertent dural puncture during the first epidural attempt. But, this cannot be applied for LUCS (obstetrics anaesthesia). Because large dose of LA agent is needed for caessarean section and this may cause total spinal block after passing through the previous dural hole which is made inadvertently by the epidural needle in previous attempt. If the level of block ascends high up, then consciousness is gradually lost as afferent impulses reaching cortex, become fewer and fewer.

Respiratory Failure

It is due to the higher spread of spinal or epidural block and may be due to the deliberate or inadvertent attempt. When the height of block reaches the level of T_1 spinal segment, then gradual progressive paralysis of all the intercostal muscles, reduction of voice to whisper, increased diaphragmatic activity, increased activity of accessory respiratory muscles of neck and tracheal tug, etc. are some of the common features of peripheral respiratory failure. But as the central respiratory drive persists and the cervical spinal segment from where the phrenic nerve originates is not blocked, so the patient continues the respiration, which is only accomplished by diaphragm. If local anaesthetic drug spreads in the cervical segment, then apnoea may also supervene due to phrenic nerve paralysis. There may be warning of this development, and this warning is patient will complain of tingling or numbness in the hands. This is due to the involvement of brachial plexus as it is formed by the cervical spinal nerve roots. This higher spinal anaesthesia causing peripheral respiratory failure is also associated with severe hypotension which causes reduced cerebral circulation. The apnoea may also be due to this hypotension and reduced blood supply to the cerebral respiratory centre, but may or may not be due to the direct spread of drug to the brain stem. So, the immediate restoration of BP is the primary physiological consideration during higher CNB. The management of complete respiratory failure is like the total spinal block. But, the speed is very vital in this treatment as the cardiac arrest may rapidly follows the respiratory arrest in cases of ischaemic medullary paralysis.

If respiratory difficulties are reported then the anaesthetist should be prepared to intubate and ventilate the patient. It is important to remember that, although the patient may be unable to breathe due to phrenic paralysis, he or she still may be conscious and a small dose of an intravenous anaesthetic agent is indicated to render the patient unconscious. Sometimes upper airway reflexes may also still be active and muscle relaxants may be needed to facilitate the intubation. The patient may require some form of general anaesthesia to maintain unconsciousness, untill the block wanes and spontaneous respiration returns. If the block is high enough then unconsciuosness will occur, but consciousness may return before the patient can breath spontaneously.

Back Pain

Back pain resulting from the spinal or epidural anaesthesia is mainly related to the needle puncture, causing tissue trauma and mild bleeding into the tissue. The tissues include supraspinous ligament, interspinous ligament, ligamentum flavum and intervertebral disc. With fine needle the backache is uncommon. Further potential changes due to injury in tissue is altered by the previous presence of any degenerative processes. The probability of back pain increases when the large bore needles are used and/or repeated attempts in same space or tissues are made. Patients with existing back pain should be made aware that a brief moderate increase in the back pain may occur.

However, any back pain after central neuroaxial block should be thought of as possible sign of more serious complication. For example, severe pain within the first several hours after resolution of anaesthesia should be considered as an early sign of accumulating haematoma. When a progressively worsening back pain is accompanied by further conduction blockade after returning from primary anaesthesia, then the possibility of neural compression by rapidly expanding epidural haematoma must be investigated. But severe back pain which begins after 24 to 48 hours of CNB and gradually progresses, then it must be evaluated as a possible sign of epidural abscess, especially if there are sign of systemic sepsis.

Previously, a local anaesthetic agent such as 2-chloroprocaine preparation had contained sodium bisulfite as preservative which has neurotoxic property. So, in the past many permanent neurological defects have been reported, following the inadvertent massive subarachnoid injection of this preparation, during attempted epidural anaesthesia. Therefore, in newer preparations of 2-chloroprocaine, sodium bisulphate is replaced by EDTA as preservative. Hence, the use of this newer preparation of 2-chloroprocaine sometimes cause severe persistent back pain and it is due to it's low pH and influence of EDTA on skeletal muscle which begin shortly after the resolution of epidural anaesthesia. This pain is described as severe muscle spasm of the paravertebral group of muscle mass and is thought to be caused by the backtracking of EDTA solution around the needle or catheter or through the intervertebral foramen to the paravertebral space.

During flexion of spine, the intervertebral disc is protruded in the spinal canal due to increased pressure on it by vertebral body. Thus, it becomes more prone to damage by the needle causing back pain due to cord compression by the prolapsed

disc. Backache also may be simply due to the musculoskeletal and sacro iliac strain which is common during obstetric delivery and if this patient has received central neuroaxial block then it is sometimes blamed. However, sometimes back pain is as common in patients who have not received spinal or epidural anaesthesia, as in those who have received it.

Haematoma

It results from the injury of epidural venous plexuses or subarachnoid vessels by needle or catheter. Damage to the epidural vessels is more likely to occur with an epidural catheter than with a needle. In patients with untreated clotting defects and 'unmonitored anticoagulant therapy', haematoma may be so large as to produce cord compression and neurological damage. So, a clotting defect should be considered as a contraindication to epidural or spinal block. This haematoma may be a nidus for infection in preexisting bacteraemia and may lead to abscess formation causing epidural abscess. Metastatic blood-borne infection may also occur, particularly in an small epidural haematoma, originating from some other focal source of sepsis. Large haematoma producing symptoms need early surgical intervention. Haematoma and abscess almost produce the same symptoms, but the differentiating point is that the symptoms of haematoma develops much more quickly than abscess. Laminectomy is urgently required to evacuate the haematoma or abscess and to avoid permanent neurological defect from cord compression.

Cord or Nerve Root Damage

Nerve roots or spinal cord can be damaged at any space during epidural or spinal anaesthesia by the needle or catheter. It may be temporary or permanent. In the distribution area due to this damage there may be pain, paraesthesia, numbness, etc. which may gradually recovers, if the injury is minor in nature and reversible.

Meningitis

Meningitis which means an infection of meninges is a very prognostically bad sequelae of spinal or epidural anaesthesia. It can be prevented by rigid aseptic technique during the procedure. On the otherhand, meningism which means aseptic meningitic reaction can also occur due to blood or injection of irritant agents in CSF. The irritant agents responsible for this aseptic meningitis (meningism) may be chemical antiseptics, starch powder from gloves, detergent, high concentration of drug, alcohol, phenol, preservatives, radio opaque agents, etc. which enter in the epidural space or CSF during the procedure. Blood responsible for meningism comes from punctured vessels present in subarachnoid space or epidural space.

Ischaemic Cord Damage

As spinal cord is supplied by end arteries, so it is more prone to ischaemic damage due to different causes. One of such cause is addition of adrenaline in local anaesthetic solution which produce vasoconstriction and ischaemia of cord. Ischaemic cord damage by adrenaline is also aggravated if it is associated with severe hypotension in arteriosclerotic subjects. Some space occupying lesion in spinal canal – such as haematoma, abscess, neoplasm, etc. also can cause compression of the functional end arteries and ischaemia of cord. When the anterior spinal artery which supplies the large part of the cord is obliterated or jeoparadised, then it produces anterior spinal artery syndrome. This syndrome is characterised predominantly by motor disturbance with sometimes loss of sphincter control and sensation. Hypotension from any cause may predispose to cord ischaemia. Preexisting arterial diseases (aorta / radicular arteries) may also aggravate this functional ischaemia of cord.

Paraplegia

After central neuroaxial blockade paraplegia has also been reported. This paraplegia can be caused by haematoma, abscess formation, chemical irritant, direct needle trauma, etc. Except CNB various anatomical abnormalities such as developmental laminar stenosis, narrow spinal canal, extradural spinal tumour, etc. may be the principal cause of paraplegia by compromising the circulation of cord. But when these are aggravated by spinal or epidural anaesthesia then regional block had to take the blame though it is merely a coincidence.

Adhesive Arachnoiditis

It may be due to the:

i. Injection of contaminated local anaesthetic,
ii. Mistaken injection of irritant solution in epidural and subarachnoid space instead of local anaesthetic agent,
iii. Injection of full epidural dose of LA agent intrathecally.

Cauda Equina Syndrome

It is due to the injury of cauda equina by the needle, catheter, or toxic effect of high concentration of local anaesthetic agent leading to:

i. Paraplegia, loss of leg reflexes,
ii. Incontinence of faces or retention of urine,
iii. Loss of sexual function,
iv. Paralysis of perineal nerve.

The causes of injury of cauda equina are the same as cord or root damage or paraplegia.

Nerve Damage due to Chemical Irritant

A number of chemical substances such as antiseptic, alcohol, phenol, preservatives, drugs, etc. cause definite nerve damage or irritation when injected in the epidural or intrathecal space. Pain is felt immediately and one is forced to abandon the procedure as soon as possible if analgesia or anaesthesia does not follow the spinal or epidural block which suggests that local anaesthetics or appropriate drugs has not

been injected. Also highly concentrated local anaesthetic agent in contact with nerve for a long time can also cause irreversible nerve damage, with histological change in nerve fibre. So, hypobaric or isobaric technique is largely abandoned because it causes deposition of large volume of drug around the nerves, displacing CSF, which is the normal enviornment of nerve roots. In total spinal, not only hypotension but also disturbances of pH, electrolyte and osmotic factors around the nerve fibres for longer time help to damage the nerve as large volume of drug has suddenly come in direct contact with the nerve.

Persistent Paraesthesia

Neurological defect should be evaluated after complete resolution of effect of the local anaesthetic drug, keeping in mind that in case of bupivacaine, the complete resolution may take 24 hours or longer. If resolution of neural blockade is followed by return of neural deficit, then a more aggressive approach is necessary. This complication first suggests the development of compressive damage to central axis. Evaluation should include predisposing factors (coagulopathy, antiplatelet medication, etc.), details of the procedure, (blood via needle/catheter, paresthesia during needle placement or catheter insertion, etc.) and history of the aggressive positioning of patient with catheter in place. Investigations should also look for the other possible aetiologies such as surgical procedure, positioning of patients devices and traction used during surgery or to position the patient. EMG before anaesthesia can detect the pre-existing neurological defects, but the exact location of defect from an acute injury of nerve is not possible with EMG, until axonal degeneration has occurred. Therefore, this is not valid until 3 weeks have elapsed.

An isolated, unilateral lesion of dermatome is more easily attributed to epidural anaesthesia than patchy multidermatomal lesion. Direct compression of cord often cross several dermatomes and causes multidermatomal lesion. Therefore, it can be differentiated from isolated nerve root injury. Absence of accompanying motor defect absolves epidural/spinal anaesthesia. Cauda equina syndrome is occurred due to either transverse chemical meningitis or vascular embarrassment of antispinal artery.

Epidural Abscess

The actual incidence of abscess after epidural or spinal anaesthesia is very low. It is unusual for an epidural abscess to form and accumulate enough to present symptoms with in 12 hours, except for unusually very virulent organisms. When excessive back pain after 24 to 48 hours of central neuroaxial blockade is accompanied by neurological irritation, focal deficit, systemic signs of toxicity, etc. then investigation is mandatory. Definitive diagnosis of abscess is made by CAT scan or MRI. Definitive treatment of it requires decompressive lamincetomy and aggressive IV antibiotic therapy to prevent the permanent neurological defect.

Wet Tap

During an attempted epidural anaesthesia, inadvertent passage of large epidural needle in subarachnoid space through the dura mater is called the wet tap. The response of an anaesthetist to possible wet tap should start immediately with confirmation and followed by next anaesthetic plan and strategies, with keeping in mind of severe PDPH. After wet tap there are several options. In first option the local anaesthetic agent with spinal dose can be injected in subarachnoid space to create a spinal anaesthesia, if it fit with the proposed surgical procedure. The second option is needle can be replaced at a different interspinous space and the epidural anaesthesia may be tried again. Second attempt of epidural anaesthesia at the same level might not be a wise choice, even if a clean reentry of an epidural needle into the epidural space through the same interspinous space is possible. This is because of the potential for massive subarachnoid deposition of local anaesthetic agent through the previous dural hole. After a wet tap, epidural anaesthesia can be followed by some manoeuvres to decrease the incidence of headache. These manoeuvres are injection of saline and blood patch through the catheter, prior to its removal, which will resist further leakage of CSF through the previous puncture site. Early epidural patch of blood is probably not indicated, because the success of this treatment is considerably higher even when applied after 24 hours.

Local Anaesthetic Toxicity

Despite proper safeguard, it is also possible to have a toxic blood level of local anaesthetic agent from a properly calculated dose in epidural anaesthesia, mainly in continuous form. For local anaesthetic agents, with low protein binding, signs of toxicity should be quite obvious and early. For example, symptoms of cranial nerve paraesthesia such as lingual paraesthesia or perioral tingling would likely to be reported rapidly by almost every patient who are given procaine (low protein binding). If the agent is of intermediate protein binding, for example, lignocaine and mepivacaine, then the gradual report of aura due to CNS toxicity could be missed, especially if the patient is not in constant communication with anaesthesiologist during dosing. Generally the signs of gradual accumulation of local anaesthetic agent in CNS include perioral numbness, gustatory paraesthesia, ringing in the ear, visual scotoma, etc. In agents with high protein binding, for example, bupivacaine and etidocaine, the aura may be very short or even absent.

Other Neurological Complication

Other than paraplegia, cord and root damage and ischaemic cord injury the other possible neurological complications

are: Pruritus, trigeminal nerve palsy, radiculitis, ascending myelitis, transverse myelitis, meningoencephalitis, intraocular haemorrage, Horner's sign, unmasking of spinal cord, neoplasm, etc.

Failed Epidural Anaesthesia

Sometimes, after successful location of epidural space and injection of full dose of local anaesthetic agent in this space, it may produce no result or anaesthesia. This is called the failed epidural anaesthesia. The speculation of such failure is that needle may pass off the midline into the muscle mass and simulate false loss of resistance during testing and injection of drug. Another speculation is that though the needle is placed correctly at midline, but any cystic degeneration in the epidural space (congenital or degeneratinve process) can create a false space where this phenomenon may occur. One way of indentification of such false space is that loss of resistance during the administration of initial dose of injection gives way to a rapid increase in resistance as the false space becomes filled, or the injection through the needle is easy but catheter placement is not possible.

Urinary Retention

Although the action of central neural blockade provided by single shot subarachnoid or epidural anaesthesia (not continuous postoperative epidural analgesia) usually lasts only for few hours, but urinary retention can sometimes be a problem, even after the block has been regressed. This retention of urine is a particular problem in the older male patients who may have pre-existing pathology, related to prostate enlargement. This problem is again exaggerated if large amounts of intravenous fluids have been administered as the part of the management of hypotension associated with central neural blockade. So, many anaesthetists routinely catheterise the bladder in patients having central neural blockade, either before or after the block has been instituted. But bladder catheterisation is often associated with a transient bacteraemia. This itself does not usually cause problems, but there are certain groups of patients in whom the administration of prophylactic IV antibiotics is advisable. These groups of patients include those having valvular heart disease and those having prosthetic joint replacements.

DIFFERENTIAL BLOCKADE

The concentrations of local anaesthetic agents required to achieve conduction blockade are different for each nerve fibre. These difference are influenced by the size of nerve fibre, myelination, and various tissue factors such as the rate of diffusion through the tissues, location of fibre within the nerve trunk (those on the surface are easier to block than those in the centre), fibrous diffusion barriers of the local anaesthetic agent and the ability of LA agent to move within the extracellular fluid. There is a general principle that the nerve fibres with smaller diameter will be blocked first than the nerve fibre with larger diameter and the nonmyelinated nerve fibres are blocked earlier than the myelinated nerve fibres. So the sensory fibres are blocked with lesser concentration of LA agents than the motors. Hence, there is only one type of nonmyelinated group C fibre which are theoretically most easier to block than the myelinated groups of comparable size nerve fibres. But, practically these C fibres are bundled in groups with significant amount of neural connective tissue (Schwann cells) around this bundle requiring higher concentration of LA agent to block these fibres than the comparable myelinated A-δ fibres.

The fibres earliest to be blocked are preganglionic B-fibres (though myelinated) that create pharmalogical sympathectomy and hypotension, associated with spinal or epidural anaesthesia. After the B group of fibres, the nerve fibres which are next sensitive to be blocked are the A group of fibres. Within the fibres of group A the concentration of local anaesthetic agent that is required to block the motor A-α fibres is double than that required to block the sensory A-δ fibres. If LA agent is injected at lower concentration or at a considerable distance from the site of action (i.e. nerve fibre), then it is found that the sensory fibres are blocked leaving the motor fibres. This explains the separation of motor block (A-α fibre) from sensory block (A-δ fibre) which thus can be elicited. So, at the edges of any area where regional anaesthesia is given due to the gradual fall of conentration of LA drug at the periphery, A-α fiber will not be blocked there, causing separation of motor block from sensory and autonomic block. This is called the differential blockade. Similarly in spinal or epidural block the injection of LA agent at the lumbar region delivers a relatively high concentration of it to the cauda equina which has very limited diffusion barrier. Hence, blockade at this level is uniformly dense for all types of fibres. Then as the agent spreads by gravity within CSF and as it moves cephalad, then the relative concentration of LA agent drops with increasing cephalad movement, and finally at a distance the agent reaches a concentration at which the myelinated largest and thickest A-α fibres are no longer blocked and no interruption of conduction of motor nerve is expected. But the fibres carring pain, touch, temperature and preganglionic sympathetic fibres are blocked. This is called the differential block. As the block precedes more cephalad, then the touch and pressure (A-β, γ fibres) are remain unblocked but the pain, temperature and preganglionic (A-δ, C, B fibre) fibres are blocked. This explain the common experience with spinal anaesthesia, when the patient retains a sense of pressure at the site of surgery, while having no feeling of sharp pain at the edges of the upper limit of block achieved. So, the classic teaching

is that there are different of two spinal segments between the motor, sensory and sympathetic block, depending on the local anaesthetic agent for spinal anaesthesia and the method of measurement of block. The simplest method of evaluation of block of different fibres which is generally used, usually brings similarity between the level of anaesthesia produced by the blckade A-δ and C-fiber. But to reflect the blockade of B fibre, the clinical tool for evaluation is patients sense of cold. If actualy sympathectomy is measured by thermography or galvanometry, the levels of it can be as much as five segments higher than the light touch.

i. A fibres
   A-α: 13-20 µm myelinated motor
   A-β: 5-12 µm myelinated touch, pressure
   A-γ: 4-11 µm myelinated muscle spindle
   A-δ: 1-4 µm myelinated pain, temperature
ii. B fibres
   1-4 µm myelinated preganglionic, sympathetic.
iii. C fibres
   0.5-2 µm nonmyelinated pain, temperature and postganglionic sympathetic.

COMBINED SPINAL-EPIDURAL ANAESTHESIA (CSEA)

This technique combines the advantages of both the spinal and epidural anaesthesia and thus makes it more versatile and flexible by removing the disadvantages of each other. This method of combined spinal epidural anaesthesia describe the placement of epidural needle in epidural space first, followed by an epidural catheter or a spinal needle through the previous needle. The history of combined spinal and epidural anaesthesia (CSEA) dates back to 1937, when Soresi, a New York surgeon, first performed an epidural block with a fine gauze needle and then he pushed the needle through the dura and arachnoid to make it a spinal block. There is no control of clinical trials at that time and Soresi had claimed that his technique had produced 24 to 48 hours postoperative pain relief from single injection of procaine both into the epidural and spinal spaces. But his claim was clearly over optimistic and failed to impress others.

Then CSEA was attempted by Curelaru, a Romanian anaesthetist, who performed both spinal and epidural blocks in a same patient, but through separate interspinous spaces. Almost simultaneously with Curelaru's work and unaware of it, Brownridge in Adelaide also performed combined spinal and epidural block for caesarean section using separate interspinous spaces by the spinal and epidural needles like Curelaru. But Brownridge's reasons for combining both the techniques were very much same as in keeping with the modern aims of combining the rapid onset, reliability and low toxicity of the spinal block with the ability of an epidural catheter to extend or prolong the block if necessary and use it for postoperative pain relief. In the following years, Coates was the first to describe the spinal needle through the epidural needle, using a single interspinous space. He used an available long spinal needle which could protrude past the tip of the epidural needle, the prototype for customised CSE sets, now provided by manufacturers. This variety of CSEA has now become the most popular. However, this needle through needle technique does not allow the placement and testing of the epidural catheter prior to the spinal injection. But when this is regarded as essential, then either a separate interspinous space may be used or another variety requiring spacialised equipment can be employed. This is the needle beside needle or 'double-barrel' needle. This equipment consists essentially of an epidural needle with a spinal needle channel guide which is soldered or incorporated in its wall. After the epidural needle has been placed and the catheter is inserted, the spinal needle is introduced through its guide channel into the subarachnoid space.

At present there are different technical combinations for combined spinal – epidural anaesthesia (CSEA). These are:

i. Use of separate intervertebral space for each epidural and spinal needles. Here catheter is negotiated through the epidural needle first and test dose is given. Then through another intervertebral space, dura is punctured by spinal needle and in subarachnoid space LA drug is deposited. The patient is then turned supine and according to the necessity of the height of block drug is injected through the epidural catheter. The same epidural catheter can be used for postoperative analgesia too.
ii. Use of the same intervertebral space for epidural and spinal needle. Here epidural needle is placed first. Then through the epidural needle a spinal needle is introduced (needle through needle) and dura is punctured. After the spinal drug is given through the spinal needle it is withdrawn and the catheter is introduced through the epidural needle in epidural space. Then the epidural needle is withdrawn and patient is turned supine (Fig. 24.39).

The disadvantages of this second technique are:

a. It does not allow the placement and testing of epidural catheter prior to the spinal injection. So, anxiety may arise about the movement of the heavy spinal LA solution which is already injected and may spread towards the cephalad or caudal

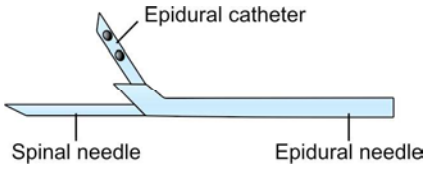


Fig. 24.39: The combined spinal epidural needle which allows the placement of 20 G epidural catheter through the modified Tuohy needle and placement of a 27 G spinal needle via an addition lumen

direction, especially if there is delay in positioning of the patient due to difficulties arising from the later insertion of catheter. This problem can be readily avoided by performing the CSEA in the Oxford position which had been introduced since 1984. Other ways of avoiding this problem are to perform the epidural first, using a separate intervertebral space or needle beside needle method. Where spinal injection is given after catheter is introduced.

b. There is controversy about the maximum possible protusion of the spinal needle beyond the tip of the epidural needle when the hubs are opposed. If spinal needle is too short it is less likely to puncture the dura, if too long it may transfix the dura and injure the cord.

c. Grazing of the tip of spinal needle against the bend of Tuohy needle.

d. Catheter may pass through the hole in dura, made by the spinal needle, in the subarachnoid space, though the possibility is very remote.

iii. To remove the above disadvantages, 'needle beside needle' technique is introduced. This equipment consists essentially of an epidural needle with a spinal needle guide channel, incorporated in its wall. After the epidural needle has been placed and catheter is inserted (also tested by test dose) spinal needle is inserted through its side channel.

Uses of CSEA

The advantages of CSEA include: Rapid onset, profound neuroaxial block, the ability to titrate the block with reduction of BP, prolongs blockade according to the necessary, postoperative analgesia and lower the total drug dose. The possible disadvantages of CSEA include: increased failure rate of SAB (approximately 5%), intrathecal migration of epidural drug and/or catheter and decreased ability and reliability of epidural test dosing. The CSEA has been most widely accepted in obstetric population. So, the concept of the 'walking epidural' has become popular among the patients, when intrathecal opioid allows the rapid onset of analgesia without motor blockade and extrathecal low concentration of bupivacaine (0.125 to 0.25%) allows prolonged analgesia. Lipid soluble opioids such as fentanyl or sufentanil are most commonly used for this purpose. Use of CSEA may reduce the incidence of instrumental vaginal delivery, lower anxiety and decreased the incidence of PDPH rate. It is demostrated that compared with lignocaine – fentanyl epidural block for caesarean section, CSEA with hyperbaric bupivacaine in subarachnoid space and fentanyl in epidural space provides more rapid onset, better motor blockade, decreased anxiety levels, decreased shivering and greater patient satisfaction.

The potential advantages of CSEA are now well known. The main uses of it are for orthopaedic and obstetric purposes. The great flexibility of CSEA has also provided its use in many other different situations.

Obstetrics

Today obstetrics is the most common indication for CSEA both as a method of pain relief during labour and for operative obstetrics. The introduction of CSEA as a pain relief during labour had lagged behind its use for caesareans section. The intrathecal use of local anaesthetics for relief of labour pain went back as early as 1900 and intrathecal use of morphine for relief of labour pain went back as late as 1980. However, a single short intrathecal local anaesthetics are only effective for limited period and a single short intrathecal morphine is only effective during first stage of labour and has a high incidence of side effects. However, continuous spinal anaesthesia (CSA) has always been associated with an unacceptably high incidence of severe PDPH. Consequently, the ability of CSEA to provide quick and reliable control of labour pain with the injection of local anaesthetic or more lipid soluble opioids than morphine or their combination in subarachnoid space and then continue the pain relief by epidural catheter provides distinct advantages of CSEA over a single shot spinal anaesthesia or continuous lumbar epidural analgesia and anaesthesia. There are two situations in which CSEA is particularly advantageous. The first of these is the delayed call for analgesia where pain relief by epidural block is slower on onset and requires high motor blocking concentrations of local anaesthetic. Secondly, CSEA has proved to be one of the most effective ways of providing analgesia with minimal motor block which is called 'walking epidural'.

The indication of CSEA for operative obstetrics essentially means caesarean section. Use of CSEA for caesarean section has two distinct advantages. The first is to use an adequate dose of spinal drug to achieve an adequate height and depth of anaesthesia for the operation and then to use the epidural catheter to modify or prolong the block, if the spinal is inadequate and/or to provide postoperative analgesia. The second is called as the 'sequential technique' in which in an attempt to reduce the hypotension a minimum amount of spinal dose which is intentionally made to be inadquate for surgery is used. The block is then deliberately extended cephalad with the epidural dose through catheter. In this two stage technique (sequential technique), the epidural catheter is not just act as a reserve for rescue anaesthesia or postoperative analgesia, but it served as a conduit for routine local anaesthetic to gradually raise the level of an intentional low subarachnoid block.

The epidural block has achieved wider acceptance as an alternative to SAB in obstetrial patients who are chronically hypovolaemic such as in pre-eclampsia. This is because incrementally giving the drugs through the epidural catheter increases the epidural sensory and motor

blockade in stages and thus minimizes the risk of hypotension. However, one large prospective study which compared the epidural and CSEA for severly pre-eclamptic patient undergoing LUCS had concluded that the changes in blood pressure are similar after epidural block or CSEA. Similarly, another study concluded that SAB produced reductions in blood pressure similar to epidural block in severly pre-eclamptic patients requiring LUCS. But, spinal anaesthesia is widely used for obstetrical surgery for technical simplicity, high success rate, minimal maternal and foetal drug exposure, minimal risk of maternal aspiration and an awake cooperative postoperative patient. However, recently many anaesthesiologist can place an epidural needle and catheter faster than they locate CSF with a small gauge spinal needle. So, subsequently administration of an epidural anaesthesia need not significantly expand operative room time.

Orthopaedics

Orthopaedic cases are the second most popular indication for the use of CSEA after obstetric cases. When CSEA is compared with individual epidural or spinal block for major orthopaedic surgeries, then it is found that CSEA has a quicker onset, better quality control and lower failure rate than the individual spinal or epidural anaesthesia alone. CSEA is also very useful for out-patient orthopaedic surgeries. It allows a minimal amount of spinal local anaesthetic agent to be used and thus hastens recovery, but with the ability of the epidural catheter to prolong the block if necessary.

Now, there are increasing number of indications for the use of CSEA other than obstetric and orthopaedic cases.

ADJUVENTS TO REGIONAL ANAESTHESIA

There was a time when our concept about pain was guided only by the simple 'door bell' theory. This theory expresses that press the switch, the bell rings and cut the wire, the ringing stops. But later, we have come to understand that such an old perception is a wrong guide to pain treatment and invariably leads to unsatisfactory results or frank failure of pain management. After the door bell theory, the 'gate control theory' of Melzack and Wall, and the concept of 'central sensitisation' has revolutionised the current management of pain. The preemptive analgesia, although proven and disproven by voluminus data, have stood the time, because clinicians have repeatedly shown satisfactory results of the preemptive analgesia from the points of view of patients and caregivers.

Based on the current datas, it is proved that the acute painful stimuli creates many changes, not only in the periphery at the site of origin, but also in the neurochemical and molecular milieu of the dorsal root ganglion and the dorsal horn cells of the spinal cord. Additionally, an increased neuronal metabolic activity in the other parts of central neurones system have been noted during acute pain, suggesting multiple dimension of pain. In 1993, Dikenson summarised the role of endogenous neurotransmitter systems in modulating and processing the pain coming from peripheral nervous system to the central nervous system and includes more than twenty-five such neurotransmitter systems in his summary. Then, if we multiply this formidable, but incomplete list of neurotransmitter by potential sites of action within the spinal cord, then a visionary can conjure up a wealth of potential ways to enhance the spinal analgesia. So inspired by the many rapidly changing knowledge of the peripheral, spinal and supraspinal responses to pain, investigators have reacted similarly by searching for the correct agonists or antagonists, and stimulants and inhibitors of pain. Thus, the drugs and pain control modalities are mixed and matched to achieve the optimal relief of pain with the least complications.

Acting directly on the proverbial door bell wire theory, regional anaesthesia is a mainstay in the armamentarium of an anaesthesiologist for the management of pain. In the last few years, several pain reliving drugs have been studied and combined with other drugs, with the objective of producing optimum analgesia and the least possible side effects. Combination of analgesic therapy in search of synergistic effect has been a common practice. Therefore, different neurotransmitter system were targeted with a combination of drugs to achieve the optimum therapeutic outcome with lower doses of drugs, thereby resulting in reduced side effects.

Hence, as adjuvents many things can be added with local anaesthetic agents in regional anaesthesia. These are: Narcotics, benzodiazepines, alpha-2-adrenergic agonists (i.e. clonidine), cholinesterase inhibitors (neostigmine) and phencyclidine (ketamine).

The aim of using adjuvents with or without local anaesthetic in spinal and epidural spaces are to:

i. Improve the analgesic intensity,
ii. Increase the duration of action,
iii. Achieve the faster onset of action,
iv. Achieve the acceptable analgesia with lower doses of drug and thus to reduce the risks and side effects.

Intraspinal or Epidural Opioids or Narcotics

Following the initial reports, in 1979, of clinical efficacy of intrathecal and epidural opioids, they have subsequently been used to control the pain following a wide variety of surgical procedures as sole analgesic agents or in combination with low dose of local anaesthetic agent. Bypassing the blood and blood-brain barrier the small doses of opioids, administered either in the subarachnoid or epidural spaces acts directly on the spinal cord to provide profound and prolonged segmental analgesia. This undoubtedly represents a major breakthrough in pain management.

Numerous studies have shown that spinal opioids can provide profound postoperative analgesia with less central and systemic adverse effects than the opioids administered systemically. Then, a large number of nonopioids analgesics have also been administered in epidural or subarachnoid space to achieve the pain relief without the risk of respiratory depression. This technique has been employed successfully to treat intraoperative, postoperative, traumatic, obstetric, chronic and acute cancer pain. Among these, management of postoperative and obstetric pain is the commonest indication for spinal opioid analgesia (Table 24.10).

The unique feature of spinal or epidural opioid analgesia is the lack of other sensory (except pain), sympathetic and motor block that allows the patients to ambulate without the risk of orthostatic hypotension or motor incoordination (walking epidural) which is usually associated with local anaesthetic agents, administered spinally or epidurally or opioids administered parenterally. These advantages of spinal or epidural opioids are particularly beneficial in high risk patients undergoing major surgery such as patients with severly compromised pulmonary or cardiovascular function, grossly obese patients and very elderly patients, etc.

For intrathecal or epidural administration, the analgesic doses of morphine are only 2 to 5% of the parenteral dose. Thus, patients can be expected to be less drowsy, more cooperative and more ambulatory. Intrathecal opioids are very easy for administration, either at the time of injection of local anaesthetic drug during spinal anaesthesia or as a separate technique when general anaesthesia is administered. With catheter the epidural route for opioids with local anaesthetic has been used much more extensively for intraoperative surgical analgesia and anaesthesia, and for postoperative pain control with or without local anaesthetic agents. The reasons for popularity of epidural opioids includes: Epidural opioids provide excellent analgesia alone or in combination with local anaesthetic agent with or without GA, willingness to leave an epidural catheter in place for extended periods to maintain analgesia and freedom from the risk of PDPH (only in epidural route).

The synergystic effect of opioid and local anaesthetic agent are best seen at the low doses of both. At higher doses the clinical synergistic effect becomes blurred and toxic effects superven. When the effects of IM or IV narcotics and epidural or spinal narcotics are compared in respect to analgesia, ambulation, GI motility, early and late pulmonary function, duration of hospitalisation and occurrence of deep vein thrombosis in the postoperative period, it is found that the average dose of IV or IM narcotics is seven times greater than that required by the epidural or spinal route. Patients, receiving epidural or spinal narcotics report superior analgesia, ambulate sooner, have fewer pulmonary complications, have earlier return of bowl function and are discharged from the hospital earlier than the patients receiving IM or IV narcotics. Mortality, overall complication, infection, time of extubation and hospital costs are all significantly lower when the narcotics are given intrathecally or epidurally than the parenteral group. Although, intraspinal or epidural opioid is not as effective as regional analgesia provided by local anaesthetic agents for controlling pain during vaginal delivery, but intraspinal or epidural only opioids for control of pain following caesarean section are widely used. These may be offered when spinal or epidural anaesthesia is chosen for surgery.

The rational for the combination of local anaesthetic agent with opioids for the relief of labour pain is that these two types of drugs eliminate pain by acting at two different distinct sites: The local anaesthetic act at the nerve roots and the opioids act at the receptor site of spinal cord. Spinal opioids alone provide good relief of pain at rest, but may not be adequet during physiotherapy and mobilisation. Although combination of local anaesthetic and opioids are used for postoperative and labour pain, but the results are more impressive in the relief of labour pain. Because it is well recognised that labour pain is different from postoperative pain as it is not relieved by epidural opioids alone. Patients receiving epidural injections of local anaesthetics combined with opioids report more rapid onset, more profound and long lasting relief of labour pain and less motor blockade than the patients receiving either drug alone. As a part of combined spinal epidural technique intrathecal opioids (e.g. fentanyl 25 µg, sufentanil 5-7 µg) combined with very small doses of local anaesthetic (e.g. bupivacaine 1 mg) provide almost instantaneous pain relief during labour and the

Table 24.10: Dose and duration of action of adjuvants to regional anaesthesia

	Single dose (mg)	*Rate of infusion (mg/h)*	*Onset of action (min)*	*Duration of action single dose (hour)*
A. *Epidural*				
Morphine	1-5	0.1-1	30	10-24
Meperidine	20-50	10-50	10	5-10
Diamorphine	5	-	5	12
Methadone	1-8	0.2-0.5	10	5-10
Fentanyl	0.025-0.1	0.025-0.1	5	2-6
Sufentanil	0.01-0.06	0.01-0.06	5	2-6
Alfentanil	0.5-1	0.2-0.5	10	1-2
B. *Intraspinal*				
Morphine	0.1-0.3	-	10	10-24
Meperidine	10-30	-	5	10-24
Fentanyl	0.01-0.025	-	5	3-5

epidural catheter is used if labour is prolonged. These low doses of narcotics and local anaesthetic agents through the both thecal and extrathecal route allow the parturients to ambulate which is called the 'walking epidurals'.

The only preservative free morphine preparations have been used epidurally or intrathecally in a wide range of concentrations with no apparent difference in efficacy. The addition of epinephrine to morphine is not recommended. The dose of intrathecal morphine is 0.1 to 0.2 mg. Epidural morphine can be used as intermittent injection or as continuous infusion. The effective doses of continuous infusion of epidural morphine may range from 0.1 to 1.5 mg/hour. Elderly patients may require remarkably small doses of epidural morphine. The relatonship between the age and the total dose of epidural morphine to achieve analgesia is: Effective 24-hour morphine dose (mg) = 18 − Age (0.15).

A more lipophilic drug such as fentanyl is also useful when rapid onset of epidural or intrathecal analgesia is important. The dose of intrathecal fentanyl is 20 to 25 µg. Intermittent boluses of 50 to 75 µg fentanyl through epidural route can also be used to achieve analgesia promptly in the immediate postoperative period, if the initial epidural dose of morphine is not adequate. Used as the sole opioid, 25 to 100 µg bolus of fentanyl in epidural space can be followed by continuous infusion of 25 to 100 µg/hr with an pump.

The adverse effects of central neuroaxial narcotics are: respiratory depression, pruritus (particularly face and upper trunk), urinary retention, nausea, vomiting and sedation (uncommon). The incidence of respiratory depression is about 0.3% at low doses of opioid which is usually used. At higher doses the incidence of respiratory depression may be higher. It results from the migration of these narcotic agent to the brainstem. So, it is more frequent with the more hydrophilic opioids than the more lipophilic opioids. This is because the more hydrophilic opioids are less absorbed by the nervous tissue which is rich in fat and remains in more water soluble form in CSF which help it to flow more to cephalad direction.

Therefore, high level of vigilance is mandatory during the use of intrathecal or epidural opioids. Intensive care facilities should be used for high-risk patients e.g. advanced age, serious underlying diseases, extensive surgery, etc. Early respiratory depression occurs within the first 2 hours following epidural narcotic injection. It is due to the result of vascular uptake from epidural and subarachnoid space and redistribution of opioid (i.e. the same mechanism that follows IV or IM injection). Delayed respiratory depression, occurring within 6 to 12 hours following spinal or epidural injection, is likely the consequence of rostral spread of opioid in CSF. Pruritus is common and sometimes becomes bothersome in few patients receiving central neuroaxial opioids. This incidence is particularly high in obstetric patients. The itching may be generalised or localised with the face being a common site. Although, pruritus caused by intrathecal or epidural opioid is probably not due to the release of histamine, still antihistamines often provide symptomatic relief.

Nausea and vomiting caused by intrathecal or epidural opioid is believed to be due to rostral spread of opioid through the CSF to the vomiting and CTZ centre, located superficially in the floor of 4th ventricle. This can be frequently treated by antiemetics.

Sedation, produced by epidural or intraspinal opioid rarely becomes a significant problem. It is due to the result of spread of the drug through CSF to the receptors in the thalamus, limbic system or cortex.

Mechanism of action of epidural or spinal opioids

The perception of pain and reaction to it are both altered by the opioids, so that pain is no longer taken as unpleasant or distressing sensation and patient tolerates it better. The analgesic action of systemic opioids have both the spinal and supraspinal components. But the central neuroaxial opioids have only spinal components. The intrathecal or extrathecal injection of opioids has been shown to cause segmental analgesia without affecting other modalities. This is because it acts only on the opioid receptors in the substantia gelatinosa (Lamina I and II) of dorsal horn and inhibit the release of excitatory neuro transmitters from the primary afferents carrying pain impulses. The action of opioid also appears to be exerted through the inter neurons which are involved in the gating of pain impulses. Release of substance P from the primary pain afferents in the spinal cord and its postsynaptic action on the dorsal horn neurones is also inhibited by the opioids. Normally, the action of systemic opioid at supraspinal sites such as in medulla, midbrain, limbic system and cortical areas is to alter the processing and interpretation of pain impulses as well as to send the inhibitory impulses through descending pathways along the spinal cord. Several other aminergic and neuronal systems appear to be involved in the action of systemic opioids and simultaneous action at spinal and supraspinal sites greatly amplifies the analgesic action of it.

When given through epidural or spinal route the uptake of opioids by the spinal cord is proportional to their lipid solubility. Highly lipid soluble opioids are quickly absorbed by the cord, resulting in lesser cephalad spread of it. So, highly lypophilic drugs have faster onset of action and quicker elimination than hydrophilic agents. Reversely, hydrophilic opioids are taken up by the spinal cord to a lesser extend and, therefore, show greater cephalad spread than the lipophilic opioids. It also shows delayed onset of action and elimination. Opioids from the subarachnoid or epidural space is eliminated by the vascular uptake.

Intrathecal Midazolam

GABA (Gamma Amino Butyric Acid) is a simple amino acid molecule which is

found as an inhibitory neurotransmitter in about 40% of the synapses – in both central and peripheral nervous system. Tissue trauma causes release of variety of chemical substances into the vicinity of the injury, such as P-substances, bradykinin, leucotrienes, 5HT, prostaglandins, etc. These substances sensitise the peripheral nociceptor, so that transduction threshold of sensitivity is decreased. Therefore, the peripheral C fibres tend to fire spontaneously and even fire in response to non-noxious stimulation, such as touching the skin. This causes a condition of primary hyperalgesia around the wound and subsequently the total spinal cord sensitisation. As a result, the pain perception gradually increases in strength even though the stimulus remains the same or absent. This phenomenon is called the 'wind up'.

Pain due to spinal cord sensitisation and wind up phenomenon is resistant to opioid. But, we know that GABA reduces this sensitisation and wind up phenomenon. GABA receptors are of two types: GABA-A and GABA-B. Among these the GABA-A receptors are present in presynaptic or primary afferent fibres and postsynaptic fibres. It is specially found in lamina II of dorsal horn of spinal cord. Whereas GABA-B receptors are found in the interneurons. So, inhibitions of selective GABA-A receptors would be ideal for analgesic action, causing powerful analgesia with no sedation. Benzodiazepines act on these GABA-A receptors and inhibit them.

Midazolam, a water soluble benzodiazepine when injected intrathecally, causes spinally meidated antinociceptive effects without any CNS effect, by combining with spinal cord GABA-A receptors. It also suppresses the visceral pain. Intrathecal midazolam probably also releases an endogenous opioid which acts on delta receptors of spinal cord and thus produces analgesia. Intrathecal midazolam causes segmentally cord level analgesia and has almost no neurotoxicity or major side effects up to the doses of 2 mg or continuous infusion of 6 mg/day. There is no significant nausea, vomiting, sedation, amnesia, itching, urinary retention, hypotension or bradycardia, etc. with intrathecal BZD.

Clonidine

Clonidine's analgesic property is known for centuries and is used extensively by veterinarians without proper knowledge of its mechanism of action. Initially it was used in humans for control of BP. Then, it was tested through epidural route on animals for analgesia with much promising results and no neurotoxicity. After that ice was broken when Tamson and Gordh first used clonidine epidurally on two chronic pain patients in 1984 and the result was very promising. The α-2 receptors are present on both pre and postsynaptically. Clonidine is α-2 adrenergic agonist and stimulation of presynaptic α-2 adrenergic receptors cause the inhibition of release of norepinephrine from the sympathetic terminals at periphery and noradrenergic neurones in CNS. These α-2 receptors are located on the superficial laminae of spinal cord and brainstem nuclei responsible for pain. So, analgesia may be produced at spinal and brainstem level. Clonidine like local anaesthetic agents also causes the blockade of conduction of nerve fibres. At spinal cord level, it also decreases the noxious afferent inputs through interaction with the α-2 adrenoreceptors. It also reduces the release of substance P and excitatory amino acid in spinal cord from peripheral nerve stimulation by noxious stimuli, suggesting presynaptic inhibitory mechanism. It also hyperpolarises the neurones in the dorsal horn and render them less responsible to afferent stimuli. In addition to brainstem and peripheral site of action, neuroaxial administration of clonidine inhibits the sympathetic preganglionic neurones in spinal cord resulting in hypotension. The sedative property of clonidine also reduces the requirement of hypnotics and is often a desirable feature.

Analgesic, hypnotic and haemodynamic effects of clonidine after central neuroaxial or systemic administration begins within 30 minutes and reaches maximum within 1 to 2 hours, but these actions last for 6 to 8 hours.

Dose

For regional anaesthesia and analgesia through epidural route the dose of clonidine with 0.5% bupivacaine is 0.5 to 1 µg/kg. It does not produce respiratory depression and does not suppress the neurohumoral secretion during stress, but produce analgesia. Postoperatively, 3 to 10 µg/Kg extradural clonidine as the sole agent results in 4 to 6 hours analgesia, but at the expense of bradycardia, hypotension and sedation.

Use

Clonidine may be used through intrathecal or extrathecal route for analgesia with or without local anaesthetic agents. It may also be used with bupivacaine, lignocaine, ropivacaine for peripheral nerve blocks, such as: molar extractions, intercostals block, brachial plexus block, etc. It gives early onset, prolonged duration of action and satisfactory analgesia and anaesthesia when used with local anaesthetic agent. In case of sympathetically maintained pain, prolonged relief of pain (9 to 10 times longer duration) is achieved by bupivacaine and clonidine combination than bupivacaine alone after stellate ganglion block.

Ketamine

Ketamine which is available in market is a racemic mixture of two enantiomer such as (R-) and (S-) form of it. Its α-elimination phase is few minutes, but the β-elimination phase is 2 to 3 hours. One of its metabolites, such as norketamine, is one- third to one-fifth as potent as the original drug and is responsible for the

prolonged analgesic effect of ketamine. It produces a dissociation state (catalepsy) in patient by electrophysiological inhibition of the thalamocortical pathways, and stimulation of the limbic system. It has good broncho-dilating and minimal respiratory depression effect. Protective airway reflexes are preserved by ketamine, but in noncoordinated way. It also increases oral secretion.

The analgesic and anesthetic properties of ketamine are mainly attributed by interaction of it with N-methyl D-aspartate (NMDA) receptors and other non-NMDA glutamate receptors. By blocking the action of other non-NMDA receptors, such as opioid receptors, cholinergic receptors, muscarinic and nicotinic receptors, adrenergic receptors and GABA receptors, etc. ketamine plays minimal role in analgesia. NMDA is the most abundant excitatory neurotransmitter causing pain sensation in CNS where ketamine acts. 'Wind up' phenomenon in dorsal horn is responsible for chronic pain and it acts through NMDA receptors where ketamine also acts.

The reduction of polysynaptic stimulation in the CNS by ketamine which is also responsible for analgesic effect of it acts through NMDA receptor at postsynaptic sites. Ketamine binds to the phencyclidine part of the NMDA receptor channel and thus inhibits the activation of glutamate and blocks NMDA receptor. NO (Nitric Oxide) plays important role in pain perception. NMDA and non-NMDA receptor activation stimulate NO synthesis. So, inhibition of NO synthesis by the blocking of NMDA and non-NMDA receptors by ketamine may be involved in its analgesic effect.

For the ubiquitous character of ketamine, it is suggested that the combination of systemic ketamine with regional or peripheral nerve block or combining ketamine with local anaesthetic agent for regional or peripheral nerve block may cause more optimal pain relief.

Neostigmine

The laboratory studies have suggested that the spinal cholinergic activation produces analgesia, because cholinergic receptors have been found in spinal cord and have been shown to have a potent antinociceptive action. So, considerable evidence exists to implicate the role of cholinergic agonists (acetylcholine) and anticholinesterase agents (neostigmine) which increases the level of ACh by inhibiting the break down of it in the spinal cord in inhibition of nociceptive transmission by stimulating these cholinergic receptors and cause analgesia. They do not act on opioid receptor, NMDA receptor or non-NMDA receptor. It does not cause axonal conduction blockade like local anaesthetic agent. It is also found that intrathecal analgesia by neostigmine is mediated through M1 and M2 muscrinic cholinergic receptor which can be blocked by atropine. Autoradiographic studies reveal the existence of muscarinic receptors such as both M1 and M2 in lamina II and III of the spinal cord. Neostigmine, as an anticholinesterase inhibitor, cause an accumulation of ACh at the muscarinic receptors in the dorsal horn when it entered into the CSF and thus cause analgesia.

Neostigmine is used both through intrathecal and epidural route with local anaesthetic agents where duration of analgesia becomes prolonged. The intrathecal dose of neostigmine is 50 µg. The 50 µg neostigmine in epidural route is less effective in prolonging the duration of analgesia. Neostigmine in a dose of 100 µg as an additive to epidural lignocaine is proved to be best in prolonging the duration of analgesia through this epidural route. The increased dose, 150 µg (epidurally) of neostigmine prolongs the duration of postoperative analgesia but at the cost of increased incidence of side effects. The common side effects of neuroaxial neostigmine are nausea, vomiting, hypotension, sweating, etc.

Epinephrine

When epinephrine is administered centrally it may potentiate the action of local anaesthetics. The mechanisms of action are:

i. Like clonidine, low doses of extradural epinephrine have direct α_2-activity on the dorsal horn cells.
ii. The vasoconstrictor properties of epinephrine reduce the vascular uptake of local anaesthetic agent and thus it helps to prolong their action.

CENTRAL NEUROAXIAL BLOCKADE (CNB) VERSUS GENERAL ANAESTHESIA (GA)

The CNB is less forgiving than GA for anything less than perfection. The choice of any anaesthetic technique such as CNB or GA is a complex medical decision which depends on many factors, such as, patient's characteristics, type of surgery, type of anaesthetic technique and its risks, anaesthetist's choice, surgeon's choice, etc. The assessment of anaesthetic risk both in CNB and GA include the consideration of anaesthetic technical factors, toxicities of anaesthetic agent, intraoperative or postoperative events, management of postoperative pain, etc. However, with proper planning and sufficient experience, it is possible to do CNB and GA with same risk and CNB as rapidly as GA. But there is one distinct advantage of CNB over GA is that the patient can be immdiately transferred to recovery room on completion of surgery after CNB. However, general anaesthesia cause prolonged emergence which can delay the next postoperative procedure.

Cardiorespiratory Effect

Many anaesthiologists think that CNB is preferable to GA for patients with pulmonary diseases. But, many published studies, comparing the pulmonary complications observed after CNB and GA have not extablished any consistent benefit of

CNB over GA. Some studies suggested beneficial effects of CNB over GA in patients with lung disease with respect to decreased morbidity from respiratory complication. However, other studies have not established superiority of either anaesthetic technique in the elderly and in patients with chronic lung disease. There is also definite evidence that excellent postoperative analgesia with continuous extradural analgesia leads to a reduction in respiratory complications. It is also possible that high quality analgesia from other than epidural (e.g. patient controlled analgesia) may also lead to a reduction in pulmonary complication. So, the provision of adequate analgesia may be more important than the method of analgesia employed.

CNB acts directly on the nerve pathway and avoids the surgical stress with its haemodynamic demands. Thus it directly avoids the myocardial depressant effect of inhalational agents of GA. Whereas GA acts indirectly through CNS to avoid the surgical stress with its haemodynamic demands. Hypotension following CNB is not always preventable and is not always without any adverse effects. So CNB is not always a safer alternative to careful GA for heart patient, particularly in inexperienced hands. CNB is particularly hazardous for patients who require well maintained preload (e.g. aortic stenosis). It is also very crucial in many cardiac patients (coronary disease) causing sudden fall in diastolic pressure with resultant fall in coronary perfusion. Conversely, reduction of afterload by CNB may be beneficial for patients with reguritant valves. But an epidural block with catheter and simultaneous intelligent use of IV fluids with vasoconstrictor can carefully titrate the fall of BP. So, always CNB may not be more hazardous in a patient then GA. Appropriate invasive monitoring of filling pressure, cardiac output and systemic vascular resistance sometimes may make CNB more safer than GA. Several studies have shown that CNB in comparison to GA is associated with less cardiac morbidity. This might be related to the reduction in thromboembolic manifestation, reduction in catecholamine levels in plasma and avoidance of cardiac depression. But, later studies concluded that CNB does not reduce the rate of cardiac complications than GA. Contrary still, many practitioner argue that individual subgroups of patients should benefit from CNB and so they continue to offer spinal or epidural anaesthesia, with or without catheter to their high-risk patients.

Metabolic and Endocrine Alterations

Surgical procedures performed under GA result in increased concentration of glucose, lactate, cortisol, aldosterone, renin, vasopresin, growth hormone, epinephrine, norepinephrine, etc. But these changes do not occur under CNB, because it completely abolishes the stress response to surgery by blocking the nerve pathway. It is observed that in CNB the markers for surgical stress, i.e. increase in protein degradation and decrease in protein synthesis were typically arrested as compared to GA. The mechanism by which CNB inhibits the metabolic and endocrine alterations during surgery is probably related to blockade of afferent and efferent pathways for nociceptive impulses. CNB also prevents central sensitisation and provides pre-emptive analgesia.

Blood Loss

In CNB decreased bleeding is observed during surgery, especially during the procedure on the lower abdomen and lower part of the body. But, there seems to be little reduction in bleeding associated with upper abdominal and thoracic surgery. Reduction of bleeding during surgery is probably due to hypotension caused by sympathetic block, reduction of venous pressure leading to reduced venous oozing, and relaxation of capillary sphincters causing reduction of arteriolar bleeding. This results in decreased requirement of transfusion and its related complications in CNB as compared to GA.

Nausea and Vomiting

Nausea and vomiting can occur with both the techniques. But, the incidence is more with GA than CNB. In CNB as laryngeal reflexes are intact (if the patient is not deeply sedated) there is less chance of aspiration if vomiting occurs. But in GA, if larynx is not properly guarded, there is every chance of aspiration if vomiting occurs. Another point is that during CNB if vomiting occurs then it is very much distressing, because abdominal and part of the thoracic muscles are paralysed.

Postoperative Pain Relief

CNB can easily be converted to postoperative analgesia. Hence, many of the prescribed benefits of CNB is actually due to this analgesia which can be extended into the postoperative period.

Thromboembolism

The CNB is associated with decrease in blood viscosity and less alterations in coagulations factors such as inhibition of coagulation and stimulation of fibronolysis which commonly occurs in GA. One can see inhibition of platelet aggregation from local anaesthetic drugs during CNB. In the postoperative period, CNB also limits the increase in factor VIII or von Willebrand factor. Thus, CNB increases the total limb blood flow, which is responsible for reduction in the incidence of thromboembolic events (mainly DVT and pulmonary embolism). This effect in CNB may be as great as 50% in reduction of thromboembolic incidence during hip surgery. In multiple studies, it is found that arterial inflow, venous emptying rate and venous capacitance are all higher in patients receiving CNB. Intraoperatively, the breathing pattern may also have a profound influence on the leg blood flow. Spontaneous breathing during CNB promotes the better venous return and this results in higher cardiac output and better blood flow in legs.

While intermittent positive pressure ventilation (IPPV) during GA impedes the venous return and this results in a low cardiac output and reduced blood flow in legs. Thus, CNB is associated with less incidence of thromboembolic phenomenon than GA.

Coagulation Profile

In GA, platelet aggregation and hypercoagulable state of blood is triggered by the neurohumoral changes which is due to stress responses during surgery. But, this is completely attenuated in CNB. On the otherhand, regional anaesthesia and analgesia also effectively attenuates the increase in plasminogen activity as compared to GA.

Hypothermia

Both GA and CNB impair temperature hameostasis. Hypothermia during CNB can nearly be as severe as that which is observed during GA. The thermoregulatory activity is reduced with advancing age during CNB, but no age related differences regarding thermoregulation were found during GA. On the otherhand, CNB decreases the vasoconstriction and shivering thresholds, possibly by producing a substantial increase in apparent leg temperature. This explains why CNB is associated with severe hypothermia.

Mortality

A number of large studies have been performed to evaluate the postoperative mortality rate following CNB or GA after major surgical procedures. The short-term mortality rate (up to one month postoperatively) is better after CNB as compared to GA. But, there is no difference in long-term survival rate (up to 1 year postoperatively) with both the techniques. Many of the deaths, occurring in GA group during the first postoperative month were related to the thromboembolic complications. However, large retrospective cohort study of elderly patients with hip fracture is unable to demonstrate that CNB is associated with better outcome than GA.

There is no general consensus that certain types of patient undergoing certain types of surgery benefit more from regional or general anaesthesia. The ultimate outcome of surgery depends on how a technique is performed rather than which technique is selected. The outcome also depends on the skill of the practitioner, patient's factor and the occurrence of side effects or complications. For many anaesthetists the benefits of regional anaesthesia appear to be self evident and worth attaining, while other practitioner virtually perform no regional technique throughout their whole life.

Discharge Criteria

The use of CNB for ambulatory surgery (or day case or out patient surgery) has gradually become more popular. The introduction of higher gauzes (more fine) pencil point spinal needles have reduced the incidence of PDPH to approximately 1% and have increased the discharge criteria. The ideal CNB for day case surgery would combine the rapid and adequate surgical anaesthesia with rapid achievement of discharge criteria, such as ambulation and urination.

CSEA can also be used for day case surgery with early discharge criteria. Availability of the epidural catheter for a rescue anaesthesia in CSEA allows the use of minimal doses of spinal local anaesthetic agent with resultant rapid recovery and discharge. However, no current data is available to assess the relative cost benefit ratio versus decreased recovery time with CSEA. Continuous spinal anaesthesia (CSA) may also have applicability in an ambulatory setting, because it has the ability to use lower amount of local anaesthetic agent which can lead to faster recovery time, especially in the elderly who are less prone to PDPH. However, with the introduction of LMA and newer anaesthetic agents with faster and more pleasant recovery profiles such as propofol, remifentanil, sevoflurane, desflurane, etc. have reduced the stress of GA and shortened the length of stay in postanaesthetic care unit than that seen for CNB.

SUBARACHNOID BLOCK (SAB) OR SPINAL BLOCK VERSUS EPIDURAL BLOCK (EB)

Technical Aspect

From the technical point of view, SAB is easier to perform and has a definite objective endpoint, i.e. the flow of CSF through the spinal needle. Conversely, the EB is not easy to perform and there is no definite objective end point, i.e. location of epidural space is confusing. The end point of identification of epidural space is loss of resistance and the presence of negative pressure. The loss of resistance is proved by the sudden easy movement of piston within the barrel. And the presence of negative pressure in the epidural space is proved by the inward movements of a drop of fluid in the hub of the needle. This is called the hanging drop technique. But, neither of these methods of locating the epidural space gurantees the proper location of the needle tip in all the patients.

Another difference between the SAB and EB from the technical point of view is that SAB is administered through the lumbar site only. Whereas, EB can be administered through the multiple sites; like lumbar, thoracic, cervical or caudal.

Onset and Spread

The onset of anaesthesia is much more rapid in SAB than EB. The spread of level of anaesthesia is more predictable and controlled in SAB than EB. The level of anaesthesia in SAB can be controlled initially by using the baricity of anaesthetic solutions and then by adjusting the patient's position. However, neither of these factors is much helpful in controlling the level in epidural block (EB). The level of anaesthesia in EB is controlled only by the use of epidural

catheter and the volume of drug though the position of patient helps little.

Duration of Anaesthesia and Analgesia

The failure to produce anaesthesia and analgesia to a desired degree and level for limited duration are inherent deficiency of a single sort technique of SAB or EB. Whereas the epidural catheter technique provides prolonged anaesthesia and analgesia, removing the previous deficiencies. The catheter technique for CSA is also available. It requires 10 to 15 times less amount of local anaesthetic agent than is needed for epidural blockade and thus virtually eliminates the possibility of systemic toxic reactions of local anaesthetic agents. The other advantages of CSA over conventional SAB are the ability to prolong the anaesthesia for long surgical procedures or even for postoperative analgesia with fewer episodes of hypotension and less need for vasopressors. With the advent of 32 G catheter that can be threaded through 26 G needle, the incidence of PDPH has decreased. Though it is reduced, still there is potential for infection, haemorrhage and nerve trauma in CSA.

Depth of Surgical Anaesthesia

The SAB provides more profound depth of surgical analgesia and anaesthesia than EB. On the otherhand the requirement for supplemental parenteral analgesia or sedation is more for EB than compared to SAB. One of the advantages of SAB over EB is that its does not suffer from the patchiness of anaesthesia which is sometimes exhibited by EB.

Unilateral Block

The SAB can be manipulated to achieve predominantly a unilateral block by keeping the patient in lateral position for 5 to 10 minutes after administration of anaesthetic agent and by controlling the baricity of anaesthetic solutions. Unilaterality in SAB also can be maximised by using a side port spinal needle and small dose of local anaesthetic agent. This facility is not available in EB.

Haemodynamic Stability

Haemodynamic parameters are better preserved during EB, particularly when catheter is used than SAB. The degree of change in MAP, stroke volume, cardiac output and heart rate is quick and more following SAB than EB.

PDPH

The PDPH is a trouble some complication of SAB, whereas EB is completely devoid of this problem. However, the potential for accidental dural puncture by thick epidural needle ever present in EB and it results in severe headache, particularly in young patients. A higher incidence of PDPH is observed in parturients after SAB.

Systemic Toxicity

One of the main advantages of SAB over EB is that small amount of local anaesthetic agent produces the desired level and effective depth of anaesthesia. Thus, the potential for central nervous system toxicity and systemic cardiovascular toxicity is almost nonexistent in SAB. On the other hand, in EB as large amount of local anaesthetic solution is used, so there is chance of systemic toxicity. Also, accidental intravascular or intrathecal injection of large amount of local anaesthetic agent in EB can lead to severe systemic toxicity or total spinal block, respectively.

Blood Loss

SAB and EB both reduces the blood loss during surgery. But, EB reduces more blood loss than SAB and results in reduced number of tranfused blood units. With hypotensive epidural anaesthesia there is approximately 50% decrease in intraoperative blood loss as compared to SAB. Coagulation function is partly better preserved during epidural block than SAB. This is indicated by higher prothrombin time in SAB. This is mainly because blood loss, dilution of circulating coagulation factors, and fibrinogen activation are greater during SAB than EB.

Spinal Cord Injury

Both the SAB and EB are associated with spinal cord and nerve root injury from mechanical trauma. But in SAB, spinal cord and nerve root damage also may result from chemical injury by local anaesthetic solution which is not found in EB. Transient neurological symptoms (TNS) have been described after SAB with any local anaesthetic agent, but is found most commonly with lidocaine. However, the recent retrospective, prospective and closed claim studies report that the incidence of postoperative neurological injury in patients undergoing SAB is between 0.7 to 1%. It has been rarely seen after epidural block and general anaesthesia.

25 Paediatric Anaesthesia

INTRODUCTION

Strictly speaking, though all the patients who are below the age of 14 years fall in the paediatric group, but only the patients who are below the 5 years of age or with a weight of less than 20 Kg need specialised anaesthetic management. This is because the newborn and infant has a number of physiological features which differ from the adult. These differences are of much relevance to an anaesthetist and anaesthetic management to this later group of patient is known as the paediatric anaesthesia. The difference in anatomy and physiology between the paediatric and the adult group of patients have many important consequences on anaesthesia, mainly with babies of 27 weeks gestation (birth weight as low as 600 gm) with some pecularities which may persist longer than the defined period after birth. Some of the peculiarities result from the fact that the infant at birth has to possess all the machineries which are required to adapt the changes from one environment in the mothers womb to a totally different one outside of it. Another important peculiarity is that such a small creature requires very special protective mechanisms to meet the hostile world outside. Other peculiarities are merely the result of adult functions being as yet underdeveloped. Thus, the neonate should not be regarded merely as an incomplete small adult, but rather, as a totally different organism. So, the provisions of a safe paediatric anaesthesia depends on the clear understanding of the anatomical, physiological, pharm ocological and psychological differences between the paediatric and the adult group of patients.

A full term neonate is one whose gestational age at birth is 37 weeks or more, whereas a preterm neonate is one whose gestational age at birth is lesser than 37 weeks. But with the passing of days, the medical and technological advances have pushed the gestational age closer and closer to 20 weeks at which the preterm neonates can be made viable (Table 25.1).

THE NORMAL WEIGHT GAIN

During the first few days after birth, the newborn infant loses upto 10% of its original birth weight. This is because of the loss of extracellular fluid. However, then the most full-term infants regain this lost weight by the age of 10 days after birth. Subsequently, they gain weight at the rate of 25 to 30 gms/day for the first 3 months of life. Thereafter, they gain about 400 gm of weight by every month for the remaining part of their first year. An infant usually doubles its birth weight by the age of 6 months and triples at the end of 1 year. Subsequently, the birth weight becomes four times at the end of 2 years and 5 times at the end of 3 years of age. At 5 years the expected weight of child is calculated by multiplying the birth weight with 6 and at 10 years with 10, respectively.

Table 25.1: Classification of paediatric patients according to their ages

Premature	:	< 37 weeks
Neonate	:	First 4 weeks after birth
Infant	:	From 5th week after birth up to 1st year
Toddler	:	1 to 3 years
Preschool	:	3 to 6 years
School age	:	6 to 10 or 12 years
Prepubescent	:	10 to 12 years (Girl), 12 to 14 years (Boy)
Pubescent	:	12 to 14 years (Girl), 14 to 16 years (Boy)

Here, there is an another easy formula for calculating the weight of a baby :

Weight = [Age (in years) + 4] × 2 in Kg, for 1 to 6 years and,

Weight = [Age (in years)] × 3 in Kg , for 7 to 12 years

(There are also many other formulae described in different books).

The most important difference between the paediatric and the adult age group of patients is the size of the body, which varies with age. But the weight is the most important determinant factor for any therapies and drugs are always prescribed as the 'doses per Kg'. Although it is rational to express the body size and therapies in terms of weight, but many physiological processes are measured in relation to surface area. But, the surface area to weight ratio of an infant is approximately twice than that of an adult. So, the metabolic rate, water and electrolyte requirement and requirements of ventilation are proportionately greater in paediatric age group of patients than that of an adult when expressed on the basis of weight. But, gradually these differences decrease, as the neonate and infant passes through the childhood (Table 25.2).

Table 25.2: The normal important milestones

4 to 6	Weeks	:	Social smile.
3	Months	:	Head holding.
6	”	:	Sits and supports, transfers object from one hand to other.
8 to 10	”	:	Crawls.
9	”	:	Stands holding furniture.
12	”	:	Walks holding furniture, says one word.
13	”	:	Walks without much support, says 3 words with meaning, feeds itself.
15 to 18	”	:	Joins 2 to 3 words into a sentence.

CARDIOVASCULAR SYSTEM

Foetal Circulation and its Changes After Birth

In foetal life blood is oxygenated in the placenta and is then returned back to the foetal heart by umbilical vein. The umbilical vein enters the foetus at the umbilicus through the umbilical cord, and then-courses through the the liver to join with the left portal vein.There is another vein called the ductus venosus, which connects the left portal vein with the inferior vena cava (IVC), and provides a low resistance pathway (bypass) between the left portal vein and the IVC. Thus, the oxygenated blood coming from the placenta through the umbilical vein has two pathways, before entering the right atrium. Most of the oxygenated blood coming from the placenta shunts through the ductus venosus to the IVC, and only a small portion of the oxygenated blood passes through the portal vein, liver parenchyma, hepatic vein and ultimately reach to the IVC. Thus, the blood of IVC comprises of blood coming from the liver parenchyma through hepatic vein, blood coming directly from the placenta through ductus venosus and blood coming directly from the lower extremities. On reaching the right atrium, the oxygenated blood of IVC is divided into two portions or streams by the inferior margins of the septum secondum, which is called the crista dividens. About 1/3rd of this total oxygenated blood of IVC enters the left atrium through the foramen ovale, and the remaining 2/3rd of the blood of the IVC mixes with the deoxygenated venous blood coming from the superior vena cava (SVC), and enters the right ventricle (Fig. 25.1).

The oxygenated blood reaching the left atrium from right atrium through foramen ovale again mixes with the small amount of blood coming from the lungs through pulmonary vein without any oxygenation, and passes to the left ventricle. The left ventricle then pumps out this oxygenated blood into the ascending aorta for distribution to the coronary arteries, head, neck and upper extremities (Fig. 25.2).

The deoxygenated blood coming to right atrium from the head, neck and superior extremities through SVC, after mixing with 2/3rd of the IVC blood, passes almost directly into the right ventricle. Then the right ventricle pumps out this deoxygenated blood into the pulmonary trunk. A small amount of this blood (10%) of pulmonary trunk enters the pulmonary circulation, and returns to the left atrium through pulmonary veins without taking any oxygen from the lungs.The rest of the blood (90%) of the pulmonary trunk passes through the ductus arteriosus into the descending aorta, and mixes with the small amount of blood reaching the descending aorta from the aortic arch. The largest branch of the descending aorta is the umbilical artery. So, 80% of the blood of descending aorta flows through the umbilical artery to the placenta through umbilical cord for oxygenation. This is favoured by the low resistance of the circulation of placenta and the remaining portion of the blood of descending aorta flows to the lower extremities.

Therefore, in foetal circulation there are two right to left shunts. One is at the level of ductus arteriosus and the other is at the level of foramen ovale. This is due to the higher pulmonary vascular resistance (PVR) than the systemic vascular resistance (SVR). It is also because the pressure developed in the right atrium and the right ventricle exceeds than that of the

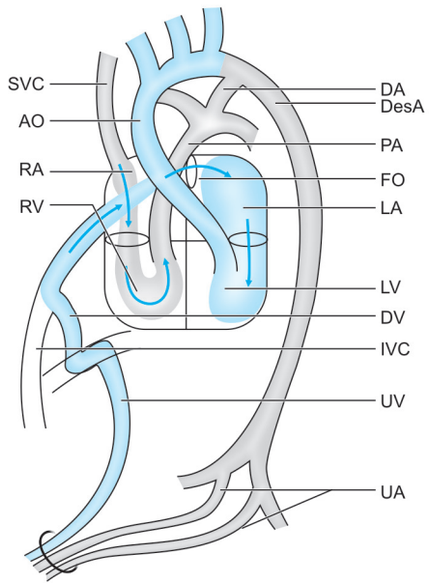


Fig. 25.1: Foetal circulation. UV-Umbilical vein, UA-Umbilical artery, DV-Ductus venosus, DA-Ductus arteriosus, IVC-Inferior vena cava, SVC-Superior vena cava, RA-Right atrium, RV-Right ventricle, LA-Left atrium, LV-Left ventricle, FO-Foramen ovale, AO-Aorta, DesA-Descending aorta, PA-Pulmonary artery

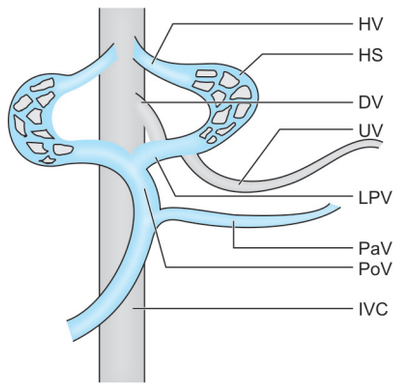


Fig. 25.2: IVC-Inferior vena cava, PaV-Pancreatic vein, PoV-Portal vein, LPV- Left portal vein, UV-Umbilical vein, DV-Ductus venosus, HS-Hepatic sinusoid, HV-Hepatic vein

left which is due to the handling of large amount of blood by the right side of the heart than the left.

As a result of this pressure difference between the two ventricles, the wall-thickness of them may be the same, or the right ventricle may be thicker than that on the left. This is in contrast to the adult situation, where the wall-thickness of right ventricle is about one-quarter of the left. As a consequence, the ECG pattern of the neonate and infant is comparable to that of an adult who has right ventricular hypertrophy.

The summary of major differences between the foetal (pre-delivery) and the neonatal (post-delivery) circulation. In this difference the foetal circulation is characterised by:

i. The presence of placental circulation which acts like adult pulmonary circulation and provides the gas exchange for foetus.
ii. The absence of gas exchange in a collapsed lung.
iii. There is very little flow of blood to the lungs, and consequently very little pulmonary venous return to the left atrium. So, the left side of the heart is a low pressure system.
iv. The presence of ductus venosus, which joins the portal vein with the IVC provides a low resistance bypass for the umbilical oxygenated blood to reach the IVC.
v. The presence of crista dividens and widely open foramen ovale provides a route for the oxygenated blood to reach the left atrium and the left venticle from the umbilical vein and the IVC for distribution to coronary arteries and the brain.
vi. The presence of a widely open ductus arteriosus which allows the right ventricular blood to reach the descending aorta and the umbilical arteries for further oxygenation, bypassing the non-functioning lungs.

After clamping of the umbilical cord and after the first breath, the high pulmonary vascular resistance which was present during foetal life falls, and at the same time the SVR rises. This causes the pressure at the right side of the heart to become less than that of the left side of the heart. This change stops the flow of blood through the foramen ovale and the ductus arteriosus, which was still maintained upto the period of birth due to the higher pressure at the right side of the heart than the left. The rise in SVR after birth is due to the elimination of the low resistance placental vascular bed from the systemic circulation, because of the clamping of the umbilical cord.

The factors responsible for the fall in PVR after birth are:

i. The unfolding of the pulmonary vasculature due to the expansions of lungs.
ii. The development of negative interstitial pressure arising from the surface tension forces.
iii. An increase in arterial oxygen tension associated with decreased CO_2 tension, following the onset of breathing which causes diminished hypoxic pulmonary vasoconstriction and reduced pulmonary vascular resistance.

The maximum decrease in PVR occurs rapidly during the first day of life and then continues to decrease gradually during the next several years, as the architecture of the pulmonary vessels change slowly.

After the first breath, lungs become inflated and PVR falls. This causes sudden increased pulmonary blood flow and subsequently increased left atrial pressure. This change in right and left atrial pressure causes the stoppage of blood flow through the foramen ovale and ductus arteriosus, and subsequently closes these right to left shunt in most cases.

As the functional or the physiological closure of ductus arteriosus results from the fall in PVR and the increase in SVR, but it is also caused by the contraction of the smooth muscles of ductus arteriosus. This is due to the increase in P_aO_2 after the first breath. The sensitivity of the contraction of the smooth muscle cells of ductus arteriosus to the P_aO_2 depends on the gestational age of neonate, and is parallel. Thismeans as the gestational age of foetus and neonate will increase, the sensitivity of contraction of the smooth muscle cells of ductus arteriosus to P_aO_2 will also increase. This closure of ductus arteriosus is completed within 10 to 15 hours after birth. But, during this period, the closure of the ductus arteriosus is reversible as it is physiological. Its anatomical closure is delayed by another 2 to 3 weeks. This closure of the ductus arteriosus is also influenced by prostaglandin E, which relaxes the ductal smooth muscles and contraction occurs with inhibition of prostaglandin synthesis. The prevention of ductal closure by the administration of prostaglandin E is used therapeutically in certain congenital heart lesions, where there is reduced pulmonary blood flow such as pulmonary atresia. In these circumstances, deliberately delaying of the ductal closure serves to maintain an increased pulmonary blood flow, until a surgical aorto-pulmonary anastomosis is established. Contrary, prostaglandin inhibitors are sometimes used to induce early ductal closure, where continued ductal shunting is undesirable.

The neonatal circulation is usually labile and sometimes may revert from the neonatal to the foetal type of circulation, with blood flowing from the right to the left side of the heart, through the functionally closed (not anatomically) ductus arteriosus or foramen ovale. So, this circulatory state of neonate is called the transitional circulation and the reverse from post delivery to predelivery state is initiated by hypoxia, hypercarbia, acidosis, anaesthesia induced changes in pulmonary or peripheral vascular tone, etc.This reversal state is caused by either an increase in PVR, or decrease in SVR in response to hypoxia, hypercarbia and acidosises. It is especially important in patients with hyaline membrane disease or congenital diaphragmatic hernia

which are responsible for the above mentioned conditions. Thus, a vicious cycle is set up between hypoxia, hypercarbia, acidosis and right to left shunt, leading to cyanosis, more hypoxia, gradual fall of cardiac output and subsequently death. This explains why the hypoxaemic events in infants during anaesthesia is dangerous and often prolonged, despite when the treatment appears to be adequate.

The risk factors that prolong this transitional circulatory state include prematurity, infection, acidosis, hypothermia, hypoxia, congenital heart diseases, etc. So, care must be taken to keep the infant warm to maintain the normal arterial O_2 and CO_2 tension and to avoid the anaesthetic-induced myocardial depression. The myocardial structure of heart, particularly the volume of the ventricular cellular mass which is responsible for myocardial contractility and cardiac output is significantly underdeveloped in neonates and infant than adults. So, the ventricles are less compliant in neonates and infants. This developmental ventricular myocardial immaturity of the paediatric group of patients account for the early tendency to cause biventricular failure. This also accounts for the high sensitivity of neonatal myocardium to volume overload, poor tolerance to an increase in afterload and heart-rate dependent cardiac output.

SUMMARY OF FOETAL CIRCULATION AND CHANGES AT BIRTH

The circulation in the foetus is essentially the same as in an adult, except for certain special differences. Here the foetal circulation is summarised with some differences from an adult.

i. The source of oxygenated blood in the foetus is not the lungs, but instead the placenta.
ii. Oxygenated blood from placenta, comes to the foetus through the umbilical vein, which joins the left branch of the portal vein, then the ductus venosus joins the left branch of the portal vein with the IVC. So a large portion of the oxygenated blood from placenta, passes through the left branch of the portal vein, ductus venosus and IVC and a small portion of the oxygenated blood passes through the substance of liver. Then it passes to the inferior vena cava through hepatic vein.
iii. The oxygen-rich blood reaches the right atrium through the inferior vena cava. It also carries the deoxygenated blood from the gut and lower limbs. Then the blood of the IVC is directed by the valve of IVC towards the foramen ovale. After that the oxygen-rich blood reaching at the foramen ovale is divided into two portions by the lower edge of the septum secundum (crista dividens).
    1/3rd of the oxygenated blood of the IVC passes through the foramen ovale into the left atrium.
    2/3rd of the oxygenated blood of the IVC gets mixed up with the deoxygenated blood returning to the right atrium from the upper limbs, head and neck, through the superior vena cava (SVC) and passes into the right ventricle.
iv. From the right ventricle, the blood (mostly deoxygenated) enters the pulmonary trunk. From the pulmonary trunk, only a small portion of this blood reaches the lungs and passes through it to the left atrium by pulmonary vein, without oxygenation. The greater part of the blood from the pulmonary trunk is short circuited by the ductus arteriosus into the aorta.
v. We have seen that the left atrium receives mainly oxygenated blood from the placenta through the right atrium and foramen ovale, and a small amount of deoxygenated blood from the lungs. The blood in the left atrium is, therefore, fairly rich in oxygen. This blood passes into the left ventricle, and then into the aorta. Some of this oxygen-rich blood passes into the carotid, coronary and subclavian arteries from the aorta and supply the brain, heart, head, neck and the upper extremities. The rest of the blood gets mixed up with poorly oxygenated blood coming from the ductus arteriosus, and supplies the trunk placenta and lower extremities. Therefore, the parts of the body that are supplied by the branches of the aorta, distal to its junction with the ductus arteriosus receive blood with only a moderate to less oxygen content.
vi. Much of the blood of the aorta, after its junction with the ductus arteriosus is carried by the umbilical arteries to the placenta where it is again oxygenated and returned to the heart through the umbilical vein, ductus venosus and the IVC.

Soon after birth, several changes take place in the foetal blood vessels, which lead to the establishment of the adult type of circulation.

The changes in the foetal blood vessels leading to the establishment of the adult type of circulation after birth are:

i. The muscles in the wall of the umbilical arteries contract, immediately after birth and occludes their lumen. This prevents the loss of foetal blood into the placenta.
ii. The lumens of the umbilical veins and the ductus venosus are also occluded. But this takes place a few minutes after birth, so that all the foetal blood in the placenta gets time to be drained back in the foetus. Though the umbilical artery, umbilical vein and the ductus venosus occlude immediately or a few minutes after birth,but this closure is physiological. Anatomical closure takes about 2 months. A patent ductus venosus decreases the delivery of the drugs to the liver, and may prolong their elimination half life.
iii. The ductus arteriosus is occluded, so that all the blood from the right ventricle now flows to the lungs where it can be oxygenated.

iv. The pulmonary blood vessels increase in size after birth due to unfolding of this pulmonary vasculature and consequently a much larger volume of blood reaches the left atrium through the lungs.

As a result the pressure inside of the left atrium is greatly increased. Simultaneously the pressure in the right atrium is diminished, because the extra amount blood from placenta no longer reaches it. The net result of these pressure changes causes the pressure in the left atrium to exceed than that of the right atrium and closure of the foramen ovale.

The vessels that are occluded soon after birth are in due course replaced by fibrous tissue and form ligaments.

The ligaments formed by the occlusion of foetal vessels are :

i. Umbilical arteries → Medial umbilical ligaments
ii. Left umbilical veins → Ligamentum teres of liver
iii. Ductus venosus → Ligamentum venosum
iv. Ductus arteriosus → Ligamentum arteriosum

THE DIFFERENCES IN CVS BETWEEN THE PAEDIATRIC AND THE ADULT GROUP OF PATIENTS

The CVS of the paediatric and the adult group of patients differ enormously. The right and the left ventricles are similar in size and thickness at birth. But, within first few days of life after birth the thickness of the left ventricular wall starts to increase gradually in response to the increased SVR and workload. On the other hand, the right ventricular wall thickness remains unchanged. So, by 3 months after birth, the mass of the left ventricle exceeds than that of the right and approaches the relative proportions of an adult. The weight of the heart of an infant doubles in the first year of life, while the body weight triples.Again, the weight of the heart doubles between the age of 4 to 5 years and between the age of 12 to 13 years of life. Thus, it gradually reaches the adult weight.

The myocardium of a newborn contains less contractile tissue and more connective tissue than that of an adult. This is reflected by the less active contraction of ventricular myocardium and a decreased compliance of the paediatric heart. It is also suggested that the limitation of myocardial contractility of paediatric heart is due to the decreased intracellular calcium influx and decreased calcium sensitivity to the contractile proteins. All these limitations of myocardial contractility in the paediatric patients tend to decrease or fix the size of stroke volume and maintain the cardiac output (CO), depending on the heart rate (CO = stroke volume × HR). In neonates and infants the resting stroke volume remains fairly constant at about 1 ml/Kg. Shortly after birth, the resting cardiac output is about 200 ml/Kg/minute depending mainly on the heart rate which declines gradually to 100 ml/Kg/minute by pubescent.

The cardiac output (CO) and cardiac index (CI = Cardiac Output divided by the body surface area) in paediatric patients are higher than that of adults and this is due to the high metabolic rate. So, the O_2 and other nutrients can be delivered easily to the actively growing tissues by increased circulation according to their increased metabolic need. In paediatric patients, this high CO and subsequent high CI is dependent mainly on the heart rate than the ventricular filling and the force of myocardial contraction, because ventricles of neonates and infants are poorly compliant. So, even though, the ventricles of a paediatric heart follow the Frank-Starling law, but the main determinant of CO is the heart rate. Thus, the neonates and infants can tolerate the higher heart rate (even 200/min) with ease. Therefore, during paediatric anaesthesia, the bradycardia should be avoided at any cost, because it represents a fall in CO (as cardiac output is heart rate dependent). So, sudden decrease of heart rate from 200/min to 50/min in an infant should be considered as cardiac arrest or as a severely compromised CO.Therefore, it should be treated immediately with cardiac massage, O_2, atropine and adrenaline. In paediatric patients, cardiac arrhythmias are rare in the absence of any persisting cardiac diseases and the most common form of cardiac arrest in such age group of patients is an asystole or EMD (not VT or VF).

Afterload is determined by the resistance of large arterial blood vessels and the tone of systemic peripheral vascular bed. As the sympathetic tone is poorly developed in a neonate and an infant, so afterload or SVR is usually low. But, it increases in parallel with the increase in systemic blood pressure with age. So, the systemic arterial pressure of neonates and infants tends to be lower than adults due to ↓SVR. The standard arterial pressure in neonate during the first day of life is about 70/50 mm of Hg, although immediately after delivery, it is slightly greater than this. Then, it rises gradually over the first week to approximately 90/50 mm of Hg and to the normal adult value of 120/70 mm of Hg by the age of 14 to 16 years. In asphyxiated neonates, the arterial pressure at birth may be higher. The rate of increase in blood pressure during the first week of life will be lower. In the preterm neonate, between 27 to 30 weeks of gestational age, the systolic pressure ranges between 45 to 55 mm of Hg. The ability of an infant to maintain his blood pressure in response to various circulatory stress is more difficult to assess than in adults. It is, therefore, not surprising that the CVP is raised even by head-up tilt of the neonates and this is reflected by the rise in aortic pressure in some infants and never by a fall (difference from adults).

The response of the neonates and infants to blood loss is perhaps that aspect of circulatory physiology, which is of greatest interest to an anaesthesiologist. All the evidences suggest that the human neonates and infants have a less active baroreceptor system, which normally

helps in the compensatory mechanism to blood loss. Also, it has been suggested that the liver serves as a buffer in the face of an increase in blood volume load in neonate. It is evidenced by the fact that gross liver enlargement may occur with little or no rise in CVP after over-transfusion which would indicate the ability of liver to take up large volume of blood from the venous system without increasing the blood pressure and manifesting heart failure.

The sympathetic system is also less developed in the neonates and infants and venodilatation occurs at rest. Thus, the sympathetic system cannot be blocked further, causing more venodilatation which is maximum at rest. So, paediatric patients who are normovolaemic at the start of anaesthesia do not exhibit a fall in the arterial pressure when spinal anaesthesia is administered. Moreover, they do not require preloading like an adult to avoid hypotension, as the further venous pooling does not occur and the venous capacitance does not further increase much from sympathectomy by spinal or epidural anaesthesia.

At birth, the autonomic innervation of heart is primarily parasympathetic, with sparse contribution from the sympathetic nervous system. But this balance of autonomic innervation matures as the child grows with the parallel increase in innervation from the sympathetic nervous system. Thus, the infant's cardiovascular system maintains a lower catecholamine store, and displays a blunted response to exogenous catecholamines. Hence, due to this reason the paediatric vascular tree is less able to respond to hypovolemia and vasoconstriction than the adults.

The decreased sympathetic neural output also explains the normally reduced BP in neonates, infants and children, and their increased susceptibility to reflex bradycardia and hypotension. Again, the diminished baroreceptor acitivity in infants may reduce their ability to adapt hypotension by an increase in the heart rate. So, the hallmark of the intravascular fluid depletion in neonates and infants is profound hypotension without tachycardia.

The potent causes of reflex bradycardia and hypotension in paediatric age group of patients during anaesthesia include easy vagal stimulation by laryngoscopy, tracheal intubation, tracheal suctioning and traction on the eye muscles, viscera, etc. This is due to the high parasympathetic tone in the paediatric group of patients. Bradycardia may also easily be caused by a variety of anaesthetic drugs, such as suxamethonium, halothane, neostigmine, etc. These effects can be successfully treated by IV atropine (20 µg/Kg).

The immature neonatal and infantile heart is also more sensitive to the calcium channel blocking properties of the volatile anaesthetic agents and opiod-induced bradycardia (Table 25.3).

HAEMOGLOBIN AND BLOOD VOLUME

Postdelivery haemoglobin (Hb) concentration of a neonate ranges from 13 to 20 gm/dl (average 18 gm/dl). Then, the concentration of Hb decreases gradually during infancy, reaching a level of 10 gm/dl by 10 to 15 weeks in full term neonates and 8 gm/dl by 4 to 8 weeks in preterm neonates. This decrease in Hb concentration in early infancy is due to the decreased erythropoiesis and shorter lifespan of the red cells. This is called the 'physiological anaemia of infancy'. Then, after reaching its plateau the Hb concentration again increases steadily throughout the infancy, touching the adult value by the end of first year. A preoperative Hb concentration of less than 10 gm/dl is abnormal and should always be investigated. Normally, the concentration of foetal haemoglobin (HbF) at 30 weeks of gestation is 95%. But, at birth this foetal haemoglobin (HbF) constitutes about 80% of the total haemoglobin. By 4 months, this falls to 10 to 15% and by 6 months this HbF disappears completely from circulation which is replaced by HbA. The synthesis of adult haemoglobin (HbA) is fully established by the age of 6 months. The differences between HbF and HbA are :

i. A higher affinity of HbF for O_2 than HbA
ii. A reduced affinity of 2, 3 – DPG to HbF than HbA
iii. The left ward shifting of the oxygen dissociation curve of HbF.

The higher affinity of HbF for O_2 in paediatric group of patients is due to the poor affinity for binding of 2,3-DPG to the Y-chain of HbF, allowing O_2 to bind strongly with it.This is reflected by low P_{50} value of the foetal Hb-O_2 dissociation curve, which is only 20 mm of Hg in a full term neonate. This low P_{50} value helps the foetus to optimise the uptake of O_2 from the placenta.It also prevents the release of O_2 from the haemoglobin at the tissue level, due to the left ward shifting of the O_2 dissociation curve. The other factors that shift the O_2 dissociation curve to the left (i.e. low P_{50}) include alkalosis, hypothermia and hyperventilation, which also limit the availability of O_2 at the tissue level. However, these demerits of HbF are removed by the increase in haemoglobin concentration, increase in the cardiac output, expanded blood volume, etc. On the other hand, the low PO_2 and increased metabolic acidosis at the tissue level due to hypermetabolic state of the paediatric patients help in the downloading of O_2 into the tissues and shift the

Table 25.3: The pulse rate and BP of paediatric patients at different ages

Age		*Heart rate*	
< 1	Months	110-160	per minute
2 to 5	"	90-140	"
5 to 12	"	80-120	"
>12	"	90-100	"
		Blood Pressure	
		S (mm of Hg)	*D (mm of Hg)*
< 1	Years	70-90	45 - 50
2 to 5	"	80-100	50 - 60
5 to 12	"	90-110	60 - 65
> 12	"	100-120	65 - 70

the oxygen dissociation curve to the right at the tissue level. Hence the leftward shifting of the O_2 dissociation curve prevents the O_2 downloading, while the rightward shifting helps in the same, thus compensating each other. Hyperventilation produces alkalosis and discourages the downloading of O_2 at the tissue level. So, hyperventilation should be avoided and normocapnia should be maintained during paediatric anaesthesia.

The normal blood volume of neonate at birth is about 90 ml/Kg. It gradually decreases to 80 ml/Kg in infants and young children. By the age of 6 to 8 yrs, an adult level of 75 ml/Kg is attained. The decision to transfuse blood in paediatric group of patients should be balanced against all other risks. In case of blood loss, usually the children can tolerate haematocrit value upto 25%. Blood loss of more than 10% of the total red cell mass should be replaced by transfusion of blood, especially if the initial haemoglobin is less than normal and further losses are expected. However, otherwise the most children who have a normal Hb concentration at the beginning of surgery can tolerate losses of upto 20% of their total red cell mass.

RESPIRATORY SYSTEM

During intrauterine life, the lungs begin to develop from the 4th or 5th week of gestation. By the 6th week of intrauterine life, lobar or secondary bronchi are developed. By the 7th week, segmental or tertiary bronchi develop and by the 8th week, subsegmental airways grow. By the 16th week of gestation, the tracheobronchial tree undergoes division upto the 16th order, terminating into terminal bronchioles and acini. At 16th week of intrauterine life, the number of airways and the number of pulmonary blood vessels in the foetus is similar to that of an adult, but the number of alveoli are less in number, and this number gradually increases towards term. From 16 weeks of gestation the lungs begin to mature as a potential gas-exchange organ, because after that onwards the pulmonary capillaries start interdigitating among the alveoli (Fig. 25.3).

Type II pneumocytes then begin to appear. It is nothing, but the differentiated epithelial cells of alveoli. The type I pneumatocytes are derived from these Type II cells. In the mature adult lungs, the Type I cells cover 25 times more surface area of the alveoli than the Type II cells. At birth, the total number of alveoli is 20 to 50 millions and each terminal bronchiole opens into a single alveolus, instead of a fully developed cluster of alveoli.In neonates, the alveoli are thick-walled and it number constitute only 10% of that of an adult. Then, the alveoli increase in number by multiplication and also increase in size until the child reaches the age of 8 years. Thus, at the end of 8 years, the total number of alveoli in children is 300 million which is equal to that of an adult. Subsequently, the growth of the lung occurs by an increase in only of the alveolar and airway size, but without any increase in number by multiplication. The granules of surfactants are produced and appear in the alveolar lining cells as early as at 24 weeks of the intrauterine life. So, after 24 weeks an independent life outside the uterine cavity becomes possible. Surfactants are lipoproteins in nature and reduce the surface tension of alveoli below 10 to 15 dynes/cm.

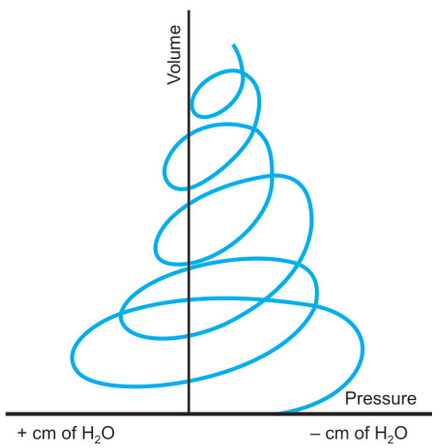


Fig. 25.3: The first few breaths of a neonate, where there is a high negative intrapulmonary pressure and low tidal volume.This is followed by a gradual reduction of this negative intrapulmonary pressure and an increase in the tidal volume

The fluid-air interface at the surface of alveoli which develops after the first breath of a newborn cannot be maintained without this surfactant. So, the lungs are unable to retain air within the alveoli without surfactant and collapses. If the pressure is measured within the alveoli of different sizes without surfactant, then it is found that the smaller alveoli have higher intra alveolar pressure than the larger ones which is explained by the Laplace law.

The Laplace law says that the pressure in each sphere or alveoli varies inversely with the radius of it (if the tension of the wall is constant). If the lung is considered as a large cluster of bubbles or alveoli in communication with each other, then it is expected that the smaller alveoli without surfactant would expand less readily on inspiration and empty more completely on expiration, than the larger ones.This is due to the high inward collapsing surface tension force of the smaller alveoli than the larger ones. Thus, the larger ones would become overdistended and the smaller ones would collapse, because smaller alveoli gradually drain into the larger ones. But, fortunately, this does not happen due to the presence of surfactant at the alveolar fluid-air interface, which reduces the surface tension to a degree, that is inversely proportional to the surface area of alveoli. Thus, the reduction of surface tension in smaller alveoli is greater than the larger ones and they remain distended or open, giving rise to a stable condition.

This Laplace phenomenon is not restricted to the consideration of just the surface tension of alveoli. But it is applicable to other hollow viscus of the body also. For example, a smaller heart does not have to develop the same tension in its wall as a larger one in order to produce the same given pressure within its cavities. A small diaphragm with a small radius can produce a larger negative intrathoracic tension, despite its paper-thin musculature which

is found during the first breath, and this negative intrathoracic pressure is as high as in the adults (-70 mm of H_2O).

The active constituents of this intra-alveolar surfactant are phospholipids, 85% of which is lecithin. Lecithin appears in the amniotic fluid towards the term. This terminal increase of lecithin in the amniotic fluid is greater than that of sphingomyelin, which is another phospholipid surfactant and is present in the amniotic fluid from the 24th week of gestation. When the ratio of lecithin to sphingomyelin is above 2, then the risk of collapse of the alveoli is less. If the child is born prematurely and these surfactant phospholipids are insufficient, then respiratory failure may follow. Glucocorticoids accelerate the production of these pulmonarysurfactant. This is proved by the fact that neonates who develop hyaline membrane disease have a low blood cortisol level, than the neonates who have a pulmonary disease.

The lungs in utero are filled with fluid. However, the composition of this fluid differs from both the amniotic fluid and the serum, since the pH is lower and the chloride content is higher than the both. This alveolar fluid is formed by an active secretory and absorption process of the alveolar epithelial cells. In the course of delivery, this alveolar fluid is expressed out of the lungs by the force exerted on the chest wall of the foetus by the birth canal and presumably it is replaced by air when the chest wall expands during first breath or first cry. The volume of fluid expressed in this way from lungs may be as much as 42 ml. With the first forceful respiratory effort after birth, most of the alveoli are recruited. Then gradually more and more alveoli are recruited in the subsequent respirations and they are expanded. Then the residual fluid in the lung is readily absorbed, as it has an extremely low colloidal osmotic pressure. This absorption of alveolar fluid takes nearly about 24 to 72 hours after birth and occurs through the transcapillary and translymphatic routes.

Within one minute of clamping of the umbilical cord, the first breath of neonate is established. For establishment of this first breath, many sensory factors such as sound, touch and temperature are needed. But, the major factor for the establishment of this first breath in newborn is sudden resetting of the respiratory centre to the new level of PaO_2 and $PaCO_2$, and the hypercapnia and hypoxia had pronounced effect in this resetting. During establishment of first respiration the sensory impulses first strike on the reticular system of brain, and cause a resetting of the respiratory centre to the new level of arterial O_2 and CO_2 concentration, so that the levels of O_2 and CO_2 tension, which had no effect on respiration before, now start effecting. The ventilatory response to CO_2 tension increases with increasing age. The ventilatory response to hypoxaemia in the neonate is more complex than its response to CO_2. The tension of O_2 in the carotid blood rises after the first few breaths from 35 mm of Hg to more than 60 mm of Hg and the CO_2 tension falls from 65 mm of Hg to 35 mm of Hg.

The tidal volume of first breath in newborn is about 20 to 80 ml and generates an extremely negative intrapleural pressure which as about – 70 cm of H_2O during inspiration. The first expiration is also active and assists in the expulsion of lung fluid. Then, progressively, each respiratory cycle shows a smaller pressure-volume loop, with steadily decreasing effort of breathing and retention of air in alveoli with every inspiration. The normal functional residual volume which is about 70 to 80 ml in a neonate is established within 60 minutes of birth.

The respiratory system of neonates and infants is less efficient and has low reserve than adults. But its O_2 consumption is 2 to 3 times as high as an adult. The two respiratory reflexes are seen in a neonate: Paradoxial Reflex of Head and Hering-Breuer Reflex. The first one is the inspiratory response which occurs after a partial inflation of the lungs. The second one is the passive expiratory response, that occurs after inflation. The respiratory pattern of some premature neonates is described as 'periodic', characterised by occasional episodes of apnoea, extending for 5 to 15 seconds. When apnoea is prolonged for more than 15 seconds, then there is bradycardia and haemoglobin desaturation (<90%). The frequency of apnoea is directly related to the degree of prematurity and 70% of preterm neonates show such periodic respiration. Among this, 50% have prolonged apnoeic episodes (>15 secs). Between apnoeic episodes, there is normal respiratory rate or tachyponea. The management of this apnoea of prematurity is theophylline. Periodic breathing and apnoea may be associated with full term neonates, but they are rarely associated with perioperative complications.

Causes of Less Efficiency and Low Reserve of the Respiratory System in the Neonates and Infants

Compared to older children and adults, the neonates and infants have less efficient system for ventilation. This is because of the weak intercostal and diaphragmatic musculature which is again due to the paucity of mature adult Type I muscle fibres, horizontal and more pliable ribs, and a protuberant abdomen. The protuberant abdomen of neonates and infants pushes the diaphragm upwards, beyond its optimal curvature for maximum contraction. This increases the total load against which the diaphragm has to work, and reduces its efficiency. So, the respiratory system of the paediatric group of patients is less efficient, with a low reserve than adults (Table 25.4).

The other causes of less efficiency of respiratory system in the paediatric group of patients are:

i. The diameter of the airways in neonates and infants is smaller. This increases the resistance to air flow, which is inversely proportional to the radius of the lumen and raised to the power of five (r^5). The airway resistance in

Table 25.4: Causes of low respiratory reserve in neonates and infants

1.	High respiratory rate.
2.	Narrow airways and high resistance to airflow.
3.	High compliance of airways and chestwall.
4.	Low compliance of lung.
5.	Sole reliance on diaphragmatic function due to weak, underdeveloped intercostal muscles.
6.	High O_2 consumption and metabolic rate.
7.	High dead space to tidal volume ratio.
8.	Infantile configuration of respiratory muscles (Type I fibres).
9.	Alveolar ventilation twice than adult.
10.	Large physiological shunt.
11.	Small lung volume.
12.	Low vital capacity (half of an adult).
13.	Weak intercostal and diaphragmatic muscles.

neonates is 30 cm of H_2O/L/sec, whereas in adults it is only 2 cm of H_2O/L/sec. Thus, the narrow airway in paediatric group of patients result in an increased resistance to the flow of air upto the age of 8 years. In children, the nasal resistance represents almost 50% of the total airway resistance. So, it accentuates the problem in children with nasal congestion, as they are obligatory nasal breathers.

ii. In children the compliance of airways and the chest wall is high and this is due to the poorly development of these structure. Thus, the high compliance of the chest wall provides little support to the lungs, and so the negative intrathoracic pressure is poorly maintained during inspiration. Hence it reduces the efficacy of the respiratory system. High compliance of airways also causes early closure of it, and the closing volume occurs within tidal breathing, i.e. functional airway closure occurs during each breath (FRC ≤ CC). Therefore, it causes an increase in alveolar and arterial O_2 tension difference ($P_{A-a}O_2$). This explains why PaO_2 in neonates and infants is lower than that of adults, and children are more at the risk of respiratory failure. On the other hand, lung compliance in neonates and infants is also very low. This is only about 6 ml/cm H_2O (adult value is 100 ml/cm H_2O) and is due to the poor development of elastic tissue in alveoli. This also accounts for greater closing capacity (CC) of the lungs and thus, predispose the neonate to increased intrapulmonary shunting of blood and higher P_aCO_2.

iii. In neonates and infants there is also high O_2 consumption and metabolic rate, which need increased ventilation. So to fulfill this high metabolic and O_2 consumption rate and to achieve adequate alveolar ventilation, neonates and infants have to maintain a high respiratory rate and subsequently increased work of breathing. High respiratory rate increases the alveolar minute ventilation. Alveolar minute volume is therefore rate-dependent, but not the tidal volume-dependent in neonates and infants. Thus the normal resulting increased respiratory rate in neonates and infants is approximately double than that of adults In neonates the average respiratory rate is 30-40 per minutes which is already at the higher limit of respiratory reserve. While in adult it is just 15 per minutes with much reserve. This explains the cause of low efficiency and low reserve of respiratory system in neonates and infants. The high alveolar minute ventilation in neonates and children also explains why the induction and emergence from inhalational anaesthesia are relatively rapid in small children. Also, a high metabolic rate explains why desaturation occurs very rapidly in children.

iv. Until the infant reaches the 2 years of age, the fibres of the main respiratory muscles, (diaphragm and intercostal) donot achieve the configuration of the adult Type 1. The adult Type 1 muscle fibres have an ability to perform repeated exercise without fatigue. As the newborns and infants are some what deficient in this adult Type 1 muscle fibres, so any factor that increases the work of breathing, results in an early fatigue of respiratory muscles and causes respiratory failure.

v. In neonates and infants there is already higher dead space to tidal volume ratio (Vd / Vt). So, any modest increase in the dead space (Vd) by equipments, such as facemasks, breathing tubes, humidifiers, etc., (or due to any cause) may have a disproportionately greater effect and reduces the efficiency of respiratory system in this group of patient.

vi. In children ventilation is solely reliant on the diaphragmatic function. This is because the ribs are soft, horizontal (i.e. perpendicular to the vertebral column), noncalcified and the intercostal muscles are poorly developed. Due to the horizontal disposition there is no bucket-handle type of movement of the ribs in children as in the adults. So, there is less expansion of chestwall and less ventilation. Diaphragm is also more horizontally attached to the ribs, reducing its mechanical advantages during contraction. Furthermore slight abdominal distension may easily cause splinting of the diaphragm, resulting in less efficient contraction of it leading to easy respiratory failure in paediatric patients.

vii. Alveolar ventilation per kilogram of body weight is twice than that of an adult in neonates. Thus it deplets the reserve and reduce the efficiency of respiratory system in neonates and infants. The normal alveolar ventilation in neonates is 150 ml/Kg/min, whereas alveolar ventilation in adults is 60 ml/Kg/min.

viii. Another important cause for less efficiences of respiratory system in the paediatric group of patients is a large physiological shunt, the value of which is nearly 20% on day-one.

ix. The lung volume in infants and neonates is disproportionately smaller in relation

to their body size in comparison to adult. But the metabolic rate is nearly twice than that of an adult. Therefore, the ventilatory requirement for per unit volume of lung is enormously high in neonates and infants. Thus, they have far less reserve for gas exchange than adults.

x. The normal O_2 consumption, CO_2 production and tidal volume (ml/Kg) of the neonate is almost double than that of an adult. The neonatal O_2 consumption is 7 ml/Kg/min as compared to 4 ml/Kg/min of an adult. Whereas, the neonatal CO_2 production is 6 ml/Kg/min as compared to 3 ml/Kg/min of an adult. Tidal volume of a neonate is 6 ml/Kg whereas in an adult it is 3ml/Kg. All these datas explain how the respiratory system of neonate and infant is using its reserve and depletes it and is less efficient than adult.

xi. The vital capacity of a neonate is half than that of the adult, i.e. only 35 ml/Kg. for neonates, whereas 70 ml/Kg for an adult.

xii. The FRC of a neonate is 30 ml/Kg, whereas the adult has an FRC of 35 ml/Kg.

xiii. Morever, hypoxic and hypercapnic ventilatory drives are not well developed in neonates and infants. Infact, unlike adults, hypoxia and hypercapnia depress the respiration in these group of patients (Table 25.5).

The different lung volumes of the neonates and infants differ from the adults. It is definitely smaller in neonates and infants than adults, but when compared with respect to their body weight and metabolic rate it is higher than that of the adult. The gas exchange area of neonatal and infantile lungs is 50 times less than that of the adults. The gas exchange area of the neonatal lung is only 3 m^2 in comparison to that of an adult, which is 150 m^2, though the metabolic rate of neonates is twice than that of the adult. The functional residual capacity (FRC) per Kg of body weight reaches the adult value during the first 48 hours after birth, but still the closing volume exceeds the FRC during normal breathing and explains the cause of low PaO_2 in neonates. When normalized for body weight, the tidal volume for both the groups is same. Dead space volume per Kg of body weight is also same for both the groups and it is about 30% of the tidal volume.

Table 25.5: Comparison of respiratory parameters between neonates and adults

Parameters	*Adult*	*Neonate*
Tidal volume (ml/Kg, in spontaneous respiration)	7-10	7
Dead space (ml/Kg)	2	2
Respiratory rate/min	15	30
V_D: V_T	0.3	0.3
Compliance (ml/cm H_2O)	100	6
Airway resistance (cm H_2O/Lt/S)	2	30
Time constant (S)	1.1	0.5
O_2 consumption (ml/Kg/min)	4	7

Spontaneous respiratory rate decreases, as the age increases. This reflects the age related decrease in ventilatory requirement which is parallel to the decrease in metabolic rate with age. This is explained by the O_2 consumption rate in neonates which is about 7 ml/Kg/minute, and is twice than that of the adult. The normal adult value is 3.5 ml/Kg/minute. Although respiratory rate of neonates and infants is high, alveolar ventilation is still inefficient than adults. Consequently, when the trachea is intubated and ventilation is constituted by mechanical ventilator, the normocapnia is only maintained by the high tidal volume of 10 to 15 ml/Kg and a low respiratory rate of 20 to 25 bpm in the healthy neonates and infants. This explains why in neonates and infants, the energy is mainly utilised for spontaneous respiration and is the major source of CO_2 production. To maintain normocapnia and a normal PaO_2 in neonates with poor respiratory gas exchange, higher respiratory rate (>15 to 25 bpm) is required. The neonatal and infantile lungs continue to grow and mature throughout there childhood and adolescence, and reach the adult value by 16 years of age.

xiv. Respiratory Rate (RR):It varies with age (Table 25.6).

The airway of the paediatric patients differs from the adults in the following ways:

i. The tongue of the paediatric group of patients is relatively larger than adults in relation to oropharynx. So, there is every likelyhood of an upper airway obstruction by this large tongue in this group of patient. It also causes technical difficulties during laryngoscopy and intubation.

ii. The larynx of the paediatric age group of patients is located highup in the neck. In neonates and infants it is situated at the level of C_{3-4} vertebrae. Whereas in adults, it is situated at the level of C_{5-6} vertebra. This is because, the neck is short and the hyoid cartilage lies in close proximity to the thyroid cartilage in paediatric patients. So, a straight blade of a laryngoscope, behind the epiglottis, becomes frequently successful to expose the vocal cords.

iii. The epiglottis of neonates and infants is long, floppy and acutely angled over the laryngeal inlet. It projects posteriorly at an angle of 45° to the base of the tongue. Whereas, the epiglottis of an adult is short, broad, flat and projects posteriorly at an angle of only 15 to 25° to the base of the tongue. So, the control of epiglottis and the exposure

Table 25.6: Respiratory rate and age in children

Preterm neonate	:	40-70	BPM
Neonate	:	40	”
2 to 5 years	:	25-30	”
5 to 12 years	:	20-25	”
> 12 years	:	15-20	”

of larynx by the blade of laryngoscope is more difficult in paediatric group of patients than the adults (Fig. 25.4).

iv. The paediatric larynx is funnel shaped and the position of cricoid cartilage in the larynx marks its narrowest portion. In contrast, the adult larynx is tubular in shape and narrowest at the level of the vocal cords, which is much above the cricoid cartilage. So, in adults an endotracheal (ET) tube which passes the vocal cord (glottic opening) will readily pass into the trachea without any hindrance at the level of cricoid cartilage. But, in neonates and infants an ET tube that easily passes the vocal cords, may be tight in the subglottic region at the level of cricoid cartilage and may not pass into the trachea. This is due to the maximum narrowing of larynx at this level, due to the presence of the cricoid cartilage from where the trachea begins. Hence, the uncuffed endotracheal tubes are preferred in patients less than 10 years of age.

The cricoid cartilage is covered with loose pseudostratified columnar epithelium. So, it is susceptible to oedema, when traumatized and inflamed by cuffed or tight tubes. As the epithelium of cricoid cartilage swells due to trauma, it occludes the lumen of the cricoid ring and severely obstructs the airflow. The resistance of airflow through a pipe is inversely proportional to the fifth power of the radius of the lumen of this tube. So, a small amount of swelling will cause a little decrease in the radius of lumen, but will tremendously increase the resistance to airflow. For example, when the radius of the cricoid lumen decreases two-folds, the resistance to airflow increases by 32 folds (i.e. $2^5 = 32$).

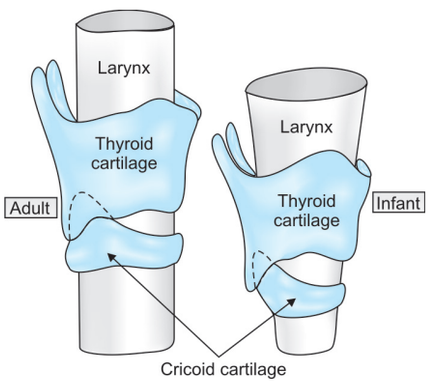


Fig. 25.4: Adult and infant larynx

v. The head of the neonates and infants is relatively large in comparison to their body size than adult. The occiput of it is most prominent and the chin is retrognathic. So, the prominence of occiput and largeness of the head of paediatric group of patient keeps already it in a 'sniffing' position without pillow which facilitates the tracheal intubation. Therefore, any pillow under the head during intubation may disturb this sniffing position and may make intubation difficult in neonates and infants.

vi. The nasal passage of the neonates and infants is relatively narrow and accounts for more than 50% of the total airway resistance. On the otherhand, neonates and infants are obligatory nasal breathers. So, they are highly predisposed to obstruction in the presence of even a very small amount of secretion in the airway.

vii. The trachea of the neonates and infants is made up of soft (compliant), short (4 to 5 cm), noncalcified, cartilaginous rings. Whereas the trachea of an adult person is long (10 to 11 cm) and made up of noncompliant cartilaginous ring which may be calcified. So, it does not easily collapse during any airway obstruction like paediatric patients.

Thus, the combination of these two characteristics, i.e a high compliance of the chestwall and the airway and a low compliance of the lung tissue in neonates and infants (opposite to that of an adult) promotes the chestwall to collapse easily during inspiration and maintain a relatively low residual lung volume at expiration,which results in a decreased FRC and low oxygen reserves (Table 25.7).

Table 25.7: Characteristics of the paediatric airway

1.	Relatively large tongue
2.	High up larynx
3.	Long acting acutely angled epiglottis
4.	Funnel shaped larynx
5.	The narrowest part of larynx is the cricoid cartilage
6.	Obligatory nasal breathers
7.	High compliance and easy to collapse chest wall and airway
8.	Retrognathic chin
9.	Short trachea and neck
10.	Prominent adenoids and tonsils

TEMPERATURE REGULATION AND MAINTENANCE IN PAEDIATRIC PATIENTS

The neonates and infants are particularly vulnerable to hypothermia. This is due to the (i) large body surface area to weight ratio, (ii) poor insulation due to thin skin and limited fat stores, (iii) immature sweat function, (iv) initial low BMR, and (v) the inability to move away from adverse thermal environment. This hypothermia causes early arterial desaturation by increasing the cellular metabolism and O_2 consumption. Previously, it was thought that this vulnerability to hypothermia is due to the ill-developed temperature regulating mechanism in paediatric patients. But, this is incorrect. Because actually, they donot have a well developed system for increasing the heat production in response to cold. The infant is able to raise the heat production in response to cold only upto 70 cal/Kg/min, as compared to an adult, who can achieve the heat production upto 90 cal/Kg/minute. Again, the vulnerability to hypothermia in neonates and infants is due to the greater heat losing surface area, than the mass of heat producing tissues i.e. larger body surface area (heat-losing) to body weight (heat-producing) ratio than adult. The premature infant is even more susceptible to hypothermia. This is because of their very thin skin and limited fat stores than mature infant and so losing more heat.

The three process of thermogenesis, producing heat in infants are:

i. Voluntary muscle activity
ii. Involuntary muscle activity
iii. Nonshivering (by cellular metabolism) thermogenesis.

The minimal ability of the neonates and infants to shiver (voluntary muscle activity) during the first three months of life makes the metabolism of brown fat (cellular thermogenesis) the principal method of heat production for this age group of patients. Brown fat is a specialised adipose tissue, capable of metabolising fat *in situ,* and is present in the newborn of most species. It develops between 25 to 30 weeks of gestation and constitutes about 25% to 30 % of the total body weight. The distribution of this brown fat varies from species to species, but in humans it is mainly found largely around the kidneys, the adrenal glands, between the scapulae, in axilla and around the blood vessels of the neck, mediastinum and the loin. The differences between brown and white fat are:

i. The blood supply is copious in brown fat
ii. In brown fat the nerve supply is abundant
iii. The cells of brown fat are multinucleated and judiciously equipped with mitochondrias.

The activities of tissues in brown fat to produce heat are mediated by catecholamines and can be abolished by sympathetic blockers. The substrate used for heat production in brown fat is mainly the fatty acids and the temperature of this tissue rises markedly, when the subject is exposed to cold. The metabolism of brown fat is severely limited in premature infants, and sick neonates who are deficient in fat stores. Furthermore, volatile anaesthetics inhibit thermogenesis in the brown adipocytes.

Newborn infants, however, cannot maintain their temperature only at the expense of brown fat consumption, but also burn their carbohydrate reserve for thermogenesis. At birth, the liver, cardiac, and skeletal muscle's glycogen content is much higher than that of an adult. Of these reserves, only the liver-carbohydrate contributes directly to the maintenance of blood sugar, and consequently to the production of heat and energy by its metabolism. However, the muscle glycogen may do so indirectly by conversion of it to lactic acid which may then become a source of glucose in the liver. Newborn infants in an adverse thermal environment tend to deplete their stored liver-carbohydrate and subsequently become hypoglycaemic and hypothermic. Hypoglycaemia which in the neonates is defined as glucose levels below 30 mg/dl may lead to grave brain damage, if untreated.

If the neonates are allowed to become hypothermic during anaesthesia, then unlike adults they try to maintain their temperature only by non-shivering thermogenesis, i.e. by cellular metabolism. Therefore, as the metabolic rate increases, O_2 consumption also increases. Then this increased O_2 consumption puts an additional burden on the cardiopulmonary system and this may become critical in neonates with a limited reserve. On the otherhand, the release of norepinephrine in response to cold stress causes vasoconstriction, which in turn causes further tissue hypoxia and lactic acidosis in the face of increased O_2 consumption and demand. This acidosis in turn favours an increase in right to left shunt, which further causes hypoxaemia. As a result, a vicious positive feedback loop of hypoxaemia and acidosis is set up.This problem of hypothermia is further compounded by cold operating room enviornment, wound exposure, intravenous fluid administration, dry cool anaesthetic gases and the direct effect of anaesthetic agents on the temperature regulatory mechanism. Thus, hypothermia is a serious problem during perioperative period of anaesthesia that has been associated with delayed awakening from anaesthesia, cardiac irritability, respiratory depression, increased PVR and altered drug response.

The Homeothermic animals have the ability to generate and lose heat, thus maintaining the core temperature in a fixed range. Heat loss from body occurs by one of the four following processes: radiation, convection, evaporation and conduction. Enviornment around a patient controls the loss of heat by this four process. The neutral thermal enviornment is defined as the range of ambient temperature at which the loss of temperature by evaporation does not occur. In this neutral thermal environment the metabolic rate is minimal. The temperature of such an enviornment is 34ºC for the premature neonates, 32ºC for the term neonates, and 28°C for an adult. These are also the temperature settings of an incubator.

Among the four processes of heat loss: radiation, convection and evaporation are the most important processes, responsible for heat loss in the OT. Radiation accounts for about 60% of the heat loss from a neonate or a infant placed in a 21°C room temperature. If the room temperature is raised to a thermoneutral environment of 34°C, the loss of heat by radiation will decrease to about 40% of the total heat loss. The reason for this is that the heat loss by radiation is a function of the difference between skin and the room temperature. So, if room temperature is raised, then the heat loss by radiation is minimum. The second major source of heat loss in the neonate is convection and this also can be reduced by increasing the room temperature to the skin temperature. Evaporative loss also can be reduced by keeping the environmental temperature at a neutral level. The neonate possesses minimum subcutaneous fat that cannot act as thermal insulation.

Many procedures and precautions can be undertaken in OT to maintain the body temperature of a neonate and an infant, mainly by reducing the heat loss. Thus the procedures taken to maintain the body temperature of a neonate and an infant by heat loss are:

i. The neonate should be transported to the theatre wrapped up by an insulator or in an incubator, set at thermoneutral temperature. Ideally, few hours before surgery the theatre should be warmed to the thermoneutral temperature. This causes the walls and the equipments of the theatre to warm up and reduces the net heat loss by radiation. Heat loss by radiation is a two-way process. The child loses heat by radiation to the walls and equipments and it also gains heat from the walls and equipments provided they are properly heated previously.
ii. All the body parts of a child that are not needed for surgical and monitoring purposes should be covered. Overhead radiant heaters should be used, if the child has to be exposed.
iii. During surgery, the child should lie on a thermostatically controlled heated blanket.
iv. Forced air-warming system by blowing filtered warm air into quilted blankets with perforations are effective in maintaining the child's temperature during surgery. This allows warm air to come into direct contact with the child.
v. Other measures such as using bonnets, to reduce heat loss from the exposed head is very effective. IV fluids and fluids used for lavage of the body cavities should be warmed to the body temperature. Anaesthetic gases should be humidified and warmed, in order to reduce the heat loss from lungs. The new born in the cold OT or Labour Room is very vulumerable to cold stress, because some heat loss is inevitable. This also can be reduced by warm wrappings, heated mattresses, overhead heaters, alluminium covers, etc.

RENAL FUNCTION AND FLUID BALANCE

The kidneys and subsequently all its functions are immature at birth. The maturation of the renal tissue occurs by hyperplasia during the first six weeks of life and then by hypertrophy during the next first year of life.

However, the complete maturation of renal tissue occurs by about two years of age. Due to low perfusion pressure and immaturity of the glomerular and tubular functions, both the glomerular filtration rate (GFR) and subsequently the renal tubular reabsorption rate are low in neonates and infants. At birth the GFR is only about 45 ml/min/1.7m^2, which increases rapidly to about 65 ml/min/1.7 m^2 by 6 months. Then, gradually it approaches the adult value of 125 ml/min/1.7 m^2 by the age of 2 years. Thus, the kidneys of neonates and mainly of premature are unable to handle the excessive water and solute load, especially Na^+ and K^+. The half life of medicines that are excreted by glomerular filtration are also prolonged. Hence, there is more chance of overtransfusion which may lead to pulmonary oedema and cardiac failure in this age group of patients. Because of the low glomerular filtration rate, poor capacity to concentrate urine, and no diuretic response to water load the infant's kidney is also less well-equipped to deal with the effects of dehydration (Table 25.8).

At birth in neonate the urine volume is about 25 ml/Kg/day. This gradually rises to about 100 to 120 ml/Kg/day by the end of 1st week. The insensible loss in normal babies is about 25 to 30 ml/Kg/day. To maintain the normal serum electrolyte concentration, the neonates and infants require about of 3 to 5 mmol/Kg of Na^+ and an equivalent amount of K^+ per day. The ability of an immature kidney in neonate and infant to eliminate excess Na^+ is limited. So, an extra load of Na^+ in the absence of loss easily results in hypernatraemia and its sequelae. The premature neonates often possess multiple renal defects including decreased creatinine-clearance, increased glucose-excretion, decreased bicarbonate-reabsorption and poor diluting-concentrating ability.

A great difference exists in the distribution of water in the body as a percentage of body weight among the neonates, infants and adults. In premature infants the water constitutes about 85% of the total body weight. In neonates, infants and adults, this percentage is 80%, 75% and 65% respectively. In neonates most of the total body water is in the extracellular compartment in contrast to adults, where most of the total body water is in the intracellular compartment. The plasma volume in percentage of body weight remains constant throughout the life and this is at about 5% of the total body weight (Table 25.9).

The approach to IV fluid therapy in paediatric group of patients should be considered in the light of their high metabolic rate, high O_2 demand and a high body surface to weight ratio. In the first week of life the requirement of fluid for maintenance increases everyday. When we relate the daily water requirement with the metabolic or caloric demand, then the general rule is that 100 ml of water is required for each 100 calories of spent energy.

On the other hand, when we relate the fluid requirement to body weight, then in infants with body weight upto 10 Kg, the fluid requirement is 100 ml/Kg/day or 4 ml/Kg/hour. For neonates and infants

Table 25.8: Distribution of water as percent of body weight

	ICF	*ECF*	*Plasma*	*Total*
Premature	30	50	5	85
Neonate	40	35	5	80
Infant	40	30	5	75
Adult	40	20	5	65

ICF= Intracellular fluid, ECF = Extracellular fluid

Table 25.9: Fluid requirements in the first week of life

Rate (ml/Kg/day)	*Day*
0	1
50	2, 3
70	4, 5
100	6
125	7

with body weight between 10 Kg and 20 Kg, this calculation requires an addition of water of 2 ml/Kg/hour for each Kg increase in body weight (Table 25.10).

As for example, for a neonate with a body weight of 15 Kg, the fluid requirement is (10×4) + (5×2) = 50 ml/hour or 1200 ml/day. Between 20 to 30 Kg, the daily fluid requirement needs an addition of 1 ml/Kg/hour, for each Kg increase in body weight above 20 Kg to the previous requirement. As for example, for a neonate or infant of 25 Kg , the fluid requirement is (10×4) + (10×2) + (5×1) = 65 ml/hour or 1600 ml/day. Of the total deficit, 50% is replaced in the first hour and 25% in each of the next 2 hours. However, this calculation does not include the previous deficit, third space loss due to surgical procedures, hyperthermia, hyperventilation, etc. Third space loss depends on surgical procedures and may vary from 1 ml/Kg/hour for a minor surgical procedure to as much as 15 ml/Kg/hour for major surgical procedures.

We also have to think about the composition of the IV fluid. There is still some controversy regarding the requirement of glucose in the IV fluid. Some reports of hypoxic brain damage have been published, due to high blood glucose levels. So, some anaesthesiologists do not recommend the routine use of glucose-containing solutions as IV fluid. This is also true that unrecognised hyperglycaemia, ketosis and high metabolic rate of neonates and infants are the motivating factors for discarding the routine use of glucose containing solutions in paediatric patients. But, this is not always true for those who have not food or fluid for a long time and also those who have a diminished glycogen store. The neonates who are at greater risk of hypoglycaemia are: premature babies or babies of small for gestational age babies receiving hyperalimentation and babies born to diabetic mothers. So, the current practice is to avoid the risk of hypoglycaemia. But, routine use of only 5% dextrose or lactated Ringer's solution is discouraged. Instead, 5% dextrose in 0·45% normal saline is used in a piggy-back infusion at maintenance rates with lactated Ringer's solution (or any balanced salt solution) for all deficits and third space losses. The IV fluids should also be administered by using a system that allows small volume to be given accurately. Anaesthesiologists usually perform this by injecting fluid using a syringe, or by a microprocessor-controlled syringe-driven infusion pump. The later method is preferable, as fluid is given at a slow but steady and accurate rate.

The Anaesthesiologists must assesses the blood loss during surgery. In minor surgical procedures the loss is minimal and the assessment is performed by visual inspection of the surgical field, swabs, mops and suction bottle. But for major surgeries where blood loss is more, then weighing of swabs and colorimetry is helpful. The estimated circulating blood volume in neonates, infants and children is near about 70-80 ml/Kg. In general, the blood loss less than 10% of the total blood volume either requires no replacement or can be replaced by crystalloid solutions. Loss between 10% to 20% should always be replaced by colloids or blood. But, over 20% of the loss must always be replaced by blood. The adequacy of blood replacement should always be assessed on the background of blood pressure, pulse rate and the central venous pressure (Table 25.11).

Table 25.10: Calculation of the fluid requirement (only for maintenance) in paediatric patients

Weight (Kg)	*Hourly requirement (ml/Kg/hour)*	*Daily requirement (ml/day)*
Upto 10 Kg	4 ml/Kg/hour	100 ml/Kg/day
10 to 20 Kg	10 × 4 + 2 (Wt in Kg – 10) ml/hour	1000 + 48 (Wt in Kg – 10) ml/day
Above 20 Kg	(10 × 4) + (10 × 2) + 1 (Wt in Kg – 20) ml/hour = 60 + 1 (Wt in Kg – 20) ml/hour	1000 + 48 × 10 + 24 (Wt in Kg – 20) ml/Day = 1480 + 24 (Wt in Kg – 20) ml/Day

HEPATIC FUNCTION

The maturity of liver function is somewhat incomplete during the birth at term.The ability to detoxify the drugs and the carbohydrate metabolism system in the liver are both poorly developed during birth. But, the capability of synthesis of albumin and coagulation factors are normal at birth. By the 6 weeks of age, the enzyme systems of liver function develops as per the adult levels, though they are not induced (stimulated) by agents which they metabolise. The conjugation reactions are often impaired in the neonates, resulting in jaundice. Because of the low glycogen stores and hepatic immaturity, hypoglycaemia (defined as blood glucose level of 30 mg/dl or less) in a term baby is common. In low birth weight or premature babies, hypoglycaemia (defined as blood glucose level 20 mg/dl or less) is more common. The condition of hypoglycaemia is usually without symptoms, unless the level is very low when the apnoeic attacks or convulsions may occur. Hypothermia also causes hypoglycaemia and vice versa. The plasma levels of albumin and other plasma proteins (necessary for binding of drugs) are low in term newborns and even more low in premature infants. This is responsible for the greater level of free drug in the plasma and neonatal coagulopathy (e.g hence the need for vit K at birth). As the infant gradually grows, the function of the liver matures in two ways: (i) The enzyme system slowly develops. (ii) The hepatic blood flow increases delivering more blood to the liver.

Table 25.11: Some important parameters of a newborn weighing 4 Kg

Heart rate	120-140 minutes
Mean blood pressure	70 mm of Hg
Respiratory rate	35-40 /minutes
Tidal volume	16 ml
Alveolar ventilation	400 ml/minute
Hb concentration	18-20 gm/100 ml
Urinary output	20-30 ml/Kg/24 hours
Fluid requirement	100 ml/Kg/24 hours

Hypocalcaemia

This condition commonly ocurrs during the first 2 days of life and this is mainly due to the immaturity of parathyroid glands and high phosphate content of some milk formulae which are usually marked. Nonspecific neurological signs, such as irritability causing tetany or convulsions etc, due to the low level of blood calcium is usually treated by intravenous infusion of 2% solution of calcium gluconate at the dose of 5 mg/Kg/hour.

GI System

Gastric secretion begins from the second trimester of pregnancy or 16 weeks of intrauterine life. Gastric pH is alkaline at birth. Then, it decreases approximately to pH 4 by 8 hours after birth. On the second day of life, the gastric pH reaches within the range of an adult. Till 4 to 5 months of age after birth, coordination between the respiration and swallowing does not develop. So, it frequently causes gastro-oesophageal reflux, laryngeal aspiration and coughing. The upper intestinal developmental abnormalities often manifest as vomiting and regurgitation, but the lower intestinal developmental abnormalities manifest as distension of abdomen and failure to pass meconium. Any developmental anomaly of the gastrointestinal tract manifests as early as 24 to 36 hours after birth.

CENTRAL NERVOUS SYSTEM

The anatomical developments of nervous system in a newborn are complete at term. But the functional development of nervous system, including myelination, synaptic connections, synthesis of neurotransmitters, etc, continues for 2 years after the commencement of extrauterine life. The cranium of the newborn is soft and pliable. It has many nonfused cranial sutures, two open fontanels (the posterior fontanel closes by 6 to 9 months and the anterior fontanel closes by 18 months of postnatal life), poorly developed cerebral cortex, fragile subependymal blood vessels, a spinal cord that ends at L_4, etc. All these peculiarities that differ from adult's CNS have important implications in the management of paediatric anaesthesia. Water is the predominant constituent of the neonatal and infantile brain tissue. Then, due to more and more myelination and dendritic proliferation water content of the brain tissue of the paediatric group of patient gradually decreases and the fat content increases, throughout the infancy and childhood. The modern inhalational anaesthetic agents are less soluble in water than fat. So, their partition coefficient is lowest in premature and newborn babies. This gradually increases with the passage of time after birth and this is due to the decrease in the concentration of water as body constituent. This explains the more rapid wash-in (induction) and washout (recovery) of inhalational anaesthetic agents from the brain tissue of the neonates and infants, when compared to adults and hence the altered requirements of it for this age group. The blood-brain barrier is immature and more permeable in the neonates and infants. So, barbiturates, opioids, antibiotics, bilirubin etc. cross this barrier more rapidly. In asphyxiated neonates and also in preterm babies, the autoregulation of cerebral blood flow is compromised, i.e. the cerebral blood flow varies directly with the systemic mean arterial pressure. But, still it is autoregulated over a wide range of change in arterial blood pressure in healthy neonates and infants. The neuro-endocrine axis of stress for pain and surgery, and the mechanism responsible for perception of noxious stimuli are well developed in neonates and infants like the adults. So an inadequate level of analgesia and anaesthesia in the perioperative period can result in marked stress response and its consequences in this paediatric group of patients.

PHARMACOKINETIC AND PHARMACODYNAMIC STATUS IN PAEDIATRIC PATIENTS

The pharmacodynamics of different drug in paediatric patients differ from that of the adults in following aspects. These are :

i. Composition of the body fluids and tissue, relative difference in tissue volume and solubility.
ii. Cardiac index and distribution of CO to different tissues.
iii. Protein-binding capacity of the blood.
iv. Maturation of blood-brain barrier.
v. Functional maturity of liver and kidneys.

In neonates and infants the total body water content (due to the large extracellular fluid and large blood volume) is disproportionately higher. Then, it gradually decreases with increasing age and this is due to the increase in fat and muscle content in body. So, the water-soluble highly ionised drugs have a larger volume of distribution and requires a larger initial dose on a weight basis in neonates and infants to achieve the desired blood level, e.g. succinylcholine. In premature babies and neonates, there is much less fat and muscle tissue than the adults. So, the drugs which depend on redistribution into fat and muscle for termination of their action (e.g. thiopentone and fentanyl) has a longer duration of action.

Thus, in general when compared to an adult, the potency of many drugs is greater in neonates and infants, requiring a lower does but this potency is lesser in children, requiring a higher dose and vice versa. Similarly, many drugs have a prolonged elimination half life in neonates and infants requiring a lower dose, but shorter half life in children over 2 years requiring a higher dose than an adult. This difference gradually equalises, as the children march towards their adulthood.

In premature babies and neonates, there is lower plasma concentration of albumin. Therefore, the ability of albumin to bind with drugs is also lower than in an adult. So, most of the IV drugs in these group of patients remain in a free-active form, requiring a lower dose. The concentration of α_1 acid glycoprotein which is the major binding protein in plasma for opioids and

local anaesthetics is also lower in paediatric patients, resulting in exaggerated and prolonged actions of these two groups of drugs in this age group of patients.

At birth the blood-brain barrier is immature and it gradually matures with increasing age. Again, the neonate's brain receives a large proportion of CO than the adult brain. So, the brain is exposed to more drugs and the concentration of drugs in the brain is higher in neonates and infants than in adults.Thus, it explains why narcotics should be used with caution and in reduced amounts in this age group of patients (Fig. 25.5).

In older children the renal functions reach an adult level by the age of 3 months and by that time the clearance of most of the drugs by kidney reaches the adult values. The activity of the liver function reaches the adult value by 6 weeks after birth. But, the volume and the weight of liver and kidney is disproportionately more than an adult, and hence receives more percentage of CO. This explains why most medications have a shorter half-life in children older than 2 years than in neonates and adults. In general, most medications will have prolonged elimination halflife in premature and term infants, shorter halflife in children and again prolonged of half-life in those approaching adulthood.

Some special characteristics of the pharmacodynamics of children during inhalational anaesthesia are:

i. Higher alveolar and minute ventilation (due to high respiratory rate) in relation to FRC.
ii. High CI. i.e. high cardiac output in relation to body weight, increases the rate of equilibrium of anaesthetic agents in the tissues.
iii. Preponderance of vessel-rich tissues (e.g. brain) and greater proportional distribution of CO to these vessel-rich organs.
iv. Reduced water solubility of inhaled anaesthetic agents in blood, i.e. blood/gas coefficients of volatile anaesthetics are lower in neonates and infants than in adults. All these cause alveolar and brain concentration of inhalational anaesthetic agents to increase and fall rapidly.

This increased rate of equilibration in neonates and infants correlates well with the earlier development of cardiovascular side effects and explains why induction and recovery by inhalational anaesthetic agents are more rapid in children.

MAC values of anaesthetic agents change with age. It is lower for premature infants and increases to a peak value at the age of 3 months. Then, it gradually declines again, until the adult value is reached. So, infants are known to have a greater anaesthetic requirement than the older children and adults. Hence, infants are in a precarious condition between the higher requirement of inhaled anaesthetic agents (say, for endotracheal intubation) and anaesthetic overdose (from cardiovascular standpoint). Use of narcotics and muscle relaxants usually widen this gap.

The blood pressure of neonates and infants tends to be more sensitive to volatile anaesthetics agents. This is probably because of the incompletely developed compensatory mechanisms (e.g. vasoconstriction and tachycardia) and an immature myocardium that is very sensitive to myocardial depression.

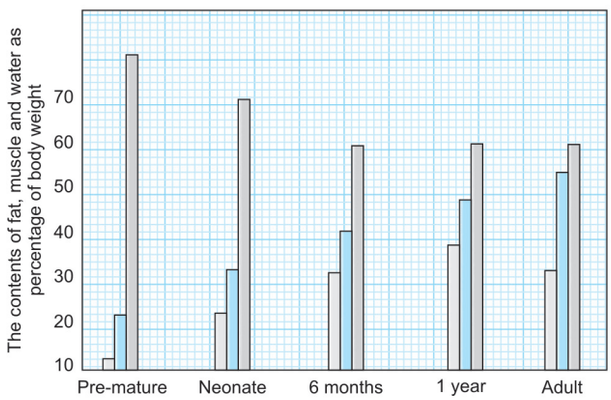


Fig. 25.5: Changes in the body composition from a premature neonate to an adult.The high water content in the body of the premature neonate causes a large volume of distribution of water soluble drugs and thus an increase in the dose requirement. Whereas a low fat and muscle content provides less redistribution of fat soluble drugs and hence prolongs their duration of action (as their effects are terminated by the redistribution of water)
Red—Total body water, Black- Muscle mass,Green- Fat

VARIOUS ANAESTHETIC AGENTS USED IN PAEDIATRIC ANAESTHESIA

Volatile Anaesthetic Agents

Halothane

Although the use of halothane in western countries has declined gradually, but is still the gold standard volatile anaesthetic agent for induction of anaesthesia in the paediatric patients in most of the other underdeveloped countries, due to its least pungent odour (it is less pungent than sevoflurane). It also allows a very smooth induction, maintenance and emergence from anaesthesia. The low blood-gas solubility coefficient (2.3) of halothane and its high potency also permits a rapid onset, as well as a rapid recovery from anaesthesia. But, many anaesthetists now consider sevoflurane as the gold standard for this purpose. Airway related problems like coughing, laryngospasm, secretions, etc. occur less frequently with halothanes and sevoflurane than with other volatile anaesthetic agents, such as: enflurane, isoflurane and desflurane. Thus, halothane like sevoflurane is the anaesthetic agent of choice for induction by mask with airway problems in paediatirc group of patients.

As most vaporisers allow high concentration like 5 × MAC of any volatile anaesthetic agent to be administered if needed, so it can be given with almost 100% O_2 without any N_2O. This is very helpful in children with an airway problem. The potency of halothane varies with age. In neonates, the MAC value of halothane is about 0·9%. But, it increases rapidly to a maximum of 1.2% at 6 months of age and, thereafter, declines gradually to the adult value of 0·8%. The lower MAC value of halothane in neonates in comparison to infants is due to the immaturity of CNS in neonates. The higher value of MAC in infants compared to older children and adults is due to the increase in brain water content in the previous group of patients. Prolonged duration of action of halothane than the other newer volatile agents (sevoflurane, desflurane) makes it simetimes specially useful in paediatric anaesthesia, as the plane of anaesthesia does not quickly lighten during intubation or instrumentation of airway.

Halothane depresses the myocardium, reduces the heart rate and decreases the CO. The hypotension produced by halothane is primarily due to its direct myocardial depression effects and bradycardia. It is, therefore, prudent to give an anticholinergic, prior to halothane administration. Another concern with halothane is that it sensitises the myocardium to exogenous and endogenous catecholamines, causing arrhythmia. But, most arrhythmias associated with halothane in paediatric anaesthesia is due to either hypoxia, hypercarbia or inadequate level of anaesthesia. Thereafter, a prudent paediatric anaesthetist must controls hypercarbia, prevents hypoxia and maintains adequate level of anaesthesia. The maximum recommended dose of epinephrine with local anaesthetic solutions during halothane anaesthesia is 5 to10 µgm/Kg. The effect of LA agent is also aggravated in paediatric anaesthesia by hypercarbia, and an inadequate level of anaesthesia.The potent myocardial depressant effect of halothane can have a profound effect on neonates and children with congenital heart diseases. It is also responsible for the occasional inability to give sufficient concentration of halothane to critically ill patients to provide anaesthesia without inducing severe hypotension. In these circumstances, the smaller concentrations of halothane and liberal doses of short acting newer narcotics generally provide a better response.

Approximately, 20% of the absorbed halothane is metabolised in liver, mainly by oxidation and produce its higher degree of metabolites. This higher degree of metabolism in liver appears to be an important factor for the aetiology of halothane hepatitis. So, repeated administration of halothane within a period of less than 3 to 6 months may be associated with hepatic dysfunction and occasionally with fulminant hepatic failure. Though the exact mechanism of this hepatitis induced by halothane is not known, but it is speculated that the oxidative metabolites of halothane acts as an antigen and are responsible for this hepatitis. These oxidative hepatic metabolites of halothane are poorly developed in children and this explains the extreme rarity of halothane-induced hepatitis in paediatric patients, though the incidence of halothane hepatitis in adults when exposed to the drug is 1:10,000 to 1:30,000. However, if a child needs a second anaesthesia within 3 to 6 months of the first halothane anaesthesia, then a risk-benefit assessment has to be undertaken (Table 25.12).

Isoflurane

Isoflurane is one of the important agent in the series of halogenated volitle ether compound and chemically it is a halogenated methyl ether. It was originally developed in the place of ether in order to improve its molecular stability and also to reduce its metabolism in liver, when compared to halothane. The metabolism of isoflurane in liver is about 1/100th of that of halothane (0·2%) and therefore there is no report of hepatotoxicity in children.

Like ether, isoflurane has an irritant and pungent odour. Thus, it is associated with an increased incidence of airway problems, such as: coughing, secretions, laryngospasm, etc. during induction, maintenance (with or without muscle. relaxant), and recovery from anaesthesia. So, despite the low blood-gas solubility coefficient (1.4) of isoflurane, when compared to halothane which dictates a rapid induction and recovery from anaesthesia, the speed of induction of anaesthesia by this agent is significantly lower in clinical practice. Recovery characteristics of isoflurane is poorer than halothane. But, the advantage of isoflurane over halothane is that an equipotent concentration of isoflurane produces similar reduction of blood pressure, without reducing the heart rate and myocardial contractility like halothane. The

Table 25.12: Physical characteristics and physiological effects of volatile anaesthetic agents

	Ether	*Halothane*	*Sevoflurane*	*Isoflurane*	*Desflurane*	*N_2O*
Odour	Most pungent	Sweet	Minimum pungent	Markedly pungent	Markedly pungent	Nil
MAC	2	1.2	2.5	1.9	9.9	105
Blood gas partition coefficient	12	2.1	0.7	1.2	0.4	0.47
Myocardial depression	↑↑	↓↓	↑↓	↓	↓	↓
Vdilation	↑↑	↓	↓↓	↓↓	↓↓	↑
Respiratory depression	↑	↓	↓↓	↓↓	↓↓	Nil
Rate of metabolism (%)	4	20	2	0.2	0.02	Nil

reduction of arterial blood pressure during isoflurane anaesthesia is due to the decrease in peripheral vascular resistance, rather than myocardial depression (like halothane). This suggests that despite similar reduction in BP, isoflurane is associated with greater cardiovascular reserve than halothane, especially in neonates, infants and children where heart rate and myocardial contractility is more important to maintain CO.

Like halothane, the MAC value of isoflurane also varies with age. It is about 1.6% in neonates, 1.9% in infants (1 to 6 months) and declines gradually to approximately 1.2% in adults.

Sevoflurane

Like isoflurane, sevoflurane also belongs to the series of halogenated volatile ether anaesthetics agent, but it is halogenated solely by fluorine. The presence of only fluorine reduces the solubility of sevoflurane in the both fat and blood. Thus, this reduces the anaesthetic potency of sevoflurane, while increases the rate of uptake and elimination. So, as an anaesthetic agent, it has the property of causing very rapid induction and recovery, due to its very low blood-gas partition co-efficient (0.68) but is a less potent volatile anaesthetic agent. The eye lash reflex is lost within 60 to 90 seconds after beginning of administration of sevoflurane at 5-6%. The blood-gas partition co-efficent of desflurane is 0.42, which also suggests that induction of anaesthesia by desflurane should be more rapid than sevoflurane. But this not so true, because the desflurane is also very irritant to the upper airway, causing breath holding, cough, laryngeal spasm, etc. just like isoflurane which results in a delayed induction.

Sevoflurane's smell is least pungent (but according to some, halothane is least pungent) than all the other currently available volatile anaesthetic agents. So, higher concentrations of sevoflurane upto a maximum of about 8% can be given to the paediatric patients without cough, increase in secretion, breath holding, laryngeal spasm and other airway problems. There is little to be gained by adding N_2O with sevoflurane during induction, as the MAC sparing effect on sevoflurane is not as great as with other agents. The MAC value of sevoflurane also changes with age. In neonates it is 3.3%, in infants it is 2.5% and in adults it is 2%. The incidence of cardiac depression, bradycardia and arrhythmias are minimal during induction and maintenance of anaesthesia by sevoflurane than halothane. So, all these favourable points of sevoflurane makes it the anaesthetic agent of choice for induction and maintenance in paediatric patients. But only the higher cost of sevoflurane restrains its use and this economic consideration dictates that sevoflurane should mainly be used for induction, followed by other cheaper halogenated agents such as halothane, isoflurane, etc. for maintenance.

The other areas of concern with sevoflurane during anaesthesia, regarding its lesser safety are: higher rate of metabolism of sevoflurane in liver which is about 2% (isoflurane 0.2%) and its instability with sodalime. It is found that after 60 to 90 minutes of anaesthesia with sevoflurane, the peak concentration of fluoride ion in plasma rises from 1/3 to 2/3 of the proposed nephrotoxic level (50 mmol/litre). With sodalime sevoflurane also produces a compound A, which is nephrotoxic and is mainly found during the use of circle absorber system with lowgas-flow anaesthesia (0·5 to 1 litre/minute, in experimental animals). But, fortunately the formation of compound A in humans is much lower than in the experimental animals with the above mentioned flow and there is no reported cases of nephrotoxicity in humans. So, the use of sevoflurane with sodalime in low-flow circle system is still debatable, but not totaly condemned (above 2 litre/minute of fresh gas flow).

Desflurane

Desflurane is another halogenated volatile ether anaesthetic agent, where a single chlorine atom of isoflurane is replaced by fluorine. So, like isoflurane it has a markedly pungent odour and is unsuitable for induction of anaesthesia, due to high incidence of airway complications such as laryngospasm, cough, increased secreion, etc. Blood-gas partition coefficient of desflurane is lowest (0.4) among all the inhalational anaesthetic agents (N_2O − 0.47). Thus, the induction and recovery is fastest with desflurane when compared to that of other inhalational anaexthetic agents. The drug is stable in sodalime and the haemodynamic responses are similar to that of halothane. But, unlike halothane the metabolism of desflurane in liver is very minimum which is approximately 0.02% (halothane 20%) and so have no incidence of hepatotoxicity. This advantage clearly sets it apart from the other currently available potent volatile anaesthetics agent. The MAC value of desflurane also changes with age such as in neonates it is 9.2%, in infants it is 9.9% and in adults it is 6%. As desflurane is stable in sodalime and provides a rapid recovery, so it is also a suitable agent for maintenance of anaesthesia in paediatric patients, using close circuit with sodalime. But, its high cost bars its use which can be mitigated by the use of low-flow rates in a circle system.

The rate of emergence from anaestheisa is fastest, following desflurane and sevoflurane. But, both the agents are associated with an increased incidence of agitation or delirium after rapid emergence, particularly in young children. So, many anaesthesiologists switch over to either isoflurane or halothane for maintenance of anaesthesia, following an induction by desflurane or sevoflurane.

Nitrous oxide

N_2O is a very less potent (MAC 105%), non-irritant, non-inflammable, sweet smelling inhalational anaesthetic agent. Due to its low potency, it is used as an adjunct with other potent anaesthetic agents and is not used as a sole anaesthetic agent. It is

very stable with little biotransformation and produces rapid induction as well as recovery, due to its low blood-gas partition coefficient (0.47).

At the equipotent anaesthetic concentrations, it is half as potent as halothane in depressing the myocardium. So, in premature babies and neonates the N_2O should not be used. In such cases, air may be substituted as a carrier gas for O_2 and other inhalational agents. N_2O also should not be used in some paediatric surgeries such as bowel obstruction, diaphragmatic hernia, lobar emphysema, eustachian tube obstruction, etc. and the cause of which is given in relevant chapter.

Intravenous Inducing Agents

All the commonly used intravenous inducing agents, like thiopentone, propofol, benzodiazepine, ketamine, etc. can also be safely used in paediatric group of patients.

Thiopentone

It produces smooth induction of anaesthesia in one arm-brain circulation time and the termination of effect occurs through distribution and redistribution of it in the muscle, fat and different tissue compartments. Termination of effect of thiopentone does not occur through quick metabolism like propofol, but gradually accumulates in different body compartments with increasing doses. So, it cannot be used as a continuous infusion for maintenance of anaesthesia and should be used very cautiously in premature neonates and malnourished infants who have less muscle and low fat stores.

The dose of thiopentone varies with age. In neonates the dose is only 3.5 mg/Kg. But it increases rapidly to 6-7 mg/Kg in infants and then it again declines gradually throughout the childhood to an adult value of 4 to 5 mg/Kg. The increased requirement of thiopentone in infants and early childhood is due to the increased cardiac output which reduces the first-pass concentration of thiopentone arriving at the brain. The reduced requirement of thiopentone in neonates is explained by the decrease in plasma protein binding capacity of them. The induction doses of thiopentone also can be reduced by 50%, with the use of other different sedative premedications. The most important drawback of thiopentone in paediatric use is its cardiovascular and respiratory depression effect. The cardiovascular depression effect of thiopentone includes reduction of myocardial contractility and it brings down the arterial blood pressure by about 15-20%. So, it should be avoided in paediatric group of patients who are dehydrated, have significant amount of blood loss or have heart failure. The other side effects of thiopentone are hiccup, cough, laryngospasm, etc.

Propofol

It also produces a rapid and smooth induction of anaesthesia in paediatric age group of patients with low incidence of serious side effects. Chemically, it is an alkyl phenol compound and marketed as 1% emulsion in a white soyabean oil base with egg phosphatide and glycerol. Like thiopentone, it is highly lipophilic and protein-bound without any analgesic properties. The dose requirement of propofol for paediatric patients is higher than adults. This is because the volume of central compartment which is responsible for distribution and redistribution of propofol is 50% larger than adult and the clearance rate of it is 25% higher than thiopentone.

The beauty of propofol in paediatric anaesthesia lies in its use as both for induction by bolus doses and maintenance by continuous infusion. Propofol is now licensed for use as an induction agent in children over 1 month, but not for use as an infusion below 3 years. Till now, the TCI (target control infusion) pump for propofol is not configured for paediatric use like that of adult use. The children upto 8 years may require almost double the adult dosage (3 to 5 mg/Kg) of propofol. The dose of propofol for continuous infusion is 100 to 300 µg/Kg/minute. Pain may occur during bolus injection of propofol for induction. But, this can be minimised by using a larger vein, injecting the solution slowly and administering IV lignocaine in the dose of 0.2 mg/Kg before the administration of propofol. There is reduction in heart rate with propofol, particularly below 2 years of age and this is due to the attenuation of baroreceptor reflex. There is also a larger fall in blood pressure, compared to equipotent doses of thiopentone. Respiratory depression and the incidence of apnoea is greater with propofol than thiopentone, although laryngeal mask insertion is easier due to more depression of the laryngeal reflexes by propofol.

Propofol is not contraindicated in epilepsy, though involuntary movements may be seen during induction with propofol. They are usually caused due to the inadequate induction dose and early stimulation. Because of its prompt wake-up characteristic, antiemetic effect, usability as continuous infusion and low incidence of serious side effects, propofol is gradually displacing the short acting barbiturates, as the induction agent of choice for paediatric out patients. It is particularly useful for maintenance of sedation during radiotherapy, or in children undergoing a radiological diagnostic procedures. Although not common in paediatric anaesthetic practice, still the technique of TIVA using propofol is very useful in children who are prone to malignant hyperthermia or children with history of porphyria. Strict aseptic technique is recommended during handling of propofol, as contamination of its intralipid and preservative free preparation produces sepsis.

Propofol is not recommended for prolonged maintenance of sedation of critically-ill paediatric patients in the NICU (neonatal intensive care unit). Because, this drug has been associated with higher rate of mortality in NICU, compared to other agents and a controversial 'Propofol

Infusion Syndrome' which is responsible for there NICV deaths has been described. The essential features of this syndrome are metabolic acidosis, haemodynamic instability, hepatomegaly, rhabdomylosis, multiorgan failure, etc. Although seen primarily in the critically ill children, but this rare syndrome has also been reported in adults and in patients undergoing long-term propofol infusion (> 48 hours) for sedation at high doses (> 5 mg/Kg/hour).

Ketamine

It is also very helpful as an inducing and an analgesic agent for paediatric anaesthesia. Intravenous administration of ketamine in the doses as low as 1 to 2 mg/Kg produces adequate analgesia and sedation. The lack of cardiovascular depression effect of ketamine allows it to be used for induction of anaesthesia in very sick children. So, it is widely used as a sole anaesthetic agent in many developing countries. The dose of ketamine should be reduced in neonates, and this is because of the reduced clearance and prolonged metabolism of it in them. Emergence phenomenon from ketamine anaesthesia are less common in children, especially when it is used in combination with midazolam. But, the incidence of PONV and salivation is higher with ketamine than other inducing agents. Increased production of both bronchial and salivary secretion by ketamine is a major side effect, and usually requires prior administration of an antisialogogue.

During ketamine anaesthesia, even though the upper airway reflexes are relatively well preserved, but still aspiration of gastric contents may occur and so it should not be used as a sole anaesthetic agent for infants with full stomach or with hiatus hernia. Emergence phenomenon from ketamine anaesthesia is accompanied by hallucination and unpleasant dreams, but this is not so well marked in paediatric patients, as children are almost always dreaming. The current available formulation of ketamine in the market is a racemic mixture of the S (+) and R (−) enantiomers. Though, it is possible to separate the two enantiomers, but there is no such commercially viable technology which can separate them for their iosolated clinical use. The aim to separate these two isomers of ketamine and to make it commercially available is : the S (+) enantiomer of ketamine is twice potent, recovery is quicker and the incidence of emergence reaction is also low in comparison to the R (−) enantiomer of it.

The contraindications for the use of ketamine in paediatric patients include : presence of active URTI, increased ICP, open globe injury, seizure disorders, etc.

Narcotics

Due to the immaturity of blood-brain barrier in neonates and infants, the high lipophilicity and lower clearance of newer narcotics and its congeners have made the neonates and infants below 6 months of age very sensitive to this group of drugs. So, narcotics should be used with caution in premature neonates, term infants and infants below 6 months who are not in the intensive care unit and whose ventilation need not be controlled postoperatively. Infants older than 6 months probably have a response to narcotics similar to that of adults.

Morphine

It is least lipophilic than meperidine and all other members of this group of drugs. So, the entry of morphies in CNS is mainly controlled by the maturity of the blood-brain barrier. Hence, in an immature blood-brain barrier morphine enters the CNS most readily than all other narcotics. In contrast, meperidine is more lipophilic than morphine and therefore is able to cross the blood-brain barrier more readily, but only after its maturation because its penetration in CNS does not depend on the maturity of blood-brain barrier, but depends on the lipophilicity of this drug. Thus, the effects of an immature blood-brain barrier would be much less significant for meperidine than for morphine, but lipophilicity would be much more significant for meperidine than morphine. When the question of entry of these two drugs in CNS will arise. On the other hand, in case of morphine this is reverse. Meperidine may not be appropriate for long term administration in paediatric group of patients. This is due to the accumulation of its active and toxic metabolites such as normeperidine.

Morphine and other narcotics (except remifentanil) are metabolised mainly in liver and their actions are terminated by conjugation of their metabolites with glucuronide. But other than metabolism in liver which is responsible for the termination and short duration of action, the very high lipid solubility of some other newer narcotics have a shorter duration of action and it is due to their rapid distribution and redistribution in the tissues, like thiopentone and propofol. So, deficiency of the microsomal enzymes responsible for glucuronide conjugation may be responsible for prolongation of the clinical effects of these oldernarcotics like morphine and others whose termination of actions depend only on the conjugation of their metabolites with glucoronide in neonates and infants. The newborns and the infants have a lower clearance rate of morphine. Therefore, a standard dose will result in higher plasma values due to longer elimination half life. In spite of all these disadvantages, still morphine remains the most commonly used opioid for the management of severe pain in children and is the gold standard with which other potent analgesics are compared. In neonates and infants who are below 6 months old and undergoing relatively brief procedures (near about 1 hour), a single dose of 25 µg/Kg of morphine usually provides adequate intraoperative and postoperative analgesia. After a more prolonged and complex surgery, the postoperative analgesia is supplemented with a continuous infusion of morphine of 5 to 10 µg/Kg/hour. For children and infants above 6 months, the adult

doses of morphine are recommended. For continuous infusion or patient-controlled analgesia, due to its long half life morphine in a loading dose of 100 µg/Kg/hour is used first (if not used intraoperatively, which is usually done), followed by a maintenance dose of 25 µg/Kg/hour.

Fentanyl

It is a synthetic, highly lipid-soluble pure opioid agonist, and is 100 times more potent than morphine. Because of its high lipid solubility and a large volume of distribution, a single dose of fentanyl has a more rapid onset and a shorter duration of action than morphine. The termination of effects of a low bolus dose of fentanyl is due to redistribution in peripheral tissues, whereas the termination of effects of a high or continuous dose of fentanyl depends on its elimination through the liver and kidney when the redistribution site is saturated. So, if fentanyl is used as an infusion or in multiple doses, then progressive saturation of the peripheral tissues by it lead to a prolonged duration of action of it as clearance of it by metabolic process in liver is slow like morphine.

Due to the rapid onset and a brief duration of action, fentanyl now is the most commonly used narcotic in paediatric anaesthesia in short bolus doses, but not by infusion. As fentanyl is more lipophilic than morphine and meperidine, so its CNS action does not depend on the maturity of blood-brain barrier. The maturity of blood-brain barrier dictates the entry of water soluble (hydrophilic) narcotics only, such as morphine. Immature blood-brain barrier of neonates and infants permits only the entry of hydrophilic morphine, but not lypophilic fentanyl. Thus, this explains fentany's lesser sensitivity in premature infants and neonates than the older ones. The volume of distribution of fentanyl in infants is similar to that of adults, but the plasma clearance and elimination half life is greater. This is due to the high hepatic blood flow in infants than adults. The dose of fentanyl producing an anaesthetic state, also produces a stable cardiovascular response. Fentanyl can be used in the dose of 2 to 10 µg/Kg with other anaesthetic agent mainly volatile agent in a surgery where postoperative ventilation is not needed. Usually, it is administered in the dose of 1 to 2 µg/Kg at the start of anaesthesia which is followed by further bolus doses as clinically indicated, or by a continuous infusion in the dose of 1 µg/Kg/hour. Higher doses of fentanyl, such as 30 µg/Kg, can be used only in a surgery (e.g., cardiac surgery). where postoperative ventilation is mandatory or to produce a full state of anaesthesia with stable haemodynamic conditions without other anaesthetic agent mainly volatile agent. Since, the cardiac output of neonates is determined by the heart rate, fentanyl-induced bradycardia may require concomitant administration of vagolytic drugs, such as : atropine or pancuronium. Fentanyl is sometimes associated with chest wall rigidity, impairing adequate ventilation.

Remifentanil

It is the newest of all the synthetic narcotics. It is an ultra-short acting drug, and its methyl ester linkage makes the drug susceptible to metabolism by non-specific plasma and tissue esterases. The pharmacokinetic profile of remifentanil in children between 2 to12 years of age is similar to that of an adult. It has rapid distribution phases, small volume of distribution, and an elimination half life of only 2 to10 minutes. The dose of remifentanil is 1 µg/Kg, followed by infusion of 0·25 µg/Kg/minute.

Still now there is very few data regarding the use of remifentanil in neonates and infants. At present, it is not licensed for use in children under the age of 2 years (Table 25.13).

Muscle Relaxants

The use of neuromuscular blocking drugs has a definite place in paediatric anaesthesia. But the responses of these group of drugs differ markedly from those in adults. All the muscle relaxants generally have a shorter onset of action (upto 50%) in paediatric patients. This is because of the shorter circulation time than adults and it is due to increased cardiac output in proportion to body surface area in neonates and infants. In general, due to this increased cardiac output in proportion to body surface area the neonates and infants are also resistant to depolarising drugs, but sensitive to non-depolarising agents.

Succinylcholine

Because of its high water solubility, succinylcholine is widely and rapidly distributed into the extracellular fluid volume of the neonates and infants containing more water which is greater than adults. This accounts for decreased sensitivity of succinylcholine in neonates and infants than the older ones and needs higher doses in the former. So, the dose of succinylcholine required for muscle relaxation and intubation in neonates and infants is approximately twice than that of the children and adults. Thus, the dose of succinylcholine for neonates and infants is 2 mg/Kg IV and for adults it is 1 mg/Kg IV. This dose of succinylcholine will produce 95% neuromuscular block within 30 seconds which is followed by 90% recovery within 5 to 10 minutes. Children are more susceptible than adults to cardiac arhythmias, hyperkalaemia, rhabdomylosis, myoglobinaemia, masseter spasm and malignant hyperthermia after administration of succinylcholine. Succinylcholine frequently causes cardiac arrhythmia in paediatric patients, mainly when used with halothane. Sometimes, severe bradycardia and sinus arrest may follow the first dose

Table 25.13: The advantages of remifentanil

1. It is metabolised by non-specific esterases in plasma and tissues.
2. The metabolites of remifentanil are inactive.
3. Half-life of this drug is short and is independent of the duration of infusion.
4. Lack of cumulative effect.

of succinylcholine. But, it is more common after repeated bolus doses. So, atropine (20 µg/Kg) should be given IV prior to the first dose of succinylcholine in children. If a child unexpectedly experiences cardiac arrest, following the administration of succinylcholine, then immediate treatment for hyperkalaemia should be instituted. However, prolonged and heroic cardiopulmonary resuscitative efforts may also be required.

There is always a tendency to develop phase II block in neonates and infants with succinylcholine. It is also one of the most potent triggering agent for development of malignant hyperthermia. The incidence of malignant hyperthermia increases, if succinylcholine is preceded by halothane induction. Fatal cardiac arrest may also occur in a small number of patients following administration of succinylcholine. It is presumed that, these patients may have unsuspected muscular dystrophies and the drug causes massive breakdown of muscle cells causing hyperkalaemia and cardiac arrest. It is also not possible to predict this group of patients who are prone to exhibit this response. So, all these complications make the routine use of succinylcholine in paediatric patients controversy. On the other hand, succinylcholine is the only commercially available short acting muscle relaxant that provides a dependable and a very rapid onset of action. So, the present status of succinylcholine in paediatric anaesthesia is that it should only be reserved for patients with full stomach, necessitating rapid sequence intubation in emergency cases or in cases of difficult intubation or for the treatment of intractable laryngospasm causing severe hypoxia and impending cardiac arrest. For the later, intramuscular succinylcholine in the dose of 4 to 6 mg/Kg is also used if IV line is not already secured. In this situation, atropine in the dose of 20/Kg IM should be administered at the same time to prevent bradycardia. Some anaesthesiologists also advocate intralingual administration of succinylcholine (2 mg/Kg in the midline), as an alternate emergency route if IV line is not available.

In contrast to depolarizing muscle relaxants (e.g. succinylcholine), the nondepolarizing muscle relaxants show higher sensitivity in neonates and infants than children and adults. So, full neuromuscular blockade occurs at a lower blood concentration and this is true for all nondepolarizing muscle relaxants. The probable explanation of this fact is immaturity of the neuromuscular junction in neonates and infants, or the difference in the bioavailability of the drug or the lesser binding of nondepolarizing muscle relaxant with the plasma proteins whose concentration is less in neonates and infants than adults. On the other hand, the clinical significance of this sensitivity may not be great, owing to the larger volume of distribution of these nondepolarising neuromuscular blocking drugs, due to the large extracellular fluid volume in neonates and infants than adults. The immaturity of renal and hepatic function in neonates and infants also cause slower excretion of non-depolarizing drugs, and hence the prolongation of the blocking effect of these agents. Only the action of non-depolarizing drugs that are metabolized in the plasma (e.g atracurium, mivacurium) doesnot vary greatly with age. So, the specific choice of a non depolarizing muscle relaxants in neonates and infants depends on the onset of action, duration of action required and the desired or undesired side effects of the relaxant. If a prolonged action and tachycardia is desired, then pancuronium is best choice, otherwise atracurium is still the chosen one for the shorter procedures. Hoffmann elimination and ester hydrolysis of atracurium make it particularly useful in newborns and infants.

Atracurium

After a standard dose of 0·5 mg/Kg through IV, atracurium produces 95% depression of the twitch-response of voluntary muscles and intubating condition occurs within 0.9 minutes in neonates and infants. But, recovery to 10% of the control twitch height after administration of atracurium occurs with in 20 minutes. The volume of distribution of atracurium in neonates and infants is 0.18 litre/Kg in contrast to adults which is 0.14 litre/Kg. The plasma clearance of atracurium has also been found to be greater in neonates and infants (9 ml/Kg/minute) than that of the adults (5 ml/Kg/minute). The adverse effects associated with atracurium is related mainly to the release of histamine. These are probably hypotension, tachycardia and or bronchospasm. The cardiovascular changes caused by atracurium are dose related, and usually occur at doses greater than 2 ED_{95} value.

Vecuronium

Vecuronium is also chosen in paediatric patients for surgical procedures which are of longer duration and also where tachycardia is not desired. This is because vecuronium induced neuromuscular block is characterised by the lack of histamine release and marked cardiovascular stability in all the age groups of patient. It is a very long acting nondepolarising muscle relaxanat in neonates and infants than adults. Vecuronium in a standard intubating dose of 100 µg/Kg maintains over 90% neuromuscular blockade for almost an hour in neonates and infants, compared to just 30 to 40 minutes in adults.

Mivacurium

Mivacurium is another very short acting nondepolarizing muscle relaxant which offers the advantage of producing satisfactory surgical conditions for brief surgical procedures like succinylcholine. But vary rapid intubating conditions as produced by succinylcholine is not provided by it. Mivacurium has the shortest duration of action among all the currently available non-depolarising drugs and its action is terminated like succinylcholine by plasma pseudocholinesterase. So, like succinylcholine, very occasionally a patient may be cholinesterase deficient,

when its duration of action may be prolonged. In a dose of 0.2 mg/Kg IV, mivacurium provides excellent relaxation within 2 minutes. Then, 20% recovery of the twitch-response occurs after 8 to 9 minutes and spontaneous 95% recovery of twitch response occurs within 20 minutes. Mivacurium is also an ideal nondepolarising muscle relaxant which can be administered by constant infusion, since there does not appear to be any accumulation of drug. As mivacurium is structurally similar to atracurium, so it has significant histamine releasing properties, which may be evident even at therapeutic doses. So, the standard dose of mivacurium which is 0.2 mg/Kg should not be exceeded.

Rocuronium

Rocuronium has the most rapid onset of action among all the currently available nondepolarising muscle relaxants. A IV dose of rocuronium in 0.6 mg/Kg produces 90% depression of the twitch-response and an intubating condition within 30 seconds like succinylcholine, but without significant changes in blood pressure and heart rate. So, it may therefore be used as an alternative to succinylcholine, when rapid tracheal intubation is desired and succinylcholine is considered as contraindicated. Whereas, the duration of clinical effects of rocuronium following a standard intubating dose (0.6 mg/Kg) is longer and is near about 40 minutes.

Therefore, atracurium, rocuronium and vecuronium, have a short, intermediate and long duration of action, making them the most commonly used muscle relaxants in paediatric anaesthesia.

Rapacuronium

Rapacuronium is a currently used new amino-steroid non depolarising muscle relaxant agent, is being evaluated in paediatric practice. Data suggest that its onset of action is similar to that of succinylcholine and its duration of action is comparable to that of mivacurium.

The general rule for the use of non depolarising muscle relaxants in neonates and infants is the careful titration of dose due to extreme variability of response. So, the intitial dose of nondepolarising muscle relaxants should be one-third to one-half of the calculated total dose for the paediatric patient. The antagonism of neuromuscular blockade in all the neonates and small infants is mandatory, even if recovery is complete clinically. This is because any compensatory increase in the work of breathing due to residual neuromuscular block may cause fatigue and respiratory failure. The useful signs of reversal of neuromuscular blockade in neonates and infants are the ability to lift the legs and arms and recovery of the train-of-four response to peripheral nerve stimulation (Table 25.14).

PAEDIATRIC ANAESTHETIC RISK FACTORS

The paediatric anaesthetic risk is best assessed from the database of a register, made by an investigating group. This register was made on reports, based on approximately one million paediatric anaesthetic cases, administered since 1994. From this register, all the cardiac arrests and deaths were investigated and analysed to find out the possible causes during anaesthesia with these incidents. It was found that approximately 300 cardiac arrests had occured, and among them 150 arrests were directly related to anaesthesia. Thus, the incidence of risk of cardiac arrest in paediatric anaesthesia is 1·5 in 10,000 cases and among these the mortality rate is 30%. Another 6% patients suffered from permanent injury. But, the majority 64% patients either did not suffer from any injury or only temporary injury. It is also important to note that age is responsible for 50% of all the anaesthesia related cardiac arrests. Among them less than one month age babies, i.e. neonates have the highest risk. About 40% babies with a physical status of ASA 3-5, suffered anaesthesia-related cardiac arrest. So like adults, the major predictors of mortality in cases of paediatric anaesthesia are: age, ASA physical status, and emergency surgery.

Among all the cardiac arrests, 80% occured during the induction of anaesthesia and is most frequently preceded by: bradycardia, hypotension, and low SPO_2 levels. The most common cause of cardiac arrest during induction is cardiovascular depression due to medications. Among the medicines, halothane alone or in combination with other drugs is believed to be responsible in 60% of cases. In another 10% cases, inadvertant intravascular injection of the local anaesthetic agent during

Table 25.14: Guidelines of doses of muscle relaxants and their antagonists in paediatric patients

Agents	*Dose for tracheal intubation ($2 \times ED_{95}$) (mg/Kg)*	*Maintenance dose (mg/Kg)*	
		N_2O/O_2	*Halothane*
Succinylcholine	2	–	–
Atracurium	0.5-0.6	0.3	0.2
Rocuronium	0.6-0.7	0.4	0.3
Pancuronium	0.1-0.15	0.08	0.06
Vecuronium	0.1-0.15	0.08	0.06
Cisatracurium	0.1-0.15	0.06	0.03
Mivacurium	0.2-0.25	0.1	0.1
Pipercurium	0.08-0.12	0.08	0.08
	Reversal agents		
Neostigmine	20 - 60 µg/Kg + Atropine (10 - 20 µg/Kg)		
Edrophonium	0.3 mg/Kg + Atropine (10 - 20 µg/Kg)		

caudal injection (still following a negative aspiration test) is blamed. In about 50% cases of cardiac arrest in paediatric anaesthesia, patients have cogenital heart disease. The respiratory causes for cardiac arrest is most often due to laryngospasm, airway obstruction and difficult intubation (in a decreasing order). In most cases, laryngospasm occurs during induction.

SOME IMPORTANT CONSIDERATIONS IN PAEDIATRIC ANAESTHESIA

Preoperative Assessment

A preoperative visit to an anaesthetic clinic and preoperative preparation for surgery of children in all ages by the anaesthetist, is very crucial. Prior to surgery, the baby's condition should be properly evaluated to determine (i) any abnormality in the CVS, (ii) the degree of respiratory distress, if any, (iii) airway problems in respect to intubation, (iv) metabolic disturbances, (v) temperature variations, (vi) the extent of planned surgical procedure matching with patient's condition, etc. Among these a detailed history and physical examination of the patient, with special emphasis on the assessment of cardiovascular and respiratory functions is most important. The neonatal history should also include problems during delivery, the severity of prematurity, the history of admission in intensive neonatal care unit after birth, etc. The infants born prematurely, especially those with history of apnoeic periods are more likely to develop apnoea following anaesthesia. So, they should not be accepted for day case procedures, until they are at least 60 weeks of gestational age. The respiratory history includes asthma, frequent colds, obstructive sleep apnoea, etc.

The cardiovascular assessment for paediatric group of patients mainly includes cyanosis, heart murmur, and whether dyspnoea is present during exercise or not. The majority of pathological murmurs are diagnosed neonatally and these children are already under the care of a cardiologist. The previously unreported murmurs were commonly heard at the age of 2 to 4 years and the majority of them were functional. Mild murmurs in a child with normal heart sounds and normal oxygen saturation, and without any limitation in exercise tolerance can be assumed to be innocent, if they are not pansystolic. Most asymptomatic patients with murmurs do not have significant cardiac pathology. Innocent murmurs may occur in more than 30% of normal children. They are usually soft, short systolic ejection murmurs and are best heard along the left lower or left upper sternal borders, without any significant radiation. The innocent murmurs at the left upper sternal border are due to the flow of blood across the pulmonary valve. Whereas, those at the lower left sternal border are due to the flow of blood from the left ventricle in to the aorta (Still's vibratory murmur). In case of any doubt, surgery should be deferred until a formal assessment has been made by a paediatric cardiologist. The paediatrician and possibly a cardiologist should carefully evaluate the patients with a newly diagnosed murmur, particularly in infancy. An echocardiogram or a colour Doppler should be obtained if (i) the patient is symptomatic (e.g. poor feeding, failure to thrive, or easy fatiguability), (ii) the murmur is a harsh, loud, holosystolic-diastolic and radiates widely or (iii) if the pulses are either bounding or markedly diminished.

The previous family history regarding anaesthesia is also important which includes malignant hyperpyrexia and prolonged apnoea caused by suxamethonium. The problems during previous anaesthesia like PONV, poor pain relief or difficult venous access are also important. The laboratory tests required for surgery depend on the severity of the existing illnesses and also the preexisting diseases (outlined from history and full clinical examination). For example, if a healthy neonate or infant is scheduled for just a minor elective surgery, such as repair of an inguinal hernia, then only a routine blood count with Hb and serum glucose estimation is needed. Some paediatric centres require no preoperative laboratory tests in healthy children undergoing minor procedures. However, obviously, this puts more responsibility on the anaesthetist, surgeon and paediatrician to correctly identify the patients who require preoperative testing or not for anaesthesia and surgical procedures. On the other hand, if the patient presents with some chronic illness or any congenital defect, then extensive investigations including complete blood count, blood biochemistry, electrolytes, coagulation profiles, etc, are required, according to the defect and surgery planned.

Mere failure to urinate within 24 hours of birth which is a very common event for a neonate usually should not direct any renal function testing. However, in the presence of other concurrent anomalies such as presence of some congenital renal anomalies then this absence of urine output should be considered as serious. In such circumstances, extensive investigations should be undertaken including serum potassium, blood urea nitrogen, creatinine, ultrasound, etc.

If children suffer from upper and lower respiratory tract infection, surgery should be delayed. The standard recommendation for this delay is 4 to 6 weeks after an episode of acute RTI, however bearing in mind that some children have frequent RTI (5 to 10 times per year). In such circumstances, each case should be dealt on the basis of its own merits, for example, whether the child has nasal discharge, inflamed tonsil, infected eardrums, fever, etc. In rare cases, the viraemic phase of illness may be associated with myocarditis. So, children who have active viral illness or children who have recently been immunized using live vaccines should not have elective anaesthesia and surgery, as these children may develop a viral myocarditis. In such circumstances,

surgery should be avoided for a week, especially following DTP and Haemophilus Influenzae Vaccination and for 2 weeks after MMR. A diagnosis of bronchiolitis and measles warrants a delay of at least 6 weeks.

However, a child with a mild cold possesses maximum difficulty in taking decisions by an anaesthetist. The history in such cases is crucial. Because it is important to decide whether the child is at the beginning or at the end of the process of URTI. A child who is apyrexial, has no chest signs and constitutionally well is probably at the end of an attack of URTI and fit for surgery too, even with a running nose. Actually, the decision to anaesthetise children with RTI remains controversial and depends on the presence of other coexisting diseases, the severity of symptoms of RTI and the urgency of surgery. If the surgery cannot be deferred, then much consideration should be given to an anticholinergic agent and branchodilator during premedication, mask ventilation, humidification of inspired gases and a longer than usual stay in the recovery room. Anaesthesia in the presence of RTI is associated with higher incidence of laryngospasm, bronchospasm, postoperative croup, pneumonia and hypoxaemia. All these are due to increased incidence of secretions and airway obstructions in the presence of RTI. These risks are increased five-folds using an LMA, and by a factor of 10 if the child is intubated. But, still some anaesthetists prefer to use ET tube considering that it is wise and easy to control the airway using an endotracheal tube which will minimise the risk of cough or laryngospasm during anaesthesia. However, generally, for minor procedures where muscle relaxants are not needed, then LMA is the better choice according to my view.

During preoperative assessment of the paediatric group of patients the anaesthetist should also keep in mind the possible intubation difficulties due to recent trauma, inflammation, tumour, etc like adult patients which are discussed in details in respective chapter. The other possible conditions and syndromes which are common to paediatric group of patients and responsible for difficult intubation should also be looked for. Patients also may present with respiratory distress which can only be alleviated by surgery and for which this surgery is proposed. These include choanal atresia, laryngeal cysts or webs, congenital diaphragmatic hernia, oesophageal atresia with or without tracheo-oesophageal fistula, pulmonary cysts producing lobar emphysema or compression of lung tissues, etc. On the other hand, patients may present with respiratory distress due to concomitant causes which are not related to the proposed surgery. But, whatever may be, the degree of this respiratory distress should always be evaluated clinically by observing the colour of mucuous membrane, the degree of intercostal and sternal recession and auscultation of the lung fields before starting anaesthesia. Radiological examination of the chest should always be undertaken in such conditions and the blood-gas status is estimated, (if needed) by using blood from an arterial puncture preoperatively. Pneumothorax, which is often present in severe cases of diaphragmatic hernia on the contralateral side (or in the cases of severe respiratory distress) should always be drained before anaesthesia by inserting a cannula into the pleural space through second intercostal space and connected to an underwater drain. Metabolic disturbances due to hypovolaemia, hypoglycaemia, acidosis, etc, should also be corrected preoperatively by the intravenous infusion of appropriate solutions.

All children should be accurately weighed after admission, because body weight is the simplest and the most reliable guide to drug doses. Haemoglobin estimation should be performed routinely. A perioperative Hb of less than 10 gm/dl does not necessarily entail cancelation of surgery, if the child is otherwise fit and the surgery is not much blood-losing. All children above 3 months of age, coming from Africa or Mediterranean countries, are likely to be the carriers of sickle-cell disease. So, they should be screened by sickle cell test and then haemoglobin electrophoresis should be undertaken, if the screening test is positive.

A nasogastric tube should always be passed in all the sick paediatric patients, because gastric distension occurs readily which may jeopardise normal respiratory function and cause regurgitation with subsequent pulmonary aspiration leading to acidosis and pneumonia (Table 25.15).

Fasting

The purpose of fasting of any patient before anaesthesia and surgery is to decrease the risk of aspiration pneumonitis from regurgitation of gastric acidic juice and asphyxia from the presence of solid food in vomitus. Aspiration pneumonitis occurs if the pH of gastric fluid is < 2.4 and the volume aspirated is greater than

Table 25.15: Some common congenital syndromes associated with difficult intubation

Syndrome	*Clinical features*
Down	Small mouth, large tongue, small subglottic area, congenital heart diseases.
Pierre-Robinson	Small mouth, retrognathia, large tongue, cleft palate, subglottic stenosis.
Turner	Short and webbed neck, narrow and high arched palate, small mandible, epicanthic fold.
Klippel-Feil	Cervical vertebral fusion, less number of cervical vertebra, rigid and short neck.
Goldenhar	Cervical spine abnormality, mandibular hypoplasia.
Treacher-Collins	Hypoplasia of the malar bone, micrognathia, coloboma, preauricular ear tags, cleft palate, malocclusion of the teeth, deformity of the middle auricles causing deafness.

0.8 ml/Kg. Neonates scheduled for surgery within 24 hours after birth are usually not fed by mouth and so they do not need any fasting protocol. But, the neonates or infants who are presented for surgery after feeding, need a fasting protocol which is extensively reviewed and different from the previous protocol. Recently, a number of studies have shown that there is no difference between the residual gastric volume and pH in children who are allowed to fast for 2 to 3 hours prior to induction of anaesthesia, and those who are allowed to fast overnight or a standard fasting for 6 hours. It is also demonstrated that fasting for more than 2 hours after oral, clear fluid ingestion does not decrease the risk of pneumonitis, if aspiration occurs. Again, the half-life of water in the stomach is only about 12 minutes which implies that 95% of ingested water leaves the stomach within 1 hour. The half-life for breast milk is about 25 minutes and that for formulated milk is 51 minutes. So, the breast milk leaves the stomach more rapidly than formulated milk. Hence, a moderate approach of allowing the children to drink clear fluid (water, apple juice, etc.) 3 hours before induction of anaesthesia has several advantages.

The advantages of allowing the children to drink clear fluid three hours before induction of anaesthesia are :

i. From psychological point of view, this approach is more human and is also more satisfactory to both the parents and children, without increasing the risk of pulmonary aspiration of gastric contents and pneumonitis.
ii. As paediatric patients have higher metabolic rate and larger body surface area / weight ratio than adults, therefore there are more chances of dehydration and metabolic acidosis in prolonged fasting. But, 2 to 3 hours fasting decreases the chances of dehydration, hypoglycaemia and acidosis.
iii. There is less chance of hypovolaemia during induction of anaesthesia.

Table 25.16: Pre-operative fasting guidelines for paediatric patients (Fasting time in hours)

Age (months)	*Clear fluid*	*Breast milk*	*Cow / formulated milk*	*Solid*
< 3	2	4	4	6
3-6	2	4	4	6
6-36	3	6	6	6
> 36	3	6	6	8

A clear fluid is defined as a fluid through which a newspaper can be read.

iv. The incidence of aspiration is very low and is reported to be approximately 1:1000 in paediatric patients. So, prolonged fasting does not necessarily decrease this risk.

However, these recommendations are only for healthy neonates, infants and children, without the risk factors of decreased gastric emptying or aspiration.

The formulated milk should be considered as solid food. So, for any form of milk other than breast the standard fasting of 6 hours or more is advised. But, there is also some evidence that infants less than 3 months may safely be given infant formula feed or cow's milk upto 4 hours, preoperatively. Infants who are breast-fed may have their last feed 4 hours prior to the anaesthetic induction. In emergency settings, e.g in a child who has sustained trauma shortly after having food, it is probably best (if possible) to wait for 6 hours before induction of anaesthesia. Clearly in this situation risk-benefit judgement has to be made, especially if the surgery is a dire emergency (Table 25.16).

Premedication

The aim of premedication in paediatric anaesthesia is to produce a calm and cooperative child before induction of anaesthesia. Premedication is also used to reduce the stress of anaesthesia and surgery and also to reduce the risk of postoperative nasusa/vomiting and behavioural disturbances. Psychological preparation is an important aspect of preoperative care, especially for younger children. So, preoperative counselling is the best form of premedication. The anaesthesiologist should avoid wearing a white coat and will explain in great details to the family and the child, how anaesthesia is administered to children and what will be done to ensure the utmost safety. The more the information the parents and the child have, the more easily they can be dealt with the stress of surgery and hospitalization. Presurgical programs, such as: videotapes, literature, booklets are also very helpful and make easy the preoperative counselling and physiological preparation. After admission in the hospital, but before anaesthesia and surgery every effort should be made to help the child to adjust the new environment by friendly interior design, availability of toys, collection of photographs, etc.

But, unfortunately, outpatients and morning-of-admission surgery, together with a busy operating room schedule often make it difficult for an anaesthesiologist to have enough time for this preoperative counselling and psychological preparation. For this reason, premedication in the form of medicine can be extremely helpful.

Sometimes, sedative premedication is required, especially in children who in spite of good preoperative counselling remains apprehensive. They include the excessively upset child, children with previous unpleasant experiences of anesthesia and surgery, and certain children with developmental delays such as with cerebral palsy, Down syndrome, etc. The preschool children are mostly at risk. They are more vulnerable to separation anxiety in a strange enviornment, but without the ability to reason himself. Older children or adolescents may request premedication. Sometimes, even when the anaesthesia and surgery are uneventful, still there may be a disturbingly high incidence of postoperative psychological problems which include: nightmares, sleeping disturbances, bed-wetting, eating disorders

and behavioural changes etc. The use of local anaesthetic cream such as EMLA, Ametop, or tetracaine gel, etc. has some advantages and reduces the necessity of sedative premedications for establishment of an IV cannula. The availability of these above mentioned topical local anaesthetic creams reduces the pain of venipuncture and greatly facilitates the intravenous induction. Emla cream is a eutectic mixture of 5% lignocaine and 5% prilocaine in a 1:1 ratio. It should be applied at least 40 to 50 minutes before any needle prick and can produce vasoconstriction. Emla cream should be avoided in children below 1 year and this is because of the risk of methaemoglobinaemia from absorbed prilocaine, due to the reduced levels of methaemoglobin-reductase in infants. Ametop is a 4% gel formulation of amethocaine. It is licensed to be used above the age of 4 weeks and has the vasodilating property. It has a shorter onset of action which is about 30 minutes and a prolonged duration of action which is about 4 hours. But, it has a higher incidence of allergic reactions.

Sedative premedication should not be used at the expense of respiratory depression. Sedative premedication is contraindicated (not absolute) in patients with respiratory insufficiency or airways obstruction. In some surgeries like cleft palate, neurosurgery, tonsillectomy, etc. sedative premedication are usually not used, because it delays the recovery of laryngeal or other reflexes which is not at all desirable for these type of surgeries for the paediatric group of patients. But this rule is not mandatory. However, much less sedation is required if the child has been carefully prepared by preanaesthetic counselling.

Sedative premedication is not used in neonates and infants usually below 6 months of age, as separation anxiety is not a concern in this age group and this group of patient is more sensitive to the respiratory and cardiovascular depressant effects of the sedative agents. But, this protocol is not followed by some group of anaesthesiologists, because the time interval between the last feed and the scheduled timing for surgery cannot be controlled properly in a busy hospital. So, the children usually cry and disturb their parents. Hence, to reduce the anxiety of parents some anaesthetists break the protocol and premedication is given to make the baby sleep.

Atropine or glycopyrrolate is sometimes used as an antisialagogue during premedication, because increased secretion in narrow paediatric airways may cause airway obstruction and respiratory distress in the paediatric group of patients. Though the vagal tone is low in neonates, but in some centres atropine is given IV routinely during induction of anaesthesia, particularly if suxamethonium and halothane is used. But, atropine is also omitted in some centres because of low vagal tone, especially in the newborns and also because of the danger of increasing the viscosity of the bronchial secretions, particularly in babies with dehydration or mucoviscidosis which may lead to the plugging of the bronchioles or even the main bronchi with inspissated mucus. They also do not use atropine routinely, because modern anaesthetic agents do not require the antisialogogue (anticholinergic) agent due to their minimal irritating and secreting effects. The absorption of orally administered atropine (40 µg/Kg) is variable. So to ensure efficacy atropine (20 µg/Kg) or glycopyrrolate (10 µg/Kg) is administered intramuscularly, 30 minutes before OT. Many anaesthesiologists prefer atropine IV at or shortly after induction. If the baby is pyrexial and toxic, then atropine should be used in small doses or may even be omitted, balancing between the risk of febrile convulsions and necessity.

Almost all the sedatives are effective as premedication. But, the choice depends on the individual anaesthetist and the protocol of the institution. The need for sedative premedication must be individualised, according to the underlying medical conditions of the patients, the length of surgery and the desired induction procedures of anaesthesia. Sedative premedications may be administered orally, IM, rectally, sublingually, nasally or IV and doses are based on the body weight of child. Among them the oral route is mostly preferred in paediatrtic patients. The disadvantage of rectal route is that the effect of such administeration is likely to be unpredictable. IM route provides accuracy of doses and certainty of actions, but very few children welcome this route.

For sedation as premedication midazolam, given orally (0·5 mg/Kg) is gaining widespread popularity. The effect of this oral preparation of midazolam occurs within 10 minutes and the peak effect reaches 20 to 30 minutes after oral administeration. However, it does not influence the discharge time in day-case surgeries as one of the disadvantages of sedative premedication is that it prolongs the discharge time. Though there is oral preparation of midazolam, but it is not available in all countries. Hence, Parenteral preparation of midazolam can also be given orally, but it has a very bitter taste. This can be eliminated by diluting it in concentrated sweet fruit juice. The paracetamol elixir is also suitable for mixing with injectable form of midazolam for oral administeration, and has the merit of incorporating an analgesic component to the premedicant. As an alternative to midazolam, in some centres the parenteral ketamine preparation is also used orally in a dose of 3 to10 mg/Kg as premedication. But, ketamine causes excessive salivation and increases PONV. So, an antisialagogue and an antiemetic should always be used with ketamine premedication. If a profound degree of sedation is required during preoperative preparation of patient, then it is also possible to combine midazolam with ketamine. A relatively new route for administration of midazolam and ketamine as premedication is the intranasal route. But, at this

stage it is still unknown how much of the drug applied through the intranasal route is absorbed directly into the CNS through the cribriform plate, and how much is absorbed through nasal mucosa. But it will have to keep in mind that preservatives present in injectable preparations of these two drugs (as preservative free special preparation for use through nasal rouse is not available) are neurotoxic when passes directly to the neural tissue through cribriform plate. So, it is better not to use this preservative added preparation of these two agents through this route at present.

The nasal and rectal doses of midazolam are respectively 0·2 to 0·3 mg/Kg and 0·4 to 0·5 mg/Kg. The nasal and rectal doses of ketamine are respectively 3 mg/Kg and 6 mg/Kg. Because of the decrease in bioavailability of the drug through the oral and rectal route, the doses of these agents must be significantly higher when using these routes than with other routes.

The use of fentanyl as premedicant through oral transmucosal route is very popular, though it can also be used through any other routes. For absorption through buccal mucosa. It is prepared by incorporating fentanyl in a lozenge like lollipop and children are allowed to suck it. It is available in doses of different range. Swallowing of saliva decreases its efficacy, because first-pass metabolism of fentanyl through the liver is high. Onset of action of fentanyl through transmucosal route is 20 to 30 seconds and duration of action is 30 minutes for a dose of 10 to 15 µg/Kg of fentanyl. The disadvantages of fentanyl as premedication are : pruritus, nausea, vomiting respiratory depression and frequent oxygen desaturation. Respiratory rate decreases within 10 minutes. So, constant observation and monitoring is required and it should be administered only in a monitored clinical setting. The principal advantage of fentanyl as premedication is decrease in the intra- and postoperative analgesic requirement, but it does not delay the discharge of patient from the hospital.

Sufentanil also can be used as a premedicant like fentanyl. But it is most successful when used through the intranasal route. However, the intranasal dose of sufentanyl is 1·5 to 3 µg/Kg and it sedates the child within 10 minutes. However, the disadvantages of sufentanil are same as fentanyl. Traditionally children undergoing cardiac surgery need heavy premedication. Naturally, the choice is morphine, because it can prevent the spasm of the right ventricular infundibulum in uncorrected Fallot's tetralogy.

There are many other drugs which also can be used for sedative premedication. These are : diazepam (0.4 mg/Kg orally), lorazepam, trimeprazine (vallergan, 3 to 4 mg/Kg orally), chloral hydrate, promethazine (1 ml/Kg), etc. Injection of Vit K_1 in the dose of 1 mg should always be given through IM to all the newborns in view of the immaturity of hepatic production of prothrombin. The longer duration of action makes lorazepam unsuitable as premedicant for day-care surgery. Chloral hydrate and triclofos are used as more for sedation than premedication. The oral doses of chloral hydrate and triclofos are 25 to 50 mg/Kg and 50 mg/Kg respectively.

Induction

The method of induction of anaesthesia in paediatric group of patients is most colourful and is determined by a number of factors, such as : age of the patient, behaviour or psycological setup of the child, ability of the child to cooperate with the anaesthetist, medical conditions of the patient, the proposed surgical procedure, the presence or absence of full stomach etc. But among these the last and the most important factor is the anaesthetic procedure with which the anaesthesiologist is most convenient or competent.

When the infants are younger than 10 to 12 months of age, then induction of anaesthesia by volatile anaesthetics agents through face masks is the procedure of choice. Fortunately, the modern, potent, volatile anaesthetic agents can render the small children unconscious within minutes. This is also usually easier in children who have been sedated prior to entering the operating room and who are sleepy enough without ever knowing what his happening (steal induction). There are also some other healthy alternatives to the above mentioned inhalational technique for induction of anaesthesia without frightening the children and these are described in table (Table 25.17).

Typically, during inhalational induction the child coax for breathing an odourless mixture of N_2O (70%) and O_2 (30%). Sevoflurane or halothane is added to this anaesthetic gas mixture graduatly in increasing concentration of 0·5% after every three to five breaths. Many, if not most, paediatric anaesthetists consider sevoflurane as the agent of choice for inhalational induction rather than halothane, because sevoflurane has a wider therapeutic safety window in terms of cardiovascular depression and has no unpleasant smell. Desflurane and isoflurane are not used for induction, because they have more pungent smell and are associated with increased coughing, breath holding and laryngospasm etc. during induction. Some clinicians use a single – breath induction technique with sevoflurane of 7 to 8% concentration to speed up induction. It produes unconsciousness after 4 to 6 breaths without any excitement, But this single-breath technique should not be used with halothane, as it has severe cardiodepressant effects. When single breath technique using high concentration

Table 25.17: More healthy options of induction without frightening the child

1. Insufflation of anaesthetic gases over the child's face.
2. Substituting a clear, scented face mask in the place of the traditional black one.
3. Placing a drop of food flavouring oil inside the mask (e.g. oil of orange).
4. Allowing the child to sit during the early stages of induction.

of halothane and svofalurane in not used, then patients typically pass through an excitement stage during which period any stimulation by premadure attempt of laryngocopy or even IV cannulation can induce laryngospasm.

In older children who allow an IV line before induction of anaesthesia then in such circumstances. IV induction is preferred. Intravenous induction is also preferred if the patient comes to the operating room with a previously inserted intravenous catheter due to other reasons. Patients with full stomach always need IV rapid induction and intubation with or without succinylcholine. In such situation induction by in halational agents even by single breath technique in never tried to prevent aspiration of gastric contents. For IV induction of anaesthesia thiopentone, propofol, ketamine, midazolam, diazepam, etc, can be used. Induction with intramuscular ketamine (5 to 10 mg/Kg) is only reserved for some specific situations, such as (i) handling of a very violent child who will not take any oral pre-medicant and (ii) refuse to co-operate during induction by volatile inhalational agents and (iii) the patient is younger and healthy enough who requires many assistant to apply force for inhalation of volatile anaesthetic agents and also (iv) there is no IV line before hand for IV induction.

The child should be accompanied by parents (or someone with whom he or she is comfortable) to the anaesthesia room. The person accompanying the child should be informed beforehand what to expect in the anaesthesia room. He should be made aware of the excitation state of the child, when inhalational induction by mask is initiated or he should be made aware of how to assist the anaesthetist when IV induction is planned by distracting the child. During mask induction by volatile anaesthetic agents, breath holding by the patient is very common and if so, then one should not attempt to assist respiration by squeezing the bag because this often elicits cough and laryngospasm. Breath holding should be differentiated from airway obstruction or laryngospasm by an anaesthetist by observing the movements of bag, chest wall and abdomen. Airway obstruction, most commonly due to the falling of tongue, can be managed by extension of the neck and by an upward thrust of the mandible, applied at the angle. But if laryngospasm occurs, then closing of the pop-off valve of anaesthetic circuit and creation of positive airway pressure of about 10 cm H_2O approximately (while allowing the child to breathe spontaneously) will often allow the gas exchange and helps to overcome the laryngospasm. If this procedure is ineffective, then administration of positive pressure ventilation avoiding inflation of stomach often disrupts laryngospasm. However in very emergency conditions, the intravenous muscle relaxant is the only answer. But if IV line is not yet instituted, then only the cricothyroid puncture can save the life of the child.

In children where difficult airway is anticipated, the induction by mask should be done very slowly, gradually increasing the concentration of the inhalational anaesthetic agent and maintaining a spontaneous respiration. As the level of anaesthesia deepens, then gentle manual assistance of ventilation by anaesthetist corraborating with spontaneous respiration, may be done. This allows an anaesthesiologist to assess whether he will be able or not to ventilate successfully by mask, when muscle relaxant is used and intubation fails. Muscle relaxant should be used only if an anaesthetist feels that he can ventilate the patient successfully by mask, if intubation fails too. A child with an airway obstruction should have a slow and prolonged induction of anaesthesia, before allowing laryngoscopy and endotracheal intubation. In some emergency conditions when the patient presents with full stomach and airway problem, then the issue of full stomach is secondary to the airway problem. Rapid sequence induction of anaesthesia and intubation is indicated in these patients. A surgical team should be prepared to perform an emergency tracheostomy, if the total airway obstruction occurs and mask ventilation or endotracheal intubation fails.

Induction of anaesthesia through rectal route is also an unique techniques in the paediatric group of patients and have many advantages over the oral route. Many different medications are used rectally for induction of anaesthesia. The main advantage of this approach is that the child falls asleep in the parent's arms and hence separation of patient from the parent is atraumatic. This technique is no more intimidating than taking a rectal temperature. Oxygen desaturation is usually not a problem, unless the child's head flexes forward causing airway problem.

Other than inhalational, IV, and rectal route many medications are also used intramuscularly for induction of anaesthesia, like premedication. But here the only difference between the induction of anaesthesia and premedication is the dose of drugs used. The main advantage of this route of administeration over the rectal and oral route is its reliability but its main disadvantage is being a painful procedure.

A child with a full stomach should be treated like an adult with full stomach. As metabolic rate is much greater, so O_2 desaturation occurs more rapidly in neonates and infants than children and more rapidly in children than adults. However, the added problem in this group of patient is that the children are usuallyunco-operative and refuse to breathe 100% O_2 prior to induction (pre-oxygenation) for denitrogenation. Like an adult all the steps of rapid induction and intubation should be followed in paediatric patients with full stomach. During induction of paediatric group of patients with full stomach, injection of atropine is mandatory. This is because atnopine will to prevent anaesthesia induced reflexes, succinylcholine induced bradycardia and delay the bradycardia due to hypoxaemia. During

induction and intubation of a patient with full stomach, cricoid pressure is also mandatory and is applied gently after the child loses consciousness.

Unlike adult practice, it is not possible to have all the necessary monitoring devices placed on the child before induction. So, the appropriate monitoring should be placed as soon as possible, after the induction of anaesthesia.

For mask induction, different types of face masks are also used. Face masks with different size and different flavours and scents are now also available to reduce the noxious smell of the anaesthetic vapours. Scented transparent silicon or plastic masks are much more acceptable to little children than the traditional Rendell-Baker or Soucek masks which are made up of black rubber or PVC. But the advantage of these later masks is that they have very small dead space of only 4 ml. On the otherhand, the transparent clear plastic masks allow an anaesthetist to observe the presence of vomitus, though they have high dead space volume. In fact, the Rendell-Baker mask was originally developed to fit around the facial anatomy of the child in an attempt to minimize the equipment dead-space. But, the flow of fresh gas in a clear mask is such that the advantage of using a Rendell-Baker mask has nowbecome minimal. On the otherhand, these Rendell-Baker masks are much more difficult to use than the transparent ones with pneumatic cushion. An alternative to use a facemask is cupping of the anaesthesiologists hand over the face of a child, while holding and directing the T-piece carrying anaesthetic gases towards the nose of the patient.

Airway Management

The ratio of the dead space and the tidal volume (V_d / V_t = 0·4) remains constant throughout the life of a healthy patient. But any increase in the dead space by anaesthetic apparatus, connectors, humidifiers, etc, also significantly increases the V_d and V_t ratio and this has significant effect on ventilation. Therefore always this should be kept at a minimum level. This is very important for a child who breaths spontaneously and has a compromised cardiovascular and respiratory systems. The anaesthetic circuit which is most commonly used in children under 5 years of age or below 20 Kg of body weight throughout the world, is the Jackson-Rees modification of Ayres T-piece. This is also called the Mapleson F system. The original Ayre's T-piece was made up of a light metal T-tube with a main lumen of 1 cm in diameter. A smaller side tube was attached at right angles to the main lumen through which the anaesthetic gas mixture was introduced. Then a length of a rubber tube was attached to the open end of the T-piece, and it acts as a reservoir of anaesthetic gases. This is the modification of Ayre's T-piece to the Mapleson E circuit. To prevent the dilution of fresh gas flow by air and to avoid rebreathing, the capacity of the expiratory limb must be greater than the tidal volume, and the fresh gas flow must be twice than the minute volume of the patient. In 1950, Jackson Rees again modified this system by attaching an open-tailed breathing bag to the reservoir tube in order to facilitate the controlled ventilation and to observe the spontaneous ventilation. This is called the Mapleson F circuit. The reservoir bag in the Mapleson F circuit helps (i) to observe the respiration, (ii) to assess the tidal volume of patient and compliance of lung, (iii) to reduce the dead space during spontaneous ventilation (as the fresh gas flow washes out the expired gas during the pause after each expiration), and (iv) allows the application of continuous positive airway pressure in a spontaneous ventiliation or PEEP in controlled ventilation which helps in improving oxygenation. The main advantages of this valveless circuit are: simplicity, light weight, low resistance, minimal apparatus dead space and helping in manual ventilation (if needed) by the open-ended reservoir bag. This circuit may be used both for spontaneous and controlled ventilation. Controlled ventilation (manually or by a ventilator) is the most satisfactory mode of ventilation for neonates and infants, because any changes in compliance, air leak or tube displacements can easily be detected. For mechanical ventilation, the bag is removed and an appropriate ventilator is attached to the expiratory limb. Scavenging system may be connected indirectly to the circuit which prevents the possibility of blockage of the expiratory flow. The disadvantage of this circuit is the absence of a pressure relief valve. It is popular for induction of anaesthesia and maintenance of short duration. The recommended fresh gas flow (FGF) to maintain normocarbia in Mapelson F circuit, during spontaneous respiration is 200 to 300 ml/Kg. But, only 70 ml/Kg produces normocarbia during controlled ventilation. Fresh gas flow (FGF) approximately equal to the normal minute volume is also sufficient to maintain normocapnia in controlled ventilation. This is because CO_2 rebreathing has no consequence during controlled ventilation and the anaesthetist can control P_aCO_2 by increasing the ventilation (Fig. 25.6).

Another recommendation for FGF rate, necessary to prevent rebreathing:
2.5 times the minute ventilation, for spontaneous breathing or 1000 ml + 200 ml/Kg in controlled ventilation.

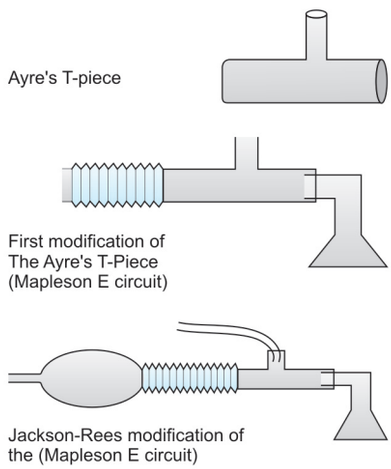


Fig. 25.6: Ayre's T-piece and modification over it

This discrepancy of recommendation of the FGF rate is dependent on the respiratory pattern. A rapid respiratory rate with minimal expiratory pause allows no time for the FGF to flush out the expired gases through the expiratory limb, before the next breath starts. This causes rebreathing of expired gases and so a higher FGF is required. Contrary, an end expiratory pause during controlled ventilation will help to flush out the expired gases in the expired limb and thus prevents the rebreathing and reduces the FGF. Most of the children require a minimum FGF of 3 litres/minute which can then be adjusted to achieve normocapnia and an inspired carbon dioxide concentration of less than 0.6 kPa. The measurement of end tidal CO_2 concentration by a capnometer may be underestimated in children below 10 Kg and this is due to dilution of the expired gases. So, sampling should be as distally in the circuit as possible. Partial rebreathing also allows conservation of heat and humidification in ventilators.

The minute volume (MV) should be calculated by:

MV = tidal Volume (10 ml/Kg) × RR

After tracheal intubation, controlled ventilation (if it is decided) can be conducted either manually or mechanically. Traditionally many institutions still prefer manual ventilation, because it allows a breath-by-breath estimation of the changes in chest compliance. But, gradually the need for manual assessment of chest compliance is pushed back and to assure adequacy of ventilation the modern non-invasive monitoring techniques such as: oximetry, capnography, pressure-volume loops, etc, are now in widespread. Moreover, the manual ventilation limits the activities of an anaesthetist, and may provide a false sense of security in detecting changes in compliance by hand. But, still the ability to hand-ventilate using the Ayre's T-piece (Mapleson F circuit) is essential in paediatric practice and such circuit should always be available in case of ventilator failure (when patient is mechanicaly ventilated) or unexpected desaturation. In a baby with gastroschisis or exomphalos, the manual ventilation can be used to assess the changes in lung compliance and can determine the volume of abdominal contents that can be reduced back into the abdominal cavity. Manual ventilation during repair of tracheo-oesophageal fistula can be timed properly, which allows the surgeon to get maximum exposure and time for the repair.

Standard adult ventilators are also suitable for paediatric patients with weight more than 20 Kg. But, below 20 Kg a paediatric version is needed with the ability to deliver small tidal volumes, rapid respiratory rate, variable inspiratory flow rate and different I:E ratio. However, the always measurement of this small inspired tidal volume is meaningless. Because, the compression of gases in the ventilator tubing and variable leaks around the endotracheal tube gives a false security. But, more sophisticated ventilators may, however, be capable of measuring expired tidal volume which is of more practical value.

Two modes of controlled ventilation are commonly used for neonates and infants.

(i) Volume controlled / time cycled.

(ii) Pressure controlled / time cycled.

The volume controlled / time cycled ventilation deliver a fixed tidal volume which is based on the inspiratory time and inspiratory flow, but is independent of the peak inspiratory pressure. It makes an allowance for changes in lung compliance, but at the potential cost of high peak airway pressure. With decrease in compliance of lungs, the tidal volume does not change, but the peak airway pressure changes. However, in contrast to volume controlled/time cycled ventilation, a pressure controlled/time cycled ventilation delivers a variable tidal volume under a fixed inspiratory peak pressure. Here, the tidal volume or minute volume varies directly with the compliance of chest and lung, and is indicated by the bellow movement or on the panel screen. As the compliance decreases, the tidal volume also decreases and vice versa. Both these ventilatory mode should be used with caution when there are chances of marked variation in the lung's compliance, due to surgery or pathological conditions such as: bronchoconstriction, pulmonary oedema, etc. To account for the changes in lung compliance when using a pressure controlled ventilation, the adequacy of alveolar ventilation can only be assessed by using a breath-by-breath capnography.

The ultimate setting of a ventilator's parameters depends on the clinical observation and the results from monitors. Inspiratory flow by changing pressure or volume can be gradually increased or decreased, until the optimum chest movement is observed. Measurement of capnography and pulse oximetry confirms normocapnia and adequate oxygenation. The peak airway pressure should always be kept at minimum level and an alarm at both the upper and lower limit side is mandatory in all ventilators. Most children are ventilated adequately with a respiratory rate between 20 to 30/minute and inspiratory pressure between 15-20 cm of H_2O. The respiratory rate should be adjusted accordingly to achieve the normocapnia.

In a ventilator the respiratory rate is set electronically between 20 to 30/min and inspiratory : expiratory ratio varies from 1:1 to 1:3. The gas flow rate required to produce a given minute volume is obtained by using a nomogram. This takes into account the voloume of gas which is lost during the expiratory phase. PEEP may be applied to the expiratory limb of the ventilator. This can also be used as a constant pressure device (CPAP) by incorporating a pressure-limiting relief valve (Fact file- I).

Non-rebreathing valves are also used in paediatric anaesthesia. But they tend to stick and produce more resistance and dead space. Circle absorber is used in paediatric anaesthetic circuit in some countries (e.g. USA). They have light tubings,

FACT FILE - I

The tidal volume of neonates is only 20 ml and the physiological dead space is just its 1/3rd. So, the amount of alveolar ventilation in neonates is only 14 ml. Hence, the addition of even a very small dead space from the anaesthetic apparatus (even a few ml) represents a very large proportional increase in dead space and tidal volume ratio. Masks are not suitable for neonates and infants for prolonged periods, because they usually require intubation. However, good fitting of the face mask is more important than its low dead space, because the latter can be reduced by increasing the FGF within the mask. The Rendell-Baker and Soucek masks do not make a good air seal on the face, though their dead space is very low.

silicone rubber valves, low gas flow with efficient humidification, warming and scavenging systems.

For the older children, over 20 Kg, it is satisfactory to use the Bains, Humphrey ADE or the circle absorber system. The ADE circuit is a hybrid system, incorporating Mapleson A, D and E types of circuits in one breathing system. Here, the E mode behaves similar to the T-piece. The A mode is efficient in children over 10 Kg of weight. Both D and E modes are suitable for controlled ventilation. The circle absorber system offers economic advantages, because a low fresh gas flow required in it. It also conserves warmth and moisture, as the reaction of CO_2 with sodalime is exothermic, producing heat and water. While using the circle absorber system in completely close circuit, then the ability to monitor the inspiratory and expiratory levels of O_2, N_2O, CO_2 and volatile anaesthetic agents is mandatory. The unidirectional valves may increase resistance to breathing and shouldnot be allowed to become damp. Paediatric circle system using a 15 mm light-weight hose, is suitable for children over 5 Kg. Till now there is no evidence of nephrotoxicity in children due to compound A, formed by the action of sevoflurane with sodalime.

In the past, much interest had been given to the resistance of the breathing system and the dead space volume of the apparatus during the use of circle CO_2 absorber system which led the paediatric anaesthesiologists to use nonabsorber (Mapleson F circuit) systems mainly. However, recently the attitude has changed and there is renewed interest in the use of circle system with CO_2 absorber in paediatric anaesthesia practice (Table 25.18).

The recent research works do not support the opinion that circle system with CO_2 absorber imposes more resistance to the breathing in infants and children during controlled ventilation. In contrast, it appears that the mechanical dead space imposed by some T-piece connectors, can be excessive during spontaneous respiration. Some problems, such as muscle fatigue, inefficient ventilation, tendency for lung collapse, etc. which were observed previously with the circle absorber system, were due to spontaneous breathing with this system. So, it can be advised that if ventilation is either controlled or assisted in neonates or infants, then a standard adult circle system which is fitted with low dead space connectors, small bore tubings and a reduced capacity reservoir bag, is appropriate for the maintenance of anaesthesia in paediatric patients of all ages.

Again, it is easy to scavenge the waste gases from all these systems with the resultant benefit of reducing the pollution of the theatre environment (Table 25.19).

An appropriately sized Guedel's airway is an important and useful adjunct in maintaining the airway when a child is being anaesthetised, but not intubated. A too small airway is ineffective and a too large airway may obstruct the larynx itself. So, an airway of correct length in used and this length is measured which is equivalent to the distance from the angle of the mouth to the angle of the mandible.

Table 25.18: Reasons for a renewed interest in the use of circle system with the absorber in paediatric practice

1.	Increased concern about economy.
2.	Enviornmental pollution.
3.	Improvement in the design of anaesthetic machines and ventilators.
4.	Use of the small bore anaesthetic circuits, reducing the anatomical dead space.
5.	Increase in availability and use of multi gas analyzers.
6.	The desire to use standard anaesthetic breathing circuits for patients of all ages.

Table 25.19: Estimation of LMA size in paediatric patients

Size of LMA	*Weight (Kg)*	*Cuff volume (ml)*
1	0-5	2-5
1.5	5-10	5-7
2	10-20	7-10
2.5	20-30	12-14
3	Large child > 30	15-20

Depending on the surgical and patient requirements, anaesthesia in the paediatric group of patients can be maintained with a face mask, tracheal tube or a laryngeal mask airway (LMA). But, the introduction of LMA offers a healthy alternative to face mask anaesthesia with Guedel's airway in patients scheduled for minor surgery. Both the indication and insertion technique of LMA for prediatric patients are similar to that of an adult. For preterm neonates who require G.A, spontaneous ventilation with face mask or LMA is avoided, because they are more prone to periodic breathing and apnoea during general anaesthesia. Neverthless, the role of LMA in neonatal surgery is limited. This is because in most instances the neonatal airway should be secured to prevent aspiration and to facilitate positive pressure ventilation, but neither of which can be properly assured with a LMA. Infants are also poor candidates for anaesthesia with spontaneous ventilation by LMA, and higher doses of volatile anaesthetics. It is because of poor pulmonary mechanics causing early respiratory failure and increased susceptibility to the cardiovascular depressant effects of volatile anaesthetic agents. These group of patients are likely to be benefited best from balanced anaesthesia offered by full dose

of muscle relaxant, intubation, controlled ventilation, minimum concentration of volatile anaesthetic agents and optimum doses of opioids. Balanced anaesthesia should also be applied to older children, undergoing surgeries for more than 45 minutes duration. Surgery lasting for less than 30 to 40 minutes of duration may be allowed to continue in children under spontaneous ventilation by LMA with a mixture of N_2O, O_2, and volatile anaesthetic agents, which is supplementated by appropriate doses of opioids, and local or regional block, where necessary.

For the maintenance of anaesthesia and the airway (from falling of tongue on the larynx), the LMA is one step ahead of face-masks with Guedel's oropharyngeal airway, but one step behind the ET tube. So, it is in an intermediate position between the face mask with oropharyngeal airway (Guedel) and the ET tube. In the maintenance of an anaesthetised airway, the LMA has certain advantages over the face mask with Guedel's airway, but also has some disadvantages when compared to the ET tube. The LMA is generally used only when spontaneous breathing is planned in a child during surgery, though controlled ventilation can be performed with LMA when necessary. It does not protect the airway against aspiration of gastric contents like ET tube. So, it is unwise to use the LMA in a patient with full stomach. The LMA is also displaced easily, causing airway obstruction. So, the present status of LMA is that it can be used in a variety of operations with spontaneous respiration or controlled ventilation, where the airway pressure is kept below 15 to 20 cm of H_2O. LMA is available in different sizes to fit all the children, including neonates. But the neonatal (size 1) LMA is not popular for different reasons such as difficulty to insert, easy displacement and increased apparatus dead space resulting in rebreathing and hypercapnia. On the other hand, due to the large cross-sectional area of the LMA tube, airway resistance increases very little. The success rate for insertion of LMA in the neonates and infants is less. In 70% unsuccessful cases it is seen that the epiglottis is not in the normal anatomical position. In most instances, the epiglottis is downfolded over the laryngeal inlet or within the bowl of the LMA. This is because the LMA used for neonates and infants is not designed according to their airway. Actually, LMA designed for the adult airway is simply scaled down in size to fit the neonates, infants and children.

Endotracheal Tube (ET Tube)

Though previously it was mandatory to intubate the trachea during artificial ventilation in neonates and infants, but now with the advent of LMA it is no more mandatory. Intubation with controlled respiration has several advantages. By intubation bronchial toileting becomes easy. It protects the lungs against aspiration of gastric contents, although when the patient is properly prepared and premedicated, then the incidence of aspiration is very low. Hence, LMA is no longer contraindicated medicolegally from the points of view of aspiration when the patient is prepared properly. However, operations in the oral cavity are not possible without tracheal intubation and with or without controlled ventilation. Even for operations outside the oral cavity, it becomes very difficult to maintain the airway of a neonate by only using airway devices and a face mask, even for the shortest surgical procedures requiring general anaesthesia. So, it is usually wise to intubate the trachea electively in most situations. But intubation results in the reduction of cross sectional area of the airway. For example, a 3·5 mm ET tube causes an increase in resistance by a factor of 16. So, tracheal intubation should not be followed by spontaneous ventilation. It always should be followed by controlled ventilation in order to reduce the work of breathing in paediatric patient.

There are different types of ET tubes which are used for paediatric patients. These are cuffed/uncuffed/Magill/Oxford/Preformed (RAE − Ring-Adair-Edwin)/Armoured/Ctole, etc, and may be made of different materials such as: PVC, silicone, rubber, plastic, etc. The RAE tubes are not recommended routinely for infants, because of the frequent inadvertent bronchial intubation caused by it. They are frequently used to facilitate the surgery around the head and neck. In RAE tube, there is a preformed bend that may be temporarily straightened during intubation.Both cuffed and uncuffed versions of nasal and oral RAE tubes are also available in various sizes. As the diameter of RAE tube increases, the total length and the distance from the distal tip to the curve of the tube also increases. Frequently, there is a mark at the bend. In majority of cases when this mark is at the level of teeth (in oral version) or naris (in nasal version), then the tip of the tube will be satisfactorily positioned in the mid-trachea, provided the proper size of the tube for the patient is selected. However, this is just a guideline and should not be used as the sole criteria for judging the correct positioning of the tube (Fact file -II).

The curvature of the nasal RAE tube is opposite to the curvature of the oral RAE tube, so that when in place the outer portion of the tube is directed over the patient's forehead. This helps to reduce the pressure

FACT FILE - II

After endotracheal intubation the controlled ventilation is the choice in neonates and in all babies upto 5 Kg of body weight, even for minor surgical procedures. This is because :

(i) Small babies are very sensitive to the respiratory depressant effects of the anaesthetic agents,

(ii) Controlled ventilation provides adequate alveolar ventilation,

(iii) Controlled ventilation maintains the normal residual lung volume.

The ventilation rate is maintained at 30 to 40/minute with a pressure of 15 to 20 cms of H_2O, PEEP of 5 cm of H_2O and FGF of 4 litres/minute to preserve the FRC. For babies above 5 kgs of body weight the spontaneous respiration with or without intubation may be allowed if the surgical procedure permits.

on the nares. This tube may also be useful for oral intubation of patients who are to be operated in prone position. The oral RAE tubes are shorter than the nasal ones. The external portion of the oral RAE tube is bent at an acute angle, so that when in place it rests on the patient's chin. These tubes are easy to secure and their use may reduce the risk of unintended extubation. The curvature of the RAE tube allows the breathing system and its connections to be placed away from the surgical field during operations, especially around the head and neck without using special connectors. The disadvantages of RAE (preformed) tubes include: difficulty in passing a suction catheter down them and these tubes offer more resistance than the comparable sized conventional ET tubes.

The spiral embedded armoured tube has a spirally winded reinforcing wire which is made up of metal or nylon and is covered internally and externally by rubber, PVC or silicone. Spirally embedded or armoured tubes are especially useful in situations where bending or compression of the ET tube is likely to occur.

The ET tubes may be either disposable or reusable. The reusable red rubber ET tubes, though possibly more irritant to the mucosa, are less liable to kinking and are easier to insert. Generally uncuffed tubes are used in children below the age of 10 years. This is because cuff pressure may cause ischaemic injury to the underlying tracheal mucosa which subsequently may lead to post-intubation croup or severe post-intubation laryngeal oedema leading to obstruction. This post-intubation laryngeal oedema may also require further intubation or even tracheostomy.

Another crucial point of paediatric anaesthesia by intubation is the determination of the size or internal diameter (ID) of the ET tube, appropriate for the given patient.

The general formula to calculate the ID or the appropriate size of tube is:

ID (in mm) = Age (years) ÷ 4 + 4.5

When using the above formula, any fractional sizes should be rounded up. This formula is only used as a rough guide to determine the size of a tracheal tube in children aged 2 years or above. But, the determination of tube sizes for neonates, infants and children who are less than 2 years of age is guided by the body weight. It is better to recall that a neonate weighing ±3 Kg will require a 3 mm (ID) tube. Low birthweight or premature babies need a 2.5 mm (ID) tube. The remainig sizes below 2 years should then be interpolated. It is advisable to keep in hand the tubes of one size both larger and smaller (0.5 mm larger or smaller) than the selected tube during intubation. For neonates, the best guide in choosing the ET tube is weight. In paediatric patients, the ideal size of a tube will be like that when it is in place there should have a small air leak around it to prevent the damage of mucus membrane of the rigid subglottic region, i.e the cricoid ring, which is the narrowest part of the child's airway. A correctly sized tube is one in which ventilation is adequate, but a small audible leak of air is present when the positive pressure is applied at 20 cm H_2O. However, this view has recently been challenged. But whatever may be the debate, it is clear that an appropriate sized tracheal tube should pass easily through the cricoid ring and there should not be excessive air leak in the working range. An alternative rough guide for the determination of the size of an ET tube is to use a tube with an external diameter similar to that of the child's little finger. As the children have a relatively short trachea, so the tube may easily enter either the right or the left main bronchus, or may even come out of the trachea easily when the neck is extended.

Certain care to be taken during intubation:

i. After intubation and intermittently during operation auscultation of both the lungs is mandatory,
ii Tube should be well secured by adhesive tapes with the immobile maxilla, rather than the movable mandible
iii The length of the tip of a ET tube from the alveolar margin (i.e. the length of the tube in the air passage) should be calculated from the formula: Age/2 + 12 cm.

This above formula is applicable only for the patients who are more than 2 years of age. However, the length of a orotracheal tube from the aveolar ridge (in cm) to the tip of the tube for patients aged less than 2 years is produced in the table below and should be memorized. But, whatever may be the length, it should allow the tip of the tube to reach the midtracheal point, while 2 to 3 cm of the tube should protrude out from the mouth for fixation. Some disposable tubes have a special marking 2 cm away from the patient's end to indicate the adequate insertion of tube into the trachea, passing below the vocal cord. Correct positioning of the tracheal tube should also always be checked by capnography and auscultation of the lung fields. The ET tube is connected with the anaesthetic machine by a connector. However, a paediatric 8.5 mm connectors are usually used, instead of the standard 15 mm connector. The catheter mount should be avoided in paediatric anaesthesia because a large dead space is involved. An alternative calculation for the length of the tube measured from the alveolar margin to the mid-trachea point is three times the internal diameter of the tube and for nasal intubation this measurement of length is : [Age (Years) ÷ 2 + 15] cm (Table 25.20).

If intubation is preceded by a period of difficult mask ventilation, then it is

Table 25.20: Estimation of endotracheal tube size in neonates and infants

Weight or age	*Length from alveolar ridge*	*Internal diameter*
1-2 Kg	7 cm	2.5 mm
2-4 Kg	8 cm	3 mm
Term neonate	9-10 cm	3.5 mm
3 months- 1 year	10-12 cm	4 mm
2 years	11-12 cm	5 mm
Over 2 years	—	Age ÷ 4 + 4.5

very common for the stomach to become inflated by ventilating gas. The inflated stomach decreases the tidal volume of the lungs, causing arterial desaturation. So, in this situation the stomach should be deflated by passing a nasogastric tube and removing it after operation.

In the first year of life a straight blade infant size Magill's laryngoscope, placed behind or posterior to the epiglottis, is more helpful for visualisation of the larynx and vocal cord. Because, in paediatric patients the larynx lies more anteriorly and is situated highup in the neck, opposite to the C_{3-4} vertebral body (in older children and adults it lies opposite to C_{5-6} vertebral body) and is covered by a large, soft and floppy (as the cartilagenous support is not yet fully developed) epiglottis, inclined at an angle of 45° to the glottis. So, visualisation of the vocal cord with a curved blade (Mackintosh) laryngoscope is difficult.The straight blade Magill's laryngoscope flattens out the curvature of the epiglottis and can be used to lift it by pushing forward directly and thus to expose the larynx. Paediatric version of Polio and McCoy blades are also available for paediatric laryngoscopy and intubation in difficult cases. For visualisation of the larynx, an anaesthesiologist has to align the three imaginary axes : one through the trachea, one through the pharynx and one through the mouth. In adults and older children this is usually achieved by placing a pillow under the head (familiar 'sniffing the morning air position') and putting the laryngoscope into the valecula in front of the epiglottis. But, in neonates and infants due to a larger head and shorter neck relative to the body, instead of placing the pillow under the head, it is usually necessary to place it under the shoulder. Laryngoscopy should be done very gently in paediatric group of patients and proper care should be taken to avoid the trapping of lips between the teeth and the laryngoscope blade which will cause injury and bleeding and distract the concentration of anaesthetist. The blade of laryngoscope also should not be levered against the upper teeth which may cause dislodging or even breaking them.

Certain considerations prior to ET intubation are:

i. Whether an awake, atraumatic intubation is possible and can be achieved easily.
ii. The possible presence of conditions making intubation difficult or impossible (e.g tracheo-oesophageal fistula).
iii. The difficulty in maintaining the airway with a face mask after induction and difficulty of maintaining ventilation by face mask after muscle relaxants.
iv. The presence of intestinal obstruction.
v. A very poor general condition of the patient (Table 25.21).

It should be noted that the concept of conscious intubation depends entirely on the clinical state of the patient and bears no relationship with age. However, in a vigorous infant and provided there is no possibility of aspiration of pharyngeal content, anaesthesia always should be induced prior to intubation. After intubation of an uncuffed tube, the laryngopharynx is lightly packed with a ribbon gauze which is slightly moistened with water or liquid paraffin to stabilise the ET tube and to prevent its kinking as well as leaking of gas.

Monitoring

The best monitoring device during paediatric anaesthesia is that which increases the contact between an anaesthetist and the patient. So, there is no substitute for an experienced and vigilant anaesthetist observing the child, and it is complimented by instrumented monitoring by modern electronic devices. Hence, for this instrumental monitoring of the paediatric group of patients the conventional adult methods of monitoring by electronic gadgets is applicable but with some special modifications for the smaller infants and neonates. With the electronic monitoring the colour changes, the movement of the chest and bag, the changes of respiratory pattern, the peripheral arterial pulses, etc, should also closely be observed clinically. It provides information about the present status of patient's oxygenation, ventilation and circulation (Fig. 25.7).

The routine instrumental monitoring of a paediatric patient should always include a precordial or oesophageal stethoscope, a blood pressure cuff of suitable width, pulse oximeter, ECG, temperature, end-tidal CO_2 tension and a peripheral nerve stimulator if muscle relaxants are administered. A precordial stethoscope and pulse oximeter should always be attached after induction, if not possible before. The precordial stethoscope should be changed to an oesophageal one, after the trachea has been intubated. The precordial or oesophageal stethoscopes assist in monitoring the heart rate, the quality of heart sounds and the pulmonary ventilation. The oesophageal stethoscope is also used for a qualitative measurement of the cardiac output, because a volume-depleted infant has soft

Table 25.21: Suggested size (ID) and length of the oral ET tube with age 72 years

Age	*Length from alveolar ridge*	*Internal diameter*
2 years	11-12 cm	4.5-5 mm
4 years	12-13 cm	5-5.5 mm
5 years	13-14 cm	5.5 mm
6 - 7 years	14-15 cm	6 mm
8 - 9 years	15-16 cm	6.5 mm
10 years	16-17 cm	7 mm
11-12 years	17-18 cm	7.5 mm
13-14 years	18-19 cm	8 mm

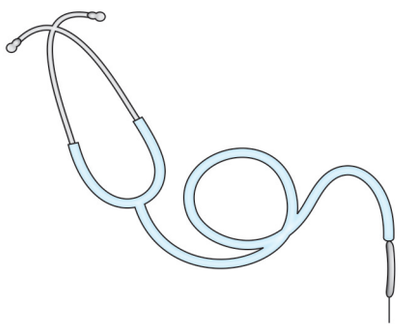


Fig. 25.7: Anaesthesia monitoring tool

heart sounds and an increase in the intensity of heart sounds after volume repletion may be recognised easily.

The sphygmomanometry method of determining BP in a small baby is difficult, and this is because of the inaudibility of Korotkoff sounds. But, the BP can be measured by automatic devices accurately, provided the width of the cuff covers at least 2/3rd of the upper arm and surrounds at least 3/4th of the limb. Many of the mechanical automatic sphygmomanometer devices are calibrated to the size of the patient, so it is important to select the proper 'neonate' mode for accurate measurement of BP.

The greatest advancement of this century in the sphere of monitoring in paediatric anaesthesia is the development of pulse oximeter by which O_2 saturation of haemoglobin can be measured continuously and noninvasively by a transcutaneous method. It is an extremely sensitive apparatus giving very early warning signs of impending hypoxia, long before clinical signs appear. The beauty of pulse oximeter lies in the simplicity of its principles upon which it works. The oximeter sensor can be attached to any site of the patient like finger, earlobe, nose, tongue, forehead, etc, and even in the medial aspect of the hand or lateral aspect of the foot in neonates. In neonates the pulse oxymeter probe should preferably placed on the right side of the body to measure the preductal oxygen saturation. The accuracy of this monitor is unaffected by the presence of foetal Hb, hyperbilirubinaemia, anaemia, etc. However, accuracy is affected by several other factors, such as the presence of met-and carboxy haemoglobin, nail polish, extraneous infrared lights (from radiant overhead heaters), hypothermia, hypotension, etc. Sometimes, the pulse oximetry results may not be accurate in cold neonates with poorly perfused extremities due to vasoconstrictions. In such situations, the application of the oximeter probe to the earlobe or nose may yield an accurate result. In addition, the use of an overhead radiant light for warming the baby may result in inaccurate oximeter results. So, the oximeter sensor should be shielded from the radiant light. The artefacts due to movement always give inaccurate measurement of O_2 saturation in neonates and infants during anaesthesia. But, now, newer algorithms have virtually eliminated motion artefacts and enables the accurate measurement of HbO_2 saturation in paediatric patients in spite of spontaneous movement.

The ECG monitoring is used in almost all the paediatric patients. The direct monitoring of arterial and central venous pressures are also easily achieved after cannulation of the radial artery and the internal jugular vein. However, such invasive direct arterial and central venous pressure monitoring are only be used in paediatric patients when such monitoring are absolutely necessary for the management of safe anaesthesia, during complicated surgery or in high-risk patients. During central venous and/or arterial cannulation all air bubbles should be removed from the pressure-tubings and only small volume of flushes should be used to prevent air embolism and circulating overload respectively in paediatric group of patient. The right radial artery is often chosen for cannulation in the neonates, because its preductal location mirrors the actual oxygen content of the carotid and retinal arteries. A femoral artery catheter or may be a suitable alternative in very small neonates when radial artery is not easily arressed. The critically ill neonates may still have an umbilical artery catheter in situ. The anaesthetists should not use these monitors simply because the patient is small or he is inexperienced. If these monitors are needed, then it can be inserted by an anaesthetist or a surgeon or even a cardiologist or a neonatologist. Pulmonary artery catheter is rarely indicated in paediatric patients, as the pressures of the right and left side of the heart are almost identical.

The end tidal CO_2 tension correlates well with the alveolar and subsequently arterial CO_2 tension. So, the measurement of end tidal CO_2 tension using a capnograph with a paediatric cuvette is mandatory in paediatric anaesthesia. Thus, the end tidal CO_2 analysis allows the assessment of the adequacy of ventilation, confirmation of ET tube placement and early warnings of malignant hyperthermia. The CO_2 partial pressure in blood can also be estimated noninvasively by transcutaneous methods. But, this technique of measurement of CO_2 tension by transcutaneous route is not commonly used in the OT, because it requires a long calibration period, responds slowly to the changes of CO_2 partial pressure in blood and does not provide breath-by-breath analysis like the end tidal CO_2 tension. For the measurement of alveolar CO_2 tension which correlates well with the arterial CO_2 tension, two types of capnometers are available. These are : sidestream and mainstream capnometers. The accuracy of capnometer reading depends on several factors such as : type of capnometer, the location of the end-tidal gas sampling port in the anaesthetic circuit, the type of anaesthetic circuit being used and the cardiopulmonary dysfunction of the patient. The sidestream capnometer aspirates gas continuously from the breathing circuit through a fine bore tubing and the main analyser lies at a distance. So, for an accurate result this side stream analyser must aspirate gas at a sufficient rate, compared to the respiratory rate and the gas should be sampled from within the tracheal tube. For this purpose, a 18 G or a 20 G IV catheter may be inserted into the 3 or 3·5 mm ID endotracheal tube.

On the other hand, the mainstream capnometer is placed directly at the junction between the ET-tube and the patient end of anaesthetic circuit and analyzes the expired gas as it passes through the sensor of it. Hence, it does not need to aspirate the gas continuously. These capnometers provide more accurate results about the end tidal CO_2 tension than the side stream capnometers. But, these are heavier than

the light-weight paediatric circuits and add more dead space. Neverthless, the small tidal volume and the rapid respiratory rate of small infants can present difficulties with both the capnograph models. Flow-through (mainstream) analysers are usually less accurate in patients weighing less than 10 Kg. Even with aspiration (side-stream) capnographs, the inspired (baseline) CO_2 can appear falsely elevated and the expired (peak) CO_2 can be falsely low. The end tidal CO_2 tension which is similar to the alveolar CO_2 tension does not correlate well with the arterial CO_2 tension in the presence of right to left cardiac shunt. But, in contrast the end tidal CO_2 tension accurately reflects arterial CO_2 tension in the presence of left to right shunt. Also, the end tidal CO_2 tension does not accurately reflect the arterial CO_2 tension in lung diseases. In such situations, the end tidal CO_2 tension should not be relied upon for accurate assessment of the adequacy of alveolar ventilation. Here the arterial blood gases should always be analysed to document the actual gas tension.

The temperature should always be measured during the surgery of small babies by nasopharyngeal, oesophageal or rectal probes due to their increased susceptibility to iatrogenic hypothermia and hyperthermia and also for early detection of malignant hyperthermia. Hypothermia can be prevented by maintaining a warm operating room environment (26° C or higher), warming and humidifying the inspired gases, using a warm blanket and also by warming all the IV fluids. The room temperature required for a neutral thermal environment varies with age. It is highest with premature newborns. However, it should also be kept in mind that during the maintenance of temperature of the paediatric patients outmost care also must be taken to prevent unintentional skin burns and iatrogenic hyperthermia from overzealous warming efforts.

Among all these routes, the nasopharyngeal probe provides an accurate reflection of the body core temperature. The oesophageal temperature may not accurately reflect the core temperature. Because, it is usually affected directly by the temperature of the inspired gases. The rectal temperature also can reflect accurately the core temperature, but it changes very slowly. The body core temperature also can be measured accurately from the external auditory meatus. But, it is not commonly used, because of the risk of trauma to the tympanic membrane. Axillary temperature does not provide the actual core temperature of body and it is very difficult to maintain the probe position over the axillary artery.

EXTUBATION AND POSTOPERATIVE CARE

At the end of the surgery when extubation is planned, then the administration of volatile anaesthetic agents should be stopped and the neuromuscular block should be anatagonised if they are used at all. The neuromuscular block should be antagonised in all paediatric group of patients, especially in neonates (preterm or full term) and infants. Because, even with the use of modern short acting neuromuscular blocking agents, the recovery from muscular paralysis in the neonates and infants remain unpredictable and any residual neuromuscular blockade may quickly lead to respiratory failure. Following anaesthesia with spontaneous ventilation under volatile anesthetics for short surgical procedures, extubation should be performed under deep anaesthesia. It is not advisable to extubate this group of patients under light anaesthesia, as severe laryngospasm is very frequent. Therefore, to maintain the level of deep anaesthesia volatile anaesthetics are continued till the child has been extubated successfully. The ET tube is extubated after thorough oropharyngeal suctioning and then the child is given 100% O_2 to breathe.

During the reveral of neuromuscular block by neostigmine (40 to 50 µg/Kg) and atropine (20 µg/Kg) or glycopyrolate (10 µg/Kg), the patients tend to follow three phases. In the begining the patient begins to breathe irregularly and tries to strain on the endotracheal tube. Next, the patient beathholds for a variable period. At that time they are at the greatest risk of hypoxia. Then, finally the regular respiration is resumed. After that the patient begins to gag on the endotracheal tube, move his limbs and contract the rectus abdominis muscle. Extubation is done after thorough oropharyngeal suctioning at this phase and 100% O_2 is administered with utmost attention for further occurrence of laryngospasm

After extubation the postoperative management of paediatric patient depends on the grade and the complications of surgery and anaestheisa and the associated medical conditions of the patient. After any surgery the patients should be monitored with a pulse oximeter, apnoea monitor and ECG in the recovery room, because the neonates are very prone to post-anaesthetic apnoea. 20% of preterm neonates may develop postoperative apnoea after general anaesthesia and the risk of which increases in the presence of anaemia and decreases with increasing postconceptual age. The risk of post anaesthetic apnoea is also high in the presence of congenital heart disease, severe respiratory distress, intracranial haemorrhage and any other major organ dysfunction. This post-operative apnoea usually occurs within 6 hours after discontinuation of anaesthesia. Though the process of maturation of respiratory centre is a dynamic process, still due to individual variations it is not surprising to face postoperative apnoea even in full term neonates. Caffeine is recommended for the management of post anaesthetic apnoea. A single dose of caffeine of 10 mg/Kg is sufficient for 18 to 24 hours to prevent postoperative apnoea. However, all patients who are prone to post anaesthetic apnoea are observed with an apnoea monitor for 24 hours or at least 12 hours after the last apnoeic episode.

NEONATAL ANAESTHESIA

Children, younger than 1 year, have a higher incidence of complications in anaesthesia than older children.

Reasons for higher incidence of complications in anaesthesia of children younger than 1 year are:

i. Usually, the neonates who are presented for surgery are of ASA 3 and 4 grade.
ii. The cardiovascular and respiratory system of the neonates, particularly the premature ones, function between the adult or extrauterine and the foetal or intrauterine type. So, any type of surgical stress or hypoxia can convert this adult to foetal type of circulation and as a consequence worsen the hypoxaemia, acidosis and cause death unless the cycle is broken immediately.
iii. Immaturity of organ systems (especially the cardiovascular, pulmonary, renal, hepatic and nervous system), high metabolic rate, high ratio of body surface area to weight, miscalculation of drug doses, etc, make taking care of these neonates and premature babies technically very difficult.
iv. The care of neonates is also always confronted with sudden changes, unexpected responses and the some unknown congenital problems.

Most of the complications that arise during neonatal anaesthesia are due to the lack of understanding of their special considerations prior to the induction of anaesthesia. So, the neonatal anesthesiologist has to be prepared for these unexpected situations and has to be ready with a variety of equipments and of proper sizes to provide highest level of care.

The controlled ventilation after endotracheal intubation is the technique of choice for neonates and for most of the babies upto the 5 Kg of body weight, even for minor procedures. The small babies are very sensitive to the respiratory depressant effects of inhalational anaesthetic agents. So, controlled ventilation ensures adequate alveolar ventilation and maintains a normal residual lung volume. But, recently many operations are done under spontaneous respiration with the LMA. During spontaneous ventilation, even the low resistance of the circle system can become a significant obstacle for the sick neonate. Unidirectional valves, long breathing tubes and absorbers account for most of this resistance. For patients weighing less than 10 Kg some anaesthesiologists prefer the Mapleson D circuit because of their low resistance and lightweight. Neverthless, as the resistance of breathing circuit can easily be overcomed by positive pressure ventilation, so the circle system can safely be used in patients of all ages if ventilation is controlled. Monitoring of airway pressure may provide an early evidence of obstruction caused by a kinked ET tube or advancement of the tube into the mainstem bronchus.

For controlled ventilation in neonates, a respiratory rate of 30 to 40 per minute with inspiratory and expiratory ratio of 1:2 (it is occasionaly necessary to reverse the inspiratory: expiratory ratio from 1:2 to 2:1 to improve gas exchange) is used with a peak inflation pressure of 25 to 30 cm of H_2O (but not more than 30 cm of H_2O). PEEP of 5 cm of H_2O (not more than 10 cm of H_2O) is also used to preserve the FRC with a fresh gas flow of 4 litres/min. Using PEEP and peak inflation pressure upto 30 cm of H_2O we should keep the inspired O_2 concentration as low as possible to maintain a P_aO_2 just between 60 to 80 mm of Hg. Early application of PEEP to the patients with hyaline membrane disease improves the gas exchange and may also decrease the severity of the disease by reducing the surfactant consumption. The net effect of PEEP on tissue oxygenation depends on the degree to which the cardiac output is reduced (PEEP than 10 cm of H_2O reduces cardiac output). For the babies over 5 Kg of body weight, anaesthesia by spontaneous breathing without intubation is possible, but only if the surgery permits and is of very short procedure.

Every effort should be made to maintain the neonate's temperature by minimising thermal loss. Operation theatre should be warmed. Electric warmer, warming blankets and heated humidification of inspired gases, particularly when nonbreathing circuit is used, minimises the heat loss.

Pulse oximeter is extremely important, not only to prevent hypoxia but also to prevent hyperoxia and retinopathy of prematurity (ROP). Oxygen saturation should be maintained between 93 to 95% (P_aO_2 between 60 to 80 mm of Hg), which keeps the patient on the steep side of oxy-heamoglobin dissociation curve. Keeping the O_2 saturation at this level, an anaesthetist will maintain a delicate balance between the potential rapid O_2 desaturation due to the absence of any reserve, and the potential development of ROP due to higher inspired O_2 concentration. So, an anaesthesiologist should be extremely vigilant and should respond quickly to any changes in O_2 saturation.

Premature neonates are deficient in surfactant production, which results in alveolar instability and atelectasis. This results in an increased intrapulmonary shunting and decreased compliance of lungs. Mild cases can be treated conservatively with humidified O_2. But, severe cases require tracheal intubation and mechanical ventilation. The decision to provide mechanical respiratory support is always made on clinical grounds such as : apnoeic attacks, respiratory rate above 60/min, signs of increasing work of breathing (nasal flaring, subcostal recession), increasing O_2 dependence (needs increased inspiratory O_2 concentration to maintain normal arterial O_2 saturation) and failure to clear secretion. Such babies are unable to maintain an arterial O_2 tension between 50 to 80 mm of Hg with increasing inspired O_2 concentration and the CO_2 tension rises above 50 mm of Hg. On the other hand, high pressure and high inspired O_2 concentration which is sometimes required for mechanical ventilation may result

in retrolental fibroplasia and damage to lung parenchyma. Factors that cause this progressive destruction of lung architecture and function (with fibrosis and cyst formation) due to high pressure and high O_2 concentration are: pulmonary hypoplasia, surfactant deficiency, the presence of L-R shunt, high ventilatory pressures (more than 30 cm of H_2O), high inspired O_2 concentration (> 60%), chronic infection and poor mucociliary function. This condition is progressive and vicious in cycle, as increased V/Q mismatching demands higher inspired O_2 concentration and falling lung compliance needs even higher inflation pressure. This high peak inspiratory pressure causes more shear injury of the lung parenchyma, creating a viscious cycle. This can be reduced only by the judicious use of PEEP and other ventilatory modes. A significant number of children who have had this type of treatment develop chronic lung disease of prematurity (previously termed bronchopulmonary dysplasia). So, the measurement of cutaneous O_2 and CO_2 tension is increasingly important and satisfactory, and is particularly helpful even when it may be difficult to obtain arterial blood for blood gas analysis. A reasonable correlation exists between the transcutaneous and arterial gas levels, when the peripheral circulation is good. But significant discrepency may occur in patients with poor tissue perfusion and with arterial O_2 tension at extremes of hypoxia and hyperoxia.

Weaning from the ventilator takes place after achievement of the cardiovascular and biochemical stability with inflation pressure of less than 25 cm of H_2O, P_aCO_2 of less than 50 mm of Hg and P_aO_2 of more than 80 mm of Hg at FiO_2 of 0·5 (i.e., the inspired oxygen concentration being 50%). Neonates must never breathe through an endotracheal tube without PEEP. Because, the zero-end expiratory pressure allows the small lungs to collapse progressively, so that the closing volume comes closer to the FRC in subsequent respirations with increased R-L intrapulmonary shunting and hypoxia. As the lung volume falls, the airway resistance to gas flow rises, so that the work of breathing and oxygen consumption also rises. With the ET tube in place, the normal mechanism is lost, whereby the glottis generates 2 to 3 cm H_2O pressure in terms of respiratory distress.

SOME SPECIAL PAEDIATRIC SURGICAL CASES

Congenital Diaphragmatic Hernia

In this condition which occurs 1 in 4000 live births abdominal visceras herniate through a defect in the diaphragm, most commonly through the Foramen of Bochdalek of the left side. Another name for this Foramen of Bochdalek is the persistent pleuroperitoneal canal. It is a free communication between the peritoneal and pleural cavities, causing a posterolateral hernia of abdominal visceras into thorax. It is due to the failure of diaphragm to develop from the lateral arcuate ligament on one or both sides, forming a triangular gap. So, a congenital diapragmatic hernia takes place through that opening and abdominal visceras herniate into the thorax, due to positive intra-abdominal pressure. In severe degree of congenital diaphnagmatic hernia almost all the abdominal visceras including stomach, intestine, liver and spleen, may be above the diaphragm and impair the development of lungs, causing hypoplasia of it. The intrauterine gestational age at which herniation begins to occur determine the severity of hernia which in turn determines the degree of lung hypoplasia. So, along with congenital diaphragmatic hernia there is also concomitant pulmonary hypoplasia associated with ↑PVR, ↑PAP and pulmonary hypertension. If the defect starts at an early gestational age, then the mediastinum is also shifted to the right and the growth of the contralateral lung is also stunted. The degree of respiratory distress at birth is related mainly to the degree of associated pulmonary hypoplasia which is indirectly related to the degree of herniation of abdominal visceras into the thoracic cavity. Infants who present with respiratory distress soon after birth, indicates severe degree of herniation and severe degree of lung hypoplasia. Usually they do not survive as they have inadequate amount of lung tissue to sustain life. After birth the midgut starts to fill with air, causing further distension of gut and compression of lungs which further increases the respiratory and cardiovascular distress. The diagnosis of congenital diaphragmatic hernia is suspected by respiratory distress after delivery and a scaphoid empty abdomen, this is confirmed by a chest X-ray.

Repair of diapragmatic hernia is not an emergency one and the child should be managed medically first. Surgery is considered only when the child's condition is optimized medically. Pulmonary hypertension should be treated with tolazoline and PGE-inhibitor before administration of anaesthesia for better result (Table 25.22).

Intraoperative P_aCO_2, reflected as $ETCO_2$ tension, reflects the severity of lung pathology and the chances of survival. It is the anaesthesiologist's duty to control the P_aCO_2 to improve the hypoxaemia and to check the hypotension.

The defect of diaphragmatic hernia is usually repaired through an abdominal incision Use of muscle relaxant and ventilation of patient by mask and bag before intubation may cause inflation of stomach and more herriation of gut in to thorax. So, an awake intubation without bag and mask ventilation is ideal (only if possible) and prevents over distension of the gut which

Table 25.22: Problems faced by an anaesthetist during perioperative management of congenital diaphragmatic hernia

1. Hypoxaemia, due to pulmonary hypoplasia, gut distension and pulmonary hypertension.
2. Acidosis due to hypercapnia.
3. Hypotension caused by kinking of major blood vessels, particularly those of the liver.

cause further herniation of abdominal visceras into the thoracic cavity. N_2O also should not be used for the same reason, as it overdistends the gut and increases the herniation of abdominal viscera into thoracic cavity. An intraarterial line is helpful in this type of sugery for blood gas analysis and continuous monitoring of the BP. Anaesthetic agents that depress the myocardium should always be avoided and stress response should be blunted by narcotics such as : fentanyl or remifentanil, which helps to establish a stable haemodynamic system. It is not always possible to introduce back all the viscera totally from the thorax into the peritoneal cavity. In such cases, a silastic silo may be used to introduce the contents gradually into the abdomen. Postoperative ventilation is essential for management of such patients.

Oesophageal Atresia and Tracheo-oesophageal (T-E) Fistula

The oesophageal atresia with or without tracheal fistula with oesophageous occurs in about 1 out of 3000 live births. It should be suspected when hydramnios complicates the pregnancy.

The infants suffering from this disease are of low birth weight and this anomaly may be the part of a larger constellation of many other congenital anomalies of structure such as vertebrae (V), anus (A), trachea (T), oesophagus (E) and renal (R) which are abbreviated shortly as VATER. Among these the cardiovascular anomalies such as : septal defects and coarctation of aorta most often coexist with this condition. So, echocardiography should always be performed before surgery of such patients. Other anomalies described above should also be excluded by thorough clinical examination and full investigations. Usually, after birth a baby who is suffering from oesophageal atresia and associated T-E fistula presents with respiratory distress or symptoms of choking during feeding and distended abdomen. Usually six types of tracheo-oesophageal fistulae with oesophageal atresia (from A-E) are described, and most of them present with an inability to swallow because of oesophageal atresia except type E. The diagnosis of this congenital anomaly is confirmed only by passing a nasogastric tube, which cannot be passed into the stomach. The main risk of life in T-E fistula comes from the soiling of lungs with saliva or gastric contents, causing pneumonitis and lack of nutrition (Table 25.23).

Table 25.23: The major issues for the management of safe anaesthesia in TE fistula repair.

1. Aspiration pneumonities.
2. Over distension of stomach by air coming through the fistula.
3. Ventilatory problems, as gases pass through the trachea and fistula to further distend the stomach.
4. Problems due to other concomitant congenital anomalies.

After birth, the corrective surgery for TE fistula should be performed as an one-stage repair and as soon as possible. Delay usually results in more soiling of the lungs, causing more pneumonitis which makes the patient gradually inoperable.

Preoperatively the child should not receive any feeding and a large bore catheter is placed in the blind oesophageal diverticulum in the A, B, C and D types of T-E fistula. It will help to drain the saliva continuously, so that the child does not swallow it. The child should be nursed in prone position with head-up tilt to prevent the soiling of lungs by gastric fluid in B, D and E types of T-E fistula. If the lungs are soiled and the child has pneumonia or pneumonitis, then the operation should be postponed until the pneumonitis improves by antibiotic and physiotherapy. Operation should be performed as soon as the child's condition is optimized medically. Sometimes, if operation is delayed for a long time due to severe illness of the baby, then initially a palliative gastrostomy should be performed to provide the means of nutrition during recovery from pneumonities and to prevent further pneumonitis (Figs 25.8A to E).

Awake intubation or inhalational induction by volatile anaesthetic agents followed by intubation is the choice of anaesthesia. Intubation after an adequate

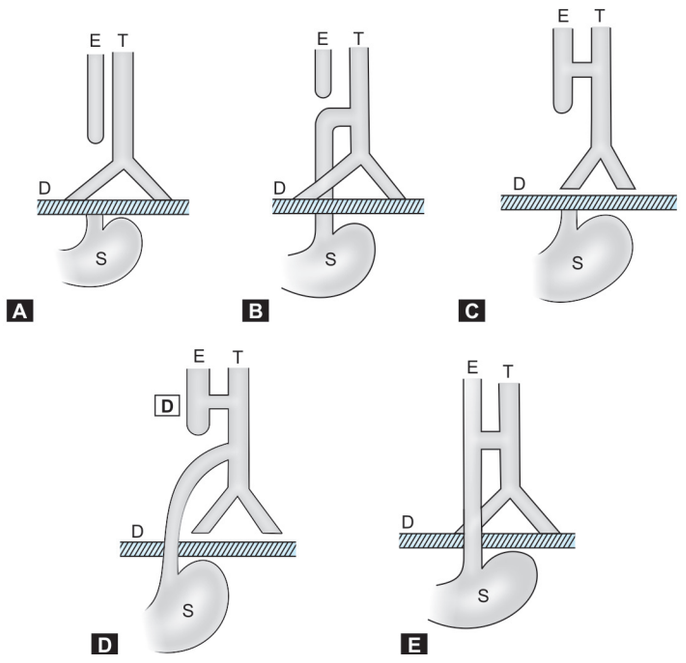


Fig. 25.8A to E: Varieties of tracheo-oesophageal fistula. E-Oesophagus, T-Trachea, S-Stomach, D-Diaphragm

dose of a muscle relaxant and followed by IPPV is contraindicated, as positive pressure ventilation causes huge distension of stomach due to passage of gas through the trachea and fistula, and subsequent compression of the diaphragm and lungs. Initially the ET tube should be inserted intentionally to deeper level beyond the fistula than predicted in any main bronchus, right or left. Tube is then withdrawn slowly, until the breath sounds are heard equally on both sides. This technique usually ensures that the tip of ET tube is placed beyond the level of fistula, but proximal to the carina. The leak of gas into the stomach caused by the placement of ET tube proximal to the fistula is easily diagnosed by auscultation of abdomen with a precordial stethoscope. The endotracheal tube should be inserted with the bevel facing up, so that the posterior wall of the tube occludes the fistula. This is because the fistula is usually situated on the posterior wall. After inhalational induction by volatile anaesthetic agents and intubation by muscle relaxant the controlled ventilation is always recommended for the surgical repair of tracheo-oesophageal (T-E) fistula. After intubation, the determination of O_2 saturation by pulse oximeter is the most useful monitoring, because any intraoperative change in the position of ET tube, as little as 1 to 2 mm from the previous position may determine whether the anaesthesiologist is ventilating the both lungs, or the one lung or the fistula. The ventilation must be monitored very carefully during surgical dissection of the fistula, as the trachea may kink during traction or manipulation and the ET Tube may be dislodged during traction. Postoperatively the neonates, especially the premature ones may have repeated apnoeic spells and this is may be due to the residual effect of anaesthesia, hypoxia, hyperglycemia, anaemia, hypocalcemia or hypothermia. Therefore, the patient should not be reversed to spontaneous respiration postoperatively for at least 12 hours.

The postoperative care of a neonate after surgical repair of T-E fistula should be given in a neonatal intensive care unit with full monitoring facilities.

Pyloric Stenosis

The incidence of pyloric stenosis is about 1 in 400 live births and males are affected in about 80% cases. It presents usually during the first 4 to 6 weeks of life after birth and is not a surgical emergency. The pathology of pyloric stenosis is the gross thickening of pyloric circular smooth muscle like a hard tumour, causing obstruction to food with increased vomiting. If untreated, the infant loses weight and becomes severely dehydrated with hypokalaemia, hypochloraemia and metabolic alkalosis. This is due to repeated vomiting of gastric secretions containing H^+ and Cl^- ions. As the obstruction is at the level of pylorus, so there is no loss of alkaline intestinal secretions. Body is thus loaded with bicarbonate and the kidney has to take this load. Bicarbonate load on the kidney at the glomerular level, exceeds its absorption power at the tubular level. Thus, the urine becomes alkaline and indicates compensatory phase. If the dehydration remains uncorrected, then hypovolaemia activates renin-angiotension-aldosterone axis to preserve the circulating volume by absorbing Na^+ and water from renal tubules. This results in an exchange of Na^+ for H^+ and K^+ (Na^+ enters, H^+ and K^+ released), which leads to the paradoxical acidic urine with worsening of hypokalaemia and metabolic alkalosis. This indicates decompensatory phase.

The surgery for pyloric stenosis (pyloromyotomy) is not an emergency one. So, it should be preceded by complete correction of fluid and electrolyte imbalance. The initial management of pyloric stenosis is gastric suction through a nasogastric tube and IV cannulation for parenteral therapy. The nasogastric suction is very important, because the stomach is always filled up with food, debris, barium sulphate (used for radiological diagnosis), etc. The initial intravenous infusion of fluid should be 5% dextrose in 0.45% saline to which 40 m.mol/L of KCl is added (2 ml/Kg of 0.9% NaCl raises the serum chloride by 1 m.mol/L). Usually, the rate of infusion of fluid is 6 ml/Kg/hour. During the preoperative preparation of patient the gastric residue is drained off continuously by nasogastric suction and stomach is washed with 0·9% saline every 4 hourly, until the aspirate is clear and odourless. Surgery should not take place until the plasma chloride level is at least 90 mmol/L and the potassium bicarbonate concentration is 25 mmol/L.

Usually, the child becomes ready for surgery within 24 to 48 hours after the commencement of treatment. Before induction of anaesthesia stomach should always be aspirated and as the children are sick but lusty, so awake intubation is not possible. However, the induction should be smooth by either the inhalation or IV route, according to the experience of the anaesthesiologist. Cricoid pressure must be used, which should be as effective in infants as in adults to prevent the aspiration of gastric contents in the lungs if there is any, even after aspiration by nasogastric tube. The postoperative oral feeding is usually re-established immediately after the patient returns to the ward. The postoperative analgesia is provided by wound infiltration with local anaesthetic agents and rectal or oral paracetamol, depending on when the surgeon decides to feed the child.

Omphalocele and Gastroschisis

It is the protrusion of a part of intestine through a defect in the anterior abdominal wall at the level of umbilicus, resulting in exposure of the viscera that are either covered (omphalocele) or uncovered (gastrochisis) by peritoneum. Whereas exomphalos is the herniation of the abdominal viscera into the unbilical cord of varying degree without any defect in the anterior abdominal wall. However, omphalocele or gastrochisis and exomphalus are embryologically two separate conditions, but present similar challanges to the anaesthesiologist.

These conditions are surgical emergencies. It is imperative that the abdominal contents should be placed in a clear sterile polythene bag, as soon as possible after birth to prevent infection, heat loss and fluid loss. Adequate intravenous access and extensive intraoperative invasive monitoring are usually necessary. This is because hypotension secondary to tension on major organs or caval compression during surgical manipulation is common. N_2O should be avoided during maintenance of anaesthesia. Muscle relaxants should be used liberally to provide optimal surgical conditions and relaxation for closure of the defect on the abdominal wall through which herniation was occurred. Nasogastric tube should be in place to decompress the stomach which will help in reduction of viscera and easy closure of the anterior abdominal wall. Postoperative controlled ventilation is mandatory, because of the reduction in compliance of the lungs, due to increased intra-abdominal pressure caused by the return of the viscera in the peritonial cavity and to provide adequate time to the abdominal wall to stretch and accommodate the viscera slowly. Intravenous alimentation play a vital role for the rapid recovery of these patients. Sometimes, it is not possible to close the defect in one sitting, then staged surgical procedures may be planned (Table 25.24).

Table 25.24: The challenges in management of omphalocele and gastrochisis

1. Massive fluid loss and dehydration. It results from the exposed visceral surfaces and from the third space loss, caused by partial bowel obstruction.
2. Heat loss.
3. Infection.
4. Difficulty in surgical closure without causing severe increase in the intra-abdominal pressure and severe compression on the lungs.
5. Frequent association of this condition with prematurity.
6. Other associated congenital defects with this condition.

Meningomyelocele

It is the herniation of a part of the meninges and the spinal cord through a defect in the vertebral column. It is a common neonatal congenital abnormality and requires an emergency surgery (Table 25.25).

Cleft Lip and Cleft Palate

Though in some centres, the total repair of both the cleft lip and cleft palate is carried out in the neonatal period, but usually the primary repair of a cleft lip is performed during the first few weeks of life and that of a cleft palate between 1 and 3 years of age. The cleft lip and cleft palate are also often accompanied by other congenital anomalies. Among them the defects of cardiac and central nervous system are of particular relevance to the anaesthesiologist. These conditions are also often associated with Pierre-Robin syndrome (micrognathia, cleft palate and glossoptosis), Treacher-Collins syndrome (cleft palate and hypoplasia of the first bronchial arch) and Klippel-Feil syndrome (fused cervical vertebrae). These may cause incipient or actual respiratory obstruction and make intubation very difficult. In Pierre-Robin syndrome, the periodic episodes of respiratory obstruction occur due to a relatively oversized tongue, blocking the airway. So, they have to be nursed in the prone position in order to overcome the obstruction. Failure to thrive as a consequence of difficulties in feeding and repeated respiratory infections is common in this group of patients.

The ideal collaboration of surgeon, paediatrician and anaesthesiologist is very much desirable in treating preoperative anaemia, malnutrition, respiratory infection, etc., which are commonly associated with these congenital anamolies and also in judging the optimal time for operation of this group of patients.

Table 25.25: Points to be kept in mind during anaesthesia of meningomyclecele

1. Possible association of meningomyelocele with hydrocephalus.
2. Possibility of cranial nerve injury during surgery.
3. Possibility of brain herniation during and after surgery.
4. Possibility of underestimation of fluid and blood loss.

Sedative premedication should be avoided during surgery of cleft palate. Induction by inhalation of N_2O, O_2 together with halothane or sevoflurane is simple and effective, although some anaesthesiologists prefer an intravenous induction. Once the child is asleep by inhalational anaesthetic agents, then an intravenous infusion line can conveniently be set up. Intubation can be performed under deep inhalational anaesthesia, but the use of muscle relaxants intravenously provide an optimum condition. But before giving relaxants of any sort, it is wise to ensure that the facial configuration of the patient will allow effective artificial ventilation with a bag and mask. It is particularly important to avoid trauma to the lips or gums in children waiting for repair of cleft lip during intubation. So, a 'tooth guard' made of several layers of sticking plaster or a custom made soft plastic mould is used. It will not only protect the gums, but also prevents the laryngoscope blade from falling into the maxillary defect. Sometimes, the use of a wad of gauze placed in the roof of the mouth will prevent the blade of the laryngoscope from slipping into the cleft.

There should be a wide range of ET tubes available to the anaesthesiologist for intubation during surgery of cleft lip and cleft palate. The surgeon requires the tube to be as unobtrusive as possible, while the anaesthesiologist requires a non-kinkable secure airway. During operation the use of one of the various modifications of the Dott-Gag will allow a good access to the surgeon, and the ET tube is retained in position by the lower (tongue) blade. But, care must be taken to check the patency of the tube after insertion of the gag, as the latter may occlude the tube by pressing it on the mandible. A preformed endotracheal tube, such as: Oxford tube is

preferred in these cases. Its strengthened proximal segment and built in pharyngeal curve offers greater resistance to kinking than the standard Magill's tube. The Oxford tube is, however, more difficult to introduce than the gently curved Magill's tube. But using a fine gum elastic bougie, threaded inside the tube as an introducer, greately facilitates intubation. The Oxford tube is tapered at the patient's end. It is, therefore, possible to force an overlarge tube through the glottis and through the narrowest part of the trachea at the cricoid cartilage unintentionally which may give rise to laryngeal oedema and postoperative croup. So, particular care must be taken to select a well-fitting tube with minimal gas leak. A small gas leak is of no significance, particularly as a pharyngeal pack is invariably used in such cases to protect against inhalation of blood.

Many anaesthesiologists allow spontaneous ventilation during surgery and maintain anaesthesia by N_2O, O_2 with any potent inhalational anaesthetic agent. Provided, the concentration of halothane is kept low and hypercarbia is not allowed to occur, then an infiltration of local anaesthetic with 1:200000 adrenaline is not a concern. Controlled ventilation using N_2O, O_2 and nondepolarising relaxants and / or opioids is a useful alternative, particularly when an anaesthesiologist is reluctant to use halothane.

With completion of surgery after pharyngeal suction, extubation should be done carefully in an awake and semiprone position which will protect against aspiration of slightly oozed blood from the operation site. Prior to extubation, auscultation of chest is mandatory which may reveal any retained secretion and occasionally a poorly expanding or blocked segment of the lung. In such conditions, careful suction of the endotracheal tube followed by gentle hyperinflation of the lungs is usually all that is needed. Children who are accustomed to breathe through the large defects in the palate have little time to accommodate the diminished airway, following operative repair. So, a bag, mask and an airway should be ready to treat any temporary obstruction of the airway, following extubation. An anaesthetic technique which will ensure rapid recovery of pharyngeal reflexes should be selected. Blood should be cross-matched as the surgical loss may exceed 10% of the total blood volume.

Postoperative airway problems after surgical correction of cleft palate are not infrequent, particularly in cases of a small mandible where the effectiveness of the genioglossus muscle is lost and the tongue falls back, partially or completely blocking the airway. In such circumstances nursing of child in the prone position is usually sufficient, although forward traction of the tongue by means of a tongue stitch may be required in refractory cases.

Inguinal Hernia

This is one of the commonest operations like circumscision in the paediatric age group of patients. At present regional anaesthesia (spinal, epidural or caudal) combined with light GA is the chosen mode of anaesthesia for repair of inguinal hernia in paediatric patients. Only general anaesthesia is indicated where regional anaesthesia is absolutely contraindicated. Regional anaesthesia combined with GA has several advantages over only GA.

The advantages of regional anaesthesia combined with GA are:

i. Decreased dose of the general anaesthetic agent required for surgery.
ii. Rapid pain free recovery.
iii. Early ambulation.
iv. Early discharge.

For RA the type of blocks and techniques chosen should have minimal side effects and should not interfere with the motor function. All the techniques of RA such as spinal or caudal or lumbar epidural with or without catheter and with or without adjunct may be applied. The child should have an IV cannula in place before the RA applied. But unlike the adult practice the volume preloading is not needed. Administeration of vasoactive drugs such as ephedrine is also not required. Spinal anaesthesia has a very quick onset of action with profound muscle relaxation, but duration of action is short. Caudal anaesthesia and analgesia has a slower onset, but lasts for a longer time. Therefore, under GA combined with caudal bilateral hernia can also be repaired and can provide postoperative analgesia too. Combined spinal-epidural (CSE) anaesthesia has both the advantages of spinal and caudal anaesthesia. Hence, in conclusion it can be said that all types of regional anaesthetic techniques adopted in adults can be administered safely in paediatric patients, combined with GA. But only strict attention has to be paid to the route of administeration, the dose of the local anaesthetic agent and the size of the proper equipment (e.g. miniature needle, fine catheter, etc.).

Caudal block with 0.25% bupivacaine in a dose of 0.75 to1 ml/Kg with or without catheter is effective for inguinal hernia repair or orchidopexy. For circumcision or hypospadious repair the caudal dose of bupivacaine is 0.5 ml/Kg as 0.25% solution. For the volumes over 20 ml the bupivacaine is diluted to 0.15%. For all the above mentioned percentage and doses of bupivacaine, analgesia lasts for 4 to 6 hours. Bupivacaine concentration higher than 0.25% offers no added advantage about sensory blockade, except adverse motor blockade. Also 0.125% bupivacaine solution is reported to produce the same quality and duration of intraoperative and postoperative analgesia as 0.25% solution and the lower concentration resulted in lesser motor blockade. For inguinal hernia repair and orchidopexy the ilioingninal and iliohypogastric nerve block which is achieved by infiltrating 0.25% bupivacaine medial to the anterior superior iliac spine also has been used successfully in paediatric patients. The penile nerve block for circumscision or hypospadius operation or any other surgical procedure on the

penis which is achieved by infiltration of 1 to 3 ml adrenaline-free 0.25% bupivacaine or adrenaline-free 1% lignocaine provides excellent intraoperative and postoperative analgesia.

The direct local infiltration of the surgical wound by long acting local anaesthetic agents is another effective method of providing pain relief (postoperative analgesia) in all children. In most institutions it is now rare for a paediatric patient to awaken from anaesthesia without some form of regional block. Parents are advised to start analgesia (oral or parenteral) when the child begins to become irritable, but prior to the complete dissipation of the block. This procedure usually provides a smooth transition and a pain free postoperative period.

POST-OPERATIVE PAIN RELIEF IN CHILDREN

Many adverse pathophysiological changes occur in children due to the acute postoperative pain. These are increase in anxiety, avoidance, certain adverse somatic signs and symptoms such as: ↑HR, ↑BP, ↑metabolic acidosis, ↑RR causing respiratory alkalosis, ↑catecholamines, etc, and the increase in parent's distress. But, unfortunately the acute pain experienced by children is often inadequately assessed and treated, inspite of our sincere efforts.

This is because pain in children had been often underestimated and undertreated. This is due to an exaggerated fear of respiratory depression caused by narcotics which are used as post-operative analgesics and other misconceptions (Table 25.26).

But, modern paediatric anaesthesia asserts on the controlling and decreasing the postoperative pain, as far as possible, without causing any harm to the child. The severity of the pain dictates the choice of the analgesic. Mild pain is treated with non-opioids, whereas the moderate and severe pain is treated with opioids and/or regional anaesthesia.

Table 25.26: Misconception governing the post-operative pain relief in children

1. Due to immaturity of the nervous system, children experience no or little pain than adults. But the nerves responsible for pain are fully developed by 27 weeks of gestation.
2. Paediatric patients, especially neonates and infants, have no memory of pain.
3. Pain is not a character building for children, which is incorrect.

The adequate pain management in paediatric patients requires the following methodical approach.

i. Pain evaluation
ii. Route of administeration
iii. Selection of drugs

Pain Evaluation

The pain in paediatric patients can be assessed by using self-report, behavioural observation and psychological changes, depending on the age of the child and his or her communication skills. In the school-going age the children can give the verbal description of severity of their pain, but it is more difficult to evaluate it in a preverbal child. So, different ages demand different methods of evaluation of pain. However, the behavioural and physiological scales are important for newborns, infants and preschool children. Their score is based on the changes in physiological parameters such as heart rate, blood pressure, respiratory rate, sweating, crying, patient's position and facial expressions, etc. The most popular scales for assessment of pain in preverbal children are : the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), the Objective Pain Scale (OPS) of Hannallah Broadman and the Children and Infants Post-operative Pain Scale (CHIPPS). In older children, the self-evaluation scores are much more suitable. Therefore, Visual Analogue Scales (VAS) can be used for this group of patient. The 'Smiling Facies' scale (from smiling to sad and then to crying facies corresponding to increasing pain) and 'The Colour's Scale' (from red to green – no pain to highest pain) are also routinely applied according to the age, verbal communication skill and intelligence of patient.

Routes of Administration

Oral analgesia is always desirable for children, whenever is possible. The standard doses of analgesics and adequate intervals through oral route provide excellent analgesia in the majority of patients. The intravenous route of administration of drugs provides rapid onset of analgesia with the advantage of incremental intravenous titration, but with no discomfort to the child. The intramuscular injections should be avoided, as children often deny repeated intramuscular injections and also because of unpredictable pharmacokinetics.

Patient Controlled Analgesia (PCA) also provides excellent analgesia for paediatric group of patients. However, preoperative education is valuable for children using PCA. This is because the patient needs the control of button to self-administer the bolus of analgesics and before using PCA adequate intravenous loading dose of the opioid is required to achieve the adequate blood levels. The two modes of PCA are used. These are (i) bolus only and (ii) bolus with continuous infusion. Various nerve blocks and epidural block are also often can be used for postoperative analgesia (Table 25.27).

Selection of Drugs

The non-steroidal anti-inflammatory drugs (NSAIDs) are taken as the first line of therapy for analgesia in paediatric group of patients. This is followed by the opioids and then local anaesthetics. Recently,

Table 25.27: Common routes of administration

Oral	:	Transmucosal preparation Fentanyl lollipop (8 to 10 µg/Kg)
Rectal	:	Paracetamol (80 to 170 mg)
	:	Diclofenac (12.5 mg)
Parenteral		Intramuscular
	:	Intravenous
		Bolus, continuous infusion, PCA, epidural, subcutaneous

the local anaesthetic agents have become the drug of choice. Recently a multimodal approach using a combination of drugs provides effective analgesia with a lower doses than any single drug.

Among the NSAIDs, paracetamol is the agent of first line management for paediatric pain control. Their action is linked to their anti-inflammatory, antipyretic and analgesic effects by inhibiting cyclo-oxygenase and thus reducing the production of pain mediators like thromboxanes and prostaglandins. Their main efficacy is in mild to moderate pain. But, they also have an opioid-sparing effect. They are metabolized in the liver and excreted by the kidneys. They should be used with caution in newborns, because their organs are still immature. Other side effects of NSAIDs are: gastric irritation and inhibition of platelet function. They also have a ceiling effect which means that above a certain higher dose there is only an increase in the side effects without increasing the analgesic effect. NSAIDs must be avoided in infants less than 1 year. Most NSAIDs can be administered by the oral or rectal route, while ketorolac and propacetamol can be used through IV. Paracetamol is the most commonly used paediatric analgesic in daily practice. A recent paper recommends the following doses of paracetamol in children: 40 mg/Kg as rectal suppositories (PR) initially, followed by 20 mg/Kg orally, followed by 30 mg/Kg orally at every 8 hours interval. The 90 mg/Kg/day dosage is not always sufficient for pain relief and 100 to 200 mg/Kg/PR may be necessary, keeping in mind that the toxicity is connected with the cumulative action of repeated doses. In the newborn the dosage of paracetamol is reduced to 40 mg/Kg/PR, followed by 30 mg/Kg/12 hours orally. Propacetamol, the injectable water soluble prodrug of paracetamol is useful for faster onset of analgesia. The recommended IV dose of Ketorolac, another NSAID whose effectiveness has been demonstrated successfully in acute pain management is 0.75 mg/Kg and provides analgesia similar to 0.1 mg/Kg of morphine. Diclofenac is used as 0.5 to 1 mg/Kg/rectal and Ibuprofen as10 mg/Kg orally, every 8 hours.

The opioids are the basis of postoperative treatment for moderate to severe pain. Their action is at the specific receptors along the CNS, inhibiting the release of neurotransmitters. The major concern for the use of narcotics in the paediatric age group of patients is the proportional increase in side effects with increased doses. These are respiratory depression, nausea, vomiting, pruritus, urinary retention, delay in gastrointestinal function, etc. The respiratory depression can occur even several hours after the administration of opioids. So, the accurate monitoring of all the vital parameters such as respiratory rate and oxygen saturation is mandatory. The evaluation of sedation score is also important for paediatric group of patients because a slight overdose of narcotics may easily cause deep sedation which is not desirable. Morphine is the gold standard opioid with which all other opioids are compared and is frequently used for postoperative pain relief in children. The doses of morphine depend on the route of administration, for example, SC → 0.01 to 0.02 mg/Kg, IV → 0.02 to 0.1 mg/Kg, continuous infusion : loading dose of 0.1 to 0.2 mg/Kg followed by 0.01 mg/Kg/hour; Epidural→ 0.03 mg/Kg/8hours. However, the above mentioned doses of morphine must be reduced in newborns and infants. Fentanyl is 100 times more potent than morphine. It has a rapid onset and shorter half life. So, it is useful for short-term therapy in acute pain in the dose of 1 to 4 μg/Kg IV. Fentanyl also can be administered epidurally at the dose of 1 to 2 μg/Kg. Remifentanyl is the most recent synthetic opioid which is mainly metabolised by a specific plasma esterase. It has a very short elimination half-life of 3 to 5 minutes. Alfentanil and sufentalil are two other important synthetic opioids. The commonly prescribed adjuvant drug for opioid's complication is naloxone (5 to 10 μg/Kg − IV) and ondansetron (0.1 to 0.2 mg/Kg /8 hourly − IV or PO).

Table 25.28: Common regional block

Caudal	: 0.5 to 1.2 ml/Kg of 0.25% bupivacaine for sacral or lumbar nerves
Penile block	: 0.1 ml/Kg of 0.25% bupivacaine on each side
Ilioinguinal block	:
Lumbar epidural	: 0.5 ml/Kg of 0.5% bupivacaine
Brachial plexua block	: 0.3 ml/Kg of 0.25% bupivacaine

The regional anaesthesia has a wide application for the management of postoperative pain in paediatric group of patients. The regional analgesia can involve epidural block, subarachnoid block, different plexus block, different peripheral nerve block wound infiltration and topical application. Blocks are safe and effective in children with the use of different local anaesthetic agent with or without adjuvants like clonidine, opioids, etc, in both as single shot or as continuous infusion technique, according to the type of surgery and the quality and intensity of the post-operative pain. It is the best technique for reducing the surgical stress. All local anaesthetics used for adults may be applied in paediatric practice too, provided the appropriate dosing regimens are followed. The lignocaine and mevacaine are suitable for short time surgeries and mild postoperative pain, while bupivacaine is used for long-term analgesia. Ropivacaine is the new aminoamide local anaesthetic agent with lesser cardiac and central nervous system toxicity than bupivacaine (Table 25.28).

To conclude for the postoperative pain management in paediatric patients, we can always say that the presence of a tender and loving care of mother by the side of the child reduces the pain to a great extent. The anticipation of pain and its pre-emptive intervention is very helpful. Using the multimodal (pharmacological, cognitive, behavioural and physical) and the multi disciplinary approach for the relief of pain, whenever possible, offers the best post-operative pain relief in children.

26 Perioperative Arrhythmia and its Management

INTRODUCTION

The incidence of perioperative cardiac arrhythmia varies from centre to centre and it depends on many factors. These factors are:

i. Types of arrhythmia (because all the types of arrhythmia are not taken into account or its incidence, as all are not potentially so harmful).
ii. Types of surveillance. Extensive surveillance increases the incidence of arrhythmia and less sensitive survilence decreases the incidence of arrhythmia.
iii. Patient's characteristics and underlying diseases.
iv. The nature of surgery.
v. The nature of anaesthesia itself with its different variabilities.

The perioperative arrhythmias are nothing different or special in type. These are the same arrhythmias that we see in everyday cardiologycal practice. But these are just named such (perioperative arrhythmia), because they are associated with operative procedures. Even the management of these arrhythmias remains more or less the same, except stoppage or alterations of some anaesthetic drugs. and stoppage of some surgical procedures such as traction on viscera, muscles (specially ocular), peritoneum, etc. The incidence of perioperative arrhythmias in cardiothoracic surgery with extensive monitoring exceeds 90% and in most of these cases requires no treatment. Whereas this incidence of perioperative arrhythmia in elective caesarean section is very low. The factors that determine how a patient tolerates perioperative arrhythmias include: heart rate, the specific type of arrhythmia, duration of arrhythmia, the presence and severity of any underlying cardiac disease, the effects of that specific cardiac rhythm on the cardiac output and the possible interaction of antiarrhythmic drugs with the drugs which are administered to produce and maintain the anaesthesia.

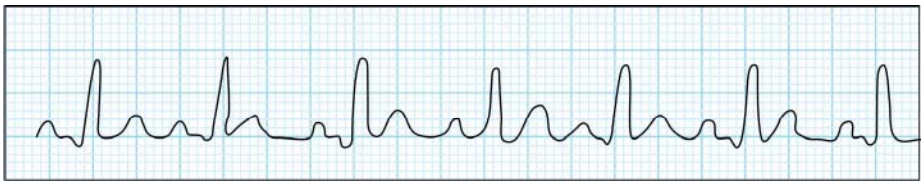


Fig. 26.1: ECG with sinus rhythm at heart rate of 100/min, because there are 3 large squares between two QRS complexes

HEART RATE

The measurement of heart rate and the identification of cardiac arrhythmia go hand in hand. This is because many abnormalities of heart rate measurement results from arrhythmias and also any wrong measurement of HR may seem arrhythmia. However, to begin with, I shall describe ways how to measure the heart rate from ECG tracing and how to diagnose the abnormalities that can affect it. It will have to remember that when there is talk of measuring the heart rate, it will mean the ventricular rate which corresponds to the patient's pulse and not the atrial rate.

Measurement of Heart Rate

Measurement of heart rate from an ECG tracing is simple and can be done in several ways.

i. When the paper speed is 25 mm/sec, then 1 sec ECG tracing covers 25 mm length of paper or 25 small squares, or 5 large squares (every small square is 1 mm and every large square containing 5 small squares is 5 mm) (Fig. 26.1). Therefore, 1 minute ECG tracing covers 1500 small squares or 300 large squares (60 sec × 5 large squares). If patient's cardiac rhythm is regular, then that have to do is to count the number of large squares between two QRS complexes and divide 300 by this number which will give the heart rate.
For example, if there are four large square between two QRS complexes, then the heart rate is 300 ÷ 4 = 75 per min. The explanation is like that 300 large squares mean 1 minute and the number of large square between two QRS complexes mean the interval between two heart beat. So, the division of 300 (i.e. 1 minute) by the interval (time in second) between two heart beat will give the heart rate.
ii. When the rhythm is irregular, this method does not work well because the number of large square between two QRS complexes varies from beat to beat. Here, that have to do is to count the number of QRS complexes within the total duration of 30 large squares which indicates the number of QRS

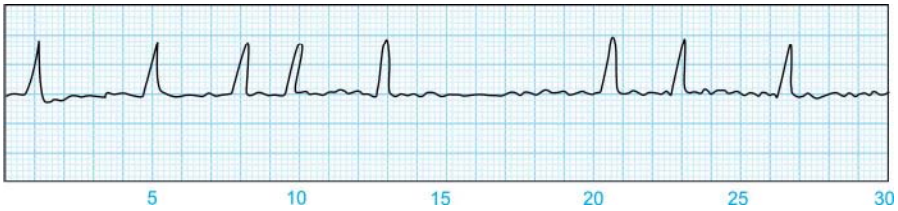


Fig. 26.2: This graph shows irregular cardiac rhythm. Here heart rate is calculated like this: We know 5 large square is 1 sec, or 1 sec = 5 large square, So 60 sec or 1 min = 60 × 5 = 300 large square, 30 large square contain 8 QRS complexes. So, 300 large square contain 8 × 10 = 80 QRS complexes. Thus, the heart rate is 80/min

complexes in 6 sec. (1 sec means 5 large squares) (Fig. 26.2).

Now, the heart rate can simply be workout by multiplying the number of QRS complexes in 6 sec (which is equivalent to 30 large square) with 10. As for example, if the number of QRS complexes within 30 large squares is 6, then the heart rate is 6 × 10 = 60 per minute.

iii. When the ECG paper speed is 25 mm/sec (i.e. 25 small squares per sec because every small square is 1 mm or 0.04 sec), then within 1 minute the tracing covers 1500 small square. Then the heart rate can easily be calculated by dividing 1500 with the number of small squares between two R waves. As for example, let the number of small squares between two R waves is 20. Then the heart rate is 1500 ÷ 20 = 75 per minute (Fig. 26.3).

These above methods of measurement of ventricular rate also can be used to measure the atrial or P-wave rate and to match the atrial rate with the ventricular rate. Usually, the two rates are same. But, in some situations the P waves are prevented to originate or are originated but are incapable of activating the ventricle and the two rates differs. This situations will be discussed later on (Fig. 26.4).

After the measurement of heart rate, one have to decide is whether: (i) it is regular or irregular, (ii) bradycardia or tachycardia, (iii) QRS complex is narrow or broad and (iv) supraventricular or ventricular in origin. As a general rule, a regular cardiac rhythm with heart rate between 60 and 100 beats per minute is considered normal. If the heart rate is regular but below 60/min, then it is called bradycardia and if the heart rate is regular but above 100/min, then it is called tachycardia.

Sinus Rhythm

Sinus rhythm is the normal cardiac rhythm in which the SA node acts as the natural pacemaker and discharging impulses at the rate of 60 to 100 times per minute (Fig. 26.5).

Sinus Arrhythmia

It is the normal physiological variation of heart rate with respiration, i.e. increase in heart rate during inspiration and decrease in heart rate during expiration. Heart rate increases during inspiration as a reflex response to the increased blood volume returning to the heart during inspiration. But during expiration reverse occurs and heart rate decreases. It is harmless and no treatment is necessary. It is uncommon after the age of 40. The characteristics of sinus arrhythmia in ECG tracing are that every P-wave is followed by QRS complex and the heart rate varies with the respiration (Fig. 26.6).

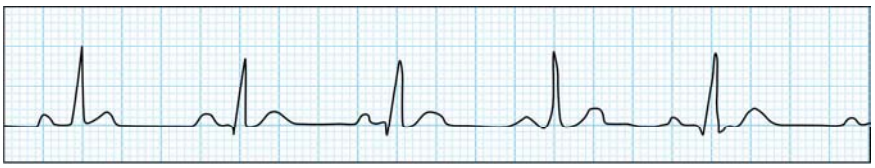


Fig. 26.3: This graph indicates 20 small squares between two R waves. So, 20 small squares indicate one heart beat. Therefore, 1500 small squares (or 1 minute) indicates 1500 ÷ 20 = 75 heart beat

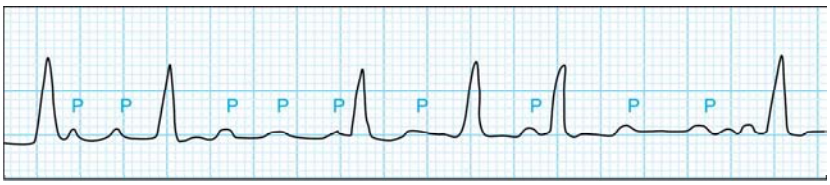


Fig. 26.4: This graph shows different P-wave and QRS complexes. To calculate the P-wave and QRS complex rate separately, we have to take the help of 30 large square

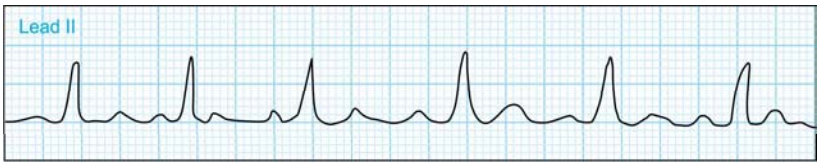


Fig. 26.5: This is a graph of sinus rhythm which is characterised by: (i) regular heart beat by any rate, (ii) P waves are upright in lead II and (iii) QRS complex after every P waves

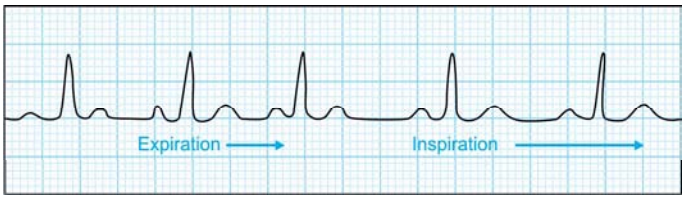


Fig. 26.6: This is a graph of sinus arrhythmia, characterised by: heart rate 100/min during inspiration and 75/min during expiration

PERIOPERATIVE DIFFERENT TYPES OF CARDIAC RHYTHM

The following types of cardiac rhythms (normal or abnormal) are usually encountered during the perioperative period.

Rhythms Arising from SA Node

Sinus rhythm, sinus arrhythmia, sinus bradycardia, sinus tachycardia, sick sinus syndrome, sinus arrest.

Rhythms Arising from Atrial Musculature

Atrial tachycardia – (supraventricular tachycardia, paroxysmal supra ventricular tachycardia) atrial flutter, atrial fibrillation.

Rhythms Arising from AV Node

AV nodal re-entry tachycardia, AV re-entry tachycardia (W-P-W syndrome), AV nodal or junctional rhythm, AV junctional tachycardia.

Ventricular Rhythms Arising from Ventricular Musculature

Ventricular extra-systoles, ventricular tachycardia, accelerated idioventricular rhythm, torsades-de-pointes, ventricular flutter and ventricular fibrillation.

Rhythm Due to Conduction Disturbance

Escape rhythm, ectopic beats (RBBB or LBBB are not varieties of rhythm. These are only due to conduction defects).

Following questions should be asked for diagnosis or identification of various types of cardiac rhythms:

The diagnosis of various types of cardiac rhythm from the tracing of ECG are not usually difficult. But, sometimes it becomes difficult. Then the following questions should be asked which will facilitate the diagnosis of different arrhythmias. These are:

(i) From where the impulses are arising?

SA node, atria, AV node or ventricles. (Table 26.1).

(ii) How the impulses are conducted?

Normal conduction, accelerated conduction (W-P-W syndrome) or blocked conduction.

(iii) If the rhythm is regular or irregular?

To determine whether the cardiac rhythm is regular or not, the distance between the two consecutive R waves is measured. If the RR interval varies, then the rhythm is irregular. The causes of irregular rhythm is sinus arrhythmia, atrial flutter with varying degree of blocks, atrial fibrillation (AF), any supraventricular rhythm with intermittent block, escape rhythm, ectopic beats, ventricular fibrillation.

(iv) If the rhythm is supraventricular (including the AV junction) or ventricular?

The supraventricular rhythm means when it originates from the site above the ventricle. All the supraventricular rhythms produce narrow QRS complexes, provided there is no conduction defects. If supraventricular rhythm is associated with bundle branch block or an accessary pathway, then the QRS complexes will be broad. The ventricular rhythm by itself originating from ventricular musculature are associated with broad QRS complex (>3 small squares). This is due to the conduction of impulses through ventricular musculature, instead of through the specified high conducting Purkinje fibres which takes less times.

Table 26.1: Different types of cardiac rhythms

1.	**SA nodal rhythms**
	Sinus rhythm
	Sinus arrhythmia
	Sinus tachycardia
	Sinus bradycardia
	Sick sinus syndrome
	Sinus arrest
	Sinus block
2.	**Atrial rhythms**
	Atrial tachycardia
	Paroxysmal atrial tachycardia
	Atrial flutter
	Atrial fibrillation
3.	**Atrioventricular rhythms**
	AV nodal or junctional rhythms
	AV junctional tachycardia
	AV re-entry tachycardia
	AV nodal re-entry tachycardia
4.	**Ventricular rhythms**
	Ventricular tachycardia
	Accelerated idioventricular rhythm
	Torsades-de-pointes
	Ventricular fibrilation
5.	**Conduction disturbances**
	RBBB, LBBB, LAHB, LPHB,
	Bifasicular block
	Complete block
6.	**Escape rhythms**
7.	**Ectopic beats**

(v) If the P-waves are present or not?

The presence of P-waves indicates atrial activity. So, careful examination of P-waves and QRS complexes gives an idea of the relationship between atrial and ventricular activity. The shape of P-wave also provides an idea of the origin of atrial depolarisation. For example – if it is upright in lead II, then it is sure that the atrial depolarisation origins in or near the SA node. On the contrary, inverted P-waves in lead II suggest its origin closer to or within the AV node. This is because here impulses pass from AV node to SA node whose direction is upwards and opposite the direction of lead II. If all the P-waves are followed by QRS complexes, then it indicates that conduction from atrium to ventricle is normal and there is no AV block. If there are more P-waves than QRS complexes, then conduction between atria and ventricles is being either partly blocked or completely blocked or atrial activity is such increased that it is beyond the normal conduction capability of AV node. More QRS complexes than P-waves indicate AV dissociation with higher ventricular rate than atrium. During the identification of P-wave always it have to bear in mind that sometimes the P-waves may be difficult or even impossible to identify clearly. Therefore, it can be difficult to say firmly that atrial activity is present or absent.

(vi) If there is bradycardia or tachycardia?

CAUSES OF PERIOPERATIVE BRADYCARDIA AND ITS MANAGEMENT

In the previous page all the arrhythmias are classified according to the site of their origin. But here from the aspect of management all the arrhythmias are classified under the two broad headings — arrhythmia causing bradycardia and arrhythmia causing tachycardia.

The common causes of perioperative bradycardia are:

i. sinus bradycardia
ii. sinus arrest
iii. sinoatrial block
iv. sick sinus syndrome
v. conduction defects – second and third degree AV block,
vi. Escape rhythm – AV junctional escape rhythms, ventricular escape rhythm,
vii. ectopics
viii. asystole

Sinus Bradycardia

Sinus bradycardia is defined as a type of sinus rhythm where the heart rate is less than 60 beats per minute. In physiological conditions it is usually found in normal persons, athletes, during sleep, etc. and is not harmful. It is unusual for the sinus bradycardia to be slower than 40 beats/min, otherwise alternative causes like heart block, drug effect, etc. should be considered. The probable pathological causes of sinus bradycardia are: drugs (digoxin, β-blockers, antiarrhythmic agents, adenosine, verapamil, diltazem, anaesthetic drugs etc.), ischaemic heart disease, M1-leading to conduction defects, sick sinus syndrome, hypothyradism, hypothermia, electrolyte imbalance, obstructive jaundice, uraemia, raised ICP, etc.

The characteristic features of sinus bradycardia in ECG are :

i. Heart rate less than 60 beats per minute.
ii. Every P-wave is followed by a QRS complex.
iii. The P-wave is upright in lead II and inverted in lead AVR (Fig. 26.7).

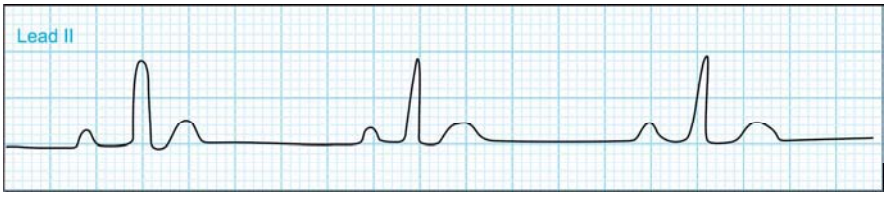


Fig. 26.7: This is a graph of sinus bradycardia, characterised by : heart rate 50/min, upright P-wave in lead II and QRS complex after every P-wave

If bradycardia is severe i.e. less than 40 beats/min, then one have to consider – sinus arrest, sino-atrial block, sick sinus syndrome and complete heart block, etc. If sinus bradycardia is severe, then escape beats or escape rhythm from the AV node or ventricles may also occur as a safe guard mechanism.

For sinus bradycardia due to physiological conditions no treatment is needed. But for the management of symptomatic severe bradycardia, the first step is to asses the urgency of situation such as syncope, falls, dizziness or breathlessness, etc. This is usually done by proper history taking, careful examination and further investigations (e.g. thyroid function, plasma electrolytes, etc.). It will also help to identify the underlying pathological causes of bradycardia and to correct it where possible by discontinuation or reduction of the dose of responsible drugs, by identification of abnormal cardiac rhythm and its management, by identification and treatment of hypothyroidism etc. When the bradycardia is severe and symptomatic with evidence of severe haemodynamic disturbance, then more urgent treatment is instituted immediately such as:

(i) Inj Atropine – 300 to 600 µg given slowly intravenously and or (ii) Inj Isoprenaline – 0.5 to 10 µg/min by intravenous infusion.

However, insertion of temporary pacemaker, later on permanent if indicated, is preferred than the prolonged infusion of isoprenaline. So, isoprenaline infusion should only be used as a short-term measure, while arranging for temporary or permanent pacing. Chronic severe bradycardia due to any cause may be an indication for a permanent pacemaker, particularly, when it is causing symptoms or haemodynamic disturbance even after removal of the aetiologies.

Sick Sinus Syndrome

The sick sinus syndrome refers to some conditions which are characterised by the combination of abnormal impulse generation and conduction problems related to the dysfunction of sinus node. As the name (syndrome) suggests, it is a collection of symptoms such as dizziness, fatigue, confusion, syncope and congestive heart failure. Any of the following ECG findings can be seen in patient with sick sinus syndrome with different combination. These are sinus bradycardia, sino-atrial block, sinus arrest and brady-tachy syndrome.

Sino-atrial block

Here, the SA node depolarises as normal rate, but some impulses fail to reach the atria from the SA node. Here, the pathology lies in the junction between the SA node and atrial muscle. The sino-atrial block may be of three degrees.

i. *First degree SA exit block*: It denotes a prolonged exit time of all impulses from SA node to the surrounding atrial tissue. It cannot be diagnosed by standard surface ECG, but requires invasive intracardiac recording.
ii. *Second degree SA exit block*: It denotes the intermittent failure of exit of impulses from the SA node to the atrium. It is manifested in ECG as the intermittent absence of P-wave. This is because the P-wave fails to appear in

the expected place. But the next usually appears exactly where it is expected.

iii. Third degree SA exit block or complete SA block. Here, all the impulses originating from SA node are blocked and fails to pass to atrium. So, it is characterised by complete lack of SA node activity in ECG and the presence of a subsidiary ectopic atrial or AV junctional pacemaker (Fig. 26.8).

Sinus arrest

Here the SA node fails to depolarise itself, but there is no abnormality of passing the impulses from SA node to atrium once it originates. So, all the manifestations of sinus arrest are like third degree SA exit block. Looking at the ECG strip we can find that a P-wave will suddenly fail to appear in the expected place and there is a gap of variable length, until the sinus node fires again which is irregular and a P-wave appears (Fig. 26.9).

Brady-tachy syndrome

It refers to a combination of sinus bradycardia, sinoatrial block, sinus arrest (all the components of sick sinus syndrome) with PSVT. In this syndrome the tachycardia often emerges as an escape rhythm in response to an episode of bradycardia and then it usually terminates with prolonged sinus pause. So, there is alternate periods of tachycardia and bradycardia. Moreover, any atrial tachycardia during which the atrial ectopic site is activated may cause overdrive suppression of the sinus node resulting in clinical appearance of this syndrome (Fig. 26.10).

The sick-sinus-syndrome usually coexists with atrial fibrillation, atrial flutter, atrial tachycardia, AV conduction disorder, etc.

Degeneration and fibrosis of SA node and conducting system due to ageing is the most common cause of sick-sinus-syndrome. The probable other causes of sick sinus syndrome are – IHD, drugs (antiarrhythmic), cardiomyopathy, myocarditis, etc. The diagnosis of this syndrome usually requires 24 hours holter monitoring. While looking at the ECG strip, a P-wave will suddenly fail to appear in the expected place and there is a gap of variable length until the sinus node fires again and a P-wave appears. The conduction problems become apparent when a patient with brady-tachy syndrome develops atrial fibrillation. During tachycardia the AV node fails to conduct all the atrial impulses at this unusual high atrial rate. Thus, AV block precipitates and the ventricular rate remains slow (Table 26.2).

An asymptomatic patient with SSS does not require any treatment. But, symptomatic patients need consideration for permanent pacemaker. This is particularly important if they also have paroxysmal tachycardia that require antiarrhythmic drugs (which can worsens the episodes of bradycardia). On the other hand, paroxysmal tachycardia which arise as escape rhythm in response to episodes of bradycardia may improve as a consequence of pacing and thus the vicious cycle is cut.

Fig. 26.8: This is a graph of sinoatrial block, characterised by: two P-waves fails to appear and next P-wave appears where it is expected

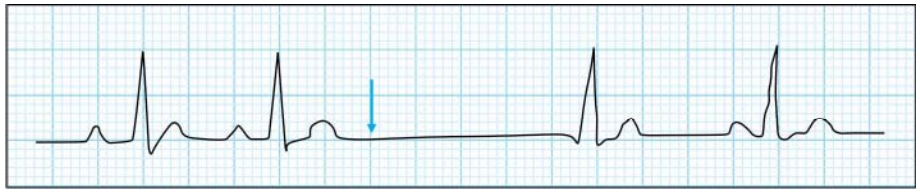


Fig. 26.9: This is a graph of sinus arrest, characterised by: P-wave fails to appear and next P-wave does not appear where expected

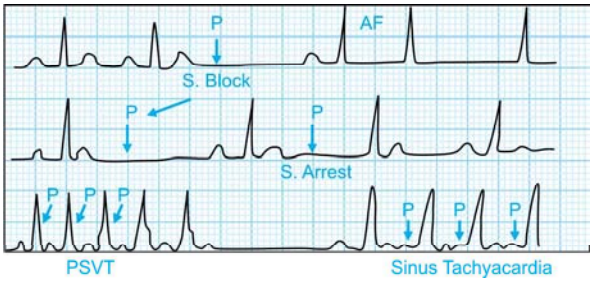


Fig. 26.10: This is a graph of sick sinus syndrome, characterised by: sinus block, sinus arrest, atrial fibrillation (AF), PSVT and sinus tachycardia

Atrio-ventricular Conduction Defects

Introduction

The specialised conducting system (AV bundle, bundle of His, Purkinje fibres) running between the atrium and the ventricle ensures smooth conduction of sinus impulses from the atrium to the the ventricle resulting in synchrous contraction of these two chambers. Hence any abnormalities of this conducting system may lead to incomplete or complete block of passage of impulses from atrium to ventricle

Table 26.2: Common features of sick sinus syndrome

Sinus bradycardia
Sinus arrest, sinoatrial block
Paroxysmal atrial fibrillation
Paroxysmal supraventricular tachycardia
Atrioventricular block

causing cardiac stand still or escape ventricular beat. Discussion on this conduction abnormalities has three significant clinical points :

i. Detection of the site of conduction disturbance.
ii. The chance of risk of progression of incomplete block to complete block.
iii. The probability of electrophysiological and haemodynamic stability of the subsidiary escape rhythm, arising distal to the block.

This last point is very important, because the symptoms which will develope depend on the stability of this escape rhythm. After AV block, the subsidiary escape beat can arise from the bundle of His or distal to the bundle in the Purkinje system. The difference between these two types of escape rhythm is that the impulse arising from the bundle of His is of 50 to 60 beats/min, whereas the impulse arising from the distal Purkinje system is 30 to 40 beats/min and unstable with broad QRS complex.

Classification

AV conduction defects or block can be classified into three degrees.

First Degree AV Block

It is also called the prolonged AV conduction defect which is characterised by a PR interval > 0.2 sec. The PR interval is the period that extends from the beginning of P-wave to the beginning of R-wave and includes the time for atrial depolarisation, the time for impulse passing through the AV node with physiological delay and the time for impulse passing through the His-Purkinje conducting system. The delay in passing of impulses through any of the structure can contribute to the prolonged PR interval (Fig. 26.11).

Delay in atrial depolarisation has no clinical significance. Delay within the AV node results in prolonged PR interval (> 0·24 sec) with normal QRS complex. Delay in His-Purkinje system results in prolonged QRS duration or broad QRS complex in addition to a prolonged PR interval. The first degree heart block does not usually need any management.

Second Degree AV Block

This is also called the intermittent AV block, as some but not all the atrial impulses fail to conduct to the ventricles through AV node. The second degree AV block is again of two types such as Mobitz type I and Mobitz type II.

In Mobitz type I (Wenckebach block) variety of second degree AV block, there is gradual prolongation of PR interval, followed by a complete block of conduction of an atrial impulse to the ventricle. This type of second degree AV block is almost always localised in the AV node and associated with normal QRS duration. This type of AV block is usually found with inferior wall infarction, β-blockers, calcium channel antagonists, drug intoxication particularly digitalis, normal individual with high vagal tone, etc. So this phenomenon may be physiological and is sometimes observed at rest or during sleep in athletic young adults. Sometimes this Mobitz type I category of second degree AV block can progress to third degree complete heart block, but it is uncommon except in acute inferior wall myocardial infarction. But still, if the Mobitz type I category of AV block progress to complete block, it is well tolerated, This is because the escape pacemaker usually arises in the proximal bundle of His and provides a stable rhythm. So, the Mobitz type I block rarely necessitates any aggressive therapy. If the ventricular rate as a consequence of Mobitz type I block is adequate and the patient is asymptomatic, then only observation is sufficient (Fig. 26.12).

In Mobitz type II variety of second degree AV block, there is sudden complete block of conduction of impulses from the atrium to the ventricle through AV node, without any previous warning of prolonged PR interval. In some varieties of this type of conduction defect, block is localized in the His-Purkinje system, but not in the AV node and is associated with prolonged QRS duration. Clinically, it is very important, because it has high incidence of progression to complete AV block with unstable escape pacemaker rhythm below the block. So, cardiac pacing is necessary in this type of block (Fig. 26.13).

Third Degree AV Block

In third degree AV block no atrial impulse propagates to ventricles from atrium. So,

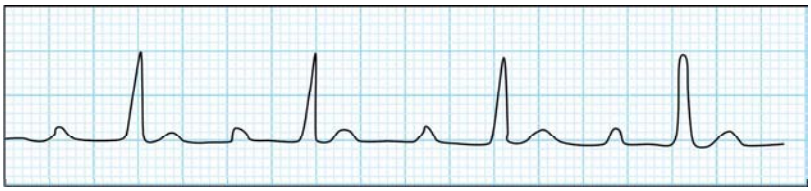


Fig. 26.11: This is graph of first degree AV block. It is characterised by: long PR interval (0.32 sec)

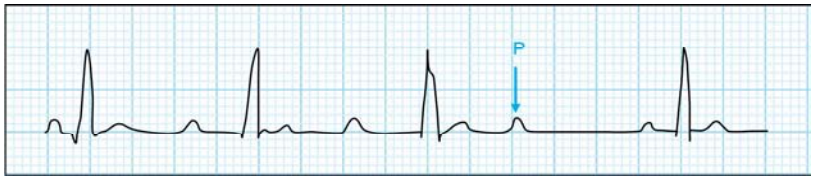


Fig. 26.12: This is graph of Mobitz type I AV block. It is characterised by: progressive lengthening of PR interval (0.16 sec, then 0.28 sec, then 0.32 sec) followed by a P-wave fails to be conducted with no QRS complex and then PR interval resets with repeated cycle

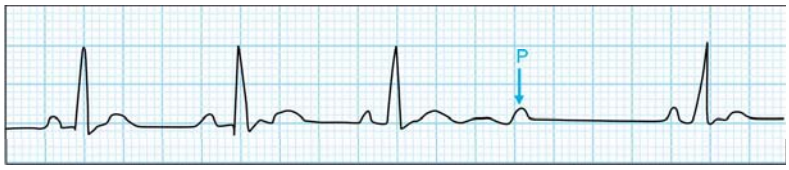


Fig. 26.13: This is a graph of Mobitz type II block. It is characterised by: all the normal and constant PR intervals and occasional P-wave fails to be conducted

the escape beat may arise from the AV node or His-Purkinje system. When the escape beat arise from AV node, the block is proximal to the origin of this escape beat in AV node and this block is called the AV nodal block. In such situation the escape ventricular beat is of normal QRS complex (as it passes through the normal Purkinje fibres) with 40 to 50 beats/min and is responsive to exercise or atropine. This is usually of congenital type. If the block is situated in the His-Purkinje system, then the escape rhythm arises from the ventricular musculature and is unreliable. It is characterised by broad QRS complexes with rate < 40/min and is usually unresponsive to atropine and exercise. This type of complete AV block mandates pacemaker implantation (Fig. 26.14).

Adams-Stokes attacks
(Adams-Stokes syndrome)

The episodes of ventricular asystole in the absence of escape beat may complicate the complete heart block or Mobitz type II second degree AV block or the sick sinus syndrome. This may be recurrent and cause syncope which is called the 'Adams–Stokes' attacks. A typical episode of Adams–Stokes syndrome is characterised by sudden loss of consciousness which frequently occurs without warning and may result in sudden fall of patient on ground. Convulsions (due to cerebral ischaemia) can occur if there is prolonged asystole. There is also death like appearance during the attack. But when the heart starts to beat again, there is characteristic regain of consciousness and flush. In contrast to epilepsy, the recovery in Adams-Stokes attack is rapid. Other diseases like the hypersensitive carotid sinus syndrome and the malignant vaso vagal syndrome may also cause similar symptoms and should be differentiated from Adams-Stokes attacks.

AV Dissociation

AV dissociation is said to be present when the atria and the ventricle are under control of two separate pacemakers. It occurs in the following three different conditions:

i. When there is complete AV block – discussed before.
ii. There is no AV block, but due to severe sinus bradycardia escape AV junctional rhythm starts. In such case, when the sinus rate and the escape rate is same, then the P-wave occurs just before the following QRS complex. This is called isorhythmic AV dissociation. Treatment of this condition is removal of causes of bradycardia. These are: (a) discontinuation of anaesthetic drugs, digitalis, β-blockers, Ca-antagonist etc, causing severe bradycardia (b) use of vagolytic agents and (c) pace making, only if patient becomes symptomatic due to severe bradycardia.
iii. There is no AV block, but enhanced lower pacemaker rate (VT, accelerated idioventricular tachycardia, etc.) which competes with normal sinus rhythm coming through AV node and frequently exceeds it. Due to rapid lower pacemaker activity in ventricle, the bombardment of the AV node by impulses arising from ventricle in a retrograde fashion, renders it refractory to the normal sinus impulse. Thus, the atrium and the ventricle beats independently. This is called interference AV dissociation, and is usually happened during myocardial ischaemia, infarction, after cardiac surgery, etc. Treatment of such condition is antiarrhythmic agent, removal of offending drugs and the correction of metabolic abnormalities or ischaemia.

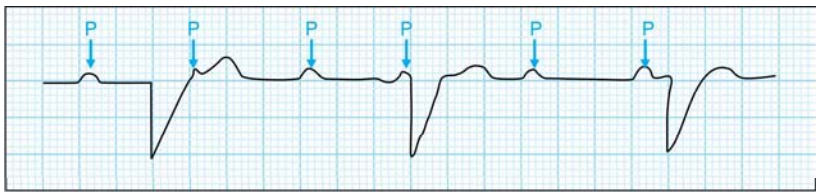


Fig. 26.14: This is a graph of third degree AV block. It is characterised by : P-wave (atrial) rate is 100/min, QRS complex (ventricular) rate is 42/min, broad QRS complexes and no relationship between P-waves and QRS complexes. There is no relationship between P-wave and QRS complex because no P-wave is conducted to ventricle through AV node due to complete AV block. QRS complexes are broad because they arise from the ventricular musculature

Role of Intracardiac ECG in diagnosis of AV conduction defects

The main indication for performing intracardiac ECG or His-bundle ECG is to determine the proper indication of pacing or to select the proper patient who will be benefited from pacing.

i. *A symptomatic third degree AV block*: In such patient the His-bunle ECG will be helpful to assess the stability of the junctional pacemaker, if it is present. If His-bundle escape rhythm is unstable, then pacing is indicated, though the patient is asymptomatic.
ii. *Patient with syncope and bundle branch or fascicular block*: If such patient shows infra-His-bundle conduction disturbance then they are indicated for pacing. But nodal conduction

disturbance are not indication for pacing. Bifascicular block with asymptomatic patient are not indicated for intracardiac ECG as these group of patients are very unusually associated with AV conduction disturbances.

iii. *Symptomatic 2nd and 3rd degree AV block* are always indication for pacing without intracardiac ECG.

iv. *Asymptomatic 2nd degree AV block* is always indicated for intracardiac or His-bundle ECG. If the block is established at the intra or infra His-bundle level, then pacing is indicated though the patient is asymptomatic.

Management of AV Conduction Defects

Pharmacological therapy

It is only indicated in acute situations of AV conduction defect. Atropine in the dose of 0·6 to 2 mg IV and isoprenaline in the dose of 1 to 4 µg/min by infusion increases the heart rate, by removing the AV block. But, they have insignificant effect only if the block is below the AV node. Moreover, the result of pharmacological therapy is not always consistent and long-term. So, pacing is the only answer for long-term management of conduction defect.

CAUSES OF PERIOPERATIVE TACHYCARDIA AND ITS MANAGEMENT

Tachycardia is defined as heart rate above 100 beat/min. Sinus tachycardia is sinus rhythm, (i.e. regular impulses arising from SA node) with heart rate above 100 beat/min. Non-sinus tachycardia means tachycardia where impulses do not arise from the sinus node, but from anywhere else. The physiological causes of sinus tachycardia are anxiety, pain, fever, exercise, etc. It is rare for sinus tachycardia to exceed 180/min, except in fit athlete. At this heart rate, it may be difficult to differentiate the P-waves from the previous T-waves, as they march on each other and then this the rhythm can be mistaken for an atrioventricular nodal re-entry tachycardia or PSVT.

Some pathological causes for sinus or nonsinus tachycardia are: (i) drugs – atropine, adrenaline, etc. (ii) heart failure, (iii) fluid loss, (iv) anaemia, (v) hyperthyroidism, (vi) MI, (vii) pulmonary embolism etc (Fig. 26.15).

The characteristic features of sinus tachycardia in ECG are:

i. Heart rate is greater than 100 beats/min.

ii. The P-wave is upright in lead II and inverted in lead AVR.

iii. Every P-wave is followed by a QRS complex, though sometimes it is very difficult to identify the P-wave. (Fig. 26.16)

The management of sinus tachycardia is the management of cause. When a patient has a compensatory tachycardia such as in blood loss, fluid loss, anaemia, low BP, etc. in such situations slowing of the heart rate with β-blockers can lead to disastrous decompensation. However, if the sinus tachycardia is inappropriate or non-compensatory in nature, as in anxiety, heart failure or hyperthyroidism, etc. then treatment with β-blockers maybe helpful or life saving.

Tachycardia also can be classified into

i. Narrow QRS complex tachycardia (<3 small squares)

ii. Broad QRS complex tachycardia (>3 small squares).

In narrow complex tachycardia impulses alway arises from above the ventricular level, i.e. they are supraventricular in origin. The QRS complexes formed by impulses arising from the supraventricular level are narrow, because these impulses pass after their origin through the normal fast conducting tissues such as AV node, bundle of His, and lastly through the Purkinje fibres. But when any impulse arise from the ventricular level and does not pass through these normal conducting path, instead goes through the myocardium then QRS complexes become broad. This is because the conduction through myocardium is not as fast as the normal conducting tissues. The causes of narrow complex tachycardia are – sinus tachycardia, atrial tachycardia, AV nodal re-entrant tachycardia, AV re-entry tachycardia, AV junctional tachycardia, atrial flutter with high AV conduction, atrial fibrillation with high AV conduction, W-P-W syndrome, etc.

In broad complex tachycardia impulses always arise below the level AV node, except supraventricular origin with bundle branch block. The causes of broad QRS complex tachycardia are: ventricular tachycardia (VT), accelerated idioventricular tachycardia, torsades-de-pointers,

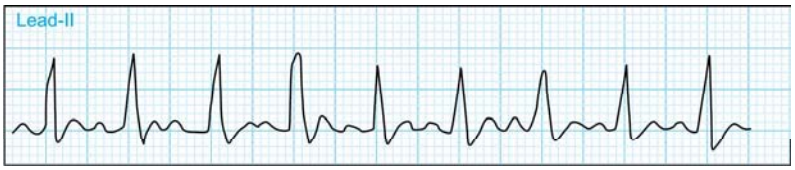


Fig. 26.15: This is a graph of sinus tachycardia. It is characterised by: heart rate 150/min, QRS complexes after every P-wave and upright P waves in lead II

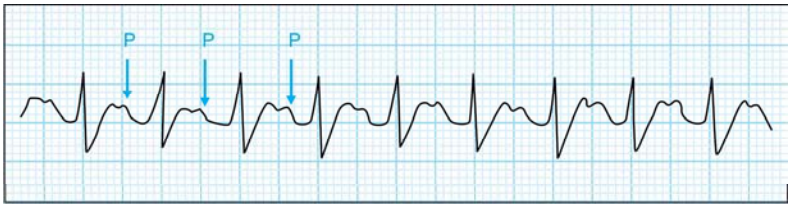


Fig. 26.16: This is a graph of sinus tachycardia with P-waves hidden within the previous T-waves

ventricular flutter, ventricular fibrillation, supraventricular tachycardia with bundle branch block, etc.

Narrow Complex Tachycardias and its Management

Paroxymal supraventricular tachycardia (PSVT) or (atrial tachycardia)

It is not sinus tachycardia as impulse originates from an ectopic focus, somewhere within the atrial myocardium, except the SA node. The characteristic features of PSVT in ECG are:

i. Heart rate greater than 100 beats/min.
ii. Abnormally shaped P-waves (Fig. 26.17).

The atrial rate (P-wave) in PSVT is usually 150 to 250 beats/min. But, when the atrial rate is above 200/min, then the AV node struggles to keep up with the conduction of impulses through it and AV block may precipitate.

The management of PSVT depends on the urgency of the situation, i.e. evidence of any haemodynamic disturbance such as hypotension, cardiac failure, poor peripheral perfusion, etc. However, the general rule is that the supraventricular tachycardia causing haemodynamic disturbance requires urgent diagnosis and treatment. Initially, carotid sinus massage (vagal stimulation) reduces the heart rate by increasing the degree of AV block and in 80% of cases it is effective. When hypotension is present with PSVT, then IV phenylephrine in the dose of 0·1 mg in incremental rate may correct hypotension and subsequently tachycardia (alone) or in combination with carotid sinus massage which correct tachycardia (Fact file -I).

FACT FILE- I

Supraventricular tachycardia (SVT)

The term SVT is often misused. So it frequently leads misunderstanding. Literally, it refers to any tachycardia which originates above the ventricle (supraventricle). Thus it encompasses : sinus tachycardia, atrial tachycardia, AF, AV re-entry and nodal re-entry tachycardia etc. But some people use this term specifically to mean only AV nodal re-entry tachycardia. So, now it is recommended that all the arrhythmias should be diagnosed as specifically as possible and the term SVT should be reserved only for those whose are not diagnosed specifically but origin is above the ventricle.

If this fails, then verapamil in the dose of 2.5 to 10 mg IV or adenosine in the dose of 6 to 12 mg IV is used as second step of management. Adenosine is preferred than verapamil, because of its extremely short half-life and without any side effects. Adenosine should not be used if patient has asthma or obstructive airway disease. Verapamil should not be used, if patient has recently taken β-blocker, otherwise severe bradycardia can result (Figs 26.18 A and B).

The β-blockers can also be used to slow or terminate the tachycardia of PSVT, but these are the agents of third choice. Digitalis also reduces the rate of atrial tachycardia but produces slower onset of action and has no role in acute therapy of tachycardia of PSVT.

If pharmacological treatment of PSVT fails or when tachycardia is recurrent, in spite of good pharmacological treatment, then temporary pacing may be used to terminate the arrhythmia. In the last resort, if severe ischaemia and / or hypotension is caused by tachycardia then DC cardioversion should be considered.

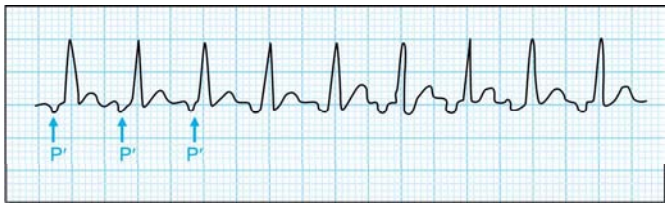
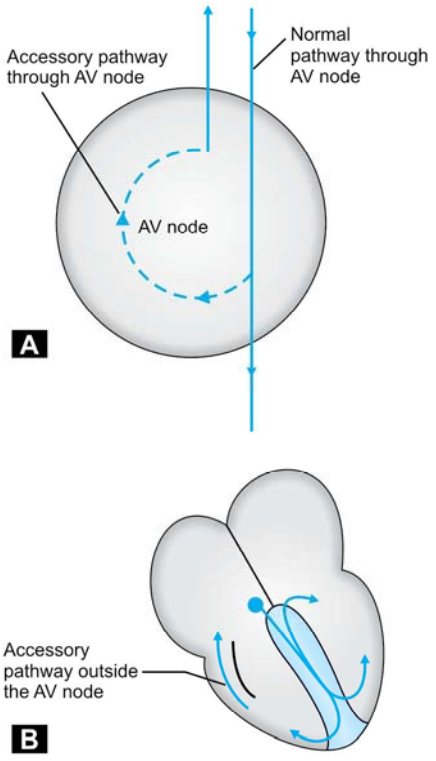


Fig. 26.17: This is a graph of atrial tachycardia. It is characterized by: heart rate 150/min and abnormally shaped P waves

AV re-entry tachycardia

AV reentry tachycardia may arise when there is a second alternate pathway for passing of impulses between the atria and the ventricles. This is in addition to the normal route for conduction of impulses other than the AV node. The presence of two different routes for conduction of impulses from atrium to ventricle creates the possibility that impulses can travel down through one route (anterograde conduction) and then return back through other route (retrograde conduction). In doing so, an impulse thus can enter into a repeated cycle of activity which circles round the two pathways continuously. Thus, it repeatedly re-enters and activates the atria and ventricles in rapid succession causing tachycardia. The extra connection between the atria and ventricles can either be an accessory pathway which is anatomically separate from the AV node (AV re-entry tachycardia, e.g. WPW syndrome) or through the AV node itself in which both the pathways lie in the AV node but are different



Figs 26.18A and B: This figure shows accessory pathway through the AV node A. and also through outside the AV node B

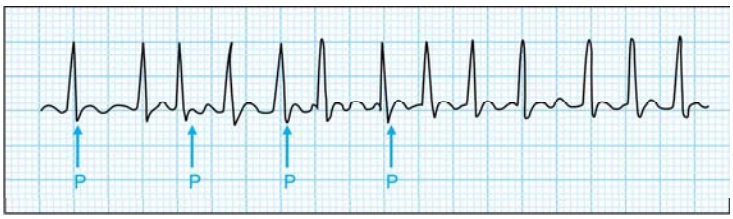


Fig. 26.19: This is a graph of AV re-entry tachycardia in WPW syndrome. It is characterised by: ventricular rate is 225/min, narrow QRS complexes and inverted P waves after QRS complexes

from their electrical activity (AV nodal re-entry tachycardia) (Fig. 26.19).

When the accessory pathways are found (like in W P W syndrome) not in the AV node, then the patients are susceptible to the episodes of AV re-entry tachycardia with anterograde conduction via the AV node and retrograde conduction via the accessory pathway. So, during the tachycardia by this type of circuit delta wave is lost. Because delta wave is only formed when anterograde conduction occurs through the accessory pathway and retrograde conduction occurs through the AV node. An AV re-entry tachycardia taking this route i.e. down the accessory pathway and up the AV node is very rare. Hence, when it does occur, then only the delta waves are seen.

Patients with AV nodal dual pathway, i.e. when both the pathway (accessory and normal) exist within the AV node, are also at the increased risk of AV re-entry tachycardia. This is called AV nodal re-entry tachycardia in which anterograde conduction usually occurs down the normal AV nodal pathway and and retrograde conduction occurs via the abnormal additional pathway within the AV node.

Both the AV re-entry and AV nodal re-entry tachycardia have the following characteristics:

i Heart rate is 150 to 250 per minute.
ii There is one abnormal P-wave (P^1) per QRS complex (although P-waves are not always clearly seen).
iii. There are regular QRS complexes.
iv. QRS complexes are narrow (in the absence of aberrant conduction).
v May have delta waves or not. Delta wave is present in the AV re-entry tachycardia where accessory pathway is present outside the AV node and anterograde conduction occurs through this accessory pathway and retrograde conduction occurs through the AV node. Delta wave is absent in AV re-entry tachycardia if anterograde conduction occurs through AV node and retrograde conduction occurs through the accessory pathway which is situated outside the AV node. Delta wave is also absent in the AV nodal re-entry tachycardia, where the accessory pathway is present within the AV node (Fig. 26.20).

In AV re-entry tachycardia the inverted P^1-waves are often seen in the middle between two QRS complexes. But, in AV nodal re-entry tachycardia the inverted P^1-waves are often difficult or impossible to find out as they follow the QRS complexes closely or are burried within them. Although the actual position of the P^1-waves may be helpful to distinguish between AV re-entry tachycardia and AV nodal re-entry tachycardia, but an ECG in sinus rhythm (i.e. when tachycardia is not present) is more diagnostic as it may reveal a short PR interval or delta wave, suggesting W P W syndrome. Truely speaking, the definite diagnosis of AV re-entry and AV nodal re-entry tachycardia is very difficult and need electro-physiological studies.

Management of AV nodal re-entry and AV re-entry tachycardia

The AV nodal re-entry tachycardia can be prevented by increasing the block within the AV node and thereby breaking the repetitive cycle of electrical activity by β-blocker or by Valsalva manoeuvre. Valsalva manoeuvre works by increasing the vagal inhibition on AV nodal conduction. Alternative of this manoeuvre is carotid sinus massage.

AV nodal re-entry can also be prevented by the use of drugs. The drugs with degree of preference are adenosine, digitalis, β-blocker and Ca-channel antagonist such as verapamil. Adenosine should not be used, if the patient suffers from asthma or any other obstructive airway disease. In emergency situation when the patient is haemodynamically compromised, then urgent DC cardioversion or overdrive atrial pacing is done.

The management of AV re-entry tachycardia is also same like AV nodal re-entry tachycardia. The patient with AV reentry tachycardia who requires pharmacological agents for chronic therapy should also be considered as the candidates for radio-frequency catheter ablation of the by-pass tract.

Wolff-Parkinson-White (WPW) Syndrome

Normally in most people impulses pass from atrium to ventricle through a distinct normal path such as AV node, bundle of His and Purkinje fibres. But, some people have additional or accessory conducting path between the atria and ventricles. This accessory path is called the bundle of Kent and the conduction of impulses through this pathway is more faster than the AV node. So, the wave of depolarisation reaches the ventricle from atrium more quickly (when it only passes anterogradely through this

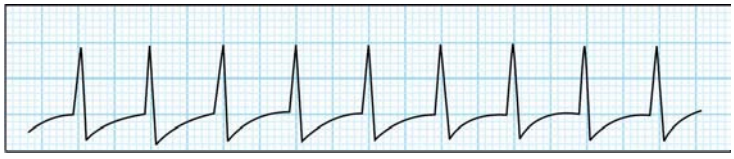


Fig. 26.20: This is a graph of AV nodal re-entry tachycardia. It is characterised by: ventricular rate 150/min, narrow RS complexes and invisible P-wave

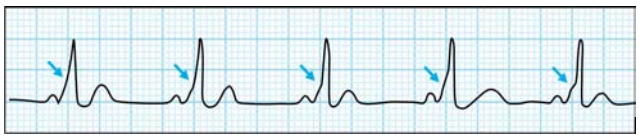


Fig. 26.21: This is a graph of WPW syndrome, characterised by: ventricular rate 75/min, short PR interval (0.08 sec) and delta waves shown by arrow

accessory pathway) than usual and thus the PR interval becomes short. A part of the ventricle is activated first by the accessory path, giving rise to Delta wave – the first part of the QRS complex. Shortly after that the rest of the ventricle is depolarised rapidly with the arrival of the normally conducted wave of depolarisation via the AV node from atrium and complete the rest of the QRS complex (Fig. 26.21).

The key diagnostic point of WPW syndrome in ECG is the short PR interval and the delta waves.

The WPW syndrome without tachycardia is found incidentally and may be asymptomatic. In these cases no action is needed. Some patients with WPW syndrome have symptoms of palpitation due to tachycardia or arrhythmia. If a symptomatic patient with WPW syndrome due to tachycardia require surgery of any kind, then the anaesthetist must be informed of the ECG finding.

The protocol of management of tachycardia in WPW syndrome is similar to PSVT. The pharmacological aim of therapy is the increase of refractoriness and reduction of conduction velocity through the components of re-entrant circuit. If there is life threatening rapid ventricular rate in response to WPW syndrome, then DC cardioversion is carried out. Alternatively, lignocaine (3 to 5 mg/kg) or procainamide (15 mg/kg) can be used, slowly intravenously over 15 to 20 min to reduce the ventricular rate. Sometimes, WPW syndrome is associated with AF. Then, IV verapamil or digitalis should not be used and if used then it should be given very cautiously, because these drugs decrease the refractoriness of accessory path and increase the ventricular rate causing VT. In chronic therapy, verapamil is not associated with increased risk. In patient with WPW syndrome and AF, the use of β-blockers are of no utility in controlling the ventricular response, when the conduction proceeds through the by pass tract. In patient with WPW syndrome and PSVT, atrial and ventricular pacing almost always terminate the PSVT immediately and regularise the ventricular rate.

The radio-frequency catheter ablation of by pass tract offers a permanent cure of WPW syndrome and is effective in 90% patient. It is the treatment of choice of WPW syndrome in patient with symptomatic arrhythmias (Fact file-II).

FACT FILE - II

Atrial fibrillation and WPW syndrome

Not only the AV re-entry tachycardia complicates the WPW syndrome, but also the AF may be precipitated. In AF due to AV re-entry tachycardia, conduction to the ventricle can occur via either the accessory pathway (commonest) or the AV node or both. When the conduction through accessory pathway takes place, it causes rapid and potentially lethal ventricular rate. Therefore, the drugs such as verapamil, adenosine, etc, which block the AV node are detrimental in such patient and increase conduction through accessory pathway. In such circumstances, DC cardio version is the treatment of choice. These conditions also can be treated by drugs which slow the conduction through accessory pathway such as sotalol, disopyramide, amiodarone etc. Ablation of accessory path also can be thought.

AV Junctional Tachycardia

The AV node is divided in three regions: (i) The central N region, (ii) the peripheral AN region where the atrial fibres enter the AV node, and (iii) the peripheral NV region where the AV node extends into the bundle of His. It had been said that the central N region show the absence of diastolic depolarisation (phase 4) and therefore automaticity does not exist in this area. So, the cells proper in the AV node cannot act as pacemakers or originate ectopic discharges. In contrast, the junctional AN zone or NV zone are the zones of automaticity and can act as pacemakers or be the site of ectopic discharges. Hence, the older terminology of AV nodal rhythms had been replaced by AV junctional rhythms. However, the more recent studies also have demonstrated the diastolic depolarisation in the N regions of AV node. Therefore, the older designation of AV nodal rhythms can be justified (Fig. 26.22).

In junctional beat the ectopic impulse arises from any junctional sites (AN or NV zones) of AV node. The impulse then spreads upward into the atrium and downward into the ventricle. This usually produces an upright P^1 wave in aVR and high oesophageal leads, and an inverted P^1 wave in aVF and low oesophageal leads. This P^1 wave can be burried in the QRS complex during tachycardia and may not be visible. The atrium is activated in a retrograde fashion prior to activation of the ventricle. This produces a normal or short P^1R interval. Such a beat is not distinguishable from an atrial ectopic beat arising from a low atrial focus near AV node and therefore is best referred to as a supraventricular beat. The finding of a short P^1R interval (less than 0.12 second) with an inverted P^1 wave in lead aVF may favour junctional origin of impulse. A P^1R

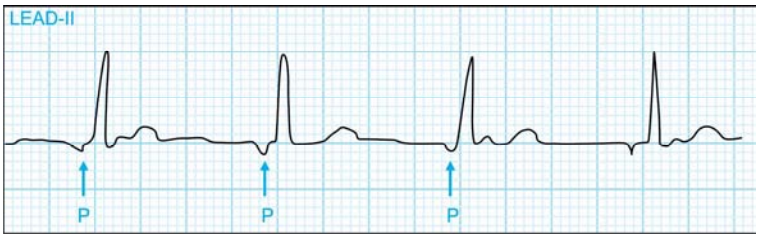


Fig. 26.22: This is a graph of AV junctional rhythm characterised by: inverted P waves in lead II, abnormally short PR interval, and narrow QRS complex

interval longer than 0.12 second with an inverted P^1 in aVF may favour ventricular excitation (Fig. 26.22A).

In AV junctional rhythm and tachycardia the QRS-T complexes are of normal configuration. The junctional beats may be either premature, i.e. occurring earlier than the next anticipated sinus beat or escape beats. The previous one occurs when increased automaticity of the junctional sites develops (e.g. digitalis toxicity) and the later occurs when the sinus rate slows. When the junctional beats act as escape rhythm, then it is regular and the rate may vary from 40 to 80 per minute (Table 26.3).

Table 26.3: Causes of inverted P waves

1. Incorrectly positioned electrodes
2. Change of axis of heart
3. Dextrocardia
4. Abnormal atrial depolarisation
   a. Atrial ectopics
   b. AV junctional rhythm
   c. Retrogradely conducted ventricular ectopic
   d. Retrogradely conducted ventricular tachycardia

The junctional escape rhythms are the form of safety net for heart. Without escape rhythms, complete failure of impulse generation from SA node and its conduction through AV node at any moment would lead to ventricular asystole and death. So, the heart has a number of subsidiary pacemaker site that can take over the responsibility if normal impulse generation from SA node or its conduction fails. The subsidiary pacemaker site are located in the AV junction or in the ventricular myocardium. If the AV junction fails to receive impulse, as a result of SA arrest or block or even during severe sinus bradycardia, then it will take over as the cardiac pacemaker. The QRS complexes generated from ventricular depolarisation by AV junctional rhythm will have the same morphology as normal, but at a slower rate of around 40 to 60 beats per minute. AV junctional pacemaker will continue until it is inhibited by impulses from the SA node. If the AV junctional pacemaker fails or its impulses are blocked to pass to ventricle then a ventricular pacemaker (from ventricular myocardium or Purkinje fibre) will take over the responsibility and this QRS complexes will be broad (Figs 26.23 and 26.24).

The AV junctional rhythm may be transient or permanent. The transient AV junctional rhythm may sometimes be seen in normal people. It may be produced by carotid sinus pressure (protective escape phenomenon) or may result form digitalis (increased automaticity of junctional site) or quinidine administration. Transient or permanent junctional rhythm also results from variety of organic heart diseases, e.g. rheumatic fever, coronary artery disease, other acute infectious myocarditis, etc. (Fig. 26.25).

In AV junction tachycardia (which is due to increased automaticity of AV junctional rhythm) the rate can vary from 120 to 200 per minute. The ventricular rhythm is regular. The P^1 waves may precede or be burried in or follow QRS complexes. The ECG pattern of QRS complex is identical with that of a junctional premature beat. With a rapid rate it is impossible to tell whether any given P^1 wave is related to the preceding QRS complex or to the following complex. Actually one can not differentiate the ECG pattern produced by junctional tachycardia from that produced by an atrial tachycardia arising from a low atrial ectopic focus near AV node. Therefore, the general term such as supraventricular tachycardia is more applicable than the specific term AV junctional tachycardia.

Thus, management of AV junctional tachycardia is like that of atrial tachycardia.

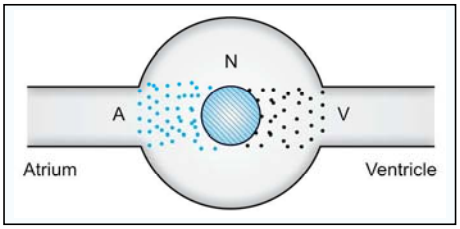


Fig. 26.22A: AV node

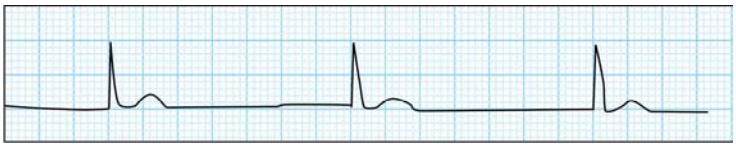


Fig. 26.23: This is a graph ofAV junctional escape rhythm, characterised by: heart rate 43/min, absent P waves and narrow QRS complexes

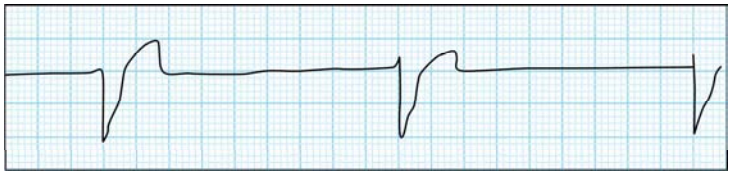


Fig. 26.24: This is a graph of Ventricular escape rhythm, characterised by: heart rate 33/min, absent P waves, and broad QRS complexes

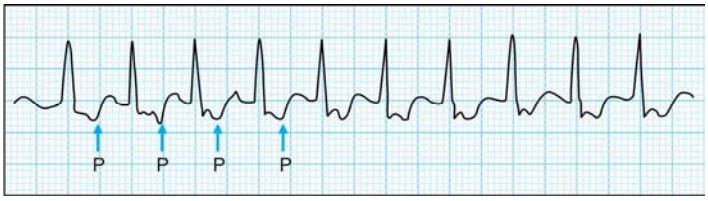


Fig. 26.25: This is the graph of AV junctional tachycardia. It is characterised by: heart rate 150/min, narrow QRS complexes, P waves hidden within the ST segments

Atrial fibrillation (AF)

Atrial fibrillation is much more common than atrial flutter. It affects 5 to 10% of elderly people and may be permanent or paroxysmal. The electrophysiological characteristic of AF is local multiple rapid chaotic depolarisation of atrial musculature which divides the atria into multiple small islands. Hence, no P-waves are seen in ECG. Instead the baseline of ECG consists of low amplitude oscillations representing chaotic electrical activity of atrium which is called the fibrillatory or F waves. Usually, the 400 to 600 atrial impulses reach the AV node per minute, but among them only 120 to 150 of these will reach the ventricles to produce tachycardia of narrow QRS complexes. This is due to the block of AV node with the traffic jam of impulses. However, due to this traffic jam and block of AV node conduction of atrial impulses through AV node is erratic which makes the ventricular rhythm irregularly irregular.

The characteristic features of AF in ECG are:

i. Absence of atrial P-waves
ii. Irregularly irregular ventricular rhythm with narrow QRS complexes. This is because transmission of atrial impulse through AV node is erratic which makes the ventricular complexes irregularly irregular (Fig. 26.26).

Once AF has been diagnosed perioperatively, then the cause of it should always be sought with careful patient's history and examination. This is because AF may be the first manifestation of many forms of organic heart disease, particularly those that are associated with enlargement or dilatation of the atria. The common causes of AF are: hypertension, 1HD, hyperthyroidism, sick-sinus-syndrome, consumption of alcohol, rheumatic mitral valvular disease, cardiomyopathy, ASD, pericarditis, myocarditis, pulmonary embolism, pneumonia, cardiac surgery, etc. When such factors are present, then the therapy of AF should be directed toward the primary abnormality.

The aims of treating AF are:

i. To control the ventricular rate.
ii. To reduce the risk of thromboembolism.
iii. If possible, restoration of sinus rhythm. (Table 26.4).

If patient's clinical status is severely compromised perioperatively by atrial fibrillation due to high ventricular rate, then electrical cardioversion is the treatment of choice. In the absence of severe cardiovascular compromised state, the slowing of ventricular rate in AF can be achieved by β-blockers, verapamil or digitalis. Both the β-blockers and verapamil prolongs the refractory period of AV node and thus slows the conduction through it. Where increased catecholamine levels or increased sympathetic tone is likely to be the cause of AF, then β-blockers are also always favoured. Digitalis is less effective in controlling ventricular rate in AF, because it takes longer time for onset of action and associated with more toxicity. Pharmacological cardioversion to sinus rhythm in AF also can be attempted by quinidine, flecainide, sotalol, propafenone or amiodarone. Among them amiodarone is probably more effective than other agents, but can lead to troublesome side effects. If medical cardioversion fails, the electrical cardio version is useful. The DC cardioversion for AF is successful when it is not long-standing and atrium is not enlarged. In patient when cardioversion is unsuccessful or in whom AF is likely to recur, then it is better to allow the patient to remain in AF and to control the ventricular response only with β-blockers or verapamil. Anticoagulation therapy appears to decrease the incidence of systemic embolization, associated with AF and cardioversion. Some advocate transesophageal echocardiography to locate the clot in atrium before cardioversion who is suffering from AF. In absence of clot, cardioversion can be undertaken and anticoagulation started immediately.

The risk of stroke due to thrombi in AF can be reduced up to 60% by anticoagulant therapy using warfarin. The use of anticoagulant in non-rheumatic AF is controversial. Patients without risk factors for thromboembolic events (previous thromboembolic episode, age > 75 yrs, hypertensive, diabetes mellitus, heart failure, large left atrium, impaired left ventricular function) may require only aspirin. In patients, below the age of 65 yrs, no anticoagulation therapy is required. The use of warfarin is most controversial in the elderly who have both the highest risk of stroke and the highest risk of bleeding when taking warfarin. The benefits and risks of anticoagulant therapy for AF must always be weighted up before initiating treatment.

Resistant atrial fibrillation can also be treated by electrical AV nodal ablation (to

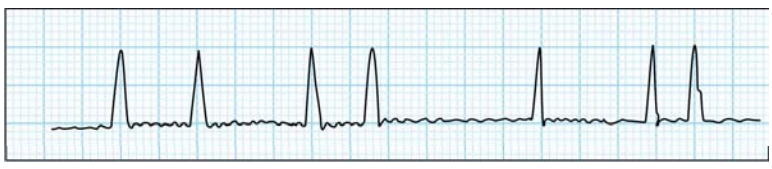


Fig. 26.26: This is a graph of atrial fibrillation. It is characterised by : absent P waves, irregularly irregular QRS rhythm as AV node fails to pass all the impulses coming from high atrial activity (>300/min)

Table 26.4: Common causes of atrial fibrillation

- Valvular heart disease (rheumatic mitral valve)
- Coronary artery disease
- Hypertension
- Sick sinus syndrome
- Hyperthyroidism
- Alcohol
- Cardiomyopathy
- Pericardial disease
- Congenital heart disease
- Pulmonary embolism
- Chest infection
- Idiopathic

prevent conduction from atria to ventricle) with insertion of permanent ventricular pacemaker.

Atrial Flutter

The characteristic features of atrial flutter in ECG are:

i. Atrial rate is around 300 per minute. This is in between atrial tachycardia and atrial fibrillation.
ii. *Sawtooth base line*: This is because of undulating P-wave due to the rapid atrial rate which gives a characteristic undulating appearance to the baseline of the ECG. This is also called the flutter waves (Fig. 26.27).
iii. AV block, usually of 2:1, 3:1, 4:1.

Atrial flutter differs from atrial tachycardia. The difference is that atrial rate or P-wave is higher (usually 250 to 350 per minute) in flutter than tachycardia and is often, almost, exactly 300 per minute. The AV node cannot keep up with such high atrial rate. So, AV block occurs. This is most commonly 2:1, although 3:1, 4:1 or other variable degrees of block may also occur. Thus, the ventricular rate is less than atrial rate and may be 150, 100 or 75 per minute.

The causes of the atrial flutter are the same as those of atrial fibrillation. The most effctive treatment of atrial flutter in emergency condition is Direct Current (DC) cardioversion. In patient who develop atrial flutter following an open heart surgery or recurrent flutter in the setting of acute MI, then atrial pacing can usually convert the atrial flutter to sinus rhythm. Atrial pacing may also convert atrial flutter to AF which allows for easier control of the ventricular response. If immediate control of atrial flutter is not mandated by patient's clinical status, then the ventricular response should first be slowed by blocking the AV node with β-blockers, or Ca-antagonist (verapamil). Once, AV nodal conduction is slowed with any of these drugs, then an attempt to convert the flutter to sinus rhythm using sotalol, flecainide, propafenone or amiodarone should be tried. The doses of these drugs which are selected are gradually increased, until the rhythm converts or side effects occur.

Broad QRS Complex Tachycardia and its Management

The causes of broad complex tachycardia are: ventricular tachycardia, accelerated idioventricular rhythm, idioventricular tachycardia, ventricular fibrillation, ventricular flutter, torsades de poindes, supra ventricular tachycardia with bundle branch block.

Ventricular Tachycardia (VT)

It is defined as broad, abnormal QRS complexes with rate more than 100 per minute (usually between 140 to 220 per minute). Usually, the episodes of VT can be self limiting. But sometimes it may be sustained or can degenerate into ventricular fibrillation. From the managemental point of view VT can be classified into sustained and non-sustained type. Sustained VT is defined as ventricular tachycardia that persists more than 30 sec with severe haemodynamic compromise. It generally accompanies with some form of serious underlying cardiac pathology such as acute MI, IHD, cardiomyopathies, myocarditis, congenital heart diseases, metabolic disorders, drug toxicity and prolonged QT syndrome, etc.

The non-sustained VT is defined as 3 or more successive ectopic ventricular beats and is sustaining less than 30 sec. It is usually not associated with any serious underlying cardiac diseases and does not produce any symptoms, i.e. without any haemodynamic compromise. (Fig. 26.28).

The ECG diagnosis of VT is suggested by tachycardia with broad QRS complexes (rate exceeding 100 beats per minute). The QRS configuration may be uniform (monomorphic) or it may vary from beat to beat (plymorphic) as in 'torsades-de-pointes'. Bidirectional VT refers to ventricular tachycardia that shows an alternation in QRS amplitude and axis, e.g VT with RBBB with alternating superior (leftward) and inferior axis (rightward).

Sometimes, the onset of ventricular tachycardia is generally abrupt and this paroxysmal VT is usually initiated by sudden multiple ventricular premature contraction (VPC). In non-paroxysmal tachycardia the onset is gradual.

The supra-ventricular tachycardia (SVT) with RBBB or LBBB may also resemble VT due to the broad QRS complex and increased heart rate. But it shoud be distinguished from original VT. Because the clinical implications and management of these two arrhythmias are totally different.

These two conditions (true ventricular tachycardia and supraventricular

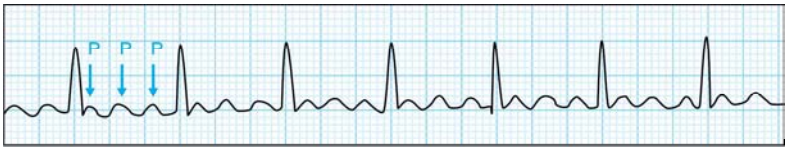


Fig. 26.27: This is a graph of atrial flutter with 3:1 AV block. It is characterised by: flutter P waves at a rate of 300/min, QRS complexes at a rate of 100/min, and 3:1 AV block (when atrial rate is above 200/min, AV node struggles to keep up with the impulse conduction and AV block may occur)

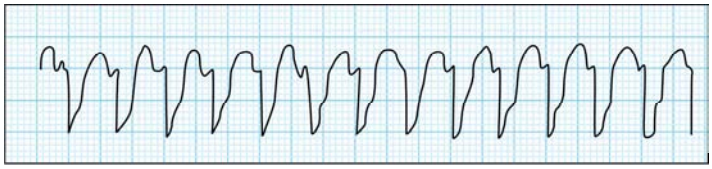


Fig. 26.28: This is a graph of ventricular tachycardia (VT). It is characterised by: Broad complex tachycardia at a rate of 200/min, QRS duration > 0.14 sec (3.5 small squares) and concordance (same QRS direction) in all the leads from V_1 to V_6

tachycardia with bundle branch block) can be differentiated apparently by :

i. Observation of intermittent canon waves in the tracing of central venous pressure monitoring and varying intensity of first heart sounds suggests AV dissociation and presence of VT.
ii. Close observation of 12 lead ECG may also be helpful.
iii. Pharmacological maneuvers such as IV administration of verapamil or adenosin (these agents terminate only the supraventricular tachycardia, but not the VT) to differentiate them can be hazardous and should be avoided. (Table 26.5)
iv. It is always useful to have a 12 lead ECG during sinus rhythm or non-tachycardia condition (i.e before development of VT) for comparison with that during tachycardia. If the QRS morphology during tachycardia is same with the previous QRS complex in ECG, i.e. when there is no tachycardia, then the diagnosis of PSVT with conduction defect is favoured.
v. An infarction pattern on the sinus rhythm tracing suggests the potential presence of VT

A characteristic feature of VT due to ventricular cause is the presence of independent atrial activity with it. This is suggested by :

• Independent P-wave.
• Fusion beats.
• Capture beats (Fact file-III and IV).

In supreventricular tachcardia the normal atrial activity is usually disturbed. So independent P-wave is absent. Whereas, in VT the independent atrial activity is indicated by the presence of independent P waves, but occurring at a slower rate than the QRS complexes. So, these QRS complexes bear no relationship to P-wave. Thus through theoretically there is definite P-ware, but, it can be difficult or even impossible to find out P waves in the jungle of multiple broad QRS complexes, originating from ventricle during VT (Fig. 26.29).

The fusion beats occur when the ventricles are activated and contracted by an atrial impulse and by an ectopic ventricular impulse at a time arriving simultaneously. The capture beats occur when an atrial impulse manages to 'capture' the ventricles for a normal contraction, causing a normal QRS complex in the jungle of broad, rapid, QRS complexes. This may be preceded by a normal P-wave (Fig. 26.30).

The characteristics of ECG that suggest tachycardia of ventricular origin (VT) are :

i. Broad complex QRS > 0.14S or 3 small squares, in the absence of antiarrhythmic therapy.
ii. Presence of AV dissociation (independent atrial and ventricular activity).
iii. Similar QRS pattern or axis in all the precordial leads.
iv. Left axis deviation with RBBB morphology or northwest axis deviation (extreme left axis deviation) with LBBB morphology.
v. Capture / fusion beat.

FACT FILE- III

Capture beat :

When there are both independent sinus and ventricular rhythm, then their impulses meet at the AV node and there interfere each other's mutual progress. So, the AV node always remains in a state of refractoriness and this is due to the prior passing of either the sinus impulses from SA node or the ectopic impulses from ventricles. But sometimes, with critical timing and due to slow ventricular ectopic rate, a sinus impulse may reach the AV node during a non-refractory phase of it and is conducted to the ventricle. Thus, it immediately activates or captures the ventricle for that beat only. This conducted sinus impulse resulting in ventricular contraction and normal QRS complex during continuous ectopic broad QRS ventricular rhythm is known as a capture beat. The QRS complex of capture beat is easily recognised, because it resembles a normal narrow sinus conducted ventricular beats inbetween the broad QRS complexes originating from ventricular ectopic site. Furthermore, the capture beat is always related to a preceding sinus P-wave.

FACT FILE - IV

Fusion beat:

Sometimes, the captured sinus impulse invades the ventricle through AV node when the ectopic ventricular impulse also tries to invade the whole ventricle, originating from ventricle. Then, each impulse will activate part of the ventricles and the resulting QRS complex will have a configuration which is in between that of the pure sinus conducted ventricular beat and the pure ectopic ventricular beat. Thus, the combination or summation of these two types of beats is known as the ventricular fusion beats. A ventricular capture and fusion beat are the most reliable diagnostic pointer to the ventricular origins of the basic ventricular tachycardia.

Table 26.5: Causes of ventricular tachycardia

1.	Ischaemic heart disease
2.	Acute MI
3.	Cardiomyopathy
4.	Myocarditis
5.	Congenital heart disease
6.	Mitral valve prolapse
7.	Drugs
8.	Electrolyte disturbance
9.	Hypoxia
10.	Idiopathic

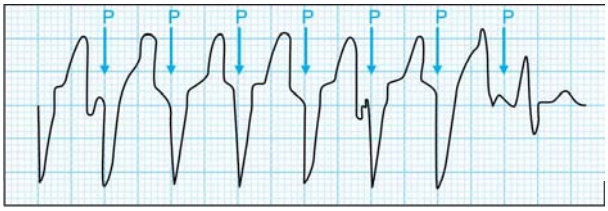


Fig. 26.29: This is a graph of captured beats in VT. It is characterised by: broad complex VT, arrows show independent P waves deforming the QRS complexes, and last beat is the capture beat

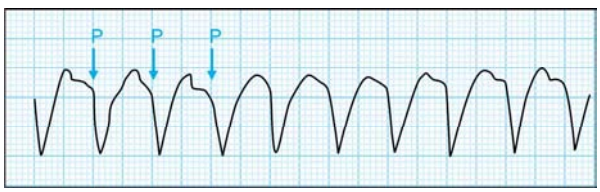


Fig. 26.30: This is a graph of fusion beat VT. It occurs when atrial and ventricular impulses arrive simulataneously

vi. No response to carotid sinus massage or IV adenosine.

The symptoms resulting from VT depend on the cardiac output which again depends on the ventricular rate, the duration of tachycardia, and the presence and extent of the underlying cardiac pathology. When the tachycardia is very rapid and is associated with severe myocardial dysfunction, then CO tremendously decreases producing hypotension, syncope, and unconciousness. Contrary, it will have to keep in mind that the presence of haemodynamic stability does not preclude the diagnosis of VT. Decrease in CO during VT may also be attributed by the loss of atrial contribution to ventricular filling (especially if atrial fibrillation is present) and by the abnormal sequence of ventricular activation.

VT without heart disease has a good prognosis with extremely low risk of sudden death. On the other hand, VT within first 6 weeks of MI have poor prognosis.

The episodes of VT can be terminated by using : (i) DC cardioversion, (ii) drugs and (iii) pacing. But the management of VT depends mainly on the risk-benefit ratio, because the antiarrhythmic agents can also produce or exacerbate the ventricular arrhythmias when they are given to prevent it. A patient with non-sustained VT without any organic heart disease and without any symptoms should not be treated, because the prognosis will not be affected. However, the patient with sustained VT, but without any heart disease may become symptomatic and require treatment (due to very low cardiac output producing hypotension and symptoms).

These tachycardias respond well to β-blockers, verapamil, procainamide, sotalol, amiodarone etc. For pharmacological termination of VT, the procainamide is the most effective agent. If it cannot terminate the tachycardia, it will always at least slow the rate. For the selection of appropriate antiarrhythmic pharmacological agent to prevent recurrence, programmed stimulation is the most effective way. In stable patients when pharmacological therapy fails, a pacing catheter can be inserted percutaneously into the right ventricular apex and the ventricular tachycardia can be terminated by overdrive pacing. Ventricular pacing to terminate VT is effective, but may sometimes also precipitate ventricular fibrillation. The VT caused by severe sinus bradycardia should also be treated by pacing at first hand. A patient with sustained VT with organic heart disease and severe haemodynamic compromise, the rhythm should be promptly terminated by DC cardioversion. Automatic implantable cardioverter defibrillation (AICD) devices can be implanted to deliver low energy shocks for recurrent episodes of VT or VF.

The development of endocardial catheter, intraoperative mapping and localization of the site of origin of arrhythmia by electrophysiological testing and then subsequent surgical ablation can better cure the ventricular tachycardia.

Some specific types of V T

Torsades-de-pointes (twisting points)

It is an unusual form of VT which is associated with long QT interval and undulating pattern of ECG with variations (polymorphic) in the direction of QRS axis. The ECG shows rapid, irregular and broad QRS complexes that oscillate from an upright to an inverted position and seem to twist around the baseline. So, it is named as the twisting point because the mean QRS axis changes. The arrhythmia is usually non-sustained and repetitive, but may degenerate into VF.

It can occur during the treatment with certain antiarrhythmic drugs (quinidine, phenothiazines, tricyclic antidepressent etc.), electrolyte abnormalities (particularly hypokalaemia and hypomagnesemia), hereditary syndromes (Jervell and Lange-Nielsen Syndrome, Romano-Ward syndrome), intracranial events and bradyarrhythmias particularly third degree AV block (Table 26.6).

Table 26.6: Causes of long QT interval and Torsades-de-pointes

Electrolyte disturbances
Hypokalaemia
Hypocalcaemia
Hypomagnesaemia
Bradycardia
Complete heart block
Sinus node disease
Drugs
Class Ia antiarrhythmic drugs (e.g disopyramide)
Class III antiarrhythmic drugs (e.g solatol, amiodarone)
Tricyclic antidepressants (e.g amitriptyline)
Phenothiazines (e.g chlorpromazine), erythromycin and other macrolides
Congenital syndrome
Jervell and Lange - Neilson's syndrome
Romano - ward syndrome (autosomal dominant)
(autosomal recessive associated with congenital deafness)

The hallmark of torsades-de-pointes in ECG are:

i. Broad complex tachycardia with polymorphic QRS complexes.
ii. Marked QT prolongation.
iii. Variation in QRS axis (Fig. 26.31).

These patients with torsades-de-points often have multiple episodes of sustained or non-sustained VT with recurrent syncope and risk of development of VF with sudden cardiac arrest. So, urgent assessment is warranted with identification and withdrawn of causative drugs prolonging QT interval and correction of electrolyte

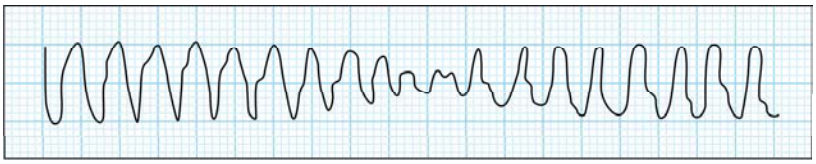


Fig. 26.31: This is a graph of torsades-de-pointes. It is characterised by : broad complex tachycardia (300/min) and variations in QRS axis

abnormalities. The management is like that:

i. The drug induced torsades-de-pointes is treated by atrial or ventricular pacing which increases the heart rate and thereby shortens the QT interval.
ii. For patients with congenital prolonged QT syndrome, β-adrenergic blocking agent is the mainstay of therapy.
iii. Cervicothoracic sympathectomy is also indicated as a form of therapy in Torsades-de-pointes by interrupting the sympathetic supply to heart.

Idioventricular Tachycardia

The idioventricular tachycardia results from the accelerated ventricular depolarization originating from ectopic foci situated in ventricle. The heart has many potential pace maker cells. These are situated in the SA node, AV node, atria, His bundle and the ventricles. But, only one of these sites with highest automaticity controls the heart rate. It is because the impulses arising from the pace maker cells of higher automaticity reaches the lower potential subsidiary pacemaker's site and abolishes their immature impulses before they have the time to fire. Thus, the subsidiary pacemaker centre with lower automaticity enjoys protection by the impulses from the fastest pacemaker centres. But, when the inherent rate of AV nodal pacemaker site is increased than SA node and goes above 100/minute, then it is called the idionodal tachycardia. Similarly, when the inherent discharge rate from the ectopic ventricular pacemaker site is increased more than SA node, and goes above 100/minute then it is also called the idioventricular tachycardia. But when the discharge rate from the idioventricular pacemaker site is below the rate of SA node, then it is called the accelerated ventricular rhythm. So, it is commonly found in incomplete atrioventricular dissociation or found in the presence of causes which decrease the sinus rate or increase the expression of nonspecific ventricular pacemaker site such as fever, carditis, etc. It is not a sudden, precipitous, dramatic event like VT and does not precipitate in VF. The idioventricular tachycardia whose rate varies around 100/m is not so pathognomic and rarely cause much decrease in cardiac output and haemodynamic embarassment. The only difference between the idioventricular tachycardia and VT is the ventricular rate (in VT the heart rate is 150 to 220/min) (Fig. 26.32).

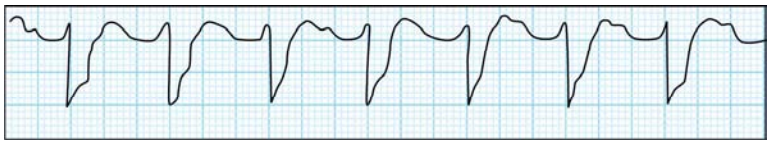


Fig. 26.32: This is a graph of idioventricular tachycardia. It is characterised by: broad QRS complexes and heart rate is 100/min. When broad QRS complex rate is <100/min, but >40/min, it is called the accelerated idioventricular rhythm. When broad QRS complex rate is <40/min, it is called the escape ventricular rhythm

The diagnosis of idioventricular tachycardia is based on the following criteria :

i. Evidence of ventricular origin — broad, bizarre QRS complexes
ii. Presence of captured beats — the captured beats are due to the relatively slow rate of idioventricular tachycardia than VT and the relatively long cycle of ventricular ectopic action potential which permits adequate recovery time and therefore a greater opportunity to capture a sinus beat. With very fast ventricular rates, as occur in VT, the refractory period frequently occupies the whole ventricular cycle and therefore, the opportunity to capture a sinus beat becomes minimal or absent.
iii. As the rate of idioventricular tachycardia is not so high, so the ectopic ventricular rhythm also begins with several consecutive fusion beats. This is also called the incomplete capture beat. Since, the rate of two rhythms (atrial and ventricular) are close to each other, so the idioventricular tachycardia tends to terminate after few successive fusion complexes.
iv. AV dissociation may be present or not. If it is present fusion or captured beats will not be found.
v. The ectopic pacemaker site for idioventricular tachycardia has great protection. This is evident from the fact that it is abolished when the sinus rhythm regains its dominance. This is in contrast to VT, where the ectopic rhythm is not abolished by the faster sinus rhythm.

Ventricular flutter

The Ventricular flutter is the expression of:

i. a very rapid and regular ectopic ventricular discharge like ventricular tachycardia but the rate is higher than VT.
ii. grossly abnormal intraventricular conduction (Fig. 26.33).

In ECG the QRS and T deflexion of ventricular depolarisation are very wide and bizarre, one merging with the other. So, that it is difficult to define or separate the QRS complex, ST segment and T wave. This is the difference between V. flutter and V. tachycardia. In V. tachycardia this separation is possible. This results in the appearance of a continuous sine like wave form in V. flutter.

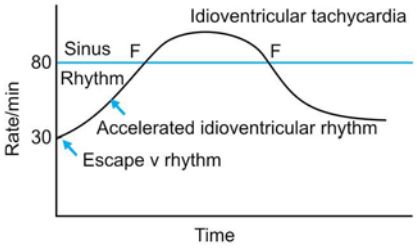


Fig. 26.33: This diagram illustrates the mechanism of ventricular tachycardia. A potential ventricular escape rhythm (beginning of red line) is enhanced to accelerated idioventricular rhythm. When it exceeds the sinus rhythm, then it becomes manifested as an ventricular tachycardia. At points F both the sinus and idioventricular rhythm will be at the same rate. Thereby, after that ventricular beat results in ventricular fusion beats. Before point F, ventricular beats are captured

The bizzare sine like wave of v flutter also may result from the abnormal intraventricular conduction alone. In ventricular flutter the coordinated activation of ventricular myocardium and sufficient contraction of it to produce a stable haemodynamic condition by giving some cardiac output is still present. However, the change from ventricular tachycardia to ventricular flutter is associated with a fall in BP and cardiac output.

Ventricular flutter is uncommon in clinical practice. It acts as a phase of tramition lying between VT and VF. So, only few examples are recorded, since the condition usually progresses or changes rapidly from ventricular tachycardia to ventricular fibrillation. Ventricular flutter differs from ventricular fibrillation in the uniformity, constancy, regularity and relatively large amplitude of QRS deflexions. Whereas the deflexions of ventricular fibrillation are small and completely chaotic and irregular.

It is well-known that V flutter and V tachycardia are the expressions of same mechanism. So their separation may nevertheless serve a useful purpose, since a diagnosis of V flutter immediately connotes a very rapid ventricular rate and / or grossly abnormal intraventricular conduction and reflects an ominous clinical state with a drop in blood pressure and a low cardiac output.

Ventricular fibrillation (VF)

Ventricular fibrillation (VF) is a very fatal condition and so it requires an immediate diagnosis and treatment. The onset of this type of arrhythmias is rapidly followed by loss of conciousness as cardiac output falls tremendously or becomes nil and if untreated, then death ensues. The 3/4th of all cardiac arrest are in the form of VF.

VF is most commonly seen after acute MI, in severe ischaemic heart disease, following administration of antiarrhythmic drugs, after electrical accidents, in severe electrolytes and acid-base imbalance, etc. (Fig. 26.34)

Genesis of VF:

i. The non-ischaemic VF begins after a short run of very rapid VT which is again initiated by subsequent multiple VPC (Ventricular Premature Contraction). The VT ultimately breaksdown into multiple wavelets of reentry circuit within the ventricular myocardium, leading to VF.
ii. In infarction or in ischaemia the VF is usually precipitated by a premature, single, early ventricular depolarisation or complex falling on T-wave (vulnerable period), which produces a rapid VT that degenerate into VF. Onset of VF within 48 hours of infarction is called primary VF and has a good long-term prognosis. Because once corrected by DC shock, this primary VT does not require prophylactic treatment (i.e low rate of recurrence). On the other hand, the onset of VF after 48 hours of infarction is called secondary VF and it merits bad prognosis due to high recurrence rate.

Electrocardiographically VF is recognised by grossly irregular undulation of waves (ventricular complexes) in ECG which is of varying amplitudes, contours and rates. The management of VF is as cardiac arrest i.e. institution of CPR immediately.

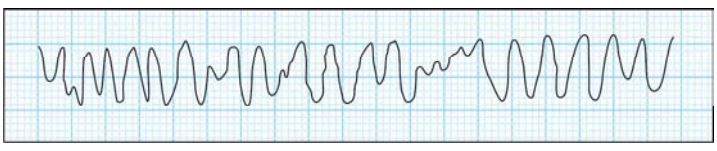


Fig. 26.34: This is a graph of ventricular fibrillation. It is characterised by: chaotic ventricular activity

CARDIAC ARREST AND CARDIO-PULMONARY RESUSCITATION (CPR)

Cardiac arrest is defined as the sudden and complete loss of cardiac function. In this condition the patient immediately loses consciousness, pulse is not palpable and respiration ceases quickly. So, death is virtually inevitable, unless an effective treatment is provided promptly. Therefore, any effective treatment which is tried immediately to start the cardiac function is called the cardio-pulmonary resuscitation.

Most frequently many cardiac arrests are managed very poorly. This is because there is lack of immediate organisation of an efficient team, lack of proper knowledge about the recommended procedures, immediate lack of proper equipments and drugs, and very frequently, different types of arrhythmias that occure during cardiac arrest are incorrectly diagnosed and treated. So, the management of cardiac arrest which is called CPR is described in a stepwise manner to prevent the haphazard way of working.

Step – I

If it is seen that a patient has been suddenly collapsed and becomes unresponsive or unconscious due to cardiac arrest, then immediate help is sought. This is because chances of successful outcome from CPR decline rapidly with the passing of time. The cardiac arrest which is manifested as unresponsiveness or unconsciousness should be confirmed first by shaking the patient and asking the questions loudly while keeping the fingers on pulse (first on radial, then if not palpable on brachial or carotid artery) and examining the eyelash or corneal reflexes. Simultaneously, the respiration should also be checked, when unresponsiveness is confirmed and pulse is not palpable. If respiration is not felt then cardiac arrest is confirmed clinically and immediate help is sought and precordial thump is delivered. If precordial thump

is started within 30 sec of confirmation of cardiac arrest, then the energy delivered by precordial thump is sufficient enough to restore an effective rhythm in 2% cases of VF and up to 40% cases of VT (provided the cardiac arrest is presented in the form of VF or VT).

If precordial thump fails to work, (usually fails) then next steps of CPR are:

i. Basic life support (BLS).

ii. Advanced life support (ALS) (Fig. 26.35).

Step – II

Though the BLS itself very rarely restores the cardiac function or patient's own breathing and circulation, still it is regarded as the cornerstone of CPR. This is because it works as stop-gap procedure to maintain the patient's minimum oxygenation and circulation until the efficient personnels, drugs and equipments needed for ALS are made available.

BLS procedure stands on : A – Airway, B – Breathing, C – Circulation.

Airway

Airway should be maintained by :

i . opening the mouth,

ii. removing or loosing any clothing around the patient's neck,

iii. removing foods, blood, froth, etc, from the mouth and cleaning the airway,

iv. lifting the chin in order to lift the tongue from the back of the throat.

Breathing

Breathing of the patient should be assessed by looking at the chest and/or by listening the mouth of the patient for breath sound and/or by feeling the patient's exhaled air on the dorsal surface of the examiner's hand. This is actually the part of the diagnosis of cardiac arrest. If the patient does not breathe, then immediate mouth to mouth artificial breathing should be started or artificial ventilation should be started by any device which is available at hand. The different types of devices which are in use for artificial ventilation has been discussed in separate chapter.

Circulation

When breathing of the patient is assessed, then peripheral pulse (brachial, carotid) also should be palpated simultaneously without wasting any time. If there is no palpable peripheral pulse then the diagnosis of cardiac arrest in confirmed and immediately full basic life support is started i.e. with mouth to mouth breathing, the cardiac compression is given. Classical cardiac compression is performed by placing the heal of one hand on the middle of the lower half of the patient's sternum and placing the heel of other hand over the first and then interlocking the fingers. After that pressure should be given vertically downwards, so that sternum is depressed by 4 to 5 cm. The rate of the chest compression should be maintained at 100 per minute. The time taken for each chest compression should be equal to the time taken to release the pressure. Every 15 chest compression should be followed by two ventilations at a ratio of 15:2. The idea behind this chest compression is that the cerebral blood flow of at least 20% of normal is needed to be maintained for a full neurological recovery and this is possible by this type of properly performed cardiac compression and artificial ventilation. Recovery of spontaneous respiration and peripheral pulse should be checked after every 10 breaths.

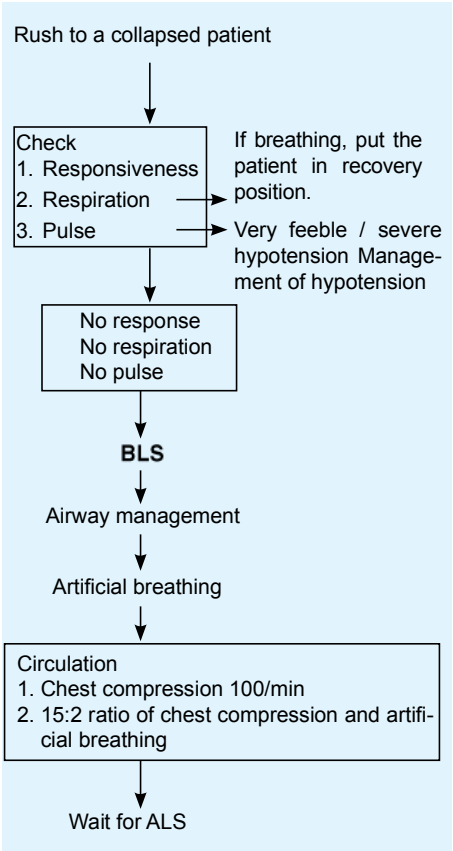


Fig. 26.35: Algorithm of adult basic life support (BLS)

Step – III

ALS is the main part of this step. ALS is commenced as soon as there is availability of proper equipments such as intubating aids, monitors, defibrillator, ventilating equipments, drugs and trained cardiac arrest management team. BLS should be continued till ALS is available and applied. Now, as the part of ALS, the defibrillator or cardiac monitor should be attached and the cardiac rhythm disorder should be studied by the other members of the team, when BLS is going on.

There are four types of arrhythmias that are usually encountered during or shortly after cardiac arrest. These are:

i. Ventricular fibrillation.

ii. Pulseless VT or sustained VT with no CO (Cardiac Output).

iii. Asystole.

iv. Electro Mechanical Dissociation (EMD).

VF

It is the most commonest form of arrhythmia in cardiac arrest and appears as a chaotic rhythm on ECG. If the monitor is faulty or the gain is turned too low, then it can also be mistaken as asystole.

Pulseless VT

It appears as broad complex rapid ventricular complexes (QRS complex) with severe haemodynamic compromise characterised

by nil or very low CO (pulseless). In such type of arrhythmia causing cardiac arrest DC shock is very helpful to convert VF and VT to normal cardiac electrical activity or to such an cardiac electrical activity which is capable of maintaining a workable cardiac output.

Asystole

It implies that there is no electrical cardiac activity and thus the ECG is simply shown as a flat or straight line. DC shock is not helpful in asystole rather it potentiates asystole (Fig. 26.36).

Electromechanical dissociation

In such condition the cardiac electrical activity is normal and the heart contract normally. But it fails to produce any CO or any effective circulation. This is mainly due to severe reduction of preload. The DC shock is also not helpful in EMD. (Fig. 26.37).

Management of VF and VT in cardiac arrest

Defibrillation converts the abnormal cardiac rhythm i.e. VF and VT (which is the most commonest > 95%) to sinus rhythm or at least to a rhythm that restores some cardiac output. So the first step of ALS is defibrillation even before the diagnosis of specific electrical activity in cardiac arrest. Defibrillation is also the coice of management for VF and VT in ICU. In addition, defibrillation can also be used if there is asystole because it cannot be entirely confirmed that it is not due to the small complex (fine) VF. So, in doubt of benefit, defibrillation should be used even in asystole as VF and VT is the most commonest (in more than 95% of cases) and treatable form of cardiac arrest. However, there is no reason in defibrillating a patient if it is confirmed that there is asystole. Because defibrillation just changes one type of cardiac rhythm to another, but it will not restart the heart where there is no initial electrical activity as in asystole. In case of EMD, defibrillation also has no role, because by definition of EMD the heart is working normally electrically, but without any CO due to some mechanical reasons such as reduction of preload.

During defibrillation the following steps should be taken. These are:

i. All nitrate patches should be removed from the patient's body.
ii. The paddles always should be placed at least 15 cm away from the permanent pacemaker.
iii. Electrode jel or gelly always should be used on the skin below the paddles.
iv. Electorde jel should not spread between the paddles as this can cause a short circuit.
v. Every body attaining this patient should stand clear of the patient and his bed just during discharging of electrical energy (Fig. 26.38).

Then, in rapid succession (i.e one after another, not measuring the time interval between the two) three DC shocks are given with the energy of 200J, 200J and 300J respectively. After that a brief pause is given to assess the patient's cardiac rhythm on monitor's screen and/or pulse and to recharge the defibrillator. These three successive DC shocks should be delivered within 45 seconds and it is not necessary to resume the basic life support as a part of ALS (i.e ventilation and chest compression) between each of these three successive shock.

After the 1st round of 3 DC shock, BLS is again started for a minute and the cardiac rhythm and pulse is assessed at the end of this minute. At this point the IV line is instituted and patient is intubated by others. BLS should not be interrupted for more than 15 sec due to any reason, when attempting intravenous line and / or intubation. If access to the IV line and intubation fails in first attempt, then it should not be tried again, till the end of the next set (2nd round) of 3 DC shocks. In between the failed attempt for IV line and intubation and DC shock, BLS should be continued for another 1 minute. The second set of 3 DC shocks should be with energy of 300J each. Before the second set of DC shock 1 mg adrenaline is given intravenously (if line is procured) or through endotracheal tube. It is not necessary to give time to adrenaline to circulate before giving the second set of DC shocks, because adrenaline does not aid in defibrillation. But it only improves the cerebral and coronary circulation by constricting the peripheral vasculature and reducing the blood flow to the skin and skeletal muscle. If adrenaline is used by endotracheal route, the total dose should be diluted to 10 ml in isotonic saline and should be used by five ventilations.

After adrenaline and the second set of DC shocks, BLS should be continued again for a minute and at the end of this minute the patient's cardiac rhythm and pulse should be assessed again. If still satisfactory cardiac rhythm has not been restored, then third set of three DC shocks should be delivered with energy of 360 J, each.

Thus, each loop [DC shock → BLS (it means chest compression and ventilation) → assessment → drug] should take no

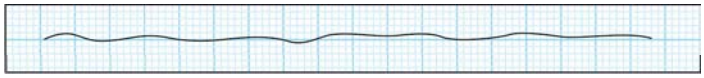


Fig. 26.36: This is a graph of asystole. It is characterised by flat line in ECG (no spontaneous electrical activity)

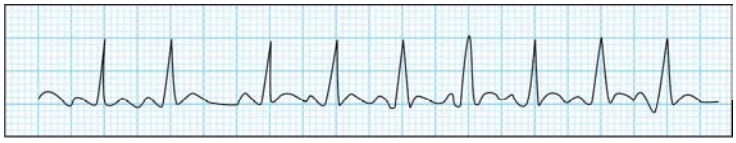


Fig. 26.37: This is a graph of electromechanical dissociation. It is characterised by normal QRS complexes in the absence of a cardiac output

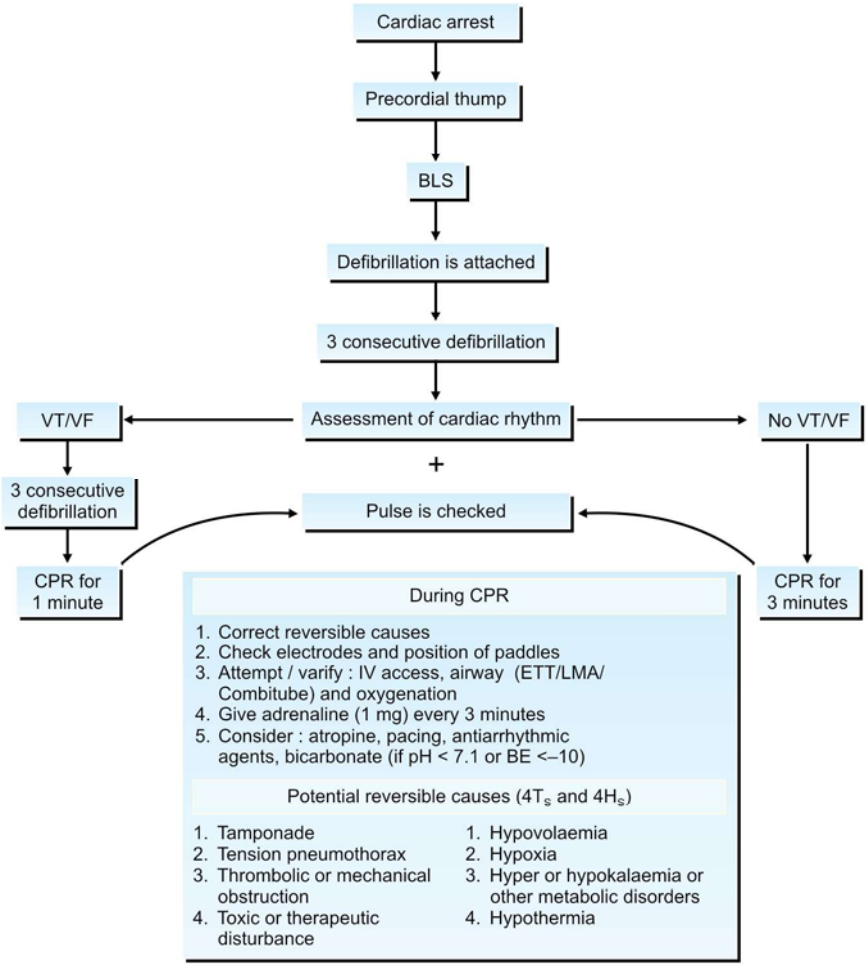


Fig. 26.38: Algorithm of adult life support

more than 2 or 3 minutes and should be repeated, untill either a effective cardiac rhythm maintaining some cardiac output is restored or it is decided that CPR would be abandoned.

After the third set of DC shocks, if VF is still continuing, then the following things can be done:

i. antiarrhythmic agents such as lignocaine, bretylium or amiodarone can be started.
ii. K^+, Ca^{2+}, magnesium should be checked and corrected.
iii. Paddle position should be changed.

Actually the benefit of the use of antiarrhythmic drugs are lacking in the management of CPR. Again the routine use of sodium bicarbonate to correct acidosis following cardiac arrest is not recommended, because paradoxically it worsens the intracellular acidosis and does not improve the final outcome. If bicarbonate is to be used then dose should be calculated from arterial pH and blood gas analysis that is discussed in acid-base balance chapter.

Management of asystole in cardiac arrest

Following cardiac arrest BLS is started immediately, while looking for ALS and if possibel the causes should be treated simultaneously with BLS and ALS. Management of aystole in cardiac arrest is not the DC shock, because DC shock does not regenerate any electrical cardiac activity. But, sometimes very fine (VF) may be misdiagnosed as aystole due to the faulty equipment or too low gain setting on the monitor. So, this wrong diagnosis is very dangerous and if there is any doubt, then for benefit of doubt three DC shocks at energy level of 200J, 200J and 360J each should be given successively to avoid missing of a potentially reversible VF. On the otherhand, application of DC shock in a confirmed asystole has no adverse effect.

Following DC shocks, the BLS and ALS should be continued again like the management of VT or VF in CPR. Intubation and access to the IV lines should be tried. Cardiac rhythm should be diagnosed as confirmed asystole. Adrenaline 1 mg should be administered intravenously and BLS should be maintained for 3 minutes with chest compression to ventilation ratio of 15:2. Then 2nd dose of adrenaline is given and patient's cardiac rhythm and pulse is again assessed. If asystole persists, 3 mg atropine in a single bolus dose is given IV. The cycle should be repeated, maintaining BLS and giving further doses of adrenaline every 3 minutes. After 3 repeated cycle, if the patient is still asystolic, pacing should be done using transvenous pacing wire or transthoracic pacing. In the mean time all the causes for cardiac asystole are searched for and removed.

Management of EMD in Cardiac Arrest

In cardiac arrest, if rhythm is diagnosed as EMD, then always the underlying remediable cause should be immediately looked for and treatment is started. The few causes of EMD are cardiac tamponade, drug overdose, electrolyte disturbance, hypothermia, hypovolaemia, pulmonary embolism, tension pneumothorax, etc.

Immediately BLS is started, while looking for ALS and if possible treating the causes. After intubating the patient and

gaining the intravenous access, the adrenaline in the dose of 1 mg is administered IV in bolus and then BLS is continued for 3 minutes with chest compression to ventillation ratio of 15:2. After that cardiac rhythm and pulse is assessed. If still EMD persists then one bolus dose of 3 mg of atropine is given IV. Cycles should be repeated, maintaining BLS and ALS and giving further doses of adrenaline after every 3 minutes interval.

Although high doses of adrenaline (5mg IV), alkalizing agents, calcium and pressor rising agents can be given, still there is no confirmed evidence for their routine use and better prognosis.

Non Drug Therapy of Arrhythmia

External defibrillation or cardioversion

The cardioversion is the process of restoration of normal electrical rhythm of heart by electrical shock and the device by which this process of cardioversion is accomplished is known as the defibrillator. This process of cardioversion can be accomplished by passing sufficiently large amount of direct electrical current through the heart from an external or internal sources. The mechanism of action of DC shock is that it will completely depolarise the heart for a fraction of a second and will temporarily interrupt any arrhythmia. Thus, it will produce a brief period of asystole which is usually followed by the resumption of normal sinus rhythm. The defibrillator usually delivers a high energy direct current of short duration via two metal paddles or gel pad, positioned over the upper right sternal edge and the apex of the heart. When this technique is used to treat organised rhythms such as atrial fibrillation or ventricular tachycardia, then the shock should be synchronised with the ECG and is normally given at 0.02 seconds after the peak of R wave. Otherwise, if energy is applied during a critical period around the peak of T wave then it may provoke ventricular fibrillation. But this precise timing of discharge of shock is not important in ventricular fibrillation as it is not an organised electrical cardiac rhythm.

In ventricular and other emergencies, the energy of the first shock should be minimum of 200 J. There is no need for anaesthesia, if the patient is unconscious such as VF in cardiac arrest. But, usually an elective cardioversion requires a general anaesthesia or sedation for conscious subject such as for correction of atrial arrhythmia. High energy shocks may cause the myocardial damage also. So, if there is no urgency, it is appropriate to begin with a low amplitude shock i.e. 50 to 100J and gradually going to larger shocks, if necessary.

Digoxin toxicity increases the risk of untoward arrhythmias after cardioversion. So, it is conventional practice to withhold the drug for 24 hours, before any elective cardioversion. Patients with long-standing atrial arrhythmias such as AF are at the increased risk of systemic embolism before and after cardioversion. So, it is wise to ensure that the patient is adequately anticoagulated for at least 4 weeks on either side of the procedure.

Implantable Cardioverter – Defibrillators (ICDs)

These are expensive and sophisticated devices which can automatically sense and terminate the life- threatening different types of ventricular arrhythmias by pacing or synchronised cardioversion with low energy shock or defibrillation with high energy shock. But, this automatic high energy shock can be painful, if the patient is still conscious. These devices also can pace the ventricles in the event of severe bradycardia and asystole. ICDs are implanted transvenously like a permanent pacemaker and are subject to similar complications. Clinical trials among the high risk patients have shown that the devices are more effective than antiarrhythmic drugs in preventing sudden death from severe cardiac arrhythmia. An ICD is used to treat the patient who present with cardiac arrest due to VT or VF or sustained VT causing syncope or severe haemodynamically compromised VT associated with poor left ventricular function (LVEF < 35%). These devices may also be used prophylactically in selected patients who are thought to be at the high risk of sudden cardiac death such as long QT syndrome, hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, etc.

Radiofrequency catheter ablation

The aim of this technique is to interrupt the re-entry circuit by selectively damaging the accessory path for conduction of cardiac impulses with endocardial tissue by radio frequency energy, delivered through a catheter that is passed into the heart through a peripheral artery or vein. This procedure is often time consuming and the patient may experience some discomfort during the time of ablation. But, it does not require any anaesthesia. Serious complications are rare and subject to similar of pacing. The radio frequency ablation eliminates the need for long-term drug therapy and is an attractive form of treatment for many arrhythmias offering the prospect of a lifetime cure. The technique has revolutionised the management of many cardiac arrhythmias and is now the treatment of choice for atrial tachycardia, AV nodal re-entry tachycardia, WPW syndrome and AF. The applications of this technique are now expanding. So, it has also been used to treat some forms of VT.

PACEMAKER

The artificial electrical depolarisation of heart is a valuable clinical means of therapies of different types of arrhythmias. So, its major uses include : (i) cardiac pacing for the control of rate and rhythm of heart and thus correcting some arrhythmias, and (ii) delivery of countershock by DC current (cardioversion) for correction of some arrhythmias which is already discussed.

The device by which the cardiac pacing for the control of rate and rhythm of heart is doen is known as the cardiac pacemaker. Anaesthesiologists must learn about pacemakers due to two reasons: (i) pacing is the mode of treatment of large number of cardiac arrhythmias facing emergencies, and (ii) pacing affects the appearance of ECG which may sometimes confuse an anaesthetist to diagnose a cardiac arrhythmia from ECG. Due to the advancement of technology more and more sophisticated kinds of pacemakers are coming out, so that a wide range of pacemaker with different mode of functions are now available. But, the two most basic functions of pacemakers for the control of cardiac rate and rhythm are

i. It provides a safety in patients who are at risk of bradycardia or asystole, and
ii. It terminates tachycardia.

There are three methods of pacing:

i. External pacing

It is effective only in very emergency situation, where internal temporary pacing is not available or if available but has no time to implant it. However, it becomes ineffective after several hours and it is painful to the conscious patient. So, patient must be sedated. Transthoracic pacing is the example of such an external pacing, and is also called the transcutaneous pacing. It functions by delivering an electrical stimulus that is sufficient to induce cardiac contraction from outside through two large adhesive gel pad or electrodes, placed over the apex and upper right sternal edge like defibrillation. These two electrodes also can be placed over the precordium and back of the patient. It has the advantage of being easy and quick to set up, but may cause discomfort and skeletal muscle contraction. Some sophisticated ECG monitor or defibrillator machines incorporate this type of transcutaneous pacing system which can be used as a temporary measure, until the temporary transvenous pacing is established.

ii. Internal pacing with power source outside the body

This is also called the temporary pacing. It can be accomplished by inserting an electrode into the heart through a large veins in neck, arm, leg or by direct puncture of the myocardium through the chest wall. These techniques are effective for emergency situations and short-term therapy. Its status lies between the external pacing and the permanent pacing. Here, the electrode placed within the cardiac cavity is connected to an external pulse generator (power source) which can be adjusted time to time to alter the energy output and pacing rate. The threshold of pacing is the lowest output that will reliably pace the heart and it should be less than 1 millivolt during initial period of implantation. It may require daily adjustment, because the threshold of myocardium tends to rise due to inflammation and oedema of cardiac tissue around the tip of the electrode.

iii. Internal pacing with power source implanted in the body

This is also called the permanent pacing. Again it can be of two types.

A. Left ventricular epicardial pacemaker : Here the electrodes are sutured directly into the left myocardium. This is done via thoracotomy or subxiphoid approach. The power source is embedded in the abdominal wall
B. Right ventricular endocardial pacemaker: Here the electrodes are introduced into the apex of the right ventricle via an axillary or subclavian vein and the power source is implanted at the pectoral or axillary area. Because of the relative simplicity and better efficacy of this procedure, insertion of this type of permanent pacemaker is preferred.

The temporary pacemaker provides pacing in an emergency situations, until a permanent pacemaker is implanted. In temporary pacing electrodes are introduced usually through the transvenous route. But transesophageal and transcutaneous temporary pacing also can be used. Here, the battery and the electronics part of the pacemaker remain outside the body. Whereas in permanent pacemaker the battery, electronics and electordes are all implanted within the patient's body. Both the temporary and permanent pacemakers are such set that it monitors the patient's cardiac activity continuously and provides impulses when necessary, because patients seldom need pacing impulse from pacemaker continuously. This helps to prolong the life of battery of pacemakers. This is called demand pacing.

All the pacemaker units mentioned above can function in an unipolar or bipolar manner. The unipolar circuit consists of a cathode end which is inserted into the myocardium and an anode end which is situated at a remote site, usually on the surface of the implanted power unit. But, the bipolar pacemaker has both the cathode and anode end within the heart which are usually at 1 to 2 cm apart.

Indications for Temporary Pacing

The indications for temporary pacing are :

i. Patients waiting for permanent pacing.
ii. Acute MI: In acute inferior wall MI complete heart block is usually developed due to the damage of artery which supplies the AV node. So, extensive infarction causes severe bradycardia or second and third degree AV block due to the damage of the bundle branches in the interventricular septum. In such situation mortality is high. So, immediate temporary pacing and inotropic support are very essential.
iii. Some tachycardia such as AV reentry tachycardia and ventricular tachycardia can be terminated by overdrive temporary pacing in emergency situations.
iv. Perioperative pacing.

Indications for Permanent Pacing

The indications for permanent pacing are:

i. Second degree AV block with an episode of symptomatic bradycardia

(syncope) regardless of whether it is Mobitz type I or II.
ii. Third degree AV block.
iii. Bi-fasicular block with a history of syncope or documented intermittent failure of the remaining fascicle. Asymptomatic patients with bifascicular block are not indicated for pacing.
iv. Sick sinus syndrome (SSS)with symptoms only. Asymptomatic patients with SSS are not indicated for pacemaker.
v. Malignant vasovagal syndrome.
vi. Carotid sinus syndrome.

DESCRIPTION OF PERMANENT PACEMAKER

The permanent pacemakers are usually described by internationally accepted code of 5 letters. Each letter describes an individual aspect of the pacemaker's different function that is shown in the table. There are different types of pacemaker available in the market. Among them some commonly available pacemakers are described here.

VVI

This pacemaker senses ventricle (V) by single lead placed within the ventricle (V). It also paces ventricle via the same lead when no cardiac electrical activity is detected. So this is also called the ventricular demand pacemakers. Otherwise, the pacemaker always senses and is inhibited (I) by normal ventricular activity and does not send impulses for ventricular contraction.

VVT

This is a triggered (T) type of ventricular pacemaker. During sinus conducted rhythm (or other spontaneous rhythm), the pacemaker also continuously discharges impulses approximately 0.04-0.08 sec after the onset of normal QRS complex. Thus, it can be seen as an artefact in the ECG and indicates pacemaker function. But it plays no role in ventricular depolarisation, because the artifact constantly falls in the absolute refractory period of the normal action potential of the ventricle. Whenever, the spontaneous sinus rhythm falls below the preset rate fixed by the pacemaker, then the pacemaker assumes its function. This is not a demand pacemaker.

AAI

The single lead of this pacemaker is situated in atrium (A) and senses atrial (A) activity. If normal atrial activity is detected, pacemaker becomes inhibited (I). But, whenever atrial activity is not detected, then it takes over the function by pacing the atria. It is also a type of demand atrial pacemaker.

AAO

This is not a demand pacemaker and the electrode is placed in the atrium. It is not a demand pacemaker, because it does not sense (O) the atrial electrical activity and in not inhibited. It continously sends impulses according to a prefixed rate for atrial depolarisation and subsequently ventricle contracts. If the patient's problem requiring pacing is due to the SA node or atrial disease, but AV nodal and His-Purkinje system conduction is normal, then this transvenously inserted atrial pacemaker is effective.

DVI

This unit paces both the atrium and the ventricle, but senses only the ventricle (V). As this pacemaker paces both the chambers of heart, so it is designated as double (D) chamber pacemaker. The pacemaker is inhibited (I) by an earlier spontaneous ventricular depolarisation. But since there is no atrial sensing, so atrial pace impulse will not be inhibited and atrial pace artefacts will appear regularly in the ECG at the programmed rate even though P-waves precede them. It cannot be used in the presence of atrial fibrillation.

DDD

This pacemaker has two leads, one in the atrium and one in the ventricle. So, it is called the dual chamber (D) pacemaker. It senses both the atrial and ventricular activity (D). It is inhibited if it senses activity in the ventricle. In complete AV block, if it senses atrial activity without ventricular activity, it can pace ventricle in sequence with atria. It can also pace the atria alone or atria and ventricle both in sequence (D). (Table 26.8)

AAIR, VVIR, DDDR

'R' indicates the rate of responsiveness. The rate of responsiveness means pacemakers adjust the HR or pacing rate according to the need of the patient during activity which mimic the physiological response. Here the patient's level of activity is continuously monitored by pacemaker through several parameters like vibration, respiration or temperature of blood. Thus heart rate is adjusted by pacemaker according to the activity.

Programmable pacemaker

The advancement of technology in the manufacture of pacemaker permit future modifications or change of many of its functions (programme) by external means, thereby sparing the need for an invasive procedure. Thus, the changes of different parameters can be made in the pacemaker from outside. These are pacing rate, sensing interval (rate hysteresis), pulse width, amplitude, etc. This facility allows the cardiologist to prolong the life of pacemaker by choosing the optimum settings and providing the means to overcome a wide range of pacing problems. For example, programming can be used to increase the output in the face of an unexpected increase in threshold or to alter sensitivity, if the pacemaker is inappropriately inhibited by electrical potentials, generated in the pectoral muscles.

The atrial pacing is appropriate for patients with sick sinus syndrome

Table 26.7: Letter codes for different functions of pacemaker

	Letter refers to	*Code*	*Meaning*
1	Chamber paced	V	Ventricle
		A	Atrium
		D	Dual or both the chambers
2	Chamber sensed	V	Ventricle
		A	Atrium
		D	Dual or both the chambers
		O	None
3	Mode of response or sensing	T	Trigeering of pacemaker (ventricular synchronus)
		I	Inhibition of pacemaker (ventricular demand)
		D	Inhibition or triggering
		O	None
		R	Rate responsiveness Reverse function: This pacemaker is silent at slow rates and activated by fast rates.
4	Programmable functions	P	Programmable for rate or output or both
		M	Multiprogrammable
		O	None
		E	External control
5	Special antitachy-cardia functions	P	Pacing of tachycardias
		S	Shock delivered
		D	Dual (pacing and shock)
		O	None
		B	Bursts of impulses

(sinoatrial disease) without AV block. Ventricular pacing is the only suitable mode for patients with continuous atrial fibrillation. In DDD (dual chamber pacing) the atrial electrode can be used to detect the spontaneous atrial activity and trigger the ventricular pacing. Thereby, it preserves the atrioventricular synchrony and allows the ventricular rate to increase together with the atrial rate during exercise and other forms of stress. Thus, though DDD is more expensive, but has many advantages when compared to only ventricular pacing. These include superior haemodynamics with better effort tolerance, a lower prevalance of atrial arrhythmias in patients with sick sinus syndrome (SSS) and the ability to prevent and cure the 'pacemaker syndrome'. The pacemaker syndrome consists of fall in BP and dizziness, precipitated by the start of ventricular pacing.

VVIMB

This is similar to VVI pacemaker but is multiprogrammable with pacing bursts for tachyarrhythmias.

DVIM

This is an atrio-ventricular pacemaker which paces both the atrium and the ventricle. It is ventricular inhibited and is multiprogrammable.

ECG FINDINGS in Pacemaker

The pacemaker depolarizes atrium and / or ventricle by electrical impulses which is generated within it and appear in the ECG tracing as 'pacing spikes'. In atrial pacing, the pacing spikes will be followed by P-wave and in ventricular pacing, the pacing spikes will be followed by broad QRS complexes (broad complex is due to the conduction of electircal impulse through the ventricular muscles like ectopic foci, but not through the normal conducting Purkinze tissue). Therefore, recognition of any specific disease state of myocardium and conducting system by ECG analysis during pacing is usually impossible. In only atrial pacing, the spikes are followed by P waves and normal QRS complexes (without ventricular spike) as the impulse conducts via the normal conducting pathway. In dual chamber pacing both the spikes will be seen. The failure of a pacing spike to be followed by depolarisation of heart indicates a problem with 'capture' (Fig. 26.39).

The ECG tracing also can help in localizing the site of electrode placement and in detecting the change of position by dislodgement of the electorde if it occurs. In right ventricular apical endocardial paceing, the depolarisation wave of heart will flow from right to left (R → L) and from apex to base. The resulting QRS vector, therefore, will be oriented to the left and superiorly. Thus the QRS complex in lead I will be positive and in lead II, III, and AVF will be negative. On the other hand, if the electrode is displaced from the apex

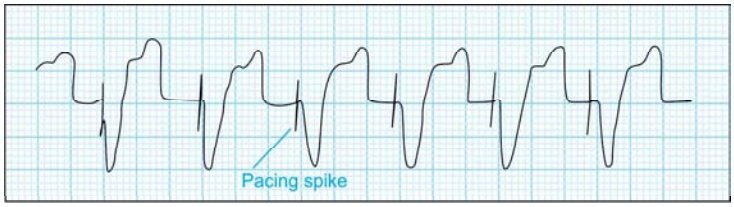


Fig. 26.39: Graph of the ventricular pacing, it is characterised by ventricular pacing spikes and followed by broad QRS complex

to the outflow of right ventricle, then the direction of depolarisation wave will be R → L, but from base to apex. So, the QRS complex remains upright in lead I, but now becomes upright in lead II, III and AVF.

Interpreting of an ECG of a patient with functioning pacemaker, the pacemaker rate should be accurately measured. Any change in rate indicates the early battery failure.

In unipolar pacemaker as the distance between the anode and the cathode is long, so the pacing spike will be large. But in bipolar unit due to the close position of anode and cathode, the spike (pacemaker artefact) will be small in ECG tracing.

For detection of any changes in the pacemaker position by dislodgement, the determination of spatial orientation of the pacing spike is also helpful. This is especially applicable to a bipolar right ventricular endocardial pacemaker. The cathode is usually distal to the anode. So, as a result of its position in the right ventricular apex, the vector of electrical artefact or spike will be oriented to the right and superiorly. Thus, it will produce negative artefact in lead I, II, AVF. If due to any cause the electrode becomes detached and floats into the right ventricular outflow tract, then the vector of artefact will be directed inferiorly. Then it will produce an upright artefact in II, III and AVF lead. The explanation is like that : the anode-cathode relation in the right ventricular pacemaker will be reversed i.e. the distal pole will be the anode. In this instance, the artefact for pacing will be oriented to the left and inferiorly, producing an upright signals in lead I, II and AVF (Fig. 26.40).

During the management of ventricular tachycardia when the antiarrhythmic drugs fail, then the ventricular pacing has been succesfully used to prevent the recurrent ventricular tachycardia and ventricular fibrillation. The mechanism is like that : when repolarization of ventricular muscle become asymmetrical due to some reason (ischaemia, infarction) leading to local potentiation of ectopic discharge, then pacing the heart at the rates of 130 to 150 per minute causes ventricular repolarization to become synchronous throughout the entire myocardium and eliminate the local potentials with arrhythmias. This type of pacing is called the 'over drive pacing'. In the treatment of refractory VT, ventricular pacing at rates slower than the tachycardia (under drive pacing) may also abolish arrhythmia by interrupting the reentry circuit that causes the tachycardia.

If the entire heart is depolarized for a moment by sufficient current, introducing in the myocardium, then the normal cardiac rhythm is re-established after depressing or breaking the cycle of arrhythmia. This countershock is delivered externally by defibrillation. This is called DC shock. But, it can be applied internally during cardiothoracic surgery or through pacemaker. It is a major life saving process by eliminating VF and VT during resuscitation process of cardiac arrest. In emergency the countershock or DC shock is also preferable to drug therapy to terminate the atrial flutter and fibrillation. This DC defibrillator introduces an electrical charge for 0·0025 sec (AC defibrillation introduces an electrical charge for 0·25 sec and due to this long duration, the charge could fall on supernormal phase of any rhythm and can produce any type of arrhythmia) and are now coupled with synchronizing device that prevent the discharge at the critical phase of cardiac cycle and thus avoides any serious arrhythmia.

Surgically implanted defibrillator are also now available which are programmed to recognize VT and VF spontaneously and discharge an internal DC shock automatically.

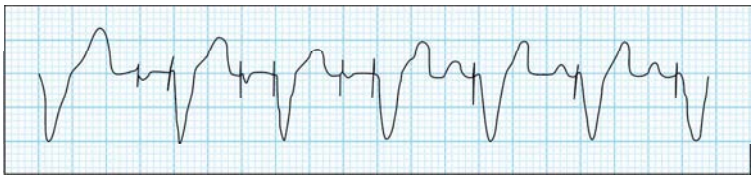


Fig. 26.40: This figure shows dual chamber pacing. The first three cardiac cycles show the atrial and ventricular pacing with narrow pacing spikes in front of each P-wave and QRS complex. The last three beats show spontaneous P waves with a different morphology and no pacing spikes. The pacemaker senses or tracks these P waves and maintain an AV synchrony by pacing the ventricle after an appropriate interval

Pacemaker and Surgery

The importance of pacemaker from anaesthetic point of view during surgery are :

i. The original indication for insertion of pacemaker should be known to an anaesthetist which may modify the mode and outcome of anaesthesia.
ii. The type of pacemaker also should be known which will help to diagnose the intraoperative arrhythmia.
iii. Checking of pacemaker before and after surgery for any 'capture beat'.
iv. To avoid interference with or damage to the pacemaker from diathermy.
v. Inappropriate pacemaker inhibition due to any intraoperative measures can cause bradycardia or even asystole.
vi. To minimize the pacemaker damage or inhibition the active diathermy electrode should be placed at least 15 cm away from the pacemaker generator box and the indifferent electrode as far from the box as possible.

Patients with certain cardiac conduction disorders who do not have a permanent pacemaker should be considered for a temporary pacemaker, if they are about to undergo general anaesthesia. These indications for temporary pacing are : (i) third degree AV block and (ii) second degree AV block. Pacing is not usually necessary for bifascicular block unless the patient has a history of syncope.

27 Ischaemic Heart Diseases and Anaesthesia

INTRODUCTION, AETIOLOGY AND PATHOPHYSIOLOGY

Ischaemia refers to the lack of O_2 which is due to inadequate perfusion. It may be absolute or relative and results from an imbalance between the O_2 supply and / or its demand. Therefore, myocardial ischaemia occurs either from a decrease in coronary blood flow (e.g. variant angina) and / or from a disproportionate increase in myocardial O_2 consumption (e.g. exertional angina). The myocardial O_2 supply is primarily determined by the coronary blood flow. The volume of coronary flow (supply) is related to both the perfusion pressure and the coronary vascular resistance which ultimately depends on the diameter of the lumen of the coronary artery. On the other hand, the four major factors which govern the myocardial O_2 demand or consumption are : ventricular wall tension, after load, heart rate and ventricular contractility. The another term such as 'double product' is a clinically useful index of myocardial O_2 demand or consumption. This is derived by multiplying the systolic blood pressure (after load) with the heart rate.

With increasing age, the people mainly suffer from cardiovascular diseases. On the other hand, cardiovascular diseases account for the majority of perioperative deaths. Therefore, the increased aging of population increases the likelihood of more and more patients undergoing surgery with co-existing cardiovascular diseases, among which ischaemic heart disease is the most common. The first and the most common presentation of ischaemic heart disease (IHD) is acute myocardial infarction (MI) in 50% of patients. The main cause of decrease in coronary blood flow (supply) causing ischaemia and infarction with increased age is the reduction of the diameter of lumen of coronary arteries by atherosclerosis. Atherosclerosis may cause an absolute decrease in myocardial perfusion in the basal state or may limit the appropriate increase in perfusion when the demand for flow is increased. The important factors for the development of atherosclerosis are: male gender, increasing age, hypercholesterolaemia, high plasma low density lipoprotein (LDL) and low plasma high density lipoprotein (HDL), systemic hypertension, cigarette smoking, diabetes, obesity, sedentary life style, and a positive family history. Coronary blood flow can also be limited by arterial thrombi, spasm, or ostial narrowing due to aortitis. The reduction of the O_2-carrying capacity of blood (e.g. severe anaemia, presence of carboxy-haemoglobin, etc.) is a rare cause of myocardial ischaemia and infarction. Myocardial ischaemia can also occur, if myocardial O_2 demands are abnormally increased, for example: exercise, tachycardia, severe myocardial (ventricular) hypertrophy due to hypertension, or aortic stenosis, etc. Not infrequently, two or more causes of ischaemia will co-exist, such as an increase in O_2 demand due to left ventricular hypertrophy and a reduction in O_2 supply secondary to coronary atherosclerosis. Often such a combination leads to early clinical manifestation of myocardial ischaemia.

The most common cause of myocardial ischaemia is the atherosclerotic disease affecting the epicardial coronary arteries. In healthy persons the epicardial coronary arteries serve largely as conduits. They undergo little constriction and relaxation. So, these vessels are referred to as the conductance vessels. On the contrary, the intramyocardial vessels normally exhibit striking changes in tone and their radius. Therefore, they are referred to as the resistance vessels. The normal coronary arterial circulation is controlled by the heart's own requirement of O_2 through these intramyocardial resistance vessels. This need is met by the ability of coronary arteries to vary its resistance (therefore blood flow) by itself, while myocardium extracts a high and relatively fixed percentage of O_2. Normally, the intramyocardial resistance vessels demonstrate an immense capacity of dilatation during needs, e.g. exercise, emotion, stress, etc. This manner of regulation of myocardial O_2 supplies is called the metabolic regulation. The coronary resistance vessels also adapt to the physiological alterations in blood pressure within certain range in order to maintain the coronary blood flow constant according to the myocardial needs. This is called the coronary autoregulation.

The atherosclerosis is caused by the dysfunction of vascular endothelium and the abnormal interaction of endothelium with blood monocytes and platelets. This leads to subintimal collection of abnormal fat,

debris and cells (i.e. atherosclerotic plaque) at different segments of the coronary artery (mainly epicardial), resulting in segmental reductions of cross sectional area. Once stenosis (of epicardial vessels) has reduced the cross-sectional area of the myocardial blood vessels by more than 70% (approximately), then the distal resistance vessels (intramyocardial vessels) dilate to reduce the vascular resistance and maintain the coronary blood flow. Thus, a pressure gradient develops across this stenosis. When the resistance vessels are maximally dilated, then the myocardial blood flow becomes dependent only on the pressure gradient in the coronary artery distal to the obstruction. In such circumstances, ischaemia in the region perfused by the stenotic artery can be precipitated by the increase in myocardial O_2 demands caused by increased physical activity. When stenosis reduces the cross-sectional area by approximately 75%, then a full range of autoregulation to increase the flow and to meet the increased myocardial demand against the increased physical activity is not possible causing ischaemia on exertion. When the luminal area is reduced by more than approximately 80%, then blood flow at rest may also be reduced and after that any further minor decrease in stenotic orifice can reduce the coronary flow dramatically, causing ischaemia at rest. Severe coronary narrowing and myocardial ischaemia are frequently accompanied by the development of collateral vessel. Usually this occurs, when the narrowing develops gradually. But when this collateral is well developed, then such collaterals can provide sufficient blood flow to sustain the viability of myocardium at rest. But, this is not possible during conditions of increased demand.

Ischaemic heart disease is often manifested as: angina pectoris, acute myocardial infarction, cardiac arrhythmias, heart failure or sudden death. Among these manifestations, angina pectoris is the most common symptom of myocardial ischaemia and is classified into the following clinical syndromes such as: (i) stable angina pectoris, (ii) variant angina (Prinzmetal's angina) (iii) mixed angina, (iv) unstable angina, (v) nocturnal, postprandial, and walk-through angina, (vi) silent angina.

DIAGNOSIS

History

The most important aspect of history, regarding the myocardial ischaemia which is an part and parcel of diagnosis is the patient's description of its own chest discomfort, i.e. its character, location, radiation, duration, precipitating and palliative factors etc. Typically, patients describe angina pectoris as a sensation of tightness or heaviness over his left precordium. The others commonly used adjectives of chest discomfort by the patient due to ischaemia include: squeezing, constricting, suffocating, crushing sensation, etc. Some patients make a tight fist over their chest to show what the pain or the discomfort is. The myocardial ischaemic pain may radiate to the inner aspects of left arm, or both arms, or shoulders, or neck and jaw. Radiation of pain to the lower abdomen is unusual and one should be caution about making this as diagnosis of angina. Chest pain which is sharp, stabbing, comes and goes in seconds, but not dull and continuous are unlikely to represent angina. The anginal syndrome usually begins gradually and goes to a peak before subsiding over several minutes. The resolution of ischaemic pain is usually due to the cessation of precipitating factors such as exercise, tension, cold exposure, etc, or use of nitroglycerine. Patients with the classical history of angina pectoris, male gender and old age increases the likelihood for the affection of left main coronary artery or multivessel disease.

Noncardiac chest pain is usually transient. It is exacerbated by the chest wall movement. It is also associated with tenderness over the involved area which is often a costochondral joint. The retrosternal sharp pain which is exacerbated by deep breathing, coughing or changing in body position suggests pericarditis. The oesophageal spasm can produce severe substernal pain. It may be confused with the angina pectoris. In such condition administration of nitroglycerine is also likely to relieve the pain, because oesophagus consists of smooth muscles.

From the severity of history, the patient's functional capacity can be determined and this has been shown to correlate well with the result of treadmill test. This patient's functional capacity is prognostically very important and can be quantified as MET (metabolic equivalents). One MET is defined as the rate of O_2 consumption by a normal person which is 3 to 5 ml/Kg/min. However, any mobility problems due to skeletal dysfunction limit this test or assessment. Patients who can exercise at 4 MET or greater present a low risk for perioperative morbidity due to ischaemia :

1. MET – eating and dressing
3. MET – light work or walk (3 to 4 Km/hour)
4. MET – climb a flight of stairs
6. MET – short run

A patient who had a CABG operation within 5 years and has no symptoms may be considered of normal perioperative risk.

Physical Examination

The physical examination is often normal in the patient with stable angina. Although frequently normal, but a careful examination may reveal some important contributory information regarding the prognostically significant co-morbidities, such as, hypertension, peripheral vascular diseases, dibetes mellitus, renal diseases, pulmonary diseases, xanthelasma, arcus senilis, etc. There may also be signs of associated anaemia, thyroid disease, etc. Physical examination by palpation can also reveal the thickened or absent peripheral associated arteries, signs of cardiac enlargement, etc. Examination of fundus of retina may reveal increased light reflexes and arteriovenous nicking as the evidence of

hypertension. Examination during an episode of chest pain may reveal a transient s_4 or s_3 heart sound and it is due to the altered left ventricular compliance or a murmur of mitral regurgitation resulting from papillary muscle dysfunction. Aortic stenosis, aortic regurgitation, pulmonary hypertension, and hypertrophic cardiomyopathy must be excluded, since these disorders may cause angina, even in the absence of coronary artery disease.

During physical examination the signs of left ventricular failure should be searched for. Peripheral oedema is usually a late finding in patients with LVF. It is often due to venous insufficiency. Examination of jugular venous pulse for abnormalities reflects right ventricular failure.

Laboratory Studies

Although the diagnosis of ischaemic heart disease (IHD) is made with confidence from typical history, but a number of simple laboratory tests can be helpful to correlate between the history and the diagnosis. The urine should be examined for evidence of diabetes mellitus and renal diseases, since both these conditions may accelerate the atherosclerosis and myocardial ischaemia. During laboratory investigations the examination of blood should include the measurement of lipids (total cholesterol, LDL, HDL), glucose, creatinine, haematocrit, thyroid function and any special test indicated by physical examination. A chest X-ray is important, since it may show the consequences of IHD, i.e. cardiac enlargement, signs of heart failure, etc. Calcification of coronary artery can sometimes be identified by X-ray (Table 27.1).

ECG

An ECG should be performed on all patients over 50 years of age who are scheduled for surgery and in younger patients who are with risk factors of IHD. Always the changes from previous ECG tracing should be investigated. The bundle branch block may predispose to brady arrhythmias or atrial fibrillation. But, 24 hours ECG monitoring is only necessary, if there is any history of palpitations or blackouts.

If patients with a known prior history of MI are excluded, then nearly 60% of patients presenting with the history of angina pectoris have a normal ECG. But, the absence of abnormalities in resting ECG does not eliminate the possibility of IHD. Repolarisation abnormalities, i.e. T-wave and ST-segment changes and intraventricular conduction disturbances at rest are suggestive of IHD. But they are nonspecific, because they can occur in any pericardial, myocardial, and vulvular heart diseases also. They are also found in anxiety, changes in posture, drugs, and oesophageal diseases. The more specific ECG changes associated with myocardial ischaemia is the ST-segment and T-wave changes which usually accompany the episode of angina pectoris and disappear thereafter. The characteristic of ST-segment changes in myocardial ischaemia is the displacement of its axis from the neutral electrical or base line. The ST-segment is usually depressed during angina, but may be elevated in its Prinzmetal's form. Along with ST segment, the T-wave changes in the ECG during ischaemia include symmetrical T-wave inversion which may be transient. In a patient with consistent inverted T-waves, in association with prior pathological Q-wave from previous myocardial infarction, may manifest a return of the T-wave to the normal upright position during ischaemic attack. This is called the pseudo-normalisation.

Exercise ECG (stress testing)

12 leads ECG before, during and after exercise on a treadmill is the most widely used test for the diagnosis of IHD. It is useful for establishing the patient's left ventricular functional reserve and thus the prognosis. The programme is usually symptoms limited. The test is discontinued with the evidence of chest pain, discomfort, severe shortness of breath, dizziness, fatigue and ST-segment depression of greater than 0.2 mV (Table 27.2). The test is also discontinued when there is fall in heart rate (exceeding > 10 beats/min), fall in systolic blood pressure (exceeding >20 mm of Hg) and development of ventricular tachycardia or arrhythmia. The significant diagnostic ischaemic ST-segment response is defined as the flat depression of it for more than 0.1 mV below the baseline and lasting longer than 0.08 second. The junctional or upsloping of ST-segment changes are not considered as diagnostic of myocardial ischaemia. It does not constitute a positive test. T-wave abnormalities alone is also not considered as diagnostic of ischaemia. This stress ECG test has a high negative, but a low positive predictive value. This test is useful for assessing the ischaemic patients, possessing high or intermediate risk than low risk group. Overall, false +ve or false −ve results is 15%. A positive treadmill test indicates that the likelihood of IHD is 98% in males over 50 years of

Table 27.1: Relation between areas of myocardial ischaemia and ECG leads

ECG leads	*Coronary artery*	*Area of ischaemia*
I, AVL	Circumflex artery	Lateral aspect of left ventricle
II, III, AVF	Right coronary artery	Right atrium, Right ventricle
V_3 - V_5	Anterior descending artery	Anterolateral aspect of left ventricle

Table 27.2: Indications of exercise ECG testing

Diagnosis of chest pain
Assessing of exercise tolerance
Assessing the response to treatment
Risk stratification of stable angina
Risk stratification after MI
Assessing the exercise induced arrhythmias

Table 27.3: Absolute contraindications to stress ECG

Unstable angina (pain within 48 hours of test)
Myocardial infarction (within 7 days)
Acute pericarditis
Acute fever
Severe aortic stenosis
Hypertrophic obstructive cardiomyopathy
Uncontrolled hypertension
(Systolic > 200 mm of Hg
Diastolic > 120 mm of Hg)
Heart failure

Table 27.4: Relative contraindications to stress ECG

Myocardial infarction (after 7 days to 1 month)
Mild to moderate aortic stenosis
Known severe coronary artery disease
Significant left ventricular dysfunction
Known serious risk of arrhythmia

age with a history of typical angina pectoris (Table 27.3).

The likelihood of IHD decreases progressively, if the patient has atypical or no chest pain. The incidence of false +ve test is significantly increased in asymptomatic male under the age of 40 with no risk factor for premature atherosclerosis. False +ve also increases when there is (i) previous changes or abnormality of the ST-segment and T-wave at rest, (ii) patient taking drugs like digitalis, quinidine, etc, with intraventricular conduction disturbances (iv) myocardial hypertrophy and (v) abnormal serum potassium level. Since the overall sensitivity of exercise stressed ECG is only about 75%, a negative result does not exclude IHD. In negative result the likelihood of three vessels disease or left main coronary artery disease is extremely unlikely.

The normal response to exercise or stress induced ECG includes a progressive increase in heart rate and blood pressure. But an important adverse prognostic part of this test is failure of BP to increase with sign of ischaemia, because it reflects ischaemia induced global left ventricular dysfunction (Table 27.4).

The presence of chest pain or severe ST-segment depression (> 0.2 mV) at a low workload which persists for more than 5 minutes after the premature termination of exercise increases the specificity of the test. It suggests severe ischaemic heart disease and high risk with further adverse events. Exercise testing is not always possible or can not be performed because of the presence of many non-cardiac causes, such as peripheral vascular diseases and associated claudication, lung disease, arthritis, other orthopaedic causes, etc. In the presence of the following conditions, such as, artificially paced ventricular rhythm, pre-existing ST-segment depression, left ventricular hypertrophy, digitalis therapy, pre-excitation syndrome etc, which interfere the interpretation of exercise ECG test, it should not be performed.

Echocardiography

The exercise induced ECG test and associated ST-segment changes indicate the presence of ischaemic heart disease. But it can not locate the site of obstruction in coronary vessels and its associated ventricular wall motion abnormalities. So, an initial, without any stress, echocardiographic cardiac wall motion analysis, and then echocardiography performed after stressing the heart by dobutamine infusion (stress echocardiography), correspond to the site of myocardial ischaemia. Thus, it tremendously helps to localise the obstructive coronary lesion. The stress echocardiography also can be done by artificial cardiac pacing which enhances the accuracy of stress echocardiography and helps to localise the obstructive coronary lesion.

Nuclear Stress Imaging

The nuclear stress imaging is very useful for assessing the coronary perfusion. After administration the tracers, like – thallium, technetium, etc, can be detected and their concentration can be measured by proton emission computed tomography (PECT) in the myocardium that correspond to the coronary blood flow. When there is lesser tracer activity, it suggests a significant coronary obstructive lesion. Exercise or stress increases the difference in tracer concentration between the normal and the underperfused regions. This is because coronary blood flow increases markedly with exercise, except in regions which is distal to the obstruction in coronary artery. The magnitude of perfusion abnormality is most important prognostic indicator of ischaemia.

Both of these, i.e. echocardiography and nuclear stress imaging are indicated for the diagnosis of IHD when the exercise induced ECG is not possible or it is difficult to interpret the ST-segment changes on the ECG. The intravenous infusion of dobutamine or artificial cardiac pacing provide progressively adequate cardiac stress for patients who can not exercise. Alternatively, the effects of cardiac stress on the extent of coronary dilatation can be assumed by artificially producing coronary dilatation by administration of coronary vasodilator, such as, adenosine or dipyridamole which dilates the normal coronary arteries, but evokes minimal to no change in the diameters of atherosclerotic coronary arteries.

Coronary Angiography (or Arteriography)

Coronary arteriography is the most definitive investigation for diagnosis, localization, and quantitation of IHD. It provides the most important information about the condition of coronary arteries. The common indications for cardiac catheterisation and arteriography are: chronic stable or unstable angina, markedly positive exercise or stress induced ECG test, postinfarction angina, inconclusive noninvasive studies, frequent hospitalisation due to cardiac causes, unexplained cardiomyopathy, high risk of IHD, angina following

thrombolytic therapy, valve replacement in patient with high risk of IHD, etc. It is also helpful for establishing the diagnosis of nonatherosclerotic coronary artery disease, such as, coronary artery spasm.

Although coronary angiography is an invasive procedure, still the risk of this test is very low in relation to the potential information which is yielded from the study. The overall mortality of angiography is 0.2%. Patients > 55 yrs of age and with an ejection fraction < 30% or with left main coronary artery disease have the greatest risk for complications.

Treatment of IHD

Medically IHD is treated mainly by the following drugs, such as, antiplatelets, anti-thrombin, β-blockers, Ca^{2+} channel blockers and nitrates. So, the preoperative awareness of an anaesthetist about these drugs is important, because these drugs may exert potentially adverse effects during anaesthesia. The aim of medical treatment of IHD is to decrease the myocardial O_2 requirement or demand and to improve the coronary blood flow or supply. When optimal medical therapy fails to control the symptoms of IHD, then revascularisation of myocardium by CABG, PTCA or placement of coronary stenting is indicated. Among these, CABG is the most promising and is performed when the occluded coronary artery is of reasonable size, free of distal plaque and a high grade proximal stenosis. It is likely to improve the survival of patient with EF < 40% and multivessel disease. But, the presence of hypokinetic or akinetic area declares the poor prognosis.

If not contraindicated, then low dose aspirin as antiplatelet agent is recommended for all IHD patients. It is used in the dose of 75 to 325 mg/day and decreases the risk of cardiac events. Clopidogrel, inhibiting platelet aggregation acts more effectively than aspirin. Patients in whom placement of intracoronary stent is anticipated, plateled glycoprotein IIb/IIIa receptor antagonists is more useful. It acts by inhibiting the adhesion, activation and aggregation of platelet.

As antithrombin the unfractionated heparin is recommended for the treatment of unstable angina. But it has many disadvantages such as variability in dose responses relationship due to its binding with plasma protein. So, instead of unfractionated heparin the low molecular weight heparin (LMWH) provides a more predictable and long half-life pharmacological profile as antithrombin. It has also advantages that it does not need monitoring by APTT (activated partial thromboplastion time) measurement and can be administered easily by the subcutaneous route. During the weeks, following the initial presentation of unstable angina, the combination of warfarin and aspirin can be used. It is superior to monotherapy with aspirin or warfarin alone.

The β-blocker (mainly the cardioselective β_1-blocker) decreases the myocardial O_2 demand or consumption and thus supports its use in the management of unstable angina. Chronic administration of β_1-blocker also decreases the risk of MI and sudden death. Now, it has been used in low doses in patients in whom β-blockers have traditionally been considered to be contraindicated, such as congestive heart failure, pulmonary disease, advanced age, etc. The β_1-blocker induced decrease in heart rate and contractility is maximum during activity than at rest. The decrease in heart rate also increases the diastolic perfusion time which may contribute to improve the myocardial perfusion. β_2-blockers can increase the risk of bronchospasm in patients with reactive airway disease and can increase the manifestations of peripheral vascular resistance. So, it (β_2-blocker) is not used in IHD patients. The most common side effects of β-blocker therapy are fatigue and insomnia. It is contraindicated in heart block, but not in diabetes mellitus, though it may mask the signs of sympathetic nervous system acitivity during hypoglycaemia.

The use of long acting calcium channel blockers for IHD are not as effective as β_1-blockers for decreasing the incidence of M1, but are comparable to β-blockers in terms of relieving the frequency and severity of angina pectoris which is due to coronary artery spasm. The short acting Ca^{2+} channel blocker such as nifedipine are not recommended for the management of IHD as they increase the sympathetic activity with associated adverse cardiac events. So, only the long acting Ca^{2+} channel blockers are used. There is adverse interactions between the calcium channel blocker and the anaesthetic drugs. For example, myocardial depression and peripheral vasodilatation effect produced by volatile anaesthetic drugs could be exaggerated by the similar effects of calcium channel blockers. The calcium channel blockers may also potentiate the effects of depolarizing and non-depolarising muscle relaxants and exaggerate the diseased states associated with skeletal muscle weakness. The pharmacological antagonism of neuromuscular transmission may be impaired in the presence of Ca^{2+} channel blocker. This is because of diminished pre-synaptic release of acetylcholine.

Nitrates dilate the coronary and its collateral arteries and improve the coronary blood flow. It also decreases the peripheral vascular resistance, resulting in decrease in left ventricular outflow impedance and myocardial O_2 consumption. The venodilating property of nitrates decrease the venous return and thus preload also. Thereby, it decreases the left ventricular filling pressure, filling volume, force of contraction (Frank-Starling law) and myocardial O_2 consumption. All the above mentioned properties of organic nitrates thus help to decrease the frequency, duration, and severity of angina pectoris. It also helps to increase the amount of exercise needed, before the onset of ST-segment depression. Nitrates are relatively contraindicated in hypertrophic obstructive cardiomyopathy and

severe aortic stenosis. The sublingual tablet or oral spray of nitroglycerine is recommended for prompt relief of angina pectoris, but not for long-term therapy. For later, long acting nitrate preparation is effective and recommended. The therapeutic value of organic nitrate is compromised or dampened by the rapid development of tolerence during sustained therapy of it. So, for long-term use nitrates should be administered with one daily nitrate-free interval of at least 8 hours to prevent the development of nitrate tolerance.

ANAESTHETIC MANAGEMENT OF PATIENTS WITH KNOWN OR SUSPECTED IHD UNDERGOING NONCARDIAC SURGERY

Assessment

The goal of preoperative anaesthetic assessment of a patient with ischaemic heart disease is to identify the individuals with increased risk of adverse perioperative cardiological outcome. The risk of perioperative death due to cardiac complications is less than 2% for patients who do not have IHD. On the other hand, this risk is double or triple in patients with known or suspected coronary or other sclerotic vascular disease. The most reliable indicator for adverse perioperative cardiac events in patients who is suffering from IHD and undergoing noncardiac surgery is myocardial ischaemia during operation and within first 48 hours following surgery. The perioperative risk for patients with IHD is usually estimated on the basis of patient's exercise tolerence. Patients who can perform strenous activities like walking, running, climbing, etc, but without any cardiac symptoms have lower risk of cardiac complications than patients who are unable to perform such strenous exercise. The limited exercise tolerence in the absence of significant lung disease is the most striking evidence of decreased cardiac reserve. The patients should always be evaluated against the background of exercise, because symptoms of ischaemic heart disease may be absent at rest. In stable patients with angina pectoris undergoing elective major noncardiac surgery, there are few independent predictors of cardiac complications. These predictors are : current complaints of angina pectoris, use of nitrate therapy, history of positive exercise test, history of M1, Q-wave in ECG, history of congestive heart failure, history of pulmonary oedema, history of paroxysmal nocturnal dyspnoea, etc. The previous CABG surgery, preoperative ST-T wave changes on the ECG, presence of critical aortic stenosis, presence of abnormal cardiac rhythm, advanced age, etc, are also the valuable predictors. It is also important to recognise the presence of incipient congestive heart faiture preoperatively, as the added stress of anaesthesia, surgery, and post operative pain may convert this incipient preoperative congestive overt congestive heart failure.

Physical examination and investigations for preoperative assessment of patient with IHD are like physical examintion and investigation of an IHD patient who is not goging for any surgical procedure which is described before.

Preoperative Preparation and Medication

High risked myocardial ischaemic patients, undergoing noncardiac surgery is probably best benefited from optimal preoperative anti-ischaemic treatment which is described before. This preoperative anti-ischaemic treatment or preparation can be achieved by pharmacological and psychological method. The patient suffering from severe myocardial ischaemia can also be treated preoperatively by CABG operation or angioplasty with or without stent before any elective noncardiac surgery. Anxiety which is part and parcel of a surgery is an another important precipitating factor of ischaemia. It acts by evoking the activity of sympathetic nervous system with accompanying increase in systemic BP and HR. Both of these increase the myocardial O_2 demand which may manifest as the myocardial ischaemia in ECG and may be first recognised when these patients arrive in the OT. These ECG changes are usually taken as the silent sign of ischaemia, because they are not accompanied by angina pectoris or haemodynamic abnormalities. This silent ischaemia is not different from those that occur in the same patients during their normal daily activities.

Anxiety is managed by both psychological and pharmacological approaches. The psychological approach for the reduction of anxiety is attempted by preoperative visit of a patient to an anaesthetic clinic during which the fearless anaesthetic sequences are explained in details. The pharmacological approach for reduction of anxiety can be achieved by many drugs. But, the choice of drug depends on the personal preference and the experience of anaesthetist. The aim of premedication for a myocardial ischaemic patient is to produce maximum sedation and amnesia without any undesirable degree of circulatory and ventilatory depression. For this purpose benzodiazepine is a very useful drug. It can be combined with morphine (10 to 15 mg IM) plus scopolamine (0.4 to 0.6 mg IM). Because scopolamine produces profound sedative and amnestic effect without any undesirable changes in HR. So, it is very valuable as a premedicant for ischaemic heart diseased patients.

Drugs used for medical management of patients with ischaemic heart disease should not be withdrawn abruptly and are continued throughout the perioperative period. For example, the sudden withdrawl of antihypertensive agents, mainly β-blocker, may result in rebound increase in sympathetic nervous system activity. Nitrates should be given preoperatively, intraoperatively and postoperatively. In high risk patients they can be continued as IV also. Otherwise, oral and transdermal route for nitrate is sufficient for low risk groups. The calcium antagonist should be

given postoperatively. The dihydropyridine group of calcium antagonist (nifedipine), especially short acting, add to the risk of acute MI. Therefore, these should be substituted to another class such as phenyl alkylamine (verapamil) or benzothiazepine (diltiazem) group of Ca^{2+} antagonist. The ACE inhibitors improve survival in patients with left ventricle dysfunction due to IHD. So, they should be given preoperatively and also should be resumed postoperatively as soon as GI absorption resumes. If they have been stopped for several days, then restarting at a reduced doses may be prudent, as most of these drugs are associated with first dose hypotension. There is theoretical possibility of H_2 receptor antagonist to produce coronary artery vasoconstriction. Because, this is mediated by unopposed H_1 receptors activity. But practically it does not seem to produce any adverse side effects in IHD patients.

Induction of Anaesthesia

The anaesthetic technique for ischaemic heart diseased patient is aimed at to minimise the incidence and severity of myocardial ischaemia by preventing the factors which predispose it such as tachycardia, hypotension, hypertension, hypoxia, etc. Induction for patients with IHD can be achieved by intravenous administration of several common inducing agents such as propofol, thiopentone, BZD, etc. Among these, ketamine is not the choice as it increases the myocardial O_2 consumption or demand by increasing the HR and systemic BP. Direct laryngoscopy and tracheal intubation may initiate sympathetic nervous system stimulation and subsequent myocardial ischaemia. It is aggravated more when there is previous existance of systemic hypertension. So the sympathetic pressure response produced by direct laryngoscopy and tracheal intubation can be minimised by the addition of following drugs. Lignocaine in the dose of 1 to 2 mg/kg, administered intravenously about 90 seconds before direct laryngoscopy, decreases the magnitude and the duration of the elevation of systemic BP. An alternative to lignocaine is nitroprusside. It is administered 15 seconds before laryngoscopy and intubation in the dose of 1 to 2 µg/kg/minute IV. Like lignocaine, nitroprusside also effectively attenuates the pressure response related to intubation, but not the HR. Another alternative to attenuate the sympathetic pressure response in patients with IHD is infusion of esmolol in the dose of 100 to 300 µg/kg/min before and during the laryngoscopy and intubation. It is especially useful for blunting the increase in HR, evoked by intubation. A small dose of fentanyl (1 to 2 mg/kg IV) or equivalent doses of other short acting opioids, administered before the direct laryngoscopy and intubation, may also be useful for blunting the circulatory responses, evoked by laryngoscopy and tracheal intubation. The continuous infusion of nitroglycerine in the dose of 0.25 to 1 µg/kg/min IV may also be used as prophylaxis against the development of coronary vasospasm and subsequent development of myocardial ischaemia in vulnerable patients. But, many controlled studies do not consistently confirm that this approach decreases the incidence of intraoperative myocardial ischaemia.

Maintenance of Anaesthesia

The choice of drugs used for maintenance of anaesthesia depends upon the preoperative evaluation of patient and the presumed left ventricular function. Sympathetic activation due to the surgical stimulation are not detrimental for normal left ventricular function. But in patients with IHD, the sympathetic activation by surgical stimulation is harmful due to increased O_2 demand in a already compromised heart. From this point of view, volatile anaesthetics (sevoflurane, isoflurane, desflurane) are useful by minimising this sympathetic stimulation and subsequent decreasing the myocardial O_2 requirement. The volatile anaesthetic may be administered alone or in combination with N_2O and opioids. If the use of volatile anaesthetics is associated with much reduction of systemic blood pressure, then it will decrease the coronary perfusion pressure and its flow which will be detrimental for IHD patients. So, excessive reduction of BP by voltile anaesthetic agents is never desirable in IHD patient.

In patients with severely impaired LV function, if slight myocardial depression by volatile anaesthetic agents is associated with much reduction of cardiac output, then in such circumstances short acting opioids in liberal doses are selected instead of volatile anaesthetics. For severly compromised patients high dose opioid such as fentanyl 50 to 100 mg/kg/IV or equivalent doses of other short acting opioids is used as sole anaesthetic agent. In such circumstances, benzodiazepine or N_2O or low-dose volatile anaesthetics can be used, if adequate amnesia can not be ensured with this high dose of opioid alone. In such situation, you will have to keep in mind that addition of N_2O and volatile anaesthetic agent to opioid is associated with myocardial depression which is not found when any of these drugs is administered alone.

Regional anaesthesia is a well accepted technique for patients with IHD. But, the reduction of systemic blood pressure should be maintained strictly within 20% of the pre-anaesthetic mean arterial pressure (MAP) value. In one sense the regional anaesthesia is beneficial for IHD patients, because it reduces the myocardial O_2 requirement by producing the sympathetic nervous system blockade. In another sense, the regional anaesthesia is not beneficial for IHD patients, because flow through the coronary arteries, narrowed by atherosclerosis, is pressure dependent. So, much decrease of mean arterial pressure (< 20% of pre-anaesthetic value) is associated with the severe reduction of blood

flow through coronary arteries which is greater than the reduction of O_2 requirement. So, prompt treatment of hypotension (that exceeds 20% of pre-anaesthetic value) by IV administration of ephedrine, phenylepherine or any other vasoconstrictive agent which is very well known to a working anaesthetist is often recommended. A disadvantage of using IV fluid load to treat the hypotension, induced by regional anaesthesia, is the interval which is necessary to become effective and the preloading by IV fluid to maintain BP is not so effective as vasoconstrictive agent.

Regarding muscle relaxants, vecuronium, rocuronium, atracurium and cisatracurium are the drug of choice for patients with IHD. Because they are associated with minimal to no effects on HR and systemic BP. Atracurium and mivacurium release histamine and there is transient alteration of BP. Pancuronium increases heart rate with BP and may precipitate myocardial ischaemia. However, it has been used without any apparent adverse effects in many patients with IHD for many decades. Pancuronium is especially used to offset the negative inotropic and negative chronotropic effect of other anaesthetic drugs, such as, volatile anaesthetic agents. The idea that simultaneous use of β-blocker therapy prevents pancuronium induced increase in HR, but it is not always correct as this drug most likely increases the HR by its vagolytic property, but not by sympathomimetic mechanism.

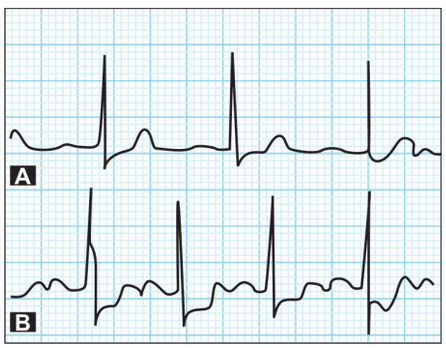
Glycopyrrolate is preferred as anticholinergic drug during reversal of nondepolarising neuromuscular blockade, if excessive increase in HR is a great concern. The combination of anticholinesterase and anticholinergic agent can be used safely for reversal of muscular paralysis in IHD patients. Myocardial ischaemia should also be anticipated during emergence and extubation due to hypertension and tachycardia. So, extubation at the deep plane of anaesthesia or the use of short acting beta-blocker during extubation should be considered. To prevent intraoperative myocardial ischaemia intraoperative blood loss needs accurate replacement and haemoglobin should be maintained by regular measurement.

Monitoring During Anaesthesia

The aim of intraoperative monitoring for patients with ischaemic heart disease is early detection of myocardial ischaemia which is influenced both by the complexity of operative and anaesthetic procedure and the severity of disease. During the routine use of expensive and complex monitors to detect intraoperative ischaemia, one should keep in mind that most of the myocardial ischaemia are not associated with any intraoperative haemodynamic abnormalities and such monitoring should not be used routinely. So, ECG is the most acceptable and cost effective methods for detecting intraoperative myocardial ischaemia. But, the sensitivity and specificity of it varies greatly.

There is good correlation between the lead of ECG used to monitor the myocardial ischaemia and the anatomical distribution of ischaemia. Usually lead II likely reflects the area of ischaemia supplied by the right coronary artery. It is also useful in identifying P waves and subsequent cardiac rhythm disturbances due to ischaemia. Whereas lead V_5 reflects the area of ischaemia supplied by anterior desending coronary artery. Lead I and aVL reflect the area supplied by the circumflex coronary artery. The diagnosis of ischaemia by ECG mainly depends on the changes of ST segment. These changes are characterised by depression or elevation of it by atleast 1 mm. The depth of changes of ST segment is parallel to the severity of myocardial ischaemia. There is also associated T-wave changes with ischaemia. But, there are numerous factors which can produce these changes without ischaemia. Except ischaemia, other factors which can produce the ST segment changes are: conduction defect, arrhythmia, electrolyte imbalance, digitalis therapy, etc. Visual detection of ST segment changes is sometimes unreliable. So, computerised analysis of ST segment changes is incorporated in some machine and offers a high modality for detection of ischaemia by a very simple and noninvasive method in high risk patient (Fig. 27.1).

Transesophageal echocardiography (TE) and measurement of pulmonary capillary wedge pressure (PCWP) is also sometimes used during complex operative procedures for detection of ischaemia. TE is gradually becoming accepted standard procedure for the intraoperative diagnosis of myocardial ischaemia. It is based on the principle that the ventricular wall motion abnormalities occur before the changes in ST-segment takes place in ECG. Whereas, other conditions responsible for ventricular wall motion changes should be excluded preoperatively. The limitation of TE for monitoring of ischaemia is its cost and the need for extensive training for its interpretation. Another limitation of it is that the TE probe can not be introduced before induction of anaesthesia. So, there is a critical period of induction during which myocardial ischaemia may develop in the absence of this monitoring. The present status of TE for monitoring of ischaemia is it provides minimal additive value over analysis of ST-segment on the ECG.



Figs 27.1 A and B: ECG of lead V5 at rest A. ECG of lead V5 after 5 minutes of exercise B. Her ST- segment is depressed horizontally 3 mm (0.3 mV), indicating a positive test for ischaemia

The value of measurement of PCWP for random or routine monitoring of ischaemia is questionable. Only the value and safety of PCWP monitoring is widely accepted in selected patients. PCWP monitoring and diagnosis of ischaemia correlates well when the left ventricular ejection fraction is more than 0.5 (or 50%) and there is no previous evidence of left ventricular dysfunction. Contrary, when the ejection fraction is less than 0.5, then there is no longer a predictable correlation between the findings and the diagnosis.

Postoperative Care

During the postoperative period, the myocardial ischaemic patients should be cared on the following aspects:

i. The relief of postoperative pain in ischaemic patient is very vital, because otherwise it activates the sympathetic nervous system leading to increased myocardial oxygen demand and ischaemia. Adequate relief of pain also facilitates deep–breathing and coughing which may decrease the likelihood of atelectasis and the development of pneumonia.
ii. In the intraoperative period patient's body temperature decreases which may predispose to shivering on awakening. This shivering leads to the abrupt increase in myocardial O_2 demand and ischaemia. So, in the postoperative period all the attempts should be made to check the shivering and O_2 administration is mandatory. It is of interest that postoperative myocardial infarction most often occurs within 48 to 72 hours after operation and this is a period that usually corresponds to the discontinuation of supplemental O_2 and less aggressive treatment of pain. So, following major surgery, all patients at risk should have supplemental O_2 for 3 to 4 days postoperatively, particularly at night.

Continuous ECG monitoring is also useful for detecting postoperative myocardial ischaemia which is often though asymptomatic.

Perioperative Acute Myocardial Infarction (MI)

Perioperative MI most frequently occurs around 3 to 4 days after surgery. Symptoms may be typical or atypical. In 20% case the symptoms may be silent. In perioperative MI, the mortality rate is very high and may rise upto 50%. The diagnostic criteria for MI may vary, but the sole reliance on CK-MB asssay for the diagnosis of MI will over estimate the incidence of it, especially in patients with ischaemic limbs or after aortic surgery. During the management of perioperative MI, the therapeutic options are reduced or limited. This is because thrombolysis is generally contraindicated during perioperative period. Other noncontraindicated possible treatment of MI are aspirin and beta-blockers. Emergency angioplasty for MI is probably atleast as effective as thrombolysis.

28 Valvular Heart Diseases and Anaesthesia

INTRODUCTION

The perioperative management of a patient with valvular heart disease is a very important aspect for an anaesthetist during his clinical practice. So, for proper management of this group of patients he must know the haemodynamic changes associated with every particular type of valvular lesion. The valvular lesion produces haemodynamic burden on left or right ventricle or both or on atrium alone. Initially, CVS tolerates this and tries to compensate the overload. But always the aim of this compensation is to maintain the adequate cardiac output. So, during examination of a patient an anaesthetist will get many findings which are due to this compensatory changes, but are not due to the actual pathology. Then, this haemodynamic burden gradually leads to cardiac muscle dysfunction and failure, when this compensatory mechanism is crossed. So, at this stage during examination of a patient an anaesthetist will get only the signs of heart failure.

More or less all the valvular lesions produce two types of haemodynamic overload such as pressure overload (MS and AS) and volume overload (MR and AR) on left or right ventricle and left or right atrium. Pressure overload produces more damage on heart and morbidity than the volume overload. Other than the knowledge regarding the haemodynamic changes, perioperative management of these group patients with valvular heart disease depends also on the knowledge, regarding the effects of different drugs used for anaesthesia purpose perioperatively on the different haemodynamic parameters such as: heart rate, rhythm, BP, SVR, PVR, etc.

MITRAL STENOSIS (MS)

Aetiology and Pathophysiology (Fig. 28.1)

Acquired mitral stenosis is almost always rheumatic in origin and particularly affects the female. However, in some elderly heavy calcification of the mitral valve apparatus can also produce an acquired form of mitral stenosis. There is also a rare form of congenital mitral stenosis. In mitral stenosis the normal left ventricular filling is restricted by the decreased area of flow from left atrium across the stenosed valve. The normal cross sectional area of the mitral valve is 4 to 6 cm^2. Symptoms appear when this area is reduced to about 2.5 cm^2 (< 50% of normal). When the valve area is measured between 2.5 to 1 cm, then mitral stenosis is recognised as moderate. But, below 1 cm^2 symptoms are severe. At this level, the left intra-atrial pressure is >25 mm of Hg and pulmonary hypertension sets up. Normally, the mitral transvalvular (between LA an LV) pressure gradient is 5 mm of Hg. When it exceeds 10 mm of Hg, then mitral stenosis is considered as severe (Table 28.1).

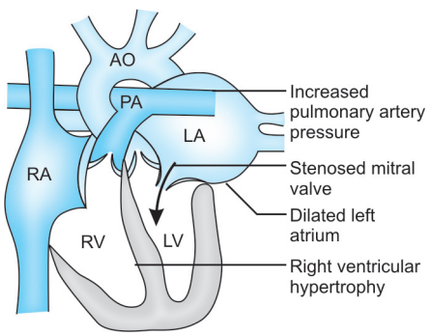


Fig. 28.1: Mitral stenosis

In the early phase of mitral stenosis, the compensation that is aimed at the LV

Table 28.1: Compensatory changes in MS

Mitral stenosis
↓
Decreased flow through mitral valve
↓ Decreased cardiac output → cold calm periphery
Increased volume and pressure of LA
↓
Increased force of contraction of LA
↓ Compensatory increase in cardiac output
Increased flow through mitral valve
↓
Hypertrophy and dilatation of LA
↓
But is limited due to the thin wall of LA chamber
↓
No valve in pulmonary vein
↓
So pressure is directly transmitted to the pulmonary vasculature
↓
Development of pulmonary congestion
↓
So dyspnoea by slight exertion (commonest symptom of MS)
↓
Pulmonary hypertension
↓
Concentric RV hypertrophy without the increase of size of it

filling and subsequently the good cardiac output is normally achieved by increasing the pressure gradient across the stenosed mitral valve. This increased pressure gradient across the stenosed mitral value increases the flow from the LA to LV and compenste this stenosis. This LV filling and cardiac output also dependent upon the increased atrial contraction or kick and the duration of ventricular diastole. So, this valvular obstruction produces increased left atrial volume and left arterial pressure (mechanism of compensation). Thus with increased volume and pressure, dilatation and hypertrophy of the left atrium occurs. The stroke volume or CO may decrease (decompensation) during stress induced trachycardia by reducing the duration of ventricular diastole and thus by reducing the time of LV diastolic filling or when an effective atrial contraction is lost by huge atrial dilatation or by the development of atrial fibrillation.

Symptomatic patients with mitral stenosis typically exhibit dyspnoea on exertion or orthopnoea or paroxysmal nocturnal dyspnoea, although left ventricular contractility is usually normal. Actually this dyspnoea in MS is due to the increased pulmonary venous pressure in response to increased left atrial pressure. This results in transudation of fluid into the pulmonary interstitial space, decreased pulmonary compliance, and increased work of breathing, leading to progressive dyspnoea on exertion, orthopnoea, or paroxysmal nocturnal dyspnoea. When the pulmonary venous pressure exceeds the oncotic pressure of plasma proteins (25 to 30 mm of Hg), then overt pulmonary oedema develops. During compensation with the increase of pulmonary venous pressure there is also concomitant increase in lymphatic drainage from the lungs. This also causes thickening of capillary basement membrane (as compensatory mechanism) which enable the patients to tolerate the increased pulmonary pressure without the development of pulmonary oedema.

Surgical correction of mitral stenosis is indicated when the symptoms increase and /or evidence of pulmonary hypertension develops. Otherwise, mild symptoms of mitral stenosis are treated by diuretics which act by decreasing the preload and subsequently the left atrial pressure. In the presence of atrial fibrillation due to LA hypertrophy and enlargement which is commonly occurs as compensatory mechanism to MS, the HR is controlled by digoxin, β-blockers or Ca^{2+} channel blockers. If pulmonary hypertension and right ventricular failure develop as a consequence to severe MS then inotropic support by dopamine or dobutamine in the dose of 1 µg/Kg/min IV and reduction of pulmonary pressure by nitroprusside in the dose of 0.1 to 0.5 µg/Kg/min IV may be useful. Catheter balloon mitral valvotomy often provides mechanical relief, if the patient is not fit for cardiac surgery. In the presence of heavy valvular calcification or when the surgery is indicated, then the treatment is open commissurotomy or valve reconstruction or mitral valve replacement.

Preoperative Abnormalities

On examination of patient with mitral stenosis the pulse may be found irregular, if atrial fibrillation develops, and this is due to the left atrial hypertrophy and dilatation. The palpation of precordium of a patient suffering from MS may also reveal a palpable first heart sound. On auscultation, there may be an opening snap that occurs during the early diastole. When the 'snap' is more closer to the second heart sound, then it is assumed that the MS is more severe. Calcification of mitral valve also may result in disappearance of the opening snap. In MS this opening snap is followed by a rumbling mid-diastolic murmur with presystolic accentuation. The loudness of the murmur is no guide to the severity of the stenosis and may be inaudible if still the stenosis is severe and cardiac output is low. Atrial fibrillation (AF) may cause decompensation of the haemodynamic changes of mitral stenosis by decreasing the left ventricular filling volume due to the ineffectful contraction of left atrium and by decreasing the left ventricular filling time. Thus, it reduces the cardiac output. This is manifested clearly by cool, cyanosed peripheries and low volume pulse (Fig 28.2).

The chest X-ray in mitral stenosis shows the left atrial enlargement with a prominent left atrial appendage and a double contour on the right border of the heart. Left atrial enlargement is also often visible on chest radiograph as straightening of the left border of the heart, widening of the carinal angle and displacement of the barium–filled oesophagus on a lateral view. The Kerley B lines may be present. The ECG may show P mitrale (large biphasic p-wave) and it is due to the left atrial enlargement. Definitive diagnosis of mitral stenosis is made by echocardiography which allows the precise measurement of mitral valve ring, left atrial dimensions and demonstration of any abnormal movement of thickened and calcified mitral valve cusps. It also permits assessment of the transvalvular pressure gradients.

In the presence of AF which is common for mitral stenosis, the systemic thromboembolism may occur. This is because of the stasis of blood in the distended left atrium (LA) which predisposes to the

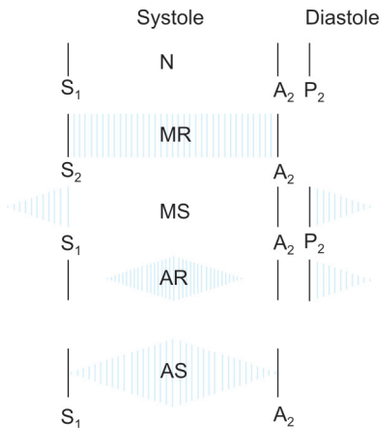


Fig. 28.2: Comparison of systolic and diastolic heart sounds in various abnormalities

formation of thrombi, especially with the onset of AF. Venous thrombosis is also encouraged by the low cardiac output and decreased physical activity, characteristic of these patients.

The patient with symptomatic mitral stemosis when comes for anaesthesia for any non cardiac surgery usually takes digoxin, diuretics, β-blockers, and anticoagulants. Digitalis is most often administered to increase the myocardial contractility and to slow the ventricular rate in responses to AF as it reduces the rate of conduction through AV node. Slowing of the ventricular rate caused by digitalis also prolongs the duration of diastole and thus improves the left ventricular filling with increased cardiac output. An adequate digitalis effect on heart is indicated by the ventricular rate, which is slower than 80 beats/min at rest. Digitalis toxicity is suggested by the prolongation of PR interval in ECG. Concomitant use of diuretics with digitalis increases the vulnerability of the development of digitalis toxicity and it is due to the total body depletion of potassium.

Symptomatic history is a good guide to the severity of disease like MS. Dyspnoea on mild exertion with episodes of paroxysmal nocturnal dyspnoea indicate the left atrial pressure (LAP) is of 15 to 20 mm Hg or greater.

Anaesthetic Problem

The anaesthetic management of a patient with mitral stenosis scheduled for non-cardiac surgery includes the avoidance of events which may further decrease the cardiac output. Tachycardia and AF reduces the LV diastolic filling time, LV filling volume and cardiac output and thus precipitate pulmonary oedema. So, they (tachycardia and AF) should be avoided at any cost. Simultaneously the large decrease in systemic vascular resistance due to any cause may result in severe hypotension, because there is limited capacity to increase the cardiac output by compensation. So, sudden decrease in systemic vascular resistance due to any cause during anaesthesia may not be tolerated well as systemic BP is maintained only by the compensatory increase in HR (which is also not tolerated in MS). Hence, if necessary, systemic BP and systemic vascular resistance should be maintained by sympathomimetic vasoconstricting drugs like ephedrine or phenylephrine. The advantage of ephedrine is its β-adrenergic effect, which increases the myocardial contractility without increasing the HR. Because any drug-induced tachycardia would be undesirable. Phenylephrine also eliminates this increase in heart rate. But increase in left ventricular afterload which follow administration of this predominantly α-agonist drug could decrease the left ventricular stroke volume.

In mitral stenosis volume overload may easily produce pulmonary oedema. Contrary, hypovolaemia accentuated by diuretics or due to any other causes may easily reduce the cardiac output. So, a fine balance should be maintained between the hyper and hypovolaemia. Myocardial depressant drugs can cause severe hypotension and should be avoided in MS. The Trendelenberg position may easily result in pulmonary oedema and hypoxia. Hypoxia and acidosis may further cause pulmonary vasoconstriction with pulmonary hypertension and thus set a vicious cycle. N_2O may be unsafe if pulmonary vascular resistance is increased. Otherwise it is not contraindicated. Bacteraemia during surgery or any instrumentation carries the increased risk of bacterial endocarditis in MS, like other valvular heart diseases.

Anaesthetic Management

Prophylaxis against infective endocarditis is the only preoperative medical therapy for mitral stenosis in asymptomatic patients. So, prophylactic antibiotics are required for any surgery performed on mitral stenotic patient which carries the increased risk of producing bacteraemia. This usually includes dental, genitourinary, intestinal surgeries, etc. If the high ventricular rate due to AF accompanies with MS preoperatively, then it should be controlled before surgery. It is acceptable to continue the anticoagulant therapy for minor surgeries if it is started preoperatively. Whereas for major surgeries which are likely to be associated with significant blood loss, then the common practice is to discontinue warfarin 3 to 5 days before surgery and it is substituted with heparin. Atropine should be avoided in mitral stenosis as tachycardia further reduces the LV filling by reducing the filling time through the already compromised stenosed mitral valve. A sedative premedication reduces the anxiety and any associated bad circulatory responses produced by tachycardia due to anxicty.

The induction of anaesthesia on patient in the presence of mitral stenosis can be achieved by any commonly available intravenous inducing agent. But ketamine should be avoided, because it has a great tendency to increase the afterload and heart rate. Tracheal intubation is usually performed by administration of muscle relaxants that are unlikely to induce undesirable cardiovascular changes due to release of histamine or affecting the conduction of cardiac impulses. The use of succinylcholine on the patient with mitral stenosis and taking digoxin is sometimes associated with ventricular dysrrhythmias, but it is not a consistent observation. So, the use of succinylcholine is not an absolute contraindication in mitral stenosis. In this regard, pancuronium is also not the choice as it causes tachycardia (Table 28.2).

During maintenance of anaesthesia an adequate depth of analgesia, amnesia and muscle relaxation is essential. This goal is most closely reached by using the combination of N_2O, opioids, and low concentration of volatile anaesthetics agents. However, N_2O can produce increased pulmonary vascular resistance by pulmonary vascular constriction. But, it seems

Table 28.2: Goals of anaesthetic management of patients with mitral stenosis (MS)

1. Avoidance of infective endocarditis.
2. Avoidance of sinus tachycardia.
3. Prevent rapid ventricular rate in response to atrial fibrillation
4. Prophylaxis of thromboembolism.
5. Avoid marked increase in IV fluid over load.
6. Avoid head down position.
7. Avoid systemic hypotension.
8. Avoid pulmonary congestion and pulmonary hypertension.
9. Avoid any such agent which depresses cardiac contractility.

unlikely that the magnitude of this change caused by N_2O would justify the avoidance of this drug in asymptomatic patients with mitral stenosis. On the other hand, when the co-existing pulmonary hypertension is severe, then N_2O may more likely to increase the pulmonary vascular resistance and should be avoided. High doses of short acting opioids such as fentanil, alfentanil, remifentanil, etc. are used for severe mitral stenotic patients. If high doses of short acting opioids are used for caessarean section with severe mitral stenosis, then the baby may suffer from severe respiratory depression, but responds well to a single dose of naloxone.

Like any other valvular diseases of heart, in mitral stenosis light general anaesthesia (which is due to not properly titrated with the level of surgical stimulation) can also produce tachycardia, systemic hypertension, and decrease cardiac output due to the increased systemic and pulmonary vascular resistance. In such circumstances, infusion of nitroprusside in the dose of 0.5 to 1µg/kg/minute may effectively decrease the systemic vascular resistance and increase the cardiac output, particularly when the severe pulmonary hypertension or mitral regurgitation coexist with mitral stenosis. There is no contraindication for the use of anticholinesterase and anticholinergic agent for the reversal of nondepolarising muscle relaxants, though the adverse effects of tachycardia deserves consideration. In this respect glycopyrrolate is better than atropine. The use of regional anaesthesia in patient suffering from mitral stenosis bears the same advantages, disadvantages and precaution as the patient suffering from ischaemic heart disease.

The degree of intraoperative monitoring of patient with mitral stenosis depends upon the severity of the lession and the magnitude of the surgery. Monitoring of asymptomatic patients does not need any special comment. On the other hand, symptomatic patients undergoing major surgery may need extensive monitoring including intra-arterial BP, trans-oesophageal echocardiography, pulmonary artery catheterisation, etc. These monitorings are helpful in confirming the adequacy of cardiac functions including cardiac output, intravascular fluid volume, ventilation, oxygenation, etc. In the absence of pulmonary hypertenssion, the changes in CVP will mirror the left atrial pressure changes. However, if it is present, then the PAWP does not correlate very well with the left atrial pressure. In the absence of pulmonary hypertension though CVP shows correctly the left atrial pressure, still it poorly reflects the left ventricular filling. This is due to the presence of stenosis in mitral valve. Intraoperative tachycardia should be treated rapidly. In such situation esmolol is very effective and easily titrable. During operation any negative inotropic effects are easily outweighed by the benefits of controlling the rate. If the tachycardia is due to new atrial fibrillation, then DC cardioversion should be considered.

MITRAL REGURGITATION (MR)

Aetiology and Pathophysiology

Acquired mitral regurgitation is mainly due to the acquired lesion of valve. This acquired lesion of valve is due to the dilatation of ring which is again due to the rheumatic disease or papillary muscle dysfunction. The haemodynamic consideration of MR from anaesthetic point of view is same as MS, but the aetiology of it may have additional consideration in anaesthesia which is not the same as MS. Rheumatic disease is the principal cause of mitral regurgitation (MR) in under developed countries like MS. So, MR is almost always associated with MS. Therefore, though MR in under developed countries is due to the dilatation of mitral valve ring caused by rheumatic pathology, but in developed countries the principal causes of this MR are: mitral valve prolapse, myocardial infarction causing damage to the papillary muscles and damage to the chordae tendinae, and dilatation of mitral valve ring due to the dilatation of heart. MR may also follow after successful surgery of MS by valvotomy or valvoplasty (Fig. 28.3).

The mitral valve prolapse is the most common cause of MR in developed countries. In developed countries MR is also caused by the congenital anomalies, myxomatous degenerative changes, bacterial endocarditis, etc. MR is sometimes a feature of connective tissue disorders such as Marfan's syndrome. The efficacy of mitral valve depends on the proper function of chordae tendinae and their papillary muscles attached to the valve cusps. So dilatation of the left ventricle due to any cause distorts the geometry of the supporting structures of the valve (i.e. chordae

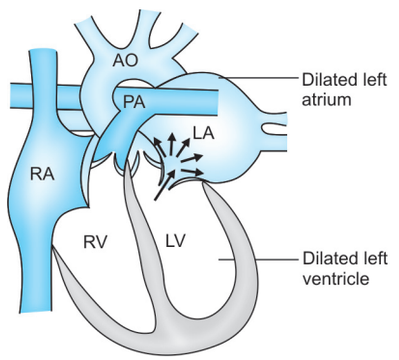


Fig. 28.3: Mitral regurgitation

tendinae and papillary muscles) and may cause mitral regurgitation. The progressive elongation of chordae tendinae due to any cause may also lead to gradual development of MR. But if MI occurs, then due to rupture of chordae tendinae mitral regurgitation suddenly becomes acute. However, this complication is rare before the 5th and 6th decade of life. In developed countries mitral regurgitation is also due to the dilated cardiomyopathy, and impaired ventricular function that results from coronary artery disease. Endocarditis may also lead to the distortion of valve leaflets and is an important cause of acute or chronic MR.

The basic haemodynamic derangement of MR is the decrease of left ventricular stroke volume in forward direction through the aortic valve. This is because a part of the left ventricular stroke volume is regurgitated back through the incompetent mitral valve into the left atrium. Patient with regurgitation fraction of more than 0.6 (> 60%) in the left atrium are considered to have severe MR. The fraction of the left ventricular stroke volume that regurgitates in the left atrium depends on: (i) the size of the mitral valve orifice. (ii) the pressure gradient across the mitral valve, and (iii) the duration of ventricular ejection, i.e. HR. On the other hand, the ventricular ejection through aorta depends on: (a) the impedence of aorta, i.e. systemic vascular resistance (SVR) and (b) the previous factors which control the amount of regurgitation. So, the pharmacological interventions that increase or decrease the SVR have an important impact on the forward ejection fraction and the backward regurgitation fraction of the left ventricular stroke volume. The pharmacological reduction of SVR increases the LV ejection fraction in the aorta and decreases the LV regurgitation fraction in the left atrium and vice-versa.

The chronic MR causes gradual dilatation of the left atrium with little increase in intra-atrial pressure and hypertrophy and, therefore, is associated with relatively few symptoms. However, rheumatic fever induced MR is associated with marked left atrial enlargement and AF. Nevertheless, the left ventricle dilates slowly in MR as the left ventricular and the left atrial pressures gradually increase as a result of chronic volume overload. Then breathlessness, pulmonary hypertension, and pulmonary oedema gradually supervene. The symptoms depend on how suddenly the regurgitation develops. Chronic MR produces a symptom complex that is similar to that of MS. But, sudden onset of isolated MR due to MI or rupture chordae tendinae usually presents with acute pulmonary oedema (Table 28.3).

Mitral regurgitation (MR) is less dependent on atrial contraction for left ventricular filling than MS. So, conversion of AF to normal sinus rhythm is of little help and produces minimal changes in cardiac output in MR. Left ventricular hypertrophy and myocardial ischaemia is unlikely in the presence of isolated MR (i.e. when not associated with MS or AS), because the left ventricular wall tension is rapidly dissipated through the incompetent mitral valve.

When MR is combined with MS, then only the increased flow rates from left atrium to left ventricle (normal amount of blood drained through pulmonary veins in left atrium plus regurgitant blood) across the stenotic valve increases the left atrial pressure and its hypertrophy. In such patient AF, pulmonary hypertension, and pulmonary oedema develop more early than those with isolated MR.

Diagnosis

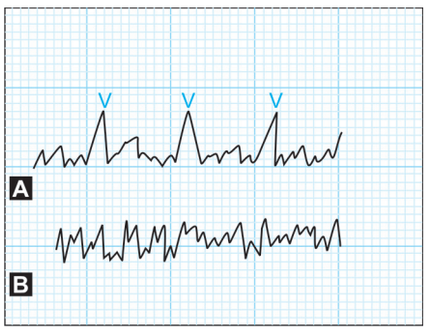
On clinical examination, the MR is recognised by the presence of apical holosystolic murmur which often radiates towards the axilla and may be accompanied by a thrill. The first heart sound is faint or silent, because mitral valve closure is abnormal. During ventricular filling

Table 28.3: Compensatory changes in MR

Mitral regurgitation
↓
Systolic leak from LV to LA
↓
No obstruction of flow through mitral valve
↓
So blood flow freely from LA to LV during diastole
↓
Mean LA pressure therefore remain normal or slight increased
↓
No increase in pulmonary venous pressure
↓
No pulmonary venous congestion
↓
Dilatation of LA and LV due to handling of large blood volume
↓
Forward flow from LV to aorta is less than regurgitation to LA due to high systemic BP
↓
So patient more complain of fatigue (due to low CD) than dyspnoea (due to pulmonary congestion)
↓
Dyspnoea occurs if MR is severe and associated with pulmonary hypertension or LV myocardial failure
↓
So presence of pulmonary hypertension in MR indicates: (i)severe MR, (ii) LVF, (iii) acute MR

increased forward flow of blood (due to normal amount of blood coming from the lungs plus the regurgitant blood) through mitral valve from left atrium to left ventricle may give rise to prominent third heart sound. The chronic MR is compensated by the development of eccentric atrial and ventricular hypertrophy and enlargement. This is detected by the apex beat which is usually displaced to the left (as a result of dilatation of LV) and feels active and rocking (due to LV hypertrophy for overload) (Figs 28.4A and B).

The radiograph and ECG in mitral regurgitation may show the features of left atrial and/or left ventricular hypertrophy. Like MS the atrial fibrillation (AF) is also common in MR as a consequence of atrial dilatation. Echocardiography provides information about the state of the mitral valve, left ventricular function and left atrial size. The severity of MR is best assessed by echocardiography. But it should be realized that the left ventricular ejection fraction as a reflection of LV performance will be overestimated in the presence of mitral regurgitation. So, doppler echocardiography is required to estimate the extent of regurgitation. During cardiac catheterisation for the tracing of pulmonary capillary wedge pressure (PCWP) the severity of MR may be indicated by the size of 'V' waves produced by the left atrium. It also can be assessed by the left ventricular angiography. The size of V wave parallels with the severity of MR.



Figs 28.4A and B: The picture shows the tracing of pulmonary artery occlusion pressure from a patient with mitral regurgitation.
A. when blood regurgitate back into the left artium through incompetent mitral valve produce large 'V' waves on tracing.
B. It shows that the magnitude of the V waves are decreased or abolished. It is due to administration of vasodilator like hydralazine. Vasodilators decrease resistance to forward ejection of the left ventricular stroke volume. As a result the stroke volume into the aorta increases and the volume of regurgitant flow into the left atrium decreases with the magnitude of the 'V' wave

Anaesthetic management

Unlike the stenotic mitral valvular lesions in MS the chronic MR causes few symptoms. So, it progresses insidiously causing LV and left atrial damage, before symptoms have developed. Thus, surgical treatment of MR is recommended when the regurgitation fraction is less than 0.6 (60%), i.e. before patient becomes symptomatic. The progressive radiological cardiac enlargement or the echocardiographic evidence of the deterioration of the left ventricular function are also the indications of surgical intervention of mitral valve. In this regard, mitral valve repair is preferred than the mitral valve replacement. This is because in mitral valve repair mortality is less and outcome is better than MS (Table 28.4).

The principles of anaesthetic management of a patient with MR for noncardiac surgery is avoidance of events that cause reduction of cardiac output. This is achieved by: (i) avoiding sudden decrease in HR, (ii) avoiding sudden increase in SVR and (iii) avoiding myocardial depression. Unlike MS, in MR the left ventricular forward stroke volume through aorta is heart rate dependent. Contrary in MS tachycardia is not desirable as it reduces the LV filling by reducing the diastolic ventricular filling time and subsequent reduces the cardiac output. But, in MR bradycardia is not desirable as it reduces the forward LV stroke volume directly due to increased back flow. So, sudden bradycardia may result in abrupt LV volume overload. Likewise, sudden increase in SVR causes reduction of LV stroke volume and causes increase in regurgitation from left ventricle to left atrium. This produces acute decompensation of LV. So, overall anaesthetic management of a MR patient is drug induced afterload reduction with nitroprusside, combined with a cardiac inotrope such as dopamine or dobutamine, and maintenance of (avoiding of bradycardia) heart rate.

Table 28.4: Goals of anaesthetic management of patients with mitral regurgitation (MR)

1.	Prophylactic antibiotic to avoid infective endocarditis.
2.	Prevent sudden decrease in heart rate.
3.	Avoid sudden increase in BP.
4.	Avoid depression of myocardial contractility.
5.	Avoid fluid overload and pulmonary congestion.
6.	Monitoring of amount of regurgitation by echo or other invasive method.

Like MS, in the patient suffering from MR prophylactic antibiotic is also started in the preoperative period to prevent the development of infective endocarditis. GA is the usual choice for MR. Induction of anaesthesia for patient in the presence of MR can be achieved with any available intravenous inducing agent, with possible exception of ketamine which should be avoided. This is because ketamine has great propensity to increase the SVR and systemic blood pressure. Thus it will reduce the forward flow from LV to aorta. Succinylcholine for intubation is not contraindicated. The anaesthetic points of view regarding the choice of nondepolarising muscle relaxants are same as MS, but pancuronium which generally produces a modest increase in HR is beneficial for MR.

Low doses of volatile anaesthetic agents can also be administered to attenuate the undesirable increase in SVR and systemic BP associated with intubation and surgical stimulation, but without depressing the myocardium. Although, any specific

volatile anaesthetic agent is not considered as superior than other, but isoflurane, sevoflurane, or desflurane (not halothane) are the choice. Because, they decrease the SVR with minimum depressant effect on myocardial contractility. In the presence of acute or severe MR when myocardial function is severely compromised, then the sole use of opioid as anaesthetic agent which minimises the likelihood of drug induced myocardial depression is the choice.

The intraoperative anaesthetic management and the maintenance of intravascular fluid volume in MR is same as the intraoperative management of MS. General anaesthesia and alterations of SVR are well tolerated unless the regurgitation through mitral valve is very severe. Other anaesthetic approaches are also well tolerated by MR. Fluid overload is a major risk factor in MR, but less than with mitral stenosis. Intraoperative monitoring of MR is also same as MS. Minor operations, performed on patients with asymptomatic MR, probably do not require any invasive monitoring. Complex invasive monitoring (such as transoesophageal echocardiography, use of pulmonary artery catheter, measurement of cardiac output by thermodilution technique, etc) are necessary for patient with severe MR undergoing a complex surgical procedure. In the tracing of pulmonary artery pressure, the presence of prominent V waves indicate appreciable regurgitation through mitral valve. Changes in V wave amplitude can also assist in estimating the magnitude of MR.

AORTIC STENOSIS (AS)

Aetiology and Pathophysiology (Fig. 28.5)

Aortic stenosis is usually idiopathic in origin, and results from the degeneration and calcification of the cusps of aortic valve. The likely aetiologies of AS vary with the age of patients. The causes of AS for infants, children and adolescents are different. The cause of AS in infants is usually congenital and it is of three types such as congenital stenosis at the aortic valve level, congenital stenosis at the subvalvular level, and congenital stenosis at the supravalvular level. The causes of AS for young adults and middle aged patients are: early calcification and fibrosis of congenitally present bicuspid aortic value and rheumatic disease. The causes of AS for elderly patients are: senile degeneration of aortic valve, calcification of bicuspid valve, and rheumatic disease (Fig. 28.5).

The aortic stenosis is more likely to occur at earlier age (below 30 to 40 years) in persons, who are born with bicuspid aortic valve than in those with normal tricuspid aortic valve. Otherwise, except the congenital forms, AS develops slowly in older age. Initially, as compensatory mechanism cardiac output in AS is maintained at the cost of steadily increasing pressure gradient across the aortic valve due to outflow obstruction. Then, the LV gradually becomes hypertrophied and maintains the cardiac output. After that when the AS becomes more severe and cardiac output gradually falls, then the coronary blood flow gradually becomes inadequate and patient develops angina, even in the absence of any coronary artery disease. It indicates increased myocardial O_2 requirement due to increased concentric myocardial hypertrophy which is again due to increased outflow obstruction. Furthermore, myocardial O_2 delivery is decreased due to the compression subendocardial coronary blood vessels by the increased left intraventricular systolic pressure. So, aortic stenosis is associated with the same risk factors as those of IHD. The fixed outflow obstruction at the aortic level limits the increase in cardiac output, which is required for increased activity. So, the effort or activity related hypotension and syncope may occur. Gradually, the LV can no longer be able to overcome the outflow tract obstruction and the left ventricular outflow failure supervenes. In contrast to MS which tends to progress very slowly, AS typically remain asymptomatic for many years. But, then it deteriorates rapidly when symptoms develop. Thus, death usually ensures within 3 to 5 years after the onset of symptoms.

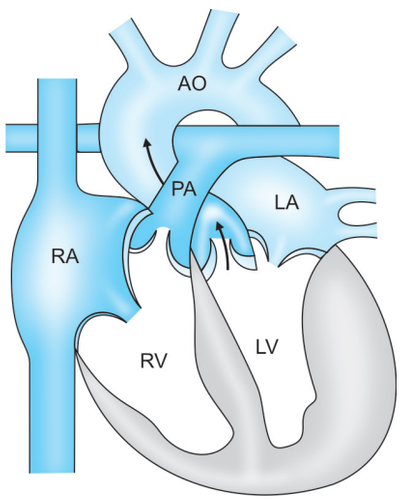


Fig. 28.5: Aortic stenosis

The severity of AS is best assessed by measuring the pressure gradient across the aortic valve by echocardiography. But, poor exercise tolerance and especially the syncope suggests severe stenosis. Critical or severe aortic stenosis, capable of causing symptoms and sudden death, is characterised by transvalvular pressure gradient higher than 50 mm of Hg and an aortic orifice area is lesser than 0.8 cm^2 (the normal aortic valve area is 2.5 to 3.5 cm^2).

The long-term prognosis of AS depends upon the degree of stenosis:
< 0.7 cm^2 – severe,
0.7 to 1.5 cm^2 – moderate,
> 1.5 cm^2 – mild.

A pressure gradient across the aortic valve of > 50 mm of Hg is considered to be severe and < 20 mm of Hg is mild. The pressure gradient between 50 to 20 mm of Hg across the aortic valve is considered as moderate. These pressure gradients are increased by tachycardia and exercise.

This pressure gradient across the aortic valve should be interpreted with the measurement of LV function, because with time the LV will fail and the measured transvalvular pressure gradient will then start to fall again. But it does not mean that AS is not severe. Aortic stenosis is almost always associated with aortic regurgitation. It is also associated with LV systolic dysfunction due to increased after load. This leads to ventricular hypertrophy and gradually progress to diastolic dysfunction due to increased LV wall thickness.

Diagnosis

The mild and moderate degree of AS is usually asymptomatic. The classical clinical symptoms of AS (which indicate severe form) are angina pectoris, exertional dyspnoea, exertional syncope, episodes of acute pulmonary oedema, etc. On clinical examination, the carotid pulse is felt as low volume and slow rising. A radial pulse is also of slow rising and of decreased amplitude. A pulse pressure of < 30 mm of Hg reflects severe AS. Contrary, if the systolic BP is > 180 mm of Hg, then the AS is not significant. Auscultation of patient with AS reveals a characteristic systolic ejection murmur over the precordium, radiating towards the neck. It is best heard on the aortic area, i.e. 2nd right parasternal intercostal space and is 'diamond' in shape. The aortic component of the 2nd heart sound is inaudible. An ejection click may be present in young patients, but not in older patients due to calcified valves. The chest X-Ray may show a prominent ascending aorta due to post-stenotic dilatation of the aortic arch. The ECG demonstrates the evidence of left ventricular hypertrophy (LVH) with the changes of ST segment. LBBB is also common in AS. In advanced cases of AS the features of LV hypertrophy are often gross and depression of ST-segment with T-wave inversion (strain pattern) may be seen in leads reflecting left ventricle.

The echocardiography examination provides a more accurate assessment of the severity of aortic stenosis. It also provides information regarding the thickening and calcification of the aortic valve, combined with decreased mobility of the valve cusps. It is also useful in determining the left ventricular ejection fraction and its extent of hypertrophy.

The doppler study permits the calculation of systolic pressure gradient across the aortic value and detects the presence or absence of aortic regurgitation. Cardiac catheterisation and coronary angiography is indicated if echocardiography studies are unsatisfactory or if it is necessary to assess the state of coronary arteries.

Anaesthetic Management

The principle of anaesthetic management of a patient with AS for noncardiac surgery is to avoid the events which causes the reduction of already jeoparadised cardiac output due to stenosis. This can be achieved by maintaining the normal sinus rhythm, avoiding tachycardia and bradycardia, avoiding sudden increase in SVR, avoiding sudden severe hypotension and optimizing the intravascular fluid volume (to maintain optimum venous return and left ventricular filling). Like anaesthetic management of other valvular disease, GA is also the choice in AS. Regional anaesthesia is not preferred, because peripheral sympathetic nervous system blockade can lead to undesirable sudden and severe decrease in venous return and and subsequently cardiac output in an already compromised patient who has limited outflow from LV. But it is not absolutely contraindicated and epidural catheter technique is often used (Table 28.5).

During anaesthetic management of a patient suffering from AS intraoperative optimum maintenance of heart rate and sinus rhythm is important, because it determines the time, available for diastolic filling of left ventricle and then subsequently the amount of ejection of blood into aorta. Sustained tachycardia can decrease the time for left ventricular diastolic filling and forward ejection, leading to reduction in CO. On the other hand, sudden severe bradycardia can also lead to acute over distension of the left ventricle. This is because the ventricle gets more time for diastolic filling. It is important to recognise that increase in SVR and BP (i.e. after load) can lead to further reduction of stroke volume and cardiac output through obstructed orifice. Contrary, sudden large decrease in SVR may be associated with large decrease in systemic BP, because cardiac output is relatively fixed. This fall in BP reduces the coronary perfusion of left ventricle which is hypertrophied and may result in ischaemia and reduced contractility. Thus, a vicious cycle sets in causing further left ventricular myocardial dysfunction, fall in BP and fall in coronary circulation.

The indications for preoperative prophylactic antibiotic and premedication for the patients with AS is like other valvular diseases. During induction of patients with AS, ketamine should not be used. All the anaesthetic drugs must be given with caution. The exact method of anaesthesia is probably less important than the care with which it is administered and the patient is monitored. The intraoperative monitoring also depends on the severity of disease and the complexity of surgery.

If the patient is symptomatic, then cardiological advice should be obtained. In symptomatic patients the aortic valve replacement or balloon valvuloplasty may be more important than the proposed

Table 28.5: Goals of anaesthetic management of patients with aortic stenosis (AS)

1. Optimization of intravascular fluid load.
2. Maintenance of preload, LV filling and cardiac output.
3. Avoidance of bradycardia and maintenance of normal sinus rhythm.
4. Prevention of sudden increase in afterload.
5. Prevention of sudden hypotension.
6. Prophylactic antibiotic.

operation. This is because mortality approaches 75% within 3 years after aortic stenosis becomes symptomatic, unless the valve is surgically replaced. Aortic valve replacement usually relieves the symptoms of aortic stenosis dramatically and the ejection fraction increases.

The dangerous feature of AS is that the signs and symptoms appear late in this disease. But once they occur, the prognosis is poor. So, an anaesthetist must be cautious during dealing of such a patient.

AORTIC REGURGITATION (AR)

Aetiology and Pathophysiology

Aortic regurgitation (AR) may be due to the disease of aortic valve cusps or dilatation of aortic root. The diseases of aortic valve cusps that causes AR are: congenital bicuspid valve, rheumatic fever, infective endocarditis, etc. The causes of aortic root dilatation leading to aortic regurgitation are: rheumatic fever, endocarditis, idiopathic root dilatation associated with systemic hypertension, ageing, dissection of aorta, aneurysm of aorta, syphilis, collagen vascular disease, Marfan's syndrome and trauma, etc. Acute aortic regurgitation is usually due to infective endocarditis. Except endocarditis other above mentioned causes are responsible for chronic MR (Fig. 28.6).

In AR there is ultimate decrease in the forward LV stroke volume due to the regurgitation of a part of ejected blood from the aorta back into the left ventricle (LV) after its ejection. Then this regurgitated blood volume in LV is added to that volume of blood which enters in LV from the left atrium and this combined volume of blood is next further ejected out into the aorta. Thus, by this compensatory mechanism the cardiac output is maintained by the increase in end diastolic LV volume during second contraction. So, gradually both the left ventricular hypertrophy and dilatation occur. The magnitude of regurgitation of blood from the aorta to the LV depends on: (i) the time available for the regurgitation to occur, i.e. HR and (ii) the pressure gradient across the aortic valve which again depends on the SVR and the diastolic ventricular pressure. Thus, the magnitude of AR can be decreased by increasing the HR upto a certain limit and by the reduction of SVR by peripheral vasodilatation.

With chronic aortic regurgitation (AR) the LV gradually dilates and hypertrophies to compensate the regurgitation. Thus, it results in large stroke volume that is entirely ejected into the aorta and a part of it is regurgitated back. So, the stroke volume of LV may eventually be doubled or tripled and the major arteries are then conspicuously become pulsatile. In some cases the stroke volume may be increased to more than 20 L/minute. As the disease progresses, then the left ventricular (LV) diastolic pressure gradually rises, at first only with exercise and then breathlessness develops. Later, the myocardium becomes stiffer, the left ventricular end diastolic pressure (LVEDP) increases, premature mitral valve closure occurs and finally the cardiac failure supervenes. A helpful indicator of the left ventricular (LV) function in the presence of aortic regurgitation is the echocardiographic determination of end-systolic LV volume and the ejection fraction. However, both of which remain normal until the LV function deteriorates. The symptoms appear late in this disease and do not correlate well with the severity of regurgitation. Severe aortic regurgitation carries a poor prognosis.

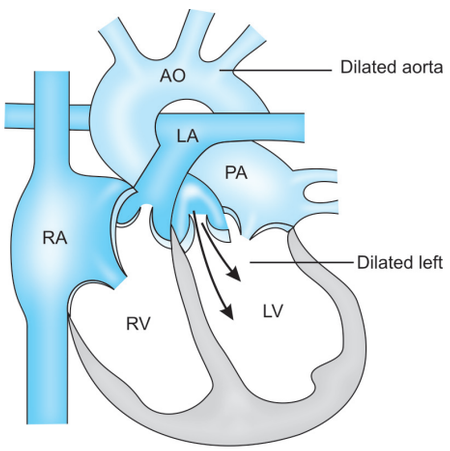


Fig 28.6: Aortic regurgitation

Diagnosis

Clinically AR is diagnosed by its characteristic diastolic blowing murmur. It is best heard along the left sternal border and is accompanied by an ejection systolic murmur due to the increased stroke volume. The peripheral signs of hyperdynamic circulation such as a widened pulse pressure, decreased diastolic BP, bounding and collapsing peripheral pulses, heaving apical impulse (volume overload), etc, are found during the clinical examination. Until the onset of breathlessness, the only symptom of AR may be an awareness of the heart beat, particularly when the patient is lying on his left side. This is only due to the hyperdynamic circulation and increased stroke volume. Clinically, dyspnoea and pulmonary oedema suggest advancement of disease. In such circumstances the diastolic BP falls in proportion to the severity of valvular lesion. In acute severe aortic regurgitation (e.g. perforation of aortic cusps due to acute endocarditis) there may be no time for compensatory left ventricular hypertrophy and dilatation to develop and the features of acute heart failure predominates. Like MR, the symptoms of AR may not appear, until the LV dysfunction is advanced. In contrast to AS, sudden death due to AR is rare.

The chest radiograph in AR characteristically shows the cardiac and aortic dilatation, together with the signs of left heart failure. When regurgitation is marked, then the ECG may show the left ventricular hypertrophy and changes in the ST segment. Echocardiography in AR typically shows a dilated left ventricle with vigorous contraction until heart failure ensues. The amount of regurgitation is readily detected by Doppler

echocardiography. Cardiac catheterisation and aortography can be helpful in assessing the severity of regurgitation and the dilatation of aorta.

Anaesthetic Management

The preanaesthetic management of AR includes the treatment of underlying conditions such as endocarditis or syphilis and prophylactic antibiotic. Aortic valve replacement is indicated if the patient is symptomatic. However, surgery is also advised for asymptomatic patients, if there is progressive radiological evidance of cardiomegaly and echocardiographic evidence of deteriorating LV function. ACE-inhibitors (as vasodilator) have been shown to prevent progressive LV dilatation and are recommended for asymptomatic patients (Table 28.6).

Table 28.6: Goals of anaesthetic management of patients with aortic regurgitation (AR)

1. Prophylactic antibiotic.
2. Avoidance of sudden increase in after load.
3. Prevent decrease in HR and maintain at higher side.
4. Use vasopressor carefully.

The anaesthesia induced fall in SVR is better tolerated by AR than with AS. The fall in SVR decreases the regurgitant flow. Contrary, an increase in SVR increases regurgitant flow and precipitate heart failure. A certain degree of tachycardia shortens the diastole and therefore, reduces the regurgitation. As the ventricle is less hypertrophied in AR, it is less at risk from tachycardia induced ischaemia. So, the goal of anaesthetic management for noncardiac surgery in patients with AR is to maintain adequate forward LV stroke volume by avoiding sudden decrease in HR, avoiding sudden increase in SVR and minimising the drug induced myocardial depression. During the whole intraoperative period, HR should be maintained above 80 beat/minute. Because, bradycardia can lead to acute left ventricular increasing the volume overload by increasing the duration of ventricular diastole and thus increasing the volume of regurgitation. Sudden increase in SVR may also precipitate left ventricular failure (LVF), requiring treatment with peripheral vasodilators, such as nitroprusside. Like other valvular diseases, GA is the choice for patients with aortic regurgitation (AR). Although, reduction of SVR due to regional anaesthesia is theoretically beneficial, but the uncontrolled nature of this response detracts an anaesthetist from the use of it in such patient. Then still if RA is decided, then epidural is safer than spinal as it can be slowly induced allowing appropriate measures to take if the BP falls. Vasopressors should be used carefully to avoid excessive increases in SVR.

Induction, intubation, maintenance and perioperative monitoring of anaesthesia in AR is like other cardiac valvular diseased patient.

29 Congenital Heart Diseases and Anaesthesia

INTRODUCTION

Congenital heart disease (CHD) is usually manifested in neonate, infant, or childhood. But, sometimes it may pass unrecognised and is not diagnosed until the adult life. Some congenital defects of heart (e.g. ASD) may cause no symptoms throughout the whole life and may first be detected incidentally during the routine preoperative examination by an anaesthetist. Very few years back, some CHD which were refused to be operated is now undergoing cardiac surgery. This is due to the better development of surgical technology, better intraoperative myocardial protection and major advances in the paediatric cardiac anaesthesia. Such many patients who have undergone corrective cardiac surgery may remain well for many years with full correction or under correction and subsequently to be presented for anaesthesia during noncardiac surgery. But many patients will still have residual problems. A study in 1992 had reported an incidence of 47% of adverse perioperative events in CHD patients, undergoing noncardiac surgical procedures who were operated before. The paediatric cardiac surgical procedures for CHD can be divided into three groups: curative procedures, corrective procedures and palliative procedures. In curative procedures the patients are completely cured without any residual problem and have a normal life expectancy, e.g. PDA, ASD, VSD, etc. In corrective procedures the patient's haemodynamic status is markedly improved, but their there is some residual problems and life expectancy may not have returned to normal, e.g. tetralogy of Fallot. In palliative procedures, the patients may have distinct abnormal circulations and cardiac physiology, but avoid the consequences if CHD remains untreated. Their life expectancy is not normal, but many are expected to reach the mid adulthood, e.g. Fontan procedures (Table 29.1).

The total incidence of congenital heart disease (CHD) is 7 to 10 per 1000 live births. About 85% of these children reach the adult life. Among all the other congenital anomalies, the CHD is the most common. It constitutes about 30% of all the congenital diseases. Previously, acquired rheumatic heart disease was the principal cause of all the heart diseases. But with the decline of rheumatic disease, congenital heart disease has become the principal cause of total heart diseases. Among the congenital heart disease the 10 to 15% of patients have associated other congenital anomalies such as the skeletal, genitourinary or gastrointestinal system, etc.

Table 29.1: Incidence of congenital heart disease

Disease	*Incidence (%)*
VSD	40
ASD	10
Pulmonary stenosis	7
PDA	6
Coarctation of aorta	5
Fallot's tetralogy	5
Transposition of great vessels	3

CHD can be classified into:

i. *Acyanotic defects:* Ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), pulmonary stenosis (PS), coarctation of aorta, and atrioventricular septal defect, etc.
ii. *Cyanotic defects:* tetralogy of Fallot, transposition of great vessels (TOGV), Eisenmenger complex, etc.

These above mentioned nine congenital form of heart diseases constitute about 80% of all the total congenital heart diseases. Other wide range of more unusual and complex congenital lesions of heart comprise the remainder 20% of CHD.

The understanding of the development of heart and foetal circulation helps to understand how CHDs occur. The heart develops as a single tube which folds back on itself and then divides into two separate circulation. Failure of this separation can lead to some forms of atrial and ventricular septal defects. Failure of alignment of the great vessel with the ventricles contributes to the transposition of great vessels, tetralogy of Fallot and truncus arteriosus, etc. Due to high pulmonary vascular resistance and as the foetus can not breath in the uterus, so it has little blood flow through the lungs during intrauterine life. The foetal circulation, therefore, allows the oxygenated blood from placenta to pass directly to the left side of heart through the foramen ovale without flowing through the lungs. This oxygenated blood then from LV passes to the ascending aorta. On the other hand, the deoxygenated blood

from RV passes through ductus arteriosus (DA) to the descending aorta and reaches the placenta through the umbilical arteries for oxygenation. The congenital heart diseases (CHD) may arise if the changes from foetal circulation to the extrauterine circulation are not properly completed. ASD occurs at the site of the foramen ovale, if it does not close. Ductus arteriosus may remain open as patent ductus arteriosus (PDA), if it fails to close after birth. The failure of aorta to develop at the point of aortic isthmas can lead to the narrowing or coarctation of aorta.

Among the causes of CHD, antenatal maternal infection, antenatal exposure to drugs or toxins, and genetic or chromosomal abnormalities are the most important factors. Maternal rubella is associated with PDA, pulmonary and/or aortic stenosis and ASD. Maternal alcohol abuse is associated with septal defects. Maternal SLE is reponsible for different forms of congenital heart block of foetus and newborn, causing CHD. However, advances in molecular biology have much helped to understand the genetic basis of CHD. Genetic abnormalities are responsible for 10% of all the congenital cardiovascular lesion. Among these two-third is due to the trisomy-21(Down's syndrome) and one third is due to the trisomy-13, trisomy-18, and Turner's syndrome. Maternal diabetes and use of lithium is also associted with high incidence of CHD. A widely used abbreviation such as CHTCH-22 depicts a syndrome of CHD which is due to the defects in chromosome 22. CATCH-22 syndrome consists of cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcaemia. Another common genetic disorder is Marfan's syndrome which results from the mutations of gene, responsible for the formation of fibrin and a component of extracellular matrix. Marfan's syndrome is characterised by skeletal disproportion (arm span greater than height), arachnodactyly (long, thin, spider like fingers), sternal depression, generalised hypermobility of joints, lens dislocation and a high arched palate. The mitral valve prolapse, aortic incompetence and aortic dissection are the most serious complication associated with Marfan's syndrome (Table 29.2).

The symptoms of CHD may be absent or the child may be symptomatic and breathless. He may fail to attain the normal growth and development. The diagnosis of CHD is apparent during the first week of life in about 50% of the affected neonates and before 5 years of age in virtually all the remaining patients. Some congenital defects of heart are not compatible with extrauterine life or if compatible it is only for a short period. The clinical signs and severity of symptoms of CHD may vary with the type, complexity, and the degree of complexity of anatomical lesion. Early diagnosis is important, because many types of CHD are amenable to surgical treatment. But, this opportunity may be lost, if the secondary changes such as the pulmonary vascular damage and pulmonary hypertension develops. Persistently raised pulmonary flow (e.g. with left to right shunt) leads to increased pulmonary resistance, followed by pulmonary hypertension. Then progressive changes (including obliteration of distal vessels) take place in the pulmonary vasculature and once established, the increased pulmonary resistance becomes irreversible. Hence, if the severe pulmonary hypertension develops, then a left to right shunt which is present from early may reverse, resulting in right to left shunt and marked cyanosis (Eisenmenger's syndrome). This is more common with large VSD or persistant ductus arteriosus than with ASD. The patients with Eisenmenger's syndrome are at the particular risk from abrupt changes in after load that exacerbate R to L shunting during anaesthesia. The younger the patient will be at the time of corrective cardiac surgery, the greater is the likelihood that pulmonary vascular resistance will normalise. In older patients, if pulmonary vascular resistance is greater than 1/3 of SVR during corrective cardiac surgery, then progressive pulmonary vascular changes can not be stopped. Cardiac dysrrhythmias are not usually a prominent feature of CHD. Infective endocarditis is the most common risk factor, associated with congenital heart disease (CHD). Sudden death sometimes occur in CHD patient who have undergone surgical correction. It reflects the myocardial scarring or damage to the cardiac conducting system.

Table 29.2: Congenital heart disease with intracardiac shunt

A. Left to right shunt	VSD
	PDA
	ASD
B. Right to left shunt	Fallot's tetralogy
	Ebstein's anomaly
	Eisenmenger syndrome

Echocardiography is the initial diagnostic step, if CHD is suspected. Both, transthoracic and transesophageal route for echocardiography facilitate the early and accurate diagnosis of CHD. Recently three dimensional echocardiography, Doppler and MRI have increased the understanding of complex cardiac malformation accurately. They also allow the visualization of abnormal blood flow and transposition of vascular structures. Cardiac catheterization and angiocardiography are also definitive diagnostic procedure for patients with CHD.

PREOPERATIVE ASSESSMENT

It helps to gain a clear understanding, regarding the anatomy and pathophysiology of the patient's congenital cardiac defect.

History

At first, patient should be asked about the limitations of his daily activities. It may define clinically the nature and the severity of cardiac lesion. The history may also provide some clue regarding the presence of other anomalies and syndromes associated with CHD.

Examination

To diagnose and to assess the severity of CHD, the patient should be properly inspected, palpated and auscultated. The cyanosis, peripheral oedema and hepatospleno megaly should be searched for. The peripheral pulses, heart and lungs are assessed for murmur, signs of failure and any infection. Cyanosed patients should have a brief neurological examination also (Table 29.3).

Investigation

The laboratory tests obviously depend on the type of proposed noncardiac surgery and the severity of cardiac disease. But, the most patients will require full blood count (FBC), coagulation profile, LFT and electrolytes estimation. Recent chest radiograph, ECG, echocardiography and doppler is done routinely. TEE, MRI and other investigation are done according to the need. For example, some patients may need pulmonary function tests. Baseline SpO_2 level while breathing air is also recorded. Data from cardiac catheterisation and angiocardiography should be kept in mind.

Factors Indicating High Risk

When a patient with CHD is undergoing a noncardiac surgery, they should be balanced between the potential risks and the benefits of proposed surgery. Admission of patient in ICU or HDU or he should be removed to the specialised cardiac centre will depend on the risk factors, playing in individual (Table 29.4).

Table 29.3: Signs and symptoms of CHD

- Asymptomatic
- Dyspnoea, tachypnoea
- Cyanosis
- Failure to gain weight
- Decreased exercise tolerance
- Murmur and thrill
- Thromboembolism
- Erythrocytosis
- Heart failure
- Sudden death

Specific Problems Found in Patients with CHD

The specific problems which are usually encountered during anaesthesia in patients with CHD are:

Myocardial dysfunction

Primarily some forms of myocardial dysfunction, mainly of ventricle, are usually present in all forms of CHD which may lead to the perioperative cardiac failure. Superimposed on it is the secondary cardiac dysfunction which is due to the poor intraoperative myocardial protection.

Arrhythmias

Perioperative all types of arrhythmias may be precipitated during noncardiac surgery on CHD patient. This may be due to the original disease or due to the some iatrogenic (surgery and medications) factors. Some CHD patients develop complete heart block following cardiac surgery and have pacemakers in situ.

Air embolism

All CHD patients are at potential risk from systemic air embolism particularly in ASD, PDA, and VSD with R to L shunt. So, all intravascular lines should be free of air.

Cyanosis

Perioperative cyanosis is common in CHD patients. It is generally due to the intracardiac mixing of oxygenated and deoxygenated blood (e.g. complete atrioventricular septal defect), or shunting of blood from the right side to the left side of heart (e.g. tetralogy of Fallot, Eisenmengers syndrome) or heart failure.

Table 29.4: Factors indicating high risks of patients

1. Unexplained dizziness or syncope,
2. Fever and recent CVA,
3. Recent worsening of symptoms of myocardial ischaemia,
4. Signs and symptoms of cardiac failure,
5. SpO2 < 75% while breathing air,
6. Haematocrit value > 60%, indicating severe polycythemia,
7. Recent onset of arrhythmia,
8. Severe aortic or pulmonary stenosis,
9. Uncorrected tetralogy of Fallot or Eisenmenger's syndrome.

Anticoagulation

Most CHD patients are under anticoagulants like aspirin, warfarin, etc. So, perioperative mangement of these patients undergoing noncardiac surgery is very difficult.

Endocarditis

Most CHD patients are at increased risk from endocarditis. So, preoperative antibiotic prophylaxis are very important.

Myocardial ischaemia

Development of perioperative myocardial ischaemia with CHD patient is very common. So, it should be protected and treated immediately.

Atrial Septal Defect (ASD)

ASD is the second most common (one third) form of all the congenital heart diseases and occurs twice as frequently in females than in males. The atrial septal defect (ASD) is of two types - ostium secundum (most common, 70%) and ostium primum. The ostium secundum involves the fossa ovalis which in intrauterine life remains as the foramen ovale. Whereas, the ostium primum results from the defect of endocardial cushion or from the defect of atrioventricular valves which are associated with the 'left mitral valve' and mitral regurgitation (MR). The more severe form of ASD is the atrioventricular septal defect (AVSD) which is associated with Down's syndrome and results in severe pulmonary hypertension, if not treated in infancy. On the other hand, ostium secundum is associated with mitral value prolapse. Surgical repair of these form of ASD occasionally results in complete heart block. Most ASDs occur as a result of the spontaneous genetic mutation (Fig. 29.1).

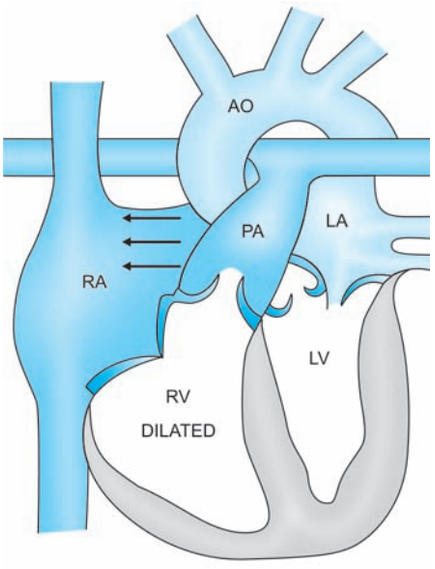


Fig. 29.1: Atrial septal defect

The right atrium and the right ventricle are much more compliant than the left side of the heart. So, a large volume of blood shunts through this defect from the left atrium to the right atrium and then through the right ventricle to the pulmonary artery. As a result, there is gradual enlargement of the right side of heart and pulmonary artery. Thus, gradually pulmonary hypertension and sometimes shunt reversal (R to L) occur in long standing cases of ASD. But it is less common and tend to occur later in life than with other types of L to R shunt such as VSD and PDA. The magnitude and the direction of blood flow through this defect are determined by the size of the defect and the relative compliance of the two atrium and the two ventricles. A small defect in the intertrial septum which is less than 0.5 cm in diameter, is associated with no haemodynamic sequelae. But, when the defect approaches ±2 cm in diameter, then clinical features appear. The ASD in which the pulmonary flow is 50% or above the systemic flow is often considered as large enough to be clinically recognisable and should be closed surgically or through trans arterial catheter technique. Severe pulmonary hypertension and shunt reversal are both taken as contraindication to corrective surgery of ASD.

The chest radiograph of ASD typically shows an enlargement of the heart and the pulmonary artery. The ECG usually shows the right axis deviation and incomplete RBBB. This is because right ventricular depolarisation is delayed as a result of its hypertrophy and dilatation. Echocardiography can directly demonstrate the defect of ASD. Sometimes atrial fibrillation and supraventricular tachycardia may accompany an ASD.

The anaesthetic management of a patient who is suffering form ASD and L to R shunt and is scheduled for noncardiac surgery, has minimal implication. The prophylactic antibiotics is needed to protect against infective endocarditis, if ASD is associated with other valvular abnormalities. During intraoperative management, the changes in SVR has an important implications on ASD. Any increase in SVR favours an increase in the magnitude of left to right shunt and right heart failure. So, it should be avoided during the perioperative period. On the other hand, any decrease in SVR tend to decrease the magnitude of left to right shunt or sometimes becomes reverse if SVR falls to a great extent. Meticulous avoidance of air entry into the intravenous line is imperative in ASD patient.

Ventricular Septal Defect (VSD)

VSD is one of the most common form of all congenital heart disease, occuring once in every 500 live birth. It occurs as a result of the incomplete septation of ventricles. Embryologically the intraventricular septum has a membranous and a muscular portion. The muscular portion is further divided into inflow, trabecular and outflow part. Most ventricular septal defects are of 'perimembranous' type, i.e. at the junction of the membranous and muscular portions (70%). Another 20% of VSD is situated in the membranous portion of the interventricular septum. Next 5% each of VSD is situated just below the aortic valve causing

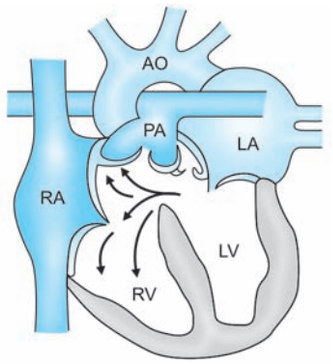


Fig. 29.2: Ventricular septal defect

aortic regurgitation and near the junction of the mitral and tricuspid valve (Fig. 29.2).

The VSD may be an isolated case or becomes a part of a complex congenital heart disease. It may be congenital or acquired. Acquired VSD may result from the rupture of interventricular septum as a complication of acute myocardial infarction or rarely from the trauma. Maximum number of small VSDs close spontaneously when a child reaches 2 years of age.

In VSD blood flows from the high pressure of left ventricle to the low pressure of right ventricle during systole, producing a holosystolic murmur. This is usually heard best at the left sternal edge, and also radiates all over the precordium. A small defect often produces a loud murmur, but contrary a large defect often produces a softer murmur, particularly if pressure in the right ventricle is elevated. This may be found immediately after birth when the pulmonary vascular resistance remains high or when the shunt is reversed—Eisenmenger's syndrome.

Symptoms, signs and pathology produced by VSD depend on the size of the defect, the difference between systemic and pulmonary vascular resistance and the rate of flow through the defect. If the defect is small, the pulmonary and systemic flow ratio is < 1.5:1 and there is no pulmonary hypertension, then there is minimal increase in pulmonary blood flow and patient is asymptomatic. On the other hand, if the defect is large enough and the

pressure in the two ventricles is equal then the flow through the pulmonary and systemic circulation depends on their relative resistance. Initially, SVR is higher than pulmonary vascular resistance and the blood flows from the left ventricle to the right ventricle (L to R shunt). These moderate sized VSD often presents with CCF, due to markedly increased pulmonary blood flow with pulmonary and systemic flow ratio 3:1 or more. These patients require early operation for closure of VSD. However, if they require anaesthesia for another noncardiac surgical procedure prior to their definitive cardiac operation, then they may present severe problems. They should must be intubated in all cases, except the very minor procedures. One should try to avoid increasing the left to right shunt (e.g. avoid hyperventilation and unnecessary high inspired oxygen levels). Care should be taken regarding the fluid administration. Inotropic support is often required. Over the time the pulmonary vascular resistance gradually increases and the pulmonary hypertension develops, causing a decline in the magnitude of L to R intracardiac shunt. Gradually, the shunt become reverse flowing right to left (R to L) with the development of cyanosis and arterial hypoxaemia. Before the development of pulmonary hypertension, these large VSD patients often require pulmonary artery banding to protect their pulmonary circulation. This band may tighten as the child grows, resulting in cyanosis. The VSDs often close spontaneously and the band may then be removed.

Like ASD, the intraoperative anaesthetic management of VSD for noncardiac surgeries includes the control of systemic and pulmonary vascular resistance on which will depend the magnitude of L to R or reverse shunt.

Patent Ductus Arteriosus (PDA)

The ductus arteriosus is a connection which arises from the arch of the aorta just distal to the left subclavion artery, and connects the arch of the aorta with the left pulmonary artery. In foetal life, the pulmonary vascular resistance is high than the systemic vascular resistance. So, the blood from the pulmonary artery, which is ejected out from the RV bypasses the deflated lungs runs through this ductus arteriosus and enters the descending aorta for oxygenation in the placenta. Normally, the ductus arteriosus closes within 24 to 48 hours after birth in a full term neonate. But, in preterm it frequently fails to close, and also sometimes in full term infant. Occassionally the persistance of this ductus arteriosus may be associated with other congenital abnormalities and is much more common in females. When the ductus arteriosus fails to close spontaneously after birth, then it results in continuous flow of blood from the aorta to the pulmonary artery, due to the reduction of pulmonary vascular resistance than systemic resistance after birth. The flow of blood through the patent ductus arteriosus after birth will depend on: the pressure gradient between the aorta and the pulmonary artery, the ratio of systemic and pulmonary vascular resistance, and the diameter and the length of the duct. As much as 50% of the left ventricular output may be recirculated through the lungs with a consequent increase in the pulmonary artery pressure which leads to progressive pulmonary vascular damage and pulmonary hypertension. If the pulmonary vascular resistance increases and the pulmonary artery pressure rises exceeding the aortic pressure, then the shunt will be reversed, flowing from the pulmonary artery to the aorta, causing central cyanosis (Eisenmenger's syndrome) (Fig. 29.3).

With small shunt there may be no symptoms for many years. This small cardiac defect is often detected accidentally during a routine preoperative physical examination. During this time a characteristic continuous systolic and diastolic murmur is heard with late systolic accentuation which is maximal in the second left

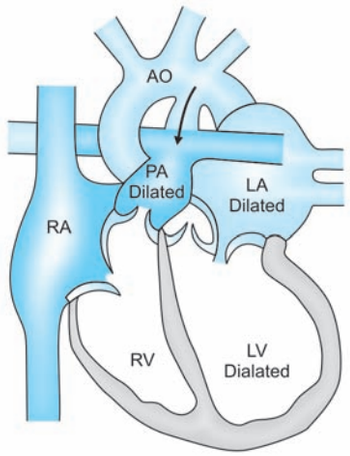


Fig. 29.3: Patent ductus arteriosus

intercostal space below the clavicle. Right ventricular hypertrophy develops, if pulmonary hypertension is apparent.

PDA can be closed surgically or through transcatheter route. Surgical correction of PDA by ligation is associated with low mortality. It is estimated that 75% of preterm infants delivered before 28 weeks of gestation require surgical closure of PDA. Alternative to surgery includes inhibition of the synthesis of prostaglandin with nonselective cyclo-oxygenase inhibitors (cox-1, cox-2). Without surgical closure, most patients with PDA remain asymptomatic, until adolescence when pulmonary hypertension and heart failure may occur. Once severe pulmonary hypertension develops, surgical correction is contraindicated. Ligation of PDA is often associated with significant systemic hypertension during the immediate postoperative period which is managed by continuous infusion of vasodilator drugs such as nitroprusside. If this systemic hypertensive persists, then long acting antihypertensive drugs will gradually substitute nitroprusside.

The first step of anaesthetic management of an uncorrected PDA patient, scheduled for noncardiac surgery, is preoperative prophylaxis by antibiotic for protection against the infective endocarditis. The principal of intraoperative anaesthetic management of PDA patient is also same like ASD and VSD, i.e. maintaining

a balance between the systemic vascular resistance and the pulmonary vascular resistance. The decrease of systemic vascular resistance improves the systemic blood flow by decreasing the magnitude of left to right shunt. But this decrease of SVR will not go below the pulmonary part when reverse shunt will flow and cyanosis will develop. Contrary, increase in SVR and decrease in pulmonary vascular resistance would increase the magnitude of L to R shunt and should be avoided. IPPV of the patient's lung is well tolerated, as increased airway pressure increases the pulmonary vascular resistance and subsequently decreases the pressure gradient between the left and right side of the heart and flow across the PDA.

Tetralogy of Fallot (TOF)

These patients have : (i) pulmonary stenosis, (ii) VSD, (iii) an overriding of aorta on the right and left ventricle and (iv) right ventricular hypertrophy. It is the most common cyanotic congenital heart disease. Right ventricular hypertrophy occurs, because the VSD permits continuous exposure of the right ventricle to the high pressure of left ventricle and pulmonary stenosis, causing right ventricular outflow obstruction. Several other anomalies may be associated with tetralogy of Fallot. These are : right aortic arch, ASD (pentalogy of Fallot), coronary arterial anomalies, etc. The cyanosis in tetralogy of fallot is due to the intracardiac right to left shunt which is again due to right ventricular hypertrophy. The magnitude of RV hypertrophy determines the severity of shunt and the severity of cyanosis. Due to pulmonary stenosis, the flow across the right ventricular outflow tract is relatively fixed. So, changes in SVR (drug induced) may affect the magnitude of the shunt. The decrease in SVR increases the R to L intracardiac shunt and increases the cyanosis with arterial hypoxaemia. Reversely, increase in SVR decreases the R to L shunt and decreases the cyanosis with increased pulmonary blood flow (Fig. 29.4).

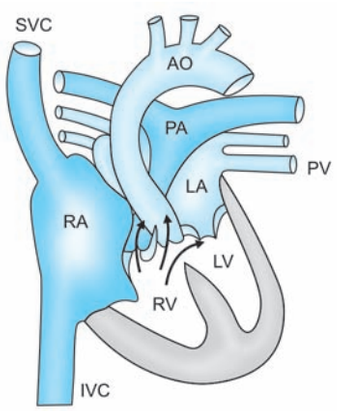


Fig. 29.4: Tetralogy of Fallot (TOF)

The diagnosis of tetralogy of Fallot is usually established by echocardiography and doppler. It assesses: (i) the presence of other associated abnormalities, (ii) the level and severity of right ventricular outflow obstruction, (iii) the magnitude of right ventricular hypertrophy, (iv) the size of the main pulmonary artery and its branches, and (v) the number, location and size of VSD. Cardiac catheterization further confirms the diagnosis by providing different anatomic and haemodynamic data. MRI of heart can also provide much of this information.

Most patients with tetralogy of Fallot present with cyanosis from birth. On examination, murmur is heard along the left sternal border due to the turbulent flow of blood across the stenotic pulmonic valve and VSD. Chest radiograph shows the evidence of decreased lung vascularity and the heart is 'boot shaped'. The right axis deviation and RV hypertrophy is the finding in ECG. Squatting position is the common picture of children with tetralogy of Fallot. Because it is speculated that squatting position increases the SVR by kinking the large arteries in inguinal area and subsequently increased SVR decreases the intracardiac R to L shunt and increases the pulmonary blood flow. The arterial O_2 tension is usually less than 50 mm of Hg. Arterial O_2 desaturation is present even when the patient is breathing with 100% O_2.

Sometimes, paroxymic cyanotic spells occur with severe arterial hypoxaemia, tachypnaea, seizures, and loss of consciousness or even death. These attacks can occur without obvious provocation. But, it is often associated with crying and exercise. The mechanism of this paroxysmal cyanotic spells is not properly known. The probable explanation is that sometimes there is sudden decrease in pulmonary blood flow due to the spasm of infundibular cardiac muscle or sudden decrease in SVR. The management of this paroxysmal cyanotic spell is administration of β-blocker such as esmolol or propranolol. It removes the dynamic infundibular obstruction by relieving the smooth muscle spasm. Cyanotic spell is also managed by intravenous administration of fluids and / or phenylephrine. It helps by increasing the SVR, decreasing intracardiac R → L shunt and increasing the pulmonary blood flow. The sympathomimetic agents with β-agonistic properties are not used. Because they may accentuate the spasm of infundibular cardiac muscle and cyanosis.

The definitive treatment of tetralogy of Fallot is complete surgical correction. Without surgery, mortality exceeds 50% by the age of 3 years. In the past, three palliative procedures were done to improve the pulmonary arterial blood flow. These palliative procedures are: (i) side to side anastomosis of the ascending aorta and the right pulmonary artery, (ii) side to side anastomosis of the descending aorta and the left pulmonary artery and (iii) end and side anastomosis of the subclavian artery to the pulmonary artery (Blalock-Taussig operation). Now, the correction of tetralogy of Fallot is done by the closure of VSD with Dacron patch and the relief of right ventricular outflow obstruction is done by placing a synthetic graft.

The aim of anaesthetic management during the noncardiac surgery of a patient with tetralogy of Fallot is to reduce the R → L intracardiac shunt and, thus, in turn to increase the pulmonary blood flow and

P_aO_2. The magnitude of R → L shunt also alter the pharmacokinetics of both the injected and inhaled drugs that by passe the lungs. The severity of R → L intracardiac shunt can be increased by: (i) decreased SVR, (ii) increased PVR and (iii) increased myocardial contractility which accentuates the infundibular obstruction to blood flow. Contrary, the R → L intracardiac shunt can be reduced by the reversed above mentioned actions. So, the pharmacological agents that decrease SVR such as volatile anaesthetics, nitroprusside, histamine releasing muscle relaxants, α-adrenergic blocking agents, etc, should be avoided. Pulmonary blood flow can be decreased by increasing the PVR that accompany many intraoperative ventilatory manoeuvers such as IPPV, PEEP etc. So, all these should be regulated and controlled. Furthermore, the loss of negative intrapleural pressure on opening the chest increases the PVR and the severity of shunt. But indeed, PaO_2 does not predictably deteriorate, either with institution of IPPV or after opening of the chest, in patients with tetralogy of Fallot and many advantages of intraoperative controlled ventilation usually offset its potential hazard.

During preoperative anaesthetic preparation of patient suffering from tetralogy of Fallot, crying should be avoided which may precipitate the hypercyanotic attack. The β-adrenergic blocker should be continued till the induction of anaesthesia to prevent the cyanotic spell. The induction of anaesthesia is usually accomplished with ketamine which improve the arterial oxygenation by increasing the SVR and thus decreasing the R→L intracardiac shunt. Ketamine also increases PVR which is undesirable in Fallot patients. But, this concern is not clinically significant. Tracheal intubation is facilitated by administration of muscle relaxants. During the use of IV drugs, it should be kept in mind that the onset and magnitude of action of drugs is more rapid in Fallot due to the R → L shunt which decreases pulmonary the dilutional effects of drugs and the metabolism of drug like fentanyl, in lungs. For this reason, it is prudent to decrease the dose of the intravenous cardiac and respiratory depressant drugs in these patients.

For intraoperative muscular paralysis, pancuronium is the agent of choice as it maintains SVR and blood pressure. Pancuronium also increases the HR which is helpful for maintaining the LV cardiac output. Use of N_2O for maintenance of anaesthesia in tetralogy of Fallot has many disadvantages. There disadvantages are: it increases PVR and decreases inspired O_2 concentration. But the advantages of N_2O are; it does not decrease SVR like volatile agents. So, balancing the advantages and disadvantages it seems prudent to limit the inspired concentration of N_2O to 50%. FiO_2 should not be reduced < 50%. Because, increased FiO_2 could decrease PVR and improve PaO_2. The use of volatile anaesthetic agents and opioids may also be considered during maintenance of anaesthesia. But the dose and the rate of administration of these agents must be adjusted to minimise the decrease of SVR.

The intraoperative ventilation for maintenance of anaesthesia should be controlled, but excessive positive pressure may adversely increase the resistance to blood flow through the lungs. The adequate intravascular fluid volume should also be maintained to avoid hypovolaemia. Otherwise, it will increase R → L shunt and cyanosis and hypoxaemia. The α-adrenergic agonist (phenylephrine) should be freely available to treat the undesirable decrease in SVR and BP. For predictable erythrocytosis due to cyanosis, it is probably not necessary to consider the blood transfusion, until about 30% of the patient's blood volume has been lost. Meticulous care should be taken to avoid infusion of air through the tubing which is used to deliver the intravenous solutions as it could lead to the systemic air embolisation.

The patients who have undergone successfully the surgical correction of tetralogy of Fallot are usually asymptomatic. But, still their life expectancy is not so hopeful. The survival rate of them is shortened due to sudden unexplained death. Cardiac dysrrhythmias, particularly ventricular are common in patients following surgical correction of tetralogy of Fallot. Pulmonary regurgitation may develop as a result of surgical repair, leading to RV hypertrophy and dysfunction.

Eisenmenger Syndrome (ES) and Anaesthesia

The persistently raised pulmonary blood flow, due to the L→R intracardiac shunt in large VSD, ASD, etc, leads to increased pulmonary resistance, followed by pulmonary hypertension. Then, progressively the changes like obliteration of distal vessels take place in pulmonary vasculature due to the presence of persistent pulmonary hypertension. Thus, once established, this increased pulmonary resistance is irreversible and pulmonary hypertension becomes permanent. Hence, when severe pulmonary hypertension develops to a level that equals or exceeds the SVR, then L → R shunt is reversed, resulting in R → L shunt and marked cyanosis which is called the Eisenmenger's syndrome. Shunt reversal occurs in about 60% of patients with an untreated VSD, 30% of patients with an untreated PDA and about 20% of patients with an untreated ASD. The murmur which was previously present associated with these cardiac defects gradually disappear when the Eisenmenger's syndrome develops. Patients with Eisenmenger's syndrome are particularly at increased risk from abrupt changes in after load that exacerbate right to left (R → L) shunting, such as vasodilatation, anaesthesia, pregnancy, etc. Central cyanosis appears and digital clubbing develops. The chest radiograph shows the enlarged central pulmonary arteries and peripheral pruning of the pulmonary vessels. The ECG shows RV hypertrophy. Palpitation is common

and is most often due to the onset of atrial fibrillation or atrial flutter. Sudden death is also not uncommon in patients with Eisenmenger's syndrome.

There are many palliative surgeries, but no treatment has proved effective in producing sustained decrease in PVR. The presence of irreversible increased PVR contraindicates the surgical correction of the original CHD that was responsible for Eisenmenger's syndrome.

The Eisenmenger's patients should be managed in a specialist centre whenever possible. The aim of anaesthetic management for patients with ES undergoing noncardiac surgery is to strictly maintain the preoperative levels of SVR and to avoid the vasodilatation by any cost. This is because the degree of shunting depends on the PVR: SVR ratio. So, reduction of SVR (epidural/spinal anaesthesia) and rise of PVR (hypoxia, hypercarbia, acidosis, cold) should be avoided. Decreasing the SVR or increasing the PVR leads to deterioration of blood oxygen saturation, rather like in patients with TOF. Desaturation episode can be treated as like TOF. To maintain the SVR, continuous IV infusions of norepinephrine can be administered during the perioperative period. The inotropic support may be required even for the shortest procedures. All the possible cares for minimisation of blood loss with the development of hypovolaemia should be taken. So, preoperative administration of antiplatelet drugs are not encouraged. Opioids can be used safely for perioperative analgesia.

Laparoscopic procedures are not recommended for ES patients. Because insufflation of peritoneal cavity with CO_2 may cause increase in P_aCO_2, resulting in acidosis and hypotension. Acidosis and hypotension increase the PVR : SVR ratio, causing more R $\rightarrow$ L shunt, cyanosis and hypoxia. Thus a vicious cycle sets up. Efforts to maintain the normocapnia may be accompanied by hyperventilation, increase in airway pressure and PVR which further increases R $\rightarrow$ L shunt. The whole thing further aggravated when IAP increases and the patients is placed in head down position. Early extubation in these patients is better to avoid the deleterious effects of IPPV.

30 Cardiomyopathies and Anaesthesia

INTRODUCTION

Cardiomyopathies are a group of diseases of unknown aetiology, affecting the cardiac muscles. It is unrelated to the usual causes of heart disease such as coronary artery disease, cardiac valvular dysfunction, essential hypertension, etc. It is common to all cardiomyopathies that they lead to a progressive life threatening congestive heart failure. Though, it is of unknown aetiology, still some probable causes for myopathies are defined. These are : idiopathic, ischaemic, infective (viral, bacterial), toxic (alcohol), systemic diseases (muscular dystrophy, collagen vascular disease, sarcoidosis, myxedema, thyrotoxicosis, pheochro mocytoma, etc), infiltrative (amyloidosis, haemochromato sis), nutritional and genetic (familial). The cardiomyopathies are classified on pathological basis into: (i) Idiopathic dilated cardiomyopathy, (ii) Hypertrophic (obstructive) cardiomyopathy and (iii) Restrictive cardiomyopathy. They can all be diagnosed by echocardiography (Table 30.1).

IDIOPATHIC DILATED CARDIOMYOPATHY (IDC)

In this type of cardiomyopathy there is gradual decrease in the contractile force of the left or right ventricle, resulting in systolic failure. It is characterised by the left ventricular (LV) or biventricular dilatation (although in early stages there may be no discernable dilatation), impaired myocardial contractility, decreased cardiac output (CO) and increased ventricular diastolic filling pressure and volume. Among these the ventricular dilatation is the most distinguishing morphological feature of IDC. Ventricular cardiac dysrrhythmias and sudden death are common in patients with idiopathic dilated cardiomyopathy. Peripartum cardiomyopathy is usually of this form and is specifically associated with late pregnancy or the first 6 months of puerperium. But, most often it is manifested in the period of first 1 to 6 weeks after delivery. The clinical course of IDC is unpredictable, although most deaths occur within 3 years of diagnosis, due to progressive congestive heart failure. There are many aetiologies of IDC such as alcohol, drugs, vitamine deficiencies, etc, but the commonest cause of IDC is IHD. The commonest problems encountered with IDC are heart failure, arrhythmias and emboli from the left side of cardiac cavities. Thus, they are treated with combinations of diuretics, ACE inhibitors, vasodilators, anticoagulants, and antiarrhythmics (Fig. 30.1).

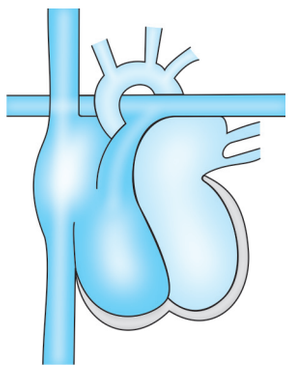


Fig. 30.1: Idiopathic dilated cardiomyopathy

In IDC there is marked reduction in the ejection fraction of the left ventricle and is most often < 0·4 (i.e 40%) when the heart failure supervenes. So, the most common initial manifestation of IDC is congestive heart failure. Though children and elders are also affected, but the most patients with IDC are first seen between 30 to 50 years of life. The haemodynamic abnormalities that predict a poor prognosis of IDC include: ejection fraction < 0.25, LVEDD (left ventricular end diastolic dilatation), hypokinetic left ventricular wall on echocardiography, PCWP > 20 mm of Hg, cardiac indess (CI) < 2.5 litre/min/m^2, systemic hypotension, pulmonary hypertension, and increased CVP.

The chest radiograph may show the evidences of cardiac enlargement, involving the all four cardiac chambers. The ECG investigation characteristically shows the evidence of LVH (left ventricular hypertrophy), ST and T wave abnormalities, and

Table 30.1: Aetiology of cardiomyopathy

- Idiopathic
- Infective – bacterial, viral
- Ischaemic
- Toxic – drugs, alcohol, poisons
- Nutritional
- Infiltrative – amyloidosis, metastasis, haemochromatosis
- Thyrotoxicosis
- Myxoedema
- Sarcoidosis
- Muscular dystrophy
- Collagen disease
- Genetic or familial

bundle brunch block. Different cardiac arrhythmias are also common in IDC. Systemic embolisation in IDC is not uncommon. It reflects the formation of mural thrombus in dilated and hypokinetic left cardiac chamber.

The preanaesthetic management of IDC includes general supportive measures which consist of adequate rest, weight control, controlled physical activity, and abstinence from tobacco-alcohol, etc. The vasodilator therapy by ACE-inhibitors, hydralazine and isosorbide dinitrate is the standard initial treatment. It helps by reducing the myocardial work for patients with symptomatic left ventricular dysfunction due to IDC. Patients with IDC are at increased risk for systemic or pulmonary embolism. As blood stasis occurs in the hypocontractile ventricle, so it leads to activation of coagulation process. Hence, long term anticoagulant therapy should be started in patient with IDC. Usually, warfarin is the drug of choice for long term anticoagulation and is often adjusted to prolong the prothrombin time to an INR (International Normalized Ratio) of 2 to 3. The risk of embolisation is greatest in patients who are suffering from : severe ventricular dysfunction, previous history of embolism, AF and present echocardiographic evidence of thrombus. Digitalis effectively controls the symptoms of congestive heart failure in patients with IDC. Other inotropes such as amrinone, milrinone, or enoxamine do not predictably improve the exercise tolerance like digitalis, when administered alone or in combination with digitalis.

During anaesthetic management of a patient with IDC, the goals are:

i. Prevention of increased ventricular afterload by controlling BP and SVR.
ii. Avoidance of drug induced myocardial depression.
iii. Maintenance of normovolaemia and preload.

During induction of anaesthesia thiopentone, propofol, etc, should be used cautiously avoiding the myocardial depression. During maintenance of anaesthesia, myocardial depression caused by the volatile anaesthetic agents must also be considered against the vasodilating properties of newer volatile anaesthetics which is desirable. Opioids are associated with benign effects on cardiac contractility. So, it can be used judiciously. However, the use of N_2O with opioids may result in unexpected depression of myocardial contractility and pulmonary vasoconstriction. So, an anaesthetist must justify himself regarding the use of N_2O in the cases of IDC according to the merit of individual patient. Skeletal muscle paralysis is provided by nondepolarizing muscle relaxants which do not release histamine and lack significant cardiovascular effects. Tachycardia should be controlled by β_1-antagonist such as esmolol, but keeping in mind the potential of these drugs to cause cardiac depression and severe bradycardia.

The perioperative monitoring of patient, suffering from IDC will depend on the extent of the surgery and the severity of the disease. For determination of cardiac filling pressure and cardiac output (CO), pulmonary artery catheterisation is necessary. It will guide the intravenous infusion of fluid and blood. It will also help in early recognition of volume overload and the need for inotropic support or administration of peripheral vasodilating drugs. On venous pressure tracings, a prominent 'A' wave reflects decreased ventricular compliance and a prominent 'V' wave indicates functional incompetance of tricuspid or mitral valve which is due to the cardiac dilatation. The intraoperative hypotension can be treated by vasopressor such as ephedrine or phenylephrine. The ephedrine provides some degree of β – stimulation, whereas phenylephrine produces α – stimulation which evoke adverse increase in LV afterload, owing to the increased systemic vascular resistance.

In selected patients the regional anaesthesia (RA) may also be an alternative to GA, but caution is indicated to avoid an abrupt onset of blockade of sympathetic nervous system and sudden severe reduction of preload and afterload. The epidural anaesthesia by a catheter produces slow changes in preload and afterload that may meet the goals of management of IDC (Fig. 30.2).

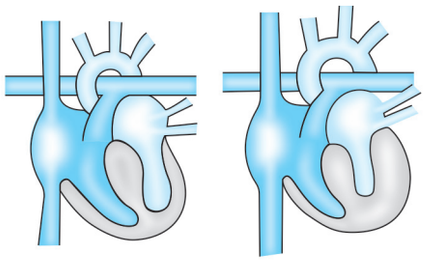


Fig. 30.2: Hypertrophic obstructive cardiomyopathy

HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY (HOCM)

HOCM is an autosomal dominant inherited condition in which there is often massive asymmetrical ventricular hypertrophy and impaired diastolic function, i.e. decreased ventricular diastolic filling causing reduction of cardiac output. It affects the patients of all ages. The excessive muscle bulk of LV wall also obstructs its outflow tract causing obstruction during systole. This HOCM is the most common form of cardiomyopathy with a prevalance of approximately 100 per 100,000 individual. In HOCM, the hypertrophy and fibroris of cardiac muscle mostly affects the septum, but may involve the whole left ventricle. Echocardiography reveals a large variation in the location and the extent of the muscular hypertrophy and fibrosis. Due to ventricular hypertrophy there is also resistance to inflow and therefore diastolic failure is the main problem. Hypertrophy of the septum may also cause dynamic left ventricular (LV) outflow tract obstruction. But, even in the presence of severe LV outflow tract obstruction, ejection fraction is usually more than 0.8 (80%), reflecting the hypercontractile condition of heart.

HOCM presents a great diversity of morphological, functional and clinical features. Some patients remain asymptomatic throughout the in life with HOCM. Some have symptoms of severe CHF and in some sudden death can occur particularly during exercise. The cause of this sudden death in HOCM is ventricular tachydysrrhythmias such as VT and VF. Symptoms and signs of HOCM is similar to those of AS. Marked left ventricular hypertrophy also makes the patient particularly vulnerable to myocardial ischaemia.

Diagnosis of HOCM is made by ECG, X-ray and echocardiography. But, suspicions always should be raised by family history, heaving or double apex, an aortic systolic murmur but without a slow rising pulse like AS. The ECG and chest radiograph are usually abnormal and may show the features of massive LV hypertrophy. ECG usually also depict wide varieties of bizarre and abnormal pattern such as pseudo-infarct, deep T-wave invertion, etc. Massive hypertrophy of intraventricular septum (IVS) presents abnormal Q-wave, mimicing myocardial infarction. The echocardiography is usually diagnostic. However, diagnosis may be difficult when the other causes of LV hypertrophy are present. When the ratio of the septal and LV free wall thickness exceed 1.3:1, then diagnosis of hypertrophic cardiomyopathy should be considered. Echocardiography is also useful for estimating the pressure gradient across the left ventricular outflow tract. Cardiac catheterisation may also demonstrate the presence of elevated LV EDP (left ventricular end diastolic pressure) as a consequence of reduced LV compliance. The reduced LV compliance also produces increased height of 'A' waves during the venous pressure tracing. It may exceed 30 mm of Hg. If severe LV outflow obstruction is present, then there is demonstrable high pressure gradient between the LV and aorta. Systemic thromboembolism is a very common complication of AF which is very commonly found in a patient presenting with HOCM.

Sudden death is an established complication of hypertrophic cardiomyopathy. The Risk factors for sudden death in HOCM are: recurrent syncope, exercise induced hypotension, marked increase in LV wall thickness, multiple episodes of non-sustained ventricular tachycardia (found in ambulatory ECG monitoring), a history of previous cardiac arrest or sustained VT and an adverse family history. Patients with above mentioned three or more risk factors are thought to be at the high risk of sudden death when they suffer from HOCM. Indeed, HOCM is the most common cause of sudden death in young athlets and ventricular arrhythmia are thought to be responsible for many of such deaths in HOCM.

Anaesthetic Management

Though pharmacological therapy to improve the diastolic filling and to decrease the myocardial ischaemia (which is due to massive muscular hypertrophy) is the primary goal of perianaesthetic management for HOCM patient, still there is no treatment that is definitely known to improve the prognosis. The β-blockers and the heart rate limiting calcium antagonists (e.g. Verapamil) have been used extensively to treat HOCM preoperatively. It can also help to relieve the angina and to increase the exercise tolerance by decreasing the heart rate (HR) with consequent prolongation of diastole and increased passive ventricular filling. But, there is no evidence that β-blockers and verapamil protect patients with HOCM from sudden death. Arrhythmias (mainly ventricular fibrillation) are common in such patients and often respond to treatment with amiodarone. Control of arrhythmias in HOCM is very important, because it causes the rapid clinical deterioration by decreasing the diastolic ventricular filling and cardiac output. Dual chamber pacing and surgery are useful in selected patients, particularly those with outflow tract obstruction due to massive muscular hypertrophy. The surgical reduction of the outflow tract obstruction is usually achieved by removing a small amount of cardiac muscle tissue from the ventricular septum. Surgery abolishes or greatly decreases the LV outflow obstruction in most patients. Digoxin and vasodilator may increase the outflow tract obstruction and should be avoided or used with caution only in failure. This is because many of these patients have diastolic dysfunction and require relatively high filling pressures to achieve adequate ventricular filling.

The intraoperative events that cause increased myocardial contractility are not desirable. Because these events may also increase the LV outflow tract obstruction. So, the use of β-stimulant to increase myocardial contractility should be restricted (only in special situation). Anaesthesia and surgery on patients suffering previously from unrecognised HOCM may manifest perioperatively as sudden unexpected hypotension. The administration of atropine in HOCM patient is questionable, as tachycardia could increase LV outflow obstruction and reduce LV filling by reducing the diastolic filling time. On the other hand, the use of scopolamine produces a desirable sedation and no increase in HR. Sedation is important, because it reduces the activation of sympathetic nervous system and LV outflow tract obstruction.

As the reduction of intravascular fluid volume causes the decrease in ventricular filling and subsequent decrease in cardiac output, so the expansion of intravascular fluid volume during the pre-operative period is useful to maintain the intraoperative stroke volume.

During induction of anaesthesia by inducing agents, the possibility of sudden decrease of SVR should be kept in mind, because it will increase the outflow tract obstruction and reduce the cardiac output. On the other hand, the ketamine is not the likely choice as it stimulates

the sympathetic system and increases the myocardial contraction (thus outflow obstruction). The activation of sympathetic system during laryngoscopy and intubation should be minimised by any cost by different procedures which are described before due to the same reasons.

The volatile anaesthetic agents which causes the reduction of myocardial contractility, but does not decrease the SVR is the ideal for HOCM patient. So, in such patient halothane is ideal. But there is no such evidence that volatile anaesthetic agents, other than halothane, is detrimental for such patients. As opioids do not produce myocardial depression, so they are likely the choice for maintenance of anaesthesia. But, the opioid and N_2O combination can not be used, because it produces the myocardial depression and increases SVR.

The nondepolarising muscle relaxants with minimum effects on cardiovascular system are the choice. In this regard, pancuronium associated with increased heart rate is not desirable. Intraoperative hypotension may be due to decreased preload or afterload or both. It should be monitered correctly by invasive method such as intra-arterial canulation, pulmonary artery catheterisation or transoesophageal echocardiography. Hypovolaemia or vasodilatation can precipitate the myocardial ischaemia and rapid decompensation. So, it should be avoided by any cost. When hypotension occurs, then drugs with predominantly α-adrenergic activity, such as phenylephrine in the dose of 50 to 100 mg IV or metaraminol are useful for normalizing the systemic BP. Drugs with predominantly β-adrenergic agonist activity such as ephedrine, dopamine or dobutamine are not recommended. Because these drugs cause increase in myocardial contractility and HR. Thus, they can increase the LV outflow tract obstruction. Intraoperative persistent increased systemic hypertension can also be treated by the gradual increase in the concentration of volatile anaesthetic agents. But, the vasodilators such as nitroprusside, nitroglycerine, etc. should not be used, as the decreased SVR produced by them can accentuate the LV outflow tract obstruction.

The factors that increase the outflow tract obstruction in HOCM are: increased myocardial contractility (β-adrenergic stimulation, digitalis, tachycardia); decreased preload (hypovolaemia, vasodilators such as nitroglycerine and nitroprus side) and decreased after load (hypotension, vasodilators, hypovolaemia).

The factors that decrease the outflow tract obstruction in HOCM are : decreased myocardial contractility (β-adrenergic blocker, volatile anaesthetics-halothane, calcium channel blockers); increased preload (hypervolaemia, bradycardia) and increased afterload (β-adrenergic stimulation, hypervolaemia).

RESTRICTIVE CARDIOMYOPATHY

It is the least common form of all the cardiomyopathies. In this rare condition, ventricular diastolic filling is impaired, because the walls of the ventricles are 'stiff'. Amyloidosis is the most common cause of stiff ventricle and the restrictive cardiomyopathy. However, the other causes of restrictive cardiomyopathy are glycogen storage disease, perimyocytic fibrosis, familial, etc. The increased stiffness of ventricular myocardium causes pressure within the ventricles to be increased precipitously with only small volume of filling. Therefore, there is impaired ventricular filling, but no apparent diastolic dysfunction. The systolic function of ventricle usually remains normal. The diagnosis of restrictive cardiomyopathy is generally considered in patients presenting with congestive heart failure, but there is no evidence of cardiomegaly or systolic dysfunction or hypertrophy.

The clinical presentation of restrictive cardiomyopathy is like constrictive pericarditis. Both the hearts (left and right) are affected equally. So, it may cause symptoms and signs of right and / or left ventricular failure. Diagnosis of restrictive cardiomyopathy is very difficult and may require investigations like complex doppler echocardiograph, CT scan, MRI, or endomyocardial biopsy. It is usually diagnosed by the method of exclusion. It also must be differentiated from the age related changes in ventricular diastolic compliance. The treatment of restrictive cardiomyopathy is symptomatic, but the prognosis is usually poor. AF is common in patient with restrictive cardiomyopathy. Angina pectoris does not occur in such patients.

The anaesthetic management of patients with restrictive cardiomyopathy includes the same principles which are described for patients with other myopathies, usually those which are associated with ventricular diastolic dysfunction. Atrial fibrillation is common in restrictive cardiomyopathy and by removing the artial contributing part to the ventricular filling, it may worsen the exiting diastolic dysfunction of LV with severe reduction of CO. So, maintenance of normal sinus rhythm is very important. It can be achieved by digitalis or amiodarone or β-blockers or cardioversion or by pace making. At the one hand, as the stroke volume tends to be fixed in the presence of restrictive cardiomyopathy, so the normal maintenance of venous return and intravascular fluid volume is essential for maintaining the normal cardiac output (CO). On the other hand, this form of myopathy is usually associated with pulmonary and systemic venous congestion which should be treated with diuretics. However this diuretics may further decrease the ventricular filling pressure and cardiac output. So, it should be used very cautiously. Anticoagulation with warfarin is likely with the aim to reduce the risk of embolic complications. The presence of anticoagulation and fixed CO may influence the decision of regional anaesthesia. The intraoperative monitoring is like other cardiomyopathies.

31 Pulmonary Diseases and Anaesthesia

INTRODUCTION

The successful anaesthetic management of patients with pulmonary or respiratory diseases depends on: (i) the accurate assessment of the nature of pulmonary diseases, (ii) the extent of functional impairment of lungs due to these diseases, and (iii) the appreciation of the effects of surgery and anaesthesia on that already impaired pulmonary function of this patient. All these factors are inter-related and among these the assessment of pulmonary function before anaesthesia and surgery is the most important. This is because on it depends the future anaesthetic plan of action. Again the proper assessment of functional impairment of lungs depends on the careful history, the careful examination of the patient the additional pulmonary functional tests, CT scan, MRI, etc.

THE EFFECTS OF ANAESTHESIA AND SURGERY ON PULMONARY FUNCTIONS

Effects of Anaesthesia

Anaesthesia affects the pulmonary functions in the following ways:

i. In normal patient general anaesthesia induces the reduction of FRC by about 450 ml (15 to 20%). The normal value of FRC in a healthy individual is 3000 ml. This reduction of FRC is due to the loss of tone of respiratory muscles, such as diaphragm, intercostal muscles, etc. In morbidly obese patient this reduction of FRC may be up to 50% of the normal value in an anaesthetised supine healthy individual. On the othe hand, ketamine does not reduce the muscle tone and consequently FRC is not reduced so much. Contrary, it is maintained at the preanaesthetic level.
ii. In normal situation anaesthesia decreases both the tidal volume and the lung compliance. This is due to the movement of diaphragm cranially and the rib-cage inwardly. Airway resistance also increases slightly after general anaesthesia due to these causes.
iii. Closing volume or capacity (CC) is the lung volume at which the closure of small airway begins. In unanaesthetized patient CC <FRC. But under general anaesthesia CC > FRC and airway closure with air trapping occurs before the lung volume reaches the FRC value. This is more common in elderly, smokers and those with underlying lung diseases.
iv. Intubation reduces the dead space to the half of the normal value by circumventing the upper airway. But the alveolar dead space rises from 50 to about 70 ml.
v. In over 80% of subjects, intubation causes atelectasis in the dependent portion of lungs. As a result 10% of the pulmonary blood flow is shunted through this areas of low V/Q ratios resulting hypoxia and hypercarbia.
vi. In anaesthesia the ventilatory response to hypoxia and $\uparrow PCO_2$ is blunted and the acute response to hypoxia and acidaemia is almost abolished by anaesthetic vapours at concentrations of as low as 0.1 MAC.
vii. Most of these adverse effects induced by anaesthesia usually improve within few hours, post-operatively. But, they are more marked and improvement is delayed in patients with lung diseases. After surgery they may last for several days.

Effects of Surgery

Surgery affects the respiratory functions in two ways—site of surgery and existing pulmonary disease.

i. The site of surgery has major implication on the respiratory functions and the incidence of complications. For example, lower abdominal surgery is associated with pulmonary complication only in 2 to 5% of cases of the general surgical population. But, this incidence of pulmonary complications in upper abdominal surgery goes up to about 20 to 40%. This incidence is more higher in thoracic surgery and it is because following thoracic and upper abdominal surgery, there is shallow respiration, inability to cough effectively and reduction of lung volumes. All these factors lead to poor basal air entry and sputum retention. Thus, this produces atelectasis and/or infection. The incidence and severity of these complications can be reduced by effective post-operative analgesia, early mobilisation and physiotherapy.
ii. Patients with already underlying pulmonary diseases are at increased risk of

developing pulmonary complications during and after surgery. Complications are minimised if the underlying conditions are identified and optimally controlled preoperatively.

HISTORY

For the assessment of pulmonary function history is very important. In history the six cardinal symptoms of respiratory diseases which are commonly asked for are: cough, sputum, haemoptysis, dyspnoea, wheeze, and chest pain. Now, among these cardinal symptoms, the detailed history regarding dyspnoea provides the best assessment for the functional impairment of lung. So, specific question is required to elicit the extent to which the activity is limited by dyspnoea. Dyspnoea at rest or during minor activities clearly indicates severe pulmonary and cardiac disease. Again for evaluating a patient with dyspnoea, one should first determine the duration over which the symptoms have become manifested. When it develops in acute form over a period of hours, the patients can have acute diseases, affecting the airways or lung parenchyma such as acute asthma, acute pulmonary oedema or acute bacterial infection – pneumonia. In other causes of acute dyspnoea, the patient can have acute diseases affecting the pleural space or the pulmonary vasculature such as pneumothorax or pulmonary embolism or the acute cardiac causes.

The subacute presentation of dyspnoea over days or weeks suggests an exacerbation of the pre-existing airway disease such as asthma or chronic bronchitis. It may also be due to the slowly progressing inflammatory process of lung parenchyma (infective or noninfective) or slowly progressing pleural diseases such as pleural effusion from varieties of possible causes or chronic cardiac disease.

The chronic presentation of dyspnoea over months or years often indicates chronic obstructive lung disease (COLD) or chronic cardiac disease. Chronic disease of airways such as COLD and asthma are characterised by periodic exacerbations and remissions of symptoms. So, patients have severe symptoms interspersed with periods in which the symptoms are minimal or absent. Ideally in such situation anaesthesia is given and surgery is performed when the patient is optimally controlled. Any respiratory symptoms suggestive of cardiac disease such as orthopnoea, paroxysmal nocturnal dyspnoea, etc, also should be noted. Dysponea can be graded using Roizen's classification. Undiagnosed dyspnoea of grade II or above should be investigated further (Table 31.1).

Among other cardinal symptoms, after dyspnoea, cough always indicates the presence of active lung disease, but does not help in differential diagnosis. The Presence of other symptoms with accompanying cough always suggests the airway diseases and may be seen in asthma, chronic bronchitis, pneumonitis, etc. A productive cough with expectoration of purulent sputum always indicates an active infection. The chronic copious sputum production may indicate bronchiectasis.

Haemoptysis can originate from the pathology of airways, lung parenchyma or pulmonary vasculatures. The disease may be inflammatory such as bronchitis, bronchiectasis, cystic fibrosis, or neoplastic such as bronchogenic carcinoma. Haemoptysis may also be due to the localised pathologies such as pneumonia, lung abscess, tuberculosis or due to diffused pathologies such as Goodpasture's syndrome, idiopathic pulmonary haemosiderosis, etc. The vascular diseases whic are potentially associated with haemoptysis, include pulmonary thromboembolic disease or pulmonary arteriovenous malformation.

Table 31.1: Roizen's classification of dyspnoea

Grade 0	No dyspnoea while walking at normal space on the ground level.
Grade I	Taking time the patient can walk as far as he likes without dyspnoea.
Grade II	Patient can move only few corners of the street without dyspnoea.
Grade III	Dyspnoea on mild exertion, i.e after walking a few steps.
Grade IV	Dyspnoea at rest.

Chest pain is another common respiratory symptom other than dyspnoea, cough and haemoptysis. It is usually due to the involvement of parietal pleura. This chest pain is often referred to as the pleuritic pain and is accentuated by respiratory movement. The common causes of this pleuritic pain are inflammatory disorders, or neoplasm. Again the inflammatory disorders may be due to the pleura itself such as pleuritis, or parenchymal disorders that extend upto the pleural surface such as pneumonia, pulmonary infarction, etc.

A history of smoking and occupational exposure to dust or fumes may suggest pulmonary pathology. The smoking history should include : the number of years and the intensity of smoking. The cigarette smoke contains highly additive nicotine and other 4700 chemical compounds. Among these 43 are known to be carcinogenic. The long-term smoking causes serious underlying problems such as COLD, IHD, vascular diseases, lung neoplasm, etc. In smokers the mucus is produced in large quantities from the respiratory tract but is cleared less efficiently due to the impaired mucociliary function. In such patients the airways remain hyperreactive and there is impairment of both the cell mediated and humoral immunity. These changes make the smokers more susceptible to respiratory complications during anaesthesia and also to post-operative atelectasis or pneumonia. The co-existing obesity with lung diseases also increases this pulmonary complications. Increased airway irritability by smoking or dust increases cough, laryngospasm and early desaturation of Hb during induction of anaesthesia by volatile anaesthetic agents, especially isoflurane. This can be avoided by using less irritant volatile anaesthetic

agents such as sevoflurane or halothane or intravenous agent such as propofol or deepening anaesthesia slowly when the volatile anaesthetic agens are used. During maintenance of anaesthesia by spontaneous respiration through ETT or LMA, it may be trouble.some due to airway irritation (Fig. 31.1).

If the patient now is not a smoker, then the duration of cessation of smoking should also be enquired. Before anaesthesia and surgery the minimum 8 weeks abstinence from smoking is required to decrease the morbidity from respiratory complications to a rate which is similar to that of nonsmokers. In very resistance cases if it is not possible, then patient can get benefit by restraining from smoking for at least 10 hours before surgery and anaesthesia. During this period the effects of nicotine, i.e activation of sympathoadrenergic system with raised coronary vascular resistance will wear off. Carboxy haemoglobin which may reach 5 to 15% in heavy smokers will also fall during this period of abstinence. Carboxy-Hb reduces the O_2 carrying capacity of blood by shifting the O_2-Hb dissociation curb towards left. Again carboxy-Hb has similar absorption spectrum to O_2-Hb. This causes the pulse oximeters to give a falsely high O_2 saturation reading. The risk of lung cancer falls progressively with increased interval following discontinuation of smoking. The loss of lung function above the expected age related decline also ceases with the discontinuation of smoking.

Fig. 31.1: Graphical representation of decline in FEV_1 annually in susceptible smokers. The blue line at the top shows the normal decline of FEV_1 within age, non smoker. The red line represents the smokers. When smoking is stopped, then the subsequent decline of FEV_1 is similar to that in healthy nonsmokers, represented by dotted red line

A detailed drug history of a patient with pulmonary diseases, going for surgery and anaesthesia, is important. The long-term steriod therapy within 3 months of the date of surgery and anaesthesia necessitates the augmented cover by steroid during the perioperative period and may cause hypokalaemia and hyperglycaemia. Bronchodilator should be continued during the perioperative period if it is used before. It should also be kept in mind that patients with corpulmonale may be receiving digoxin and diuretics which may interact with anaesthetic drugs.

The recent history of respiratory tract infection is also very important like other histories before administering any anaesthesia. There is some evidence that the incidence of laryngospasm is increased in patients with a recent history of upper respiratory tract symptoms. The patients who have active respiratory tract infections producing fever and cough, and with or without chest signs on auscultation, should not undergo elective surgery under general anaesthesia. Because it is associated with increased perioperative risk of pulmonary complications. But adult patients with simple coryza are not at the significantly increased risk of developing perioperative pulmonary problems, unless they have preexisting respiratory diseases or are having major abdominal and thoracic surgery compared with asymptomatic patients. Children with symptoms of acute or recent URTI are more likely to suffer from more incidences of laryngospasm, ronchi, creps and post-operative hypoxaemia (SPO_2 < 93%). This is more marked when intubation is performed.

EXAMINATION

For the assessment of lung condition and pulmonary function like history the physical examination is also very important. A full physical examination of patient is done with the aim of detecting the signs of airway obstruction or increased work of breathing or active infection or evidence of heart failure, because all these can be treated preoperatively. The full physical examination of a patient includes: inspection, palpation, percussion and auscultation of the respiratory system. But among these examinations, the auscultation is most important. During auscultation, both the quality and intensity of breath sounds in both the lungs should be looked for the presence of any extra or adventitious sounds. Normal breath sound is heard through the stethoscope at the periphery of the lung. These are dscribed as vesicular. In it the inspiration part is louder and longer than expiration. When the sound transmission is improved through the consolidated lung, then the resulting bronchial breath sound is of more tubular in quality and is characterised by more pronounced expiratory phase. The primary adventitious or abnormal sounds that can be heard by stethoscope during auscultation include crackles (rales), wheezes and ronchi. The crackles represent the sound which is created when the alveoli and the small airways open and close during respiration. Therefore, often they are associated with interstitial lung disease, microatelectasis or filling of alveoli by liquid.

Wheezes which are generally more prominent during expiration than inspiration reflect the oscillation of the walls of the airways that occurs when there is obstruction of airflow. Thus, it is produced by bronchospasm, airway oedema, collapse or intraluminal obstruction by neoplasm or secretions. Ronchi is the term applied to the sounds which is created when there is free liquid in the airway lumen. The interaction between the free liquid in the airway lumen and the moving air through it creates a high-pitched vibratory ronchi sound. Other adventitious sounds during auscultation of lung include pleural friction rubs and

stridor. The gritty sound which is produced by the pleural friction indicates inflamed pleural surfaces, rubbing against each other. It is heard both during inspiratory and expiratory phases of respiratory cycle. Stridor represents the flow of air through a narrowed upper airway which occurs primarily during inspiration.

After the meticulous examination of respiratory system, a careful general physical examination of the whole body is also mandatory. This is because a number of systemic diseases such as systemic lupuserythematosus, scleroderma, rheumatoid arthritis, etc. may affect the respiratory system. So, they may be associated with pulmonary complications, even though their primary clinical manifestations and physical findings are not related to lungs. Conversely, other diseases that most affect the respiratory system, such as sarcoidosis, can have findings on physical examinations with other systems which are not related to the respiratory system. So, they have findings which are not related to the lungs such as ocular findings (uveitis, conjunctival granuloma) and skin findings (erythema nodosum, cutaneous granulomas).

INVESTIGATIONS

X-ray

To evaluate the respiratory system of a patient who is presented for anaesthesia and surgery with the history of pulmonary diseases, chest radiograph is often the initial and the most important diagnostic procedure. This is because it can provide the initial evidence of pulmonary disease in patients even who are still free of respiratory symptoms at present. The example of this is the accidental finding of one or more nodules or a big mass when chest X-ray is performed due to reason other than the evaluation of the respiratory symptoms. Radiographhic findings even in the absence of respiratory symptoms often indicate localised disease affecting the local airways or a discrete disease affecting the whole pulmonary parenchyma. One or more nodules, or a large mass may suggest intrathoracic malignancy. But they can also be the manifestation of a current or previous infective process. On the other hand, the patients with diffuse parenchymal lung disease, evidenced by radiographic examination, may be free of symptoms, as is sometimes seen in the case with pulmonary sarcoidosis.

A localised opacity involving the lung parenchyma is usually characterised by having an alveolar or a nodular pattern. In contrast, the increased radiolucency can be localised as occurs with a cyst or bulla, or generalised as seen with emphysema. The chest radiograph is also particularly useful for the detection of pleural disease. An abnormal picture of the hila and / or the mediastinum structure can suggest a mass or enlargement of lymph nodes. Patients with respiratory symptoms, but a normal chest X-ray most commonly have diseases of airway. This is happened in asthma, COPD or interstitial lung disease, etc. Chest X-ray is also normal in respiratory symptoms when there is disorder of respiratory pump mechanism, i.e chest wall and neuromuscular apparatus controlling the movement of chest wall. Here, the pulmonary function test is helpful for diagonosis.

The preoperative chest X-ray is a poor indicator of the functional impairment of lungs. But, still it is important for several following reasons for the preoperative evaluation of respiratory system:

i. It helps as baseline to assess the postoperative radiographs.
ii. It helps to discover any localized disease of lungs and pleura which are not symptom producing and are not detected on clinical examination such as small neoplasm, small collapse or consolidation, not symptoms producing effusion, etc.
iii. To reveal the underlying generalised lung disease in patients presenting with acute pulmonary symptoms such as pulmonary fibrosis, emphysema, etc.

CT

For proper diagnosis of pulmonary diseases which have tremendous impact on the mode and the result of anaesthesia, preoperative CT (Computerised Tomography) offers several advantages over the routine chest X-ray. It is better for characterising the tissue densities which helps in distinguishing the subtle differences between the adjacent structures and providing accurate assessment of the size of the lesions. It is particularly valuable in assessing the hilar and mediastinal structure and its diseases, in identifying diseases adjacent to the chest wall or spine, in identifying the areas of fat bodies (pulmonary fat embolism) in lungs and calcification of pulmonary nodules. For the diagnosis, assessment and staging of malignant mediastinal diseases, CT is the most important tool among all. By the use of contrast material, CT also makes it possible to distinguish vascular from nonvascular structures. Helical CT scanning which is more informative than conventional CT allows the collection of continuous data over a large volume of lung tissue, during a single breath-holding manoeuver. With High Resolution CT (HRCT) the thickness of individual cross- sectional images is approximately 1 to 2 mm, rather than the usual 10 mm. Images in HRCT are reconstructed using high spatial resolution algorithms. The detail that can be seen in HRCT scans allows better recognition of any subtle parenchymal and airway diseases such as bronchiectasis, emphysema and diffuse parenchymal diseases.

MRI

MRI provides less described view of the airways and pulmonary parenchyma than CT. So, the role of MRI in the evaluation of pulmonary diseases is less well defined. But, MRI has certain advantages over CT in certain clinical circumstances. For example by MRI the vascular structures can be easily distinguished from the nonvascular structures without the need of

contrast media. Flowing blood does not produce signal on MRI. So, vessels appear as hollow tubular sturctures in MRI. This feature is helpful in determining whether abnormal hilar or mediastinal structures are of vascular origin or not. For diagnosis of aortic lesions such as aneurysm or aortic dissection, MRI is extremely helpful. Another advantage of MRI over CT is that it can be reconstructed in sagittal, coronal and transverse plane, whereas CT is constracted only in transverse plane.

Other radiological investigations except X-ray, CT and MRI for accurate diagnosis of pulmonary diseases are: scintigraphic imaging and pulmonary angiography. In scintigraphic imaging, the radioactive isotopes such as albumin macro aggregates lavelled with technetium 99 m or radio labeled xenon gas are administered either through intravenous or inhalational route, respectively. It is most commonly used in ventilation – perfusion lung scanning (V/Q scan), and for evaluation of pulmonary embolism. The IV isotopes demonstrate the distribution of blood flow. Whereas the inhaled isotope demonstrates the distribution of ventilation. Thus, perfusion – ventilation mismatch is constructed. One such example is pulmonary embolism where there is defect in perfusion, but no defect in ventilation. Another common use of such radioisotope scan is for the diagnosis of impaired lung function which is being considered for lung resection. The distribution of isotope also can be used to assess the regional distribution of blood flow and ventilation. The pulmonary arterial system can also be visualised by pulmonary angiography, in which radio opaque contrast media is injected into the pulmonary artery through a catheter which is previously threaded. Pulmonary angiography demonstrates the intravascular clot (pulmonary embolism) either as filling defect in the lumen of vessel (filling defect sign) or as an abrupt termination of a vessel (cut off sign). In patients with abnormal chest radiograph this test is often difficult to interpret.

The ultrasound imaging is not useful for evaluation of the pulmonary parenchymal diseases. Because the ultrasound energy is rapidly dissipated in air. USG is only helpful for detection and localisation of pleural fluid and as a guide for placement of a needle for thoracocentesis.

Measurement of Diffusing Capacity or Transfer Factor (TLCO)

The transfer factor or diffusing capacity is the measurement of lung's ability to transfer gas from alveoli to blood. This test utilizes the uptake of carbon monoxide by a single breath from a 0.3% mixture of it in the air. This gas is chosen, because it combines rapidly with Hb and provides a true estimation of diffusion or transfer across the alveolar capillary membrane. The diffusing capacity or transfer factor is reduced in patients with disease, principally affecting the alveoli such as fibrosis, alveolitis, emphysema, etc. The transfer coefficient is the measurement of diffusing capacity expressed per volume of ventilated lung during the single breath test. This is useful to confirm that a low diffusing capacity is due to alveolar disease rather than maldistribution of ventilation. The high values of diffusing capacity may be seen in alveolar haemorrhage (Table 31.2).

The measurement of H^+ ion concentration, P_aO_2, P_aCO_2 and bicarbonate concentration in arterial blood is essential in assessing the respiratory function, the degree and type of respiratory failure and for measuring the overall acid-base status. A preoperative baseline provides a guide- line for the further patient's management. It should be measured in anyone suffering from mild to severe dyspnoea on minimal exertion. CO_2 retention will be detected and the efficiency of oxygenation is assessed. A resting P_aCO_2 > 6 kPa suggests pulmonary complications and pending ventilatory failure.

Table 31.2: Patterns of abnormal ventilatory capacity in spirometry

	Asthma	*Emphysema*	*Lung fibrosis*
FEV_1	↓	↓	↓
VC	↓	↓	↓
FEV_1 / VC	↓	↓	N
TLCO	N	↓	↓
KCO	N	↓	↓
TLC	↑	↑	↓
RV	↑	↑	↓

↓ = Decreased, N = Normal, ↑ = Increased

Pulmonary Function Test (PFT)

From anaesthetic point of view, the PFT (Pulmonary Function Test) is very helpful for determination of pulmonary functional reserve which deteriorates due to different pulmonary airways and parenchymal diseases and the effect of bronchodilators on these diseases. So, the pulmonary function test is discussed in detail in separate chapter. But few parameters of it are discussed here. These are : peak flow, spirometry and flow volume loops.

Peak flow

For evaluation of airway obstruction, the measurement of airway resistance is specific and sensitive. But the measurement of resistance is not easy and is very cumbersome. So, the airway obstruction is commonly evaluated by the measurement of maximal forced expiration or maximal midexpiratory flow rate (MMEFR). The simplest of such measurement is the peak expiratory flow rate (PEFR). This is conveniently measured by a variable orifice flow meter at bed side. The main disadvantage of this peak flow value is that it is highly dependent on personal effort and subject's cooperation. So the result vary significantly. However, as the variation of measurement in the same subject is surprisingly low, so the peak expiratory flow is fairly a reproducible test of airway function. A single result of peak expiratory flow has no value. So, serial measurement only indicates deterioation. PEF of less than 200 L/m indicates that effective coughing is difficult and pulmonary complications rate are high (Fig. 31.2).

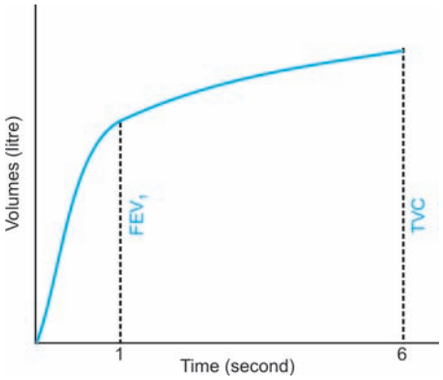


Fig. 31.2: Graph represents the peak expiratory flow, demonstrating forced expiration in first one second (FEV1) and total vital capacity (TVC) in next part of expiration

The another extensively used indirect evaluation of airway obstruction is FEV_1 (forced expiratory volume in first 1 second). It is the fraction of VC which is expired during the first second of a forced expiration. So, it is also called the timed vital capacity. The VC is the largest amount of air that can be expired after a maximal inspiratory effort. The FEV_1 is frequently measured clinically as an index of pulmonary function and gives a useful information about the strength of the respiratory muscle. FEV_1 also gives additional information, because the VC may be normal but the FEV_1 reduces in diseases such as airway obstruction (e.g. asthma) in which the airway resistance is increased by bronchial constriction (Table 31.3).

Table 31.3: Abbreviation used In pulmonary function testing in spirometer

Abbreviation	*Stands for*
TV	Tidal volume
IRV	Inspiratory reserve volume
ERV	Expiratory reserve volume
VC	Vital capacity
RV	Residual volume
IVC or IC	Inspiratory vital capacity
FEV_1	Forced expiratory volume in first 1 sec
FVC	Forced vital capacity
PEF	Peak (maximum) expiratory flow
TLC	Total lung capacity
FRC	Functional residual capacity
TLCO	Gas transfer factor for CO
KCO	Transfer coefficient for CO
TV	Volume of air inhaled or exhaled during normal breathing.
VC	Maximum volume of air that can be exhaled after a forced inspiration, i.e. VC = TV + IRV + ERV
RV	Volume of air that remains in lungs after ERV (maximum expiration).
IRV	Maximum volume of air that can be inhaled after a normal tidal inspiration.
ERV	Maximum volume of air that can be exhaled after a normal tidal expiration.
FRC	Volume of air that remains in lungs after a normal tidal expiration.
FEV_1	Volume of air exhaled in first one second during complete forced expiration.

Spirometry

Simple spirometry should be a routine procedure and carried out by all the doctors when assessing a patient who is breathless. It has been widely used to assess the functional reserve of lungs and magnitude of risks in patients with significant pulmonary diseases, scheduled for major surgery and anaesthesia. It can also be used as a bedside method using a device of bellow or in the investigating centre using sophisticated instrument. In spirometer different pulmonary volumes are studied by recording graphically the changes of volume of lungs under different condition of respiration. This graphical recording of different volume of lungs is called the spirogram or spirography which is represented in picture. The different abbreviations used in PFT by spirommeter is also shown in table. All the present results of spirometry are compared with the predicted normal values which are based on age, sex, height and ethnic group. Normally, the forced vital capacity (FVC) is measured along with forced expiratory volume in 1 second (FEV_1) and the ratio of FEV_1 / FVC is measured as percentage. Normally the FEV_1 / FVC ratio is > 70%. But when it is less than 70%, it indicates airflow obstruction. In obstructive symptoms the reversibility using inhaled short-acting β_2-adrenoreceptor agonists (e.g. salbutamol or terbutaline) also can be tested. Full reversibility is diagnostic of asthma. If time permits and the patient has undertreated obstructive disease, then a course of steroids (prednisolone 20 to 40 mg daily for 7 days) should be assessed for effectiveness (Fig. 31.3).

Recently, the evidences suggest that spirometry does not always predict perioperative pulmonary complications, even in patients with severe COPD. Only specific subgroups may be benefited such as (i) those with unclear diagnosis or those with equivocal clinical and radiological findings, (ii) those where functional impairment of lungs cannot be assessed due to extreme disability.

There are no spirometric values which should be considered as prohibitive for surgery. Despite poor preoperative spirometry result, many series of patients undergoing thoracic and major non-thoracic surgery are being increasingly reported. A FEV_1 less than 1000 ml indicates that post-operative coughing and secretions clearance will be poor and increases the likelihood of a period of respiratory support following major surgery.

Flow-volume loop (F-V loop)

Sometimes, there is no clinical evidence of bronchial asthma, COPD, etc. but findings of reduced peak flow rate and FEV_1

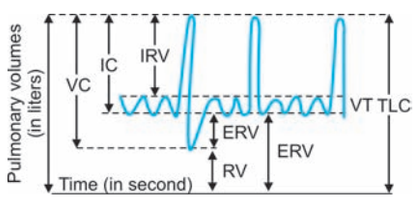


Fig. 31.3: Schematic diagram of normal spirogram showing different pulmonary volumes

is present. This indicates the presence of upper airway obstruction such as in larynx, pharynx or trachea. In such situation F-V loop is helpful in differentiating between the upper airway obstruction in pharynx, larynx or trachea (extrinsic obstruction) and diffuse airway obstruction such as asthma, COPD, etc. (intrinsic obstruction). In addition, they also provide useful data about the severity of obstruction of airway and restrictive pulmonary diseases. The F-V loop not only helps in suspecting upper airway obstruction, but may also help to localize the site and the nature of obstruction (Fig. 31.4).

In F-V loops the flow and volume are plotted on an X and Y axis respectively. Several characteristic patterns of F-V loop have been described among which few are discussed below. In fixed obstruction such as a growth in larynx, no significant change in airway diameter occurs during inspiration and expiration. As a result the inspiratory and expiratory phase shows a plateau of constant flow over the effort dependent portion of vital capacity. In variable upper airway obstruction (extrathoracic) such as in vocal cord paralysis, pharyngeal muscle weakness, chronic neuromuscular disorders, etc. the inspiratory and expiratory phases are not equal. The period of inspiration is reduced more than the expiratory period which is reflected in loop. This is because during forced inspiration the negative transmural pressure inside the airway tends to collapse the airway with increasing effort and reduce the inspiratory flow. But during expiration the positive pressure in the upper airway tries to reduce the obstruction. So, the expiratory flow is not reduced and may even be normal. In variable airway obstruction (intrathoracic) such as tumour in trachea and major bronchi, the expiration becomes longer and plateau usually occurs. This is because during expiration compressed airway lumen assumes its minimal size at the area of lesions. But the inspiratory portion of F-V loop may be quite normal. In diffuse airway obstruction the F-V loop takes a characteristic appearance which is shown in Figure 31.4.

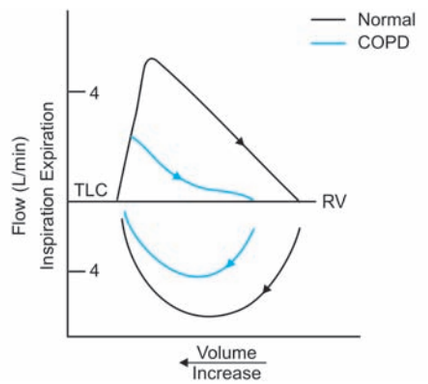


Fig. 31.4: Schematic flow-volume curve in a normal subject and in a patient with COPD

PREDICTING PERIOPERATIVE PULMONARY COMPLICATIONS

The multiple large and rigorous studies, identifying the risk factors for perioperative pulmonary complications are still lacking, though comparison of large prospective studies to identify the pulmonary risk factors are performed. This is because comparison between the studies on pulmonary function is very difficult. Still, some risk factors are identified (described below) and the incidence of perioperative complications can be reduced, if these patients are treated properly preoperatively (Table 31.4).

Formerly, spirometry was considered as an important tool for the assessment of risk factors. But, recent evidence suggests that it does not properly predict the risk of perioperative pulmonary complications.

Table 31.4: Risk factors to predict the perioperative pulmonary complications

i.	Increased age > 60 years.
ii.	Symptoms of chronic bronchitis.
iii.	Smoking within 8 weeks.
iv.	Body mass index > 30.
v.	Abnormal clinical findings in chest.
vi.	Abnormal finding in chest X-ray.
vii.	History of pulmonary malignancy.
viii.	P_aCO_2 > 6 kPa
ix.	Upper abdominal and thoracic surgery.

Therefore, it should not be used alone to determine the risks. The general scoring system such as ASA grading system, Goldman cardiac risk index and Charlson comorbidity index, etc. which assess the overall comorbidity are also the best predictors of pulmonary complications. The abnormal chest findings on clinical examination and in X-ray reflect significant lung disease and are independent predictors of pulmonary complications.

GENERAL PRINCIPLE OF POST-OPERATIVE CARE IN PULMONARY DISEASE

The post-operative care of all patients with pulmonary disease can be guided by the following principles.

Early Mobilization

Early mobilization is the corner stone of post-operative management of a patient suffering from respiratory diseases. It reduces the incidence of pulmonary thromboembolic menifestations. Lung performance, FRC and clearance of secretions are also improved when the patient is sitting or standing in comparison with the supine position.

Physiotherapy

As a part of pulmonary physiotherapy the incentive spirometry and breathing exercise helps to clear the bronchial secretions and thus reduce atelectasis and its pulmonary complications.

Oxygen Therapy

In patients with lung disease the dose dependent depression of respiratory function and the dose dependent depression of the sensitivity of central chemoreceptors to the stimulatory effect of CO_2 on ventilation can occur for up to 72 hours post-operatively. It is mostly found at night. So, supplemental O_2 should be delivered for at least this period of time. COPD patients chronically retain CO_2. Therefore, they depend on hypoxaemia

for their main ventilatory drive due to down regulation of central chemoreceptors to CO_2. Hence, O_2 therapy should be controlled and guided by adequate monitoring such as blood gas analysis. A preoperative data of P_aO_2, SaO_2 and P_aCO_2 are essential to establish a realistic target for each patient. O_2 must be humidified to help sputum clearance and physiotherapy.

Fluid Balance

Patients with lung diseases are at increased risk of fluid overload and pulmonary oedema. This is caused by dilated and hypertrophied Rt. ventricle due to commonly associated pulmonary hypertension with pulmonary disease. Thus, it may mechanically compromise the function of left ventricle leading to pulmonary oedema. So a high index of suspician regarding the fluid overload leading to pulmonary oedema should be maintained clinically. Reading of CVP as a guidence of fluid therapy are misleading in the presence of pulmonary hypertension.

Pain Management

Good analgesia is very essential for the best post-operative management of patients suffering from pulmonary diseases. This properly titrated post-operative analgeria helps by maintaing the early mobilization, increasing the compliance of physiotherapy, increasing the proper respiratory function and minimising the cardiac stress with heart diseases. Patients with respiratory diseases are best benefitted by local or regional analgesia. It helps by avoiding the sedative and respiratory depressive effect of narcotics. Risk benefit ratio of opioid based analgesia and regional analgesia should be weighted against each other. Paracetamol and other NSAIDs are not absolutely contraindicated in pulmonary airway disease. They should be used where possible.

Regular Clinical Review

Regular clinical review always allows early detection of respiratory deterioration and resolution of problem.

INDIVIDUAL PULMONARY DISEASE AND ANAESTHETIC MANAGEMENT

Bronchial Asthma

Etiology and pathology

Bronchial asthma is primarily the disease of airways which is characterised by reversible obstruction of airflow due to increased responsiveness of the tracheobronchial tree to a number of stimuli. All aspects of pulmonary functions are virtually compromised during an acute attack of it. This disease is manifested clinically by paroxysms of dyspnoea, cough and wheeze following generalised narrowing as well as inflammatory changes of air passages. As it is an episodic disease, so acute exacerbation is interspersed with symptom free periods. Usually, most of the acute attacks of bronchial asthma are mild and last for few hours. Sometimes, it becomes much more serious with severe obstruction when this condition is called the status asthmaticus. However, during symptom free phase, the patient may also experience some degree of airways obstruction daily.

Bronchial asthma is the commonest chronic obstructive pulmonary airway disease and is one of the leading causes of death in our country. High mortality from bronchial asthma is due to the ineffective or inadequate treatment, leading to gradual irreversible changes of the airways. Bronchial asthma occurs at all ages, but more common at early life. About one half of the cases develop before the age of 10 and another third develop before the age of 40. In childhood when the incidence is very high, the male-female ratio is 2:1 and it gradually equalises at the age of 30. The presence of symptoms at childhood, cough which wakes the patient at night, diurnal variation, specific trigger factors (especially allergic), abscence of smoking history and response to previous treatment, etc. may all be helpful in differentiating bronchial asthma from COPD (now called COLD).

Bronchial asthma is a heterogenous disease from the etiological point of view. It can be described under two broad headings (i.e types of asthma): allergic and idiosyncratic. In allergic type of bronchial asthma, patients should have (i) personal/or family history of allergic disease such as rhinitis, urticaria, eczema, etc. (ii) ↑level of IgE, (iii) positive skin reaction to intradermal antigen test, (iv) positive response to provocative tests involving specific antigens by inhalation, etc. On the other hand, in idiosyncratic variety no such positive history or test will be present.

In general, the bronchial asthma that has its onset in early life falls in the allergic group. Allergic asthma is dependent on an IgE response, controlled by T and B lymphocytes. It is activated by the interaction of antigen with the mast cells bound IgE molecules. Most of the allergens that provoke bronchial asthma are airborne. To induce a state of sensitivity (first reaction in the body), the allergens must be reasonably abundant for considerable period of time. Once sensitisation of body has occured, then the patient can exhibit exquisite hyper responsiveness, so that next exposure to the minute amounts of the offending agents can produce significant exacerbations of the disease. This allergic variety of asthma is most often observed in children and young adults and is usually seasonal. A nonseasonal form of bronchial asthma may result from the allergy to feathers, animal danders, dust mites, molds and other antigens that are present continuously in the environment. From the above discussion it is clear that the inhaled antigens cause an antigen-antibody reactions on the surface of bronchial mast cells to provoke an acute episode of asthma.

In idiosyncratic group of bronchial asthma, there is (i) no personal or family history, (ii) level of IgE is not elevated and (iii) negative skin test to antigen. So, this group does not depend on immunological

mechanism (antigen-antibody reaction) for its manifestation. The initial insult in idiosyncratic group is usually the common cold or upper respiratory tract illness, leading to paroxysms of wheez and dyspnoea. Bronchial asthma that develops late in life usually falls in this group. Again this idiosyncratic group cannot be confused with the group where symptoms of bronchospasm superimposed on chronic bronchitis or bronchiectasis. On the other hand, in practice there are many patients that do not fit clearly into any of the above mentioned group and they are classified as mixed group.

Though basic mechanism is still unknown, the main denomination of pathophysiology of bronchial asthma or bronchospasm is nonspecific hyperirritability of tracheo-bronchial tree and its neural control pathways. The intensity of this hyperactivity of bronchial tree is directly proportional with the intensity of symptoms and aggresiveness of therapy. Following a viral infection of the respiratory tract, the reactivity of airway rises and remains elevated for many weeks, even after recovery from infection though seemingly trivial. This is very important from the anaesthetic point of view. In this hyperactivity period, any exposure to antigen or chemical irritants (those who have no history of asthma) cause bronchospasm.

The most popular hypothesis of bronchial asthma now is that of airway inflammation with increased number of mast cells, eosinophils, lymphocytes, neutrophils and epithelial cells. This is because, even when acute episode of bronchial asthma is in remission, bronchial biopsy reveals large infiltration of mucosa by inflammatory cells and epithelial shedding. But, if this increased number of cells and inflammation is the effect or cause of antigen-antibody reaction (for allergic group) is still unknown, because increased cellularity and elevated capillary density (i.e. findings of inflammatory process) is the most ubiquitous findings even in asymptomatic group of patients. In idiosyncratic group of patient, inflammation is the effect of asthma. However, bronchospasm during anaphylactic reaction should not be confused with idiosyncratic asthma.

For pathogenesis of asthma, the above mentioned cells (mast cell, eosinophil, macrophage, lymphocyte and neutrophil) and chemical mediators (histamine, bradykinin, leukotrienes, prostglandians – E_2, $F_2\alpha$, platelet activating factors) which are released from these cells play an important role causing inflammatory reaction. This inflammatory reactions involve mucous production, bronchospasm, vascular congestion and oedema formation. These chemical mediators bring more and more eosinophils, platelets and polymorphonuclear leucocytes to the site of reaction by their chemotactic effects. Thus, these infiltrating cells, the resident macrophages and the airway epithelial cells produce additional mediators in vicious cycle and cause immediate and delayed cellular phase reaction. This local inflammatory reaction exposes the nerve endings and initiates a neurogenic inflammatory pathways, converting primary local event into a generalised reaction by reflex mechanism. This is an alternative explanation of bronchial asthma due to abnormal autonomic nervous system function. This hypothesis is supported by increased expiratory airflow obstruction in patients with bronchial asthma, being treated with a β-agonist, suggesting the presence of an imbalance between the excitatory and inhibitory neural output. It is likely that the chemical mediators released from the mast cells interact with the autonomic nervous system. Some chemical mediators can stimulate the airway's irritant receptors to trigger the reflex broncho-constriction. While the other mediators sensitize the bronchial smooth muscle to the effects of acetylcholine. In addition, stimulation of muscarinic receptors facilitates the release of mediator from the mast cells, providing another positive feedback loop for sustained inflammation and bronchoconstriction. The stimuli that interact with airway reponsiveness and incite acute episodes of bronchial asthma can be grouped into seven major categories and thats are : allergenic, pharmacologic, environmental, occupational, infective, exercise related and emotional.

The allergenic factors as the aetiology of bronchial asthma are already discussed. Among the pharmacological allergic factors, the important drugs that are commonly associated with the induction of episodes of bronchial asthma are aspirin, tartasine (colouring agent in food products), sulfiting agents (used as preservative in food preparation), beta adrenergic antagonist, etc. It is important to recognise that the drug-induced bronchial asthma is often associated with greater morbidity and sometimes with mortality. There is a great deal of cross reactivity between aspirin and other NSAID, such as ibuprofen, fenoprofen, indomethacin, phenylbutazone, etc. The exact mechanism by which aspirin and other drugs produce bronchospasm is still unknown. But the probable explanation is generation of leukotrienes which act as chemical mediator by aspirin or other drugs. This is proved by inhibition of leukotriene synthesis or receptor activity during the treatment of this type of problem. On the other hand, paracetamol (acetaminophen), sodium salicylate and propoxyphene are well tolerated by these aspirin sensitive group of patient. On exposure to even small amount of aspirin, sensitive individual develop ocular and nasal congestion and often acute severe airway obstruction. The aspirin induced hypersensitivity usually starts with perineal vasomotor rhinits that is followed by hyperplastic rhinosinusitis with nasal polyp. Progressive asthma then appears. Several sulfiting agents such as potassium metabisulfite, sodium and potassium bisulfite, etc. used in different food and pharmacological industries as preservatives, also can produce acute airways obstruction in sensitive individuals. Patients become

sensitised after first exposure. Then, after subsequent exposure, patients develop acute bronchial asthma. Exposure usually follows by ingestion of food and beverages which also contain different sulfiting agents such as shellfish, wine, salad, fruit preparations, etc. Some topical ophthalmic solutions, IV glucocorticoids preparations and bronchodilator solutions for inhalation also contain some sulfiting agents which produce bronchospasm.

The enviornmental causes of bronchial asthma are usually due to pollen (airborne antigen) and atmospheric pollutants such as ozone, nitrogen dioxide, sulphur dioxide, etc. This environmental cause of bronchial asthma can be treated by mast cells stabilising drugs. Occupation related bronchial asthma is due to exposure to large number of compound used in different types of industrial process. Respiratory infection is also an important stimuli to evoke exacerbation of bronchial asthma. Among the infections, viruses such as syncytial virus, rhino virus, influenza and parainfluenza virus, etc, are the predominant pathogens. Simple colonization of viruses do not cause bronchial asthma, but attacks of asthma occur when symptom of respiratory tract infection are present. The mechanism of virus induced exacerbation of bronchial asthma is due to the production of T-cell derived cytokines that help in the infiltration of inflammatory cells into the already susceptible airways.

Exercise also precipitates acute onset of bronchial asthma by provoking bronchospasm to some extent in asthmatic patient. When such patients are followed for sufficient periods, then it is found that they often develop recurring episodes of airway obstruction which is independent of exercise. So, onset of exercise induced bronchial asthma may be the first manifestation of the later full blown asthmatic syndrome. Exercise induced asthma is not due to the smooth muscle contraction, but due to the obstruction produced by thermal induced hyperemia and engorgement of the microvasculature structure of the bronchial wall.

Pathophysiology

The hallmarks of pathophysiology of bronchial asthma are: vascular congestion, oedema of tracheo-bronchial wall, thickening of mucous membrane, reduction of airway diameter due to contraction of smooth muscles, copious tenacious secretions and plugging of airways (mainly the small airways), hypertrophy of the bronchial smooth muscle, hyperplasia of mucosal and submucosal vessels, eosinophilic infiltration of bronchial wall and denuation of surface epithelium. All these pathological changes lead to increased airway resistance, decreased forced expiratory volume, decreased flow rates, increased work of breathing, hyperinflation of the lungs and thorax, decreased elastic recoil, altered ventilation and perfusion ratio, altered arterial blood gas concentration (Fig. 31.5).

When the forced vital capacity of an asmatic patient with acute episode goes below or becomes equal to 50% of the normal value, FEV_1 comes down to 30% or less of the predicted value and maximum midexpiratory flow rates are reduced to 20% or less of the expected, then he presents for therapy. In acutely ill patient with status asthmaticus, residual volume (RV) frequently approaches 400% of normal value and functional residual capacity (FRC) becomes double. Flow-volume loop of asthma shows characteristic downward scooping of the expiratory limb of the loop. The flow-volume loops where the inhaled and exhaled portion are flat help to distinguish the wheezing caused by upper airway obstruction such as foreign body, tracheal stenosis, mediastinal tumour, etc, from bronchial asthma. During moderate to severe attacks of bronchial asthma, the functional residual capacity may increase as much as 1 to 2 litres, whereas the total lung capacity usually remains within the normal range.

The mild bronchial asthma is usually accompanied by normal arterial O_2 and CO_2 tension. Tachypnoea and hyperventilation which is observed during a mild asthmatic attack, therefore, do not reflect the compensatory phase of arterial hypoxaemia, but, rather neural reflexes of the lungs. During moderate to severe form of attack, the abnormal blood gas analysis is the universal finding. This is associated with hypoxia, hypocapnia, and respiratory alkalosis. As the severity of obstruction to expiratory airflow increases, the associated gradual ventilation-perfusion mismatching may result in P_aO_2 less than 60 mm

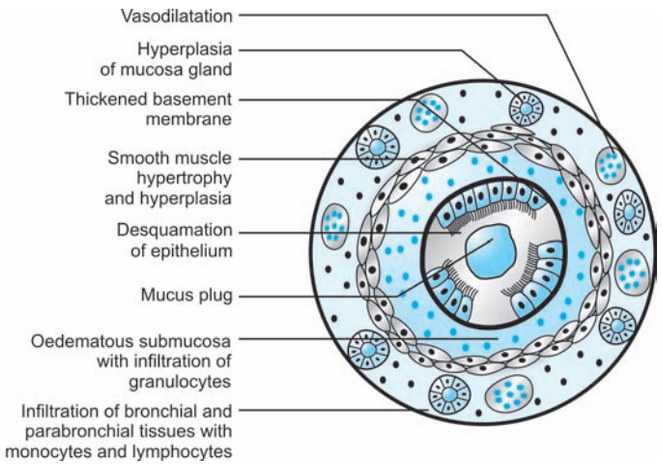


Fig. 31.5: Changes in bronchial wall during asthma

of Hg but normocapnia, while breathing room air. This is followed by compensatory hyperventilation which results in hypocapnia and normal P_aO_2. Then gradually when hypocapnia comes to normal level, it indicates severe airway obstruction. The P_aCO_2 is likely to increase when the FEV_1 is less than 25% of the predicted value and indicates impending respiratory failure. Equally, the presence of metabolic acidosis in the setting of acute bronchial asthma signifies severe hypoxia due to acute obstruction. Cyanosis is very uncommon and is late sign of bronchial asthma. Clinically hypoxia can go undetected. So, clinical indication should not be relied upon with any confidence. Therefore, in any acute condition with suspected alveolar hypoventilation, arterial blood gas tension must be measured (Fig. 31.6).

Drugs

Drugs used for treatment of bronchial asthma are classifed as:

A. Bronchodilators

1. Adrenergic stimulants –
   i. Catecholamines: Epinephrine (adrenaline), Isoproterenol (Isoprenalin), Isoetharine, Rimiterol, Hexoprenaline.
   ii. Resorcinols: Terbutaline, metaproterenol (orciprenaline), Fenoterol
   iii. Saligenin: Salbutamol (albuterol), Salmeterol

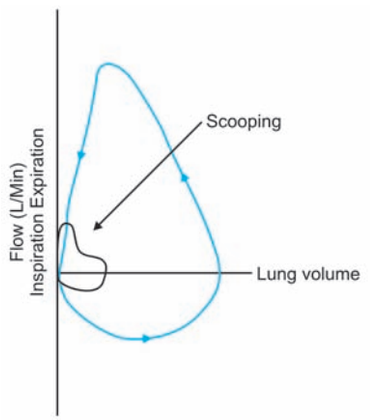


Fig. 31.6: Flow-volume curve of a normal (blue line) and an asthmatic (red line) individual

2. Methylxanthines: Theophylline, aminophylline
3. Anticholinergies: Atropine, ipratropium

B. Mast cell stabilisers

Sodium chromoglycate, ketotifen

C. Corticosteroids

1. Systemic: Hydrocortisone, prednisolone and others
2. Inhalational: Beclomethasone, budesonide, fluticasone, Triamcinolone

CATECHOLAMINES

This group of drugs causes bronchodilatation through agonistic action on β-receptor and activation of G-protein, with the resultant increased in formation of cAMP in bronchial muscle cell leading to relaxation of it. Increased cAMP in mast cells also reduces antigen: antibody reaction which inhibits the release of chemical mediators responsible for smooth muscle contraction. The catecholamines which are in wide spread clinical use for bronchial asthma are: epinephrine, isoproterenol and isoetharine. Among the catecholamines the epinephrine is the mainstay of treatment for reversible airway obstruction, but should be reserved for refractory cases and used cautiously in hypertensive patients, cardiac patients and in those receiving digitalis. They are the fastest acting bronchodilators when inhaled.

Epinephrine (adrenaline) is an α (α_1 + α_2) and β (β_1 + β_2) agonist and causes prompt but short-lasting bronchodilatation. The duration of action of epinephrine is 30 to 90 minutes and are effective only when is administered by inhalational or by parenteral routes. The α-action (weakly bronchoconstrictor) of it is masked by dominant β_2 mediated action. As epinephrine is not selective β_2 agonist, so it has considerable chronotropic and inotropic cardiac (β_1) actions also. Inhalation of adrenaline or spray of it may afford additional benefit by producing mucosal decongestion (α-action). The usual parenteral dose of epinephrine in acute bronchial asthma is 0.3 to 0.5 ml of 1:1000 solution, administered subcutaneously.

Another catecholamine such as isoproterenol is devoid of α-activity and has both β_1+β_2 activity. It is also a very potent bronchodilator and is usually administered in acute asthmatic patient as 1:200 solution by inhalation. Then in 1960, sudden deaths among the asthmatics were increased markedly when the high doses of isoprenaline was used. This is because of inhalation of several doses of isoproterenol in succession during escalation of symptom and respiratory acidosis is probably resulted in cardiac arrhythmia and asystole. Then death rate has dropped following the restriction of these inhalers and development of more selective β_2 agonists which have replaced isoprenaline. Isoetharine is the most β_2 selective compound, but is a relatively weak bronchodilator. It is employed as an aerosol and supplied as 1% solution.

RESORCINOLS AND SALIGENIN

The most commonly used resorcinols are metaproterenol, terbutaline and fenoterol. The most commonly used saligenins are salbutamol (albuterol) and salmeterol. With the exception of metaproterenol, these group of drugs are highly selective for the β_2-receptors of respiratory tract and are virtually devoid of any significant cardiac (β_1) effects, except at high doses. Their major side effect is tremor. They are active by all the routes of administration. Their peculiar chemical structure allows them to bypass the metabolic processes which degrade the catecholamines in liver when used through oral route. So, their effects are long-lasting (4 to 6 hours) than catecholamines.

The differences in potency and duration of action among these agents can be eliminated by adjusting the doses and/or administration schedules. Inhalation is the preferred route of administration of these group of drugs. Because through this

route, it further increases the bronchial selectivity of action of these drugs and allows the maximal bronchodilation with fewer systemic side effects. This is also true during the treatment of severe acute airway obstruction and making the IV therapy obsolete during emergency. The IV administration of β_2 selective agonistic agent such as terbutaline and salbutamol offers no advantages over the inhalational routes (Table 31.5).

The orciprenaline (metaproternol) also resembles to isoprenaline and is somewhat selective β_2-agonist. But as it is not a substrate for COMT like isoprenaline, so it is orally effective and longer lasting (3 to 4 hours). Now, orciprenaline (metaproterenol) is less favoured than other more selective β_2 agonists.

Both salbutamol and terbutaline are highly selective β_2-agonists. So cardiac side effects of these two agents are less prominent. Bronchial selectivity is further increased by inhaling these drugs. Muscle tremor caused by salbutamol and terbutaline is their dose related side effect. Palpitation, restlessness, nervousness, throat irritation and ankle oedema may also occur. Salbutamol and terbutaline undergo presystemic metabolism in gut wall. So, oral bioavailability of this drug is only 50%. They are longer acting and safer than isoprenaline but similar in efficacy. Inhaled salbutamol and terbutaline are currently the most popular drugs. By inhalation the peak bronchodilatation effect produced with these agents, occurs within 10 min and lasts up to 6 hours. They are convenient, effective in most mild to moderately severe cases and produce few side effects.

Table 31.5: Comparison of β_1 and β_2 activity of commonly used bronchodilators

Drugs	*Adrenergic activity*	
	β_1	β_2
Epinephrine	+ + + +	+ +
Isoproterenol	+ + +	+
Metaproterenol	+ +	+ + +
Albuterol (salbutamol)	+	+ + +
Fenoterol	+	+ + +
Isoetharine	+ +	+ + + +
Formaterol	+	+ + + +
Bitolterol	+	+ + + +
Salmeterol	+	+ + + +
Terbutalin	+	+ + + +

The regular use of inhaled β-agonists does not reduce the bronchial hyperactivity, but may even worsen it. Regular use also down regulates the bronchial β_2-receptors. This may be responsible for the gradually diminshed responsiveness seen after the long term use of these drugs. It is felt that the use of β_2-agonist inhalers should be restricted to the symptomatic relief of wheezing.

Salmeterol is the recently introduced long-acting (9 to 12 hours) congener of salbutamol and selective β_2-agonist with slow onset of action (30 minutes). As it is long-acting (12 hours), so is effective in producing sustained symptomatic relief. Therefore, it is used on a twice daily schedule for maintenance therapy and for nocturnal and exercise induced asthma, but not for acute symptoms. It should not be used as a rescue drug for breakthrough symptoms. In addtion, its long half-life means that administration of extra doses can cause cumulative side effects.

METHYLXANTHINES

The drugs used from this group of agent is theophylline and aminophylline. Theophylline and its various salts are bronchodilator of medium potency and work through an undefined mechanism. The probable explanation for their mechanism of action is direct effect on their receptors, as well as due to the release of adrenergic transmitters. The previous theory of their action that these drugs increase cyclic AMP by the inhibition of phosphodiesterase is no longer correct. Before the era of salbutamol, theophylline and its compounds have been extensively used in bronchial asthma. But, now it is not considered as first line of drugs anymore. Theophylline is one of the three naturally occuring methylated xanthine alkaloids, such as caffeine, theophylline and theobromine which are present in tea leaves, coffee seeds and coca. The therapeutic plasma concentration of theophylline traditionally have been thought to lie between 10 to 20 µg/ml. But some schools recommend a lower therapeutic plasma concentration, ranging between 5 to 15 µg/ml to avoid its toxicity.

The dose required to achieve desired therapeutic level and to reduce toxicity of methylxanthines varies widely from patient to patient. This is due to the differences in metabolism of theophylline in different patients. Theophylline clearance and thus its dosage requirement is decreased substantially in neonates, elderly, and those who are suffering with acute and chronic hepatic dysfunction, cardiac decompensation, corpulmonale and febrile illness. On the other hand, theophylline clearance increases in children. In addition, a number of important drug interaction can alter the theophylline metabolism. The clearance of methylxanthines (theophylline) also fall with the concurrent use of erythromycin, other macrolite antibiotics, quinolone antibiotics, cimetidine, etc. Clearance of theophylline also increases with the use of cigarettes, marijuana, phenobarbital, phenytoin and other drugs that induce microsomal enzymes of liver. At therapeutic concentration, the $t_{½}$ of theophylline in adults is 7 to 12 hours. Children eliminate it much faster with $t_{½}$, 3 to 5 hours, but for the elderly $t_{½}$ is more than 12 hours. In premature neonates and infants the $t_{½}$ of theophylline extends from 24 to 36 hours. Long-acting theophylline compounds are also available for maintenance of therapy and are usually given once or twice per day (Fig. 31.7).

The dose of this group of drug is adjusted on the basis of clinical response and the measurement of serum concentration. Now, the effectivenss or the role of aminophylline in the management of acute asthma is in debate. Still, in severe asthma it is used as infusion perioperatively. Both

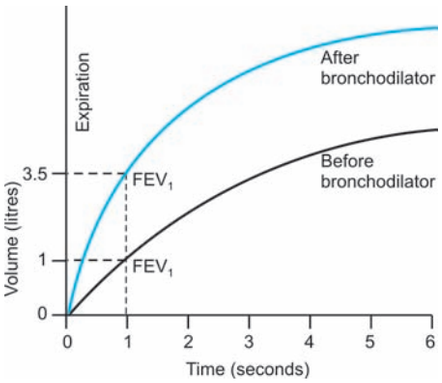


Fig. 31.7: Schematic representation of change in FEV_1 before (red line) and after (blue line) administration of bronchodilator

aminophylline and theophylline are available for IV use. The recommended intravenous dose of theophylline is 6 mg/kg as loading, followed by an infusion of 1 mg/kg/hour for the next 12 hours and then 0.8 mg/kg/hour thereafter. For older, heart failure, liver disease and corpulmonale patients the IV loading dose remains the same, but the maintenance dose is reduced to between 0.1 to 0.5 mg/kg/hour. Sometimes, for patients who are already receiving theophylline, the loading dose is frequently withheld.

The most common side effects of aminophylline and theophylline are nervousness, nausea, vomiting, anorexia and headache. At plasma levels of theophylline greater than 30 µg/ml, there is risk of seizures and cardiac arrhythmias. Very rapid IV injections of methylxanthines causes precordial pain, syncope and even sudden death and these are due to marked fall in BP, ventricular arrhythmias or asystole. Theophylline has been found to reduce the frequency and duration of episodes of apnoea that occur in some preterm infants in the first few weeks of life. So, for premature neonates, to prevent or to abolish the episode of apnoea closely monitored IV treatment by theophylline or aminophylline is employed for 1 to 3 weeks.

ANTICHOLINERGIC

The anticholinergic drugs such as atropine sulphate produces bronchodilation in patients with bronchial asthma. It acts by blocking the cholinergic constrictor tone of vagus. But its use is limited by its systemic side effects and less effectiveness than sympathomimetic agents. But after the introduction of nonabsorvable quaternary ammonium congener such as atropine methylnitrate and ipratropium bromide, the anticholinergic agent has been found to be both effective in the management of acute bronchial asthma and free of untoward side effects. The Patients of asthmatic bronchitis, COPD and psychogenic asthma respond better than pure bronchial asthma to anticholinergic agents. Because, reflex vagal activity is an important factor causing bronchoconstriction and increased secretion in chronic bronchitis and COPD, but to a lesser extent in bronchial asthma. It may also be particularly beneficial for patients with coexistent heart diseases, in whom use of methylzanthines and beta-adrenergic stimulants may be dangerous. Anticholinergic also enhances the response, achieved by sympathomimetics and produce better bronchodilatation. Ipratropium bromide given by aerosol also has been shown not to dry up the secretions (like atropine) in the respiratory tract which may lead to inspissation and plugging of bronchioles, resulting in alveolar collapse. However, the major disadvantage of inhaled anticholinergics are that they produce slower response (60 to 90 minutes may be required before peak bronchodilatation is achieved) with modest potency. So, anticholinergics are better suited for regular prophylactic use than for control of an acute attack.

GLUCOCORTICOIDS

They are not bronchodilators. But they act by (i) reducing the bronchial hyperirritability, (ii) reducing the mucosal oedema and (iii) suppressing the inflammatory response produced by AG:AB reaction or other stimuli. The indication of glucocorticoids in asthma are: (i) when severe airway obstruction is not resolving or is worsening, despite intense optimal bronchodilator therapy, (ii) in chronic disease when there has been failure of a previously optimal regimen with frequent recurrences of symptoms and increasing severity and (iii) to restore the responsiveness of sympathomimetics, once resistance to them has developed (Fact file).

FACT FILE

At the cellular level glucocorticoids act by the following mechanism:

1. Induction of synthesis of lipocortins in macrophages, endothelium and fibroblasts → ↑lipocortins inhibits phospholipase A_2 → decreases synthesis of PGs, LTs and PAF (LT - leukotriene, PAF - platelet activity factor).
2. Negative regulation of genes for cytokines in macrophages, endothelial cells and lymphocytes → decreased production of IL - 1, 2, 3, 6; TNFα, GM-CSF, γ - interferon → inhibition of fibroblast. (IL - Interleukin, TNF—Tumour Necrosis Factor, GMCSF—Granulocyte Macrophage Colony Stimulating Factor)
3. Complement function is inhibited.
4. Decreased production of ELAM (Endothelial Leucocyte Adhesion Molecule) and ICAM (Intracellular Adhesion Molecule) causing supression of adhesion and localization of leucocytes.
5. Inhibition of IgE mediated release of histamine and LT - C_4 from basophil by which AG : AB reaction is inhibited.
6. Inhibition of production of collagenase and stromelysin → prevention of tissue destruction.

The glucocorticoid molecule penetrates the cell membrane and binds to the glucocorticoid receptor (GR) which is a protein in nature and normally resides in the cytoplasm of cell. The glucocorticoid receptor is practically distributed in all the cells and made up of 800 aminoacids. The GR has a steroid binding domain near its carboxy terminus and a DNA binding domain having two 'zinc finger' at mid region. Each zinc finger is made up of a loop of aminoacids with chelated zinc ion. Normally the GR remains in cytoplasm in association with 3 proteins such as HSP_{90}, HSP_{70} and IP (HSP – Heat Shock Protein, IP – Immunophillin).

These proteins have inhibitory influence on GR and prevent its dimerization. The binding of steroid molecule to GR dissociates these three complex proteins and the dimerization region is exposed. Thus, dimerization of two GR with glucocorticoids molecule occur. Now, the diamer of two GR with steroid molecules translocate within the nucleus of cell and interacts with the sepecific DNA sequences or region called GRE (Glucocorticoid Responsive Elements). These are the regulatory region of a appropriate gene of DNA. Thus, the expressions of these genes is consequently altered resulting in promotion or supression of their transcription. The specific mRNA thus produced from genes (whose expression is altered) is directed to the ribosomes. In the ribosome the message carried by mRNA is translated for a specific pattern of protein synthesis, which in turn modifies the cell function.

Thus, in summary the corticosteroid molecules penetrate the cells and bind to high affinity cytoplasmic glucocorticoid receptor protein → a structural change occurs in the steroid receptor complex → allows its migration into the nucleus and bindings to specific sites on the DNA → transcription of specific mRNA → regulation of protein synthesis → alterations of function of cells. This process takes at least 30 to 60 minutes. So, effects of steroids are not immediate and once the appropriate proteins are synthesized, then the effects persist much longer (Fig. 31.8).

All the natural and synthetic corticosteroids, except deoxycorticosterone acetate (DOCA) are effective by the oral route. Water soluble esters of corticosteroids, e.g. hydrocortisone hemisuccinate, dexamethasone sodium phosphate, methylprednisolone, etc. can be given IV or IM. They act rapidly and achieve high concentration in tissue fluids. Insoluble esters, e.g. hydrocortisone acetate, triamcinolone acetonide, etc. cannot be injected IV. They are slowly absorbed from IM site and produce more prolonged effects (Fig. 31.9).

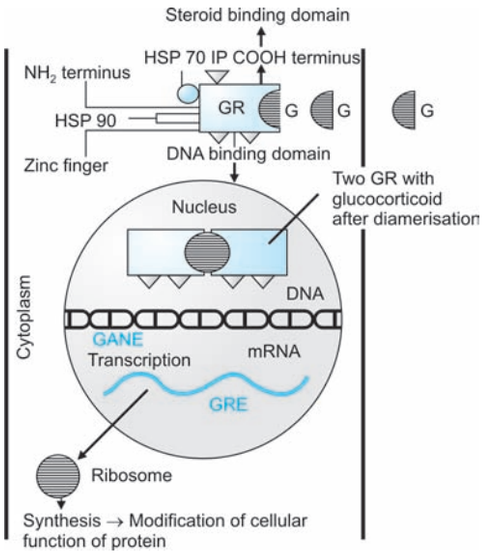
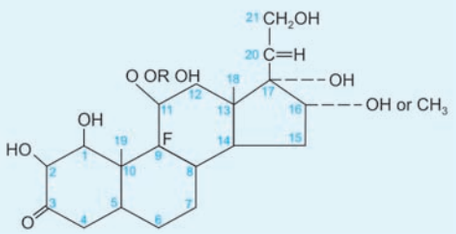


Fig. 31.8: The glucocorticosteroid molecule (G) first penetrates the cell membrane. Then it binds to the receptor GR. Normally GR resides in the cytoplasm in association with 3 another proteins - HSP 90, HSP 70 and IP. The GR has two domain, one is steroid binding domain near the carboxy terminus. Another is DNA binding domain having two zinc fingers at the middle. Binding of the G to GR dissociates the complex proteins (HSP 90, HSP 70, etc.) from GR and thus remove the inhibitory influence on it. Thus a dimerisation region is exposed. It helps dimerisation of two GR. Then the steroid molecule bound diamer of receptor translocates into the nucleus and interacts with specific DNA sequence which is called glucocorticoid responsive elements (GREs). Then expression of the genes in DNA is altered. This results in promotion or supression of their transcription and production of specific mRNA. The specific mRNA thus produced is directed to the ribosome and gives direction for specific pattern of protein synthesis which modifies cell function



Corticosterone	DOC	+	OH at 11
Hydrocortisone	DOC	+	OH at 11 and OH at 17
Cortisone	DOC	+	O at 11 and OH at 17
Prednisolone	DOC	+	OH at 11, OH at 17, Δ 1,2
Triamcinolone	DOC	+	OH at 11, OH at 17, 1,2 and F at 9, OH at 16
Dexamethasone	DOC	+	OH at 11, OH at 17, Δ 1,2, Fat at 9, CH_3 α at 16
Betamethasone	DOC	+	OH at 11, OH at 17, Δ 1,2, Fat at 9,CH_3 β at 16
Fludrocortisone	DOC	+	Hydrocortisone + F at 9
Aldosterone	DOC	+	Corticosterone + CHO at 18

Fig. 31.9: Chemical structure of corticosteroid. Black lined structure is deoxycorticosterone (DOC). Important substitutions which yield other compounds are shown by blue colour

The chemical structure of different natural and synthetic glucocorticoids are depicted in picture. Among all the glucocorticoids, hydrocortisone (naturally occuring, daily rate of synthesis 10 mg/day) undergoes high fast pass liver metabolism. So, it has low oral: parenteral activity ratio and is mainly used through IV route. Whereas oral bioavailability of other synthetic corticosteroids are high. Hydrocortisone acts rapidly, but has short duration of action ($t_{½}$ < 12 hours). In status asthmaticus the dose of it is 100 mg IV in bolus plus 100 mg 8 hourly by infusion. Prednisolone is 4 times more potent and more selective glucocorticoids than hydrocortisone, but is not used through IV route. While methyl prednisolone (solumedrol)

is available for slow IV use for its anti-inflammatory action. Triamcinolone is more potent and selective glucocorticoids than prednisolone, but IV preparation of it is not available. It is used only by oral, IM or intra-articular route. Dexamethasone is also potent and selective glucocorticoids without fluid retention and hypertensive action (mineralle corticoid actions). It is long-acting ($t_{½}$ > 36 hours) and its IV preparation is also available. As it has no fluid retention property, it is used for the management of cerebral oedema like betamethasone. Betamethasone is also available as IV preparations. Its action is like dexamethasone but is long-acting ($t_{½}$ > 36 hours). Fludrocortisone is a potent mineralocorticoids with some glucocorticoid activity. DOCA (Deoxycorticosteron Acetate) has only mineralocorticoid activity. Beclomethasone and budesonide are used by inhalation in bronchial asthma patient as spray. They have high topical potency and reduce airway reactivity. The realization that bronchial asthma is primarily an inflammatory disease which accentuates with time. So, the availability of inhaled steroids that are less hazardous in long term use have led to more extensive use of such glucocorticoids in chronic bronchial asthma (Fig. 31.10).

It should be emphasized that the effects of steroid in acute bronchial asthma are not immediate and may not be seen for 6 hours or more after the initial administration. Also the correct dose of it to use in acute situations is a matter of debate. The available data indicates that very high doses of glucocorticoids do not offer any advantage over the more conventinoal doses. So, the recommended dose of methylprednisolone is 40 to 60 mg IV every 6 hours. Since, IV and oral administration produce the same effects, prednisolone 60 mg every 6 hours orally can be used instead of IV. In UK, acute bronchial asthma is treated with dose of prednisolone 30 to 40 mg given once daily.

For bronchial asthma the corticosteroids can also be used through inhalation route and is preferred than oral administration, because it is associated with less systemic side effects than oral administration. Inhaled corticosteroids have direct anti-inflammatory action on the bronchial mucosa and thus decrease airway hyperresponsiveness. This decrease in airway hyper responsiveness is not maximum until treatment has passed several months. The corticosteroids which are used through inhalation are: beclomethasone, fluticasone, budesonide, etc. (Table 31.6).

Anaesthetic Management

The anaesthetic management of a patient with bronchial asthma requires an exhaustive understanding of the pathophysiology of this disease and pharmacology of the drugs, being used for the management of it which are already discussed. There is also evidence that the frequency of perioperative bronchospasm and laryngospasm is common in patients with the history of bronchial asthma, but where there is no symptoms before induction. Whereas symptomatic bronchial asthma patients are at increased risk for morbidity and mortality.

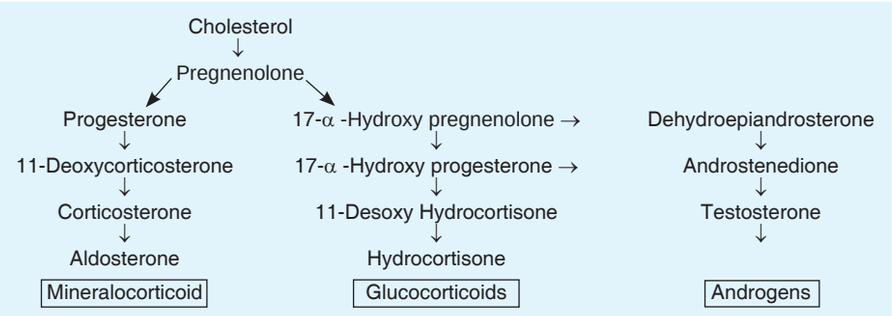


Fig. 31.10: Activity of glucocorticoids in chronic bronchial

Table 31.6: Equivalent doses of glucocorticoids

Glucocorticoids	*Dose (mg)*
Betamethasone	3
Dexamethasone	3
Methylprednisolone	16
Triamcinolone	16
Prednisolone	20
Prednisone	20
Hydrocortisone	80
Cortisone acetate	100

Perioperative assessment

The purposes of proper preoperative anaesthetic assessment of a bronchial asthma patient are: (i) to assess the degree of respiratory dysfunction, (ii) to assess the efficacy of treatment and (iii) to formulate the proper anaesthetic plan and management. Preoperative information should be obtained regarding the frequency and severity of attacks, drug history and any recent episode of respiratory tract infection. Acute recent viral respiratory tract infection increases the bronchial reactivity and increases the incidence of intraoperative bronchospasm. Physical examination of chest may be normal, though a forced expiration may provoke some end expiratory wheeze. Signs of cardiac and respiratory failure may or may not be present.

In addition to the routine tests such as complete blood count, coagulation screening, urine analysis and ECG, sometimes special attention should also be paid to the pulmonary function tests, arterial blood gases and X-ray chest. The comparison of chest X-ray with previous one is often useful to evaluate any further change in the recent disease process. In pulmonary function tests, the timed vital capacity (FEV_1) curve and flow volume loop give the most valuable information regarding : (i) the degree of airway obstruction and (ii) the degree of reversibility of obstruction with bronchodilators. Pulmonary function tests show reduction in forced vital capacity, FEV_1, FEF (25 to 75%) and PEFR. The FEF at 25 to 75% is defined as the forced expiratory flow at 25 to 75% of forced vital

capacity. FEV_1 is a relative crude indicator of small airway obstruction compared to PEFR. Normal value of PEFR is 600 to 650 L/min in adult male and 450 to 500 L/min in adult female. Comparisons with previous measurements are invaluable. FEV_1 values are normally more than 3L for men and 2L for women. FEV_1 / FVC should normally be >70%. An FEV_1, FEV_1 / FVC or PEFR less than 50% of normal is indicative of moderate to severe bronchial asthma.

A single peak flow reading can also be helpful for preoperative assessment of an bronchial asthma patient. But serial measurement is more helpful than a single result. The response to bronchodilators should also be measured. When the peak flow rate is > 80% of the predicted value with minimal symptoms, then bronchial asthma is considered as mild and patient requires little extra treatment prior to surgery. Results of peak flow rate and spirometry should always be compared with the predicted values based on age, sex and height. Anaesthesia should not be given for elective surgery, when the patient's asthma is less than optimally controlled. Viral infection are potent triggers of bronchospasm. So, postponement of elective surgery is considered with symptomatic URTI (Table 31.7).

Depending upon the spirometric pulmonary functional impairment and arterial blood gas level, the bronchial asthma has been classified into five grades (Table 31.7).

Preoperative blood gas analysis may be helpful in providing base line for further management in asthma patients. Hypoxia and hypercarbia are seen only in patients with very severe asthma. In X-ray of chest, the hyperinflation, increased lung markings and peribronchial thickening are the common radiological findings. It also helps to detect the presence of certain complications such as pneumonia, emphysema, cyst, etc.

Preoperative preparation and premedication

The proper preoperative preparation helps to reduce the perioperative morbidity and mortality in bronchial asthama patients. Preoperative chest physiotherapy, systemic hydration, appropriate antibiotics and bronchodilator therapy are some of the important points which may improve the reversible components of asthma and may reduce the intraoperative and postoperative complications. Elective surgery should not be undertaken unless and until the bronchial asthma is well controlled. The incidence of perioperative bronchospasm and laryngospasm in asthmatic patients undergoing routine surgery is less than 2%, especially if they continue their routine medication. The frequency of complications is increased in patients over 50 years and in those with active disease.

The bronchodilator drugs used to treat bronchial asthma should be continued at the time of premedication. Salbutamol and ipratropium should be changed to its nebulized form. Chromoglycate, used as mast cells stabilizer preoperatively, can be continued safely during perioperative period as it does not interact adversely with any drugs, used during anaesthesia. Leukotriene inhibitors can also be continued as preoperative medication and must restart when patient is taking oral medications post-operatively.

Exogenous corticosteroids should be continued or supplemented (if stopped before) before anaesthesia for major surgery to combat the hypothalamia – pituitary – adrenal suppression which is likely in patient taking long term oral corticosteroids and to control the hyper-reactivity of tracheo-bronchial tree to different anaesthetic drugs. It is found that hypothalamic -pituitary-adrenal suppression is unlikely as a result of long-term inhaled corticosteroids. The preoperative supplementation of steroid (if stopped before) is considered only when the previous daily dose is > 10 mg of prednisolone or inhaled beclomethasone >1.5 mg/day. Preoperatively oral prednisolone should be converted to IV hydrocortisone (1 mg prednisolone is equivalent to 5 mg hydrocortisone). When preoperative FEV_1 is less then 80%, than a preoperative course of oral corticosteroids must be used, even if patient does not get steroid before.

Opioids have a number of actions on airway. It releases histamine and other vasoactive substances from mast cells and produces bronchoconstriction. It also increases the bronchial smooth muscle reactivity and tone due to the increase in vagal nerve activity. So, the clinical use of opioids in asthmatic patients is controversial. But there is no evidence that opioids, especially the newer synthetic opioids used in doses for preanaesthetic medication or before intubation, stimulates the release of vasoactive substances from mast cells (histamine, LT, PAF) and produce bronchoconstriction. Moreover, it helps to increase the depth of anaesthesia which is mandatory for anaesthetic management of an asthmatic patients and tilts the balance in favour of use of opioids as premedicants or during induction and before intubation. On the other hand, it depresses the ventilating efforts and supresses the ventilating responses to hypoxia and hypercarbia but not in premedicant doses. So, newer opioids are safe in asthmatics in premedication doses.

The use of anticholinergic drugs in the perioperative period is also controversial and should be individualized, remembering that these drugs can increase the viscosity of secretions and make it difficult to remove, causing plugging of smaller

Table 31.7: Classification of severity of bronchial asthma

Severity of asthma	*P_aO_2 (mm of Hg)*	*P_aCO_2 (mm of Hg)*	*FEV_1 (% predicted)*
Normal patient	> 60	< 40	> 80%
Mild asthma	> 60	< 40	65 - 80%
Moderate asthma	> 60	< 45	50 - 64%
Severe asthma	< 60	> 50	35 - 49%
Status asthmaticus	< 60	> 50	< 35%

airways and alveolar collapse. On the otherhand, it decreases the airway resistance by inhibiting the postganglionic cholinergic receptors. Hence the use of anticholinergic agents such as atropine and glycopyrollate depends on the balance between their merits and demerits. The use of H_2 receptor blocker as premedicant to increase the gastric pH in bronchial asthma patient is also controversial. Histamine mediates bronchochonstriction through H_1 receptor and mediates bronchodilatation through H_2 receptor. So, H_2 receptor blocker can potentiate the H_1 receptor induced bronchospasm. But, in clinical practice it has no effect.

Anxiety may precipitate an acute attack of asthma. BDZ acts on GABA receptors present in the airway and attenuate the reflex mediated bronchoconstriction. They also relax airway smooth muscle directly. Therefore, perioperative BDZ are used to provide anxiolysis, but keeping in mind that in acutely ill patients the risk of depressing alveolar ventilation by BDZ is greater and respiratory arrest has been reported to occur shortly after their use. Admittedly, most individuals are anxious and frightened, but experience has been shown that they can be calmed equally well by the physician's presence and reassurances without using benzodiazepine. Hence, the use of benzodiazepine in preoperative preparation will depend on anaesthetist's choice. It should also be kept in mind that a large number of asthmatic patients react adversely to aspirin or any NSAID. So, NSAIDs should be used cautiously during the post-operative period for the treatment of surgical pain.

Intraoperative management

Normally, surgical and anaesthetic stimuli that do not evoke bronchoconstriction in the absence of asthma may precipitate the life-threatening bronchospasm in patients with bronchial asthma. For example, intubation (mechanical stimulus) can precipitate bronchoconstriction easily in asthmatic patient, if reflexes are not obtunded properly by deepening anaesthesia. Different drugs (chemical stimuli) used in anaesthesia can also increase the airway reactivity and precipitate bronchospasm which is not found in normal patient. So, the goal during induction and maintenance of anaesthesia in patients with bronchial asthma is to depress the airway reflexes sufficiently by increasing the depth of anaesthesia and by avoiding the drugs which can precipitate bronchoconstriction if not absolutely necessary or to balance between the prevalance of bronchoconstriction and its beneficial effect.

Regional Anaesthesia

Regional anaesthesia (RA) is an attractive alternative procedure for the patients of bronchial asthma when the operative site is superficial, lower abdominal or on the extremities. Because it avoids instrumentation of airways (intubation) and the use of multiple drugs, responsible for bronchospasm. RA such as low spinal, low epidural or caudal should be preferred for the surgeries on perineum, lower extremities, pelvis, or intra and extra peritoneal organs restricting below umbilicus. Respiratory complications are also quite common with high regional anaesthesia (T_6–T_4) like GA in bronchial asthma patient. So it is not alternative to GA. This is because high RA paralyses the normal and the accessory respiratory muscles in a already compromised patient, necessitating artificial ventilation where GA has great advantage. High RA is also not possible without sedation which further jeopardise the already compromised ventilation process. So, significant differences are not observed in asthmatic patients anaesthetized with high RA and those undergoing GA with ketamine, cisatracurium and isoflurane or sevoflurane. Nevertheless, it must be kept in mind that failed RA and the subsequent need to induce GA is always a possibility.

General Anaesthesia

During GA, induction and intubation in a bronchial asthmatic patient should be done under deeper plane of anaesthesia, because patient may develop bronchospasm in lighter plane. The cuff of an ET tube should be placed just below the cord but not touching it and without irritating the carina. Also the patient should be extubated at deeper plane of anaesthesia avoiding coughing and bucking. However, the risk of aspiration, airway obstruction and hypoventilation due to extubation at deeper plane of anaesthesia should be weighted against its benefits.

For GA, induction is most often accomplished by intravenous injection of short-acting inducing drugs like thiopentone, propofol, benzodiazepine or ketamine. But the effects of barbiturates (thiopentone) on the bronchial smooth muscle varied from relaxation to no effect to constricton. Some evidences also support that thiopentone produces a dose dependent constricton of airways by releasing histamine. Some school again thought that if thiopentone at all does not cause bronchospasm, but it fails to supress the upper airway reflexes and airway instrumentation can trigger bronchospasm. On the other hand, propofol relaxes the airway smooth muscle. But the mechanism of propofol's relative bronchodilating effect is not known. Incidence of wheezing is significantly lower in asthmatic patients induced with propofol than with barbiturates. Even, respiratory resistance following tracheal intubation in healthy patients is lower after induction of anaesthsia with propofol than after induction of anaesthesia with thiopentone. So, based on these observation it can be concluded that propofol is the agent of choice for induction of anaesthesia in patients with bronchial asthma who are haemodynamically stable. Haemodynamically unstable patient can be induced by adequate dose of benzodiazepine. Ketamine depresses the neural airway reflex pathways and directly relaxes the smooth muscle by reducing the intracellular calcium concentration. The catecholamines, released by ketamine have also bronchodilating effect. Again ketamine has also been

used successfully to decrease the airway resistance and to treat the status asthmaticus. So, alternatively ketamine can be used for induction of patients who are actively wheezing. Some generic formulation of induction agents which are available in market contain metabisulfites as preservative and the presence of these metabisulfites causes bronchospasm in patients with hyperactive airways. So, an anaesthetist should be careful of these generic formulation (Table 31.8).

After hypnosis and unconciousness, established by IV inducing agents, it is better to ventilate the patient's lungs with gas mixtures (N_2O and O_2) containing volatile anaesthetic agents. The goal is to further produce a deeper plane of anaesthesia that depresses the hyperactive airway reflexes sufficiently and permit tracheal intubation without precipitating bronchospasm. Otherwise, bronchospasm can be precipitated if tracheal intubation is done without establishing sufficient depth of anaesthesia. It is often assumed that any volatile anaesthetic agent at comparable doses is equally effective producing bronchodilation. Lesser pungency of halothane and sevoflurane (compared with isoflurane) may make coughing less likely as coughing may trigger bronchospasm. On the other hand, halothane is not ideal as it sensitizes the myocardium to catecholamines which remain at high level in asthmatic patients causing arrhythmias. Again, it is also known that the effect of sevoflurane on the airways resembles those of halothane and isoflurane. So, at conclusion, considering all aspects, it is thought that sevoflurane is the more suitable agent in patients with bronchial asthma. However, some school thought that halothane has the maximum bronchodilating effect and is more potent than sevoflurane. So, it is the best suitable agent in asthma patient producing deeper plane of anaesthesia easily and maximum bronchodilatation. The mechanism of bronchodilating effect of volatile anaesthetic agents is due to their direct effects on the airway smooth muscles. This is explained by the fact that they block the intracellular calcium influx, impair calcium release from the sarcoplasmic reticulum and disrupt the mechanism that sensitizes the myofilament contractile system to calcium. Except bronchodilatation, they also attenuate the responses of bronchial smooth muscle to broncho constricting stimuli. This action is due to the alteration of liberation of acetylcholine and the depression of ganglionic transmission in the vagal pathway.

An alternative technique to the administration of volatile anaesthetic agents which supress the airway reflexes before muscle relaxant, laryngoscopy and tracheal intubation may be the intravenous injecton of lignocaine. Lignocaine in the dose of 1 to 1.5 mg/kg through IV, administered 2 to 3 minutes before muscle relaxant, laryngoscopy and tracheal intubation is helpful for preventing reflex bronchoconstriction. Intravenous lignocaine antagonises both the reflexes and antigen induced bronchospasm in hyper reactive airway. It also relaxes the smooth muscles of airways in higher concentration. But lignocaine spray over the larynx and vocal cords before intubation has both advantages and disadvantages. The beneficial effect is surface anaesthesia produced by lignocaine block the stimuli from the laryngoscopy and intubation. But, the disadvantage is that lignocaine spray itself produces bronchospasm by placing the solution like foreign body into hyperactive airway of asthma patients which is not found in normal individuals. However, clinical evidences show that at good level of anaesthesia, lignocaine spray does not initiate bronchospasm.

The skeletal muscle relaxation for intubation and maintenance of anaesthesia is often obtained by nondipolarizing muscle relaxants. The selection of muscle relaxant for bronchial asthma patient depends mainly on the property of the release of histamine by these drugs. Drugs which release minimum amount of histamine or none is preferred for asthma patients. Non-depolarising neuromuscular blocking drugs which cause histamine release should be avoided and they are listed on the table. After tracheal intubation, it is sometimes very difficult to differentiate between in sufficient muscular paralysis from bronchospasm as a cause of decreased lung compliance. This can be helped by adding additional dose of muscle relaxant (Table 31.9).

Succinylcholine also causes the release of histamine, but to a lesser extent. Hence, there is no evidence that this drug is associated with increased airway resistance when administered in patients with bronchial asthma. Reversal of neuromuscular blockade by neostigmine and other cholinesterase inhibitor could theoretically

Table 31.8: Substances influencing bronchial smooth muscle tone

A. Bronchodilatation

1. β_2- sympathomimetics:
   Salbutamol, terbutaline, isoprenaline, adrenaline, ephedrine, etc.
2. Xanthine derivatives:
   Aminophiline, theophylline, caffine, etc.
3. Volatile anaesthetics:
   Halothane, isoflurane, sevoflurane, ether, etc.
4. Nitrites :
   Amyl nitrite, glyceryl trinitrate.
5. Prostaglandin E_1 and E_2:
   Allergic reaction, infusion, etc.
6. Muscarinic cholinergic receptor blockers :
   Atropine, glycopyrrolate, etc.

B. Bronchoconstriction

1. Muscarinic cholinomimetics
   (a) Anticholinesterases:
   Neostigmine, pyridostigmine, physostigmine, edrophonium, etc.
   (b) Choline esters and alkaloids:
   Pilocarpine, carbacol, methacol, etc.
2. β_2-adrenergic blockers:
   Atenolol, propranolol, etc.
3. Autacoids:
   Histamine, 5-HT, kinins, PG-$F_2\alpha$, etc.
   (a) Histamine releasing drugs:
   Pancuronium, atracurium, morphine, thiopentone, etc.
   (b) Allergic reactions
   (c) Carcinoid tumours
   (d) Prostaglandin administration

Table 31.9: Benzylisoquinoline and steroidal compounds

Muscle relaxants	*Doses causing release of histamine*
A. Benzylisoquinoline compound	
d - Tubocurarine	0.6 × ED_{95}
Metocurine	2 × ED_{95}
Doxacurium	4 × ED_{95}
Mivacurium	3 × ED_{95}
Atracurium	2.5 × ED_{95}
Cisatracurium	None
B. Steroidal compound	
Pancuronium	Minimum
Vecuronium	None
Pipecuronium	None
Rocuronium	None

cause bronchospasm. However, when administered with the anticholinergic drugs like atropine or glycopyrrolate, then neostigmine does not significantly change the airway resistance.

Intraoperatively the desired level of P_aO_2 and $ETCO_2$ is best maintained by mechanical ventilation. Ventilation should be controlled with warmed humidified gases whenever possible. Airflow obstruction during expiration due to bronchospasm is apparent on capnography as a delayed rise of the end-tidal CO_2 value. The severity of obstruction is generally inversely related to the rate of the rise in end-tidal CO_2 tension. For ventilation in asthma patient low inspiratory flow rate is used which provides optimal distribution of ventilation against perfusion. Severe bronchospasm is manifested by rising peak inspiratory pressures and incomplete exhalation. In the past, tidal volumes of 10 to 12 ml/kg with ventilatory rates of 8 to 10 breaths/minute were considered desirable. However, currently, minimizing the tidal volume (<10 ml/kg) with prolongation of expiratory time may allow the more uniform distribution of gas flow to both the lungs and may help to avoid air trapping during expiration. This is because during expiration sufficient time should be given to prevent air trapping in alveoli in the presence of expiratory air flow obstruction which is a characteristic of bronchial asthma. PEEP is not ideal for asthma patient as it may impair exhalation in the presence of narrowed airways (Fig. 31.11).

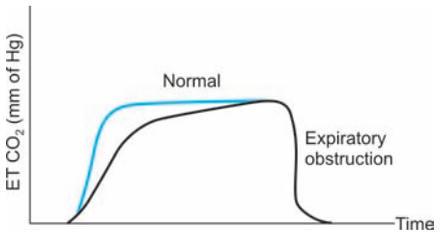


Fig. 31.11: Capnograph of a normal patient compared with expiratory airway obstruction patient (red line)

Humidification and warming of inspired gases is very vital. Nevertheless, it must be appreciated that sometimes humidification as produced by ultrasonic nebulisers and pneumatic aerosols can produce bronchospasm. Liberal use of IV fluid is mandatory during perioperative period. It helps adequate hydration and ensures the presence of less viscous secretions which can be expelled more easily. For patients with history of bronchial asthma, it is prudent to remove the endotracheal tube while anaesthesia is still in deep level. It avoids hyperreactive airway reflexes, causing bronchospasm during extubation. If there is risk of gastric aspiration, then extubation should be done when the patient is awake, but there is chance of reflex bronchospasm. However, it can be managed by continuous IV infusions of lignocaine in the dose of 1 to 3 mg/kg/hour.

Intraoperative bronchospasm

When the bronchospam occurs during intraoperative anaesthetic period, then it should be differentiated from other conditions which also reduce the pulmonary compliance and mimic bronchospasm.

For example, the conditions which mimic the intraoperative bronchospasm are:

i. mechanical obstruction of tracheal tube due to kinking, secretions, etc.
ii. endobronchial intubation,
iii. pulmonary oedema,
iv. pulmonary aspiration,
v. pulmonary embolism,
vi. pneumothorax,
vii. during spontaneous respiration, active expiratory efforts due to inadequate depth of anaesthesia.

When the diagnosis of intraoperative bronchospasm is established, then the priority should be given to increase the depth of anaesthesia by increasing the inspired concentration of volatile anaesthetic agents. Intravenous agents such as ketamine, propofol and lignocaine may also be useful to increase the depth of anaesthesia. Then, the conditions which are mimicking the acute bronchospasm should be searched for and treatment should be instituted according to the cause.

If it is confirmed that there is definite bronchospasm, then β_2-agonist should be nebulised through the endotracheal tube, keeping in mind that the requirement is more due to decreased efficiency of the drug delivery system to the lung compared to unanaesthetised ambulatory patients. In extreme circumstances, inhaled β_2-agonist are ineffective due to inadequate tidal volume. In such circumstances intravenous adrenergic agonists such as epinephrine may be necessary. Intravenous aminophylline does not provide any additional benefit over halothane. Further, it may produce dysrythmias that may accompany severe bronchospasm. Parenteral corticosteroid may be administered but it takes several hours (3 to 4 hours) to get the effect. The parameters of mechanical ventilation should be adjusted accordingly to prevent the gas trapping and barotrauma by minimising the airway pressure and prolonging the expiration.

Post-operative management

The post-operative respiration of a bronchial asthma patient must be monitored very carefully. Venturi mask with FiO_2 of 0.24 to 0.40 should be used for oxygen therapy during the immediate post-operative period. Regional nerve blocks and TENs may be used to provide post-operative analgesia without using narcotics and

depressing respiration. Following the major abdominal or thoracic surgery, good pain control is important and epidural analgesia is frequently the best choice, provided the widespread intercostal block is avoided. The narcotics for analgesia should be used very carefully for post-operative bronchial asthma patient, because respiratory depression may further compromise the airway. Morphine is contraindicated due to their histamine release property. Pethidine is safer than morphine and can be used in PCA. Fentanyl or its congeners may be the better choice. Ideally NSAIDs are to be avoided, though precipitation of bronchospasm due to the production of leukotrienes is not very common (only 5 to 10% cases). But they can be used if they have been tolerated before. If there is increasing dyspnoea and wheezing after surgery, then other conditions such as LVF, pulmonary embolism, fluid overload, etc, which may mimic bronchospasm should also be considered.

Drugs which are considered safe for bronchial asthma patients are:

Inducing agents: Propofol, ketamine, midazolam
Narcotics: Pethidine, fentanyl, sufentanil, etc.
Muscle relaxants: Succinylcholine, vecuronium, rocuronium, pancuronium, etc.
Volatile agents: Halothane, isoflurane, sevoflurane.

Prophylaxis of perioperative bronchospasm can be instituted by the following measures:

i. Continued bronchial asthma pharmaco-therapy upto the time of anaesthesia and surgery.
ii. Inhalation of β_2-agonists before induction.
iii. Corticosteroid replacement therapy.
iv. Preoperative anxiolysis.
v. Prefer regional anaesthesia, if possible.
vi. Tracheal intubation at deeper plane of anaesthesia but never at light plane.
vii. Avoid anaesthetic agents, which increase the airway reactivity.

Emergency surgery

The Bronchial asthmatic patient waiting for emergency surgery is a two-way sword. Because patients are presented usually with full stomach. So, one way of the sword is that intubation in light plane of anaesthesia or awake intubation to prevent pulmonary aspiration triggers bronchospasm. Second, if anaesthesia is deepened to prevent the reflexly initiated bronchospasm, then there is higher risk of pulmonary aspiration. So, an anaesthetist have to balance between these two and the intensity of emergency of the surgery. Furthermore, there is often insufficient time to optimize the bronchodilatation and corticoid therapy prior to surgery. So, regional anaesthesia is always preferred, if the site of surgery suits properly and permits in such situations.

CHRONIC OBSTRUCTIVE LUNG DISEASE (COLD) OR CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

The symptoms of COLD usually start after the age of about 55 years. The most common symptom of it is breathlessness. But there is often a combination of cough, wheeze and increased production of sputum with the shortness of breath in COLD. The majority of patients having COLD are tobaco smokers for a significant period of their lives. Other factors associated with COLD include: (i) occupational exposure to dusts and atmospheric pollutions, (ii) poor socioeconomic status, (iii) repeated viral infections, (iv) α-1-antitrypsin deficiency, etc. Chronic bronchitis, airway obstruction and emphysema are the three distinct components of COLD and they are most often present in different combination. Among these three pathologies, chronic bronchitis progressively lead to chronic obstructive bronchitis with extra addition of obstruction to airflow which is not fully reversible. Chronic obstructive bronchitis is also termed as chronic asthmatic bronchitis and when it is developed, then COLD consists of two components – chronic asthmatic bronchitis and emphysema (Fig. 31.12).

The chronic bronchitis is defined as a condition where there is excessive tracheobronchial mucus production for atleast 3 months of the year and for more than 2 consecutive years due to inflammation of airways, (but at this phase there is no bronchoconstriction and obstruction). The chronic bronchitis has two parts: hypersecretion of mucus and inflammatory changes. Chronic obstructive bronchitis which is the 2nd phase of COLD is also defined as the condition where there is both the excessive secretion of mucus and inflammation due to chronic bronchitis and obstruction due to bronchospasm, and experience both the severe dyspnoea and wheezing. Such patients are also said to have chronic asthmatic bronchitis as there is both the picture of chronic bronchitis (secretion and inflammation) and asthma (obstruction). It is characterised by partial reversibility of air flow obstruction with bronchodilator and abatement of inflammation. These group of patients also show the hyper responsiveness of airway to nonspecific stimuli, like bronchial asthma patients. So, confusion may persist between the chronic bronchitis with obstruction (chronic asthmatic bronchitis)

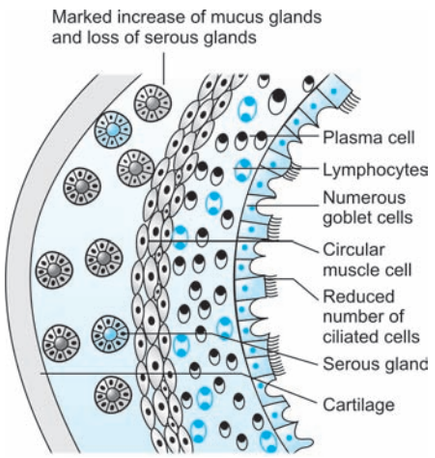


Fig. 31.12: The microscopic picture of airways of patient suffering from COLD

and those of pure bronchial asthma who also may have chronic airways obstruction with inflammation. Thus the difference between the two is that patients with chronic asthmatic bronchitis have a long history of sputum production and cough (i.e. only bronchitis part at beginning) with a later onset of wheezing (asthmatic part). Whereas the bronchial asthma patients with chronic obstruction will first give a long history of wheezing with later onset of chronic productive cough. Emphysema which is the third component of COLD is defined as the permanent, abnormal distension of air spaces distal to the terminal bronchiole with destruction of alveolar septa.

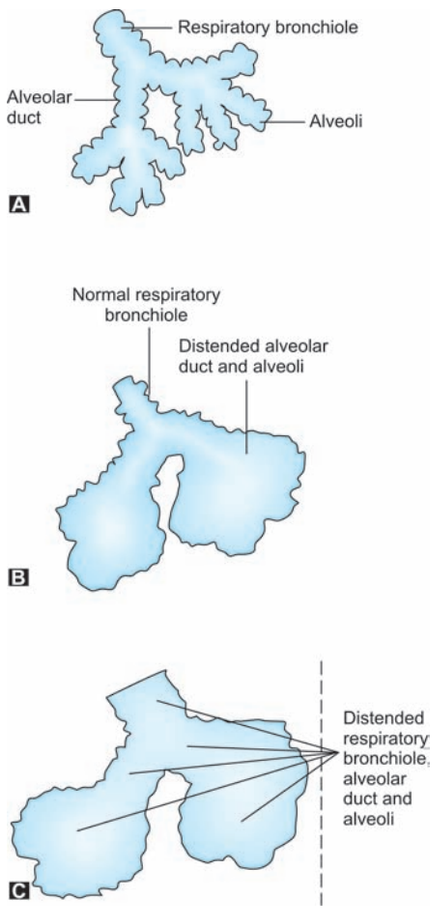
So, COLD = Chronic Obstructive bronchitis or Chronic Asthmatic Bronchitis (chronic bronchitis + asthma) + emphysema.

Patients suffering from COLD with predominant emphysema is thin, tachypnoeic and breathless at rest. They are described as 'pink puffer'. Though they are hypoxic, but CO_2 retention develops only as a late or terminal event. Whereas, patients suffering from COLD with predominant chronic bronchitis are frequently overweight with marked peripheral oedema, poor respiratory effort and CO_2 retention. They are described as 'blue bloater'. This classical two stero typed picture of 'pink puffer' and 'blue bloater' are relatively infrequent as majority of patients have a combination of features. In 'pink puffers' which is associated with emphysema P_aO_2 is usually higher than 65 mm of Hg though hypoxic and P_aCO_2 is normal to slightly decrease. Whereas, in 'blue bloaters' which is associated with bronchitis P_aO_2 is usually lower than 65 mm of Hg and P_aCO_2 is increased to more than 45 mm of Hg.

Pathology of Bronchitis and Emphysema of Cold

The hypertrophy of mucus producing glands in the submucosa layer of large cartilaginous airways, increase in number of goblet cells, reduced number of ciliated cells, increased number of neutrophil – lymphocyte-plasma cells are the usual findings of chronic bronchitis of COLD. So, it is characterized by hypersecretion of mucus, less secretion of serous fluid and inflammatory changes in bronchi. This causes daily cough and large sputum production. On the other hand, due to loss of ciliated epithelium and decrease of serous secretion, a large quantities of viscid mucus secretion becomes difficult to eliminate. Thus, there is always a tendency of retention of secretion in the airway which encourages the bacterial growth. So, a viscious cycle may be set up which leads to chronic bronchitis. This viscious cycle is like that increased and retention of secretion → bacterial growth → repeated attack of infection and inflammation → repeated attack of chronic bronchitis. Thus, with repeated acute exacerbation of inflammation and increasing retention of secretion, there is gradual spread of chronic inflammatory changes along the bronchial tree and more and more damage is encouraged. When the terminal bronchioles are affected, then more serious changes take place. These are : seepage and retention of exudate in alveoli → leading to bacterial infection → leading to patches of pneumonia during acute exacerbations. All these factors with lack of ciliary function make the airway difficult to get rid of exudate which hinders resolution. Healing takes place by organisation of fibrosis, causing obliteration of small alveoli and bronchioles and leading to obstruction during expiration. Thus, emphysema develops. Chronic bronchitis is most common in industrial areas with high rain fall. In its serious form, it usually occurs in males over the age of 40, but the onset can be dated many years earlier. The prognosis of chronic bronchitis is poor. The death often occurs within 5 years, after the first episode of acute respiratory failure (Figs 31.13A to C).

Emphysema is a condition where there is a permanent increase in the size of air spaces, distal to the terminal bronchiole. With the increase in size of air spaces, there is also destructive changes in the walls of the air spaces. Usually emphysema is of two types: alveolar or centrilobular emphysema and panacinar emphysema. In centrilobular emphysema there is no enlargement of lung. The distension and destruction are mainly limited to the respiratory bronchioles with relatively less changes in the acinus at periphery. So, there is little radiological evidence of emphysema, because the alveolar tissue is normal. These changes are extremely common in normal lungs of persons who are above the age of 50. In panacinar emphysema, where the process is extensive, distension eventually spreads to involve the respiratory bronchiole and the whole acinus. Thus the whole lungs



Figs 31.13A to C: A. Normal lung parenchyma, B. Alveolar emphysema, C. Panacinar emphysema

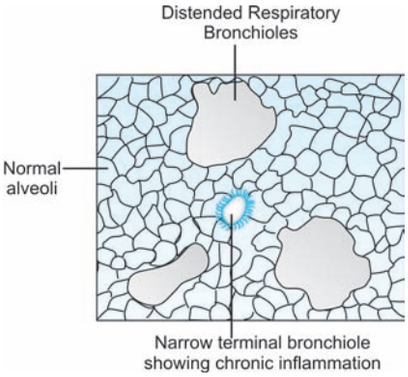


Fig. 31.14: Centrilobular emphysema. Chronic inflammation of the terminal bronchioles is an important feature. In this type of leison there is little radiological evidence of emphysema because the alveolar tissue is normal for a considerable time

become distended with definite radiological findings (Fig. 31.14).

Pathophysiology

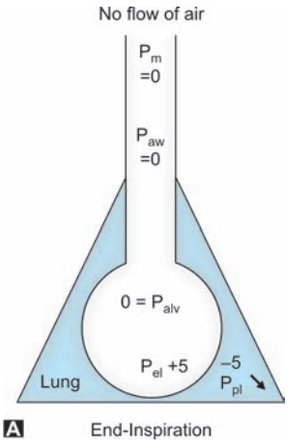
In COLD patients, initially both the chronic bronchitis and emphysema can exist without any evidence of obstruction in airways. But later by the time when a patient begins to experience dyspnoea as a result of these processes, then obstruction is always demonstrable. Thus when the two processes (bronchitis with obstruction and emphysema) are combined, then one process may dominte over the other. The therapeutic improvement of this condition depends on the extent of inflammatory airway disease, the quantitative presence of secretions and bronchospasm. Both the chronic bronchitis and emphysema result in airways narrowing. The airways narrowing in chronic bronchitis is due to inflammation, secretions, hyperactive reflexes, etc. But loss of elastic recoil of the lung in emphysema accounts for a decrease in airway caliber through the loss of radial traction on airways. In both situations (i.e. chronic bronchitis and emphysema) narrowing of airways (abstruction) is often associated with an increase in airways resistance and a diminuation of maximal expiratory flow rates.

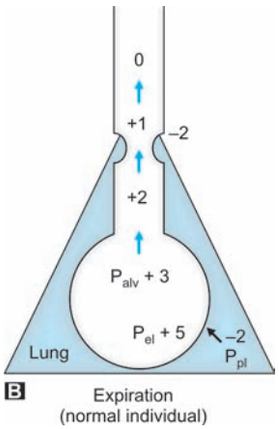
Mechanism of Diminution of Expiratory Flow Rate

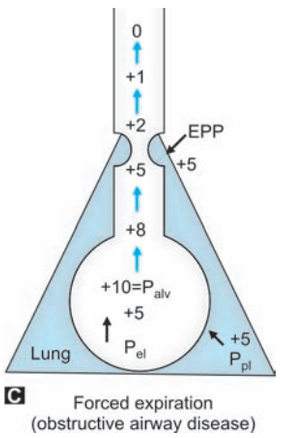
The failure to increase the flow rate by augmented expiratory effort during expiration results from the dynamic compression of airways. This can be described by a point named EPP (equal pressure point). During expiration the pressure head that helps to move the air from alveoli to mouth is provided by the P_{alv} (intra alveolar pressure). At any fixed state of the dynamic process of respiration and at any given lung volume the P_{alv} is the sum of distending P_{pl} (negative intra pleural pressure) and recoiling Pel (lung's elastic recoil pressure). At the end of inspiration, when there is no flow of air, then the P_{alv} becomes zero, i.e becomes equal to the pressure of atmosphere at the level of mouth. At that condition, P_{pl} is maximum subatmospheric (i.e −ve) but equal to and counter balances the P_{el} (which is always +ve). During expiration due to passive reduction of thoracic volume, P_{pl} (intrapleural pressure) becomes less negative and P_{alv} rises. This increased alveolar pressure head gradually decreases along the airway and finally reaches to zero at the level of mouth. When this pressure is gradually decreasing along the airway from alveoli to mouth then at some point on the airway the intraluminal pressure comes to a level that is equal to the surrounding P_{pl}. This point is called as the EPP and airways start to collapse at this level. During normal expiration the P_{pl} does not usually become equal to the intraluminal pressure at any point through out the airway from alveoli to mouth and the EPP never develops and the airway closure usually does not occur. But during forceful expiration P_{pl} rises and sometimes may become +ve. Intra-alveolar pressure (P_{alv}) also rises with forceful expiration, but it is gradually coming down along the airway towards the mouth and at mouth it becomes zero, i.e. equal to the atmospheric pressure. Along the airway when the intraluminal pressure is gradually coming down, then at point situated anywhere on the airway between the alveoli and the mouth the P_{pl} becomes greater than the intraluminal pressure and EPP develops and airways start to close at that site. If the EPP falls on the airway where cartilages are present, i.e. proximal to the eleventh generation of airways, then airways do not collapse. But, if the EPP falls on the airway where there is absence of cartilages, i.e. distal to the 11th generation of airway, then only these airways are vulnerable to collapse. However, EPP is not a fixed point on airway, but a dynamic one. It changes according to different conditions such as P_{pl}, P_{alv} force of expiration, compliance, etc. (Figs 31.15A to C).

In normal lungs airway usually does not close and if closes it occurs first at the basal portion of lungs and in the small airways of 0.5 to 0.9 mm of diameters. In normal healthy lungs airway does not collapse at the end of expiration, because P_{pl} is though high (i.e. less −ve) than begining of expiration but still subatmospheric (or negative). During forceful expiration airways closer occurs first in the basal region because the distending negative or subatmospheric P_{pl} becomes first positive in this region and volume changes during expiration is greater.

Early or premature airway closer and reduction of expiratory flow rate with air trapping in alveoli occurs with slight active expiration in patients suffering from emphysema, bronchitis, asthma, and interstitial oedema. In these four conditions, airway resistance is increased which causes a quick and larger decrease of pressure gradient from alveoli towards mouth. Therefore, it causes potential negative intraluminal and P_{pl} pressure gradient and early collapse of airways with shifting of EPP more towards the alveoli. In addition, the structural intigrity of airways is diminshed due to chronic inflammation and scarring which also causes early closure of airways with shifting of EPP towards alveoli at high lung volumes in the above mentioned diseases. Thus FRC is increased.







Figs 31.15A to C: The concept of EPP (equal pressure point). Also it tries to explain the mechanism of diminuation of expiratory flow during forced expiration.
A. End of inspiration,
B. Expiration in normal individual,
C. Forced expiration in obstructive pulmonary disease.
P_m =Pressure at mouth, P_{aw} = Airway pressure

In COLD patients RV (residual volume) and FRC are almost always higher than normal. Normal FRC is the volume at which inword elastic recoil force of lung is balanced by the outward distending force of chest wall. So the loss of inward elastic recoil property of lung in emphysema results in higher FRC. Again, prolongation of expiration due to obstruction and initiation of inspiration before the respiratory system reaches its static balance point during expiration, causes dynamic increase in FRC. With the increase of RV and FRC due to decreased elastic recoil of lung, total lung capacity (TLC) also increases (Fig. 31.16).

Both the increased airway resistance (due to mechanical obstruction – spasm) and increased lung compliance (due to loss of recoil lung eleasticity – emphysema) is responsible for prolonged expiration and long time constant (which is described later). Prolonged time for expiration signify insufficient time for expiration especially during tachpnoea, and even at normal respiratory rate. So, after every expiration lungs fail to return to their previous FRC. Thus this leads to progressive increase in lung volume which, in turn, push the tidal volume to a higher less compliant portion of the pressure-volume curve and increaes the work of breathing. Intrinsic PEEP (PEEPi) or auto PEEP is a common finding in such patient with chronic airflow obstructive disease. Additionally, hyperinflation of lungs cause flattening of the diaphragm and places it at a mechanical disadvantageous position. This disadvantageous position of diaphragm is due to the length tension relationship of diaphragmatic muscle fibres, the angle of diaphragmatic insertion with the lower ribs and Laplace's law. This is always presented as mismatched ventilation/perfusion ratio. When these mismatches are severe, then the impairment of gas exchange is reflected in the abnormalities of arterial blood gases.

There are some regions of lungs that have deficit of perfusion in relation to ventilation and it increases the wasted ventilation. Alternatively, there are some regions of lungs that have deficit of ventilation in relation to perfusion and it increases the wasted perfusion. Thus, in chronic bronchitis with obstruction and emphysema, there are increase in both the wasted ventilation and wasted perfusion. The resultant effect of this wasted ventilation and wasted perfusion is different for different patients. Some patients at the cost of extremely high effort of breathing and chronic dyspnoea maintain a strikingly increased minute volume which results both in a normal to low artrial PCO_2 and a relativley high arterial PO_2, despite high V_d / V_t and high $P_AO_2 – P_aO_2$ difference respectively. Other patients show only modest increase in minute volume and effort of breathings with less dyspnoea, which results in high

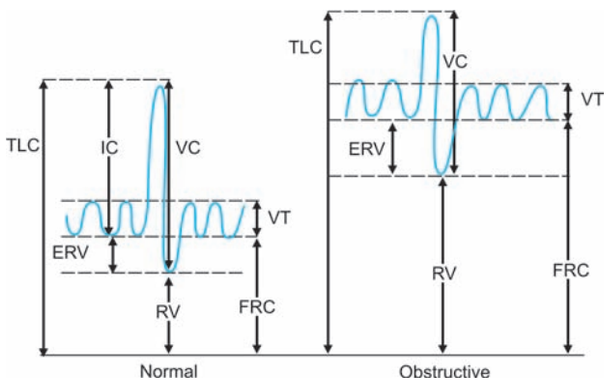


Fig. 31.16: Different lung volumes in spirogram during chronic obstructive pulmonary disease compared with normal values. In the presence of obstructive lung disease, VC is decreased, RV and FRC is increased, TLC is increased, RV / TLC ratio is increased

P_aCO_2 and severly depressed P_aO_2. The explanation behind this patient to patient difference is that the patients who maintain low arterial PCO_2 levels are of highly responsive type and have increased ventilatory drive in response to their high blood gas values. Those who chronically maintain high P_aCO_2 and low P_aO_2 levels have a diminished ventilatory drive in relation to their more severly deranged blood gas values (Table 31.10).

COLD is often associated with mild to severe pulmonary hypertension. Pulmonary hypertension is due to the reduction of total cross sectional area of pulmonary vasculature. This can be attributed to anatomical changes and constriction of vascular smooth muscle in pulmonary arteries and arteriols as well as destruction of alveolar septa with loss of capillaries. The most important is constriction of the pulmonary capillaries in response to alveolar hypoxia and this vasoconstriction is reversible which depends upon the alveolar PO_2.

According to the arterial blood gas analysis, the COLD patients are divided into 'pink puffers' where P_aO_2 is usually higher than 65 mm of Hg and P_aCO_2 is normal to slightly decreased and 'blue bloaters'where P_aO_2 is usually lower than 65 mm of Hg and P_aCO_2 is chronically increased to more than 45 mm of Hg. 'Pink puffers' individuals are typically thin build, free of signs of right heart failure and are usually found to have severe emphysema. On the other hand, 'blue bloaters' typically exhibit excessive cough and sputum production, frequent respiratory tract infections and recurrent episodes of cor pulmonale. In pink puffers, emphysema component predominates over bronchitis with obstruction component. Whereas the blue boaters individual more often meet the criteria of chronic bronchitis with obstruction than emphysema. But the common denominator in all these patients is chronic cigarette smoking. The Blue bloater patients usually develop pulmonary hypertension due to arterial hypoxaemia and respiratory acidosis which evoke pulmonary vasoconstriction. In response to chronic pulmonary hypertension, right ventricular hypertrophy and corpulmonale is developed. Later on right ventricular failure results with jugular venous congestion, peripheral oedema, systemic venous hypertension, etc. Patients with COLD who are characterised as pink puffers experience emphysematous lung destruction leading to loss of pulmonary capillaries as a result of destroyed alveolar walls. The subsequent loss of the pulmonary capillary vascular bed is manifested as decreased diffusing capacity, although the PaO_2 is typically only mildly depressed such that pulmonary vasoconstriction is minimal and cor pulmonale develops only rarely in these patients.

Table 31.10: Classification of COLD

Severity	*Spirometry*	*Symptoms*
Mild cold	FEV_1 60-80% of normal	Cough ± breathlessness on exertion
Moderate COLD	FEV_1 40-60% of normal	Cough + Breathlessness on exertion, ± Wheeze, ± sputum
Severe COLD	FEV_1 <40% of normal	Prominent cough, wheeze and breathlessness

What is time constant?

It is defined as the time taken by the alveoli to reach its final volume if the initial gas flow rate is maintained throughout the inflation. Usually the normal inspiratory time is 1 to 1.5 second. A long inspiratory time increases the mean intrathoracic pressure and reduces the venous return with reduction of cardiac output. On the otherhand, short inspiratory time causes poor distribution of the inspired gases throughout the lungs.

If the airway leading to an alveoli is narrowed and the resistance is increased, then the alveoli will still reach the same volume when inflated at same pressure. But it will take longer time to reach the final volume. Again if the wall of the alveoli is stiffened and compliance is decreased, then the alveoli will also take longer time to reach the final volume when inflated at same pressure. Thus the time constant depends on the resistance and compliance of the system and the relation is:

Resistance × compliance = Time constant

Typical values of resistance and compliance for an anaesthetized patient are 10 cm H_2O/L and 50 ml/cm H_2O (or 0.05 L/cm H_2O). So, the normal time constant is 10 × 0.05 = 0.5 second.

An increase in resistance and decrease in compliance result in longer time constant. Usually 94% of the final volume of lungs reaches within the 3 time constant due to different types of alveoli. This scattering of time constant is exaggerated in some forms of lung diseases such as asthma and emphysema. In such circumstances a short inspiratory time will result in poor ventilation of those zones of lung having a long time constant. Thus there will be a resulting increase in V/Q mismatch (Table 31.11).

Anaesthetic Management of COLD

The anaesthetic management of patients suffering from COLD and waiting for surgery include :

i. preoperative evaluation of pulmonary function – by history, clinical examination, investigation and PFTs (pulmonary function test),
ii. treatment of COLD in the preoperative period to optimise the pulmonary function,
iii. intraoperative management aimed at minimizing pulmonary complications and minimizing residual depressant effects of anaesthetic drugs on respiration post-operatively,
iv. post-operative pain control and pulmonary care to reduce the pulmonary complications.

Table 31.11: Difference between pure chronic bronchitis and emphysema (component of COLD)

Features	*Ch. bronchitis*	*Emphysema*
Airway obstruction (mechanism)	Due to mucus or inflammation	Nil
Cough	Frequent	Very less frequent
Dyspnoea	Less frequent	More frequent
Sputum	Copious	Scanty
P_aO_2	Markedly decrease (blue bloater)	Less decrease (pink puffer)
P_aCO_2	Often elevated (> 40 mm of Hg)	Usually normal or hypo (<40 mm of Hg)
FEV_1	Decrease	Decrease
TLCO	Normal	Decrease
Haematocrit	Increase	Normal
Elastic recoil	Normal	Decrease
Airway resistance	Increase	Normal to slightly elevated
Chest radiograph	Increased lung markings	Hyperinflation
Cor pulmonale	Early manifested	Late manifested
Prognosis	Poor	Good

Preoperative evaluation

Preoperative evaluation of patients with COLD is based on the recognition that perioperative pulmonary complicatoins are of predictable risks, with increased morbidity and mortality due to pneumonia, atelectasis, bronchospasm, acute respiratory failure requiring mechanical ventilation, etc. So the history, clinical examination, investigation and PFT of patients suffering from COLD provide a more accurate assessment of the likelyhood of perioperative pulmonary complications. History and clinical examinations are more important than the PFT and blood gas analysis for assessment of risks and complications. History of exercise intolerance, chronic cough, unexplained dyspnoea, etc. are very important and is directly related to the increased mortality. Decreased breath sound, wheezing and prolonged expiratory phase on clinical examination predict increased risk of perioperative pulmonary complications. However, the value of PFTs done as a routine preoperaitve evaluation of perioperative risk is in doubt. Usually, PFT is taken as a reference point during management and optimisation of pulmonary function in perioperative period, but not as a means to assess the risks. Preoperative lung function tests (PFTs) are also useful tools for assessing the lung functions and responses to the therapy. But these tests do not provide predictive information as to the likelyhood of the rate of postoperative pulmonary complications. This is because, patients defined as high risk by PFT (FEV_1 < 70% of predicted value, FEV_1 / FVC less than 65%, P_aCO_2 > 45 mm of Hg) can undergo surgery with an acceptable risk of perioperative pulmonary complications. Potential risk factors of patients with COLD for development of perioperative pulmonary complications are: smoking, operative site, anaesthetic drugs, advanced age, poor general health, etc.

Smoking increases perioperative pulmonary complications many fold in patient who is suffering from COLD. So, cessation of smoking before operation is advised strictly, although the sufficient time required for reversible changes to occur after cessation of smoking is not correctly known. Operaive site is also the most important predictor of the perioperative pulmonary complications. Upper abdominal and thoracic surgery create the greatest risks. Perioperative pulmonary complications are less likely following operations outside the thorax and the abdomen. Duration of surgery is also an important factor for the development of pulmonary complications. Duration of surgery more than 3 hours increases the risks. Anaesthetic drugs and surgical trauma disrupts the normal activity of respiratory muscles causing persistant decrease in FRC and VC with atelectasis that can last for several days after surgery, leading to increased pulmonary complications.

Preoperative preparations

The preoperative preparations of patients suffering from COLD include:

i. Stoppage of smoking,
ii. Treatment of expiratory outflow obstruction such as bronchospasm,
iii. Eradication of bacterial infection,
iv. Physiotherapy regarding lung volume expansion manoeuvres.

To stop the cigarette smoking is strongly recommended for patients before undergoing elective surgey, as the risk of post-operative pulmonary complications predictably increases many-fold with smoking. Till now the optimal period of abstinence from smoking before elective surgery is not clearly known. But, it is clear that even a brief period of abstinence from smoking improves the oxygen carrying capacity of arterial blood. Because the adverse effects of CO (carbon monoxide) on O_2 carrying capacity of Hb and adverse effects of nicotine on CVS are short-lived. Sympathomimetic effects of nicotine on CVS are transient, lasting for only 20 to 30 minutes. The elimination half-life of CO is 4 to 6 hours. So, the smoke free intervals of at least 12 hours should result in substantial decrease in carboxy haemoglobin levels. Experimentally, it is seen that 12 hours abstinence from smoking increases P_{50} value of Hb (the PO_2 at which Hb is 50% saturated) from 22 to 26 mm of Hg and the plasma levels of carboxy haemoglobin decreases from 6 to 1%. Increased levels of carboxy haemoglobin in blood can cause the pulse oximeter to falsely overestimate the SPO_2 level. Cigarette smoking also causes the hypersecretion of mucus, impairment of mucociliary transport activity and narrowing of the smaller airways. So, abstinence from smoking definitely decreases the sputum production, and improves ciliary action and smaller airway function. But these actions of

recovery occur slowly over period of weeks, after cigarette smoking is stopped. Only the effects of smoking on COHb improves faster with short-term abstinence. It is found that when abstinence from cigarette smoking in longer than 8 weeks, then the incidence of post-operative pulmonary complications decreases significantly.

Smoking also interferes the function of immune system and increases the incidence of post-operative pulmonary infections after anaesthesia and surgery. Return of normal immune function may require at least 6 weeks of abstinence from smoking. Smoking also stimulates the hepatic enzymes which increases the post-operative analgesic requirement. Like immune response, 6 to 8 weeks of abstinence from smoking makes return of the hepatic enzyme to normal level. Cessation of smoking helps to diminish the symptoms of chronic bronchitis. It also helps to eliminate the accelerated loss of lung functions observed in those who continue to smoke. For preoperative preparation of COLD patients, chronic administration of O_2 (2 L/min for few hours per day) is recommended if the P_aO_2 is less than 55 mm of Hg (the goal is to achieve P_aO_2 between 60 to 80 mm of Hg), the haematocrit is more than 55% or there is evidence of cor-pulmonale. Relief of arterial hypoxaemia by administration of O_2 is very effective than any drug in decreasing pulmonary vascular resistance and preventing excessive erythrocytosis with associates increase in blood viscoity.

Preoperative administration of broad spectrum antibiotics is indicated if there is acute episodes of worsening of clinical symptoms which is marked by increased dyspnoea, excessive purulant sputum production, wheezing, etc. Vaccinations against influenza and possibly pneumococcus may be beneficial. If exacerbations of COLD is due to the viral infections of upper respiratory tract, then preoperative antibiotic treatment will not be helpful. Drug induced diuresis may be considered for patients with cor-pulmonale and right ventricular failure (peripheral oedema). Diuretic induced chloride depletion may also result in hypochloremic metabolic alkalosis that depresses the ventilatory drive and may aggravate the chronic CO_2 retention.

Another mainstay of preoperative preparation of patients suffering from COLD is bronchodilation. Though it causes only a small increase in FEV_1 in patients with COLD, but these drugs reduce the symptoms and dyspnoea. Bronchodilators such as mainly β_2-agonist improves exercise tolerance, though there is little improvement in spirometric measurements or values. β_2-agonist also decreases the exacerbation of infections by reducing the adhesiveness of bacteria such as haemophilus influenze with epithelial cells. But anticholinergics are more effective in the treatment of COLD than β_2-agonist which is more effective in the treatment of bronchial asthma.

Another risk reduction strategy during preoperative preparation to decrease the incidence of post-operative pulmonary complications is to initiate the patient's education, regarding the lung volume expansion manoeuvres. Prophylactic lung volume expansion manoeuvres such as deep breathing exercise, incentive spirometry, chest physiotherapy, positive pressure breathing techniques, etc, are of proven benefit for preventing post-operative pulmonary complications in high-risk patients. These physiotherapy of chest reduces the risk of atelectasis, facilitates the removal of secretions from airways and increases the pulmonary functions. The institution of preoperative lung expansion manoeuvers definitely decreases the incidence of perioperative pulmonary complications than if education begins after surgery. Measurement of FRC is the most important lung volume parameter during post-operative period that provides a specific goal of therapy. Positive pressure breathing technique may be of two types—intermittent or continuous. Both are effective in reducing the incidence of perioperative pulmonary complications, but its cost has resulted in decreased usuage. Continuous positive airway pressure (CPAP) is usually reserved for very sick patients who are unable for intermittent positive pressure breathing (IPPB). Another type of positive pressure breathing such as nasal positive airway pressure – also minimises the post-operative reduction of lung volume, incidence of atelectasis and acute respiratory failure.

Intraoperative management

There is no specific drugs or anaesthetic technique for the better management of patients suffering with COLD. During management of COLD patients, always it should be kept in mind that these patients are highly susceptible to the development of acute respiratory failure during intra and post-operative period. Among the general and regional anaesthesia, regional anaesthesia is the mostly desired method. But, unfortunately it is only restricted to the surgeries of lower abdomen and extremities. Because higher RA required for upper abdominal or thoracic surgeries paralyses the more and more intercostal muscles and impairs ventilation in a patient whose respiratory system is already compromised. GA is the usual choice for upper abdominal and intrathoracic operations which are associated with high incidence of pulmonary compilations. There is some debate or controversies between the incidence of pulmonary complications and duration of anaesthesia. But the general aggreement is that operation and anaesthesia lasting longer than 3 hours are more likely to be associated with pulmonary complications. So, where there is chance of post-operative respiratory failure, tracheal intubation and mechanical ventilation should be continued post-operatively. Alternatively, post-operative epidural analgesia by narcotics or local anaestheics permit painfree breathing which allows early tracheal extubation and decreased systemic analgesic requirement with their associated depressant effects on ventilation and consciousness.

When GA is applied, then volatile anaesthetic agents, proper humidification of inspired gases and mechanical ventilation

are the cornerstones of technique. Intraoperative use of volatile anaesthetic agents is more preferable than narcotics because of the patient's ability to eliminate these drugs rapidly through the lungs and thus minimising the early post-operative residual respiratory depression and pulmonary complications. Moreover, the volatile anaesthetic agents cause bronchodilatation which has a distinct advantage over narcotics. The narcotics or opioids are less useful for COLD patients, because of their prolonged depression effects on ventilation.

COLD patients are often associated with emphysema. So, one should use N_2O carefully. Because it will diffuse in the pulmonary bullae which is commonly associated with emphysema and can lead to enlargement and rupture resulting in the development of tension pneumothorax during anaesthesia. The another disadvantage of administration of N_2O is that it limits the concentration of inspired O_2. Inhaled volatile anaesthetic agents attenuates hypoxic pulmonary vasoconstriction. This hypoxic pulmonary vasoconstriction is beneficial for maintenance of arterial oxygenation in nonanaesthetised patient by shifting the blood from hypoxic to nonhypoxic zone. But as the volatile anaesthetic agents attenutes this hypoxic pulmonary vasoconstriction, so its beneficial effect is lost and thus increase the degree of right to left intrapulmonary shunt. So, increased inspired concentration of O_2 is necessary to off-set this anaesthesia induced pulmonary changes, which can be hindered by the use of N_2O.

Intubation which bypasses nearly the entire natural airway humidification system and high flows of dry anaestheties gases greatly intensify the need for humidification of dry inspired gases to prevent drying of secretions in airways. The systemic dehydration due to inadequate fluid administration during the perioperative period also can result in excessive drying of secretions in the airways despite humidification of inhaled gases. Controlled ventilation is useful for COLD patients receiving GA. During controlled vantilation, large tidal volume (10 to 15 ml/kg) combined with slow inspiratory flow rates and low breathing rates (<10 breaths/minute) maintains the optimum ventilation-perfusion ratio.

Low breathing rates helpes by:

i. allowing complete expiration and preventing air trapping which is characteristic of COLD patients,
ii. preventing hyperventilation which causes more reduction of P_aCO_2,
iii. increasing venous return,
iv. reducing the likelihood of turbulent flow in airways.

PEEP should be avoided as a ventilatory mode in COLD patients, because it affects the expiratory flow. But large tidal volume, slow inspiratory flow and low breathing rates act as alternative to and as effective as PEEP. If any time high positive airway pressure is required to provide adequate ventilation and proper oxygenation of blood, then pulmonary barotrauma and rupture of emphysematous bullae should be kept in mind. During spontaneous ventilation of COLD patients, ventilatory depression by volatile anaesthetic agents should be observed carefully, because depression of respiration produced by narcotics and other anaesthetic agents are more sensitive than normal individual. So, whatever may be the ventilatory mode, arterial blood gases, pH, SPO_2 and $ETCO_2$ should be maintained at normal level.

The risk of pulmonary complication is often viewed as less, following surgery performed under regional anaesthesia. But, regional anaesthesia technique that produces sensory block above T_7 level are not recommended, as this high level leads to decrease in expiratory reserve volume. In turn, this decreased expiratory reserve volume causes impairment of cough which leads to reduction in clearance of secretions from airways. Also block above T_7 level produces a feeling of suffocation and uneasiness requiring sedation which further depresses the respiration. But different types of nerve blocks, field blocks, infiltration anaesthesia, etc. carry much lesser risks than epidural or spinal anaesthesia. Nevertheless, the regional anaesthesia remains a useful selections in patients with COLD only when large doses of sedative drugs are not given, because such patients are extremely sensitive to the ventilatory depressant effects of sedative agents.

Post-operative care

The aim of post-operative care of COLD patients is to reduce the incidence and the severity of post-operative pulmonary complications. This can be achieved by lung volume expansion exercise, analgesia preferably by neuraxial approach and mechanical ventilation, if needed for respiratory failure. It is stated previously that post-operative complications are greatest following upper abdominal and intrathoracic surgery. This is documented from the data that following upper abdominal surgery, the VC decreases about 40% from the preoperative value on the first post-operative day which does not return to preoperative level for next 10 to 15 days and FRC does not decrease to normal level in first 24 hours. Astonishingly, it is also found that complete analgesia does not restore VC and FRC to the preoperative levels which suggests that surgical trauma is the main determinant factor for diminution of VC and increase of FRC. Altered VC and FRC are the main responsible factors for decrease in P_aO_2 and increase in P_aCO_2 in the immediate post-operative period than the depression of ventilation by narcotics, inhalational anaesthetics, anaesthesia induced impair regional hypoxic pulmonary vasoconstriction and anaesthesia induced dimination of ventilatory responses to CO_2 and hypoxia. The incidence of post-operative pulmonary complications, however, is dramatically less after laparoscopic cholecystectomy than after open cholecystectomy.

BRONCHIECTASIS

Bronchiectasis is a chronic suppurative airway disease with focal or diffuse abnormal

permanent dilatation of bronchi and airway obstruction during expiration like COLD. It is either congenital, caused by the genetic factors, e.g. cystic fibrosis or acquired following damage to the lower respiratory tract, especially during severe early childhood infection. Most patients suffering from bronchiectasis have a chronic productive cough which may present throughout the year, despite the wide-spread availability of broad spectrum antibiotics. In bronchiectasis there is frequently a component of asthma associated with chronic inflammatory changes in the airways. It often affects the lungs at the segmental or subsegmental level. The focal bronchiectasis involves the airways supplying a limited region of pulmonary parenchyma, but diffuse bronchiectasis involves a wide spread area of lungs (Figs 31.17A and B).

The dilatation of bronchi is due to the destructive (destruction of cartilage, muscles and elastic tissue) and inflammatory changes, mainly of the walls of the medium sized airways. Thus, the dilated airways frequently contain the pools of thick and purulent material, while distal portion of it is often occluded by this secretions and is replaced by fibrous tissue. The lung parenchyma supplied by the affected airways also contains varying combinations of fibrosis, emphysema, pneumonia and atelectasis. The affected bronchial wall becomes highly inflamed and vascular with associated enlargement of bronchial arteries, causing sometimes severe haemoptysis.

Aetiology of bronchiectasis may vary from:

i. infective → by microorganisms,
ii. noninfective → due to exposure to toxic substances,
iii. obstructive → due to foreign bodies,
iv. impaired host defence mechanism → by immunoglobulin disorders causing panhypogammaglobulinemia,
v. ciliary dysfunction→ primary ciliary dyskinesia, Kartagener's syndrome and cystic fibrosis.

Whatever may be the aetiology of bronchiectasis, the infection of airways by microorganisms is the cornerstone of its pathology. Once the disease process is established, the bacterial infection can be difficult or impossible to eradicate. Pseudomonas aeruginosa is the most common pathogen that may be present for many years and be associated with intermittent exacerbations of respiratory symptoms. At the pathological site the microorganisms produce pigments, proteases and other toxins that injure the respiratory epithelium and impair mucociliary clearance. Again as a result of infection the inflammatory response of host induces epithelial injury, largely as a result of mediators, released from neutrophils. On the other hand, as protection against infection is compromised (in immunoglobin disorders patient), so the dilated airways become more and more susceptible to colonization and growth of bacteria. Thus, a reinforcing vicious cycle can result with again and again infection and inflammation, producing further damage, impaired clearance of microorganisms and further infection which then completes the cycle by inciting more inflammation.

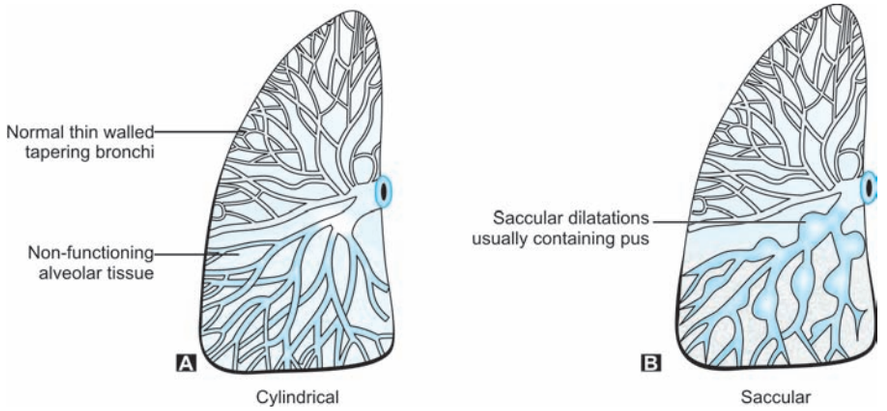
Anaesthetic management of patients with bronchiectasis invokes the same principles as outlined for patients with COLD. Prior to elective surgery, status of pulmonary function of patients should be optimized by appropriate therapy.

Preoperative therapy for bronchiectasis includes:

i. elimination of an identifiable underlying causes,
ii. improving the clearance of tracheobronchial secretions,
iii. control of infections, particularly during acute exacerbations,
iv. reversal or removable of airflow obstruction.

Appropriate treatment for bronchiectasis should be instituted when a treatable cause is found. For example:

i. If cause is the foreign body, it should be removed
ii. Acute infection should be controlled by antibiotics, guided by Gram's stain and culture of sputum
iii. Treatment of hypogammaglobulinemia by immunoglobulin
iv. Treatment of tuberculosis with antitubercular agents and allergic bronchopulmonary aspergillosis (ABPA) with glucocorticoids.



Figs 31.17A and B: Bronchiectasis means a permanent dilatation of one or more bronchi. The main bronchi upto 4th division possess large supporting cartilage rings. So, bronchiectasis only affects the bronchi beyond this point. Two main anatomical varieties of bronchiectasis are described. But, these may have similar causes and frequently both are found in the same lung.
A. This type of bronchiectasis is almost always found in the lower lobes. The bronchi are grossly dilated throughout their whole length. Intervening lung tissue is much reduced and much of it is fibrosed.
B. In this type of bronchiectasis, as the name suggests, the dilatations of bronchi tend to be more localised and exaggerated. They are roughly rounded and may be single or multiple.

In bronchiectasis due to cystic fibrosis, there is also malabsorption syndrome and it is due to pancreatic insufficiency. So appropriate advice regarding the diet and pancreatic supplements are essential. In cystic fibrosis induced bronchiectasis the secretions are typically copious and thick and contribute to the symptoms. Chest physiotherapy by chest percussion, vibrations or postural drainage frequently help the patients with copious secretions. Mucolytic agents to produce thin secretions and to allow better clearance are controversial. Antibiotics have an important role in the preoperative management of bronchiectasis. But which antibiotics should be given and the frequency and duration of administration are not well- established. When patients present with frequent exacerbation of infection, characterised by an increase in quantity and purulence of the sputum, then antibiotics are commonly used. Although, antibiotic should be choiced by culture and Gram's stain of sputum, but empiric coverage is often given initially. When *P.aeruginosa* is suspected, the appropriate treatment is oral quinolone or parenteral aminoglycosides or third generation cephalosporin. In patients with chronic purulent sputum, despite short course of appropriate antibiotic therapy, more prolonged course or intermittent but regular courses of a single or rotating simple antibiotics have been used. Bronchodilators are particularly useful in patients with airway hyperreactivity and reversible airflow obstruction. It improves the obstruction and aids the clearance of secretions. The intraoperative anaesthetic management of bronchiectasis is same as COLD. But only the especial point is that double lumen endobronchial tube may be used in severe cases and it is to prevent the spillage of purulent sputum into the normal areas of lungs.

RESTRICTIVE LUNG DISEASES (RLD)

Restrictive lung diseases are conditions where the total lung capacity (TLC) is reduced. It may be of two types, intrinsic and extrinsic. In intrinsic variety of restrictive lung disease (IRLD), there is alterations of the elastic properties of lungs, causing the lungs to be stiffed. Again IRLD may be of acute and chronic. The example of acute IRLDs are : ARDS, pulmonary oedema, aspiration pneumonitis, etc. The examples of chronic IRLDs are : sarcoidosis, silicosis, asbestosis, eosinophilic granuloma, extensive pulmonary fibrosis, etc. Initially in chronic IRLD there is an inflammatory reaction in response to different stimuli which is centered on the alveoli, impairing gas exchange. Then over a period of time which can vary from days to years, collagen fibres are formed in and around the alveoli causing more marked impairment of gas exchange and smaller, stiffer lungs. Then, pulmonary fibrosis is the final response of lung. The causes of these stimuli include those which are associated with autoimmune disorders (e.g rheumatoid arthritis, scleroderma), inhaled dusts (e.g asbestos) or ingested substances, especially drugs (e.g amiodarone, chemotherapy agents, etc.). Allergic response to inhaled substances can also cause fibrosis and chronic IRLD if exposure is prolonged.

The extrinsic variety of restrictive lung disease (ERLD) reflects the disorders of chestwall (obesity, flail chest, deformity such as severe Kyphoscoliosis, etc.); pleura (pleural effusions, pneumothorax, etc.), mediastinum (mediastinal mass), etc. Intra-abdominal pressure changes producing significant splinting of the diaphragm and small group of neuromuscular disorders where lung movement is restricted from outside are also the examples of ERLD.

The pathology of restrictive lung diseases are:

i. In RLD vital capacity is decreased (normal VC is 70 ml/kg). But, in contrast to obstructive lung disease the expiratory flow rate in RLD remains normal. So, FEV_1 remains normal and the ratio of FEV_1:FVC is preserved in restrictive lung disease. While in obstructive lung disease the ratio of FEV_1:FVC is reduced.
ii. The patients with restrictive lung disease like obstructive lung disease also complain of dyspnoea, reflecting the increased work of breathing which is necessary to expand the poorly compliant lung.
iii. Tidal volume decreases in restrictive lung disease. So, to compensate this reduced tidal volume respiratory rate increases. Despite the increase in respiratory rate, the alveolar ventilation decreases which produces proportionate increase in P_aCO_2 and decrease in P_aO_2 (Fig. 31.18).
iv. Resulting hypercarbia and associated hypoxia causes vasoconstrictive pulmonary hypertension and corpulmonale.
v. The intrinsic and extrinsic varieties of restrictive lung disease can be differentiated from each other by the measurement of elastic properties of lungs. Elastic properties of lungs can be quantitated by measuring the lung compliance which is defined as the change in volume of lung per unit change in pressure. The compliance of normal lung is 0.1 to 0.2 L/cm of H_2O, whereas in patients with intrinsic restrictive lung disease, the compliance comes down to as low as 0.02 L/cm of H_2O. The flow-volume curves are shifted downwards and to the right in patients with increased lung stiffness (Fig. 31.19).

The anaesthetic management of restrictive lung diseases includes preoperative diagnosis, assessment of the severity of impairment of lung function and treatment of the reversible components. A preoperative history of dyspnoea that limits the day-to-day activity and that can be referred to restrictive lung disease may be taken as an indication for the performance of PFTs and measurement of arterial blood gases, in additon to the routine investigation such as X-ray, CT-scan, etc. for the diagnosis

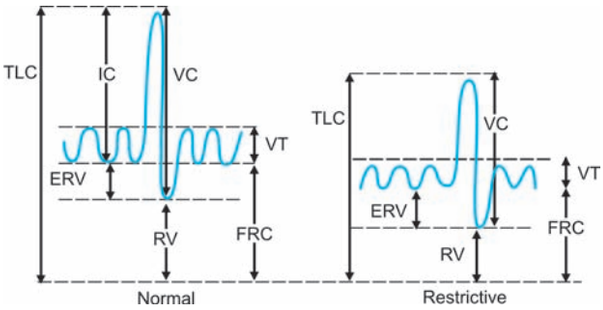


Fig. 31.18: Lung volumes in restrictive lung disease compared with normal values. In the presence of restrictive lung disease TLC, FRC, RV and VC are all decreased.

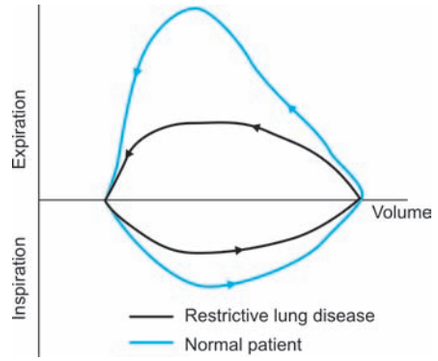
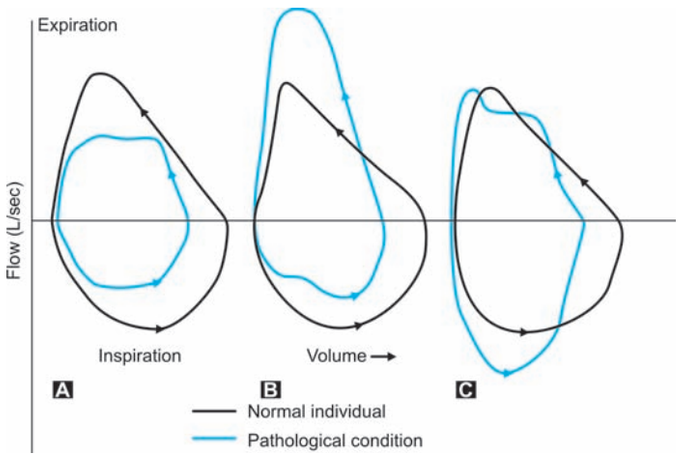


Fig. 31.19: Schematic representation of flow-volume loop in a normal patient (green line) and in the presence of a restrictive lung disease (red line)

of RLD. Restrictive lung diseases should be differentiated from obstructive lung diseases by the analysis of PFTs and flow-volume loop. If VC is reduced to < 15 ml/kg (where normal value is 70 ml/kg) and resting P_aCO_2 rises than normal, then there is more chance of developing exaggerated perioperative pulmonary complications. Like COLD and bronchiectasis, the preoperative preparations of RLD also include: eradication of pulmonary infections, improved sputum clearance, treatment of cardiac dysfunction, exercise to improve the strength of breathing muscles, and other specific treatments like the drainage of pleural effusion, management of pneumothorax, etc. If there is mediastinal tumour, then the size and the degree of tracheal compression by the tumour should be assessed by CT scan or MRI. The prediction of tracheal compression by tumour mass is a useful assessment for difficult airway management. So, in such circumstances flexible fiberoptic laryngoscope/bronchoscope under topical anaesthesia is a good preoperative method for evaluating the airway obstruction. A number of asymptomatic patients have developed unexpected airway obstruction during anaesthesia without any previous warning (Figs 31.20A to C).



Figs 31.20A to C: Different flow-vloume loops in different conditions
A. Flow-volume loop in fixed obstruction
B. Variable extrathoracic obstruction
C. Variable intrathoracic obstruction

Without bronchospasm, the presence of restrictive lung disease does not influence the choice of drugs for induction and maintenance of anaesthesia. During induction and maintenance of anaesthesia, a high index of suspicion for the presence of pneumothorax and the need to avoid or continue with N_2O must be assessed. Intraoperative controlled ventilation is prudent for optimal oxygenation of patients with RLD due to their poorly compliant lungs and as sometimes high inflation pressure is needed to inflate the low compliant lungs. Regional anaesthesia is suitable for lower abdominal operations or surgeries on extremities, but sensory block should be kept below T_7 to T_{10} level, above which level regional block is associated with impairment of the respiratory muscle activity which is necesssary to maintain acceptable amount of ventilation and oxygenation. Tracheal tube must not be removed until the patients have met established criteria for extubations. Post-operative respiratory depression should be avoided by proper selection of intraoperative narcotics and sedative drugs. Post-operative pain is best managed by epidural analgesia.

Lung Cyst

These are fluid or air-filled cyst, located in the pulmonary parenchyma or adjacent to the tacheaobronchial tree. They may be asymptomatic or may be the site of recurrent pulmonary infections or may be the cause of life-threatening airways obstruction. The anaesthetic interests of the lung cyst are: the use of N_2O and the use of positive pressure ventilation. N_2O usually diffuses into the cyst and causes its expansion leading to rupture and life-threatening respiratory/cardiovascular decompensation due to pneumothorax. Institution of positive pressure ventilation may have a ball value effect causing expansion of cyst and compression of lung parenchyma or rupture leading to pneumothorax. Despite all these concerns, clinical experience confirms that N_2O, muscle relaxant induced skeletal paralysis and IPPV may all safely be utilized in patients with lung cyst.

32 Liver Diseases and Anaesthesia

INTRODUCTION

Liver is the largest gland of our body. It consists of both an exocrine or excretory and endocrine or secretory parts. The exocrine part of liver excretes bile which is conveyed by the biliary passages into the deodenum. On otherhand, the endocrine part of the liver liberates some useful chemical sustances such as glucose (from glycogen), ketone bodies, fatty acids, plasma proteins (except the immunoglobins), heparin, etc. directly into the blood stream. In addition, cholesterol which is secreted by the liver presents the cyclo-pentinoperhydro-phenanthrene nucleus for the synthesis of different steriod hormones. Liver is also involved in the various metabolic activities of all the nutritional substances of our body such as carbohydrate, proteins, lipids, vitamins and minerals, etc. These metabolic acitivities dissipate much heat and thus the liver subserves an important function for the regulation of body temperature.

The liver is a wedge-shaped organ with a broad base, directed to the right and a narrow apex, directed to the left. It occupies the whole of the right hypochondrium, upper part of the epigastrium and a part of the left hypochondrium upto the left lateral plane.

The weight of a liver in an adult person is approximately 1.4 to 1.8 Kg (average 1.5 Kg) and that in a newborn is approximately 150 gm. It is relatively larger in children than an adult. This is due to its increased haematopoietic function during fetal life and occupies about 2/5th of the abdomen. The weight of a liver represents 2% of the total body weight in adults and almost 5% of the total body weight in neonates. The liver is a highly vascular organ and so also acts as a reservoir of blood. When it is ruptured then bleeding continues, because the hepatic veins are unable to collapse as it is directly attached to the plate of liver cells. The liver cells undergo rapid mitosis and regeneration when a part of this organ is removed. Surgical removal of 2/3 of a liver may be compatible with life. But the disorganised growth of the liver cells during regeneration after degeneration or removal of a part of it or in cirrhosis is detrimental and culminates into portal hypertension. Patients with liver disease, undergoing anaesthesia and surgery, face a number of significant intraoperative and postoperative complications. This is because liver disease can alter the patient's response to anaesthesia and surgery in many ways which is discussed later. Thus, it is important to understand the applied anatomy and physiology of liver, factors altering the hepatic blood flow, details of liver functions, alter pharmacokinetics and pharmacodymnaics of anaesthetic drugs due to liver disease, etc. for proper perioperative management of these group of patients.

MACRO- AND MICROANATOMY OF LIVER

The outer surface of a liver is lined by a serous coat, which is derived from the visceral peritoneum. Beneath this serous coat there lie a thin layer of connective tissue, known as the Glissons capsule and it encloses the entire organ. It also extends into the interior of the liver as numerous branching septa and trabeculae. The radicles or branches of portal vein, hepatic artery and bile duct run together within these septa, ensheathed by the Glisson's capsule, in the form of portal triads (also called portal canals or portal tracts). On the otherhand, the hepatic veins and their tributaries, called the central vein from where the hepatic vein starts and draws the blood from liver to inferior vena cava run independently. They are not ensheathed by Glisson's capsule, but is surrounded by the laminae of hepatic cells (Fig. 32.1).

Conventionally, the liver is imagined to be composed of regular lobules. Each lobule is arranged around a central vein with portal tracts at the periphery. Thus, each hepatic lobule consists of hexagonal mass of liver cells and measures about 1 mm in width. The central vein which is a tributary of hepatic vein occupies the central axis of each hepatic lobule. Portal triads or portal canals, covered by Glisson's capsule are found in the interlobular spaces

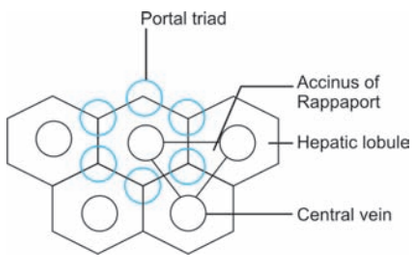


Fig. 32.1: Schematic anatomy of liver

i.e. at the meeting place of three adjacent liver lobules. Therefore, in a typical case six portal triads or portal canals are found at the periphery of a hexagonal liver lobule. The blood vessels and bile ductules of the portal canals give rise to a number of terminal branches. They arise at right angles to them and pass transversely along the sides of the two adjacent liver lobules.

The liver cells are arranged and radiate outwards as multiple sheets or plates from the central vein. These sheets or plates of hepatic cells are called the hepatic laminae. At the periphery of each lobule these multiple lamina joins together with one another and form an another plate of liver cells, called the limiting plate. The spaces between the multiple laminae or the sheets of hapatic cells are known as the hepatic lacunae which are occupied by hepatic sinusoids. These hepatic sinusoids receive a mixture of blood from both the portal vein (coming from intestine) and hepatic artery (branch of coeliac artery). The limiting plates which surround or make the periphery of each hepatic lobule presents numerous perforations. Through these perforations passes the branches of the portal vein and hepatic artery and opens into the sinusoids. After providing nutrition and O_2 to the liver cells, the blood of the sinusoids drain into the central vein. Then the central veins from the adjacent lobules join together to form the hepatic veins which finally drain into the inferior vena cava. Truely speaking, each liver lobule centered around a central vein is neither a structural nor a functional unit of liver. It is infact an independent venous unit and includes the area of liver whose venous blood drains into a particular central vein.

The sinusoidal walls (or hepatic laminae) are also fenestrated and communicates with one another by some holes, through which blood passes freely. among each other The sinusoidal walls are also lined by flattened endothelial cells. Stellate shaped Kupffer's cells, derived from the bone marrow are attached to these endothelial cells. These Kupffer's cells are actually mobile macrophages and capable of phagocytosing foreign particles, bacteria and denatured proteins. They also scavenge the breakdown products of RBCs and have an important role in the metabolism of drugs and intermediary metabolites. Along with the Kupffer's cells, there are also Pill cells which are highly mobile lymphocytes. They act as defence against virus, other infective agents and tumour cells. At the peripheral end of the sinusoids, i.e. at the periphery of hepatic lobule where the hepatic arterioles and portal venules enter, there pressure of the portal venule is about 8 to 10 mm of Hg and that of the hepatic arteriole is about 90 mm of Hg. Whereas the central veins maintain a pressure of about 5 mm of Hg or less. Inspite of this pressure differences between the portal vein and the hepatic artery, the sinusoids convey a mixture of blood from both the vessels. This is because the sinusoids act as a huge vascular reserver like sponge with intersinusoidal communication through multiple fenestretion and damp down any gradient of vascular pressure. Thus, any disease of liver, reducing the capacity of this vascular sponge, produces portal hypertension. Thereafter any small changes in hepatic venous pressure result in massive fluid transudation as the lymph and subsequent leakage of it into the outer surface of the capsule and into the peritoneal cavity. This fluid contains 80 to 90% of protein (Fig. 32.2).

The walls of the sinusoids which are made by hepatic lamina are covered by endothelial cells. Between the endothelial cells and the hepatic cells of lamina there exists a potential space known as the space of Disse. This space is filled with plasma and chylomicrons which percolate from the blood of the sinusoids into the space of disse and then enter the liver cells. Liver cells manufacture plasma proteins (except immunoglobin) and this is delivered directly into this space of Disse and from there into the sinusoidal blood. Moreover, chylomicrons are taken up by the liver cells from the space of Disse and are converted into lipoproteins. These are then again subsequently delivered into the circulating blood of the sinusoids through the space of Disse. The space of Disse also contain Ito cells. These Ito cells secrete a collagenous matrix, named proteoglycans which provides growth factor for the regeneration of the damaged liver cells and their subsequent reorganisation as hepatic laminae. It also replaces the defunct liver cells with collagen fibres (as found in cirrhosis) and store the fat-soluble vitamin A in their lipid vesicles (Fig. 32.3).

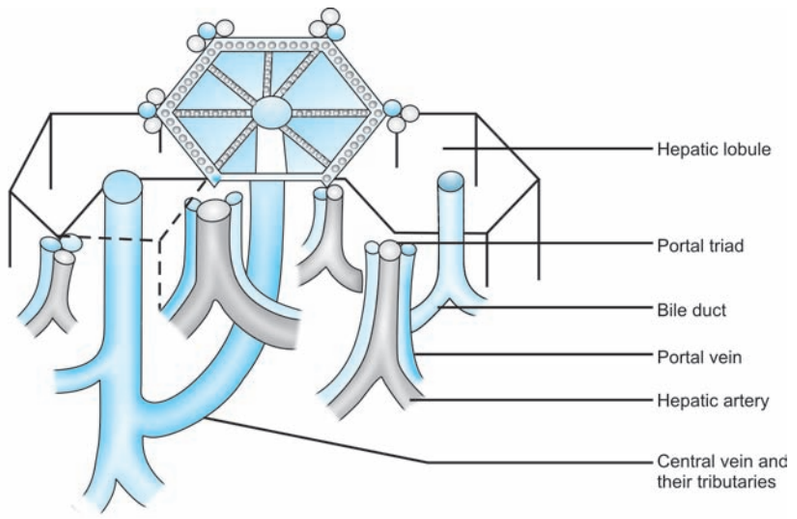


Fig. 32.2: Vascular anatomy of liver

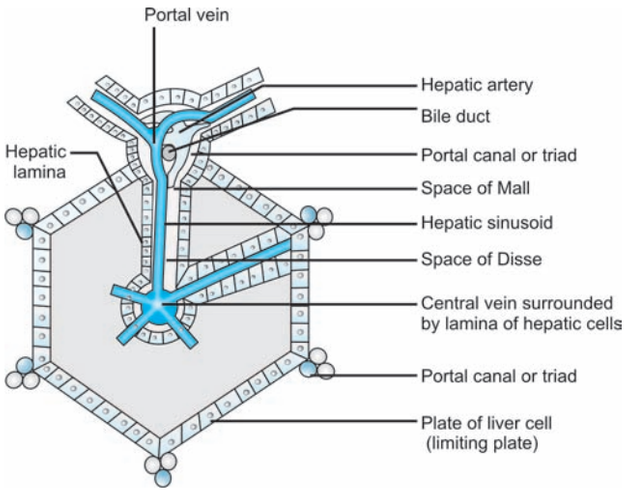


Fig. 32.3: Structures of hepatic lobules

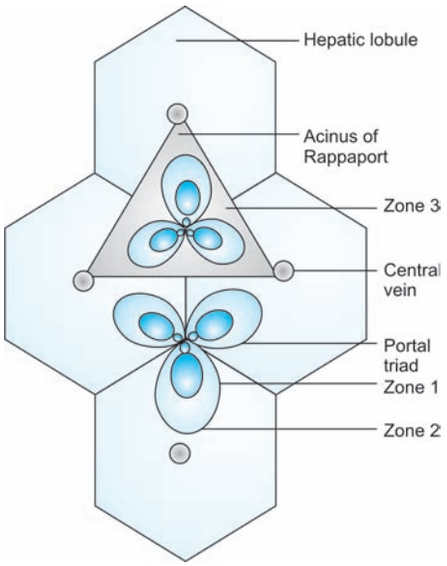


Fig. 32.4: Structural unit of liver

Between the Glisson's capsule of the portal canal and the plate of hepatic cells, around the Glisson's capsule there exist another set of potential space, called the space of Mall. At the periphery of the liver lobule the space of Disse is continuous with the space of Mall. The lymphatics of the liver begin in the space of Mall as blind radicles. During excess accumulation of plasma in the Disse's space, it is reabsorbed by the lymphatics of the space of Mall (Fig. 32.4).

The individual liver cell is roughly cuboidal in shape and presents with six surfaces. Out of these six surfaces, two surfaces are related to the blood of sinusoids and the remaining surfaces are surrounded by the polygonal network of bile canaliculi. Actually, these bile canaliculi are not the separate channels, but they are formed by the separation of plasma membranes of the adjacent liver cells. Numerous microvilli project into the walls of these bile canaliculi from the liver cells and increase the surface area of its secretion, through which the liver cells can secrete more bile. The liver cells take up the lipid soluble unconjugated serum bilirubin from the blood of sinusoids through the space of Disse and then deliver the water soluble conjugated bilirubin glucuronide into the bile with the help of an enzyme named glucuronyl transferase. The borders around the bile canaliculi are sealed by the tight junctions of cell membrane between the adjacent hepatocytes, and prevent the bile from entering the intercellular spaces of the liver, the space of Disse and the blood of sinusoids. Thus this forms the blood-bile barrier network of bile canaliculi. Bile after flowing through the canaliculi ultimately passes to the periphery of the hepatic lobules and drain into the bile ductules of the portal canal. Thus the bile canaliculi are intralaminar and centrifugal in direction, whereas the hepatic sinusoids are interlaminar and centripetal in direction (Fig. 32.4).

A new concept of functional structure of liver is now in use. According to this new concept the functional hepatic unit is called the acinus of Rappaport. It is an area of liver tissue centered around a portal triad and is drawn by joining the central veins of three adjacent liver lobules. The centre of the acinus of Rappaport is formed by the portal triad consisting of the portal vein, hepatic arteriole, biliary ductule, nerve fibre and lymphatics. This area of the acinus of Rappaport gets nutrition and O_2 from the radicles of portal vein and hepatic arterioles. Bile is collected in the bile ductule of the aforesaid portal canal. Blood flows perpendicularly from the portal triad through the sinusoids to the central vein. Each of these transverse vessels and ductules form the backbone which provides nutrition to and collect bile from an unit area of liver parenchyma which is known as the acinus of Rappaport. This acinus of Rappaport forms the structural and metabolic unit of the liver. In terms of supply of O_2 and other nutrients, an acinus of Rapport is subdivided into three zones. The most inner zone (zone-1) which is situated just around the portal triad, receive the blood with highest O_2 saturation and show maximum metabolic activity. They are thought to be involved in protein anabolism and catabolism. The intermediate zone (zone-2) being intermediate in position is moderately oxygenated. The outer zone (zone-3), which is situated close to the central vein is least oxygenated and most susceptible to anoxic injury. This site is responsible for drug biotransformation (Fig. 32.5).

BLOOD SUPPLY AND NUTRITION OF LIVER

Under normal resting conditions, the total hepatic blood flow is approximately 1500 ml/min or 1 ml/gm (of liver tissue) /min. Out of this, about 1200 ml of blood is

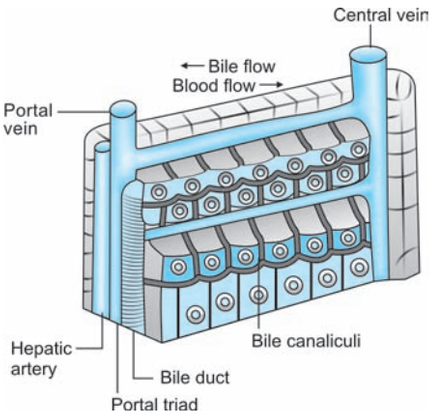


Fig. 32.5: Metabolic unit of liver

derived from the portal vein at a pressure of about 8 to 10 mm of Hg. The hepatic artery circulates blood at a pressure of about 100 mm of Hg and supplies about the remaining 300 ml of blood to liver tissues per minute. The total blood flow in a liver per minute represents about 25% of the total cardiac output. Liver receives 20% of its blood supply and 30% of its O_2 supply from the hepatic artery. On the otherhand, it receives 80% of its blood supply and 70% of its O_2 supply from the portal vein.

The hepatic arterial blood contains about 19 ml O_2 per 100 ml (95% saturated) and hepatic venous blood contains about 13.4 ml O_2 per 100 ml. So, the hepatic arteriovenous oxygen content difference is about 5.6 ml/100 ml. The portal venous blood contains about 17 ml O_2/100 ml (85% saturated) and the 'portal vein – hepatic vein' O_2 difference is 3·6 ml per 100 ml. Hence, 300 ml of hepatic arterial blood supplies 3 × 5.6 = 16.8 ml O_2 per minute of the liver's requirement. Likewise, 1200 ml of portal venous blood supplies 12 × 3.6 = 43.2 ml O_2 per minute of the liver's requirement. Thus total O_2 usuage of the liver is 43.2 + 16.8 = 60 ml per minute, of which about 70% is supplied by the hepatic portal system and 30% is supplied by the hepatic arterial system. Before entering the liver, the hepatic artery and portal vein divide into right and left branches. Within the liver they divide and redivide to form the segmental and

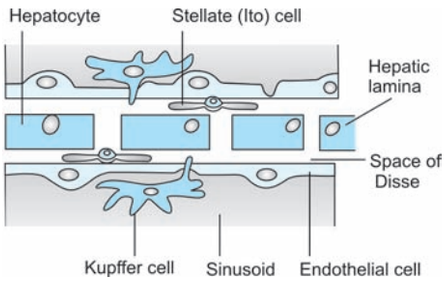


Fig. 32.6: Hepatocyte and hepatic lamina

then interlobular branches which run in the portal canals or triads. The further ramifications of these interlobular branches open into the hepatic sinusoids. The sinusoids are the hepatic capillaries bounded by the two hepatic laminae and formed by the merging of the hepatic artery and the portal vein. Thus the hepatic arterial blood mixes with the portal venous blood in the sinusoids. There are no anastomoses among the tributuries of the hepatic artery and hence each hepatic arterial branch is an end artery (Fig. 32.6).

VENOUS DRAINAGE, LYMPHATIC DRAINAGE AND NERVE SUPPLY OF LIVER

Hepatic sinusoids drain into the central veins (interlobular veins) which then subsequently join to form the sublobular veins. These sublobular veins again reunite to form the hepatic vein which ultimately drain directly into the inferior vena cava.

Liver lymph is rich in protein. Lymphatics of the liver begin blindly around the portal canals in the spaces of Mall. Probably the liver lobules are devoid of lymph capillaries and the interstitial fluid of the lobules reaches the lymphatic radicles via the spaces of Disse and spaces of Mall. In obstruction of hepatic veins the flow of the liver lymph increases. The lymphatic network of liver consists of two sets – superficial and deep. The superficial lymphatics net work run on the surface of the liver, beneath the visceral peritoneum and terminate into the caval, hepatic, paracardial and coeliac lymph nodes. The deep lymphatic net work partly end in the nodes around the end of the IVC and partly in the hepatic nodes.

The liver receives its nerve supply from the hepatic plexus. It enters the liver through the porta hepatis and contains both the sympathetic and parasympathetic fibres. The sympathetic fibres are derived from the branches of coeliac plexus and the parasympathetic fibres are derived from both the right and left vagus and right phrenic nerve.

REGULATION OF LIVER BLOOD FLOW

Liver blood flow is regulated by two mechanisms: Intrinsic and Extrinsic.

Intrinsic Mechanism of Regulation

The intrinsic mechanism for regulation of blood flow in liver does not depend on the nerves or any blood borne vasoactive compounds. It is operated mainly by three mechanisms: autoregulation, metabolic regulation and hepatic arterial buffer response.

Autoregulation

It causes local regulation of blood flow in the liver and maintain a constant pressure of hepatic artery and its branches in spite of the wide range of changes. This is also called the local pressure-flow autoregulation. It is probably performed by the hepatic arterial vasoconstriction and dilatation and is due to the myogenic response of arterial smooth muscle to stretch, imposed by increased arterial perfusion pressure. It is mainly found in the metabolically active (i.e. postprandial) liver, but not in the fasted liver. Unfortunately, as anaesthesia and surgery is performed under fasting condition, so pressure-flow autoregulation does not exist in this situation. However, this pressure-flow autoregulation is not evidenced in portal venous system. Instead there exists a linear pressure-flow relationship which means when pressure in protal vein increases, then flow in it also increases and vice versa.

Metabolic Control

Here, the metabolic factors, but not the pressure in the vessels of liver regulate the hepatic blood flow. In this mechanism both the portal venous flow and hepatic arterial flow is controlled by the changes in the composition of blood, flowing within them due to metabolism. These factors include the changes of blood PO_2, PCO_2, pH and osmolarity. The liver blood flow is increased during hypoxaemia, hypercarbia, decreased pH, postprandial hyperosmolar state, etc. and vice versa.

Hepatic arterial buffer response

Here, one flow compensates the other. Thus, when the portal blood flow decreases, then the hepatic arterial blood flow increases and maintains the total hepatic blood flow at constant level. This is called the buffer response. This reciprocal relationship between the flow of hepatic artery and portal vein tends to maintain a constant hepatic O_2 supply which is essential for the hepatocyte's function. Thus, when the portal venous flow decreases, then the hepatic arterial resistance also decreases by dilatation and hepatic arterial flow increases and vice versa. It is postulated that this is due to the locally produced adenosine

Extrinsic Mechanism of Regulation

The extrinsic mechanism for regulation of liver blood flow depends on both the neural and humoral factors.

Neural Control

The sympathetic and the parasympathetic nerves which supply the liver through the hepatic plexus terminates on the arterioles and the venules of hepatic vessels. Stimulation of this sympathetic nervous system reduces the liver blood flow and expels near about 500 ml of blood into the systemic circulation, immediately from liver. The liver in this way represents a major reservoir of whole blood, during emergency. But, the parasympathetic innervation influences the regional distribution of blood flow within the liver by exerting effects on the perisinusoidal sphincters, rather than by affecting the total liver blood flow.

Humoral Factors

The hepatic arterial bed has both the α and β adrenergic receptors, whereas the portal vasculature has only α receptors. So, epinephrine, norepinephrine and other catecholamines administered exogenously induce vasoconstriction via the α-receptors which is partially compensated by vasodilation mediated by β-receptors. Dopamine has little effect on liver vasculature due to the absence of dopamine receptors on them. Vasopressin also induces marked splanchnic vasoconstriction in the liver. Consequently, there is reduction in venous flow through the portal system and reduction in inflow resistance in the portal vasculature occuring after vasopressin administration. Thus, vasopressin becomes very effective in alleviating the portal hypertension.

EFFECTS OF ANAESTHESIA ON LIVER BLOOD FLOW

Anaesthesia alters the blood flow in liver. It is due to the effects of individual anaesthetic agents, types of anaesthesia, mode of ventilation and the type of surgery. Most of the anaesthetic agents which reduce the BP and cardiac output decreases the liver blood flow. However, among all the volatile anaesthetic agents, halothane is the most significant. Incontrast, isoflurane increases the hepatic blood flow at the inspired concentration of 1 or 2 MAC. During general anaesthesia, as the splanchnic vascular resistance increases, the liver blood flow decreases. Application of PEEP further decreases the hepatic blood flow by increasing the systemic and subsequently the hepatic venous pressure.

Regional anaesthesia definitely decreases the liver blood flow, but it depends on the extent or the height of the block. This is because higher level of regional block is associated with more hypotension and more hypotension is associated with more reduction of liver blood flow. For example, the sensory block up to T_4 level reduces the hepatic blood flow up to 20%. But, this is not significant and runs parallel to the decrease of mean arterial pressure. It is also found that up to 40% reduction of MAP, there is no significant change of blood flow in liver, as there is contribution from both the portal and hepatic vascular system. Moreover reduction of MAP by more than 40% ensues the ischaemic insult on the liver. Among the type of surgery, upper abdominal surgery causes the maximum reduction of hepatic blood flow.

Thus, in conclusion it can be said that although all the forms of anaesthesia decrease the liver blood flow, but simultaneously the O_2 requirements by the liver also decreases. So, anoxic injury does not routinely occur during anaesthesia.

FUNCTIONS OF LIVER

The liver acts as a well equipped biochemical laboratory where practically metabolism of all the nutritional substances such as carbohydrates, fats, proteins, vitamins, minerals, etc. are taken place and heat is produced. So, its functions are numerous which are briefly summarised below.

(I) In Connection with the Blood and its Circulation

1. RBC formation—in foetal life.
2. RBC destruction—in adult life.
3. Storehouse of blood and regulation of blood volume.
4. In relation with blood clotting—(i) Virtually all coagulation factors which are protein in nature are synthesised in the liver, (ii) Mast cells of liver produce heparin and prevent intravascular clotting.
5. It helps in immune mechanism through its RE system.
6. It transfers blood from portal to systemic circulation
7. It manufactures all the plasma proteins (except immunoglobulins).

8. It stores iron, copper and other haematinic factors which help in the formation of red cells and haemoglobin.

(II) Synthesis of Bile

Bile with their different constituents are synthesised and excreted continuously from the liver and is stored in the gall bladder. Cholesterol is synthesised in the liver from active acetate and is also excreted from it. Bile acids such as cholic acid, deoxycholic acid and lithocholic acid have been considered to be the derivatives of cholanic acid and are formed in the liver. These bile acids in conjugation with glycine and taurine form the compounds such as glycocholic acid and taurocholic acid respectively. Bile salts are the Na – salts of these taurocholic acid and glycocholic acid and have very important function during the process of absorption of fat. This function is performed by the emulsification of ingested fat and concurrent production of greater surface area which enables the lipase and other fat metabolising enzymes to act more efficiently (Table 32.1).

Bile pigments, named the biliverdin and bilirubin are the breakdown products of haemoglobin and are formed in the RE system in various parts of the body. Bone-marrow, liver and spleen have been considered to be the part of of this RE system and so is the site of formation of bile pigments. These bile pigments are insoluble in water. So, these are then carried to the liver and is congugated to water soluble bile pigments (bilirubin glucuronide) which are then next excreted in the bile and is responsible for the normal colour of stool.

(III) In Relation with Carbohydrate Metabolism (Fig. 32.9)

Liver is immensely related to the carbohydrate metabolism in the following way.

i. It converts non-glucose monosaccharides such as galactose, fructose, mannose, etc. to glucose and glycogen.
ii. It converts lactic acid, pyruvic acid and glycerol to glucose and glycogen.
iii. It stores carbohydrates in the form of glycogen by glycogenesis and when the blood sugar tends to be low, then it mobilises this glycogen by glycogenolysis and produce glucose.
iv. It takes an important part in regulation of blood sugar.
v. It is the seat of neoglucogenesis.
vi. It manufactures fats from carbohydrates.
vii. Glucose is metabolised here through TCA cycle and other alternative pathways such as HMP shunt.
viii. In liver glucorinic acid is formed from uridine diphosphate glucose (UDPG) and plays an important role in the conjugation of bilirubin (Fig. 32.7).
ix. Alcohol metabolism: The liver is the main site of alcohol metabolism. In it an enzyme named alcohol dehydrogenase catabolises alcohol to acetaldehyde. Then, acetaldehyde dehydrogenase an enzyme which is present in liver converts acetaldehyde to acetyl CoA. Acetyl CoA may be oxidised to CO_2 and H_2O through TCA cycle or converted to other biochemical compounds including fatty acids. When alcohol is converted to acetaldehyde and then to acetyl CoA, NAD acts as cofactor, i.e. hydrogen acceptor and forms NADH. The ATP is generated during the oxidation of this NADH by the electron transport chain (ETC) and provides energy for the synthesis of fatty acids. Thus reduced NADH ($NADH^+ + H^+ = NADH$) which is produced during the metabolism of alcohol can alter the intracellular NADH/NAD ratio appreciably. In turn, this altered ratio can affect the number of important intracellular metabolic reactions that use these 2 co-factors. High level of NADH favour the formation of lactate from pyruvate, accounting for the lactic acidosis. This diminishes the concentration of pyruvate and thus inhibits gluconeogenesis. In severe cases, when liver glycogen is depleted due to less intake of carbohydrate and is no longer available for glycogenolysis, then this will result in hypoglycemia (Fig. 32.8).

Under the influence of alcohol the hepatic microsomes help in the

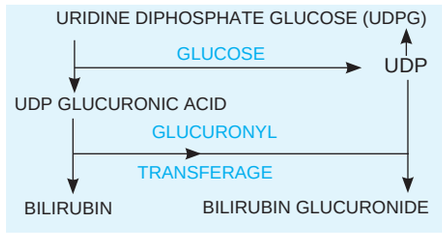


Fig. 32.7: Schematic diagram showing the conjugation of bilirubin by liver as glucuronide

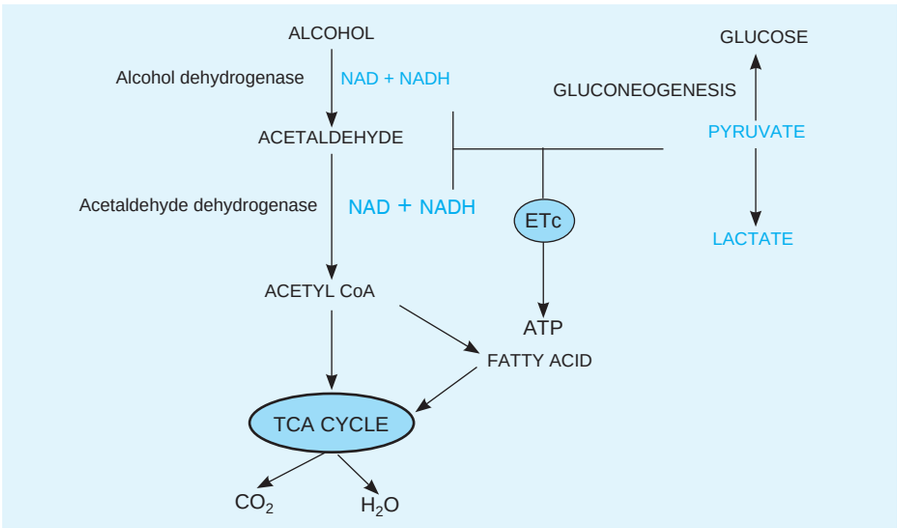


Fig. 32.8: Schematic representation of metabolism of alcohol in liver

esterification of fatty acids to triglycerides, rather than phospholipids. So the direct effect of alcohol may be alcoholic fatty liver which is due to the increased hepatic fat synthesis as well as decreased hepatic fatty acid oxidation.

(iv) In Relation with Fat Metabolism (Fig. 32.9)

Liver is related to fat metabolism in the following way.

i. It stores fats.
ii. It helps in the oxidation of fat, releasing energy in the form of ATP through TCA cycle.
iii. It is the site for synthesis of cholesterol from acetate.
iv. It is the site of synthesis of phospholipids.
v. It is the site for synthesis of fats from carbohydrates and proteins.
vi. It is the site of ketone body formation.
vii. The unused free fatty acids (FFA), which are released from the fat depot, is converted to triglycerides and other lipids in liver. These are then metabolised to meet the energy requirement when necessary (Fig. 32.10).
viii. The glycerol is oxidised in liver via the pathway of carbohyd–rate metabolism.
ix. In carbohydrate deficiency, the fat metabolism in liver is increased and fat is partially converted to glucose or glycogen.
x. Fat-soluble vitamins, e.g. A, D, E and K are stored here.

(v) in Relation with Protein Metabolism

i. Liver is the chief site for deamination of amino acid which constitute the principal step of protein metabolism.
ii. It is the main site of urea and uric acid formation.
iii. Synthesis of certain amino acids takes place in liver.

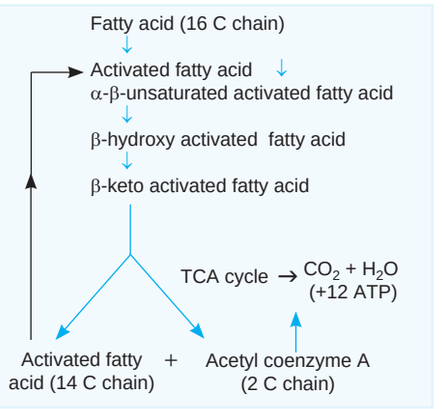


Fig. 32.10: Schematic diagram of fatty acid metabolism. During every cycle two carbon atoms are reduced and thus the fatty acid chain gradually becomes smaller and consists of less carbon atoms

iv. Plasma proteins are manufactured in liver except immunoglobulins.
v. Coagulation factors in addition to fibrinogen and prothrombin are manufactured here.

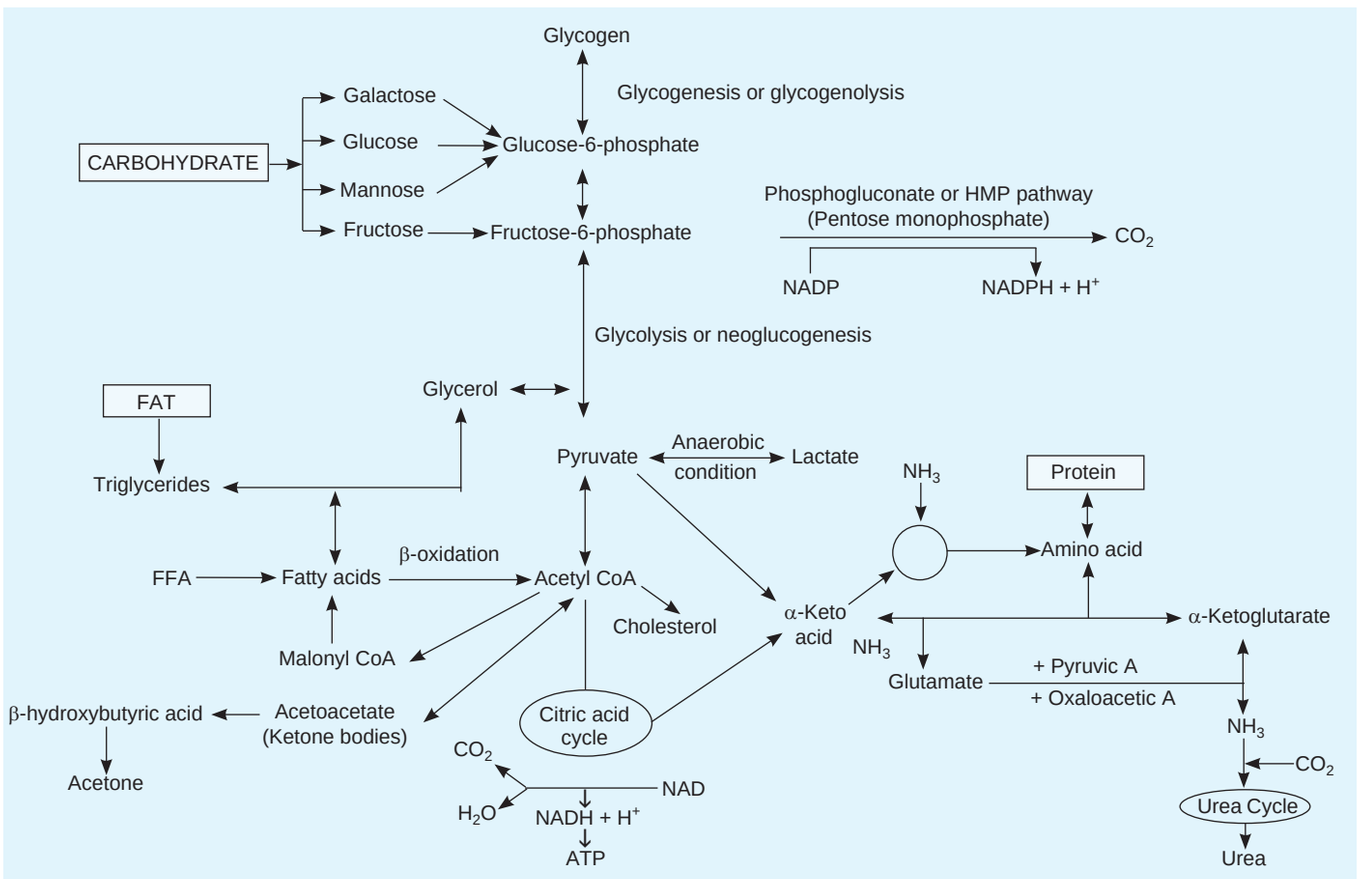


Fig. 32.9: Carbohydrate and fat metabolism in liver

Deamination is the process by which the amino radicle ($-NH_2$) is taken away from the amino acid. It is carried out chiefly in the liver with the help of an enzyme named deaminase. Deamination may also take place by the enzyme transaminase which transfers the amino group from the amino acid to a keto acid, converting the latter into an amino acid and the former into a keto acid. By this process the amino acid molecule is broken down into two parts: (i) the nitrogenous part (ammonia) and (ii) the non nitrogenous part (α-keto acid) (Fig. 32.11).

(i) The nitrogenous part of an amino acid has the following fate

a. Formation of urea: Most of the NH_3, under normal condition is converted to urea by K-H Ornithine cycle. So, about 80% of the total urinary nitrogen is found in the form of urea. Urea is mainly formed in the liver.

b. Formation of ammonium salt: A small part of ammonia combines with acids, (such as sulphuric acid, phosphoric acid, etc.) other than carbonic acid in renal tubles and appears in the urine in the form of ammonium salts, such as ammonium phosphate, sulphate, urate, etc. It is obvious, therefore, that the amount of ammonium salts which will be formed will not depend upon the amount of ammonia, but on the relative proportion of the acids or bases in the body. In acidosis more ammonia is needed to neutralize the excess acids and so there will be proportionate increase in the formation of ammonium salts. In alkalosis opposite changes will occur (Fig. 32.12).

c. Ammonia may also be used for synthesis of some simple amino acids, such as glycine, alanine, etc, and also for the amination of glutaric acid to give glutamine.

d. Ammonia may also be used for the synthesis of various nitrogenous substances such as creatine, purine, uric acid, pyrimidine, lecithine, etc.

(ii) The non-nitrogenous part of an amino acid has the following fate

a. Some will have the fate of carbohydrate. So, these amino acids increase the sugar level in blood. For this reason, in a diabetic subject about 60% of food protein is converted into sugar. These amino acids are called the antiketogenic amino acids. Because they act as carbohydrate in the body and prevents the formation of ketone bodies. They are also called the glucogenic amino acid. Glycine, alanine, serine, cysteine, arginine, lysine, valine, histidine, etc. belong to this group.

b. Some undergo the fate of fats. These amino acids are broken down in the body as fatty acids, from which the ketone bodies are formed. These amino acids are therefore known as the ketogenic amino acids. It is known that in a diabetic subject about 40% of proteins are converted into ketone bodies. Phenylalanine, tyrosine, isoleucine, etc. fall in this group (Table 32.1).

c. The sulphur and phosphorous, derived from the non-nitrogenous part of the amino acids are converted into various sulphur and phosphorous compounds and are excreted through urine.

(VI) Excretory Function

i. The cholesterol and bile pigments are excreted from liver through the bile.

ii. Various toxins, bacteria and drugs are also excreted by liver through the bile.

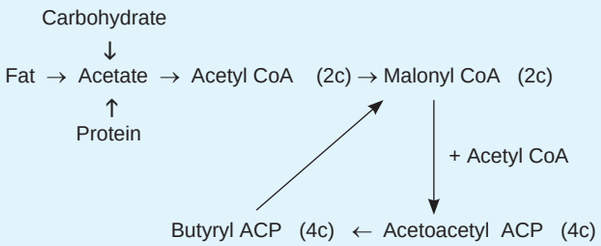
(VII) In Relation with Vitamin

i. Liver manufactures prothrombin with the help of vitamin K.

ii. It forms vitamin A from carotene and stores both the vitamin A and D.

iii. The liver is the principal storage organ of vitamin B_{12}. Therefore, in any hepatocellular disease, the uptake and storage of vitamin B_{12} by the liver tissue is decreased.

A. Synthesis of fatty acid



The two carbon (2C) acetate is thus elongated to four carbon (4C) butyryl ACP. This four carbon butyryl ACP is further elongated by 2C in each cycle by adding malonyl CoA. Finally, fatty acids with 16C are formed. For unknown reasons elongation of fatty acid stops when the chain is 16C atom long.

B. Synthesis of glycerol

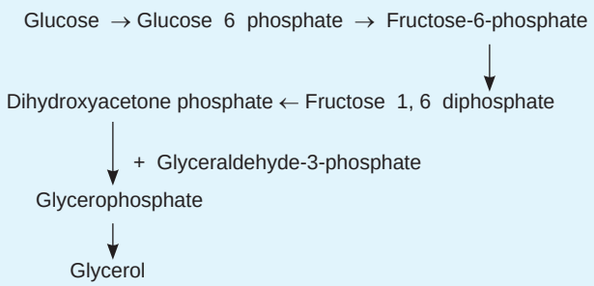
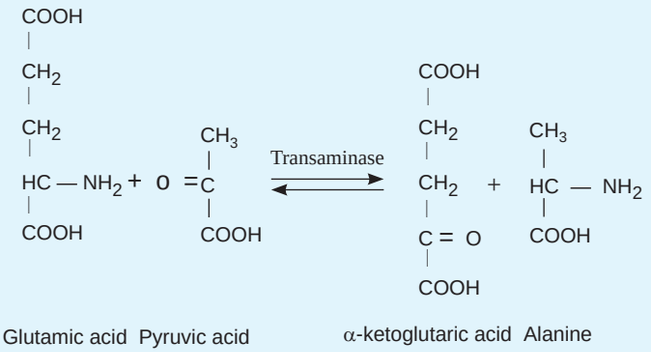


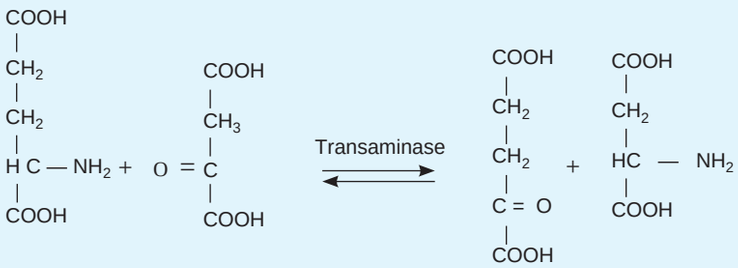
Fig. 32.11: Synthesis of fat (Triglycerides = Fatty acid + glycerol)

A. The example of glutamic-pyruvic transminase



Glutamic acid Pyruvic acid α-ketoglutaric acid Alanine

B. The example of glutamic-oxaloacetic transminase



Glutamic acid Oxaloacetic acid α-ketoglutaric acid Aspartic acid

Transaminase is recently referred to as aminotransferase. Transamination is reversible and combined process which is made up of deamination and amination. In most cases, there is transfer of amino group from amino acid to keto acid which is derived from either amino acid, carbohydrate and fat.

Fig. 32.12: Transamination or deamination

iv. Chronic liver disease is always associated with folic acid deficiency. It is known that the liver converts folate to its active form – tetrahydrofolate. Tetrahydrofolate is the storage form of folic acid. In liver disease this enzymatic transformation of tetrahydrofolate becomes impossible and thus folic acid is excreted through the urine.

(VIII) Detoxicating and Protective Functions

Liver is the principle site for the biotransformation of different toxic substances. They are either produced in the body during metabolism or taken along with the food. Again the liver converts some nonpolar compounds (lipid soluble) to polar compounds (water soluble), so that they are not reabsorbed by the renal tubules after filtration through the glomerulus and are thus excreted through the urine. But, many water soluble drugs such as streptomycin, neostigmine, etc. are not bio transformed by liver and are excreted unchanged through the urine. Though, the primary site of drug metabolism is the liver, still other sites are also available for drug biotransformation. These are kidney, intestine, lungs and plasma, etc. Biotransformation reaction of drug can be classified into nonsynthetic or phase I reaction and synthetic or phase II reaction.

Nonsynthetic or Phase I reaction

This is also called the functionalisation reaction. In this phase, metabolites becomes either active (mostly) or inactive. Activation is caused by the introduction of carbonyl, epoxide or hydroxyl groups into the parent compound. Phase-I reaction involves oxidation, reduction, hydrolysis, cyclization and/or decyclisation. Oxidation is the most common form of reaction in this phase, accounting for more than 90% of all the reactions. It is catalysed by the cytochrome P-450 system of liver cell and to a lesser extent by the mixed function of other oxidases present in the hepatocytes. Many of the reduction pathways in the liver are also catalysed by cytochrome P-450 system of hepatocytes.

Oxidation reaction involves addition of oxygen (negatively charged radical) or removal of hydrogen (positively charged radical) from the compound. Barbiturates, phenothiazines, paracetamol, steroids, phenotoin, benzodiazepines, theophylline and many other drugs are oxidised in this way in liver. Some other drugs, e.g. adrenaline, alcohol, mercaptopurine, etc. are also oxidized by the mitochondrial and cytoplasmic enzymes of hepatocytes. Reduction is the reverse of oxidation and also involves P-450 chytochrome enzymes. But, it works in the opposite direction. Drugs primarily reduced

Table 32.1: Synthesis of ketone bodies

Fatty acid oxidation
↓
Acetyl CoA
↓ Acetyl CoA
Aceto actyl CoA
↓ Liver
Aceto acetic acid
↓Reduced
β -hydroxybutyric acid
↓ Decarboxylation
Acetone

It has been observed that acetyl CoA produced during fatty acid oxidation, condenses with oxaloacetic acid for oxidation through TCA (or citric acid) cycle. But the formation of oxalo acetic acid is depressed when glucose supply is restricted (starvation) or glucose metabolism is impaired (diabetes). In this condition acetyl CoA cannot be properly metabolised through citric acid cycle. Thus acetyl CoA condenses to form acetoactyl CoA which next in the liver produces acetoacetic acid. Then this aceto acetic acid in form β-hydroxybutyric acid which after decarboxylation forms acetone. This aceto acetic acid, acetone and β -hydroxybutyric acid are called ketone bodies

are chloralhydrate, chloramphenicol, halothane etc.

Hydrolysis is the process of cleavage of a drug molecule by water, e.g.

Ester + $H_2O \rightarrow$ Acid + Alcohol

Amides and peptides are also hydrolysed by amidases and peptidases. Hydrolysis also occurs in liver, intestine, plasma and other tissues. Examples of hydrolysis are choline esters, procaine, lidocaine, procainamide, pethidine, oxytocin, etc. Decyclisation is opening up of ring structure of the cyclic drug molecule, e.g. barbiturates, phenytoin, etc. This is generally a minor pathway. Cyclisation is the formation of ring structure from a straight chain compound, e.g. proguanil.

Synthetic or Phase II reaction

This phase of metabolism involves conjugation of drugs or substrates, derived from phase I metabolism to form a polar, highly ionised organic acid which is easily excreted through the urine or bile. Conjugation reactions require high energy. This phase II reactions include glucoronide conjugation, acetylation, methylation, sulfate conjugation, glycine conjugation and glutathione conjugation.

Glucoronide conjugation is the most common form of all the phase II reactions. Compounds are easily conjugated with glucuronic acid which is derived from glucose. Examples are chloramphenicol, aspirin, phenacetin, morphine, metronidazole, etc. Not only the drugs, but also many endogenous substrates like bilirubin, steroidal hormones and thyroxine, etc. also undergoes transformation through this pathway. After conjugation these glucoronide compounds are excreted through the bile and can also be hydrolised by bacteria in the gut. Then the liberated drug is reabsorbed and undergoes enterohepatic circulation and its action is then prolonged, e.g. phenolphthalein, oral contraceptives etc. Some compounds are also conjugated with the help of acetyl coenzyme-A. This is called acetylation. The examples of this acetylation are sulfonamides, isoniazid, PAS, hydralazine, etc. Multiple genes control acetyl transferase an enzyme which is needed for this reaction and the rate of this acetylation shows genetic polymorphism. Amines and phenols are conjugated by methyl group which is donated by methionine and cysteine. This is called methylation. The examples are adrenaline, histamine, nicotinic acid. Chloramphenicol, adrenal and sex steroids undergo sulfate conjugation.

(IX) In Relation to Body Temperature

Liver produces a large amount of heat from metabolism of carbohydrate, protein and fat and thus takes part in controlling the body temperature.

(X) Hormone Metabolism

Liver metabolises the circulating hormones of adrenal gland (cortical and all sex hormones) by reduction and conjugation reaction. Steroid hormones like oestrogen, cortisol, testosterone, etc. are insoluble. Their solubility is increased and made excretable after being conjugated with glucorinic acid and sulphuric acid in the liver. The liver normally extracts about 97% of delivered aldosterone and inactivates it. Inactivation of insulin, glucagon, ADH and other hormones also occur here. In liver disease levels of all these hormones are increased.

CLASSIFICATION OF LIVER DISEASES

No single classification for all the types of liver diseases is entirely satisfactory. Because in many instances the aetiology and the pathogenic mechanism of liver diseases are obscure. As a consequence, one finds an abundance of nomenclatures and labels, applied to the same hepatic disorders. For example, some individuals use the term 'hepatitis' to imply the viral infection. Whereas, others use it simply to mean the evidence of hepatic inflammation. Similarly, the oftenly used words such as acute, subacute and chronic are also ambiguous. Chronicity is referred to the continuation or recurrence of the disease. Whereas the active is referred to evidence of the full presence or perpetuation of disease. This is most easily identified by the elevation of serum transaminase and by the degree of hepatocellular necrosis on biopsy. As there are many difficulties involved in defining the aetiology of many types of liver diseases, so, in most instances the disease process is best defined and described by an examination of the morphologic character of the lesion. Therefore, a morphologic classification of liver diseases is outlined in the table, which appears at present the more practical than one based on aetiology (Table 32.2).

LIVER FUNCTION TESTS

The liver has enormous capability to regenerate. So, it has a large functional reserve. Therefore, the liver disease in man does not become clinically apparent till well advanced. In addition, liver function tests (LFTs) which reflect the intracellular contents in circulation may be abnormal in the presence of relatively normal functions of liver. Many disease processes of liver may lead to the severe impairment of certain liver functions, while others remain entirely unaffected. Since, as no battery of tests is universally applicable, so those most appropriate to a given clinical problem must be selected. Also their potential value and risk should be considered and the results are interpreted in relation to the clinical findings. Thus, LFTs are only crude indicators of the real hepatic state and should always be correlated with the clinical picture. One isolated biochemical abnormality is insignificant. Tests should be done serially in order to evaluate the course of the disease process. Abnormal LFTs may also be due to the effect of some systemic diseases of liver

Table 32.2: Classification of liver diseases

Parenchymal

1. Hepatitis (viral, drug induced, toxic, ischaemic)
   a. Acute
   b. Chronic (persistent or active)
2. Cirrhosis
   a. Alcoholic (portal, nutritional)
   b. Postnecrotic
   c. Biliary
   d. Haemochromatosis
   e. Rare type (Wilson's disese, galactosemia, cystic fibrosis of pancreas, α-antitrypsin deficiency)
3. Infiltration
   a. Glycogen
   b. Fat
   c. Amyloid
   d. Lymphoma
   e. Leukemia
   f. Granuloma
4. Space-occupying lesion
   a. Hepatocellular carcinoma
   b. Metastatic tumour
   c. abscess
   d. Cyst
   e. Gummas
5. Functional disorder associated with jaundice (hereditary or acquired)
   a. Gilbert's syndrome
   b. Crigler-Najjar syndrome
   c. Dubin-Johnson and Rotor syndromes
   d. Cholestasis of pregnancy
   e. Benign recurrent cholestasis

Hepatobiliary

1. Extrahepatic biliary obstruction (by stone, stricture)
2. Cholangitis (septic, primary biliary cirrhosis, drug, toxic)

Vascular

1. Chronic passive congestion and cardiac cirrhosis
2. Hepatic vein thrombosis (Budd-Chiari syndrome)
3. Portal vein thrombosis
4. Pylophlebitis
5. Arteriovenous malformations
6. Veno-occlusive disease

(e.g. chronic heart failure, malignancy, etc.) and this also must be taken into consideration, while deciding on the anaesthetic plan.

Usually, the liver function tests are carried out for both the screening and identification of the type of liver disease with the aim of (i) detecting intrinsic hepatocellular damage, (ii) detecting cholestasis, (iii) detecting and differentiating between the types and causes of jaundice, (iv) assessing the synthetic functions of liver, and also (v) diagnosing of primary carcinoma (Fig. 32.13).

Bilirubin

Bilirubin is the degradation product of the heme part of haemoglobin (Hb) which is derived after the breakdown of aging erythrocytes by the mononuclear phagocytic system (MPS) or the reticuloendothelial system (RES). Bilirubin is the yellow pigment which is oxidised again into the green pigment biliverdin. According to some, biliverdin is formed first from heme and later by reduction forms bilurubin This unconjugated bilirubin (or indirect bilirubin) is bound to serum albumin because it is insoluble in the aqueous solution at the physiological pH. So, it is not excreted by glomerular filtration through the urine. On reaching the liver cells via the blood of sinusoids, the albumin is dissociated from bilirubin and free bilirubin enters the liver cells, where it is bound to the cytoplasmic protein, named ligandin. This cytoplasmic liver cell protein, ligandin, then assists in the transfer of bilirubin to the endoplasmic reticulum (ER) of liver cell for conjugation. In ER of liver cell, bilirubin is conjugated with glucoronic acid which is catalysed by the enzyme glucoronyl transferase. Then, this conjugated bilirubin glucoronide (or direct bilirubin) which is water soluble, is actively transported to the bile canaliculi. A small amount of conjugated bilirubin (bilirubin glucuronide) escapes in the blood of sinusoids. Therefore, the total plasma bilirubin normally includes free unconjugated bilirubin which is bound to

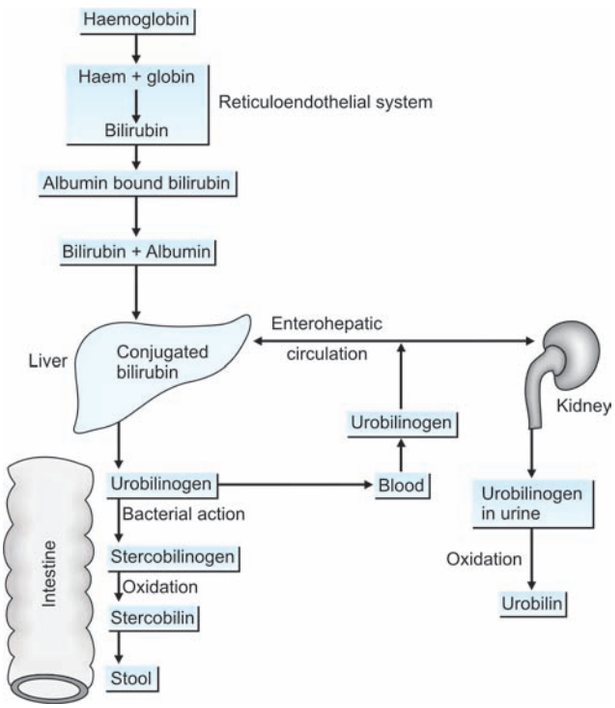


Fig. 32.13: Pathway of bilirubin formation and excretion

albumin and a small amount of conjugated bilirubin which are circulating in blood. The normal value of total plasma bilirubin is 0.2 to 0.8 mg/dl. Out of which the level of conjugated is 0.00 to 0.2 mg/dl and the level of unconjugated is 0.2 to 0.6 mg/dl.

The conjugated Bilirubin imparts the brilliant yellow colour to the bile. Most of the conjugated bilirubin passes via the bile duct into the intestine. In the intestinal mucosa, then most of the conjugated bilirubin glucoronides are again deconjugated by the intestinal bacteria and form the colourless urobilinogen. The urobilinogen and the residues of some intact pigment are then largely excreted through the faeces as stereobilinogen and stercobilin which are responsible for the brown colour of the stool. Some of the urobilinogens are reabsorbed from intestine and excreted through the urine as it is conjugated and water soluble. Some are also returned to the liver. Complete bile duct obstruction blocks the excretion of conjugated bilirubin from liver into the gut and results in disappearance of urobilinogen and stercobilinogen from the urine and stool. Thus, the assessment of urobilinogen in a freshly collected 2-hour urine specimen may distinguish the biliary tract obstruction from the parenchymal dysfunction of liver. But this test has been largely superseded by other methods. In complete bile duct obstruction as the pressure in the bile canaliculi is increased, so the conjugated bilirubin from the bile canaliculi flows back from the liver cells into the blood of sinusoids and enters the systemic circulation. So, the level of conjugated bilirubin in blood becomes very high.

The disorders of bilirubin metabolism can be divided into four major categories: (i) increased pigment production in RE system, (ii) reduced hepatic uptake of unconjugated bilirubin, (iii) impaired hepatic conjugation in the liver cell, (iv) decreased excretion of the conjugated pigment from the liver into the bile. However, the last three points can be clubbed under the heading of impaired excretion of bilirubin. The first three disorders are associated predominantly with the unconjugated hyperbilirubinaemia and no bilirubinuria. The fourth group is associated predominantly with the conjugated hyper bilirubinaemia and bilirubinuria. Now, the increased plasma concentration of unconjugated bilirubin may be due to the increased production, e.g haemolysis (factor 1) or reduced liver uptake, e.g Gilbert's syndrome and Crigler-Najer's syndrome (factor 2 and 3) or those in whom both the mechanisms operate. In haemolytic anaemia, jaundice due to unconjugated bilirubin appears only when the rate of bilirubin production exceeds the amount that can be conjugated and removed by a normal liver which has an enormous reserve. In most cases of uncomplicated haemolytic states, the mean serum bilirubin (unconjugated or indirect) level will be in the range of 3 to 4 mg/dl. Rarely, higher levels may be seen, if the haemolysis is associated with fever, sepsis, hypoxaemia, etc., or if the ability of the liver to handle the pigment load is compromised (i.e. when haemolytic disease is associated with liver disease).

Jaundice due to increased pigment production may also be seen as a consequence of large tissue infarction (e.g. pulmonary infarcts) or large collection of blood in the tissues. If hypotension or hypoxaemia supervene, then the jaundice is usually more pronounced and the resulting impairment of liver function may lead to a significant increase in the serum unconjugated bilirubin level. Except in early infancy, the elevation of serum unconjugated bilirubin levels is not harmful. Rather the prognosis depends on the haemolytic process itself than the level of the unconjugated bilirubin. However, in the neonatal state and infancy, the unconjugated bilirubin levels above 20 mg/dl may lead to kernicterus. This is due to the deposition of this water insoluble (fat soluble) bilirubin in the lipid rich basal ganglia of brain as blood brain barrier is not well developed in neonates like adults.

Currently, there are three syndromes such as Gilbert's, Crigler-Najjar II and Crigler-Najjar I which fall in the category of hereditary glucoronyl transferase enzyme deficiency disorders. In these disorders there is impairment of conjugation of bilirubin by the liver parenchymal cells. These three syndromes reflect progressive decrease in the activity of glucuronyl transferase enzyme and thus may be the part of a spectrum of a single disease, i.e. from minimal deficiency to complete absence of glucoronyl transferase enzyme (Gilbert's is the mild, Crigler-Najjar II is the moderate and Crigler-Najjar I is the severe form). These three syndromes are characterised by unconjugated hyperbilirubinaemia, normal liver function tests and no overt or clinically recognisable haemolysis. The liver cells during liver biopsy usually appear normal by light microscope.

Normally, between the 2nd and 5th days of life, almost every neonate shows some transient unconjugated hyperbilirubinaemia. During intrauterine period, the placenta serves to clear the unconjugated bilirubin from the fetus. But after birth, neonates detoxify the pigments themselves by their liver. However, at this stage the hepatic enzyme, named glucuronyl transferase, remains immature. As a result, the unconjugated hyperbilirubinaemia develops (usually not exceeding 5 mg/dl). Within several days to weeks after birth, the activity of glucouronyl transferase enzyme increases and concomitantly the serum unconjugated bilirubin level returns to normal. In infants with erythroblastosis (a superimposed haemolytic process), the excessive pigment load leads to more pronounced jaundice and unconjugated bilirubin level may go upto 20 mg/dl or above. Neonatal jaundice is not present at the time of delivery. If jaundice is present at birth, then other causes must be considered. During

neonatal period if unconjugated bilirubin level exceeds 20mg/dl, the patient usually develops Kernicterus (bilirubin encephalopathy) and eventually dies. This condition results from the deposition of unconjugated bilirubin in the lipid rich basal ganglia (as unconjugated bilirubin is fat soluble and not water soluble). The current therapeutic approach of this unconjugated hyperbilirubinaemia is phototherapy, in which the strong white or blue light leads to the photoisomerisation of nonwater soluble bilirubin to its water soluble isomers that are rapidly excreted in the bile without prior need for conjugation. Another novel approach involves decreasing the bilirubin production from heme by inhibitors of heme oxygenase. Synthetic protoporphyrins such as tin protoporphyrin also have been administered successfully to the patients with neonatal unconjugated hyperbilirubinemia, causing marked reduction in the serum bilirubin level with no major side effects (Table 32.3).

In jaundice, due to primary or parenchymal liver disease, the plasma usually exhibits the elevated levels of both the conjugated and unconjugated bilirubin, but urine contains the only water soluble conjugated bilirubin. The relative proportion of these two pigments are highly variable. Such serum bilirubin pigment pattern is also seen with extrahepatic biliary obstruction. One cannot differentiate the intrahepatic and extrahepatic causes of jaundice only by the levels of unconjugated and conjugated bilirubin in serum, but from the prehepatic causes of jaundice. Thus, the main purpose of the initial fractionation of the serum bilirubin is to distinguish hepatic parenchymal and biliary obstructive diseases from the prehepatic disorders which are associated with predominantly unconjugated hyperbilirubinaemia. In many familial hepatic abnormalities such as Dubin-Johnson syndrome (autosomal inheritance), the jaundice is largely due to the increase in conjugated bilirubin. Functionally, in Dubin-Johnson syndrome there exists a defect in excretion of bilirubin into the biliary canalienli from the liver cells after conjugation (at cellular levels). But, there is no defect in the conjugation process of unconjugated bilirubin. So, bilirubin after conjugation flows back from the liver cells into the blood due to the defect in excretion into biliary canaliculi. Other familial defects in hepatic excretory function where conjugated hyperbilirubinaemia occur are Rotor syndrome (actually this syndrome is due to impairment of storage capacity), benign recurrent intrahepatic cholestasis, recurrent jaundice during pregnancy, etc. Acquired defects of hepatic excretory function at cellular level where conjugated hyperbilirubinaemia occur are drug induced cholestasis (e.g. use of oral contraceptives), hepatitis and cirrhosis. Hepatitis and cirrhosis are the most common disorders associated with jaundice. When the liver cells are damaged as in viral hepatitis, then there is often impairment in all the three major hepatic phases of bilirubin metabolism, namely uptake, conjugation and excretion. This is due to the impairment of function of liver cells. There is also little increase in the level of serum unconjugated bilirubin. The acquired defects of biliary excretory function at extrahepatic level may be due to stones, tumours or strictures in biliary tree. The clinical pictures of this obstructive jaundice are quite similar to that of intrahepatic cholestasis, with pronounced elevation of serum conjugated bilirubin.

Table 32.3: Mechanisms producing jaundice

A.	Increased production of bilirubin
	• Haemolysis
B.	Impaired excretion of bilirubin
	Congenital non-haemolytic hyperbilirubinaemia
	• Gilbert's syndrome
	• Crigler-Najjar type I and type II
	• Dubin-Johnson syndrome
	• Rotor's syndrome
	Hepatocellular jaundice
	• Acute parenchymal liver disease
	• Chronic parenchymal liver disease
C.	Cholestasis or obstruction
	• Stone in CBD
	• Stricture of CBD
	• Cirrhosis
	• Pregnanct

Serum Enzyme Assays

A number of serum enzymes have been used to distinguish and assess the hepatocellular functions. But, none can truly distinguish or assess these processes definitely and especially all have inherent limitations in sensitivity and specificity. On the otherhand, the elevation of these enzyme acitvities may also be seen in association with nonhepatic disorders. Nevertheless, with proper and careful interpretations, a number of serum enzymes provide important clinical tools regarding the assessment of liver functions. These enzymes are:

Aminotransferase (Transamines)

As an indicator of hepatocellular function, assays of many serum enzymes have been proposed. But among these, AST (aspartate aminotransferase, previously called SGOT) and ALT (alanine aminotransferase, previously called SGPT) enzyme activities have been proven to be the most useful. In contrast to ALT which is found primarily in the liver, AST is also present in many tissues, including heart, skeletal muscle, kidney and brain. Thus, AST is somewhat less specific as an indicator of liver function than ALT.

In a hepatocyte, ALT is found exclusively in the cytosol, while different isoenzymes of AST exist in mitochondria and the cytosol. The normal level of AST and ALT in serum is 35 U/L. The source of normal serum AST and ALT level is still unclear. Although the elevated serum levels of AST or ALT may also be observed in a variety of non-hepatic disease, notably in myocardial infarction and skeletal muscle disorders, but these disorders can usually be distinguished clinically from liver disease. In contrast, uremia may also lead to a falsely low aminotransferase value.

The absolute levels of aminotransferase correlates poorly with the severity of liver disease or its prognosis. Only serial determination of value is usually most useful. Very high level of these enzymes suggests the development of cholangitis with resultant hepatic cell necrosis. Modest elevation of transaminases occur in alcoholic hepatitis. Minimal elevation of AST and ALT is found in association with the biliary tract obstruction. In general, serum AST and ALT levels are parallel with each other, with some exceptions (e.g. in alcoholic hepatitis AST/ALT > 2) (Table 32.4).

Alkaline Phosphatase

Alkaline phosphatase is a plasma membrane derived enzyme of uncertain physiological function that hydrolyses synthetic phosphate esters at pH 9. Human serum contains several forms of it and different techniques of assesment of alkaline phosphatase have been developed that utilize different substrates. Alkaline phosphatase usually arises from the bone, intestine, liver and placenta. In the absence of bone disease or pregnancy, the elevated levels of alkaline phosphatase reflect impaired biliary tract function. In liver diseases the increased level of alkaline phosphatase is due to the increaed synthesis of this enzyme by hepatocytes and biliary tract epithelium, or due to the regurgitation of this enzyme by biliary obstruction. The probable explanation of it is that bile acids play a role both in inducing the synthesis and promoting the solubilisation of this membrane's associated enzyme activity.

Slight to moderate rise of alkaline phosphatase level occurs in parenchymal liver disorders such as hepatitis and cirrhosis. But very high level of it is found in infiltrative disorders, e.g. myobacterial infection of liver. However, consistently and striking increase in alkaline phosphatase level which is 10 times greater than normal value (normal value is 30 to 120 U/L) occurs with the extrahepatic biliary tract (mechanical) obstruction or with intrahepatic (functional) cholestasis, (as in drug induced cholestasis or primary biliary cirrhosis). Conversely, it is unusual for the serum alkaline phosphatase to remain normal when there is obstructive jaundice. On the otherhand, a normal alkaline phosphatase enzyme level argues strongly against the presence of cholestasis or obstruction.

In metastatic or infiltrative liver diseases such as leukaemia, lymphoma and sarcoidosis, etc. the alkaline phosphatase level is usually mildly elevated. Sometimes alkaline phosphatase level is also elevated in nonhepatic disorders, most commonly in some bone disorder such as Paget's disease, osteomalacia, bone metastasis, etc. and sometimes with malignancy. Several methods can distinguish different isoenzymes of alkaline phosphatase of different origins. For example, in contrast to that of alkaline phosphatase which is derived from bone, the hepatic isoenzyme of alkaline phosphatase is stable on treatment with heat (56°C for 15 minutes). These isoensymes can also be distinguished by electrophoresis. But, this is not practical for the diagnosis of specific diseases. Because the parallel determination of serum 5′-neucleotidase helps in diagnosis. An increase of both 5′-neucleotidase and alkaine phosphatase diagnose hepatobiliary disease.

Table 32.4: Abnormalities shown by tests of liver function

Test	*Type of liver disease*	
	Obstructive	*Parenchymal*
AST and ALT(SGOT and SGPT)	↑	↑ to ↑↑↑
Alkaline phosphatase	↑↑↑	↑
Albumin	N	↓ to ↓↓↓
Prothrombin time	N to ↑	↑ to ↑↑↑
Bilirubin	N to ↑↑↑	N to ↑↑↑
γ-glutamyl transpeptidase (GGT)	↑↑↑	N to ↑↑↑
5' - nucleotidase	↑ to ↑↑↑	N to ↑

Correctable with parenteral vitamin K if elevated. N = Normal , ↑ = Elevated , ↓ = decreased

5-Nucleotidase

It is an enzyme which catalyzes the hydrolysis of phosphate at the position 5 of a pentose component of a nucleotide. The enzyme 5 nucleotidase is widely distributed in all the tissues, but the hepatobiliary disease is associated with higher elevation of this enzyme. The normal value of this nucleotidase enzyme is 1 to 18 U/L. The principle importance of 5-nucleotidase measurement is to confirm the hepatic origin of an elevated alkaline phosphatase level in children or pregnant women or in those settings where coincident bone disease may be present. In the contrary, lack of elevation of 5 nucleotidase always does not exclude an hepatic source of elevated serum alkaline phosphatase level.

Gamma (γ)-Glutamyl Transpeptidase (GGT)

The GGT plays a major role in amino acid transport and catalyses the transfer of γ-glutamyl group from peptides such as glutathione to other amino acids. It is distributed in various tissues, as well as in the hepatobiliary system. In liver disease, the plasma level of GGT correlates well with that of the alkaline phosphatase levels and is the most sensitive indicator of biliary tract disease. GGT levels are also elevated in pancreatic, cardiac, renal and pulmonary disorders, as well as in diabetes and alcoholism. So, overall lack of specificity of GGT has constrained its usefulness.

Serum Proteins

Extensive liver cell damage or injury leads to decreased blood levels of albumin, prothrombin, fibrinogen and other serum proteins which are exclusively synthesised by the hepatocytes. So, in contrast to the measurement of serum enzymes which reflect directly the liver cell injury, estimation of serum proteins also reflect the synthetic dysfunctions of liver cells.

During interpretation of serum protein levels in hepatic diseases, there are three important principles:

i. Liver proteins are neither early, nor sensitive indicators of liver disease. This is because of the huge hepatic reserve and the prolonged half-live of serum proteins.
ii. Decrease in serum protein levels is not specific for liver disease, because there are many other factors which cause the decreased level of serum proteins such as nutritional deficiency, malabsorption, etc.
iii. Liver proteins are of little value in the differential diagnosis of liver diseases.

Albumin and Globulin

The normal serum value of albumin ranges from 35 to 55 g/L and it is the most important protein, synthesised by the liver. The half-life of albumin is 14 to 20 days and daily turn over is < 5%. Moreover, there is a substantial power of reserve for synthesis of albumin by hepatocytes. Thus, adequate synthesis of albumin may continue, though there is extensive hepatocellular injury. So, albumin estimation is not a good indicator for acute and mild hepatocellular injury. On the other hand, serum levels of albumin are also influenced by a variety of non-hepatic factors such as nutritional status, hormonal factors, kidney diseases (nephrotic syndrome), protein losing enteropathy, etc. which are not associated with the dysfunction synthesis of albumin by liver. Still, reduction of serum albumin levels provide an excellent indicator of chronic liver disease (provided other systems remain free of diseases).

Serum globulins are a heterogenous group of proteins (α, β, γ, etc) which are synthesised in a variety of tissues. The normal serum globulin level is 20 to 35 g/L. It is often elevated in association with chronic liver disease, e.g. cirrhosis hepatitis, fatty liver, etc. This reflects the increased stimulation of synthesis of immunoglobin by the peripheral RE system, due to the shunting of the antigens which bypass the liver and are not cleared by the hepatic Kupffer cells. There are many other nonhepatic conditions where globulin levels are also elevated. The albumin/globulin ratio has no physiological significance.

Clotting factors

Virtually all the coagulation factors, which are protein in nature are synthesised in the liver and requires the presence of vitamin K as cofactor (factor V, XII, XIII do not need vitamin K for synthesis). Like serum protein, these coagulation factors are also normally present in plasma in excess concentration. So, impaired coagulation is usually seen only in severe liver disease. Impaired coagulation can be most efficiently determined by the one-stage prothrombin time (PT). PT measures the rate of conversion of prothrombin to thrombin in the presence of thromboplastin and calcium and requires the integrity of other vitamin K dependent clotting factors (Table 32.5).

Thus, prothrombin time (PT) depends on sufficient intestinal uptake of Vit-K and normal synthesis of clotting factors by liver. Absorption of vitamin K requires adequate dietary intake, normal function of intestinal mucosa and normal biliary secretions (as vitamin K is a fat soluble vitamin). As coagulation factors are of shorter half-life than that of serum proteins, so the prothrombin time may be an early indicator than serum albumin level in hepatic injury. In both acute and chronic hepatocellular injury, an increase in the prothrombin time serves as an ominous prognostic sign. As vitamin K is a fat soluble vitamin, so the prolongation of prothrombin time can also result from vitamin K malabsorption which may occur with cholestasis due to biliary tract disease or due to malabsorption of any cause (e.g. pancreatic insufficiency, steatorrhoea, etc.). Poor dietary intake, antibiotic therapy and use of warfarin type of anticoagulants are additional causes of prolonged prothrombin time, owing to the deficiencies of active vitamin K. These process can be distinguished from the failure of hepatic synthesis by demonstrating the normalisation of prothrombin time (within 24 to 48 hours) after parenteral injection of vitamin K. The partial thromboplastin time (activated PTT) which reflects the activity of fibrinogen, prothrombin and clotting factors such as V, VIII, IX, X, XI, XII may also be prolonged in severe liver disease. Before any surgical procedure on patient with liver disease including liver biopsy, clotting functions should always be assessed in all of them (Fig. 32.14).

Table 32.5: Numerical system for International Nomenclature of blood coagulation factors

Clotting Factor	*Synonym*
I	Fibrinogen (100)
II	Prothrombin (80)
III	Tissue thromboplastin
IV	Calcium
V	Labile factor (18)
VI	Accelerin (6)
VII	Stable factor (6)
VIII	Antihaemophilic factor (AHF) (10)
IX	Christmas factor (24)
X	Stuart factor (50)
XI	Plasma thromboplastin antecedent (PTA) (25)
XII	Hageman factor or Surface factor (60)
XIII	Laki-Lorand factor (LLF) (90)

Blood Ammonia

Liver is the major site of amino acid or protein metabolism and their interconversions. It synthesises proteins from amino

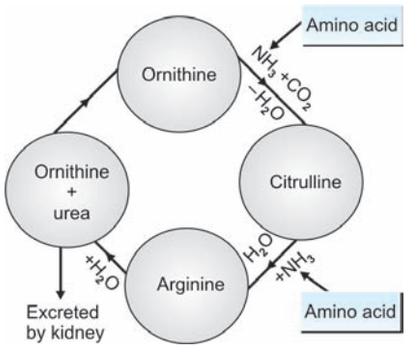


Fig. 32.14: Krebs-Henuseleit ornithine cycle. Formation of urea → Krebs- Henuseleit cycle. In this cycle one acid (carbonic acid) and two molecules of NH_3 are neutralised

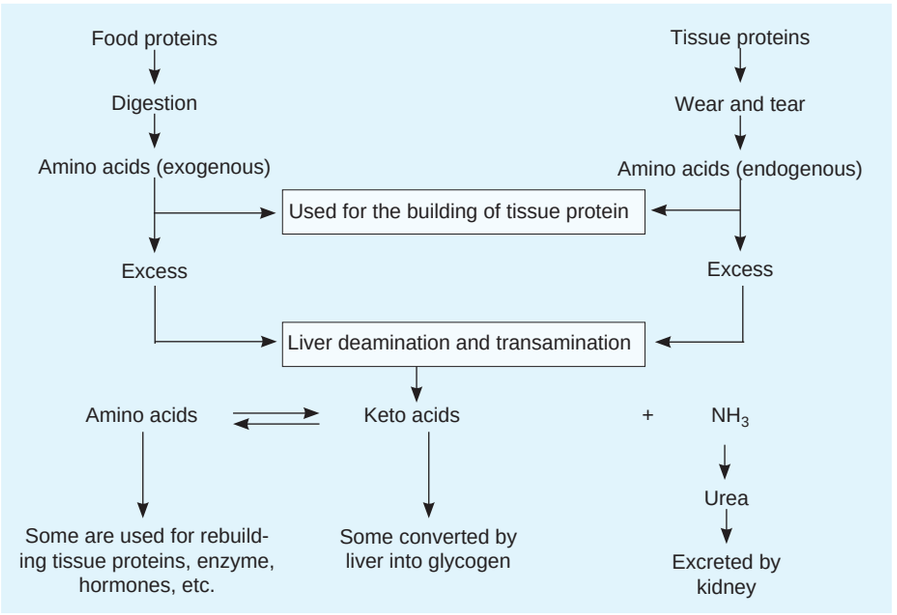


Fig. 32.15: Synthesis of proteins and amino acids in liver

acids supplied from dietary source or from metabolic turnover of endogenous protein (primarily from muscle). Protein is also directly synthesised in the liver. The dietary amino acids enter the liver through portal vein and are also catabolised to urea. In liver diseases, disruption of this normal amino acid metabolism pathway leads to elevated plasma amino acid concentrations.

Liver handles the amino acids by two major reactions: transamination and oxidative deamination. In transamination amino acid enters the citric acid cycle. But in oxidative deamination amino acids are converted to keto acids and ammonia. This ammonia is the toxic product of nitrogen metabolism. So it is converted to urea by Krebs-Henuseleit or ornithine cycle and is of very clinical importance in a patient with severe liver disease. In advanced liver disease, urea synthesis is often depressed, leading to an accumulation of NH_3 in blood. This is sometimes associated with a significant reduction of blood urea nitrogen (BUN) which is an ominous sign of liver failure. Urea is mostly excreted by the kidney. 25% of the formed urea is also diffused into the lumen of intestine from blood where it is again converted to NH_3 by bacteria named urease. The intestinal production of ammonia also occurs from the bacterial deamination of unabsorbed amino acids and also from the protein which are derived from the diet, from the exfoliated cells of intertine or from the blood in the GI tract. NH_3 from the GI tract is reabsorbed and transported to liver by portal system and again converted to urea. Kidney also produces the varying amounts of amonia. The contribution of gut and kidney in ammonia synthesis has important implications in the management of hyper-ammonaemic state, frequently seen in patients with advanced liver disease. Hyper-ammonaemia usually leads to hepatic encephalopathy (Fig. 32.15).

EFFECTS OF LIVER DYSFUNCTION ON PHARMACOKINETICS AND PHARMACODYNAMICS OF ANAESTHETIC DRUGS

Liver plays a critical role in nutrition, drug metabolism, synthesis of plasma proteins, detoxification and elimination of many endogenous and exogenous toxic substances, etc. which are described before. So, acute and chronic liver dysfunctions usually alter the pharmacokinetics and pharmacodynamics of anaesthetic drugs. It is due to the result of portal hypertension, reduced level of serum albumin and other proteins causing altered drug binding, altered volume of distribution of drugs due to the increased total body water, reduced metabolism of drugs secondary to abnormal function of hepatocyte, etc. Enzyme induction due to chronic alcohol ingestion, changes of hepatic blood flow and the severity of the underlying hepatic diseases also influence the effects of drugs. In addition, the influence of liver disease differs for elimination of enteral and parenteral group of drugs. Portal hypertension causes reduction in the portal venous blood flow to the liver and hence the drugs given by the oral route will have prolonged half-life.

The clearance of drugs by liver is dependent on its availability to the liver cells, which in turn is dependent on the liver blood flow. So, the metabolism of drugs like lignocaine and pethidine which have high clearance ratio are affected more than the drugs like benzodiazepines (BDZ) which have low clearance ratio. On the other hand, these drugs are more affected by altered protein binding, intrinsic hepatic clearance and metabolism.

Premedicants

The advent of day care anaesthesia has virtually reduced the number of patients who are routinely subjected to premedication. The trend is now either no premedications or oral administration of short acting benzodiazepines in very small doses. The recovery time and elimination kinetics of a sedative dose of benzodiazepines is prolonged in patients with liver dysfunction. It is due to reduced protein binding and reduced metabolism of BDZ in liver disease. Therefore, these drugs should be used with caution when repeated injections or infusions are required. However, their effects may be reversed by flumazenil.

IV Inducing Agents

Most intravenous inducing agents undergo extensive hepatic metabolism. However, studies suggest that after a single bolus dose, pharmacokinetics of these agents is not much altered. But, there are no studies showing that the duration of action of weight adjusted dose of thiopentone is altered in patients with liver dysfunction. Propofol has a very large volume of distribution and is extensively protein bound. So, there is little difference in pharmacokinetics of propofol between the normal and liver dysfunction patients. Though the kinetics of thiopentone and propofol is not affected after a single bolus dose, but prolonged mean clinical recovery time has been reported mainly after propofol infusion in liver dysfunction.

Opioids

Opioids are extensively metabolised by the liver. Therefore, their duration of action is significantly prolonged in liver disease. Decreased plasma protein binding capacity in liver disease also leads to potentially exaggerated sedative and respiratory depressant effects of opioids. Doubling of half-life has also been observed in morphine and pethidine in hepatic dysfunction and, therefore, it is recommended to increase the administration interval by 1.5 to 2 folds for these group of drugs. In addition, decreased clearance of norpethidine in patients with advanced liver disease may precipitate neurotoxicity more commonly. Fentanyl and sufentanil are highly lipid soluble synthetic opioids and are extensively metabolised in the liver. However, their single dose pharmacokinetics is not much altered in liver diseases. But, continuous infusion or repeated dosing may prolong their effect. Unlike these drugs, the half-life of alfentanil is almost doubled in patients with cirrhosis of liver which can lead to prolonged duration of action and enhanced effects. The remifentanil is rapidly hydrolysed in plasma by tissue esterases, leading to rapid recovery which is independent of dose and duration of infusion. So, the available data indicates that its elimination is unaltered in patients with severe liver disease or in those undergoing liver transplantation.

Muscle Relaxants

Suxamethonium and mivacurium are the substrates for hydrolysis by plasma cholinesterase enzyme. Plasma cholinesterase is synthesised in liver. So, low plasma cholinesterase concentration in liver dysfunction may prolong the half-life of succinylcholine and mivacurium. However, the reduction of plasma cholinesterase level is such that, even in fulminant hepatic failure, the action of succinylcholine is unlikely to be prolonged significantly. But, care should be taken if mivacurium or succinylcholine is administered by infusion.

The non-depolarising muscle relaxants are highly water soluble (e.g. d-tubacurarine, galamine and pancuronium atracurium, vecuronium, rocuronium, etc.) and are therefore easily excreted through the urine. However, increased volume of distribution in patients with liver disease leads to an apparent resistance to these agents with prolonged elimination. The modern steroid based drugs such as vecuronium and rocuronium show little alteration in their pharmacokinetics in a jaundiced patient. The atracurium and cisatracurium undergo organ independent elimination by ester hydrolysis and spontaneous Hoffman degradation in the plasma. So, they have no change in elimination half-life or clinical duration of action, even in patients with both hepatic and renal failure. But, many of the newer non-depolarizing drugs are given by infusion and their effect may be unpredictable in patients with hepatic disease. So, careful monitoring of neuromuscular function should be carried out with a nerve stimulator during anaesthesia when muscle relaxants are used, especially by infusion in liver dysfunction patients.

PREOPERATIVE EVALUATION AND RISK ASSESSMENT OF PATIENT WITH LIVER DYSFUNCTION

Liver diseases can alter the responses of patients to anaesthesia and surgery in many ways. So, it is important to understand the applied anatomy and physiology of liver, the factors altering hepatic blood flow, the liver functions and the pharmacokinetics and pharmacodynamics of anaesthetic drugs for proper perioperative management of these patients. But, the complex functions of liver, the effects of perioperative stress and strain on the liver function and the unpredictable effect of drugs in patients with liver disease has made the preanaesthetic evaluation and the risk assesment is challenging. The perioperative risk assessment should take into account the type of liver disease, the degree of hepatic impairment and the intrinsic surgical risk associated with the procedure. Patients with liver disease undergoing nonhepatic surgery and anaesthesia face significant postoperative complications also.

For the assessment of risk, liver disease can be graded (according to Child's classification which is modified by Pugh) on the basis of the impairment of the synthesis functions of liver, mainly plasma

albumin levels and prothrombin time. Mild hepatic disease consists of positive clinical history and evidence of liver pathology coupled with normal plasma albumin and prothrombin times. Other tests of hepatic function such as aminotransferase may be elevated. Moderate liver disease consists of plasma albumin level of at least 3 g/dl and prothrombin time is not greater than 2.5s. Severe liver disease is defined as when albumin level falls below 3 g/dl and prothrombin time is above 2.5s. The perioperative risk assessment of patient according to the type of liver disease is described below under the heading of asymptomatic and symptomatic patients and under the heading of individual disease (Table 32.6).

Asymptomatic Patients

Asymptomatic patients with abnormalities of standard liver enzyme tests including asperate aminotransferase (AST), alamine aminotransferase (ALT) and alkaline phosphatase occur in 0.1 to 4% of the general population. The incidence is as high as 36% in patients with history of alcohol and drug abuse. Minor elevations of these enzymes less than twice of the normal value in asymptomatic patients, who have normal serum bilirubin and INR do not warrant additional testing before anaesthesia and surgery. On the other hand, larger elevations of transaminases during routine preoperative investigations signify a subclinical acute process such as viral hepatitis or a chronic disorder such as chronic hepatitis. So, they require additional analysis starting from the careful history and physical examination of patient to the history of previous surgeries, jaundice, blood transfusion, use of alcohol and other recreational drugs, sexual history, etc. Careful attention should also be paid to the systemic effects of liver disease including pruritus, excessive bleeding after minor trauma, abdominal distention and weight gain. Physical examination should also focus on the signs of liver disease such as icterus, pallor, hepatomegaly, splenomegaly, testicular atrophy, palmar errhythema, spider nevi and gynecomastia. Further investigations should also be carried out to assess the hepatic functions such as coagulation profile, electrolytes and liver enzymes. AST/ALT ratio may also be helpful in distinguishing between the viral and alcohol related hepatitis. Alcohol tends to preferentially damage the mitochondria of hepatocyte, therefore causing much elevation in AST which is usually greater than twice of the ALT values. In contrast, a decrease in this ratio is more consistent with a diagnosis of viral hepatitis. Elevated alkaline phosphatase with abnormal bilirubin and GGT indicate hepatobiliary disease. Asymptomatic patients with significant abnormal liver function should have elective surgery postponed and is further investigated to reassess the perioperative risks.

Symptomatic Patients with Acute and Chronic Hepatic Diseases

Patients with acute liver disease or failure rarely represents for anaesthesia and surgery. This is because mortality rate is very high and is near about 10 to 100%. Acute hepatic failure during postanaesthetic period is due to the decompensation of previously apparent well patients with chronic liver disease. Paradoxically, hyperacute hepatic failure (encephalopathy within 7 days) has the best prognosis.

Table 32.6: Spectrum of liver disease

	Early stage	*Late stage*
1.	Inflammatory response in liver usually predominates	Fibrotic response in liver usually predominates
2.	Drug resistance is often observed	Drug sensitivity is often observed
3.	No portal hypertension is observed	Portal hypertension is the dominant feature
4.	Major laboratory abnormalities are elevated enzymes such as aminotransferase	Major laboratory abnormalities are disorders of hepatic synthetic functions such as abumin, prothrombin time, etc.

Bilirubin level in plasma is elevated in both the stages

Some causes of acute liver disease or failure presenting for surgery and anaesthesia are:

i. Viral hepatitis: Type A to G , cytomegalo virus, herpex simplexvirus, Epstein – Barr virus, etc.
ii. Drugs: Halothane, paracetamol excess, idiosyncratic reactions, etc.
iii. Toxins: Carbon tetrachloride, mushrooms poison etc.
iv. Others: Acute fatty infiltration of pregnancy, HELLP syndrome, Wilson's diseaese, REYE's syndrome, etc.

Some causes of chronic hepatic diseases presenting for surgery and anaesthesia are:

i. The commonest cause of chronic liver disease is cirrhosis. Cirrhosis can be acquired such as due to alcohol, viral hepatitis, drugs, secondary biliary disease etc. Or cirrhosis can be inherited such as due to primary biliary cirrhosis, haemochromatosis, Wilson's disease, galactocaemia, sickle cell disease, etc.
ii. Chronic hepatitis is also wide spread. It is defined as any hepatitis lasting longer than 6 months. The causes of chronic hepatitis are: viruses, alcohol, autoimmune, metabolic and drugs (isoniazid, methyldopa). Chronic hepatits B develops in 3% of those infected. It is widespread in the Far East, Africa and infects 300 million people world wide. Other high risk groups include — homosexuals, IV drug abusers, haemophiliacs, haemodialysis patients. Chronic hepatitis B may progress to cirrhosis or hepato – cellular carcinoma. Chronic hepatitis C develops in 75% of those infected. Risk groups are

similar to hepatitis B and cirrhosis or hepatocellular carcinoma can develop.

Hepatitis

A hepatitis patient should always be taken seriously for anaesthesia. So, an accurate diagnosis of the cause of hepatitis is exceedingly important during preanaesthetic investigations. There are two points of serious concern in a patient suffering from acute viral hepatitis and who may require surgery and anaesthesia. These two points are:

i. The combination of surgery, anaesthesia and acute viral hepatitis is associated with high mortality rate. Available data indicates that perioperative mortality rate ranges from 10 to 100%, if a patient with acute viral hepatitis requires surgery and anaesthesia. Thus, a disease of low to moderate mortality is converted by the surgery and anaesthesia to one of high mortality.
ii. Hepatitis B and C can be highly contagious via parenteral inoculation to the operating theatre personnel.

However, the exact time of surgery and anaesthesia which is safe after an acute attack of viral hepatitis is still unknown. It is usually said that surgery is permissible some 30 days after the liver function studies have returned to normal. It is prudent to postpone the elective surgery in the acute phase of hepatitis and wait for the level of transaminases to return to the normal ranges. In case of hepatitis B and C, there should be sufficient time to ensure that the patient does not enter into the phase of chronic persistent or chronic active hepatitis. A jaundiced patient waiting for anaesthesia and surgery should be differentiated between acute viral hepatitis and posthepatic biliary obstruction as a cause of jaundice where in one condition early surgery is necessary and in one condition where early surgery and anaesthesia is associated with high mortality rate.

There are three principal hepatitis viruses: A, B and C (older nomenclature of C is non-A / non-B). Hepatitis A is the classic oral-faecal, food-borne hepatitis with low mortality rate and does not progress to chronic hepatitis. Hepatitis B and C have higher mortality rate and can progress to chronicity. The chronic phase of these viral hepatitis may be either chronic persistent hepatitis or chronic active hepatitis. Chronic persistent hepatitis is a mild non progressive disease. In most cases it is due to either hepatitis B or C viruses. This chronic persistent viral hepatitis may be due to some unknown reasons and is slow to resolve, at times taking as long as 18 months. Then, these patients eventualy do resolve and the prognosis is generally favourable. Since these patients are eventually cleared of liver disease, usually with in a year, so it is prudent to defer the elective surgery until their liver function studies become normal, for at least 1 month. If emergency surgery is required, then the risk in these patients is probably not increased (but there is no data to confirm this point).

Chronic active hepatitis has also been termed as chronic aggressive hepatitis. It is produced by hepatitis B and C viruses and progress in most patients to cirrhosis and hepatic failure. Patients with chronic active hepatitis will eventually die of liver failure within 2 to 10 years, unless other causes of death supervene. The bilirubin level increases and aminotransferase levels fluctuate between 200 to 800 U/L. There will be elevated prothrombin time and hypoalbuminaemia. Purely elective surgery is not wise in chronic active hepatitis and they fall within the domain of severe hepatic impairment (Table 32.7).

Table 32.7: Causes of hepatitis

A. Viral infections	
• Hepatitis A virus	• Hepatitis E
• Hepatitis B virus	• Herpes simplex virus
• Hepatitis C virus	• Cytomegalovirus (CMV)
• Hepatitis D virus	• Epstein-Barr virus (EBV)
B. Toxins	
• Alcohol	• Drugs, e.g. methyldopa, isoniazid, halothane, amiodarone, herbal drugs
C. Miscellaneous	
• Wilson's disease	• Haemochromatosis
• Autoimmune hepatitis	• α_1-antitrypsin deficiency

Alcoholic Liver Disease (Alcoholic Hepatitis)

Patients with alcoholic liver disease or alcoholic hepatitis tend to have increased postoperative complications such as poor wound healing, infections, delirium and bleeding. Alcoholic hepatitis similar to other forms of liver disease or hepatitis runs as continuum and the severity of complications depends upon the severity of the liver pathology. The end result of alcoholic hepatitis is cirrhosis. Patients with alcoholic fatty liver tolerate surgery well. While those with cirrhosis have increased postoperative morbidity and mortality. Asymptomatic alcoholic hepatitis produces some hepatomegaly with minimal alterations of liver functions tests. Mild alcoholic hepatitis adds mild jaundice with liver tenderness. Some acute alcoholic hepatitis adds increasing jaundice, fever, leucocytosis and elevated prothrombin time. If patient is considered to have mild alcoholic hepatitis, evidenced by slightly elevated aminotransferase, lactate dehydrogenase, alkaline phosphatase and mildly elevated bilirubin with little or no change in prothrombin time, then the patient should be advised to abstain from alcohol to improve liver functions and then surgery and anaesthesia can be proceeded with.

Cirrhosis

The table illustrates the polarisation of the spectrum of liver disease. A chronic inflammatory process of liver initiated either by virus infections or by toxins (alcohol) or due to any other causes shown in table produces an inflammatory response in hepatocytes. After a variable

period of time this chronic inflammation is replaced by scar tissue (fibrosis) leading to cirrhosis. Cirrhosis is then the end stage of chronic liver inflammatory disease which is characterised by severe fibrosis and irregular nodular regenerations of the remaining liver parenchyma. The bundles of scar tissue infringes on the hepatic sinusoidal space, increasing their pressure. This increased sinusoidal pressure is transmitted to the low pressure, high flow portal venous system and in turn increase its pressure (portal hypertension). As a result, this increased pressure forces portal blood out of the liver. The blood is then diverted through the other vessels, such as gastric and oesophageal veins where there is communication between the portal and systemic circulation producing oesophageal varices. Therefore, increased portal venous pressure causes portal hypertension and other stigmata of it. Patients with cirrhosis have altered and reduced hepatic blood flow, that further worsens the liver functions and decreases the metabolism of commonly administered drugs. Associated with cirrhosis they have also nutritional disorders, ascites, coagulopathy, renal dysfunctions and high risk of developing encephalopathy (Table 32.8). There is no question that patients with advanced liver disease are at severe risk if they require major surgery and anaesthesia. The risks of surgery in these patients correlate well with the Child's classification of risk assessment. This classification is not only applied in cirrhotic patient, but also in other liver dysfunction. In this classification, there are five factors affecting mortality and infuencing the gradings. These are ascites, albumin, bilirubin, encephalopathy and nutritional status. However, this Child's classification is modified by Pugh who added prothrombin time as another risk factor. Prolongation of prothrombin time greater than 2.5s from control, implies increased anaesthetic risk and if greater than 4.0s implies severe risk. AST and ALT levels are not included in this list of risk factors, because elevation of these plasma enzymes do not imply acute injury. For each factor, score of 1 to 3 is alloted and usually three classes – A, B and C are described. Mortality rate in group A, B and C are respectively < 10%, 30% and > 40%. The causes of mortality in the perioperative period in patients with eirrhosis of liver or liver dysfunction are: sepsis, renal failure, bleeding, hepatic failure and hepatic encephalopathy. However, this score is simple, but lacks linearity. Because it does not take into account any specific underlying disease process. Although three of these factors such as ascites, encephalopathy and nutritional status are purely subjective, but this score still remains a useful tool for preanaesthetic assessment of patients with cirrhosis (Table 32.9).

Table 32.8: Causes of cirrhosis

- Any cause of chronic hepatitis
- Primary biliary cirrhosis
- Secondary biliary cirrhosis (stones, strictures)
- Alcohol
- Wilson's disease
- Haemochromatosis
- Cystic fibrosis
- α_1-antitrypsin deficiency

ANAESTHETIC MANAGEMENT OF PATIENT WITH LIVER DISEASE AND JAUNDICE

The most common liver disease encountered during anaesthesia is inflammatory hepatitis (alcohol or virus) leading to cirrhosis. If these patients require anaesthesia during an acute attack of hepatitis, mortality can be extremely high. Among them some patients with chronic hepatitis may remain in some stages of progression to cirrhosis and portal hypertension which require anaesthesia for nonhepatic surgical events. Sometimes patients present for surgery with acute biliary tract obstruction and jaundice (e.g. stone in CBD, etc.) without any hepatitis. The pathognomonic features of advanced jaundice due to hepatitis or posthepatic obstruction or due to other causes which frequently anaesthetists have to encountered and manage are hyperdynamic circulation, hypoxaemia, metabolic alkalosis, clotting abnormalities, altered hepatic blood flow, cirrhosis, ascites, renal impairment, hepatic encephalopathy and altered drug handling.

Table 32.9: Child's classification (modified by Pugh) of risk for cirrhotic patients undergoing major surgery

	Group A	*Group B*	*Group C*
Serum bilirubin (mg/dl)	< 2	2 - 3	> 3
Serum albumin (g/dl)	> 4	3 - 4	< 3
Ascites	None	Controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced
Nutritional status	Excellent	Good	Poor
Prothrombin time (seconds)	< 2.5	2 - 4	> 4
Surgical risk	Good	Moderate	Poor
Mortality risk	< 10%	30%	> 40%

Group A → 1point each,
Group B → 2 point each,
Group C → 3 point each.

Grading

Grade 5 – 6 : Good risk (30% mortality)
Grade 7 – 9 : Moderate risk (40% mortality)
Grade 10 – 15 : Poor risk (90% mortality)

Hyperdynamic Circulation

The striking features of a patient with advanced liver disease with or without jaundice is decreased systemic vascular resistance and increased cardiac output, resulting in a bounding pulse. The increase in cardiac output is proportional to the decrease in SVR, which is again proportional to the severity of liver disease. But, if tense ascites is present, then cardiac output (CO) will decrease due to the reduction of preload due to pressure on IVC and it will not improve, until paracentesis is done. The decreased vascular resistance is due to the arteriolar vasodilatation in hepatic diseased patient. Blood pressure tends to be normal or may even be a bit lower. So, hypertension is very unusual in a jaundiced patient. The atherosclerotic changes in the vascular system are generally minimum in liver dysfunction. Deficiency of cholesterol and abnormal lipid metabolism are responsible for this. The tragedy is despite having the increased cardiac output in jaundiced patient, many patients have overt signs of an underlying cardiomyopathy. So, the low peripheral resistance of a liver-dysfunction patient exerts a protective effect on left ventricular function. Thus, an abrupt return of vascular resistance to normal values due to any cause can unmask the acute left ventricular decompensation. Cardiac glycosides are not of any benefit to cardiomyopathy in liver dysfunction patient. Plasma levels of catecholamines are increased, indicating hightened sympathetic tone (compensatory mechanism) to compensate the blunted baroreceptor reflexes, which occurs in jaundice. These appears to be due to the decreased numbers of adrenergic receptors by down regulation. So, there is a rightward shift of the dose response curve, in contrast to normal patient causing increased dose requirement of pressure raising drugs. Thus, for the planning of anaesthetic management several considerations regarding the cardiovascular system in liver dysfunction or jaundiced patients should be kept in mind.

Table 32.10: Effects of liver dysfunction on respiratory system

- Decreased alveolar ventilation
- Hypoxaemia: Hepatopulmonary syndrome (intrapulmonary shunting)
- Pulmonary hypertension: PPS, hypercapnoea, acidosis
- Pulmonary aspiration: Gastro-oesophageal reflux
- Require postoperative ventilatory support

Table 32.11: Effects of liver dysfunction on haematology

- Blood loss: Varicose vein, peptic ulcer
- Anaemia: Chronic illness, haemolysis
- Platelets: Dysfunction, ↓ number
- Coagulation abnormality
- Fibronolysis
- Blood and blood products should be ready for management

Drugs such as isoflurane and sevoflurane which depress the myocardial contractility are not absolutely contraindicated in liver dysfunction patient, but should be used with great care. Since the decreased peripheral resistance seems to be somewhat of compensatory safe guard, so correction or normalization of this variable may not be in the patient's interest. If catecholamines or pressure raising agents are used, then the dose should be more than of normal patients. This is because of the down-regulation and decreased number of receptors. Liver disease causes various types of shunt such as from cutaneous spider angioma to portal systemic arteriovenous shunts. These shunts, in combination with reduced SVR and increased extracellular fluid due to activated renin angiotensin system, increases the cardiac output often by 50%. In contrast, some alcoholics may have decreased cardiac output secondary to cardiomyopathy (Table 32.10).

Hypoxaemia

In a jaundiced or liver diseased patient arterial hypoxaemia is common. This hypoxaemia is primarily due to the diffusion and perfusion mismatch in lungs. Thus, arterial oxygen partial pressure usually remains < 70 mm of Hg. This diffusion – perfusion mismatch is due to the increased intrapulmonary shunting, and this is because of the dilatation of the pulmonary precapillary or capillary bed. This hypoxaemia is further exacerbated in upright position, because gravity further increases the blood flow in the bses of lung where perfusion is greater than ventilation, causing more diffusion – perfusion mismatch. This peculiar hypoxaemia can also be due to the true pulmonary shunt. Incidence of pleural effusion is more common in jaundice or may develop frequently in the post-operative period, especially if the abdominal right upper quadrant surgery has been performed. Lung infections are also common in a liver disease patient.

From the anaesthetic point of view, hypoxaemia is never allowed in liver compromised patients for any reason. So, always a high inspired O_2 concentration (FiO_2) should be employed during anaesthesia. Sometimes splinting of diaphragm by ascites, causing a decrease in P_aO_2 cannot be improved by increasing the FiO_2. However, this should be managed by diuretics or paracentesis. Pulmonary problems should be resolved in the preoperative phase by (i) stopping smoking, (ii) giving appropriate antibiotics for lung infections, (iii) paracentesis, (iv) physiotherapy, etc. For moderate to major surgeries, the anaesthetist should also consider the placement of an indwelling arterial catheter for perioperative blood–gas analysis (Table 32.11).

Metabolic Alkalosis

Patients with liver dysfunction and jaundice often have metabolic alkalosis (compensatory). The explanation of this metabolic alkalosis is like that in liver dysfunction aldosterone levels remain high. This hormone causes excessive renal absorption of Na^+ in exchange of urinary

potassium with H^+ loss and renal retention of ammonia causing azotemia. This K^+ loss is of particular importance, if the patient is under diuretic therapy preoperatively specially. So, an anaesthetist must be careful about potassium replacement in hepatic failure patient. Failure to replace potassium perioperatively can lead to cardiac arrhythmias, increased plasma ammonia and difficulty in reversing the neuromuscular block.

Clotting and Bleeding Abnormalities

As liver is the site of synthesis of vit-K dependent clotting factors such as II, V, VII and X ; so their levels are reduced in hepatic disease or in jaundiced patient. Thus, the prothrombin time which measures the activities of these factors and the extrinsic pathway is increased. Activated partial prothrombin time (aPTT) which measures the activities of II, V, VIII, IX, X, XI, XII clotting factors and intrinsic pathway is also increased. Thus, they provide an excellent assessment of the risk of surgery. So, Vit-K should be given parenterally for atleast 72 hours before surgery when prothrombin time (PT) increases. When PT is greater than 2.5 s, in a patient facing a major surgery, then the fresh frozen plasma (FFP) is probably indicated. Still, if there is persistent hepatic dysfunction, then repeated doses of FFP may be required. The rational approach in bleeding disorder is to administer 2 to 6 U of FFP at 6-12 hour interval in an attempt to bring the PT to 2 to 3 s of control. If surgery progresses with enough bleeding, then FFP requirement certainly increases. If correction of PT is not obtained, even after what would seem to be adequate by recommended FFP therapy, then there may probably exist fibrinogen degradation product in the circulation. As factor VII has a half-life of only 4 to 8 hours, so the response to FFP measured by PT may not be long lasting.

Disorders of bleeding also develop in patients with liver diseases due to absolute deficiency in number and quality of platelets. Redistribution of platelet to the spleen is also considered to be the most important factor leading to absolute thrombocytopenia in liver compromised patient. The platelet infusions may be indicated when platelet count is less than 40,000 to 50,000/cu mm. Platelet function is best assessed by bleeding time. There would appear to be no problem in insertion of an epidural catheter, if the PT has been corrected to 2 to 3 s of control value and the platelet count is > 40000/cumm, with normal bleeding time.

Hepatic Blood Flow

The total hepatic blood flow is the result of hepatic arterial flow plus portal venous flow. Among these, the portal venous flow is responsible for 70% of the total O_2 supply to the liver. Buffer response autoregulates the total hepatic blood flow, i.e. when BP drops due to any reason (e.g. haemorrhage), then blood flow in the portal venous system drops first due to low pressure system. Then, due to dilation of the hepatic artery, blood flow through it again increases, so as to keep the total hepatic blood flow within normal limits. Again the liver cells have unique property to increase the oxygen extraction from blood when blood flow drops.

General and regional anaesthesia cause the reduction of liver blood flow and it is generally parallel with the drop of systemic blood pressure and cardiac output. So it seems that BP is the major determinant factor of blood flow in liver. So, during anaesthesia on a liver dysfunction patient blood pressure should be maintained strictly whithin its normal range. During inhalational anaesthesia at equi-anaesthetic concentrations, halothane compromises the hepatic blood flow to maximum extent than other inhalational agents. This is due to the absence or attenuation of buffer response during inhalational anaesthesia as hepatic artery does not dilate in reponse to decreased portal venous blood flow and hypotension by volatile agents. Isoflurane and sevoflurane produce lesser reduction of hepatic blood flow than halothane. Hepatic blood flow is best preserved during anaesthesia, if there is proper maintenance of CO and BP. Intravenous anaesthesia by newer synthetic opioids and propofol is considered to be the best technique in this regard. But, patients with compromised liver functions respond poorly to opioids due to decreased clearance and increased CNS susceptibility. Thus, a high-dose of fentanil or sufentanil is rarely an option for anaesthesia in patients with poor liver function.

Except anaesthetic agents, other factors that alter the hepatic blood flow are controlled ventilation, hypocapnia and surgical intervention. Controlled ventilation, particularly PEEP can cause upto 30% reduction in hepatic blood flow. Hypocapnia is also associated with a significant reduction in hepatic blood flow. This is due to the increase in hepatic arterial vasoconstriction and simultaneously the increase in resistance. So, $ETCO_2$ tension should be kept as near normal as possible. Surgical manoeuvers, especially in upper abdomen decrease the splanchnic and total hepatic blood flow to a greater extent and even more than the general anaesthetic agents. So, during surgical manoeuvers care should be taken to avoid undue pressure and strain on the supplying vessels of the liver by manual traction, packs, retractors, etc.

Ascites

The presence of ascites with liver disease indicates advanced pathology and carries a bad prognosis. So, preoperative amelioration of ascites considerably improves the surgical prognosis. Thus, forced sodium and water excretion by diuretics is the corner stone of preoperative therapy for ascites. Spironolactone is a weak diuretic and acts by inhibiting the action of aldosterone at distal tubule. It inhibits Na^+ reabsorption at distal tubule, but spares

K^+ (potassium sparing diuretic). Thus, conservation of K^+ is helpful in a jaundiced patient who has hypokalemia due to increased aldosterone level. The dose of spironolactone required to induce diuresis is proportional to the plasma aldosterone concentration. Like spironolactone, other K^+ sparing and distal tubular acting diuretics such as triamterene or amiloride are also the drugs of choice. Frusemide is not well tolerated in patients with ascites, cirrhosis or other liver dysfunctions. Because, it prevents reabsorption of both Na^+ and K^+ at proximal tubule. So, though natriuresis, induced by frusemide is helpful, but hypokalemia is not helpful for liver dysfunction or jaundiced patient. Hypokalaemia produces a dangerous situation in liver disease. So, K^+ level should be monitored and maintained strictly within normal level. Following aggressive diuretic therapy an anaesthetist will often find low serum Na^+ level in patients scheduled for surgery. This is probably without hazard, if the sodium is not less than 130 m.mol/L.

In some patients, diuresis can not be initiated, despite the maximal dose of diuretic agents (e.g. 400 mg of spironolactone) which act on distal tubule. This is because of the avid proximal tubular sodium reabsorption. Then, more potent, proximally acting diuretics (frusemide, thiazide, etc.) can be added cautiously to this regimen. In such situation, spironolactone plus frusemide (20 to 80 mg per day) is usually sufficient to initiate a diuresis in most patients. However, such aggresive therapy must be used with great caution to avoid plasma volume depletion, azotaemia and hypokalaemia which may lead to encephalopathy.

Except diuresis, paracentesis may also be employed successfully to reduce ascites. Paracentesis is considered as complimentary to diuretic therapy and makes the patient definitely comfortable. Ascites can also be controlled by peritoneovenous shunts which moves the ascitic fluid into the vascular compartments, causing over expansion of vascular volume, ↑CO, ↑renal blood flow, ↑excretion of Na^+ and water. More recently, transjugular intrahepatic portosystemic shunting (TIPS) has been used effectively to control the refractory ascites and may improve the postoperative outcome in these patients.

Renal Impairment

There are varieties of changes in renal function, induced by advanced liver disease. Among these the hepatorenal syndrome and acute tubular necrosis are common. These are due to the increased renin-angiotensin activation, which produces excessive sodium and water retention. The hepatorenal syndrome is a unique pathological condition of kidney which is seen only in advanced liver disease. It is a functional renal failure, occurs spontaneously and is more commonly due to the fluid shifts, particularly in patients with obstructive jaundice. However, the kidney is normal histologically and functions normally following a liver transplantation or if this kidney is transplanted into a healthy recepient. All the pathological changes seen in ascites (renal sodium and water retention and plasma volume expansion) are present in an extreme form in the hepatorenal syndrome. So, maintenance of an adequate urine output by fluids and diuretics is the mainstay of prevention of this syndrome. It is a serious complication in patients associated with cirrhosis and ascites. It is characterised by worsening azotemia with avid Na^+ and water retention and oliguria in the absence of identifiable specific causes of renal dysfunction. Once renal failure occurs due to any cause in the presence of cirrhosis, then mortality is usually 100% (Table 32.12).

Table 32.12: Renal effect of liver dysfunction

- Water overload
- Hypernatraemia
- Hyperkalaemia
- Circulatory decompensation
- Oedema and ascites
- Hepatorenal syndrome

The exact cause of this syndrome is not fully known, but altered renal haemodynamic appear to be the probable explanation. The kidneys are structurally intact and renal biopsy is also normal. The risk is great, if the serum bilirubin levels are high and there is endotoxemia from infected bile. The hallmark of this hepatorenal syndrome is intense sodium retention, oliguria, hypotension and intense azotemia. The patient hardly excretes any Na^+. The onset of this syndrome is very rapid. Urine analysis reveals little sodium (< 10 m.mol/L). Sometimes, in severe liver dysfunction patients can also develop acute oliguric renal failure due to haemorrhage, hypotension, etc. This oliguric renal failure can be differentiated from the hepatorenal syndrome as urinary sodium is > 30 m.mol/L in oliguric renal failure. Diagnostic criteria of hepatorenal syndrome are: (i) urinary sodium < 10 m.mol/Litre, (ii) urine : plasma osmolarity and creatinine ratios > 1, (iii) presence of chronic liver disease and ascites.

The anaesthetic management of this problem includes adequate preoperative evaluation of fluid, electrolyte and renal status. Urinary output is measured by bladder catheterisation. Central venous pressure measurement is strongly advised during extensive operative procedure to guide the fluid therapy. The most important factor predisposing to renal failure in the presence of hyperbilirubinaemia is hypovolaemia. Therefore, patients should not be allowed to be dehydrated. IV fluid (0.9% normal saline) should be used liberally to ensure moderate to high CVP and urine output of 1 ml/Kg/hour or 50 ml/hour (in adult). If despite hydration, the urine output is low, then 20% mannitol administered intravenously is the treatment of choice. The dose of mannitol is 0.5 g/Kg over 30 minutes.

A suitable antibiotic should be given preoperatively along with premedication, if there is endotoxaemia. As there is activation

of aldosterone – renin – angiotension system, these patients are avid Na^+ retainers. Thus, Na^+ containing IV fluid should be administered cautiously during perioperative period. The use of nephrotoxic drugs such as NSAIDs and gentamicin in repeated doses should be avoided. Worsening of hepatorenal failure may result in death, despite haemofiltration or dialysis and can only be corrected by liver transplantation.

Hepatic Encephalopathy

Sometimes hepatic encephalopathy is seen in individuals with severe liver disease. It is characterised by decrease in consciousness, fluctuating neurological signs, flapping tremor and distinctive EEG changes. This occurs in hyperacute (within 7 days), acute (7 to 28 days) and subacute (28 days to 6 months) hepatic failure. This classification does not include fulminant hepatic failure, where encephalopathy developed within 8 weeks of precipitatory illness. In severe cases of hepatic encephalopathy irreversible coma and death may occur. Generally, this is a lethal syndrome with more than 90% mortality.

In hepatic encephalopathy, there are two issues of interest to the anaesthetist. First is the high level of ammonia which is most often incriminated in the pathogenesis of hepatic encephalopathy. Second is the excessive concentration of GABA which is an inhibitory neurotransmitter of CNS and is responsible for the reduced level of consciousness. In severe liver dysfunction, due to intrahepatic and extrahepatic shunting of portal venous blood into the systemic circulation, liver is largely bypassed. As a result of this process various toxic substances, mainly NH_3, absorbed from the intestine are not detoxified by the liver and lead to elevated blood ammonia level, causing metabolic abnormalities in CNS. The salient point for an anaesthetist regarding hepatic encephalopathy is hyperventilation, producing respiratory alkalosis which strongly helps in conversion of ammonium ion (NH_4^+) to ammonia (NH_3). Ammonia (NH_3 not the ammonium ion NH_4^+) is the form that can cross the blood-brain barrier and cause or exacerbate encephalopathy (Table 32.13).

Increased GABA level in CNS reflects the failure of liver to extract precursor amino acid which synthesise GABA in brain or to remove GABA which is produced in the intestine. It has been also recognised that benzodiasepine receptors (BDZ) are closely associated with GABA receptor and also facilitate GABA transmission. Thus, BDZ sometimes can precipitate hepatic encephalopathy or coma. This finding can be substantiated by the fact that injection of flumazenil ameliorate the symptoms of clinical coma and EEG signs in a high percentage of cases. Thus the clinical information to the anaesthetist is that CNS depressant drugs such as sedatives (BDZ), narcotics, barbiturates, etc, which are related to GABA receptors may precipitate hepatic encephalopathy and coma. The mechanism behind the increased CNS susceptibility of these drugs which may be amplified by other altered drug handling phenomenans are ↓biotransformation, ↓albumin binding, etc., in liver diseases. So, large doses of these drugs should be avoided in late stages of liver dysfunction. Thus, a typical high dose of narcotic technique used for cardiac anaesthesia has no role in liver disease and may be detremental. In such situations, inhalational anaesthetics have no limitation and are favoured.

Other factors which can precipitate hepatic encephalopathy are GI bleeding, azotemia, hypokalaemia (directly stimulating ammonia production by kidney), hyponatremia, hypoxia, infection, surgery, etc. In severe encephalopathy, the decreased level of consciousness may compromise the airway and intubation may be required if cerebral oedema develops.

Table 32.13: Grades of hepatic encephalopathy

Grade 0	Alert and oriented
Grade I	Drowsy and oriented
Grade II	Drowsy and disoriented
Grade III	Stupour and restlessness
Grade IV	Coma-Nonresponsive to deep pain

Cirrhosis

Before surgery and anaesthesia cirrhotic patients may be benefited from increased aggresive preoperative treatment of coagulopathy are done which are usually associated with cirrhosis, ascites and encephalopathy are done which are usually associated with cirrhosis. Patients with cirrhosis develop coagulopathy as a result of decreased synthesis and shortened half-life of Vit-K dependent coagulation factors and abnormalities (both qualitative and quantitive) of platelets. Vit-K administration normally corrects the prolongation of prothrombin time. However, it is not effective when the decreased synthesis of coagulation factors is due to the nutritional deficiency. In these cases FFP infusion usually brings the prothrombin time to normal. If this also fails, then cryoprecipitate is helpful to reduce the prothrombin time within 3 seconds to normal.

The cirrhosis is the most common cause of portal hypertension. In cirrhosis the vascular bed of liver is distorted and blood flow is mechanically obstructed. So, the normal portal venous pressure which is about 7 mm of Hg is raised upto 50 mm of Hg. As the portal venous system lacks valves, so the resistance at any level between the right side of the heart and the splanchnic vessels in intestine results in retrograde transmission of this elevated pressure. This facilitates retrograde blood flow from the present high pressure portal venous system to the lower pressure systemic venous system or circulation. The major sites of this collateral flow of blood between the portal and the systemic venous system involve the veins around the rectum (haemorrhoids), cardio-oesophageal junction (oesophagogastric varices), retroperitoneal space and falciform ligament. The major clinical manifestations of portal

hypertension include: haemorrhage from the gastroesophageal varices, splenomegaly with hypersplenism, ascites and hepatic encephalopathy.

Cirrhosis is thought to be a major risk factor for patients undergoing non-hepatic surgery. Elective surgery is contraindicated in Child-Pugh class C patients. Surgery should also be avoided in patients with severe hypoalbuminaemia, evidence of infection and encephalopathy. Alternatives to surgery should be considered, as it is associated with high mortality rate.

PREOPERATIVE LABORATORY INVESTIGATION

The following preoperative laboratory investigations should be done before anaesthesia and surgery for a liver dysfunction patients. These are:

i. Full blood count and studies of clotting profile: among these the prothrombin time is the best marker of liver dysfunctions.
ii. Electrolytes, urea and creatinine: the urea level in blood is falsely low due to decreased hepatic production.
iii. Blood glucose level: Hepatic stores of glucose and glycogen are often affected. Patients frequently suffer from hypoglycaemia.
iv. Liver function tests (LFTs): LFTs must always be interpreted against the careful history and examination of that particular patient. The liver has large reserve of its functional capacity and can often withstand considerable damage before LFTs become deranged. On the other hand, serum liver functions tests are rarely specific. So, the serial measurements are useful and indicate trends. Among the liver function tests, prothrombin time, albumin level and bilirubin level are the most sensitive markers. It is important not to give the fresh forzen plasma, unless there is active bleeding before the LFTs are performed. Because, it will alter the prothrombin time which is an excellent guide to overall liver functions. AST and ALT (liver transaminases) are sensitive markers and can even indicate mild liver damage. But, they have no role in mortality prediction. Although, the levels of transaminases increase in liver diseases, but it may also decrease in severe liver disease. Alkaline phosphatase is increased with biliary obstruction. Antinuclear antibody is present in 75% of patients with chronic active hepatitis. Smooth muscle antibody is present in nearly all the cases of primary biliary cirrhosis. α-fetoprotein is a marker of hepatoma.
v. Imaging techniques: Ultrasound is the main initial investigation of obstructive jaundice. Other useful investigations include ERCP, CT, MRI and CT or MRI guided – cholangiograms.
vi. Arterial blood gases.
vii. Urine analysis.
viii. Hepatitis screening (Table 32.14).

SOME PERIOPERATIVE CONSIDERATIONS

During anaesthsia of patients suffering from liver diseases there are some principles or guide lines. These guide lines are given below. H_2 antagonists or proton pump inhibitors should be routinely used preoperatively in liver dysfunction patients. Rapid sequence induction of anaesthesia will reduce the risks of gastric aspiration. Hepatic blood flow is often altered during anaesthesia and surgery. This is due to the effect of anaesthetic drugs, positive pressure ventilation, PEEP and surgical technique. In most cases anaesthesia reduces liver blood flow, particularly if halothane is used. However, isoflurane actually seems to improve the hepatic blood flow. Sevoflurane is also a preferred volatile agent for liver disease. Regional techniques can be used as long as coagulation is not much deranged and it should be remembered that all the local anaesthetics are metabolised by liver.

POSTOPERATIVE JAUNDICE

The occurrence of postoperative jaundice is a problem of increasing incidence. It is perhaps seen more frequently now than in earlier years. This is because many patients are now undergoing more major surgical procedures and survive too. The incidence of postoperative jaundice varies from 1%

Table 32.14: Preoperative preparation of liver dysfunction patient

- Restore and maintain euvolaemia.
- Correct electrolyte imbalance, if any.
- Maintain normal glucose level.
- Correct coagulopathy with FFP and platelets.
- Use Vit-K, according to the laboratory test.
- Use DDAVP and aminocaproic acid as necessary.
- Optimize the patient's nutritional and medical status.
- Ascites if massive - abdominal paracentesis is preferred. Otherwise, treated with Na^+ and water restriction and diuretics. Rate of reduction of ascitic fluid should be 0.5 kg of body weight per day.
- Administration of thiamine to patients experiencing acute withdrawal of alcohol and prophylaxis for delirium and tremors.
- Prevent hepatorenal syndrome by avoiding dehydration, avoiding nephrotoxic drugs like aminoglycosides and NSAID, using dopamine infusions, using powerful diuretics, avoiding renal contrast, paracentesis of tense ascites, etc.
- Iotrogenic factors, precipitating encephalopathy should be used cautiously like injudicious use of sedatives like BDZ, opioids, etc.
- Lactulose and neomycin should be used to limit bacterial toxins.

of all the patients undergoing abdominal surgery to 17% of all the patients undergoing major surgery. Although postoperative jaundice is relatively common, but significant postoperative liver dysfunction is relatively rare. This rare postoperative liver dysfunction has varied aetiology and often resolves without treatment. It should be remembered that hepatitis due to volatile anaesthetic agents is extremely rare and is largely diagnosis of exclusion.

There are three major pathological mechanisms for postoperative jaundice. These are: postoperative increased pigment load, postoperative impaired hepatocellular function and postoperative intrahepatic/posthepatic obstruction of bile flow. Most of the etiologies for postoperative jaundice become apparent within three weeks of surgery and can be classified as mild or severe if the serum bilirubin is less than 4 mg/dl or greater.

Increased pigment load occurs as a result of haemolysis following blood transfusions, drugs (which sometimes induce haemolysis) and also from reabsorption of blood from the extravascular space. Approximately 10% of stored whole blood undergoes haemolysis within 24 hours of transfusion. Each 0.5 L of stored blood yields 7.5 g of haemoglobin, which is then converted to 250 mg of bilirubin. Multiple blood transfusions may, therefore, limit the ability of liver to conjugate and excrete this bilirubin load i.e. reserve of the liver function (Table 32.15).

Hepatocellular damage and impaired hepatocellular functions postcoperatively are caused by nonanaesthetic drugs used during anaesthesia, anaesthetic agents (mainly halothane), ischaemia due to hypotension, sepsis and viral hepatitis, etc. With lesser degree of hypotension and hypoxaemia, morphological changes may be slight, but significant impairment of function may occur in severe hypotension and hypoxemia. Prior shock or hypotension plus pigment overload may produce significant liver dysfunction and jaundice. Extensive sepsis also can produce jaundice of cholestatic type. Concurrent renal impairment due to hypotension and hypoxaemia may also enhance the degree of liver dysfunction and jaundice, and this is because of decreased renal excretion of conjugated bilirubin. Drug induced hepatotoxicity is primarily due to idiosyncratic reactions or alterations in bile flow by drug, resulting in cholestasis.

Table 32.15: Causes of postoperative liver dysfunction or jaundice

1. Bilirubin overload (haemolysis)
   - i. Blood transfusion
   - ii. Haematoma reabsorption
   - iii. Haemolytic anaemia :

     Sickle cell, G-6-P deficiency, mismatched transfusion etc.
2. Hepatocellular injury
   - i. Exaccerbation of pre-existing liver disease
   - ii. Hepatic ischaemia due to hypovolaemia, hypotension and cardiac failure
   - iii. Septicaemia
   - iv. Hypoxia
   - v. Viral hepatitis
   - vi. Drug induced (halothane, antibiotics)
3. Cholestasis (Obstruction)
   - i. Intrahepatic:

     Benign, infective, drug induced, pregnancy, etc.
   - ii. Extrahepatic: Retained stone in bile duct, postoperative cholecystitis, bileduct injury, pancreatitis, etc.

The extrahepatic obstruction flow of bile due to surgical damage of biliary passage or stones within if causing postoperative jaundice need to be considered and may be excluded by sonography. Benign postoperative intrahepatic cholestasis mimics biliary obstruction and usually occurs after major surgery associated with hypotension, hypoxaemia or multiple transfusions.

GUIDELINE FOR ANAESTHESIA IN PATIENTS WITH DECOMPENSATED LIVER FUNCTION

An anaesthetist should always show a considerable degree of latitude when making a mind to administer anaesthesia in patients with advanced liver disease. The choice of drugs and monitoring of patient during anaesthesia of patient suffering from liver dysfunction mainly depends upon the severity of the disease, the type of surgery and the experience of anaesthetist. The surgical procedures can be divided into two groups: surgery on diseased liver to correct dysfunction of it and extrahepatic surgery with liver dysfunction. The surgery on liver may extend from a simple biopsy to liver transplantation. Whereas the extrahepatic surgery with liver dysfunction include different general surgeries with jaundice or asymptomatic carrier state of hepatitis and various surgeries to correct the complication which is developed due to liver dysfunction e.g. making portacaval shunts, trans-oesophageal ligation of varices, etc.

The type of anaesthesia in liver dysfunction can be divided into regional and general. The regional anaesthesia plays a significant role in patients with liver disease. The main limitation of regional anaesthesia in liver dysfunction is clotting and bleeding abnormalities causing haematoma in epidural or subarachnoid space. Otherwise, it is very safe, if it fits well with the type of surgery, i.e. lower extremities, obstetric and gynaecological operations (lower abdomen), or some upper abdominal surgeries such as cholecystectomy, etc. Now, mastectomy and other cardiac and thoracic surgeries also can be done by cervical or thoracic epidural anaesthesia. Different types of nerves and plexus blocks such as brachial or cervical plexus block are also very safe for liver dysfunction patients. Clotting and bleeding abnormalities of patients with liver disease should be corrected before administering anaesthesia, especially regional anaesthesia. Otherwise, it is sheer madness to operate upon them. If regional anaesthesia is selected as the ultimate choice, then the guidelines for detection of clotting and bleeding abnormalities are: prothrombin

time must be less than 2.5s of control value, platelet count should be > 40,000 / Cu.mm, bleeding time which measure the both platelet quantity (number) and quality should not be greater than 12 minutes. If bleeding and clotting parameters are within these guidelines; then spinal, epidural and other regional blocks with epidural catheter for postoperative pain control can be employed safely after major surgeries.

During administration of GA care should be taken by the anaesthetist when he uses CNS depressant drugs like sedatives, narcotics, etc for induction. Large doses of them always should be avoided. Titrating dose is mandatory. Regarding premedications, none to small amount is suggested, according to the severity of liver dysfunction and physical status of the patient. If premedications are needed at all, drugs handled by phase II biotransformatione such as morphin, lorazepam or oxazepam, etc. are recommended. Glycopyrrolate is preferred to atropine as it does not cross the blood brain-barrier. Regarding induction, the preferred inducing agent is propofol. Thiopentone also can be used safely. Regarding the neuromuscular block, many anaesthetists still use succinylcholine during elective surgery for intubation. This is because there is only theoretical speculation that the action of succinylcholine can be prolonged due to deficiency of plasma cholinesterase in patients with liver disease. It is true, but seems clinically insignificant, because the action of succinylcholine rarely becomes prolonged and cause any problem of overwhelming magnitude. Vecuronium, cis-atracuronium and atracurium are ideal muscle relaxants for patients with liver dysfunction. Vecuronium is used for longer surgical procedures and atracurium is used for shorter ones. Isoflurane and sevoflurane are the backbones of anaesthetic regimens for patients with liver disease, but doses should always be adjusted so as not to depress much the cardiovascular system. N_2O does not produce any injury to the hepatocytes and can be used safely even in severe liver dysfunction patients, if there is no contraindication, e.g. bowel distension, middle ear surgery, etc. Small doses of opioids play an important role in the anaesthetic regimen by reducing the need of inhalational anaesthetics, particularly if there is hypovolaemia and central pump failure. But, larger doses of opioids should always be avoided. There is no contraindication for use of neostigmine for reversal of neuromuscular block and it responds well in normal fashion in patients with liver dysfunction.

The monitoring of liver dysfunction patients during perianaesthetic period include all the standard monitoring, depending on the gravity of the surgical procedures and the physical status of the patient. PT, aPTT, platelet count and haematocrit values are required periodically. Standard monitors include pulse oximeter, ECG, $ETCO_2$, HR, BP, etc. Urine output should always be monitored with a catheter. Invasive monitors such as intra-arterial catheter, CVP, Swan-Ganz catheter, TEE, etc, are also indicated depending on the clinical circumstances. Coronary vasoconstriction caused by vasopressin which is used to control the variceal haemorrhage can be reversed by conventional doses of nitroglycerin. Somatostatin can be used instead of vasopressin and causes less coronary vasoconstriction. Where there is concern about renal perfusion, then dopamine drip in the dose of 1 to 2 µg/Kg/min may be of immense value.

HALOTHANE AND HEPATIC TOXICITY

The liver dysfunction produced by halothane is called the halothane associated hepatitis (HAH). This HAH is defined (though the definition is unsatisfactory) as the appearance of liver damage within 28 days of halothane exposure in a person in whom other known causes of liver disease have been excluded. Two syndromes are recognised in HAH or halothane induced liver dysfunction: (i) The first is associated with the transient rise of the values of liver function tests and has low morbidity. This occurs often after the initial exposure to halothane. (ii) The second is associated with repeated exposure and high rise of values of liver function tests. It has an 'immune' mechanism with the development of fulminant hepatic failure (FHF) and is associated with high mortality rate. FHF is rare with an incidence of 1 in 35,000 after halothane anaesthesia.

Halothane induced liver dysfunction may be due to (i) the direct effect of drug on the hepatocytes itself or (ii) the effect of metabolites of drug on the hepatocytes or (iii) an immune reaction following repeated exposure to halothane. Indirect cause for liver dysfunction after halothane exposure is due to hypotension, diminished liver blood flow and subsequent reduced hepatic O_2 availability. These also appear to be of genetic susceptibility for halothane induced hepatotoxicity as shown by *in vitro* test.

Metabolic cause for liver dysfunction is also due to the metabolites, produced by metabolism of halothane in the hepatocytes. Up to 20 to 40% of halothane is metabolised in human liver. Whereas enflurane 2 to 8%, isoflurane 1%, sevoflurane 0.2% is metabolised in liver. The metabolism of halothane in liver takes two pathways: One is the oxidative pathway and another is the reductive pathway. The the metabolites of reductive pathways do not produce any injury to hepatocytes. But metabolites of oxidative pathway bind to liver microsomes which contain the cytochrome P-450 system and induce hepatotoxicity. The chance of metabolic reaction causing hepatotoxicity by volatile agents is thought to be related to the amount it is metabolised. As for example enflurane only 2 to 8% is metabolised, it should therefore cause 10 times fewer reactions than halothane. Isoflurane is only 1% metabolised. There is, therefore, a theoretical risk for reaction to isoflurane and indeed there have been only a few case

reports of isoflurane induced hepatotoxicity. So isoflurane is considered safe for use in patients at risk of hepatic failure. Sevoflurane and desflurane also appear to be safe in liver failure.

The immunological mechanism of hepatitis, particularly fulminant hepatic failure (FHF) is evidenced or proved by the presence of antibodies to halothane in the sera of patients suffering from FHF after exposure to halothane and are present in 70% of such patient. Antibodies have not been found in patients with liver disease of other etiologies. It is also not found in patients exposed to halothane but without developing FHF. The antibody is not directed against the reductive metabolites of halothane, but only against an oxidative metabolite compound such as trifluroacetyl halide (TFH). These are IgG type of antibodies and react with the cell surface of hepatocytes, making them susceptible to antibody dependent cell mediated toxicity. Halothane is a small molecule and itself is unlikely to be immunoreactive. It is postulated that binding of oxidative metabolite of halothane to the liver cytochrome which act as a hapten induce a hypersensitivity reaction. FHF which carries a high mortality rate is particularly due to immune reaction following repeated exposure. Any time interval between two exposures are not considered safe, as the mechanism is immunological and any exposure after the first could trigger an immunological response.

HAH is usually present in two forms. One is characterized by moderate elevation of liver transaminase and transient mild jaundice with low morbidity and no mortality. Another is characterised by development of FHF with high mortality and is associated with repeated exposure to halothane (or isoflurane, enflurane, sevoflurane due to cross sensitivity).

33 Thyroid Diseases and Anaesthesia

INTRODUCTION

The hypothalamus, pituitary and thyroid gland, making an axis are involved in the regulation of various cellular activity in the body. In this axis as the target organ, the thyroid gland is very important. The different forms of thyroid diseases are very common and it affects 5 to 10% of total general population, of which females are more affected than male. The thyroid gland is not so essential for life. But its absence causes impairment of cellular activity or metabolism and as a consequence produce several defects such as slowing of both physical and mental growth, reduction of cardiac contractility, poor resistance to cold, etc. In children mental retardation and dwarfism is manifested in the absence of thyroid hormone. In the contrary, excess thyroid secretions lead to nervousness, body wasting, tremor, tachycardia, excess heat production, etc.

The thyroid hormones are synthesised in the body from iodine and an essential amino acid, named tyrosine. After absorption from GI tract, the dietary iodine is converted to iodide and actively transported to thyroid gland. The thyroid gland has also the special capacity of abstracting iodide from the circulating blood. In the thyroid gland this iodide is again oxidized to iodine by peroxidase enzyme and combines with tyrosine to form monoiodotyrosine (MIT) and di-iodotyrosine (DIT). In the gland these two compounds are again coupled to form tri-iodotyrosine (T_3) and tetraiodotyrosine or thyroxine (T_4). The last two compounds are released from the thyroid gland and are called the thyroid hormones. But, the T_4 is formed in far excess in amount than T_3. After their formation, the T_4 and T_3 are immediately attached or conjugated to thyroglobulin which is also a specific protein, secreted by the thyroid cell. This conjugated material is popularly known as the colloid substance and it is in this form that the T_4 and T_3 is stored in the acini of thyroid gland. When required by the body, this conjugation breaks and large amount of T_4 with little amount of T_3 is liberated into the circulation (Fig. 33.1).

Physiology

The thyroid gland predominantly secretes two hormones, named tetraiodothyronine or thyroxine (T_4) and a small amount of tri-iodothyronine (T_3). But 85% of this small amount of circulating T_3 is also produced from T_4 by the process of monodeiodination in other peripheral tissues such as muscle, liver, kidney, etc. *In vivo* T_3 is more potent than T_4 and metabolically is more active. While T_4 is probably metabolically inactive and may be regarded as prohormone of T_3. The 99% of circulating T_4 and T_3 are bound to a special transport protein in plasma, called the thyroxine binding globulin (TBG). The remaining small fraction of circulating thyroid hormones remains as unbound or free form and diffuses into tissues to exert their metabolic function.

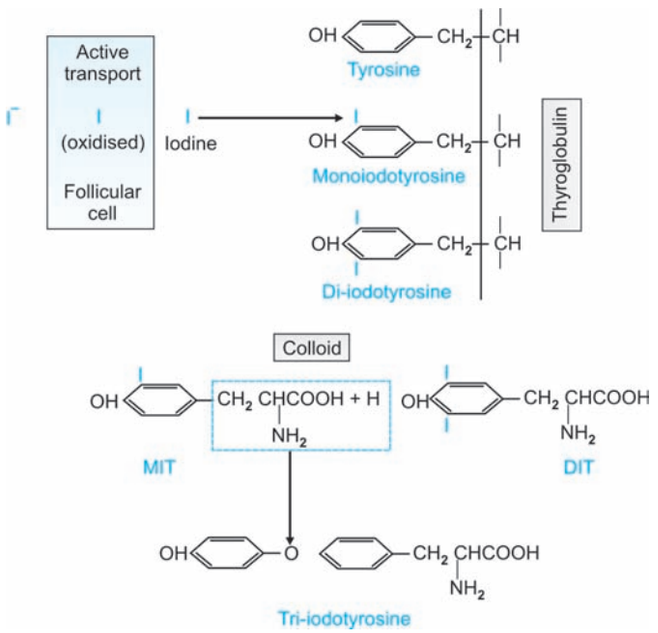


Fig. 33.1: Synthesis of thyroid hormones

It is possible to measure the total, bound (with TBG) and unbound (free) fraction of thyroid hormones, i.e. T_4 and T_3 in plasma. But, the advantage of measurement of free hormone is that they are not influenced by the changes in the concentration of TBG or plasma protein. For example, during pregnancy the TBG level is increased and with it the total T_4 and T_3 level may be increased. But, the free thyroid hormone level may remain normal.

The production of thyroid hormones from the thyroid gland is stimulated by another hormone named TSH (thyroid stimulating hormone). This TSH is released from the anterior pituitary gland in response to another thyrotrophin releasing hormone (TRH), secreted from hypothalamus. A circardian rhythm for the secretion of TSH is found with the peak at 0100 hour and 1100 hour of the day. But, this circardian variation is small and does not influence the timing of blood sampling for the assessment of thyroid function. There is some negative feedback response of thyroid hormones on the secretion of TSH from the anterior pituitary. So, when the plasma concentration of T_4 and T_3 are raised in primary hyperthyroidism, then the TSH level is reduced. Similarly, when the plasma concentration of T_4 and T_3 are decreased in primary hypothyroidism, then the TSH level is raised. In subclinical hyper- and hypothyroidism the T_4 and T_3 level remain normal, but the TSH level suppressed or raised. This is because the anterior pituitary gland is very sensitive to minor changes in thyroid hormone level, though it remains still within its normal range.

The three major forms of thyroid diseases that are frequently encountered in clinical practice by an anaesthetist are hyperthyroidism, hypothyroidism and goitre. Although no age group is exempted from thyroid disease, but the patient most likely to be affected are middle aged and female. In addition, the increasing tendency to screen the population and ready access to accurate tests of thyroid functions have led to the identification of many patients with abnormal result who are either asymptomatic or with nonspecific complaints such as tiredness, more sleep, weight gain, etc. (Table 33.1, Fact file-I).

HYPERTHYROIDISM

In over 90% of patients the principal cause of hyperthyroidism is Graves disease. The other causes of hyperthyroidism are multinodular goitre, thyroiditis, some drugs, etc, which are displayed in Table 33.2. The most common symptoms of hyperthyroidism are: loss of weight, heat intolerance, palpitation, tremor, etc, which are also displayed in table. Although the diagnosis of this disease, i.e. hyperthyroidism can usually be made clinically, but still it is important to confirm this disease by laboratory tests such as by measuring the levels of circulating thyroid hormones and TSH. The serum T_4 and T_3 level are elevated and TSH level is reduced in majority of patients. But, T_4 is in the upper part of the normal range and T_3 is only raised in 5% of hyperthyroidism patient. This special condition is called the T_3 thyrotoxicosis and is found particularly in those who are suffering from recurrent hyperthyroidism, or following thyroid surgery or after a course of antithyroid drugs. Other tests which are also performed to establish the aetiology of hyperthyroiroidism include the estimation of TRAB (TSH – receptor antibody) which is elevated in Graves disease, isotope scanning, etc. Diagnosis of hyperthyroidism during pregnancy is very

Table 33.1: Patterns of thyroid function tests in different thyroid diseases

Thyroid disease	*T_3*	*T_4*	*TSH*
1. Hyperthyroidism (Graves disease)	H	H	L
2. T_3 hyperthyroidism	H	N	L
3. Subclinical hyperthyroidism	N	N	L
4. Primary hypothyroidism	L	L	H
5. Subclinical hypothyroidism	N	N	H
6. Secondary hypothyroidism	L	L	L
7. Secondary hyperthyroidism	H	H	H

FACT FILE - I

The thyroid gland secretes three hormones -thyroxine (T_4), Triidothyronine (T_3) and calcitonin. The first two are secreted by the follicular cells of thyroid gland and have the same biological activity. So, they are termed as thyroid hormones. While the last one is secreted by the interfollicular cells and its biological activity is entirely different from thyroid hormone. It takes part in Ca^{2+} metabolism.

Both T_4 and T_3 are the iodine containing derivative of a chemical compound, named thyronine which is produced by the condensation of two molecules of amino acid, called tyrosine. The total body content of iodine (I_2) obtained from food product is 40 to 50 mg. Out of this, 1/4th is present in the thyroid gland. Concentration of iodine in blood is low (0·2 to 0·4 μg/dl). But the thyroid follicular cells have an active transport process and concentrate it in the gland. This trapping of I_2 in the gland is stimulated by TSH and exceed the gradient of more than 100 fold between plasma and gland. The total iodine content of thyroid gland also regulates the uptake of it by the gland. Little store of iodine stimulate and the large store inhibits the uptake of iodine by the gland. This iodine concentrating ability is also found in other organs such as salivary gland, skin, intestine, gastric mucosa, placenta, breast, etc. But their uptake of iodine is not regulated by TSH.

Dietary iodine is first absorbed by the GI tract. Then it is converted to iodine ion (I^-) and actively transported to the thyroid gland. After trapping of iodide (I^-) by the follicular cells of thyroid gland, it is further oxidised to iodine (I). Then it combines avidly with the tyrosine residue of thyroglobulin, and form MIT and DIT. Then the pairs of iodinated tyrosyl residues couple together to form T_4 and T_3. Normally, much more T_4 is formed than T_3. But during the iodine deficiency, relatively more T_3 (active form) is formed.

The thyroid hormones are synthesised and also stored as colloid in the cavity of the thyroid follicle, (but not in the cells of the follicle) as a part of thyroglobulin molecule. Thyroglobulin is glycoprotein in nature and is also synthesised by the thyroid follicular cells. Then, the thyroglobulin is transported from the cells to the cavity of the follicle, where MIT, DIT and by further coupling T_3 and T_4 are formed. During the release of thyroid hormones, colloid is taken back into the follicular cells from the cavity by endocytosis and broken down into T_4, T_3, DIT and MIT. T_4 and T_3 so released from thyroglobulin is secreted into the circulation, while MIT and DIT residues are deiodinated and the released iodine is reutilised. The uptake of colloid and breaking down of it is stimulated by TSH. The resting thyroid gland has follicles distended with colloid and the cells are flat or cubical. While the TSH stimulated gland has columnar cells and colloid virtually disappears.

difficult. This is because in pregnancy oestrogen induced increase in TBG results in increased total protein bound T_4 and T_3 level (Table 33.2).

The symptoms and signs of hyperthyroidism reflect the excessive effect of T_4 and T_3 hormone on the cellular activity, particularly its metabolism which are also listed in the table. It mainly increases the carbohydrate and fat metabolism. Thus, the thyroid hormone determines mainly the growth and the metabolic rate of the body. But from the anaesthetic point of view the important thoughts are that the increase in metabolic rate is associated with an increase in O_2 consumption and CO_2 production which indirectly increases the minute ventilation. The cardiac contractility and HR are also increased. This is due to the alteration in physiology of adrenergic receptor and other internal proteins or receptors by increased circulating level of thyroid hormones, as opposed to the increases level of plasma catecholamines (Table 33.3).

The patients suffering from hyperthyroidism are usually treated by antithyroid drugs, inorganic iodine, β-adrenergic antagonist, radioactive iodine and / or surgical removal of thyroid gland. During the period of treatment of hyperthyroidism, patients are continuously monitored by the measurement of plasma TSH level which indicates if hypothyroidism is developing or not and the plasma T_4 level which indicates if hyperthyroidism is developing or not.

Table 33.2: Causes of hyperthyroidism

A.	*Thyroid overactivity*
	Graves disease
	Toxic multinodular goiter
	Solitary toxic adenoma
	Hashimoto's thyroiditis
	Thyroid cancer
	TSH - secreting pituitary tumour
B.	*Extrathyroidal*
	Administration of thyroid hormones (iatrogenic)
	Ectropic thyroid tissue
	Choriocarcinoma and hydatidiform mole

Table 33.3: Clinical features of hyperthyroidism

Goiter - diffuse or nodular
Weightloss, diarrhoea, nausea and vomitting.
Tachycardia, atrial fibrillation, angina, heart failure.
Tremor, nervousness, anxiety, hyperreflexia, myopathy.
Heat intolerance, fatigue.
Exophthalmos, and other eye signs.

The commonly used drugs for the medical management of hyperthyroidism are: (i) the antithyroid drugs such as carbimazole, methimazole, propylthiouracil, etc. (ii) iodine containing compounds such as potassium iodide, Lugol's solution of iodine, etc (iii) lithium, and (iv) glucocorticoids. The other modes of treatment of hyperthyroidism are: use of radioactive iodine and surgery (Table 33.4).

As antithyroid agent, the thiourea derivatives are first discovered in 1940. Subsequently, the methyl and propyl thiouracil derivatives and thiomidazole derivatives such as methimazole and carbimazole were discovered and found to be safe and effective for the treatment of hyperthyroidism. All these antithyroid drugs bind to thyroid peroxidase enzyme and inhibit the iodination of tyrosyl residue of thyroglobulin. Thus, they inhibit the production of MIT and DIT. They also stop the coupling of iodotyrosine residue of MIT and DIT to form T_3 and T_4. Thus, the thyroid colloid is gradually depleted of thyroid hormones i.e. T_4 and T_3 overtime and blood levels of T_3 and T_4 are reduced. However, they do not interfere with the trapping of iodine by thyroid gland from plasma and do not modify the action of T_3 and T_4 on peripheral tissues or on pituitary gland. The antithyroid drugs also do not affect the release of T_3 and T_4 from thyroid gland which are already synthesised in the cell. Hence, their effects are not apparent, till the thyroid gland is depleted of its hormone content. Propylthiouracil also inhibits the peripheral conversion of T_4 to T_3. In India only carbimazole is available and routinely used. But, it acts largely by getting converted into methimazole by the peripheral tissues.

Table 33.4: Mechanism of action of antithyroid drugs

	Drugs	*Mechanism of action*
A.	Antithyroid drugs Propylthiouracil Carbimazole Methimazole	Inhibit the thyroid hormone synthesis
B.	β-adrenergic agonist Esmolol Propranolol	Impair the peripheral action of T_4 and T_3
C.	Iodine compounds Potassium iodide Lugol's solution	Inhibit the release of T_4 and T_3
D.	Lithium	Inhibits the release of T_4 and T_3
E.	Glucocorticoids	Immunosuppressive action Impair the peripheral action of T_4 and T_3

Though iodine is a constituent of the thyroid hormones, but still it is the fastest acting thyroid inhibitor. All the facets of thyroid function seem to be affected by iodine. But the most important function of it is inhibition of the release of thyroid hormone from the follicular cells which has been already synthesized. The endocytosis of colloid and proteolysis process of thyroglobulin with the attached MIT, DIT, T_3 and T_4 which help in the release of thyroid hormones comes to a halt. Thus, the enlarged gland slowly shrinks, and then, it becomes firm and less vascular (Table 33.5).

With daily administration of iodine the thyroid status starts to return to normal slowly and peak effects are seen within 10 to 15 days after starting of iodine. After that the 'thyroid escape' may occur spontaneously and thyrotoxicosis may return with greater severity. So, this group of drugs i.e. iodine is only used temporarily for the preoperative preparation of patient before thyroiectomy. It is generally given for 10 days just before surgery with the aim

Table 33.5: Differences between propylthiouracil and carbimazole

	Carbimazole	*Propylthiouracil*
1.	More potent (3 times).	Less potent
2.	Plasma half-life 6 to 10 hours.	Plasma half-life 1 to 2 hours.
3.	Less plasma protein bound.	High plasma protein bound.
4.	Large amount crosses the placenta.	Little amount crosses the placenta.
5.	Duration of action 12 to 24 hours.	Duration of action 4 to 8 hours.
6.	So single daily dose is used.	Multiple daily dose is used.
7.	Produces active metabolic - methimazole.	No active metabolite.
8.	Does not inhibit the peripheral conversions of T_4 and T_3.	Can inhibit the peripheral conversion of T_4 to T_3

to make the gland firm, less vascular and easier to operate on. Though iodine itself lowers the thyroid status, but it cannot be solely relied upon to attain euthyroidism which is done by the concomitant use of carbimazole before starting iodine. Propranolol may be given additionally for the control of symptoms of hyperthyroidism, especially tachycardia before anaesthesia and surgery if needed (Fact file-II).

The commonly used radioactive isotope of iodine for the treatment of hyperthyroidism is I^{131} (other isotopes are I^{127}, I^{125}, etc). Its half-life is 8 days and emits both the γ-rays and as well as β-particles. The former are useful in tracer studies as they traverse the tissues and can be monitored by a counter. While the later are utilized for their destructive effect on the thyroid cells. After administration the radioactive I^{131} is actively concentrated by the thyroid gland, incorporated in their colloid and then emits radiation from within the follicles. The β-particles penetrate only the 0·5 to 2 mm of tissues. Thus, the thyroid follicular cells are affected from within the gland and undergo pyknosis and necrosis. Then the necrosed tissues undergo fibrosis when a sufficiently large dose of I^{131} has been administered, without damage to the neighbouring tissues. Hence, with the careful selected doses of radioactive iodine it is possible to achieve the partial ablation of thyroid gland without surgery. It is used as sodium salt of I^{131} which is dissolved in water and taken orally. The response of radioactive iodine is slow. Its action starts after 2 weeks of administration and gradually increases to reach a peak effect at 3 months. The common indications for the use of I^{131} are: (i) patient above 45 years of age, (ii) recurrence of hyperthyroidism after surgery, (iii) hypersensitive or refractory to antithyroid drugs, (iv) patient unfit for surgery (Fact file -III).

For surgical management of hyperthyroidism, two types of surgeries are advocated. These are subtotal thyroidectomy and excision of only toxic nodule. Surgical treatment for hyperthyroidism is only indicated when there is large goitre, causing tracheal compression and cosmetic concerns and medical or radioiodine therapy have failed. Any patient with hyperthyroidism scheduled for surgery should be rendered first euthyroid by drugs before anaesthesia. This is because toxic patients cannot be dealt as such for the fear of development of thyroid crisis during surgery and anaesthesia. Therefore, the principles of preparation of a hyperthyroid patient before surgery and anaesthesia are as follows:

i. Patients suffering from mild hyperthyroidism :
   They are usually treated by only iodine preparation 14 days before operation. For this purpose Lugol's iodine (10%) is used in the dose of 5 drops 3 times per day.
ii. Patient suffering from severe hyperthyroidism :
   They are usually treated by carbamizole. But it takes long time, usually 8 to 12 weeks to make the patient euthyroid. However, with this treatment the size and vascularity of the gland increase and make the operation very difficult. Some surgeons, therefore, stop or reduce the dose of the antithyroid drug 14 days prior to the surgery and for these 14

FACT FILE - II

Advantages and disadvantages of antithyroid drugs over surgery and I^{131}.

A. Advantages

i. Can be used in young adults and children.
ii. No surgical risk such as injury of nerve, parathyroid gland, haematoma and airway obstruction.
iii. No anaesthetic risk.
iv. Used in pregnancy.

B. Disadvantages

i. Prolonged treatment is needed.
ii. Release rate is high.
iii. Not applicable in psychiatric patient.
iv. Drug toxicity can occur.

Thyroidectomy and I^{131} are contraindicated during pregnancy. Propylthiouracil is preferred than carbimazole during pregnancy. This is because its greater protein binding capacity allows less transfer to the foetus and less chance of foetal hypothyroidism and goiter caused by antithyroid drugs. Due to the same reason it is also preferred in the nursing mother after delivery.

FACT FILE - III

Advantages and disadvantages of radioactive I^{131}.

A Advantages

i. Treatment is simple, inexpensive and outpatient procedure.
ii. No surgical and anaesthetic risk.
iii. Cure is permanent.

B Disadvantages

i. Delayed response.
ii. Contraindicated during pregnancy.
iii. Not suitable for young patients.
iv. More likely to develop hypothyroidism and needs life long T_4 treatment.

I^{131} is the treatment of choice after 35 to 40 years of age and if chronic heart failure, angina or any other contraindication to surgery is present. In some centre the cut off age for the treatment of hyperthyroidism by radioactive iodine has been lowered to 25 years.

days they administer only iodine with the idea that iodine will cause diminution of the size and vascularity of thyroid gland. While this is true, but others do not favour the use of iodine, since it causes an increased friability of the gland which proves troublesome during operation.

iii. During an emergency, patients also can be prepared for surgery in less than 1 hour by IV administration of esmolol or propranolol.

The common complications of thyroid surgery which may concern an anaesthetist are: damage to the recurrent laryngeal nerve, airway obstruction, postoperative bleeding, thyroid crisis and postoperative hypoparathyroidism. The most common nerve liable to damage during thyroid surgery is the adductor fibres of recurrent laryngeal nerve. When this type of nerve damage is unilateral, then it is characterised by the paralysis of vocal cord of one side which assumes an intermediate position and produce hoarsness of voice. Whereas the bilateral injury of this nerve causes paralysed vocal cord of both side which can then collapse together, producing apnoea and total airway obstruction during inspiration.

Airway obstruction is also a common complication following thyroid surgery. It may be due to (i) adducting malfunction of vocal cords caused by recurrent laryngeal nerve injury of both side described above or (ii) collapse of trachea for tracheomalacia, reflecting weakness of tracheal ring due to chronic pressure from goitre or (iii) haematoma formation at surgical site causing tracheal compression. This emergency condition caused by haematoma at operative site is promptly treated by the removal of surgical stitches and evacuation of blood clot or reintubation.

Another complication followed by thyroid surgery and is important from the anaesthetic point of view is thyroid crisis. It is a medical emergency situation and is characterised by tachycardia, hyperthermia, dehydration, tremor, congestive heart failure, shock, etc. It can occur intraoperatively or 6 to 10 hours postoperatively. When the thyroid crisis occurs intraoperatively then it mimicks the malignant hyperpyrexia. But unlike malignant hyperthermia, thyroid crisis is not associated with muscle rigidity, raised creatinine kinase, metabolic (lactic) acidosis, and respiratory acidosis. It generally occurs when the patient is not properly made euthyroid prior to the surgery. This condition usually results from the sudden entry of huge quantity of thyroid hormones into the circulation due to: (i) pumping out of thyroid hormone from the gland by manipulation during surgery, and (ii) absorption of thyroxine from the raw cut surface of the thyroid gland (Fig. 33.2).

The immediate treatment of thyroid crisis is very important and life saving. It includes:

i. sedation by morphine, or pethidine, or benzodiazepine,

ii. control of hyperpyrexia by infusion of IV – cooled crystalloid solution, continuous ice sponging, air conditioning of room, etc,

iii. control of severe tachycardia by propanolol or continuous infusion of esmolol, until the HR is < 100 per minute,

iv. control of cardiac failure by digitalis,

v. control of hypotension by IV fluid and glucocorticoids (100 to 200 mg every 8 hours) from coexisting adrenal gland suppression,

vi. control of increased plasma T_4 and T_3 level by potassium iodide (1 gm IV over 12 hours) which block the release of T_4 and T_3 from thyroid gland and propylthiouracil (200 to 600 mg every 6 hours orally or by nasogastric tube) which inhibit the extrathyroidal convertion of T_4 to T_3.

Hypoparathyroidism causing tetany due to hypocalcaemia may also occur following thyroidal surgery. It results from either removal of the parathyroid glands with the thyroid tissue or impairment of blood supply to the parathyroid glands during thyroid surgery. If two of the four parathyroid glands remain intact, then tetany does not develop. If damage to all the parathyroid

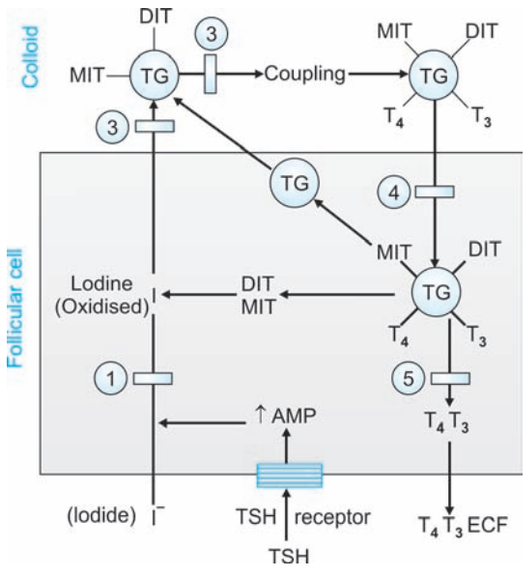


Fig. 33.2: The pathways of synthesis and secretion of thyroid hormones and the different sites of action of antithyroid drugs, such as: 1 = Potassium perchlorate, 2 and 3 = Carbimazole, propylthiouracil, 4 = Lithium, 5 = Iodide. (TG = Thyroglobulin, MIT = Monoiodotyrosine, DIT = Diiodotyrosine)

glands occur during thyroid surgery then symptoms of hypoparathyroidism typically develop 24 to 72 hours after operation. But, it may manifest as early as 1 to 4 hours postoperatively. Laryngeal muscles are most sensitive to hypocalcaemia. So, inspiratory stridor which gradually leads to laryngospasm may be the first manifestation of the surgically induced hypoparathyroidism. Treatment of this emergency condition consists of prompt administration of calcium through intravenous route, until laryngeal spasm or laryngeal stridor ceases.

Anaesthetic Management

When surgery is indicated due to any reason (on thyroid or any other organ than thyroid) on a patient suffering from hyperthyroidism, then it should be deferred until an euthyroid state is achieved. This can be performed by some preoperative preparation which are discussed before. Usually it is the dictum that all the drugs used to maintain the euthyroid state should be continued throughout the perioperative period. During emergency, when the surgery cannot be deferred and there is a state of hyperthyroidism, then the hyperdynamic cardiovascular system has been controlled by continued IV infusion of esmolol in the dose of 100 to 300 µg/kg/minute. The poor control of hyperthyroidism and surgery may precipitate life-threatening condition of thyroid crisis.

Preoperative medication and preparation

Proper evaluation of a hyperthyroid patient prior to surgery is the corner stone of anaesthetic management of it. Among these the full thyroid function tests, the assessment of cardiovascular system and the assessment of airway are most vital. For evaluation of airway, otherthan clinical examination, CT scan or MRI is very helpful. Benzodiazepine is the choice of agent for sedation as preoperative medication and should be used judiciously. It will reduce both the anxietly and HR. The use of anticholinergic agent as premedicant is not always the choice, because it contributes to the increased HR. But it is also not always absolutely contraindicated and where possible glycopyrolate is preferred than atropine.

Induction and maintenance of anaesthesia

Among all the inducing agent for hyperthyroid patient, thiopentone is the most choiced agent. Because its thiourea structure provides some antithyroid activity. However, it is also unlikely that a significant antithyroid effect can be produced by an induction dose of thiopentone. Propofol also can be used for induction of anaesthesia in hyperthyroid patient. But, ketamine is never used, except in some special situation like hypotension, shock, etc, where it is only indicated. This is because it can stimulate the sympathetic nervous system and increase the HR, SVR, BP, etc. Other drugs that also stimulate the sympathetic nervous system should also be avoided because of the possibility of exaggerated elevation in HR and BP. Before the use of any muscle relaxant, depolarizing or non-depolarizing, for tracheal intubation the possible obstruction of airway by a huge goitre and failed intubation should be kept in mind. Otherwise, their use is not contraindicated in hyperthyroid state, provided they do not affect the cardiovascular system.

Throughout the whole perioperative period, the hyperthyroid patient should be monitored for its full cardiovascular function and body temperature. The patient should be positioned with 15° to 20° head raised. It will help by increasing the venous drainage and reducing the blood loss from operative site. But it may increase the chance of venous air embolism. Patient's eyes should be well covered, because exophthalamos in Graves' disease may increase the chance of corneal injury. Adequate depth of anaesthesia during intraoperative period must be achieved to prevent the exaggerated sympathetic response due to laryngoscopy, intubation and surgical stimulation which is already present in hyperthyroid patient. Among the volatile anaesthetic agents isoflurane, sevoflurane, and desflurane are the attractive choice for the maintenance of anaesthesia with adequate depth. This offsets the increased response of sympathetic nervous system due to surgical stimulation and also not sensitise the heart to catecholamines. An alternative choice to volatile anaesthetic agents, where it is contraindicated, is short acting narcotics combined with N_2O. There is clinical impression that the MAC value of volatile anaesthetic agent is increased in hyperthyroid patient. This is due to the increased alveolar circulation caused by increased cardiac output. But practically there is no change in MAC value or anaesthetic requirements of volatile anaesthetic agents.

Thyrotoxicosis is often associated with an increased incidence of myasthenia gravis and myopathies. Therefore, any muscle relaxants should be used cautiously and monitored closely by peripheral nerve stimulator. Pancuronium is not the choice as muscle relaxant for hyperthyroid patient in view of the ability of this drug to stimulate the sympathetic nervous system and to increase the HR with BP. Hence, administration of muscle relaxant with minimal effect on cardiovascular system is always preferred for hyperthyroid patient. Antagonism of neuromuscular blockade by anticholinesterase combined with anticholinergic agent in hyperthyroid patient introduces a great concern regarding the drug induced tachycardia. So, it should be controlled by using glycopyrrolate which has less chronotropic effect than atropine and by β-blocker.

The management of hypotension due to any cause during surgery should be treated by cautious use of sympathomimetic agents with the possibility of exaggerated responses in a hyperthyroid patient. For

these reasons the use of decreased dose of phenylephrine is more logical than ephedrine. This is because the former is direct acting and does not act in part by releasing the endogenous catecholamine like the later. During the immediate and delayed postoperative period the patient should be closely monitored for any thyroid crisis, recurrent laryngeal nerve injury causing respiratory difficulty, airway obstruction by formation of haematoma at the surgical site, hypoparathyroidism, etc, which are specific to thyroid surgery. The management of this complications are discussed before.

HYPOTHYROIDISM

It is a condition where the body tissues are exposed to decreased circulating concentration of thyroid hormones such as T_4 and T_3. It may be the end result of number of diseases of the thyroid gland (primary hypothyroidism), or it may be secondary to pituitary failure (secondary pituitary hypothyroidism) or hypothalamic failure (secondary hypothalamic hypothyrodism). The syndrome of adult hypothyroidism is also known as myxoedema. But sometimes this is used mainly to refer specifically to the skin changes in hypothyroidism. However, when hypothyroidism is present since birth or before it during intrauterine life, then this hypothyroidism is called the cretinism.

The prevalance of hypothyroidism in general population is 1:100. But, if the subclinical hypothyroidism (characterised by normal T_4 and raised TSH) are included, then the prevalance rate may rise to 1:500. Females are more affected from hypothyroidism than male and the male female ratio is 1:6. There are many causes of hypothyroidism and these are displayed in the table. Among these the spontaneous atrophic hypothyroidism, thyroid failure following the use of I^{131} or surgical removal of thyroid gland for hyperthyroidism and the hypothyroidism due to Hashimoto's thyroiditis account for about 90% of cases in those parts of the country which are not significantly iodine deficient (Table 33.6).

The clinical features of hypothyroidism depends on the duration and the severity of it, because the complete thyroid failure may develop over months and even years insidiously. The main consequence of hypothyroidism is the infiltration of body tissues by many substances such as mucopolysaccharide, hyaluronic acid and chondroitin sulphate, etc, causing thickening of it. Thus, there is development of low pitched voice, poor hearing, slurred speech, large tongue and compression of median nerve at wrist, etc. The infiltration of dermis by the previously described substances give rise to non-pitting oedema or myxoedema which is most marked on the skin of the hands, feet and eyelids. There is also periorbital puffiness which is often striking of hypothyroidism. When this is combined with facial pallor due to vasoconstriction or anaemia and parchment paper like lip, then the clinical diagnosis of hypothyroidism is simple. But, most of the cases of hypothyroidism are not so obvious. However, sometimes the diagnosis of hypothyroidism is possibly entertained in the middle aged woman by the complain of tiredness, weight gain, depression, carpal tunnel syndrome, etc, which provide an opportunity for early treatment, otherwise missed.

In the most common form of hypothyroidism such as primary hypothyroidism, there is low serum T_4 and high serum TSH level. The serum T_3 level is not important for hypothyroidism, so is not measured. Other nonspecific biochemical abnormalities of hypothyroidism include the elevation of enzyme lactate dehydrogenase (LDH), elevation of creatine kinase, raised cholesterol level, raised triglyceride concentration, low Na^+ concentration, etc. In severe prolonged hypothyroidism the ECG shows sinus bradycardia, low voltage complexes, and ST and T wave abnormalities. In rare secondary hypothyroidism there is both low T_4 and TSH level. The treatment of hypothyroidism consists of oral administration of thyroid hormone T_4. The optimal therapy of hypothyroidism is characterised by the disappearance of all the symptoms, and normal T_4 and TSH level.

Table 33.6: Causes of hypothyroidism

A.	**Primary**
	• Spontaneous atrophic
	• Hashimoto's thyroiditis congenital
	• Excess iodine (inhibits release)
	• Dietary iodine deficiency
	• Previous subtotal thyroidectomy
	• Previous radioiodine therapy
B.	**Secondary**
	• Hypothalamic dysfunction
	• Ant pituitary dysfunction

Anaesthetic Management

In our day-to-day practice, the likely presence of undiagnosed subclinical hypothyroidism in many patients who undergoes uneventlful anaesthesia and the lack of increased morbidity and mortality during anaesthesia of diagnosed mild hypothyroid patient indicates that there is no reason for delaying elective surgery in these patients. It also indicates that the patients suffering from mild to moderate hypothyroidism are not extra sensitive to inhaled anaesthetic agent and opioids and have no prolonged recovery time or do not experience increased cardiovascular complications. So, elective anaesthesia and surgery should not preferably be deferred in patient suffering from mild to moderate hypothyroidism. However, this is not applicable for severe hypothyroidism patient with some present complication due to it such as pericardial effusion, severe bradycardia, hypotension, etc, provided the surgery is not emergency.

Most patients suffering from hypothyroidism usually receive thyroid hormone replacement therapy and are in euthyroid state during elective surgery and

anaesthesia. So, they must continue it preoperatively and at the morning on the day of anaesthesia. The serum T_4 is a long acting agent and its half-life is 7 to 8 days. So, its scheduled morning dose on the day of surgery is optional. Whereas, T_3 is a short acting drug and its half-life is 1 to 2 days. Therefore, a patient must not omit its usual morning dose of T_3 on the day of surgery and anaesthesia. Hypothyroid patients are more prone to respiratory depression in response to sedatives and narcotics. They also fail to response to hypoxia by increasing the rate and depth of respiration, i.e. minute ventilation. So, they usually do not require much sedation as preoperative medication. Regarding the anticholinergic agent, they are helpful to counter the usually present sinus bradycardia and for this purpose atropine is preferred than glycopyrrolate. Hypothyroid patients usually suffered from increased gastric emptying times (i.e. delayed process of gastric emplying). So, premedications of hypothyroid patients by H_2 histamine antagonist and prokinetic agent such as metoclopramide is very essential. Theoretically, myocardial ischaemia may be worsened by the thyroid hormone replacement therapy. Because it increases the myocardial O_2 demand due to its inotropic and chronotropic effects on myocardium. But the recent available data shows that the symptoms of angina pectoris actually decrease with the thyroid hormone replacement therapy. So, a controversy may condense regarding the use of thyroid hormone from outside as a preoperative medication in such patient.

The induction of anaesthesia of a hypothyroid patient can be performed by the usual inducing agents such as thiopentone, propofol, ketamine, benzodiazepine, etc. But it depends on the severity of the disease and the presence of associated complications. This is because hypothyroid patients are more susceptible to hypotensive effect of inducing agents as there is blunted baroreceptor reflex, diminished intravascular volume, and reduced cardiac output. Therefore, ketamine is frequently recommended as the choiced inducing agent for severe hypothyroid patient and in myxoedema coma. Benzodiazepine is also a good choice as inducing agent in severly ill patient. Sometimes, the possibility of coexistant congestive heart failure and adrenal insufficiency should be taken into account in cases of refractory hypotension in a hypothyroid patient. Theoretically, decreased cardiac output may speed up the induction of anaesthesia by inhalation anaesthetic agents and decrease the MAC valve. But, practically the MAC value of inhalation anaesthetic agents does not truly decrease in hypothyroid patient. In such patient tracheal intubation can be facilitated by muscle relaxation produced by succinylcholine or any nondepolarising agent. But, it will have to keep in mind that the coexisting skeletal muscle weakness may be present in association with hypothyroidism and may potentiate the action of muscle relaxant. Other potential problems which should be kept in mind during induction and intubation of a hypothyroid patient include: large tongue, compression of trachea by large goitre, anaemia, hypoglycaemia, hypothermia due to low BMR, hyponatraemia, etc.

The maintenance of anaesthesia of a hypothyroid patient is usually achieved by using the mixture of N_2O and O_2 which is supplemented by short acting narcotics or volatile anaesthetic agent. However, the excessive volatile anaesthetic agent is not recommended because it may cause the excessive cardiac depression and peripheral vasodilatation, causing abrupt decrease in systemic blood pressure. Therefore, adequate muscle relaxation by the judicious use of neuromuscular blocker (NMB) and minimum use of IV and inhalation anaesthetic agent is the appropriate goal for the management of severe hypothyroid patient. Among the NMB agents, pancuronium is preferred for hypothyroid patients due to its cardiovascular stimulating effect. On the otherhand, the short and intermediate acting NMB agents are also preferred. This is becasue they are less likely to produce prolonged neuromuscular blockade as the reduced skeletal muscular activity is associated with hypothyroidism. Controlled ventilation is preferred than spontaneous ventilation in hypothyroid patient, because they are more prone to hypoventilation and hypoxia in response to anaesthetic drugs. On the other hand, hypothyroid patients are more vulnerable to less production of CO_2 due to decreased BMR. This when again is associated with mechanical ventilation, then it causes decreased P_aCO_2 and subsequently low $ETCO_2$ value.

The aim of perioperative monitoring of a hypothyroid patient is directed to the prompt recognition of any exaggerated depression of cardiovascular system and early detection of onset of any hypothermia. So, continuous monitoring of BP (noninvasive or invasive according to the gravity of necessity), HR, ECG, temperature, $ETCO_2$ etc. is mandatory. In addition, the glucose solution used as IV fluid should contain Na^+ to decrease the incidence of hyponatraemia, because the hypothyroidism is usually associated with the later. In the face of hypothermia which is common in hypothyroidism the body temperature is maintained by increasing the temperature of OT, by using a warming device placed under the patient, by warning the inhaled anaesthetic gases and IV fluid by warmer, etc.

` The perioperative hypotension of a hypothyroid patient is treated mainly by IV fluid, sympathomimetic agents and glucocorticoids. Regarding the sympathomimetic agents, the α-adrenergic agonist such as phenylephrine could adversely increase the systemic vascular resistance in the presence of a heart that cannot reliably increase its contractility. On the other hand, β-adrenergic agonist may precipitate the cardiac arrhythmia. Therefore, a useful approach for the management of

hypotension in a hypothyroid patient is small dose of IV ephedrine (2.5 to 5 mg) while continuously monitoring the CVS. The possibility of acute adrenal insufficiency is thought when there is persistent hypotension despite adequate treatment with IV fluid and sympathomimetic agents. Then, glucocorticoids should be used.

Antagonism of nondepolarising neuromuscular blockade by anticholinesterase combined with anticholinergic agent usually does not pose any extra hazard to hypothyroid patients. But, recovery from general anaesthesia and extubation may be delayed in such patient. This is due to hypothermia, respiratory depression or slow drug biotransformation in hypothyroid patients. Patients should remain intubated until they respond appropriately and the body temperature is near 37°C. Hypothyroid patients often require prolonged ventilation, because they are at increased vulnerability to respiratory depression. Despite all these facts, comparing patients who have mild to moderate hypothyroidism with euthyroid patients fails to demonstrate any significant difference in respect to the incidence of cardiac dysrhythmias, the time to tracheal extubation, the need for vasopressor, hypothermia, and the need for the postoperative ventilatory support.

Myxoedema coma

This is a rare and acute presentation of hypothyroidism in which there is loss of deep tendon reflexes, hypoventilation, hypothermia, cardiovascular collapse, coma and death. Body temperature may be as low as 25°C and convulsions are not uncommon. Myxoedema coma is a medical emergency condition. Sepsis and exposure to cold may be an initiating factor of it. However, treatment must begin before the biochemical confirmation of this medical emergency condition is established. For this situation T_4 is not usually available for parenteral use. T_3 is given as an intravenous bolus stat in the dose of 20 µg. It exerts its physiological effect within 6 hours and is repeated 8 hourly, until there is definite clinical improvement. Administration of T_3 is accompanied with administration of cortisol, if adrenal insufficiency is suspected. In responders, there is gradual rise of body temperature within 24 hours. After 48 to 72 hours it is possible to start substitution by oral thyroxine. Other measures of management in myxoedema coma include slow rewarming, IV fluid, high flow of O_2, broad spectrum antibiotics, etc. During fluid replacement it is important to remember that these patients may be vulnerable to water intoxication and hyponatraemia. Occasionally, assisted ventilation may be necessary (Fact file- IV).

Hashimoto's thyroiditis

It is an autoimmune disease. Hence, it is also known as autoimmune thyroiditis. In 90% of patients with this disease antibody against thyroid peroxidase are present in the serum. This condition is also not infrequently associated with other autoimmune diseases such as autoimmune gastritis, pernicious anaemia, mysthenia gravis, etc. This is the most common cause of goitrous hypothyroidism. It typically affects in the age between 20 to 60 years of old women who present with small or moderately sized diffuse goitre. At this stage it may be impossible to differentiate Hashimoto thyroiditis from simple goitre by palpation alone. Usually this disease runs in two stages. At first, there is moderate and uniform enlargement of gland with soft to firm feel. Then, usually it turns hard and nodular which depends on the relative degree of lymphocytic infiltration, fibrosis and follicular cell hyperplasia of the gland. The thyroid function is usually low. But, in some patients the serum T_4 is normal and TSH is normal or raised. This patients are at increased risk of developing hypothyroidism in future.

Hypothyroid state which is common for this disease is treated by thyroxine therapy. It also helps to shrink the goitre. The dose of thyroxine should be sufficient to suppress the serum TSH to undetectable levelw ithouti nducinghype rthyroidism.

FACT FILE - IV

Graves disease

It accounts for 70 to 80% of the cases of hyperthyroidism. It is distinguished from other forms of hyperthyroidism by the presence of diffuse thyroid enlargement, ophthalmopathy, and pretibial myxoedema (rare). It most commonly affects the 30 to 50 years age group of people. However, it may occur at any age but unusual before puberty. It mostly affects the women, but the cause of this predilection is still unknown. In Graves disease the hyperthyroidism results from the increased production of IgG antibodies directed against the TSH receptor on the thyroid follicles which stimulate the receptor. This produces marked T_4 and T_3 secretion and enlargement of thyroid gland (goitre). However, due to feedback effects of T_4 and T_3, the plasma TSH level is low.

Another hallmark of this disease is exophthalmus. It occurs in 50% of patients suffering from Graves disease and often precedes the development of hyperthyroidism. The cause of this ophthalmic manifestation is still properly not known. But the probable explanation is that there is cytokine-mediated proliferation of fibroblasts which secrete hydrophilic glycosaminoglycans. This results in increased interstitial fluid content which combined with chronic inflammatory cell infiltration causes marked swelling of the orbital tissues and increased retrobulbar pressure. The other antithyroid antibodies which are present in Graves disease also include antibodies to thyroglobulin and thyroid peroxidase. In Hashimoto's thyroiditis the autoimmune antibodies ultimately destroy the thyroid gland. But during the early stage of inflammation of gland it causes excess thyroid hormone secretion and thyrotoxicosis.

34 Psychiatric Diseases—Pharmacology and Anaesthesia

INTRODUCTION

The term 'psyche' means mental process. So, the 'psychiatric disorders' mean the mental disorders. The term 'mental disorders' encompasses a broad range of conditions which are characterised by abnormal patterns of behaviour with psychological signs and symptoms that result in mental dysfunction. Mental disorders are highly prevalent in medical practice, although they are frequently ignored or untreated and may present either as a primary disorder or as a comorbid condition. Approximately 20% of people in UK suffer from psychiatric ill health and apparently 1% of them will have a major disorder.

The important considerations during anaesthetic management of a patient with psychiatric diseases are :

i. The psychotropic drugs that the patients are taking may have potential serious interactions with the anaesthetic agents.
ii. As the patients are frequently depressed, so they have little understanding or appreciation of the course of anaesthesia.
iii. Patients suffering from psychiatric diseases may have associated co-pathology as the consequence of frequent alcohol or drug abuse by them.
iv. Patients who require ECT may require repeated anaesthesia.
v. History taking from a psychiatric patient may be difficult. So, the relatives or care givers of this patient may need to be present during preoperative assessment. The consent for surgery or anaesthesia can only be given by a competent relative, though the majority of patients with psychiatric disorders can give consent themselves normally.
vi. Psychiatric patients are often surprisingly healthy strong muscular and may become suddenly aggresive by unfamiliar faces or surroundings.
vii. Adequate sedative premedication should always be considered and adequate personnel should always be present during induction and emergence from anaesthesia of such patient.
viii. Many patients are on the long term medication and this should be continued throughout the perioperative period, whenever possible and have definite effect on anaesthesia.

During the last 50 years, psychiatric treatment has witnessed many major changes due to the advent of many specific drugs for specific illness. It has also changed the trend from custodial care of patient towards the restoring of individual patient in his own place in the community. Before 1952, the aim of psychiatric treatment was to quieten and sedate the agitated and violent patients. But, the introduction of chlorpromazine in that year had changed the situation and most schizophrenics could now be rehabilated to their productive life. Next in the year of 1957 – 1958 came the tricyclic antidepressants and MAO inhibitors which successfully covered the another group of psychiatric patients. Then, after 1980 many novel antipsychotics and antidepressants have been introduced. After that development of meprobamate and chlordiazepoxide has proved that anxiety could easily be tackled without producing any marked sedation. Now, the goal of treatment of psychiatric patient has been more realised by the development of benzodiazepine (BDZ) in 1960. Buspirone is a recent significant addition.

CLASSIFICATION OF PSYCHIATRIC DISEASES

Like any growing branch of medicine, the psychiatric illnesses have also seen the rapid changes in its classification. This is only to keep up with the growing research data and to deal with the changing epidemiology, symptomatology, prognostic factors, treatment methods and new theories for causation of psychiatric disorders. Now, all the principal types of psychiatric disorders are classified as psychosis, affective disorder and neuroses.

Psychosis

These are severe mental illnesses, characterised by the serious distortion of thought, behaviour, incapacity to recognise the reality and perception (delusions and hallucination), and misconception. This psychotic patient is unable to meet the ordinary demands of life.

Psychoses can be classified again into two disorders: cognitive disorder and functional disorder.

Cognitive disorder (Acute and chronic organic brain syndrome)

The prominent features of this cognitive disorder are confusion, disorientation, defective memory and disorganised behaviour. Examples of this disroder are delirium and dementia. Some toxic or pathological basis can often be found for this disorder, otherwise no definite aetiology can be detected.

Functional disorder

No underlying cause or pathology can often be found for this disorder. Memory and orientation are mostly retained, but emotions, thought and behaviour are seriously altered. This disorder is again classified into schizophrenia and paranoid states.

Schizophrenia (split mind)

It is characterised by inability to think coherently. There is also splitting of perception and interpretation from reality (hallucination).

Its prevalence rate normally varies between 2 to 4 per 1000 normal population. Schizophrenia is characterised by the presence of any one of the Schneider's first rank symptoms in the absence of any physical disease. Schneder's first rank symptoms include auditory hallucination, thought withdrawl, insertion or broadcasting, delusional perception, somatic passivity and feelings, etc. Chronic schizophrenia is characterised by the presence of 'negative symptoms' such as withdrawal, catatonic disturbances and lack of emotion. It commonly begins in late adolescence of either sex and is found in any social group. In the acute phase, patients may be highly delusional and / or aggresive and may not be able to give informed consent. Controlled schizophrenics may be completely lucid and rational, but care must be taken to ensure that their medication is continued where and when possible. Some chronic schizophrenics have predominantly negative symptoms and it is difficult to communicate with them.

Paranoid states

It is characterised by the loss of insight into the abnormality and false believes.

This is also called the delusion disorder. This disorder is characterised by:

i. persistent delusions of persecution (being persecuted against), grandeur (inflated self-esteem), jealousy,
ii. absence of hallucination
iii. personality disturbances,
iv. no underlying organic causes,
v. absence of schizophrenia and mood disorder.

Affective Disorder

The primary symptom of affective disorder is the change in mood. It may be manifested as mania and depression.

Mania

It is characterised by the elation, hyperactivity, uncontrollable thought and uncontrolled speech. It may be associated with violent behaviour.

Depression

It is characterised by the sadness, guilty, physical slowing, mental slowing, melancholia, self destructive idea, etc. Affective disorder may be bipolar (manic and depressive) with cyclically alternating manic and depressive phases. It may also be polar (manic or depression) with a waxing and waning of any single disorder.

Neuroses

This disorder represents the most largest proportion of all the psychiatric illness, attending psychiatric out patients department (75%). These are less serious condition. Here, ability to comprehend reality is not lost, though sometimes patient may undergo extreme suffering. In these disorders catecholamine levels may be very high or the patient may suffer from hyperventilation. These patients require only a great deal of reassurance, but no drug. Premedication is often required to smooth the induction for these patients. Depending on the predominant feature, it may be classified as: anxiety, phobic states, obsessive - compulsive and hysterical.

Anxiety

It is an unpleasant emotional state or thought for the future.

Phobic states

It is characterised by fear for unknown or some known specific objects, person or situation.

Obsessive, compulsive

It is defined as abnormality of thought or behaviour where the patient has limited ability to overcome, even on voluntary effort.

Hysterical

It is a drama like symptom, resembling serious physical illness. But, it is situational and always in the presence of others. The patient does not pretend and actually undergoes the symptoms against his or her will, though the basis is only psychic and not physical.

MULTIAXIAL CLASSIFICATION OF PSYCHIATRIC DISORDERS

Labelling a patient with a diagnosis of psychiatric disorder is not enough. This degrades the patient just as a diseased individual in hospital, but does not give any direct attention to the whole individual in a society. So, a recent classification is adopted by APA (American Psychiatric Association) in DSM-IV (Diagnostic and statistical Manual – IV). This method of classification helps in more holistic assessment of a patient as a whole human. In this system an individual patient is diagnosed on 5 axes.

Axis–I: Presence or absence of any major mental disorders (clinical psychiatric diagnosis).

Axis – II: Presence or abscence of any underlying developmental and personality disorders.

Axis – III: Presence or abscence of general medical disorders.

Axis – IV: Presence or abscence of psychological and enviornmental or social problems (psychosocial disorder).
Axis – V: Overall rating of general psychological functions.

PSYCHO-PHARMACOLOGY AND ANAESTHETIC DRUGS INTERACTION

Till recent years the exact pathophysiology of many psychiatric illnesses are not clear. But some ideas have been formed. As for example, dopaminergic overactivity in the limbic system may be involved in schizophrenia and mania. On the otherhand, the monoaminergic (NE,5-HT) deficit may underlie the depression disorder. So, treatment of psychiatric diseases are emperical, symptom oriented and not disease specific. However, this emperical and symptom oriented management is highly effective in many situations. The drugs which are used for psychiatric diseases and have a significant effect on higher mental functions are also called as psycoactive or psychotropic drugs (Fact file I).

The psychotropic drugs can be classified as follows :

Antipsychotic Drugs

They are useful in all types of psychosis, especially schizophrenia. They are also called neuroleptics, major tranquillizers or antischizophrenic drugs.

Antianxiety Drugs

These are also called anxiolytic, sedative or minor tranquillizer. They are useful for anxiety and phobic states.

Affective Disorder Drugs

i. Antidepressant drugs.
ii. Antimanic or mood stabilizing drugs.

Psychotomimetics or Hallucinogens

Now they are seldom used therapeutically to produce psychosis like states. But, majority are the drugs of abuse.

FACT FILE - I

Tranquilizer is an old term. It means 'a drug which reduces the mental tension and produces the calmness without inducing sleep or depressing mental facilities'. This term is confusing and should not be used any more. Its division into major and minor tranquilizers is also not justfied. Because the 'minor tranquilizers' are not less important drugs. They are more frequently prescribed and carry higher abuse liability than the 'major tranquilizers'. Instead of tranquilizer, the newer terms such as sedative and hypnotic are more commonly used. Sedative is a drug that subdues the excitement and produces the calmness without inducing sleep, though drowsiness may be produced. Sedation also refers to the decreased responsiveness of CNS to any level of stimulation. It is associated with some decrease in motor activity and reduction of formation of idea, but does not induce sleep. Whereas hypnotic is a drug that induces and / or maintain sleep (similar to normal arousable sleep). This should not be confused with 'hypnosis' which means a translike state where the subject becomes passive and highly suggestible. Both sedatives and hypnotics are more or less general CNS depressants with different time action and dose action relationship. Those with quicker onset, shorter duration and steeper dose response curve are referred to as the hypnotics. Whereas, more slowly acting drugs with flatter dose response curve are referred to as the sedatives. However, there is considerable overlap. A hypnotics at lower dose may act as sedative and sedative in higher dose may act as hypnotic.

ANTIPSYCHOTIC DRUGS

The antipsychotic drugs are those agents which are used for the treatment of psychoses or psychotic symptoms. These are also known as the major tranquilizers, neuroleptics or antischizophrenic drugs. But, the term antipsychotic is the most appropriate. These drugs have salutary effect on psychosis.

Classification

i. Phenothiazines
- a Chlorpromazine (CPZ), and triflupromazine (aliphatic side chain)
- b Thioridazine (piperidine side chain)
- c Fluphenazine and trifluoperazine (piperazine side chain)

ii. Butyrophenones
Trifluperidol, Haloperidol, Penfluridol, Droperidol.

iii. Thioxanthenes
Flupenthixol, chlorprothixene, Thiothixene.

iv. Miscellaneous
Pimozide, Molindone, Loxapine

v. Atypical
Risperidone, Clozapine

The pharmacological and mechanism of action of all these drugs in this group is more or less same, like chlorpramazine (CPZ). So, the pharmacology of chlorpromazine is described here as the prototype of all the antipsychotic drugs. However only they differ from each other in varying degree of actions (Fig. 34.1).

Mechanism of action

The exact mechanism of action of all these antipsychotic drugs is still unknown. But most probably, one of the major mechanism of action of these agents is the antidopaminergic activity. The dopaminergic projections to the temporal and prefrontal areas, constitute the limbic system of brain and is responsible for the psychological state. Also the dopaminergic projection to the mesocortical areas are probably responsible for emotional reactions. Over activity of this dopaminergic

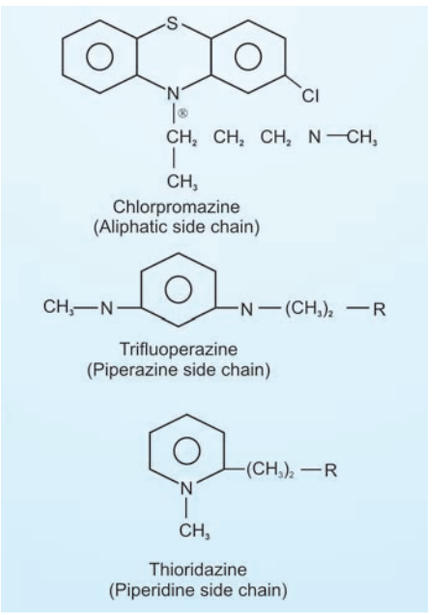


Fig. 34.1: Structure of various phenothiazines

pathway is responsible for this psychiatric illness. All the antipsychotic drugs have potent dopamine D_2 receptor blocking action and act at these areas. So the antipsychotic potency of these agents has shown good correlation with their affinity and blocking property to this dopamine D_2 receptor. Phenothiazines and thioxanthenes also block D_1, D_3 and D_4 receptors. Clozapine has weak D_2 blocking action, but is selective for D_4 receptors and also has significant $5HT_2$ and α_1 blocking action. The extrapyramidal symptoms (EPS), caused by this group of drugs is due to the blockade of D_2 receptors, situated in the extra pyramidal system (basal ganglia). Antiemtic action of these group of drugs is also due to the D_2 receptor blockade action in CTZ area. Sedation produced by these agents is caused by adrenergic blockade action which is maximum for chlorpromazine and thioridazine.

Pharmacological action

These antipsychotic group of drugs reduce the irrational behaviour, the agitation and the aggressiveness of patient. They control the psychotic symptomatology. Disturbed thinking of patient is corrected. Disturbed behaviours are gradually normalised. Difficulties in attention and concentration are slowly corrected. Anxiety is relieved. Hyperactivity, hallucination and delusions are suppressed.

All phenothiazines, thioxanthenes and butyrophenones have the same antipsychotic effects. But potency among them differs in term of equieffective doses. The aliphatic and piperidine side chained phenothiazines (CPZ, triflupromazine, thioridazine) have low antipsychotic potency than piperazine side chained phenothiazines (trifluoperazine), but produce more sedation and cause greater potentiation of hypnotics and opioids. The sedative effect of these antipsychotic drugs is produced immediately, while the antipsychotic effect takes weeks to develop.

In normal individuals, the antipsychotic drugs also produce indifference to the surroundings, paucity of thought, psychomotor slowing, emotional quietening, reduction in intiative and tendency to go off to sleep from which the subject is easily arousable. Spontaneous movements are minimised but slurring of speech, ataxia or motor incordination does not occur. This has been referred to as the 'neuroleptic syndrome' and is quite different from the sedative actions of barbiturates, benzodiazepine and other similar drugs. These effects are appreciated as 'neutral', but 'unpleasant' by most of the normal individuals (Table 34.1).

Performance and intelligence of the patient are relatively unaffected by this group of drugs, but vigilence is impaired. They lower the seizure threshold and can precipitate fits in untreated epileptics. Like sedatives and hypnotics the medullary respiratory and other vital centres are not affected by these agents except at very high doses. They have potent antiemetic action which is exerted through the centre of CTZ, but are ineffective in motion sickness.

All the neuroleptics also have the varying degree of α-adrenergic blocking activity. This may be graded as CPZ > triflupromazine > thioridazine > fluphenazine > haloperidol > trifluoperazine > clozapine > pimozide. Thus it is concluded that more potent compounds have lower propensity for α-adrenergic blocking activity. All the neuroleptics also have anticholinergic property in varying degree. The gradation of anticholinergic property is like that : thioridazine > chlorpromazine > triflupromazine > trifluoperazine = haloperidol. The phenothiazines also have weak H_1 antihistaminic and anti-5HT actions as well (Fact file II).

The neuroleptics produce hypotension by central, as well as by peripheral blocking action of sympathetic tone. The hypotensive action is more marked after parenteral administration of this agent. It is roughly parallel to the α-adrenergic blocking property of this group of drugs. This is accentuated by hypovolaemia. Reflex tachycardia accompanies hypotension (Table 34.2).

The release of ACTH in response to stress is diminished by the use of these drugs. So, Corticosteroid levels fail to increase under circumstances of stress. High doses of CPZ directly depress the

Table 34.1: Comparative properties of antipsychotic drugs

Drugs and doses (in mg)	*Sedation*	*Extrapyramidal*	*Hypotension*	*Antiemetic*
Chlorpromazine(100-800)	S	M	S	M
Thioridazine (100-400)	S	L	S	N
Triflupromazine (50-200)	S	S	M	S
Fluphenazine (1-10)	L	S	L	S
Trifluoperazine (2-20)	L	S	L	S
Thioproperazine (5-30)	L	S	L	M
Trifluperidol (1-8)	L	S	L	S
Haloperidol (2-12)	L	S	L	S
Flupenthixol (3-15)	L	S	L	L
Chlorprothixene (50-400)	S	M	M	M
Molindone (50-150)	L	M	N	N
Pimozide (2-6)	M	S	L	L
Loxapine (20-100)	L	S	M	L
Risperidone (2-12)	L	N	L	N
Clozapine (25-300)	L	N	L	N

Note: S= strong, M= moderate, L= less, N= Nil

FACT FILE - II

The antipsychotic drugs most likely exert their effects by inhibiting the binding of dopamine at their post synaptic receptors. So, they have an array of effect of overdose such as neuroendocrine, autonomic, cardiac, ophthalmic etc. But still their therapeutic index is high and the overdose effects are rarely irreversible and serious. The most troublesome (but not serious) side effects of antipsychotic drugs are : parkinsonism and dystonia. 50 to 70% of patients receiving antipsychotic drugs manifest some form of extrapiramidal system. It gradually diminishes after 2 to 3 months of initiation of treatment. Acute dystonia manifested by contraction of skeletal muscles of mouth, neck, tongue, etc, is treated by diphenhydramine, 25 to 50 mg IV.

Table 34.2: Side effects of antipsychotic drugs

Cardiovascular system	Hypotension Tachycardia ↑ PR interval ↑ QT interval
CNS	Sedation Extrapyramidal symptoms (dystonia, parkinsonism) Cognitive impairment Seizure
ANS	Blurred vision Urinary retention
GI	↓ Bowel motility Cholestatic jaundice
Ophthalmic	Opacities of lens and cornea ↑ IOP
Haematology	Agranulocytosis Leukopenia
Endocrine	Weight gain Amenorrhoea Galactorrhoea

heart and produces some ECG changes. These changes are : increased PR interval, QT prolongation, widening of QRS complex and T wave suppression. CPZ also exerts some antiarrhythmic action and probably it is due to some membrane stabilization property of it. However, arrhythmia may still occur in overdose of these agents especially with thioridazine.

Most of the antipsychotic agents have a narrow therapeutic window. If the blood level is below than the lower limit of window, then the drug is ineffective and if the blood level is higher than the upper limit of the window, then there is toxicity. All the antipsychotic agents are highly lipophilic and highly protein bound in nature. So, half-life of all the antipsychotics are long and theoretically a single dose administration per day is enough to produce sustained therapeutic blood levels. Once the drug is withdrawn, it may remain in the body for many days to many months.

Drug Interactions (Anaesthetic Implications)

As all the neuroleptic agents have central sedative properties, so they potentiate the actions of all the CNS depressing agents, like hypnotics, anxiolytics (sedative), alcohol, opioids, antihistaminics and analgesics. Therefore, overdose of symptoms may easily occur and the requirements of the anaesthetic drugs should be decreased. As all the antipsychotic agents have the potent dopamine receptor blocking action, so they block the actions of levodopa and other DA agonists which are used in Parkinsonism. So the doses of drugs used in parkinsonism should be increased. The central anticholinergic effects of all the antipsychotic agents are additive with those of atropine and hyoscine. So, the glycopyrrolate is the preferred antisialogogue where antipsychotic drugs are used. The α-adrenoreceptor blockade action of antipsychotic agents also aggravates the hypotensive effect of an anaesthetic agent. This may be an important consideration during the management of anaesthesia. This is particularly true with acute blood loss or institution of IPPV or regional anaesthesia, as the compensatory sympathetic nervous system mediated vasoconstriction is attenuated by the antipsychotic drug induced α-adrenergic blockade. Seizures may occur often with clozapine than with other antipsychotic agents. When considering GA, especially administering succinylcholine, then the patients with the history of neuroleptic malignant syndrome are more vulnerable to develop malignant hyperthermia, due to the common pathology. The neuroleptic malignant syndrome consists of marked mascular rigidity, immobility, fever, fluctuating BP and HR, myoglobin in blood etc. It is presumed due to drug induced interference with the dopamine's role in central thermoregulations.

ANTIANXIETY DRUGS

Anxiety is an emotional state which is associated with uneasiness, discomfort and fear about some defined or undefined objects. The antianxiety drugs are also called minor tranquillizers or anxiolytics. They are all illdefined mild CNS depressants, without interferring the normal mental or physical functions. This group of drugs differ markedly from the antipsychotic group of drugs and more closely resembles to sedative or hypnotics. Anxiety is very unpleasant in nature and some degree of it is always part and parcel of life. Treatment of anxiety is always not necessary. But it is needed when anxiety is disproportionate to the situation or excessive.

Characteristic of Antianxiety Drugs

i. They cannot control thought disorder of schizophrenia.
ii. They do not produce extrapyramidal side effects.
iii. They have anticonvulsant property and produce skeletal muscle relaxation.
iv. They produce physical dependence.
v. They carry abuse liability.

Classification of Antianxiety Drugs

i. **Benzodiazepines**
Chlordiazepoxide, diazepam, oxazepam, alprazolam, lorazepam, temazepam, midazolam, etc.
ii. **Azapirones**
Buspirone, gepirone.
iii. **Other sedatives**
Meprobamate, hydroxyzine.
iv. **β-blocker**
Propranolol (Fig. 34.2).

Benzodiazepine (BDZ)

All the BDZs have the selective taming effect and supress the induced aggresion. They have slow and prolonged action and relieve anxiety at low doses without producing global CNS depression. In contrast to barbiturates, BDZ are more selective for limbic system. They have also been proved to be clinically better in both quality and quantity for improvement of anxiety and stress related symptoms. However, they have very little effect on other body systems. Withdrawal syndrome is milder and delayed due to their long half-life. They reduce nightmare and have been found to be relatively save even in gross overdoses. They have least cardiovascular and respiratory depression effect at antianxiety doses.

The benzodiazepines act through BDZ receptors which is a part of the $GABA_A$ (which is discussed in Chapter 14) receptors and so facilitates the release and action of major inhibitory neurotransmitter such as GABA. Thus, it produces antianxiety, muscular relaxation and anticonvulsant action. Among all the BDZs the most commonly used agents in anaesthesia practice are midazolam, alprazolam, lorazepam, diazepam and temazepam.

Azapirones (Buspirone)

It is a new class of non BZD, antianxiety agents and buspirone is the first of all the azapirone group of drugs. The characteristics of buspirone is that it does not produce sedation or functional impairment and does not act through BZD or GABA receptors. It has no muscle relaxant or anticonvulsant property and does not produce physical dependence.

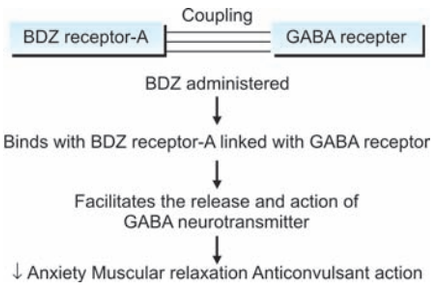


Fig. 34.2: Probable mechanism of action of benzodiazepine (BDZ)

The mechanism of action of buspirone is not exactly known. But the probable explanation is that it acts by selective partial agonistic action on $5HT_{1A}$ receptors. It has no antipsychotic or extrapyramidal effects. Buspirone relieves only mild to moderate anxiety, but is ineffective in severe cases. The therapeutic effects of buspirone develops slowly over 2 weeks. Occasionally a mild mood elevating action of buspirone has also been noted and it is due to the facilitation of central noradrenergic system.

Buspirone is rapidly absorbed through oral route and undergoes extensive hepatic first pass metabolism. Hence, the oral bioavailability of it is only less than 5%. It may cause rise in BP in patients on MAO inhibitors. But, it does not potentiate the action of CNS depressants, like benzodiazepine and barbiturates.

DRUGS FOR AFFECTIVE DISORDER

Affective disorders are also called the mood disorders and the two extremes of this pathological states are depression and mania. So, the classification of the drugs used in this disorder are similarly divided into antidepressants (mood elevators) and antimanias (mood stabiliser). Antidepressant agents again are of two types, i.e. tricyclic antidepressants (TCA) and MAO inhibitors (MAOI). The main antimanic agents is lithium.

Antidepressant

Antidepressants are those psychiatric drugs which are used for the treatment of depressive illness. They are also called mood elevators. The first antidepressant to be discovered was imipramine in 1958. It is different from phenothiazines only by a replacement of a sulphur atom with an ethylene linkage. Due to this small structural difference, imipramine was no longer effective as an antipsychotic agent, instead was quite beneficial in depressed patients. Since 1958, the number of antidepressants discovered has been gradually increasing.

The mechanism of action of imipramine (tricyclic compound) is to inhibit the NA and 5HT (seretonin) reuptake by the presynaptic neurons at nerve terminal, thus increasing the NA and / or 5HT concentration at the receptor site on the past synaptic membrane. So, tricyclic compounds are also called Mono Amine Reuptake Inhibitors (MARI). As the large number of congeners of imipramine or tricyclic compound were soon added, so they are collectively called Tricyclic Antidepressants (TCA). But it includes very few tricyclic compounds in structure as well. Some of these compounds have relatively greater inhibition on NA reuptake than 5HT or greater inhibition on 5HT reuptake than NA. Most significant development in this subject in the past 15 years is the introduction of highly Selective Serotonin Reuptake Inhibitor (SSRI) and also some atypical antidepressants. Most of the TCA compounds do not inhibit DA reuptake, except maprotiline and buproprion. Moreover, amphetamine and cocaine (which are not antidepressants, but CNS stimulants) are strong inhibitors of DA uptake. So, at the end, it can be summarised that inhibition of DA reuptake correlates with the stimulant action of CNS and is not involved in antidepressant action. Whereas inhibition of NA and 5HT reuptake is associated with antidepressant action, but not correlates with CNS stimulant action. Inhibition of 5HT reuptake is also responsible for sedation.

On the otherhand, MAOI act on the monoamino oxidase (MAO), which is a mitochondrial enzyme and is responsible for the degradation of NA, DA and 5HT after their reuptake at the nerve terminal. Thus, MAOI allow NA, DA and 5HT to accumulate in their respective neurons in

the brain and periphery. Two isoenzyme forms of monoamino oxidase (MAO) have been identified. These are MAO-A and MAO-B. The MAO-A preferentially deaminates 5HT, adrenaline and NA, whereas the MAO-B preferentially deaminates all the nonpolar aromatic amines such as phenyl ethylamine, etc. The tyramine and dopamine are deaminated by both. Their distribution also differs. Both these enzymes are present in neural and non neural tissue with a preponderance of MAO-A enzyme in the brain and MAO-B enzyme in the liver and lungs. MAOI inhibit both these MAO enzyme and thus the resultant increased amine level (NA, DA, 5HT) in brain is probably responsible for the antidepressant action. Older MAOIs are non selective (inhibiting both MAO-A and MAO-B isoenzyme) and irreversible. However, newer types of MAOIs are selective for the MAO-A isoenzyme and cause reversible inhibition (reversible inhibitor of monoamine oxidase A or RIMA) (Fig. 34.3).

Classification of Antidepressant Agents

Tricyclic antidepressants and related compounds

i. **Both noradrenaline (NA) and serotonin (5HT) reuptake inhibitors**
Imipramine, trimipramine, amitriptyline, clomipramine, doxepin etc.

ii. **Selective noradrenaline reuptake inhibitors (NA>5HT)**
Nortriptyline, protriptyline, desipramine, amoxapine.

iii. **Selective serotonin (5HT) reuptake inhibitors (SSRI)**
Fluoxetine, fluvoxamine, paroxetine.

iv. **Atypical**
Trazodone, mianserin, bupropion, tianeptine.

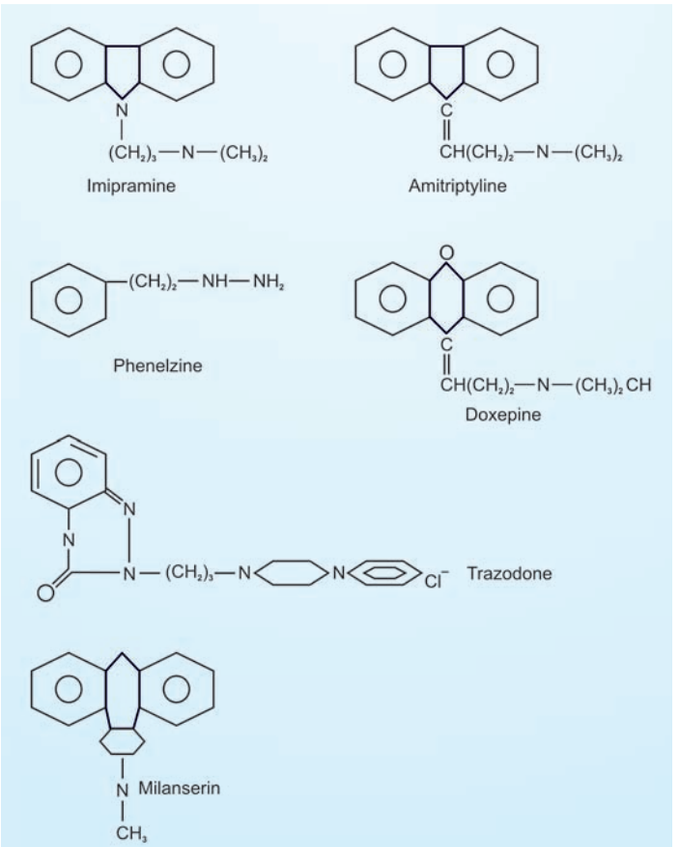


Fig. 34.3: Structural formula of some commonly used antidepressant

MAO inhibitors (MAOI)

i. **Nonselective inhibitors**
Phenelzine, isocarboxazid, tranylcypromine.

ii. **Selective inhibitors**
a. Selegiline (deprenyl) – Selective MAO-B inhibitors.
b. Moclobemide and clorgiline – Selective MAO-A inhibitors.

Pharmacological action of TCA

The older TCAs inhibit the reuptake of both the monoamines (NA,5HT) and also interact to block the variety of other receptors such as muscarinic, α-adrenergic, histamine (H_1), $5HT_2$ and occasionally dopamine (D_2). So, they have properties which include α-antagonist, anticholinergic, antidopaminergic and antihistaminic. However, relative potencies to block these receptors differ among different compounds. The newer selective serotonin reuptake inhibitors (SSRI) and atypical tricyclic antidepressants interact with fewer receptors and have more limited spectrum of action. So, they produce fewer side effects. The action of imipramine is described as prototype of all the TCAs and their related compounds (Fig. 34.4).

In depressed patients the TCA gradually elevates the mood. Patients become more communicative and start to take interest about their surroundings. Thus, TCAs are only antidepressants, but not euphoriants. They produce sedation, but this sedative property varies among different compounds. Most TCAs are potent anticholinergic and

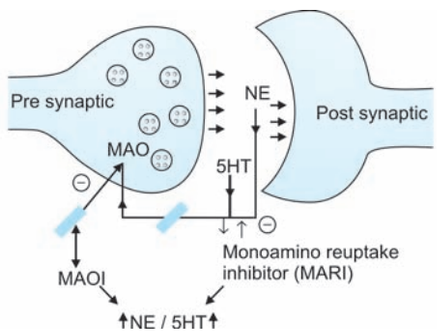


Fig. 34.4: Mechanism of action of antidepressant

cause dry mouth, blurring of vision, constipation, and urinary hesitancy. The tolerance to anticholinergic effects develop gradually, but antidepressant action is maintained. They also potentiate the action of exogenous catecholamines. All the TCAs cause tachycardia and it is due to anticholinergic and NA potentiating actions. Postural hypotension caused by TCAs is due to the inhibition of cardiovascular reflexes and α-blocking effect. The effects of TCA on CVS are common and prominent. It occurs at therapeutic concentration and may be dangerous in overdose. ECG changes due to TCAs are: T wave suppression or inversion (most consistant changes), prolongation of PR interval and widening of QRS complex. Arrhythmias may occur in overdose of TCAs. It is due to the interference to intraventricular conduction and NA potentiating action, combined with Ach blocking actions. The SSRI and atypical antidepressants are safer in this regard, but tolerance to these atypical antidepressants are higher and develops quickly. Increased appetite and weight gain is noted with most TCAs and trazodone, but not with SSRI and bupropion. Seizure threshold is lowered and fits may precipitate by TCAs. Cardiac arrhythmias induced by TCAs (especially in patients with ischaemic heart disease) may be responsible for sudden death in these patients (Fact file III).

Anaesthetic implications and drug interaction between anaesthetic agents and TCA

The interactions of TCAs with anaesthetic drugs are common and generally predictable. The increased catecholamine concentration at the central sites by TCA may lead to increased anaesthetic requirements and exaggerated response to endogenous or exogenous catecholamines. Similarly, the increased concentration of NA at post-synaptic sites in the peripheral sympathetic nervous system is responsible for the increased systemic blood pressure. This potential for hypertensive crisis is maximum between the first 14 to 21 days, during acute treatment with TCA for acute depression. Whereas, the subsequent chronic management by TCA is associated with down regulation of receptors and decreased risk of hypertensive crisis, even after administration of sympathomimetic agents. The threshold for ventricular dysrhythmias may also be lowered during chronic management by TCA. Still where possible, administration of catecholamine or drugs causing release of cathcholamines (e.g. ephedrine, mephentermine) should be avoided. Therefore, if augmentation of blood pressure is necessary, then direct acting agents such as methoxamine or phenylephrine may be used but with caution. If hypertensive episode occurs, then alpha blockers such as phentolamine may be used. However peripheral vasodilating agent such as sodium nitroprusside is better alternative.

Although, it has been recommended that TCAs should be discontinued 2 weeks before anaesthesia, but this may not be possible in many psychiatric patients as illness will be aggravated. They abolish the antihypertensive action of clonidine by preventing their transport into the adrenergic neurons. They potentiate the effect of other CNS depressants, including alcohol and antihistamines. By their anticholinergic property, they delay gastric emptying. Centrally acting anticholinergic drugs (atropine, hyoscine, not glycopyrolate) should be avoided as premedication for patients taking TCA, because their additive effect may precipitate confusion postoperatively, especially in the elderly. Dangerous hypertensive crisis with excitement and hallucination may occur, if MAOIs are used with TCAs.

FACT FILE- III

Tricyclic antidepressants and cardiovascular system

In addition to producing anticholinergic effect and sedation, TCA may cause CVS abnormalities. It includes arrhythmias and orthostatic hypotension. TCA compounds try to slow the both ventricular and atrial depolarization. This is manifested as increased PR interval, QT interval and wide QRS complex. These changes are benign and gradually disappear with continued therapy, in the absence of excessive plasma concentration. So, the previous thought that TCA increases the risk of cardiac arrhythmias is not now correct in the absence of overdose. In the presence of co-existing cardiac dysfunction such as heart block, prolonged QT interval, etc, there may be increased risk. So, sometimes when the TCA therapy is contraindicated due to patient's bad cardiac status, then ECT may be advised.

SSRI (Selective serotonine reuptake inhibitors)

This group of drugs was first introduced in 1987 and is now the most commonly prescribed antidepressant agents. They are highly selective for the inhibition of serotonin (5HT) reuptake at the presynaptic nerve terminal and are considerably less toxic than TCAs. The CVS side effects of it are very rare. Bradycardia has occasionally been reported. In patients with coronary artery disease, SSRI may precipitate coronary artery vasoconstriction. Nausea, vomiting and diarrhoea are common side effects of SSRI due to the inhibition of serotonin reuptake in the GI tract. Platelet aggregation may occasionally be inspired. 'Serotonine syndrome' may sometimes be precipitated by the addition of drugs such as MAOIs, TCAs, pethidine or pentazocine, etc, with SSRI. It is due to increased concentration of serotonin at synaptic levels in the brainstem and spinal cord. This syndrome consists of confusion, agitation, rigidity, autonomic instability, arrhythmias and sometimes coma. The treatment of these symptoms is supportive. Acute withdrawal of SSRI after use of many years may precipitate a syndrome of anxiety, agitation and increased sweating. Unlike TCA, the SSRI lacks anticholinergic effects. They also do not cause postural hypotension or delayed conduction of cardiac impulses. SSRI does not reduce the seizure threshold level.

Among the SSRI, fluxetine is the potent inhibitor of certain cytochrome P_{450} enzymes. Hence, it may increase the plasma concentration of drug that depends on hepatic clearance. So, the addition of

fluoxetine to TCA may result in 3 to 5 fold increase in plasma concentration of TCA. This mechanism may also be responsible for 'serotonine syndrome'.

Pharmacological actions of MAOI

MAOI are the toxic psychopharmacological agents. So the nonselective MAOI are rarely used nowadays. However the selective MAO-A inhibitors possess antidepressant property and is still used now in some countries. They are indicated in patients suffering from major depression, not responding to TCA and in whom ECT is contraindicated or refused. In contrast to TCA, the MAOI has negligible anticholinergic effects and do not sensitize the heart to cardiac dysrhythmogenic effects of epinephrine. Orthostatic hypotension is the most common side effect, observed in patients being treated with MAOI. The mechanism for this hypotension is unknown, but it may reflect the accumulation of some false neurotransmitters such as octopamine which are less potent than norepinephrine.

Anaesthetic implication and drug interaction of MAOI

Certain varieties of cheese, beer, wines, pickled meat and fish, etc. contain large quantities of tyramine and dopa. They are the precursors of norepinephrine (NE or NA). In MAO inhibited patients, these indirectly acting sympathomimetic amines escape their degradation in the intestinal wall and liver during absorption. Then reaching into the systemic circulation, they displace the large amount of NA from transmitter loaded adrenergic nerve endings, causing hypertensive crisis. This is called 'cheese reaction'. It can be treated by IV injection of rapidly acting α-blocker, e.g. phentolamine, prazosin or chlorpromazine or directly acting vasodilators. Certain cold and cough preparations also contain some indirectly acting sympathomimetic amines (which act by stimulating the release of NE), e.g. ephedrine which causes in hypertension. So, any indirectly acting sympathomimetic agent such as ephedrine and metaraminol which may potentiate the hypertension leading to crisis should be avoided. Excitement and hypertension also occur due to the increase in biological t½ of DA and NA that are produced from levodopa. Action of barbiturates, alcohol, opioids and antihistamines are also intensified and prolonged.

The interaction between MAOI and pethidine is also important, though uncommon. In this reaction high fever, sweating, excitation, restlessness, rigidity, hypertension, delirium, convulsion and severe respiratory depression with coma may occur. So, morphine appears to be the safe in this purpose. Other opiates which can safely be used with MAOI include fentanyl, alfentanil and remifentanil. The most accepted explanation of the reaction between MAOI and pethidine is MAOI retard hydrolysis of pethidine, but not its demethylation. Thus, excess of norpethidine (normally a minor metabolite but increase when hydrolysis is inhibited) is produced by demethylation of pethidine which has excitatory actions. Other possible explanation of this reaction is mass discharge form sympathetic nervous system, caused by the excess opioid and increased CNS concentration of serotonine (secondary to blockade of 5HT uptake). These hypertensive responses may be eliminated by withdrawal of MAOIs, 2 weeks before anaesthesia or by avoiding administration of pethidine. But like TCA, this also may not always be practical in the psychiatric patients, because withdrawal of these agents so long before surgery and anaesthesia will produce recurrence of depression in more severe form. So, it is no longer recommended that these drugs (MAOI) should be stopped 2 weeks preoperatively. But, care should be taken to avoid interaction with the anaesthetic drugs (Fig. 34.5).

Benzodiazepines are acceptable for preoperative treatment of anxiety in these group of patients. Induction of anaesthesia in these patients can safely be performed with drugs like thiopentone and propofol. But, it will have to be kept in mind that CNS depression effects and depression of ventilation may be exaggerated. Ketamine is exception to this as it stimulates the sympathetic system. N_2O combined with volatile anaesthetic agent is acceptable for maintenance of anaesthesia. But, halothane is not preferred as it may cause cardiac arrhythmia. Anaesthetic requirement in these patients is usually increased due to the increased level of catecholamines in the CNS. The spinal and epidural anaesthesia is acceptable in this group of patients. But, hypotension and subsequent administration of vasopressors may put direction in favour of GA. If vasopressor is needed, then direct acting agent such as phenylephrine is the choice, though ephedrine can be used with no apparent adverse effects. But, the dose should be reduced to minimise the likelihood of an exaggerated hypertensive response. The choice of nor depolarising muscle relaxant is not influenced by MAOI with the possible exception of pancuronium.

Pancuronium should be avoided in patients taking MAOIs, as it releases the stored adrenaline. Tranylcypromine is the most hazardous among all the MAOIs due to its stimulant action. Phenelzine has been shown to decrease the pseudocholiner esterase concentration and so there have been isolated reports of prolonged action of suxamethonium. This appears to be unique to phenelzine.

The new generation of selective MAO-A inhibitors such as RIMA (reversible inhibition of monoamine oxidase type A) are now being increasingly used. They are of short half-life, well tolerated, have

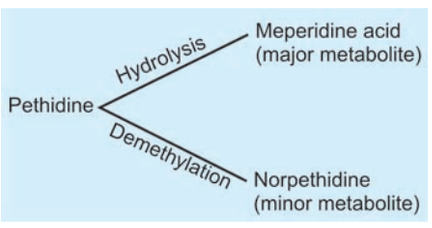


Fig. 34.5: Metabolism of pethidine

anticholinergic effects and do not cause postural hypotension. They have no central excitatory side effects, no interactions with tricyclic antidepressants and a clinically insignificant response to ingesting tyramine. RIMA may still cause an excitatory response to pethidine. So, pethidine should be avoided in patients taking RIMA. Indirectly acting sympathomimetics (e.g. ephedrine, metaraminol) should also not be used with RIMA. Selegiline is a selective MAO-B inhibitor, used in the treatment of Parkinson's disease. Interactions of it with anaesthetic agents are fewer than with the MAO-A inhibitors. Still, pethidine is best avoided and vasopressor should be used with care with MAO-B inhibitors.

Postoperative pain management is influenced by the interaction between MAOI and opioids. If they are needed, then morphine and fentanyl is the drug of choice. But, the dose should be titrated according to necessity to achieve desired analgesia. On the otherhand, alternative to opioids is the NSAID (nonopioid analgesics), peripheral nerve block or transcutaneous electrical nerve stimulation (TENS). In such circumstances, the use of opioids through spinal or epidural route is not well studied.

Antimanic Agents

Mania is an autosomal dominant disease with variable penetrance among the offsprings. It is manifested by inflated self esteem, flight of ideas, short attention, decreased sleep, increased verbalization, etc. Lithium is the mainstay of antimanic treatment. Alternative treatment is the carbamasepine or sodium valporate.

Lithium

It is a small monovalent cation (Li^+) and is the drug of choice for the management of bipolar manic depressive illness (MDI). It is extensively used at centres where its serum levels can be measured accurately. Practically, it has no effect on normal individuals and is neither sedative, nor euphoriant. On prolonged administration, it acts as a mood stabilizer in patients suffering from MDI. However, the mechanism of action of lithium is still not exactly known. Therefore, the probable explanation of action of lithium are :

i. As the lithium resembles sodium ion, so it penetrates the voltage sensitive Na^+ channel and accumulates inside the cell, causing partial depolarisation. Hence, Li^+ replaces body Na^+ and is equally distributed inside and outside of the cell. Thus, it affects the ionic movement across the cell membrane (mainly the brain cells) and modify the transmission of impulses imparing the action potential of nerve cells.
ii. It decreases the release of NA and DA in brain, without affecting the release of 5HT. Thus, it may correct the imbalance in the turnover of brain monoamine.
iii. Li^+ inhibits the hydrolysis of inositol-1-phosphate. Thus, it results in reduction of supply of free inositol for regeneration of membrane phosphatidyl-inositides which are the source of IP (Inositol triphosphate) and DAG (Diacyl glycerol). Thus, hyperactivity of neurons which is responsible for manic states is reduced as supply of the inositol from extracellular sources is meagre.

However, the hypothesis (i) and (ii) can not explain why Li^+ has no effect on normal people, not suffering from MDI. Only hypothesis (iii) can explain this.

Li^+ is efficiently absorbed from stomach after oral administration. It has a very low therapeutic window. So, as the margin of safety is narow, therefore, the monitoring of serum Li^+ concentration is essential for optimal therapy. Hence, the use of it without monitoring the serum levels is associated with unaccepted toxicity of lithium or no therapeutic effect. The therapeutic serum concentration of Li^+ for acute mania varies between 1 to 12 mEq/L. But, for prophylaxis this level may fall to 0.6 to 0.8 mEq/L. Monitoring of serum lithium concentration by flame photometry, usually 12 hours after the last oral dose, is recommended. Because it decreases the likelihood of toxicity.

Toxicity of Li^+ occurs when the serum concentration of it exceeds than 2 mEq/L. Toxicities are manifested as skeletal muscle weakness, ataxia, sedation, widening of QRS complexes, AV block, hypotension and seizures. Lithium treatment can also cause hypothyroidism and vasporessin resistant diabetes insipidus like syndrome (polyuria, polydipsia). Toxicity of lithium is also made worse by sodium depletion and dehydration.

Li^+ is handled in the body by kidney in much the same way as Na^+. So, most of the filtered Li^+ is reabsorbed from the proximal convoluted tubule and inversely related to the concentration of Na^+ in the glomerular filtrate and its reabsorption. Therefore, the loop diuretics and thiazides increases the serum lithium concentration by enhancing the renal Na^+ excretion and increasing the reabsorption of Li^+. Hence lithium toxicity may ensure in hyponatraemic states, when there is intense attempt of renal conservation of sodium and consequently in the absence of Na+ intense absorption lithium. When Na^+ is restricted then a large fraction of the filtered Li^+ is also reabsorbed and vice versa. So, IV administration of sodium containing solution or osmotic diuretics favours renal excretion of lithium in patients who show evidence of lithium toxicity.

Anaesthetic implications

During preoperative evaluation of manic patients, specially those who are under lithium treatment, the search for evidence of lithium toxicty is an important consideration and recently measured serum lithium concentration should be reviewed. In the perioperative period, Na^+ containing solution should be administered intravenously and judiciously to reduce the serum Li^+ level. Loop and thiazide diuretics should not be used or used very cautiously in patients receiving lithium. Monitoring of these patients by ECG for evidence of lithium induced changes is useful to recognise the toxicity. Li^+ potentiates sedative effect

of intravenous and inhaled anaesthetic agents and, therefore, their dose should be reduced. As lithium tends to act as an imperfect Na^+ ion, so potentiation of both depolarizing and non depolarizing muscle relaxants occurs in patients receiving lithium and hence close monitoring of neuromuscular function in necesary. Lithium is contraindicated in sick sinus syndrome.

Anaesthesia and Electroconvulsive Therapy (ECT)

For the first time in the year of 1934, Von Mednna used 25% camphor (prepared in oil) intramuscularly to produce convulsions for therapeutic purpose of depression. Later, he used metrazol for the same purposes. Then, in the year of 1938, Cerletti and Bini used a safer form of convulsive therapy for the management of severe depression by using electric current and they called it as electroshock therapy (EST) which now came to be known as the electroconvulsive therapy (ECT). Thereafter, this year 1970s saw a widespread criticism of ECT, restricting the use of it and making some modifications. Following this modifications, now the ECT technique has become the much more safer mode of treatment for severe psychiatric diseases which are unresponsive to drugs or when the patient becomes acutely suicidal.

Some physiological effects of ECT are:

i. Cardiovascular effect:
   Immediate cardiovascular effects of ECT are bradycardia and hypotension. It is due to the immediate parasympathetic stimulation following ECT. After 1 minute of parasympathetic stimulation, there is sympathetic stimulation which is characterised by tachycardia, hypertension, dysrhythmias, increased myocardial O_2 consumption, etc.
ii. Cerebral effect:
   The cerebral effect of ECT are: increased cerebral blood flow, increased ICP, increased cerebral O_2 consumption, etc.
iii. Others:
   Increased intragastric pressure, increased IOP, etc.

The contraindications of ECT are:

i. Absolute :
   Recent myocardial infarction, recent CVA, ↑ICP due to intracranial mass lesion.
ii. Relative:
   Uncontrolled angina, congestive cardiac failure, severe pulmonary diseases, pheochromocytoma, severe hypertension, severe osteoporosis, major bone fractures, glaucoma, retinal detachment, etc.

The pretreatment or preanaesthetic assessment of patient waiting for ECT consists of (i) informed consent, (ii) detailed medical and psychiatric history, (iii) general and systemic physical examination, (iv) routine laboratory investigation on the light of history and examination, (v) ECG and plasma pseudocholinesterase level, (vi) examination of funds oculi (to rule out papilledema), etc.

So, some important points regarding the preoperative assessment before ECT are:

i. ECT is usually carried out in elderly patients who have a variety of coexisting diseases. So, an anaesthetist must be very careful.
ii. The majority of patients are taking psychiatric drugs which have the potential to interact with anaesthetic agents, used during GA for ECT.
iii. Patients are mostly non cooperative. So, histories are not reliable, even regarding preoperative fasting.
iv. Sedative premedication is not always indicated as it prolongs the recovery.
v. ECT is a repeated procedure. So, previous anaesthetic note should be studied carefully to see the effect of anaesthesia on previous ECT (Table 34.3).

The exact mechanism of action of ECT is still unclear. But one hypothesis states that ECT possibly affects the catecholamine pathways between the diencephalon (site of seizure generation) and limbic system (responsible for mood disorder), involving hypothalamus which is responsible for severe psychiatric illness. The previous concept of the therapeutic benefit of ECT on psychiatric illness depend on the production of generalised tonic clonic seizures, but that is not correct. Because, now it is established that therapeutic efficacy of ECT is related to the amount of electric current passing through the brain, but not on the production of tonic clonic seizures. The electrical stimulus given during ECT produces grand mal seizure which consists of brief tonic phase followed by long clonic phase. The EEG changes during ECT is similar to that of spontaneous grand mal seizure and typically 8 to 10 ECT is necessary which show 80% favourable response.

The techniques used for administration of ECT are of two types: direct ECT and modified ECT. In direct technique, ECT is given in the absence of muscular relaxation and general anaesthesia. This is infrequently used now. In the later technique, ECT is modified to reduce or avoid generalised tonic clonic seizure by drug induced muscular relaxation and general anaesthesia.

General anaesthesia is usually administered to ensure the patient's safety and comfort during ECT. Patients are fasted as in GA. Sedative premedications are usually not used, because it prolongs the period of recovery following ECT. Anticholinergic (atropione or glycopyrolate) is given before induction of anaesthesia or delivery of electric current. This is to

Table 34.3: Side effects of ECT

Parasympathetic stimulation
Bradycardia
Hypotension
Sympathetic stimulation
Tachycardia
Hypertension
Dysrhythmias (cardiac)
↑ Myocardial O_2 consumption
↑ Cerebral blood flow
↑ Intracranial pressure
↑ Cerebral O_2 consumption
↑ Intragastric pressure
↑ Intraocular pressure

decrease the oral secretions and to prevent the vagal stimulation during ECT which can cause severe bradycardia or even cardiac arrest. Bradyarrhythmias are also particularly common during stimulus titration where subconvulsive stimuli are used to determine the seizure threshold. Centrally acting anticholinergic drugs such as atropine may have synergistic effects with central and peripheral anticholinergic effects of TCA (Tricyclic antidepressant) which the patients are already taking and manifests as delirium and confusion during postanaesthetic period. For this reason, glycopyrrolate is preferred to atropine when ECT is administered to patients being treated with TCA. Sympathetic stimulation during ECT in patients with cardiovascular disease may be undesirable. So, high rise of blood pressure and tachycardia during intubation and electric current therapy can be controlled by esmolol (50 to 200 µg/kg/min) or nitroglycerin or nitroprusside. Monitoring of ECG is useful for recognising ECT induced cardiac dysrhythmias.

For induction during ECT, the commonly used agents are thiopentone, propofol or methohexital. Among these, methohexital is the inducing agent of choice and is used most commonly in the dose of 0.5 to 1 mg/kg through IV. Thiopentone has no advantage over methohexital and may be associated with longer recovery time, but it can be used. Prior treatment of patients with TCAs or MAOIs could enhance the sedative effects of thiopentone. Propofol in the dose of 1 to 2 mg/kg is now also the agent of choice, giving rapid onset and recovery. Like thiopentone, ketamine and etomidate have also been successfully used for induction of GA in ECT.

The use of muscle relaxants in ECT has virtually eliminated the potentially dangerous skeletal muscle contractions and the fracture of bone that can be produced by seizure activity. Succinylcholine in a dose of 0.3 to 0.5 mg/kg through IV route is the most commonly used muscle relaxant for ECT. This lower dose of succinylcholine is particularly selected, because it helps in sufficient visual confirmation of seizure activity during ECT. When it is not possible to visualise the seizure activity due to higher doses of muscle relaxants, then the most reliable method to confirm electrically induced seizure activity is the EEG. Alternatively, one limb can be isolated from the effect of muscle relaxant by applying tourniquet before its administration to see the seizure activity. Low dose of mivacurium (0.08 mg/kg) has also been tried. But although the recovery in case of mivacurium was found to be good, still seizure modification was inadequate. Therefore, if mivacurium is used, the dose should be at least 0.15 mg/Kg and reversal will probably be necessary. Longer acting muscle relaxing agents are not generally suitable for ECT.

Provided there are no risk for aspiration, then the airway and arterial oxygenation can normally be maintained with an oral airway and mask, unless muscle relaxants are used. Ventilatory support and delivery of supplemental O_2 by mask and IPPV is recommended both before production of seizure and until the effects of succinylcholine or mivacurium have been dissipated. After induction of anaesthesia (but before application of ECT stimulation) hyperventilation of the patient's lungs by bag and mask lowers the seizure threshold and prolongs the duration of seizure. Thus, it increases the effectiveness of ECT. When the limbs are flaccid by muscle relaxant, then a rubber 'bite block' is inserted into the mouth between the teeth before electrical stimulation is applied. This will prevent damage to the lips, tongue and teeth during convulsion by electrical stimulation which is given after induction and muscular paralysis by muscle relaxant. During seizure, artificial ventilation with O_2 is continued to avoid arterial desaturation, until adequate spontaneous ventilation has returned. Denitrogenation of the patient's lung by 100% O_2 before production of convulsion by ECT decreases the likelihood of arterial hypoxaemia if it becomes difficult or impossible to support the ventilation in the presence of seizure induced skeletal muscle contractions. Patient should be recovered in the lateral position by trained nursing staff with equipment available immediately for treatment of any emergency. Furthermore, it is important to keep in mind that apnoea may last for 2 to 3 minutes following ECT, requiring ventilation even in the absence of succinylcholine. Monitoring of arterial O_2 saturation by pulse oximetry is mandatory to guide the need for supplemental O_2 and mechanical ventilation for patients undergoing ECT. It is confirmed that ECT does not increase the succinylcholine induced release of potassium. But, monitoring of the neuromuscular blockade by succinylcholine by peripheral nerve stimulator is also sometimes necessary, because repeated anaesthesia is given by it for ECT. The use of peripheral nerve stimulator may help to identify the degree of blockade by succinylcholine with previously unrecognised atypical cholinesterase enzyme. It is also possible to establish the dose of the anaesthetic inducing drug and succinylcholine that will produce the most predictable and desirable effects in each patient.

Special attention should be given to the patients with permanent pacemaker, waiting for ECT. But, fortunately most pacemakers have inbuilt safety measures such as a shield which are not affected by the electrical currents necessary to produce seizures. During ECT of a patient with pacemaker, an external magnate should be kept ready for converting pacemaker to synchronous non demand modes if malfunction occurs in response to the externally delivered electrical current. The continuous monitoring of cardiac activity by ECG and peripheral arterial pulses by palpation is very impotant for uninterrupted function of artificial cardiac pacemaker.

35 Obstetrics Analgesia and Anaesthesia

INTRODUCTION

The obstetric anaesthetic care usually accounts for approximately 10 to 15% of total anaesthetic procedures. It always should be kept in mind that the patients who enter the obstetric wing of an hospital may potentially require the anaesthetic care either for labour analgesia or for CS which may be an emergency or may be a planned one. Hence, anaesthesiologist should be cautious about the relevant history of all the parturient patients. This history will include the present and past medical, surgical and obstetrics history, parity, age, duration of pregnancy etc. The patient should also be examined previously with the potential idea of future planned or emergency surgery. These preanaesthetic examinations include general survey with special attention to BP, airway assessment, examination of spinal cord for regional anaesthesia (RA), etc. Regardless of the time of last oral intake, all obstetric patients should be considered to have a full stomach. So, they are all at the increased risk of pulmonary aspiration, if surgery is at all needed. Therefore, those patients who are specially at high possibility of operative delivery should take nothing permouth during the progress of labour. On the other hand, if the labour is uncomplicated then small amount of clear fluid can be provided during the prolonged labour. However, if there is any doubt, then prophylactic oral administration of 0.3 M sodium citrate at every 2 to 3 hours interval will help to maintain the gastric pH above 2.5 and decrease the chance of aspiration pneumonitis. This prophylaxis also can be taken by oral or parenteral use of H_2 blocker and metoclopramide in high risk patients who are expected to receive GA. H_2 blockers reduce the volume of gastric secretion and pH after its administration. But it has no effect on the gastric contents which is already present. On the other hand, metoclopramide reduces the gastric volume which is already present by accelerating the gastric emptying. But it can not increase the gastric pH. Contrary it increases the lower oesophageal sphincter tone and reduces the incidence of gastric regurgitation. All parturient patients should be placed in 15° left lateral position by an wedge, placed under the right hip to avoid inferior vena caval compression by gravid uterus and reduction of preload.

The majority of obstetric patients are in child bearing age and therefore are healthy. So, they are considered to be at very less anaesthetic risk. But, certain changes in body due to pregnancy such as PIH (pregnancy induced hypertension), PET (pre-eclamptic toxaemia), excessive weight gain, oedema, etc; and certain other medical diseases which are aggravated by pregnancy increases the obstetric anaesthetic risk. The obstetric meternal mortality rate is calculated as the number of maternal death divided by the number of live birth. Recently, this rate has decreased tremendously and now approximately this number has touched to 6 to 12 per 100,000 live birth. The principal causes of maternal death associated with live birth are: pulmonary embolism (20%), PIH (20%), sepsis (15%), cardiomyopathy (10%), haemorrhage (5%), cerebrovascular accident (4%), anaesthesia (3%) and other medical condition (20%). On the other hand, the common among these causes of maternal morbidity which are encountered during obstetric practice is severe haemorrhage and severe pre-eclampsia. Anaesthesia accounts for approximately 2 to 4% of total obstetric maternal death. The anaesthetic risk factors for this maternal death include: age over 35 years, multiple pregnancy, black patients, PIH, previous PPH, emergency LUCS, etc. Among the anaesthetic causes the most maternal deaths occur during or after LUCS. Recently this figure has been reduced due to frequent use of RA than GA.

PHYSIOLOGICAL CHANGES DURING PREGNANCY

Before any discussion regarding the anaesthesia in obstetrics, every clinician should have a profound knowledge about the changes which occur during the whole period of pregnancy and delivery. Because pregnancy affects virtually all the organs of body and brings about multiple changes which alter the usual responses to anaesthesia. These changes occur due to mechanical and hormonal influences and are appeared to be useful to meet the demands of placenta, uterus, foetus and to tolerate the increased stress during pregnancy, labour and delivery. For example, during the whole period of pregnancy

(280 days calculated from the first day of last menstrual period) the uterus itself increases in weight from 30 gm to 1000 gm which has profound implication on anaesthesia that is discussed later.

Changes in Cardiovascular System (CVS)

The changes in CVS that occur during pregnancy serve two functions. These are: (i) to maintain increased uteroplacental circulation which are necessary to continue pregnancy, and (ii) to maintain the increased exchange of O_2, CO_2, nutrients, and other waste products between the mother and foetus.

The maternal blood volume increases by about 40% during the whole period of pregnancy. But the plasma volume increases in excess than that of the red cell volume. Therefore, it apparently reduces the Hb concentration and produces the dilutional anaemia in pregnancy which is physiological in nature. This dilution of blood reduces its viscosity and causes better perfusion in tissues, which thus offsets the side effects of anaemia by increasing the delivery of O_2 to tissues. This drawback of anaemia is further offset by the increase in cardiac output and the shifting of O_2-Hb dissociation curve towards right. The blood volume increases by about 1000 to 1500 ml at term and this will allow a woman to tolerate the blood loss during delivery which is near about 400 to 500 ml in vaginal delivery and 800 to 1000 ml in CS (Table 35.1).

During pregnancy cardiac output also increases by about 40%. This increase in cardiac output is due to both the increase in heart rate (10%) and stroke volume (30%). The increased stroke volume is again due to myocardial hypertrophy and enlargement of cardiac chambers. Most of this changes in cardiac output is observed during 1st trimester and to a lesser extent during 2nd trimester of pregnancy. In 3rd trimester, cardiac output does not appreciably increases except during the process of labour and delivery. After 28 weeks of pregnancy the cardiac output decreases in supine position. This is due to the compression of inferior vena cava by gravid uterus and impairment of venous return to the heart. This is called the supine hypotension syndrome and is found in 20% of patient. This syndrome is characterised by dizziness, restlessness, hypotension, pallor, sweating, nausea and vomitting, etc. when the patient lie directly on his back. Turning the patient on her side typically improves these symptoms. So, a pregnant patient with more than 28 weeks gestation should never be placed supine without left uterine displacement. This can be performed by placing a wedge (> 15°) under the right hip. The trendelenburg position of patient due to any cause increases the compression on inferior vena cava and the risk of supine hypotension syndrome. The abdominal aorta is also compressed by a gravid uterus when the woman lies in supine position. This results in decreased circulation in femoral artery and more importantly the uteroplacental flow. This reduction in uteroplacental blood flow produced by aortocaval compression causes decreased cardiac output (due to reduction of preload), decreased uterine arterial perfusion (due to compression of aorta), increased uterine venous pressure (due to vena caval compression) and increased sympathetic tone. All these factors result in foetal hypoxia and acidosis. During the process of labour, contraction of uterus relieves this compression on inferior vena cava, but increases the compression on aorta. These problems of aortacaval compression will be grossly aggravated following sympathetic blockade during subarachnoid or epidural anaesthesia. Therefore, strict avoidance of supine position and adequate IV fluid to increase preload are the very essential part of any technique of RA.

Table 35.1: Cardiovascular changes during pregnancy

Parameters	*Changes*
Heart rate	+ 10 to 15%
Stroke volume	+ 25 to 30%
Cardiac output	+ 35 to 40%
Systolic pressure	– 5 to 10 mm of Hg
Diastolic pressure	– 15 to 20 mm of Hg
Systemic vascular Resistance (SVR)	– – 15 to 20%

Due to elevation of diaphragm by the enlarged gravid uterus, heart is also displaced upwards, laterally, and forwards. This results in the appearance of a normal heart to an enlarged heart on a plain chest X-ray and also left axis deviation in an ECG. Thus, the usual changes in ECG during pregnancy show the flattened T-waves or Q-waves in lead III and as well as innocent depression of ST segment. Sinus tachycardia, premature ventricular contractions, or bouts of paroxymal atrial tachycardia are also more common in pregnancy. In pregnancy, SVR is reduced. It decreases both the diastolic and systolic blood pressure, but reduction of diastolic BP is more than systolic BP. During pregnancy, the central venous pressure, pulmonary artery pressure and pulmonary capillary wedge pressure are all usually remain unchanged.

The physical examination of a pregnant patient often reveals splitting of 1st heart sound, audible 3rd heart sound, and a soft systolic ejection flow murmur (grade I and II).

Respiratory System

With the progressive enlargement of uterus, diaphragm is gradually elevated towards thorax which is about 4 to 5 cm in height. This reduces the volume of lungs. But, usually, it is compensated by an increase in both the anteroposterior and transverse diameter of thoracic cavity due to hormone induced relaxation of the costal ligaments. This explains why thoracic breathing is favoured over abdominal breathing in pregnancy. In pregnancy, O_2 consumption is increased by 20%. Therefore, to meet this increased need of O_2 the minute and alveolar ventilation is also increased by 50% and 70%, respectively. This is again due to the increase in both

tidal volume and respiratory rate. In pregnancy, the vital capacity (VC) and closing capacity (CC) remain unaltered, but FRC is reduced by 20%. This is prinicpally due to the reduction in expiratory reserve volume as a result of a larger than normal tidal volume. Therefore, CC exceeds FRC in 50% of pregnant women and early airway closure occur during normal respiration with normal tidal volume. This is again more usual when the patient lies in supine position and so atelectasis with hypoxaemia occurs more readily in this position. This phenomenon along with the increased O_2 consumption explains the cause of rapid O_2 desaturation during the periods of apnoea, and explain why preoxygenation with 100% O_2 prior to induction of GA is mandatory to avoid hypoxia in pregnant woman. However, FRC returns to normal within 48 hours of delivery.

Due to increase in ventilation P_aCO_2 decreases up to 25 to 30 mm of Hg, causing respiratory alkalosis. This is compensated by decrease in the plasma HCO_3^- level. Pregnancy induced respiratory alkalosis reduces the unloading of O_2 in tissue level. But this is compensated by increase in P_aO_2 due to hyperventilation, increase in 2,3-DPG level which decreases the O_2 affinity to Hb and increase in cardiac output which enhances the delivery of O_2 to tissues.

Pregnancy is associated with decreased airway resistance and pulmonary compliance. Dead space usually remains unaltered in pregnancy, but intrapulmonary shunt increases towards term. The flow-volume loops of lungs are unaffected by pregnancy. A chest X-ray during pregnancy often reveals prominent vascular markings due to increased pulmonary blood volume increased pulmonary circulation and raised diaphragm.

During pregnancy capillary dilatation and oedema of mucous membrane occurs throughout the respiratory tract. This easily predisposes the upper airway to trauma, bleeding, and obstruction. Hence, small ET-tube than the calculated one and gentle laryngoscopy is essential during administration of GA in pregnancy (Table 35.2).

Table 35.2: Respiratory changes during pregnancy

Parameters	*Changes*
Respiratory rate	+ 15%
Tidal volume	+ 40%
Alveolar ventilation	+ 70%
Minute ventilation	+ 50%
Airway resistance	– 35%
Total compliance	– 30%
Residual volume	– 20%
Closing capacity	Unchanged
Vital capacity	Unchanged

Central Nervous System

The pregnancy has also profound effects on CNS, the actual mechanism of which is still not known. But probably it is due to the high concentration of progesterone associated with pregnancy. It decreases the dose of inhaled anaesthetic agents. The MAC value of all the volatile anaesthetic agents decreases upto 40% in pregnancy which again returns to normal on the 3rd day after delivery. Like volatile anaesthetic agents, LA agents also show higher sensitivity to neurons during pregnancy. Therefore, less amount of LA agents (30% reduction) is required during RA (spinal or epidural) to produce the same level of analgesia and anaesthesia. This event can be explained by two mechanism – hormonal and mechanical. The hormonal effect is mediated by progesterone which make the nervous tissue more sensitive to LA agents. The mechanical effect causing reduced dose of LA agent during spinal or epidural anaesthesia is due to the obstruction of inferior vena cava by gravid uterus. This causes distention of epidural venous plexus. Therefore, the volume of the potential epidural space and CSF are reduced. This enhances the more cephalad spread of same volume of LA agents during both the spinal and epidural anaesthesia in pregnant than non-pregnant state and needs the reduced doses of drug.

GI Effects

Pregnancy places the parturient women at higher risk for regurgitation and pulmonary aspiration. This is again due to the hormonal and mechanical effects. The hormonal effect is due to the higher level of progesterone and gastrin, secreted from placenta. This high level of progesterone decreases the tone of lower gastroesophageal sphincter and increases the chance of regurgitation. On the other hand, gastrin increases the secretion of HCl in stomach. The enlarged gravid uterus displaces the stomach upwards and anteriorly. This again promotes the incompetence of lower gastroesophageal sphincter. Thus, the above mentioned three factors (progesterone, gastrin, and upward displacement) increases the risk of severe aspiration pneumonitis during GA in pregnancy. Nearly all pregnant patients have gastric pH < 2.5 and the residual volume of gastric secretion is > 25 ml. Thus, it has also a profound effect on causing pulmonary complication.

The effect of pregnancy on gastric emptying time is in controversy. It is particularly delayed following administration of opiates for labour analgesia and onset of labour. Otherwise, gastric emptying takes place at widely variable rates during pregnancy. Anticholinergic agents delay the gastric emptying and reduce the tone of lower gastroesophageal sphincter. Contrary, prokinetic agent like metoclopramide usually speed up the gastric emptying, but is unable to reverse the effects of opiate and anticholinergic agent. However, the spinal and epidural anaesthesia do not affect the gastric emptying time. It is the loss of tone of lower gastroesophageal sphincter and not the rise of intra-abdominal or intragastric pressure which is the common cause of high incidence of gastroesophageal reflex (heart burn) and oesophagitis occuring during prganancy. Intragastric pressure remains unchanged throughout the pregnancy.

Haematological Changes

The maternal blood volume increases markedly during pregnancy. This increase

in blood volume results from both the increase in plasma and erythrocyte volume. The usual pattern is that there is initial increase in plasma volume and this is followed by an increase in the volume of circulating erythrocytes due to increased erythropoiesis. But the increase in plasma volume is much more than the increase in volume of erythrocytes. So, the concentration of Hb apparently (falsely) decreases during pregnancy due to the dilutional effect. The average Hb concentration at term is 12 gm/dl, as compared with a level of 13 gm/dl for nonpregnant women. The Hb concentration below 11 gm/dl, especially in late pregnancy, is suggestive of an abnormal process. The blood leucocyte count varies considerably during normal pregnancy. Usually, it ranges from 5000 to 12000 per cumm of blood. But during labour and the early puerperium it may become markedly elevated, attaining the levels of 25000 per cumm.

The plasma levels of several coagulation factors are increased during pregnancy. The concentration of plasma fibrinogen (factor I) increases by about 50%. The normal value of it ranges between 200 to 400 mg/dl (average 300 mg/dl). In pregnancy, it increases to an average value of 450 mg/dl (ranges between 300 to 600 mg/dl). The other clotting factors, and activation of which are increased appreciably during pregnancy are: factor VII, factor VIII, factor IX, factor X and factor XII. But the level of factor II (prothrombin) does not increase or increases only slightly during pregnancy. Whereas those of factors XI and XIII are decreased during pregnancy. Prothrombin time and partial thromboplastin time (PTT) are both shortened slightly as pregnancy progresses (Table 35.3).

Although some investigators have described a moderate decrease (10%) in the number of platelets, but still there is some controversy regarding this fact. This is because clotting time does not differ significantly between the normal pregnant and non-pregnant women. Pregnancy is associated with lower level of antithrombin III and increased level of plasminogen (profibrinolysin).

Table 35.3: Haematological changes during pregnancy

Parameters	*Changes*
Plasma volume	+ 40%
Red cell volume	+ 20%
Total blood volume	+ 45%
Haematocrit	– 15%
Plasma albumin	– 15 %
Plasma globulin	↑
Plasma fibrinogen	+ 50%
Plasma cholinesterase	– 30%

Renal Changes

Apparently the kidney increases in size slightly during pregnancy. Glomerular filtration rate (GFR) and renal blood flow (RBF) increase upto 50% during early pregnancy. The elevated GFR has been found to persist upto term, whereas the RBF decreases towards the non-pregnant value during the 3rd trimester of pregnancy. Pregnancy is associated with increased renin and aldosterone secretion which subsequently promotes the increased Na^+ and water retention. This causes the increased circulating volume of blood during pregnancy. During pregnancy, the concentration of creatinine and urea in plasma decreases upto the level of 0.5 to 0.6 mg/dl and 8 to 9 mg/dl, respectively as a consequence of increased GFR. Some times, the urea concentration during pregnancy may be as low as to suggest impaired hepatic synthesis, which often occurs with severe liver disease. So creatinine clearance is the most useful test for renal function during pregnancy.

The glycosuria which often found during pregnancy is not necessarily always taken as abnormal finding. The appreciable increase in glomerular filtration rate, together with the impaired renal tubular reabsorption capacity this huge amount of filtered glucose is responsible in most cases for glycosuria in pregnancy. Even though glucosuria is common during pregnancy, still the possibility of diabetes mellitus which has separate inplication on pregnancy can not be ignored. Proteinuria does not occur normally during pregnancy, except occasionally a mild one (< 300 mg/dl) during or soon after vigorous labour. If not the result of contamination during collection, blood cells in the urine during pregnancy indicates the disease somewhere in the urinary tract.

Hepatic Changes

During pregnancy there is no distinct change in size and morphology of liver. The overall hepatic function remains unchanged throughout the whole period of pregnancy, except minor increase in the serum transaminases and lactic dehydrogenase level in plasma during 3rd trimester. The total alkaline phosphatase activity in serum approximately becomes double during normal pregnancy and commonly reaches the levels that would be considered abnormal in the nonpregnant woman. Much of this increase in serum alkaline phosphatase level is due to the secretion of it from placenta. Pregnancy is associated with decrease in plasma albumin level, showing it to average 3 gm/dl, compared with 4 to 6 gm/dl in nonpregnant woman. This probably is due to the expanded plasma volume. But, globulin level in plasma increases in pregnancy and results in a decrease in the albumin to globulin ratio, similar to that found in certain hepatic diseases. There is also 30% reduction in serum (pseudo) cholinesterase activity in pregnancy. But, rarely it is associated with prolonged action of succinylcholine. This decreased activity of pseudocholinesterase persists upto 6 weeks after delivery. But, the breakdown of mivacurium by pseudocholinesterase does not appreciably alter during pregnancy.

Metabolic Changes

In response to the rapidly growing foetus and placenta and their increasing metabolic demands, the pregnant woman undergoes some metabolic changes that are numerous

and intense. This is because the altered carbohydrate, fat and protein metabolism favours the foetal growth and development. The first and foremost metabolic changes that occur in pregnancy is weight gain of mother. The large increament in maternal body weight during pregnancy is the result of metabolic alterations, especially retention of water, and deposition of fat and protein. The average total gain of body weight in a pregnant woman during the whole period of pregnancy is about 11 Kg and the minimum amount of extra water that an average pregnant woman could be expected to retain is about 6.5 L. The total accumulation of protein throughout the whole pregnancy is 1 gm, out of which 500 mg is needed for the development of foetus and placenta and another 500 mg is required for the development of rest such as in the form of uterus (as contractile protein) plasma protein, Hb, etc.

The pregnancy is potentially a diabetogenic process. So, a already present diabetes mellitus is aggravated by pregnancy or a clinical asymptomatic individual becomes an overt one. The diabetogenic effect of pregnancy is principally due to the lactogen secreted from placenta which is called placental lactogen. It opposes the action of insulin and produces or aggravates the diabetes mellitus. Thus, the ability of placental lactogen to oppose the action of insulin leads to increased maternal secretion of insulin. Therefore, hyperplasia of the beta cells of pancreus occurs in response to an increased demand for insulin secretions. The placental lactogen also promotes lipolysis which brings about an increase in the level of plasma free fatty acid. These plasma free fatty acids provide alternative source of energy other than glucose in mother. Hence, in pregnancy starvation induces much more intense ketonaemia and ketonuria.

The plasma lipid level increases appreciably during the later half of pregnancy. This increase involves the total lipids, esterified and nonesterified cholesterol, phospholipids, neutral fat and lipoproteins, etc.

UTEROPLACENTAL CIRCULATION

The delivery of most of the substances essential for the growth and metabolism of foetus and placenta, and as well as the removal of most of the metabolic wastes from them depends upon the adequate perfusion of these. This is called the uteroplacental circulation and in turn it depends upon the blood flow through the uterus by uterine and ovarian arteries and through the placenta by umbilical arteries and veins. There is progressive increase in uteroplacental blood flow throughout the pregnancy. It represents about 10% of total cardiac output or 500 ml/min in late pregnancy. Among these 80% of the flow goes to the placental circulation and the rest goes to the growing myometrium of uterus.

During pregnancy due to the maximum dilatation of uterine vasculature, its autoregulation is lost. Then, the blood flow through uteroplacental circulation is directly proportional to the difference between the uterine arterial and venous pressure, and inversely proportional to the uterine vascular resistance. During autoregulation uterine arteries are under the neural control which are mediated by mainly α-adrenergic receptors and to a lesser extent by β-adrenergic receptors. Therefore, α-adrenergic agonistic agents cause uterine vasoconstriction and decrease the uteroplacental blood flow. The example of some α-adrenergic agonists are adrenaline, noradrenaline, phenylphrine, mephentermine, etc. As β-receptors are sparse on uterine vasculature, therefore predominant β-adrenergic agonists such as ephedrine does not decrease much the uteroplacental blood flow. Hence, it is the vasopressure of choice to treat hypotension during obstetric regional analgesia and anaesthesia. However, practically many clinical studies suggest that predominat α-adrenergic agonists though constricts the uteroplacental vasculature, still are associated with less foetal acidosis than ephedrine. This is becasue they maintain the adequate uterine blood flow by maintaining systemic blood pressure and a pressure head to flow, provided excessive vasoconstriction is avoided.

The three major factors which decrease the uteroplacental blood flow during pregnancy are: (i) systemic hypotension by decreasing the difference between uterine arterial and venous pressure, (ii) uterine vasoconstriction by increasing the uterine vascular resistance, and (iii) uterine contraction by decreasing the difference between uterine arterial and venous presure by elevating the uterine venous presure. The intense uterine contraction decreases the uteroplacental blood flow by compressing the uterine arterial vessels as they traverse through the myometrium. Hypertonic uterine contractions by oxytocin infusion or due to other causes can critically reduce the uteroplacental blood flow and compromise the foetus.

Effects of Anaesthetic Agents on Uteroplacental Blood Flow (UPBF)

More or less all the anaesthetic agents affect the UPBF by acting directly or indirectly. Among the intravenous anaesthetic agents thiopentone, benzodiazepines and propofol reduce the UPBF. This is due to indirect effect of systemic hypotension, produced by these agents in high doses. But the clinical inducing dose of these group of drugs does not produce any alteration in UPBF, if the BP is maintained with in normal level. However, a small inadequate dose of these inducing agents may reduce the UPBF and it is due to the stimulation of sympathetic system during laryngoscopy. Injection ketamine causes the activation of sympathoadrenal axis and may reduce the UPBF by vasoconstriction. But the increase in BP by ketamine counter acts the effect of vasoconstriction and ultimately the UPBF remains the same. This explanation is applicable when the dose of ketamine is kept below 1 to 1.5 mg/Kg of body weight. But, when

the dose of ketamine is increased to >2 to 3 mg/Kg, then it causes the hypertonic contraction of uterus and drastically reduces the UPBF.

The effects of volatile anaesthetic agents on UPBF also depend upon the interactions between the effect of these agents on systemic BP and direct uteroplacental vasodilatation with uterine myometrial relaxation produced by them. In clinical doses (around the value of 1 MAC) they produce the maximum vasodilatation effect and uterine relaxation than the sytemic reduction of BP. Therefore, in these doses the UPBF does not decrease, rather increases till systemic BP falls to a greater extent. N_2O has negligible effect on UPBF. Regional anaesthesia (central neuroaxial block) does not directly affect the UPBF, provided the systemic BP is maintained. In severe hypotension, the UPBF is proportional to the fall of BP. In pre-eclampsia, the RA has very beneficial effect on UPBF and this is due to reduction of the uterine vasoconstriction by cutting down the sympathetic supply to it. But again this beneficial effect on UPBF is maintained upto a certain level of hypotension, below which the uterine and placental circulation is severly compromised. The use of recommended dose of epinephrine with LA agent during CNB is not contraindicated for obstetric analgesia and anaesthesia. Becasue the intravascular uptake of epinephrine from epidural space is so small that it only produces the β-adrenergic effects and dilate the uterine vessels, instead of vasoconstriction.

Transfer of Anaesthetic Agents Through Placenta

Most of the drugs used during anaesthesia can cross the placental barrier except the muscle relaxants. Because they are highly ionised and placental transfer of them is impaired causing minimum or no effect on foetus. The transfer of any anaesthetic agent through placenta depends on multiple factors such as the route of administration, the total dose, the method of administration (single shot large, multiple small boluses, continuous infusion, etc), and the timing of administration. But the effect of anaesthetic agent on foetus depends on the above mentioned factors (placental transfer) plus the maturity of foetal organs (liver and brain). For example, giving a drug many hours before delivery is least likely to produce any foetal effect after delivery. Similarly, a single IV bolus dose of any anaesthetic agent during uterine contraction and just prior to delivery also produce minimum concentration of it in foetus. Foetal effects of any anaesthetic agent is evaluated by observing the foetal heart rate variability, intrapartum acid-base status and by Apgar score and neurobehavioral examination during postpartum period.

All the opiates cross the placenta barrier, but the newborns are most sensitive to morphine regarding the respiratory depression effect of it than any other opiates. The maximum respiratory depressions effect of meperidine which occurs 1 to 4 hours after administration is higher than other opiates, but still less than morphine. Fentanyl readily crosses the placental barrier, but produce minimal respiratory depression effects if the dose of it is kept below 1µg/Kg. Remifentanil also crosses the placental barrier readily like fentanyl, but foetal blood concentration is generally half than that of the mother. Butrophanol and nalbuphine produce less respiratory depression than morphine and pethidine (meperidine), but have significant depressed neurobehavioral effect on focus.

The commonly used inducing agents in GA such as thiopentone, propofol, ketamine and benzodiazepines, etc, readily cross the placental barrier. But, except benzodiazepines, other agents in the usual induction dose do not cause any significant effect on foetus due to their characteristic distribution, metabolism, and placental uptake. Only benzodiazepines in the induction dose have profound effect on foetus regarding the respiratory depression and neurobehavioral effect. All the inhalational agents freely cross the placenta. But, they produce minimal foetal depression, if the dose is kept below the value of 1 MAC and is used for less than 10 minutes before delivery.

LA agents also freely cross the placenta barrier, but it depends on three factors such as: pK value of this agent, maternal and foetal pH, and the degree of protein binding of LA agents. Bupivacaine and ropivacaine are more protein bound than lignocaine. So, these LA agents diffuse poorly across the placenta and causes lower foetal blood level than lignocaine. Foetal acidosis causes higher concentration of LA agent in the foetal blood. This is because H^+ binds with the nonionized form of LA agents and causes trapping of it on the foetal side of placenta. Other drugs which are used during anaesthesia such as ranitidine, metoclopramide, atropine, antihistamine, phenothiazines, β-blocker, vasodilator, etc; can cross the placenta. But, glycopyrrolate can not, because it is an ionised quaternary ammonium structure.

EFFECTS OF ANAESTHETIC AGENTS ON UTERINE ACTIVITY

Intravenous anaesthetic agents such as thiopentone, propofol, benzodiazepines have no effect on uterine contraction. Opiates minimally decrease the uterine muscular activity. Ketamine in the dose of > 2 mg/Kg through IV increases the uterine contraction. Below this dose, it has also little effect on uterine contraction. All the volatile anaesthetic agents such as halothane, isoflurane, sevoflurane, desflurane, etc. decreases the uterine muscular activity equally at equipment doses, and causes dose dependent myometrial relaxation. Thus, they produce uterine atony and increases the postpartum blood loss. But, at concentration < 0.7 MAC (low doses) they do not interfere the action of oxytocin on myometrium. N_2O has no effect

on uterine activity. Uterine myometrium also contains both the α and β receptors which respectively produces the muscular contraction and relaxation. Therefore, the α-adrenergic agonistic agents such as phenylephrine, mephentermine, ephedrine, etc. augments the uterine contraction. But this effect is found only in high doses. Whereas, the β-adrenergic agonistic agents such as salbutamol, retordrine, etc; produce the uterine relaxation and is used to treat the premature labour.

Regional anaesthesia (RA) has little effect on uterine contraction. Therefore, it does not affect the course of labour. Regional analgesia using the combination of low dose of local anaesthetic agents such as bupivacaine 0.125% and low dose of opiates such as fentanyl 5 µg/ml does not prolong the labour and does not increase the chances of instrumental delivery or CS. But when the higher concentration of LA agents are used, it prolongs the labour by only affecting the second stage. This is indirect effect and is due to the loss of Ferguson reflex which produce motor weakness and impair the expulsive or bear down effort. This is not the direct effect of RA on the course of labour. Epinephrine has both the α and β action. But in low concentration, β action predominates over α action. Therefore, epinephrine containing LA agent used for obstetric RA may produce prolongation of labour as it is used in very low concentration producing only β effect. But clinically prolongation of labour is generally not observed as it is used in very very low concentration, e.g. 1:200,000 to 1:400,000 dilution.

CONSEQUENCES OF PAIN IN LABOUR

Pain is a noxious and unpleasant stimulus. It produces great fear and anxiety. Which again aggravate the pain. Thus, a vicious cycle sets up. Pain during labour causes reduction of uterine blood flow, ↓FHR, ↓foetal oxygenation, foetal acidosis, etc. All these are mediated by the activation of sympatho-adrenal axis of mother. So, painful labour is associated with increased maternal plasma cortisol and catecholamine levels which are responsible for the reduction in uteroplacental blood flow. Thus, effective pain relief during labour reduces the plasma cortisol and catecholamine concentration with their bad effects. Pain relief also prevents the metabolic acidosis of mother by reducing the rate of rise of plasma lactate, pyruvate, and decreasing the maternal consumption of O_2 up to 15%.

Pain during labour also produces hyperventilation and hypocapnia of mother. This causes the reduction in uteroplacental blood flow and even tetany in some parturient patients. This respiratory alkalosis further impairs the fetomaternal gas exchange by shifting the oxy-Hb dissociation curve to the left. Thus, foetal PaO_2 may fall producing foetal acidosis (Fig. 35.1).

PAIN PATHWAYS IN LABOUR

Pain during the First Stage of Labour

Pain during the first stage of labour is due to the stretching, distortion, tearing, and possibly the ischaemia of uterine tissues. It is also due to the simultaneous dilatation of cervix with stretching of lower uterine segment. The intensity of pain during the first stage of labour increases progressively with the rising of the strength of contraction and stretching of the uterus and cervix. These painful stimuli are transmitted through A-delta and C affarent fibres accompanying the sympathetic pathway. It passes gradually through the pelvic and the inferior, middle, and superior hypogastric plexus → lumbar sympathetic chain → the white rami of T_{10} to L_1 spinal nerves → posterior root of these spinal nerves → T_{10} to L_1 segment of spinal cord. During the early part of the first stage of labour, only the nerve roots of

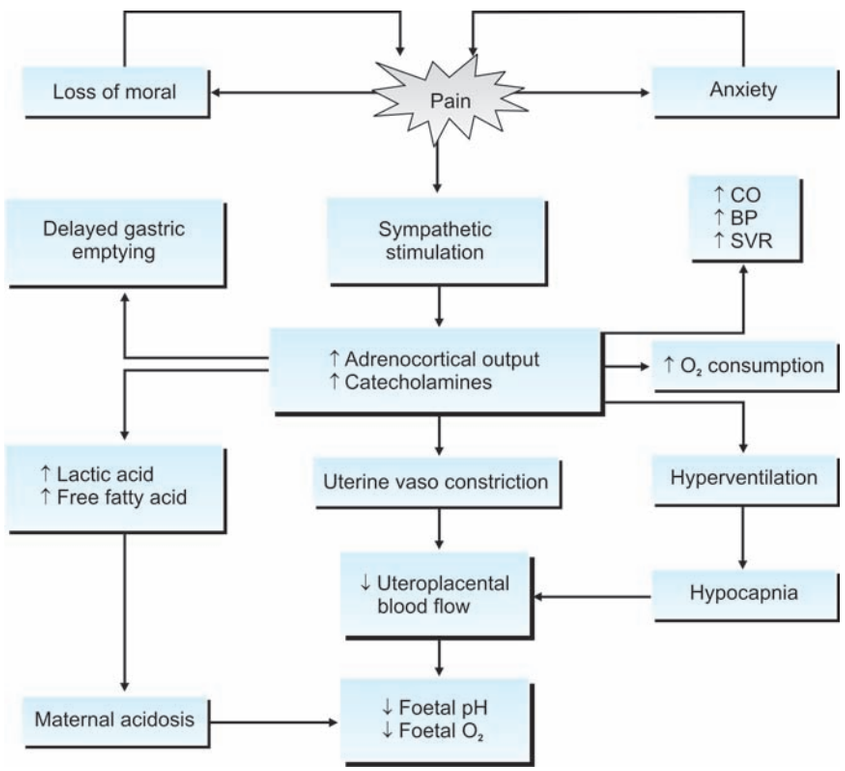


Fig. 35.1: Effect of pain on mother and foetus

T_{11} and T_{12} spinal segment are involved. But as the intensity of uterine contraction increases, then gradually the T_{10} and L_1 nerve roots with their corresponding spinal segments are recruited.

Backache is a frequent complain during the progress of labour. It may be caused by one or other of these two mechanisms which is explained below. Pain originating from the uterus or cervix may be referred to the cutaneous branches of the posterior divisions of T_{10} to L_1 spinal nerves which migrate caudally for an appreciable distance before they innervate the skin overlying the vertebral column. For example, the posterior cutaneous branches of T_{11} spinal nerve supply the skin overlying the L_3 and L_4 vertebrae. Pain due to pressure on the periuterine tissues by foetal head which is found in association with the foetal malpresentation or unusual shape of sacrum is referred to the L_5 and S_1 segment of spinal cord which is felt as very low back pain.

Pain During the Second Stage of Labour

In the second stage of labour, pain is mainly caused by the distension and stretching of the pelvic structure and perineum which is due to the descent of foetal presenting part. This is also added to the pain of uterine contraction of the first stage of labour. Once the cervical dilatation is complete, the pain induced by uterine contraction may become less intense. The pain initiated by uterine contraction is continued to be referred to the T_{10} to L_1 dermatones. But the pain produced by stretching and pressure exerted on the intrapelvic structure including the pelvic floor (levator ani), bladder, urethra, rectum is referred to the sacral segment. With the above manifestation, the direct pressure on the root of the lumbosacral plexus by the foetal presenting part is also manifested as a pain which is felt low on the back or on the inner side of thighs. The pain produced by the stretching of perineum is transmitted through the pudendal nerve ($S_{2,3,4}$), posterior cutaneous nerve of thigh ($S_{2,3}$), genitofemoral nerve ($L_{1,2}$), and the illioinguinal nerve (L_1).

During the first stage of labour, an epidural block in which the level of anaesthesia is limited only to the $T_{11,12}$ segment of spinal cord (in very early stage) and later is extended to the T_{10} and L_1 spinal segment is sufficient to provide excellent pain relief. While the neural blockade of sacral segment is not necessary for the relief of pain in the first stage of labour. Premature blockade of sacral segment in the early stage of labour can result in the loss of stimulating effect of Ferguson's reflex which initiates more contraction and helps in the rotation of foetal presenting part. Thus, premature blockade of sacral segment cause more incidence of instrumental delivery and CS.

ANALGESIA FOR VAGINAL DELIVERY

Pain during vaginal delivery can be alleviated by different processes. These are:

i. Psychological and non pharmacological technique,
ii. Pharmacological technique,
iii. Nerve block technique – central or peripheral (Table 35.4).

Psychological and Non-pharmacological Technique

In this technique, exhaustive counselling of mother is done from 6 weeks before delivery, regarding the normal anatomy of reproductive system, physiology of pregnancy, physiology of normal delivery and postpartum advice, etc. By this psychological counselling, pain during the process of labour and vaginal delivery can be reduced by recognising or preconditioning the cerebral cortical activity or thought of patients. Usually fear of unknown or previous unpleasant experience aggravates the labour pain. Thus removal of this fear by proper counselling helps to reduce the pain. The patient concentrates her mind away from the delivery process and tries to relax herself. This distraction of mind from the process of normal delivery inhibits the incoming painful stimulus from uterus and thus subsequently reduces the pain sensation, associated with uterine contraction.

Some common psychological techniques used to reduce the labour pain are: Lamaze, Duola, Dick Read, Le Boyer and Bradley etc. Among these, Lamaze technique for relief of labour pain is the most popular. In this technique, patient is trained to take deep breath at the begining of each uterine contraction. This is followed by

Table 35.4: Pain pathway in labour

Site of origin	*Pathway*	*Site of pain*
Uterus and cervix	Affarent fibres which accompany the sympathetic pathway to T_{10} - L_1 spinal segments	Whole abdomen and groin
	Dorsal rami of T_{10}-L_1 spinal nerves. This is referred to cutaneous branches of posterior divisions	Mid back
Pressure by presenting part of foetus on periuterine tissue	Lumbosacral plexus	Low back, thigh
Bladder, urethra, rectum	Pudendal nerve ($S_{2,3,4}$)	Referred to perineum and sacrum
Vagina	Pudendal nerve ($S_{2,3,4}$)	Perineum
Perineum	Pudendal nerve ($S_{2,3,4}$) Genitofemoral nerve ($L_{1,2}$) Ileoinguinal nerve (L_1) Post cutaneous nerve of thigh ($S_{2,3}$)	Perineum

gentle exhalation in a shallow pattern until the uterine contraction ends. Other psychological techniques used to reduce the labour pain are: hypnosis, mesmerism, acupuncture, TENS (transcutaneous electrical nerve stimulation) etc. But, success of all these techniques varies from patient to patient and frequently needs combination of some of these techniques or addition of some newforms of pain relieving method.

Pharmacological Technique

Nearly all opioids and non opioid analgesics and sedation can be used to alleviate the labour pain. But, all these agents relieve the labour pain to different extent and have their own advantages and disadvantages. They all cross the placenta and affect foetus.

Opioids

Opioids are the most commonly used agents for the relief of labour pain. But, foetal depression limits the use of these agents at the early stage of labour. They are also used where RA techniques are not possible and not used. Among the opioids the most commonly used agents are: meperidine, morphine, fentanyl, butorphanol and nalbuphine etc. and they produce more or less comparable pain relief. But the choice of drugs for clinical use depends on their potential side effects, desired onset of action, duration of action and the familiarity of these agents by the anaesthetist. The main drawbacks of the use of opioids for the relief of labour pain are: foetal respiratory depression, foetal respiratory acidosis, abnormal neurobehavioural pattern of foetus, loss of beat to beat variability of foetal HR, decreased foetal movement, ↓Apgar score, ↓SPO_2 of foetus, maternal respiratory depression, maternal nausea and vomiting, maternal delayed gastric empting, etc. The loss of beat to beat variability of foetal heart rate and decreased foetal movement by opioids make the intrauterine monitoring of foetal well being difficult.

Though, morphine is the gold standard of all the opioid analgesics, still it is not commonly used in the practice of obstetric analgesia. This is because it appears to cause more respiratory depression of the foetus than any other opioids in equipotent analgesic doses. The other drawbacks of morphine are delayed onset of action and prolonged duration of action. The peak effect of it occurs 20 to 30 minutes after IV administration and 1 to 2 hour after IM injection. The duration of action of morphine is 4 to 6 hour. The most commonly used opioids in the practice of obstetric analgesia is meperidine. The peak effect of it occurs 5 to 10 minutes after IV and 30 to 60 minutes after IM administration. The usual IV doses of meperidine for obstetric analgesia is 25 to 50 mg and IM dose is 50 to 100 mg. The duration of action of meperidine of this dose is 2 to 4 hour. Therefore, the meperidine is given during early stage of labour when delivery is not expected at least within 4 hours after its administration. The fentanyl is also used to relief labour pain through IV or IM route and the usual dose is 25 to 50 µg and 50 to 100 µg respectively. After IV administration the peak effect of fentanyl occurs within 2 to 4 minutes after its administration and duration of action lasts for 40 to 60 minutes. It is found that the above mentioned doses of fentanyl does not cause: neonatal respiratory depression, ↓Apgar score, adverse effects on neonatal neurobehavioural score and adverse effect on umbilical cord blood gas analysis. So, it is concluded that the fentanyl may be used as analgesics to reduce the labour pain, as an alternative to either RA or GA. Another two commonly used opioids for obstetric analgesia are butorphanol and nalbuphine. They are synthetic agonist and antagonist opioids in nature. The analgesic dose of butorphanol is 2 mg and nalbuphine is 10 mg which is equivalent to 10 mg of morphine, 100 mg meperidine and 100 µg fentanyl in respect to the respiratory depression. But the advantage of these two drugs is that increasing the doses of them does not produce more respiratory depression with cumulative action (ceiling effect). On the other hand, large doses of these two compounds may produce excessive sedation, dizziness, somnolence, etc.

Benzodiazepines

Benzodiazepines are also used in the practice of obstetric analgesia. The indications are: to reduce anxiety, as anticonvulsant in eclampsia, as adjunct to opioids and as premedicant for CS. Among all the BDZs, the commonly used agents in obstetric analgesia and anaesthesia are: diazepam, lorazepam, midazolam etc. and they all cross the placental barrier readily. Within 1 minute after IV administration, the maternal and foetal plasma concentration of all these BDZ approximately becomes equal. The use of BDZs in obstetric practice has also many advantages and disadvantages like opioids. The advantages of the use of benzodiazepines are the reduction of maternal anxiety and subsequently its consequences such as ↑catecholamines, ↓uteroplacental circulation due to constriction of uterine artery, foetal acidosis, etc. It also reduces the requirements of opioids (it is used to alleviate the labour pain) and cuts down its complication. But the disadvantages of the use of BDZ are mainly on foetus. These are foetal respiratory depression, hypotonia, lethergy, hypothermia, depressed feeding, ↓SPO_2, etc. These adverse effects are found when the unusual large nonobstetric doses of BDZs are used for obstetrics analgesia and anaesthesia. But, small doses of BDZs have minimal effects on foetus and neonats, though beat to beat variability is markedly decreased even in small doses.

Lorazepam does not offer any extra advantages over diazepam in obstetric analgesia and anaesthesia practice except that only less than 1% of it is transformed to other pharmacologically active metabolites. If the total maternal dose of diazepam during labour exceeds than 20 to 25 mg

then the drug itself and its pharmacologically active metabolites persist above the therapeutic level for about atleast 1 week. The usual nonobstetric doses of lorazepam (1 to 2 mg) is associated with adverse effects on neonates. The advantage of midazolam over the other BDZ is that it is water soluble and rapid onset and short duration of action.

Another usual drawback of the use of BDZ in obstetric practice is the anterograde amnesia of mother produced by it. But all the mothers desire to recall the birth of their baby and it is highly pleasure to them. So, amnesia produced by BDZ is an unwanted effect in obstetric practice, though it is highly desirable in other surgical patients.

Ketamine

Ketamine is also used in obstetric practice to reduce the labour pain, because it has strong analgesic effect, even though in very low doses (0.1 to 0.25 mg/Kg). But in higher doses (1 mg/Kg), it causes induction of anaesthesia. In very low doses it produces only analgesia without any effect of sedation or unconciousness. In both the above mentioned doses, ketamine does not affect the uterine blood flow, foetal Apgar score and uterine muscle tone. But in higher doses than 2 mg/Kg, ketamine can produce hypertonic uterine contraction. The main drawback of use of ketamine in obstetric practice is its unpleasant effect of hallucination which some obstetricians do not like. But this hallucination is usually not found in very low doses which is used in obstetric analgesia, but not in anaesthesia.

Phenothiazine derivatives and hydroxyzine

Among the phenothiazine derivatives, promethazine is the most commonly used agent in the practise of obstetric analgesia and anaesthesia. Other phenothiazine derivatives which are also used in obstetric analgesia and anaesthesia practice are: promazine, chlorpromazine, prochlorperazine etc. But, they are not popular because they possess high α-adrenergic blocking activity and frequently cause hypotension. Hydroxyzine is not a phenothiazine derivative. But it has similar property of ataraxia (a state of detached serenity without depression of mental faculties or impairment of consciousness) like promethazine. So, it is frequently used in combination with promethazine and meperidine. However, both these drugs reduce the requirement of opioids, anxiety, nausea, and vomiting of mother. Also they do not appreciably produce neonatal depression. These are the advantages of promethazine and hydroxyzine. The principal disadvantage of hydroxyzine is that IV preparation of it is not available. So it is only administered through IM route causing delayed onset and prolonged action. The usual dose of promethazine and hydroxyzine used for obstetric analgesia and anaesthesia are 25 to 50 mg and 50 to 100 mg IM respectively.

Barbiturates

The short and medium acting barbiturates such as pentobarbital (nembutal), secobarbital (seconal), amobarbital (amytal), etc, are not used now a days in obstetric practice to reduce anxiety and labour pain, because they have prolonged effect of depression on neonates, even with smaller doses that does not cause clinical maternal depression. NSAID such as ketorolac is not recommended to relief the labour pain, because it suppresses the uterine contractions and promotes the premature closure of ductus arteriosus.

Inhaled analgesic

The inhalation of different volatile anaesthetic agents is also a popular method for alleviation of labour pain. Through this inhalation route different inhaled anaesthetic agents are administered alone in subanaesthetic concentration, only to reduce labour pain but without any loss of consciousness or as supplementation to regional or local anaesthesia. This form of relief of labour pain should not be confused with inhalational anaesthesia where patient losses his consciousness with the loss of protective laryngeal reflexes. With this technique patient remains conscious and co-operative with the presence of full laryngeal reflexes, while she enjoys the analgesic effect of inhalational agent. Usually the volatile pharmacological agent is administered either by patient herself or by anaesthetist via a face mask in intermittent or continuous way. However, the main disadvantage of this method is that as the inhalational anaesthetic agents are used in subanaesthetic concentration, so this method does not always provide adequate amount of pain relief. Hence, it is usually used as an adjunct to other methods of pain relief.

The commonly used inhaled anaesthetic agents are: N_2O and O_2 mixture (50:50 N_2O-O_2 mixture called entonox), desflurane (0.2%) isoflurane (0.25%), enflurane (0.2%), etc. Entonox has been used for many years to relief the labour pain as a sole analgesic agent or as an adjunct to other systemic or regional analgesic technique. But, truly speaking, and is unfortunate to say that the analgesia provided by 50% N_2O alone is not reliable. The maximum analgesic effect of N_2O occurs within 30 to 60 seconds after the starting of its inhalation. It is, therefore, advised that patients should start to inhale the gas at the early onset of uterine contraction and discontinue it after the peak of contraction, if intermittent method is applied. During the use of entonox the lack of proper use of scavenging system put the labour room staff at the unnecessary risk of exposure to the excessive level of N_2O over a prolonged period.

The subanaesthetic concentration of other volatile anaesthetic agents such as desflurane, isoflurane, enflurane etc. has also successfully been used to provide labour analgesia, and their effectiveness also appears to be comparable to that of

N_2O. The above mentioned dose of these volatile anaesthetic agents are not fixed. It depends on the response of patient. If the patient becomes drowsy, non-cooperative, confused and gradually progresses to unconsciousness then the inspired concentration of volatile anaesthetic agents should be lowered quickly. The major risk of this method of obstetric analgesia and anaesthesia is accidental anaesthetic overdose producing unconsciousness. So, a trained person must remain in continuous verbal contact with the patient and monitor the consciousness.

Nerve Block

Two types of nerve block are used to relief the labour pain for vaginal delivery. These are: peripheral nerve block and central neuraxial block.

Peripheral nerve block

Among the peripheral nerve block for obstetric analgesia and anaesthesia the pudendal nerve block is most commonly used. This is often combined with local infiltration of subcutaneous tissue of perineum by local anaesthetic agents, if other forms of anaesthesia are not applied or is inadequate. Thus, it provides complete perineal anaesthesia only for the 2nd stage of labour. The pudendal nerve is derived from $S_{2\text{-}4}$ nerve roots and provides sensory innervation to the valva, lower part of the vagina and perineum. It also provides motor innervation to the perineal muscles. The pudendal nerve can easily be blocked through transvaginal route by depositing LA agents behind the sacrospinous ligament. This nerve block provides adequate local anaesthesia only for the 2nd stage of vaginal delivery, outlet forceps manipulation, episiotomy and its repair etc. But it does not provide adequate analgesia for mid forceps manipulation, repair of upper vaginal laceration, exploration of uterine cavity etc. The pudendal nerve block is associated with low complication, but high incidence of failure rate.

Another technique of peripheral nerve block for obstetric analgesia and anaesthesia is the paracervical block. In this technique, the paracervical ganglion (or FranKenhausen's ganglion) which transmits all the visceral sensory nerve fibres from uterus, cervix and upper vagina is blocked. So, this technique provides pain relief for the later part of the first stage of labour and the first part of the 2nd stage of labour. The paracervical ganglion is situated lateral and posterior to the junction of the cervix and the body of the uterus. Hence, for this technique LA agent is deposited through the vaginal route into the fornix of vagina, lateral to the cervix. However this block does not affect the somatosensory fibres from lower vagina, perineum and valva. Therefore, it does not afford any pain relief during the second stage of labour. On the other hand, it does not adversely affect the dilatation of cervix and the progress of labour.

Recently, this paracervical plexus block is not used for obstetric analgesia and anaesthesia. This is because it is associated with high rate of foetal bradycardia, foetal acidosis, decreased foetal oxygen saturation and increased likelihood of foetal depression. However, the probable explanation of these complications in paracervical block is the close proximity of injection site to the uterine artery which result in uterine arterial vasoconstriction, uteroplacental insufficiency and high levels of LA agent in the foetal circulation. The foetal bradycardia usually develops within 5 to 10 minutes after the injection and it lasts for 10 to 30 minutes.

Central neuraxial block (CNB)

Recently, the CNB is the most commonly used technique for obstetric analgesia and anaesthesia. Compared to the pharmacological method and GA, this technique of obstetric analgesia and anaesthesia is less likely to produce drug induced depression of foetus and aspiration pneumonitis of mother. It also provides relief in labour pain, while allow the patient to remain awake and to participate actively in labour and delivery. CNB is associated with lower level of catecholamines in maternal circulation which is beneficial to the foetus. The most common forms of CNB for obstetric analgesia and anaesthesia are lumbar epidural, caudal epidural, subarachnoid, and different combination of these techniques, such as combined spinal and epidural by LA agents and/or opioids with their different concentration. Though, LA agents and opioids alone can provide adequate labour analgesia, still the combination of these two agents at different concentration is most popular. This is because the synergistic effect due to the combination of these two types of agents decrease the individual dose requirement with few or nil maternal and foetal side effects if these agents are used alone.

Lumbar Epidural Anaesthesia — Analgesia for Vaginal Delivery

This is the most commonly used regional anaesthesia-analgesia technique to relief pain in all the stages of labour. It can be provided by a single shot or by continuous technique using catheter. Continuous epidural anaesthesia-analgesia by catheter provides the greater flexibility than the single shot technique. For obstetric analgesia and anaesthesia epidural catheter is placed at lumbar region and analgesia is achieved when the patient wants it during any stage of labour. But, it is often advantages if the catheter is placed in early stage of labour when the patient is comfortable and can be positioned easily. Moreover, if emergency LUCS is needed at any time during the progress of labour, then it can be converted into epidural anaesthesia and again this can be exended for postoperative analgesia. A more conservative approach for the commencement of epidural labour analgesia (recommended by some obstetrician) is to wait till the labour is well established, which is characterised by: regular uterine contraction at 3 to 4 minutes interval and lasting for 1 minute,

minimum cervical dilatation of 3 to 4 cm, no foetal distress and engagement of foetal presenting parts.

For lumbar obstetric epidural anaesthesia-analgesia, the optimal interspinous space is L_{2-3} or L_{3-4} which is used by maximum anaesthetist. This is because this space helps to achieve the level of analgesia with minimum amount of drug extending between T_{10} to S_5 dermatomes. Any position of patient, i.e. lying or sitting can be used. But sitting position is more helpful for identifying the midline in obese patient. Sitting position also helps for better sacral spread of analgesia, if lumbar epidural is given at second stage of labour. One disadvantage of sitting position for epidural block is that as in this position there is more CSF pressure, so there is increased incidence of unintentional dural puncture. Most anaesthetists prefer midline approach, while some favour the paramedian approach for epidural placement of catheter. The incidence of wet tap during lumbar epidural procedure varies between 0.2% to 10%, depending on the skill of anaesthetist. If unintentional wet taps occur, then the clinician has two choices: (i) he can try again at the another higher or lower interspinal space, or (ii) he can put the epidural catheter in the subarachnoid space and convert the continuous epidural to continuous spinal anaesthesia-analgesia. For detection of epidural space by the loss of resistance technique, usually air or normal saline is used. But the amount of air injected in the epidural space should be as little as possible, probably less than 3 to 5 ml. This is because injection of large amount of air in the epidural space is associated with headache, and unilateral or patchy anaesthesia-analgesia.

In obstetric epidural anaesthesia-analgesia, the commonly used drugs to relief the labour pain are local anaesthetic agents in different concentration with or without combination of opioids. These two agents such as LA agents and opioids have synergistic effect on each other and have separate sites of action. Opioids act on the opiate receptors situated at the dorsal horn cells of the spinal cord, while LA agents act directly on the neuronal axons of the nerve roots. This synergistic effect helps to reduce the concentration or doses of these two agents. Therefore, the incidence of side effects of both the LA agents and opioids are reduced. For example, hypotension due to chemical sympathectomy and motor block due to the block of conduction of motor nerve fibres which are common adverse effects of LA agents in higher concentration in epidural space are absent in lower concentration of there agents. Therefore, the patient can help from herself in 2nd stage of labour by bearing down and accelerating the normal vaginal delivery. In some low concentration of bupivacaine such as 0.062 to 0.125%, patients even can walk during the first stage of labour because in this lower concentration bupivacaine only block the sensory fibres, sparing the motor. So, this is called the 'walking or mobile epidural'.

Similarly the nausea, vomiting and respiratory depression which are the common side effects of opioids are also absent in low doses of opioid in epidural space. When opioid is omitted then the higher concentration of LA agent such as bupivacaine in 0.25 to 0.5% or ropivacaine in 0.2% is needed. This high concentration of LA agent reduces the normal pelvic muscle tone by blocking the motor nerve which normally help in rotation and engagement of foetal presenting parts and thus impair normal vaginal delivery. This high concentration of LA agent abdominal muscles and will impair the mother's ability to bear down as the labour progress.

Among the LA agents, bupivaciane, levobupivaciane and ropivacaine are the drug of choice for obstetrc analgesia by most of the anaesthetist. Bupivaciane is choiced for obstetric analgesia and anaesthesia because it produces optimal clinical effect in very low concentration, long duration of action, apparent lack of tachyphylaxis and high protein bound causing less placental transfer. But, the main disadvantage of bupivacaine is its cardiotoxicity. Bupivacaine is also effective for only sensory block but without any motor block in concentration as low as 0.125% or 0.0625% when it is combined with opioids for early labour. But some higher concentration of bupivacaine such as 0.125% with opioid or 0.25% alone without opioid are needed in later stages of labour. The concentration of 0.5% bupivacaine is only reserved for use during CS which causes both the sensory and motor block producing obstetric anaesthesia. Ropivacaine is a newer amide local anaesthetic agent with near similar in structure and pharmacodynamics to bupivacaine. It is the first levo isomer (levo isomer of bupivacaine is levobupivacaine) LA agent to be marketed. It is less soluble than bupivacaine. Therefore is less potent. Cardiotoxicity of ropivacaine appears to be intermediate in position between those of lignocaine and bupivacaine. Unlike bupivacaine, progesterone does not appear to enhance the cardiotoxicity of ropivacaine. Clinically only for obstetric analgesia to alleviate labour pain it is used in the concentration of 0.2%. It is now thought that the reduced toxicity and reduced motor block produced by ropivacaine is due to its low potency.

Levobupivacaine is now used to provide the epidural labour analgesia. It is the levo isomer of bupivacaine. The normally marketed bupivacaine contains the mixture of R-enantiomer (racemic bupivacaine) and S-enantiomer (levobupivacaine). It is confirmed that levobupivacaine is long acting and possess more safety profile than the recemic mixture of bupivacaine. The lethal dose of levobupivacaine is 1.5 to 2 times higher than that of its racemic mixture i.e. bupivacaine. The usual concentration of levobupivcaine used in clinical practice is 0.25 to 0.5%.

The addition of epinephrine to the LA agent during epidural anaesthesia-analgesia to relief labour pain is a controversial topic. It is known to all that epinephrine reduces

the systemic absorption of LA agent and subsequently its toxicity. Therefore, it can increase the total dose of LA agent without increasing without toxicity, provides longer duration of action and intensify the sensory and motor block. But, all these advantages of epinephrine by adding to LA agent is unnecessary during epidural analgesia by catheter for vaginal delivery. This is because small amount of LA drug in the form of low concentration is used for epidural analgesia to relief labour pain in vaginal delivery as motor block is not needed and prolonged or indefinite period of action of LA agent is obtained by catheter without adding epinephrine. Only the advantages of adding epinephrine to the LA agent for epidural anaesthesia-analgesia to relief labour pain is acts as a marker in test dose during testing of inadvertment placement of catheter into blood vessel. The other disadvantage of epinephrine is its β-mimetic action which decreases the uterine contraction and unnecessarily prolongs the duration of labour. On the contrary, many anaesthetists prefer epinephrine in the concentration of 1:200,000 to 1:400,000 with LA agents for epidural anaesthesia-analgesia during CS where large amount of drug in the form of higher concentration are used to obtain profound both motor and sensory block.

Like LA agents, opioids are also not used alone clinically for epidural labour analgesia, because opioids alone frequently does not provide satisfactory and complete result. On the other hand, high doses of opioids are also needed when used alone for obstetric analgesia and this high doses have many adverse effects such as maternal and foetal respiratory depression, nausea and vomiting of mother, loss of beat to beat foetal heart rate variability, etc. So, the combination of LA agent in low concentration and opioids in low dose has now become very popular for obstetric analgesia and anaesthesia. Among the opioids the most commonly used agents are fentanyl and sufentanil in the doses of 25 to 50 µg and 10 to 20 µg respectively. The most significant advantage of this combination of LA agent and opioid in low doses is the striking lack of motor blockade which allow a mother to experience a pain free, unparalysed, pleasant vaginal delivery. Till now the maximal total dose of fentanyl and sufentanil when used continuously by catheter through epidural route is not clear. But some believe that the maximum dose of sufentanil in continuous epidural should not exceed beyond 30 to 50 µg. For fentanyl this maximum dose may go upto 200 to 300 µg.

After successful placement of epidural catheter a preliminary test dose is mandatory. This test dose helps to diagnose, if there is any unintentional subarachnoid or intravascular placement of needle or catheter. For the test dose, 2 to 3 ml of local anaesthetic agent with 1:200,000 epinephrine as marker is used. This test dose should be given at the interval between two uterine contractions. This will help to reduce the false +ve sign of an intravascular injection of marker, (i.e. epinephrine) manifested by tachycardia which can also occur due to the painful uterine contraction if it is given during the period of contraction. This test dose will also help to diagnose the unintentional subarachnoid placement of needle or catheter by extensive block like spinal anaesthesia with this small amount of drug used in this test dose.

After 5 to 10 minutes of test dose, the principal mixture of LA agent and opioid can be administered by three methods. The first choice is administration of bolus 10 ml mixture of local anaesthetic agent and opioid which is given in two incremental doses (5 ml each) with an interval of 1 to 2 minutes between two injections. This initial mixture usually contains 0.0625 to 0.125% bupivacaine or 0.1 to 0.2% ropivacaine with 10 to 20 µg sufentanil or 50 to 100 µg fentanyl. This will achieve sensory block extending upwards upto T_{10} level of dermatomes if the catheter is placed through L_2-L_3 interspinous space in horizontal lying down position. After the first bolus dose patient should be monitored continuously by BP, heart rate, SPO_2 level, etc, for the first 30 to 40 minutes or until the patient becomes stable. This bolus dose can be repeated several times according to the need, till the total process of vaginal delivery is completed. Epinephrine in concentration of 1:400,000 to 1:800,000 can also be added with the LA solution to prolong analgesia with fewer additional doses.

The second choice is instead of repeated bolus injection continuous infusion of local anaesthetic agent and opioid mixture is employed at the rate of 10 to 15 ml/hour which may contain bupivacaine (0.0625 to 0.125%) or ropivacaine (0.1 to 0.2%) with fentanyl (1 to 2 µg/ml) or sufentanil (0.2 to 0.4 µg/ml). Later this dose is adjusted according to the patient's response and progress of labour.

The third choice is patient's control epidural analgesia (PCEA). In this method, the patient itself administered the mixture of drug (i.e. LA agent and opioid) through epidural catheter. There are different PCEA settings which can be changed by the patient himself according to the response. But a typical setting is 5 ml/hour as basal infusion rate and 5 ml as bolus at 10 to 20 minute lockout interval. Thus, within an hour 20 to 30 ml of 125% bupivacaine and 50 kg of fentanyl may be administered. The great advantage of PCEA is that the total drug requirement is less and patient's satisfaction is greater in this method. For the relief of pain during second stage of labour, the sensory block should be extended below upto $S_{2\text{-}4}$ level of dermatomes. For this, the drug should be administered in semirecumbent or sitting position of patient through epidural catheter which will reduce the total dose of LA agent.

Caudal Epidural Anaesthesia and Analgesia for Vaginal Delivery

Caudal epidural block is also administered to relief the pain during any stage of labour. But it is usually accomplished only when the labour is well established and is in

second stage. To relief the pain during first stage of labour, i.e. to extend the sensory block upto T_{10} level through caudal epidural route, large volume of LA agent is required. So, this epidural route is usually not used to relief the labour pain during first stage. It is performed on patient, positioned either prone or on their sides. For caudal epidural block coccyx is always used as landmark and then for next successful result the sacral cornu and the sacro-coccygeal ligament, covering the sacral hiatus is palpated. After successful placement of an epidural needle in sacral canal through sacral hiatus, rectal and vaginal examination is mandatory. This is because it will exclude the possibilities of accidental puncture of foetal presenting part by the needle and its subsequent sequelae. Through this epidural needle epidural catheter can also be passed into the sacral canal for continuous caudal block. A test dose of LA agent mixed with epinephrine is also mandatory to use through needle or catheter, since it is possbile to enter the needle or catheter in an epidural vessel or dural sac which ends at S_1 or S_2 vertebral level producing spinal anaesthesia. The volume of LA agent and opioid mixture to provide labour analgesia (not anaesthesia) through sacral route during the first stage of labour should extend upto the T_{10} level of dermatome. Therefore, the volume of drug is very high through sacral route which varies from 10 to 20 ml in first bolus dose. The subsequent doses of drug to maintain labour analgesia is also very high which is 15 ml for every sitting. Hence, to achieve the T_{10} level of block through sacral route with smaller volume of drugs, placing the patient in head down position is necessary.

The lumbar epidural route to relief labour pain is preferred to caudal route because:

i. The level of analgesia extending between T_{10} to L_1 dermatomes which is necessary during first stage of labour can be achieved easily through lumbar route and spare the block of sacral dermatomes which is not desired for the first stage of labour.
ii. Less amount of drug is required through lumbar route than caudal anaesthesia-analgesia during the whole delivery process through vagina.
iii. In lumbar epidural obstetric analgesia pelvic muscles retain their tones. This help in the rotation of foetal presenting part and normal vaginal delivery.
iv. Placement of lumbar epidural needle is technically more easier than caudal procedure, though in the previous technique there is more chance of dural puncture. On the contrary, the advantage of caudal epidural analgesia placed just before the vaginal delivery if it is not placed before over lumbar epidural block is that the onset of perineal analgesia and muscle relaxation is more quick in the previous one.

Subarachnoid Anaesthesia-Analgesia for Vaginal Delivery

The subarachnoid block is not so popular to relief the labour pain for vaginal delivery. But, it has some definite indications, advantages and disadvantages. It is particularly indicated in a very distress (from pain) parturient patient where placement of epidural catheter is very difficult or impossible. In such circumstances, single shot subarachnoid anaesthesia-analgesia produced by LA agent or opioids or their mixture is very useful for emergency instrumental vaginal delivery in patient who does not have epidural catheter before. But, the disadvantages of this technique is that it does not provide flexibility of an epidural catheter. The other problem of subarachnoid anaesthesia-analgesia to relief the labour pain is that it is very difficult to titrate the dose and concentration of LA agent or opioid by which we can get only the sensory block where motor block is not at all desirable for 1st and 2nd stage of labour or both motor and sensory block in 2nd and 3rd stage of labour where operative intervention is needed. The another advantage of single shot subarachnoid injection of LA agent or opioid or their mixture is that unlike epidural it provides effective and rapid onset of labour analgesia or anaesthesia. If only opioid is given in subarachnoid space to relief labour pain then it needs very small dose than the only opioid given in epidural space (though this dose is greater than when used with LA agent). This is because it directly acts on the dorsal horn cells of the spinal cord, without usual systemic effects of narcotics. Thus, the only intrathecal opioids have the potential advantage (unlike only narcotic through epidural space which needs larger doses and may have systemic effect) of providing effective and safe labour analgesia with no motor and sympathetic block. Hence, there is no hypotension, no adverse effects on uterine contraction and no maternal and foetal respiratory depression (due to small doses). So, this technique of using opioids alone in subarachnoid space to relief the labour pain is especially indicated in patients with cardiac disease who require adequate analgesia without motor block and hypotension. Thus it will prevent the potentially dangerous increase in HR and myocardial O_2 consumption associated with painful labour.

The continuous subarachnoid anaesthesia-analgesia to relief labour pain by using conventional epidural catheter in subarachnoid space (but not the microcatheter which is specially designed for continuous spinal anaesthesia) is also considered in cases of accidental (during attempt of continuous epidural) or deliberate dural puncture for high risk patients. But, surprisingly due to unknown reason the incidence of PDPH is very low in this continuous spinal labour analgesia and anaesthesia using conventional epidural needle and catheter, during accidental or deliberate dural puncture. In 1980, spinal micorcatheter was first introduced for continuous spinal anaesthesia. Then it quickly gained popularity because of the fast onset of block, convenience and low incidence of PDPH. But, it causes high incidence of cauda equina syndrome because of improper mixing of

local anaesthetic agent of relatively higher concentration with CSF than that of used for epidural space. This is again also due to less turbulance of flow produced during injection of drug within the intrathecal space through the microcatheter. Hence, there is controversy regarding the use of micro-catheter for continuous subarachnoid analgesia-anaesthesia.

To relief labour pain through subarachnoid route for vaginal delivery, the commonly used LA agents are hyperboric lignocaine (25 to 50 mg or 0.5 to 1 ml of 5% hyperboric lignocaine), bupivacaine (5 to 10 mg or 1 to 2 ml of 0.5% hyperboric bupivacaine) and tetracaine (4 to 5 mg). This dose provides analgesia or anaesthetia extending from T_{10} to S_5 dermatomes. But small doses of hyperboric LA agents such as lignocaine (15 to 20 mg), or bupivacaine (2 to 5 mg) or tetracaine (3 mg), administered in subarachnoid space in sitting position, provides only sacral anaesthesia and analgesia (saddle block) which is sometimes helpful only during 2nd stage of labour.

For the subarachnoid labour analgesia the commonly used opioids and their dose when used alone or with LA agents are morphine (0.25 mg), meperidine (10 to 20 mg), fentanyl (25 µg) and sufentanil (5 to 10 µg). When morphine is used alone without LA agent, the onset of analgesia is slow, taking 40 to 60 minutes and lasting for 24 hours. The side effects of intrathecal morphine are frequents and these include: dizziness, pruritus, nausea, vomiting, drowsiness, retention of urine, respiratory depression, etc. Pruritus produced by intralhecal morphine can be lessened by the use of IV naloxone in the dose of 0.4 to 0.8 mg, followed by infusion of it in the dose of 0.4 mg/hour. But this naloxone does not effect the analgesia caused by narcotics. Increasing the subarachnoid dose of morphine from 0.25 mg to 1 mg does not prolong the analgesia, instead increase the complications. Intrathecal 25 µg fentanyl alone also provides labour analgesia within 5 minutes and lasts for 1 to 2 hour. When it is used with LA agent the dose of fentanyl should not be reduced. Intrathecal 10 µg sufentanil alone also provides analgesia within 5 minutes and this action lasts for 3 hours. The onset of action of intrathecal 10 mg meperidine is 10 minutes and it lasts for approximately 2 to 4 hours. However, intrathecal opioids only do not provide adequate analgesia for episiotomy or for the use of forceps. Therefore, it needs supplemental anaesthesia by mixing opioids with LA agents. Addition of 0.2 mg epinephrine to intrathecal opioid does not prolong the duration of pain relief. But it decreases the severity and incidence of pruritus, while increases the incidence of nausea and vomiting.

Combined Spinal Epidural (CSE) Analgesia to Relief Labour Pain

This technique is also widely used now to provide the optimum and prolonged analgesia to relief labour pain and if necessary anaesthesia in obstetric practice. By this method we obtain the benefits and remove the disadvantages of each technique such as spinal and epidural. It offers rapid onset, and effective analgesia, minimum risk of toxicity of LA agent and opioids, and minimally impaired or no motor block. The rapid onset of action performed by the spinal part of CSE overcome the disadvantage of delayed onset of action by epidural part of it. This delayed onset of action by epidural part of CSE may sometimes be thought as incomplete or patchy analgesia, causing unnecessary increase in the dose of LA agent and subsequent motor blockade. Furthermore, this method make possible to prolong the duration of analgesia as necessary by the use of epidural catheter which can not be obtained from the spinal part of it. Patients found greater satisfaction with CSE than the only continuous epidural analgesia. This is perhaps because of rapid onset and greater feeling of self control by patient. In addition, if an operative delivery is necessary, then the same epidural catheter may be used to provide operative obstetric anaesthesia. The onset of action of analgesia in CES is almost immediate due to its spinal component. The duration of this spinal analgesia lasts for 2 to 3 hours, but depends on which opioid (alone) or which mixture of opioid and LA agent is used. The addition of isobaric bupivacaine to the opioids in the subarachnoid space during CSE produces a greater density of sensory blockade and minimum or nil motor blockade. Conventionally in subarachnoid space 25 µg fentanyl or 10 µg of sufentanil is used only for spinal analgesia. But 15 µg fentanyl or 5 µg sufentanil produces same effect when either of these agents is mixed with isobaric bupivacaine and is injected in the subarachnoid space. Another potential advantage of CSE technique for obstetric analgesia is that it may be associated with the significantly reduced duration of first stage of labour. On the other hand, the use of continuous epidural infusion by dilute LA agent such as 0.0625 to 0.125% bupivacaine plus opioid such as fentanyl 15 µg provides only sensory analgesia without any motor block which may permit many obstetric patients to ambulate during labour. Then it is termed as ‘walking epidural’. This is becaue any form of central neuraxial block or analgesia where there is no motor block is termed as like that. But, before ambulation every patient should be assessed carefully for the maternal and foetal well being and also the adequate motor function of mother.

GENERAL ANAESTHESIA FOR VAGINAL DELIVERY

To relief pain during labour GA is usually avoided for normal vaginal delivery. This is because of the increased risk of gastric aspiration in lungs in an unprepared patient and complete absence of mother’s co-operation which is a part and parcel of normal vaginal delivery. But, sometimes it is necessary in the following emergency situation such as acute foetal distress

requiring immediate expulsion of baby, instrumental vaginal delivery, manual removal of retained placenta, tetanic uterine contraction, replacement of inverted uterus, psychiatric patients who become sudden uncontrollable, etc; and where epidural catheter is not in place before. If epidural catheter is in place before for labour analgesia then obstetric regional anaesthesia is rapidly instituted through this catheter instead of analgesia.

If sudden decision of GA for vaginal delivery is taken, then previous important medical history of patient is quickly taken and a naso or orogastric tube is put into the stomach to aspirate the gastric contents, provided the patient is not properly prepared. After that the tube is removed. This is followed by quick preoxygenation of patient by 100% O_2 for 3 to 5 minutes or 4 full breaths, while monitors are applied by assistant. Once all possible monitors are applied and obstetrician is ready, then rapid sequence induction is instituted, applying cricoid pressure when patient becomes unconscious and reflexes are lost. For rapid induction the commonly used drugs are thiopentone (4 to 5 mg/Kg), propofol (1 to 2 mg/Kg) or ketamine (1 mg/Kg, used only if there is hypovolaemia or hypotension) which is followed by succinylcholine (1 to 1.5 mg/Kg). The fasiculation produced by succinylcholine is usually not prevented by the use of small dose of nondepolarising agent. Because most pregnant patient usually do not fasciculate and moreover this fasciculation does not appear to promote regurgitation as increased intragastric pressure caused by fasciculation is matched by similar increase in the tone of gastro-oesophageal sphincter by succinylcholine.

After a successful intubation with a 7 or 7.5 ET-tube, patient is ventilated by 100 O_2 and 1 to 2 MAC of any potent volatile anaesthetic agent. After the action of the succinylcholine is over if skeletal muscle relaxation is needed, then any short to intermediate acting nondepolarising muscle relaxing agent is used. Once foetus and placenta is delivered then N_2O and opioids are added or propofol infusion is started to avoid recall. Simultaneously, concentration of volatile anaesthetic agent is reduced to 0.5 MAC or discontiued and oxytocin infusion is started at the rate of 10 to 20 U/L in IV fluid. At the end of surgical procedure, the action of nondepolarising muscle relaxant is reversed by anticholinesterase and the patient is extubated, while reflexes are fully returned.

ANAESTHESIA FOR CAESAREAN SECTION (CS)

There are lots of medical and obstetric indications for CS which are done under RA or GA. But, the choice between these two type of anaesthesia is determined by multiple factors which include: indication for CS, the severity of urgency, skill of anaesthetist, patients preference, surgeon's preference, etc. However, now, RA is most frequently preferred than GA for ELUCS, because the later is mostly associated with increased maternal mortality and morbidity. But recently many studies has showed that morbidity and mortality in these two types of anaesthesia is equal. Death or severe maternal morbidity in RA is mainly due to severe hypotension, or epidural haematoma or sepsis of spinal cord. Death associated with GA is mainly due to airway problem, failed intubation, failed ventilation, aspiration pneumonitis, pulmonary oedema, etc. The advantages of GA over RA for caesarean section are: very reliable, rapid onset, better control of airway, better control of ventilation, less incidence of severe hypotension and better management of patient in the face of severe bleeding such as in placenta praevia, accidental haemorrhage, etc. Whereas the advantage of RA over GA are: minimal risk to pulmonary aspiration, less neonatal depression due to minimal or no exposure of foetus to potentially depressant general anaesthetic drugs, provide better option for postoperative analgesia, pleasant experience by mother during birth of her child.

After taking decision for RA in CS next question arises whether spinal or epidural. Except for few special indications for each technique, usually the decision between the spinal or epidural anaesthesia depends on the physician preference. Continuous epidural anaesthesia allows slow, better and prolonged control of sympathetic, sensory and motor block which is very helpful for severly ill patient, prolonged surgery and postoperative analgesia. Contrary, the spinal anaesthesia has more rapid onset, is easier to perform, produce more intense motor, sensory and sympathetic block and because of small dose of LA agent it does not have the potential for serious drug toxicity.

Now at the end of discussion, we can say that whatever may be the type of RA, patient should always be prepared for GA, because at any time during the process of applying RA it may be needed. Though, the principle disadvantage of GA is drug induced foetal depression, but the present technique of it limit the dose of IV inducing agent and reduces the foetal depression. Clinically, it is not significant in GA if delivery of foetus occurs within 10 minutes of induction of it. On the contrary, whatever may be the type of anaesthesia such as regional or general, if the baby is delivered within 3 minute of uterine incision then there is better Apgar score.

Regional Anaesthesia

The CS performed by RA (spinal or epidural) requires sensory block upto the level of T_7 dermatomes. Therefore, it blocks more than half of the sympathetic outflow (this is because sympathetic block is always two dermatomes above the sensory block) and causes high incidence of severe hypotension. So, patients waiting for RA during CS must receive 500 to 1000 ml of crystalloid IV fluid (usually Ringer's lactate) prior to central neural blockade. But, small volume of IV administration of colloid is more effective than

huge volume of crystalloid. Whatever may be, the prophylactic IV administration of fluid (crystalloid or colloid) does not consistently prevent hypotension induced by sympathectomy in RA. So, if hypotension still persists in spite of adequate preload, then 10 mg IV ephedrine should be used to maintain the systolic BP above 100 mm of Hg or MAP should not be reduced < 20% of previous one. Instead of epihedrine, 25 to 100 µg of IV phenylephrine can also be used safely. Some anaesthesiologist use the ephedrine or phenylephrine prophylactically to avoid the immediate precipitous fall of BP after regional block which sometimes can cause cardiac arrest. This prophylactic measure is more applicable in spinal anaesthesia than epidural. But, it may produce severe hypertension if the severity of proposed hypotension is not properly titrated with the doses of pressure rising agent and given at proper time which is matched with the peak level of hypotension. Therefore many anaesthetists do not like it. Slight 10 to 15° head down position of patient reduces the chances of hypotension by encouraging the venous drainage and increasing preload. But it does not increase the extension of sensory and sympathetic block by allowing more cranial flow of LA agent. During continuous epidural by using catheter for CS, if there is unintentional dural puncture, then it can be converted to continuous spinal anaesthesia by advancing the epidural catheter through this needle in subarachnoid space. It during first attempt of epidural anaesthesia there is unintentional dural puncture then another attempt through the spaces above or below the previous one is again tried.

The commonly used drug for spinal anaesthesia in CS are lignocaine (50 to 100 mg), bupivacaine (10 to 15 mg) or tetracaine (5 to 10 mg). But 0.1 mg epinephrine can also be used with this LA agent for spinal anaesthesia which enhances the quality of block and prolongs the duration of action of it. The addition of 25 µg fentanyl or 10 µg sufentanil or 0.2 mg morphine with the LA agent enhances the intensity of block and prolongs the duration of action without adversely affecting the neonatal outcome.

The commonly used drug for epidural anaesthesia in CS are: 15 to 20 ml of 2% lignocaine or 0.5% bupivacaine, or 3% chloroprocaine. Similar to spinal block addition of 50 to 100 µg of fentanyl or 10 to 20 µg of sufentanyl or 5 mg of morphine, etc, with the LA agents greatly enhances the intensity of block and prolongs the duration of action of it without adversely affecting the neonatal outcome. For epidural anaesthesia the 15 to 20 ml of the recommended initial volume of drug is not injected quickly as bolus. It is injected slowly in 5 ml incremental doses at 1 to 2 minute intervals. If due to any reasons sensory levels recede and pain develops, then LA agent is further added through catheter in 5 ml incremental doses to maintain a sensory block upto T_7 level. Patchy epidural blocks due to some unknown reasons is usually treated by small doses of IV ketamine, prior to deliver of baby. But after delivery of baby, it is managed by adequate doses of opioids, propofol; etc. However, if pain remains intolerable, inspite of these above mentioned measures, then it necessities GA with ET-intubation (Fig. 35.2).

General Anaesthesia

In recent decades the use of GA for CS has declined dramatically. But still it is used in some circumstances where RA is contraindicated such as when patient refuses to give consent, coagulopathy, local sepsis, systemic infection, etc; or anaesthesiologist has failed to provide RA due to some technical difficulties or there is no time to institute RA, for example, during life threatening severe maternal haemorrhage, life threatening foetal compromise etc. Several recent studies also have found that the maternal death rate associated with properly managed RA has dramatically declined, but not in GA. Therefore, the difference in rate of maternal mortality between RA and GA has increased to 16 times. There are no absolute contraindications for GA in CS like RA. But, there are certain conditions such as malignant hyperthermia, very difficult airway, etc; where modified general anaesthetic technique is required. The two principal problems associated with GA for CS are failed intubations and pulmonary aspiration of gastric contents.

Failed intubations

The most common causes of maternal death related to GA during CS are failed intubations with concomitant, failure to ventilate by mask or failure to recognise oesophageal intubation. On the otherhand, the common causes of failed intubation in obstetric patient compared with nonobstetric surgical patients are: weight gain, oedema of the airway, large breasts obstructing the manipulation of handle of laryngoscope, short neck (due to oedema); etc. Therefore, anticipation of difficult airway and subsequent difficult intubation may help to reduce the incidence of maternal hypoxaemia and death during GA. Hence, careful assessment of airway before CS under GA is very crucial and anticipation of difficult intubation may help to reduce this catastrophy. Among all the methods of evaluation of airway Mallampatti classification is the most useful predictors. It has been found that airway of Mallampatti class IV, protruding maxillary incisions, short neck, mandibular recession, etc; are associated with greatest risk for failed intubation. Hence, simple examination of oropharynx, neck, mandible, dentition, etc; often helps to predict which patient will produce problem or not. The patient which has normal airway before pregnancy, becomes problematic during this pregnancy. Again it has been demonstrated that labour is associated with changes in the maternal airway. So, all the patients must have a repeat airway assessment before induction of anaesthesia for CS, though the patient is examined initially. Last, it may be said that the experience of anaesthetist is the key factor for general anaesthesia related maternal mortality.

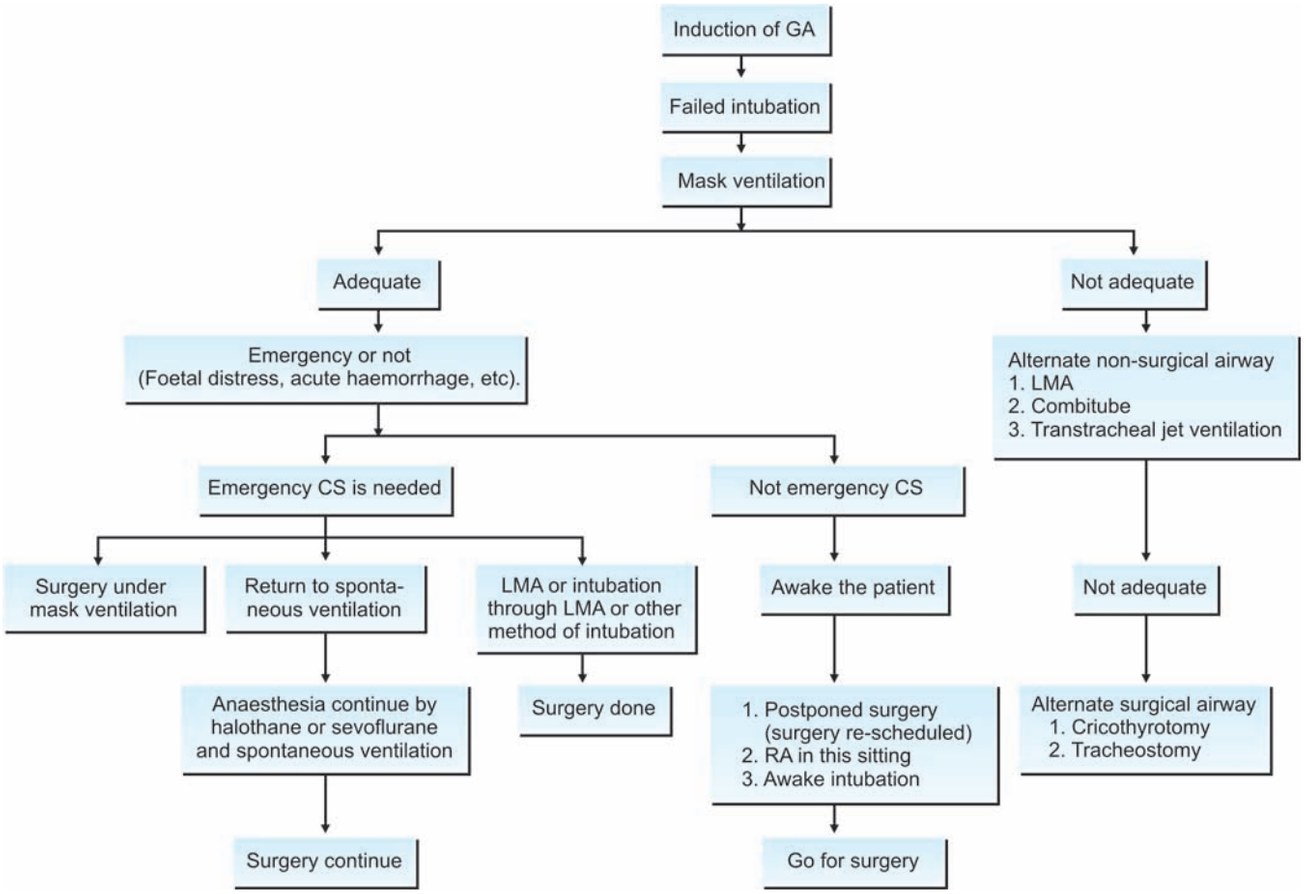


Fig. 35.2: Algorithm for difficult intubation in obstetric practice

Because, in one vast study in a big teaching hospital it is found that the most cases of failed intubation is occured when patients are cared by less experienced anaesthetist.

Anticipating difficult intubation, varieties of laryngoscope blades, different sizes of ET tube, stylettes, bougies, classic LMA, intubating LMA (fastrach), fibreoptic laryngoscope, combitube, kit for cricothyrotomy and tracheostomy etc. should be made ready. Proper positioning of the head and neck may facilitate tracheal intubation in difficult cases. These manipulations are: flexion of cervical spine, elevation of shoulder and extension of atlanto-occipital joint etc. When difficult intubation is anticipated, then anaesthesiologist must have a clear plan and obviously mother's life will get priority over foetus. After failed intubation if mask ventilation is possible, then different methods of intubation should be tried. Or in the absence of foetal distress patient can be awakened and later an awake intubation by infiltration of LA agents can be tried. If mask ventilation is not possible, then other methods of ventilation by using LMA, combitube, etc; are tried. But still if ventilation is not adequate then cricothyroitomy or tracheostomy or awakening the patient can be tried to save the mother's life.

Pulmonary aspiration of gastric contents

Another important cause of maternal death related to GA during CS is pulmonary aspiration of gastric contents. Therefore, increase of gastric pH and decrease of its volume in a labour patient is prime important for an anaesthetist. However both of these effects can be accomplished by the following methods. Generally, gastric pH can be raised by routine use of antacids prior to induction of anaesthesia. But use of antacids does not reduce the risk of pulmonary aspiration. Because though antacids increase gastric pH, but as most antacids contain suspension of particulate matter so they may produce severe pulmonary reaction if they are aspirated. So, instead of nonclear antacid, clear antacid such as 0.3 M sodium citrate is used. The advantage of both these type of antacids is that they act immediately. But disadvantage is that they immediately increase the volume of gastric content after their use.

Except antacids, gastric acidity is decreased (or pH is increased) and volume of gastric content also can be decreased by using H_2 receptor blocker (ranitidine) or proton pump inhibitor (omeprazole, pentaprazole etc). But both of these drugs do not act immediately like antacids. Therefore, atleast 1 to 2 hours of interval after oral administration or 45 to 60 minutes of interval after

IV or IM administration of these drugs is required. It should also be kept in mind that both these drugs can not change the pH and volume of gastric contents which is already secreted into the stomach.

Metoclopramide is an another prokinetic agent that increases the emptying of stomach and raises the lower gastro-oesophageal sphincter tone. Thus, it reduces the gastric volume (not the gastric pH) and decreases the subsequent chances of aspiration of gastric contents by regurgitation or vomiting. On the other hand, it does not raise the gastirc pH and has no adverse effects on foetus or neonates. To prevent pulmonary aspiration of gastric content the use of IPPV before intubation should also be avoided. Because it can inflate the stomach by air and thus can make the patient more vulnerable to regurgitation and pulmonary aspiration of gastric contents. Another mechanical way to reduce the risk of pulmonary aspiration of gastric contents is Sellick's manoeuver (cricoid pressure) which occludes the oesophagus. Finally, the risk of pulmonary aspiration of gastric contents can also be minimised by intubating the trachea with an ET-tube and extubating the patient only after she is fully awake with good return of laryngeal reflexes (Table 35.5).

Table 35.5: Some strategies to reduce maternal mortality in obstetric anaesthesia

1. Less experienced anaesthetist should not take sole responsibility for obstetric anaesthesia.
2. The anaesthetist must have a skilled help irrespective of his or her experience.
3. Antacid does not give full protection aganist Mendelson syndrome. Therefore H_2 blocker and prokinetic agent are mandatory.
4. Cricoid pressure must be applied.
5. Failed intubation drill should be exercised by all obstetric anaesthetist.
6. No matter how urgent the obstetric anaesthesia, history and monitoring must not be neglected.
7. Epidural labour analgesia should be supervised by a skilled person and an anaesthetist should be available immediately in emergency.

Steps of general anaesthesia in CS

- Taking of history and airway assessment meticulously.
- Proper preparation of patient by oral antacid or H_2 blocker or proton pump inhibitor and metoclopramide.
- The patient is placed supine with 15° left uterine displacement by putting a wedge under the right buttock.
- Starting of IV infusion by large bore cannula.
- Preoxygenation by 100% O_2 with high flow rate (> 6 lit/min) for 3 to 5 minutes. 4 full vital capacity breaths of 100% O_2 is also adequate for denitrogenation.
- Monitors are applied.
- The patient is prepared by antiseptic dressing over abdomen and is draped.
- The surgeon is ready to begin surgery and an assistant of anaesthesist should apply cricoid pressure.
- Rapid sequence induction and muscular paralysis is performed, by using thiopentone (4 to 5 mg/Kg) or propofol (1 to 2 mg/Kg) or ketamine (1 mg/Kg, in hypovolumic or asthmatic patient) and succinylcholine (1 to 1.5 mg/Kg). Defasciculation is not necessary in CS.
- Trachea is intubated by a proper sized ET-tube and cuff is inflated. Cricoid pressure is maintained till trachea is sealed off. Proper placement of ET-tube is confirmed by capnography.
- Maternal P_aCO_2 below 25 mm of Hg by hyperventilation is avoided. Because it can reduce the uterine blood flow by vasoconstriction and subsequently foetal acidosis. Hyperventilation also causes a leftward shift of the maternal O_2-Hb dissociation curve and decreases O_2 availability to the foetus.
- Respiration is maintained by IPPV using 50:50 N_2O:O_2 mixture with any potent volatile anaesthetic agent in low concentration (0.5% halothane or 0.75% isoflurane or 1% sevoflurane or 3% desflurane). This low concentration of volatile anaesthetic agent helps to produce amnesia and does not cause excessive uterine relaxation or impair uterine contraction by oxytocin.
- Non-depolarising muscle relaxant of intermediate duration of action such as rocuronium, atracurium, cisatracurium or mivacurium are used when necessary.
- The 20 to 30 unit of oxytocin per litre of IV fluid is infused after the neonate is delivered. Then, the umbilical cord is clamped and placenta is removed.
- Anaesthesia is deepened by increasing the percentage of N_2O in inspired gas mixture by upto 70% and by further adding narcotics, benzodiazepines or propofol.
- If there is hypotonicity of uterine muscle, then halogenated volatile anaesthetic agent should be discontinued.
- If there is still relaxation of uterine musculature, then 0.2 mg of methylergonovine or 0.25 mg of 15 methyl prostagland in $F_2\alpha$ IM may also be given.
- At the end of surgery, the effect of muscle relaxant is reversed by anticholinesterase with glycopyrolate and extubated when there is full return of laryngeal reflexes.

Acid Aspiration or Mendelson's Syndrome

It was first described by Mendelson in 1946 in which gastric contents had been regurgitated and aspired in the lungs and initiated a series of characteristic pulmonary signs and symptoms constituting a syndrome. So, now it bears his name. The morbidity and mortality of this syndrome is very high and it depends upon the volume, nature, acidity and the nature of distribution of aspirated material in lungs. If the inhalation of gastric contents is of sufficient quantity or solid, then it will cause asphyxia due to obstruction. Otherwise, if the gastric content is of very low pH (< 2.5), though is of small amount (as small as 25 ml) causes serious pulmonary reaction and death without producing asphyxia. It has been found that 60% of the obstetric patients at term have more

than 40 ml of gastric juice and pH is less than 2.5 in empty stomach.

The pathophysiological consequences and the clinical picture of this syndrome following aspiration of gastric acids fit with the acute respiratory distress syndrome (ARDS). But this ARDS may also develop due to other causes. These other causes are pulmonary injury by other substances except acid which enter through airway or by indirect blood borne insult to lungs. Some severe form of this syndrome may develop immediately and patient collapse. But sometimes the symptoms following aspiration of little to moderate amount of liquid gastric contents with low pH may become apparent slowly over 6 to 8 hours after the incident (Table 35.6).

After aspiration of gastric acid content in lungs there is severe inflammation of pulmonary tissue and simultaneously there is also release of large number of mediators which include cytokines (such as tumour necrosis factor, interleukins 1 and 6, platelet activation factor), prostaglandins, leukotrienes, lysosomal enzyme, etc. These mediators trigger a complex interactions between the endothelial cells, platelets, coagulation pathways, and WBC which become activated and damage the vascular endothelium. Then fluid and cells pass across the damaged endothelium from the blood vessels into the interstitial space, causing pulmonary oedema and further tissue inflammation. Thus, a vicious cycle of endothelial injury, intravascular coagulation, microvascular occlusion, tissue damage and further release of inflammatory mediators ensues. Patient often suffers from cough, tachypnoea, weeze, ronchi, hypoxia and all the other features of pulmonary oedema. The criteria defining ARDS are: (i) hypoxaemia which is defined as P_aO_2 < 200 mm of Hg, (ii) chest radiograph showing diffuse bilateral infiltrates, (iii) absence of raised left atrial pressure: PAWP < 15 mm of Hg, (iv) impaired lung compliance.

Table 35.6: Conditions predisposing to ARDS

Direct through airway
• Aspiration of gastric contents
• Toxic gases
• Near drowning
Indirect by bloodborne
• Severe sepsis
• Multiple trauma
• Anaphylaxis
• Pancreatitis
• Drugs
• Ammiotic fluid and fat embolism

The term ARDS is often limited to the patients requiring ventilatory support. But the less severe form of ARDS is conventionally referred to as the acute lung injury (ALI). Suction through an endotracheal tube which reveals bile stained fluid is often diagnostic. While over the longer term, serial chest X-ray and serial arterial blood gas estimation will reveal progressive changes.

Management of this Mendelson's syndrome is very difficult. It includes: proper arterial oxygenation by ventilation through ET tube, suction through ET tube, correction of blood volume and acid base balance, steroid, antibiotics, etc and adequate monitoring in ICU.

As prevention is better than cure, so an anaesthetist will always try to take measure which will prevent to develop it. This is described in table.

PRE-ECLAMPSIA, ECLAMPSIA AND ANAESTHESIA

Pre-eclampsia is also termed as pregnancy induced hypertension (PIH). Hypertension in pregnancy may be due to PIH or chronic essential hypertension existing before pregnancy or recent development of essential hypertension during this pregnancy or chronic hypertension with superimposed pre-eclampsia. Pre-eclampsia complicates upto 8 to 10% of all pregnancies and is the most common difficult condition encountered by an anaesthetist during his practice of obstetric anaesthesia where otherwise a previously healthy patient suddenly becomes severely ill. The classic triad of pre-eclampsia are: hypertension, proteinuria (> 500 mg/day) and oedema (hand and face). Hypertension in pre-eclampsia is usually defined as systolic and diastolic BP above than 140 mm of Hg and 90 mm of Hg respectively, or persistent increase in systolic and diastolic BP by 30 mm of Hg and 15 mm of Hg respectively above the normal baseline value. The other characteristic features of pre-eclampsia are: (i) hypertension occuring after 20 weeks of gestation and resolving within 48 hours after delivery or develops in the early postpartum period and returning to normal within 3 months of delivery, (ii) oliguria, (iii) serum and urine creatinine concentration ratio > 0.09 mm/L, (iv) headache with visual disturbances, (v) increased level of liver enzymes, (vi) ↑lactate dehydrogenase, ↑thrombocytopenia, ↑haemolysis, and DIC. When convulsions occur in pre-eclampsia then this condition is called eclampsia where prognosis of both the mother and foetus worsens. But it is less common. Severe PIH contributes about 30 to 40% of maternal death and 15 to 20% of perinatal death. The principal causes of maternal death in pre-eclampsia are: stroke, pulmonary oedema and hepatic failure. There are some predisposing factors for pre-eclampsia. These are: a family history of pre-eclampsia, chronic renal disease, chronic hypertension, multiple gestation, age > 40 years, diabetes, etc. (Table 35.7).

HELLP syndrome found in pre-eclampsia is a pathological condition which is characterised by haemolysis (H), elevated liver enzymes (EL) and low platelet count (LP). This represents a severe form of pre-eclampsia with above mentioned signs. It occurs in 20% of pregnant patients who develop severe pre-eclampsia with many of the manifestations occuring in the post partum period. Its severity ranges from a mild self limiting condition to a fulminant process leading to multiorgan failure. No signs and symptoms of this syndrome are diagnostic, because all these signs and symptoms are found in patients with

Table 35.7: Measures to avoid acid aspiration

Decreasing the acidity of gastric fluid
- Use of antacid to neutralise the existing acid.
- Use of H_2 blocker to stop secretion of acid and elevate pH.

Decreasing the volume of gastric fluid
- By restricting intake.
- By increasing emptying of stomach by metoclopramide.
- By decreasing the gastric secretion.
- By physical mean - suction through large bore tube.

Preventing the regurgitation of gastric secretion
- Increase in intragastric pressure should be avoided.
- Increase in tone of lower gastro-oesophageal sphincter.
- Induction in upright position.

Preventing the inhalation of regurgitant material
- By applying cricoid pressure.
- By suction.
- By induction in Trendelenberg position.

Avoiding GA
- RA avoid gastric aspiration.

Avoiding difficult intubation
- By proper assessment of airway.
- By appointing skilled anaesthetist.

severe pre-eclampsia-eclampsia, but without HELLP syndrome.

Pre-eclampsia may be classified as mild or severe according to the severity of symptoms and signs which are demonstrated in table. Assuming no presence of any coagulopathy, haemostasis is not usually a problem unless the platelet count is decreased below 40,000/cumm in pre-eclampsia. In such circumstances, RA is contraindicated. This abnormal platelet count usually returns to normal within 72 hours of delivery. But this thrombocytopenia may persist for longer periods (Table 35.8).

Pre-eclampsia is the disease of theories, as the precise cause of it is still unknown in spite of excessive resreach. It is mainly associated with abnormal activities of trophoblastic cells and abnormal placentation. Thus, it leads to maladaptation of maternal spiral arteries and is particularly found in

Table 35.8: Classification of pre-eclampsia

	Mild	*Severe*
Systolic pressure	< 160 mm of Hg	> 160 mm of Hg
Diastolic pressure	< 110 mm of Hg	> 110 mm of Hg
Urine output	> 500 ml/24 hour	< 500 ml/24 hour
Urinary protine	< 5 gm/24 hour	> 5 gm/24 hour
Platelet count	> 100,000/cu mm	< 100,000/cu mm
Pulmonary oedema	Absent	Present
Headache	Absent	Present
Epigastric pain	Absent	Present
Visual disturbance	Absent	Present
HELLP syndrome	Absent	Present

women with vascular disorders. The secondary pathology in pre-eclampsia is also linked to immunological basis and endothelial dysfunction (vascular hyper- reactivity), causing excessive activation of coagulation. This is due to abnormal metabolism of prostaglandin. This pre-eclamptic patient has increased production of TXA_2 (thromboxane A_2) which is a potent vasoconstrictor and help in platelet aggregation and decreased production of PGI (prostacyclin) which is a potent vasodilator and reduce platelet aggregation. Another mechanism of action of endothelial dysfunction is decreased production of nitric oxide (NO) which is a potent vasodilator and increased production of endothelin 1 which is a potent vasoconstrictor. Thus, marked endothelial immunological injury due to its hyperreactivity leads to wide spread systemic manifestation as well as reduced placental perfusion (Table 35.9).

The systemic manifestation of pre-eclampsia include: generalised oedema with special importance to airway, ↑SVR, ↓intravascular volume, hyperdynamic circulation, decreased GFR, ↑uric acid, liver dysfunction, pulmonary oedema etc. The pulmonary oedema in pre-eclampsia is due to: (i) high left atrial and pulmonary capillary wedge pressure, (ii) low plasma colloid and osmotic pressure, and (iii) increased pulmonary capillary permeability. Increased level of uric acid in pre-eclampsia results from decreased renal excretion, tissue ischaemia and oxidative stress. Acute renal failure is rare in pre-eclampsia, but is mostly associated with

Table 35.9: Complications of pre-eclampsia

CVS	Hypertension, ↓ intravascular volume, ↑ vascular resistance, ↓ cardiac output, heart failure, stroke.
RS	Airway oedema, pulmonary oedema.
Kidney	↓ GFR, Oliguria, proteinuria, renal failure.
NS	Hyperexcitability, convulsions, headache, visual disturbance, intracranial haemorrhage, cerebral oedema.
Liver	Elevated liver enzymes, impaired functions, haematoma, rupture of blood vessels.
Haematology	Thrombocytopenia, coagulopathy.

HELLP syndrome. Liver dysfunction is also mostly associated with HELLP syndrome. Cardiac output in pre-eclampsia may be high, normal or low depending on the severity of increase of SVR, severity of diminution of intravascular volume and hyperdynamicity of cardiac function (contractility).

Immediate delivery of foetus and placenta is the definitive and principal way of treatment for pre-eclampsia and eclampsia during life threatening condition of mother at any stage of gestation. Otherwise (i.e. when there is no life threadning condition to mother), the aim of treatment of pre-eclampsia is control of hypertension and prevention of convulsions. The drugs used to treat hypertension in pre-eclampsia are: hydralazine, labetalol and methyldopa (250 to 500 mg orally). The other agents

Table 35.10: Pharmacology of labetalol and hydralazine

	Labetalol	*Hydralazine*
Mode of action	Slight α blocker mainly β blocker	Direct vasodilatation
Dose	10 to 20 mg IV	5 to 10 mg IV
Maintenance	20 to 160 mg/hour	2 to 20 mg/hour
Speed of onset	Quick	Gradual
Tachycardia	Absent	Present

used during emergency are: nitroglycerine, Na-nitroprusside, esmolol. Nitroprusside is helpful only for short-term basis, because prolonged infusion of it is associated with increased risk of cyanide toxicity. Ca^{2+} channel blocker are usually not used because they are contraindicated in pregnancy (Table 35.10).

$MgSO_4$ is the agent of choice to control convulsions and for prevention of recurrent eclamptic fits. It is effective in more than 50% of patients, without serious maternal morbidity. Another beneficial effect of $MgSO_4$ is that it causes vasodilatation and decrease SVR, causing increased cardiac output. The initial bolus dose of $MgSO_4$ is 4 gm and is administered IV slowly over 10 minutes. This is followed by infusion at the rate of 1 to 3 g/h. $MgSO_4$ has low therapeutic index with serum Mg^{2+} level between 4 to 6 mEq/L, being safe and effective. It is excreted through kidney. Therefore, in the presence of renal failure the dose of $MgSO_4$ should be reduced and guided by serum magnesium level. During the use of $MgSO_4$, the level of plasma Mg should be monitored carefully in conjunction with the clinical signs which include respiratory depression and decreased tendon reflex, indicating toxicity. If toxicity of $MgSO_4$ occurs, then 10 ml of 10% calcium gluconate is given IV slowly which counteract the side effect of Mg.

Anaesthetic Consideration

The first step during anaesthetic management of a pre-eclamptic – eclamptic patient includes: detailed history taking regarding the severity of condition, degree of systemic involvement, fluid status, airway assessment, cardiovascular status, renal condition, coagulation status, etc. It also includes: complete blood count, liver function tests, renal function tests, platelet count, coagulation profile, etc. But routine coagulation screening is not recommended by all clinicians, except the presence or suspected of coagulopathy clinically. Central neuraxial block (CNB) is contraindicated in the presence of coagulopathy or low platelet count (< 100,000/cu mm). But, some anaesthetists take this lower count of platelet as 70,000/cu mm for contraindication of CNB.

Pre-eclampsia – eclampsia is associated with exaggerated Na^+ and water retention. But still it is characterised by decreased intravascular volume (hypovolaemia). This is due to the shift of fluid and protein in the interstitial space from intravascular compartment. Thus, the intravascular fluid volume is inversely proportional to the severity of hypertension in pre-eclampsia and eclampsia. So, measurement of CVP in the presence of severe pre-eclampsia – eclampsia will be a false guide. Therefore, before any mode of anaesthesia patient should be hydrated properly by IV infusion. This will improve maternal tissue perfusion, increase cardiac index, decrease SVR, and increase GFR, etc.

Regarding the mode of anaesthesia in pre-eclampsia-eclampsia, it is found that any form of anaesthesia (RA or GA) is equally safe, if they are properly conducted with extra caution. But, there should be some choice as both these modes of anaesthesia have their own advantages and disadvantages. But in the absence of coagulopathy the first choice of anaesthesia for most patients with pre-eclampsia-eclampsia during the process of labour, vaginal delivery and CS is continuous epidural analgesia and anaesthesia. It offers the advantage of gradual onset of sympathetic blockade, gradual hypotension, cardiovascular stability due to gradual compensation with passing of time and no neonatal depression that cab be caused by general anaesthetic drugs. Reduction of hypertension and diminution of vasospasm (due to sympathetic block) caused by RA will improve uteroplacental blood flow, provided severe hypotension is avoided. The RA also reduces the risk of upward exaggerated haemodynamic alterations associated with intubation and extubation and airways complications. On the other hand, if CNB is badly managed, then it frequently associated with extensive sympatholysis and profound hypotension (if not controlled) which may lead to decreased cardiac output, decreased uteroplacental blood flow and in extreme condition even foetal and maternal cardiac arrest. This is more likely with single shot spinal anaesthesia if severe hypotension is not corrected immediately. Hence, even though the single shot spinal block is considered acceptable by many anaesthetist, but is still taken by others to be relatively contraindicated for women with severe pre-eclampsia–eclampsia. However, multiple recent studies have suggested that the magnitude of decline of maternal BP after spinal and epidural block appears to be similar. Hence, spinal block is not contraindicated and can easily be instituted on a severe pre-eclampsia patient undergoing CS. Hypotension induced can easily be avoided by meticulous attention, use of IV colloid infusion and / or use of vasopressor (ephedrine 5 mg) in a titrable fashion, because pre-eclamptic patients tend to be very sensitive to these agents. It is also true that hypotension associated with CNB can easily be controlled than the exaggerated surge of hypertension in GA during laryngoscopy, intubation and extubation which can only be controlled by appropriate treatment with labetalol, nitroglycerine, nitroprusside, hydralazine, trimethaphan, etc. In GA, the risk of failed intubation also should be weighed against the risk of hypotension when deciding between GA and RA for CS of patient who is suffering from

severe pre-eclampsia-eclampsia. If GA is instituted on a pre-eclamptic-eclamptic patient receiving $MgSO_4$, then anaesthetist should be careful regarding the use of muscle relaxant – depolarising and non depolarising. This is because the action of both will be potentiated by $MgSO_4$. Hence, the use of muscle relaxant in a patient receiving $MgSO_4$ should be guided by the peripheral nerve stimulator. $MgSO_4$ also blocks the release of catecholamines after sympathetic stimulations and blunts the response of vasoconstrictor. Therefore, there is also more chance of severe hypotension after CNB in a patient receiving $MgSO_4$. All the pre-eclamptic and eclamptic patients associated with severe hypertension, pulmonary oedema, refractory oliguria, receiving IV vasodilators, etc, should must be monitored by intra-arterial BP, CVP, PCWP, etc.

OBSTETRIC HAEMORRHAGE AND ANAESTHESIA

Obstetric haemorrhage is one of the leading cause of maternal morbidity and mortality, necessitating immediate anaesthesia and surgical intervention. The common causes of this obstetric haemorrhage are placenta praevia, abruptio placentae, uterine inversion, uterine rupture, and uterine atony. Placenta praevia and abruptio placentae account for about 0.5 and 1 to 2% of total pregnancies, respectively.

In placenta praevia, the placenta is situated on the lower uterine segment, covering the internal os which may be complete or partial. The complete placenta praevia is more dangerous than the partial one, regarding the severity of bleeding. Placenta praevia presents usually as painless vaginal bleeding and stops spontaneously in mild cases usually in partial one. But severe bleeding can occur at any time usually in complete placenta praevia. During severe bleeding there is two problems : on the one hand the life of mother and on the another hand the life of the foetus. If the duration of pregnancy is less than 37 weeks and bleeding is mild to moderate, then conservative management may be allowed by bed rest and close observation. Whereas the definitive management of obstetric haemorrhage for any cause after 37 weeks of gestation is CS.

In abruptio placentae there is premature separation of placenta causing painful bleeding which may be revealed through vagina or concealed. Occasionally, the blood may extend into the myometrium which is called the couvelaire uterus. Any vaginal bleeding of a pregnant woman is assumed to have placenta praevia, until proved otherwise. The actual diagnosis is performed by ultrasound. Uterine rupture is another cause of obstetric haemorrhage causing emergency. It is relatively uncommon and can occur as a result of dehiscence of a previous scar on uterus or due to any intrauterine manipulation or due to very prolonged labour. It can present as acute foetal distress, frank haemorrhage, loss of uterine tone, or severe hypotension with occult bleeding into the abdomen.

In all the acute obstetric haemorrhage the mother should be assessed first about its haemodynamic status. If the bleeding is mild to moderate, resuscitation by fluid is adequate and the condition of patient is stable when decision for surgery is taken, then RA may be considered. Otherwise, acute bleeding or a patient with unstable haemodynamic status may require surgical intervention under GA. All these patients should be tackled with atleast two largebore (16 or 18 G) intravenous catheter. Intravascular volume deficit must be replaced vigorously. A central venous line is especially useful for monitoring of preload and rapid transfusion. Two units of whole blood should be immediately available.

The choice between the regional and general anaesthesia during surgery to tackle obstetric haemorrhage depends upon the urgency for delivery and maternal haemodynamic stability. In such situation close communication is very necessary with the concerned surgical team regarding about the mother, foetus, or both who are in immediate danger requiring GA or there is time to safely administer RA. If epidural catheter is already in place for painless labour (labour analgesia), then severe hypotension due to massive bleeding and delay in establishing adequate anaesthesia by further adding anaesthetic dose of LA agent through this epidural route may prohibit its use.

In acute emergency if GA is decided, then adequate pre-oxygenation is quickly achieved by four full breaths of 100% O_2, while possible necessary monitors are being applied during this period of preoxygenation. For induction instead of thiopentone and propofol, ketamine in the dose of 1 mg/Kg is used for hypotension. Other steps for emergency CS are also taken which will help in prevention to develop aspiration pneumonitis (Mendelson's syndrome) and will also help to develop proper ventilation with adequate oxygenation if failed intubation occur. Continuous precise foetal monitoring is very essential, becasue it may help by avoiding the unnecessary GA as emergency for acute foetal distress, diagnosed by imprecise monitoring. Otherwise extra time may be allowed to institute RA. For example, in most of the cases the foetal distress is diagnosed by foetal heart rate variability. But, it has high false positive result and may land in GA showing acute distress, giving no time for RA. Hence, careful interpretation of other parameters such as foetal pulse oxymeter or foetal scalp pH is necessary which may change the mode of anaesthesia.

In abruptio placentae, RA is contraindicated if there is coagulopathy, particularly following foetal demise. This coagulopathy is due to activation of circulating fibrinolysin (plasminogen) and the release of tissue thromboplastin. This may precipitate DIC which is characterised by low fibrinogen level, low platelet count, and high fibrinogen degradation product. Fibrinogen level is mildly reduced with level between 150 to 250 mg/dl in moderate abruptio placentae. But in severe one the fibrinogen level may go below 150 mg/dl.

36 Anaesthesia in Laparoscopic Surgery

INTRODUCTION

Due to the development of better surgical equipments and anaesthetic facilities and also due to the increased knowledge and understanding of the anatomy and pathophysiology of different diseases, the different surgical procedures gradually also have improved. Thus, it reduces the trauma to the patient with the reduction of morbidity, mortality, hospital stay and consequently the reductions in health care costs by the concept of 'minimally invasive or endoscopic surgery'. Endoscopic procedures had first started in the early 1970's for various gynaecological operations (for diagnosis and treatment). Then it soon becomes very popular among the gynaecologists only. But, during this period it was not very popular among the general surgeons, until 1987, when, laparoscopic cholecystectomy was first described in late 1980's by Phillipe Mouret in France. After that gradually it became a well established technique for cholecystectomy in this country (France). Then, very soon this technique was accepted by surgeons all over the world and now more than 80% of all the cholecystectomies are done by laparoscopic procedure with less postoperative pain, reduced hospital stay, reduced cost and earlier return to the work. During that period acute cholecystitis, obesity and previous intra-abdominal surgeries were considered as the contraindications for cholecystectomy by laparoscopic procedure. But these are now no longer considered as contraindications like before for laparoscopic cholecystectomy and the procedure has become quite safe in the hands of experienced surgeons. Subsequently, many other new intra- and extra-abdominal laparoscopic or endoscopic surgical techniques have been developed such as gastrointestinal surgeries (oesophagectomy, vagotomy, appendi sectomy, fundoplication, colonic, gastric, splenic, hepatic), gynaecological surgeries (hysterectomy), urological (nephrectomy), hernia repair, testicular surgeries, etc.

So, these new minimum invasive endoscopic surgical techniques have created the new interests to anaesthetist with separate anaesthetic considerations for the management of such patients. Gradually, the list of the surgical procedures which are now commonly performed endoscopically has grown rapidly. The laparoscopic surgical techniques which are included in this list are now extending from intraperitoneal to transabdominal preperitoneal to totally extra-peritoneal procedures. For example, a laparoscopic fundoplication procedure which is performed as antireflux surgery proves a very cost effective technique for patients suffering from gastroesophageal reflux and on long-term medical management. Pathophysiological changes due to pneumoperitoneum, different patient's position (required during laparoscopic surgeries), long duration of some laparoscopic surgeries, risk of some unsuspected visceral injury, the difficulty in evaluating the amount of blood loss during surgery and some other factors make the anaesthesia for laparoscopic surgery a potentially high-risk procedure. Young healthy women are the largest group of patients who are undergoing the different gynaecological and different surgical (mainly cholenystectomy) laparoscopic surgery. Usually they are associated with minor to moderate cardiorespiratory changes which are of little concern to an anaesthetist. But, older patients with known or latent co-existing systemic diseases waiting for endoscopic surgery are prone to more risk, necessitating intensive care and thorough knowledge of pathophysiological changes associated with laparoscopic surgery.

Compared with the open laparotomy the major advantages of laparoscopic surgery are: Reduced tissue trauma (as less surgical exposure), reduced wound size, reduced postoperative pain due to small wound, reduced incidence of postoperative ileus, earlier mobilisation of patients, shorter hospital stay, improved postoperative respiratory function, etc. For example, following open cholecystectomy forced vital capacity (FVC) is reduced by approximately 50% and changes are still evident up to 72 hours postoperatively. Contrary following laparoscopic cholecystectomy FVC is reduced by approximately only 30% and becomes normal within 24 hours postoperatively.

On the other hand, technically the laparoscopic surgery differs from the open laparotomy by the following points:

i. Laparoscopic surgery needs gravitational displacement of abdominal viscera from the operative site by Trendelenburg or anti-Trendelenburg position.

ii. It needs pneumoperitoneum which separates the abdominal wall from viscera. For pneumoperitoneum the upper limit of IAP (intra-abdominal pressure) is 15 to 20 mm Hg. Modern pneumoperitoneum producing equipment has the ability to maintain continuously this upper limit of IAP automatically. Older laparoscopic equipment which may not have this automatic adjustment for upper limit can deliver uncontrolled gas flows, producing a very high intra-abdominal pressure (sometimes greater than 40 mm Hg).
iii. It needs decompression of abdominal viscera, especially the stomach by nasogastric tube and the bladder by catheter to prevent the injury during insertion of trocar.

PATHOPHYSIOLOGICAL CHANGES OF RESPIRATORY AND CVS DURING LAPAROSCOPY

Two systems of our body are mainly affected during laparoscopic surgery. These are: respiratory system (RS) and cardiovascular system (CVS).

Changes in Respiratory System During Laparoscopy

The insufflation of CO_2 (current routine practice) in to the peritoneal cavity to create pneumoperitonium for laparoscopic surgery results in ventilatory and respiratory changes in patients. Dure to pneumoperitoneum the resulting increase in intra-abdominal pressure (IAP) displaces the diaphragm upwards and causes decrease in compliance of both the chest wall and the lungs, increase in airway resistance, and an increase in peak inspiratory pressure. There is also increase in the risk of gastric regurgitation during pneumoperitoneum.

The compliance of lung is reduced to 30 to 50%, but the shape of the pressure – volume loop of it does not change. Once the pneumoperitoneum is created upto the surgeon's desired level and IAP is kept constant, then further lung compliance is not affected or reduced after reaching its upper limit either by the subsequent patient tilting or by the increase of minute ventilation which may be required to avoid intraoperative hypercapnia. That means compliance decreases and becomes fixed at a given increased IAP. Then, further decrease or deterioration of compliance cannot be detected by increasing IAP. After that point if there is any deterioration of lung's compliance occurs, then it will be only due to the lungs pathology. Therefore, continuous compliance and pressure volume loop monitoring are helpful in diagnosing any second complication resulting from the increased airway pressure due to bronchospasm, changes in muscle relaxation, endobronchial intubation, or pneumothorax, etc. Which are responsible for decrease in compliance of lungs (Fact file-I).

The elevation of diaphragm and subsequently the increased intrathoracic pressure also causes diminished FRC, increased ventilation-perfusion mismatch (preferential ventilation of nondependent areas of lungs can be associated with intrapulmonary shunting and hypoxaemia), increased physiological dead space and increased intrapulmonary shunt contributing to decrease in arterial oxygenation. Such changes would favour the development of atelectasis of lungs. But these changes are generally not found or minimal in normal healthy individuals. On the contrary, in obese patients, in respiratory disabled patients or in patients with cardiovascular problems, these changes may be more significant.

FACT FILE - I

Pneumoperitoneum → ↑IAP → ↑Diaphragm → ↓Compliance of lung → ↑ Airway resistance and ↑airway peak pressure → ↓ FRC → ↑ V/Q mismatch, ↑shunt, ↑dead space, and ↑atelectasis → ↑ hypoxia and ↑$PaCO_2$.

Pneumoperitoneum →↑ IAP and ↑diaphragm → compression of venous capacitance vessel, ↑intrathoracic pressure, compression of arterial resistance vessel (↑SVR) → ↓venous return → ↓ CO → ↑ sympathetic neurohormonal response → ↑ SVR → ↓ CO → vicious cycle.

Due to increased systemic absorption of highly soluble CO_2 by the vasculature of peritoneum, arterial CO_2 tension ($PaCO_2$) increases. It reaches a plateau value at 15 to 30 min after the beginning of CO_2 insufflation of peritoneum under general anaesthesia and this is found only in anaesthetised patient with spontaneous ventilation and in head down (Trandelenburg) or head up tilt position. But, during laparoscopy under local anaesthesia where the patient is not under GA, $PaCO_2$ remains unchanged or remains normal. It is due to the compensatory increase in minute ventilation (hyperventilation) by the stimulation of the respiratory centre by hypercapnia. In such condition, hyperventilation in unanaesthetised patient is achieved by increasing the respiratory rate, rather than by increasing the tidal volume. Usually, the mechanical factor (decreased tidal volume) is compensated by the increase in respiratory rate (in unanaesthetised under local anaesthesia patient), or by controlled ventilation (in anaesthetised paralysed patient) except in anaesthetised spontaneously ventilated patient where both the increase in respiratory rate and tidal volume is jeopardised. This is because if laparoscopy is performed under general anaesthesia with spontaneous ventilation, the compensatory hyperventilation is not achieved. This is again due to anaesthesia induced depression of respiratory centre causing reduction of both respiratory rate and tidal volume. As it takes 15 to 30 minutes for $PaCO_2$ to reach a plateau value after the starting of pneumoperitoneum by CO_2, so GA with spontaneous respiration can be considered only for short laparoscopic procedures with low intra-abdominal pressures.

Like local anaesthesia, during laparoscopy under regional anaesthesia, $PaCO_2$ remains also unaltered due to the absence of ventilatory depressant effects provided the level of block is not much high up. For monitoring of $PaCO_2$ and oxygen saturation, capnography and oximetry are two

reliable devices for a healthy patient. But in sick patients (ASA III – IV) $ETCO_2$ tension is not always reliable, because $PaCO_2$ and ET CO_2 tension gradient increases due to the inadequate capacity of excretion of CO_2 through alveoli. So, for higher risk patients preoperative pulmonary function tests and intraoperative arterial blood gas sampling is recommended as preoperative assessment and as a guide line for intraoperative monitoring of patient respectively (Table 36.1).

The increase in $PaCO_2$ during pneumoperitonium by CO_2 gas is due to: (i) increased absorption of CO_2 from the peritoneal cavity because of its high diffusibility and large absorption area (the absorption of any gas from peritoneal cavity depends on its diffusibility, the absorption area and the perfusions of the walls). (ii) Impairment of pulmonary ventilation and perfusion by mechanical factors such as abdominal distension, patients's position, depression of ventilation by premedicant and anaesthetic drugs. (iii) Accidental events such as CO_2 emphysema, capnothorax (pneumothorax by CO_2), CO_2 embolism, etc. The $PaCO_2$ does not increase if other gases like N_2O, helium, O_2, etc. are used for pneumoperitoneum instead of CO_2 which indicates that the absorption of gases through the peritoneal cavity plays a vital role for increase in $PaCO_2$ rather than the impaired mechanical ventilatory factors due to ↑IAP, in healthy patients. This is because in healthy patient the mechanical factors responsible for ↑$PaCO_2$ is compensated by hyperventilation in unanaesthetised patient or controlled ventilation by IPPV in anaesthetised patient except in anaesthetised patients with spontaneous respiration. Whereas in cardiorespiratory compromised patient both absorption of CO_2 and compromised mechanical factors play vital role (mechanical factor cannot be compensated) for ↑$PaCO_2$.

Table 36.1: Causes of ↑$PaCO_2$ during laparoscopy surgery

i.	Increased physiological dead space and V/Q mismatch • Steep head down position • Abdominal distension • Reduced cardiac output • Reduced ventilation
ii.	Absorption of CO_2 through peritoneal cavity
iii.	Depression of respiration by anaesthetic drug in a spontaneous ventilated patient
iv.	Increased metabolism for stress due to inadequate anaesthesia
v.	Accidental events such as: • Capnothorax • CO_2 emphysema • CO_2 embolism • Change of position of ET tube

Haemodynamic Changes During Laparoscopy

The haemodynamic changes observed during laparoscopic surgery result from the combined effects of anaesthesia, ↑$PaCO_2$ due to CO_2 absorption from peritoneal cavity, ↑IAP due to pneumoperitoneum, patient's position, intravascular volume status and the preexisting cardiorespiratory status of the patient. Peritoneal insufflation raising IAP higher than 10 to 12 mm Hg (the 12 mm of Hg of abdominal pressure is the threshold pressure and up to that level it has minimal effects on haemodynamic function) causes major haemodynamic alterations. These are characterised by ↓ cardiac output, increased systemic vascular resistance (↑SVR), increased pulmonary vascular resistance (↑PVR), increased mean arterial pressure and pulmonary hypertension. Cardiac output is reduced by 10 to 30% whether the patient was placed in the head down or head up position and this is well tolerated by a healthy patient. The causes of this reduction of cardiac output are: (i) pooling of blood in the legs due to increased IAP, (ii) reduced venous return due to compression on inferior vena cava, and compression on both the venous capacitance system and the arterial resistance vessels (this compressive mechanical effect on the venous system will involve in the reduction of venous return to the heart and on arterial resistance vessels will involve in increase in systemic vascular resistance) and (iii) decreased venous return due to increased intrathoracic pressure.

All these above mentioned factors lead to reduced venous return to heart and this reduced venous return to heart causes reduction in left ventricular end diastolic volume (preload) and reduced cardiac output. But, paradoxically, CVP (central venous pressure) and PCWP (pulmonary capillary wedge pressure) rises due to increased intrathoracic pressure inspite of reduction of preload. So, in pneumoperitoneum the measurement of right atrial pressure and pulmonary artery pressure which is generally taken as the cardiac (left ventricle) filling pressure cannot be a proper guide for the left ventricular end diastolic pressure and cardiac output. Following pneumoperitoneum, due to this mechanical factors both the right and the left sided filling pressure of heart (but not the filling volume) will substantially increase. Decreased cardiac output associated with pneumoperitoneum and ↑IAP is also associated with decreased stroke index, since heart rate is not significantly affected. Normally, cardiac index is reduced to 30% from the baseline when the patient is kept in anti-Trendelenburg position and is further reduced to 50% by starting of pneumoperitoneum in this position provided the laparoscopy surgery is done in head up tilt position. Then, the cardiac index gradually comes to normal within 10 minutes after insufflation. The magnitude of reduction of CI is directly proportional to the increased IAP, caused by insufflation (Fig. 36.1).

The pneumoperitonium and ↑IAP is associated with ↑SVR (afterload). Increase in mean arterial pressure (MAP) reflects the increased afterload with an associated deterioration in CI. The magnitude of reduction of CI is directly proportional to the insufflation pressure. The threshold of intraperitoneal pressure that had minimum effect on haemodynamic function is 12 mm Hg. The causes of ↑SVR due to pneumoperitoneum are: (i) compression of intra-abdominal aorta and arterioles by raised IAP

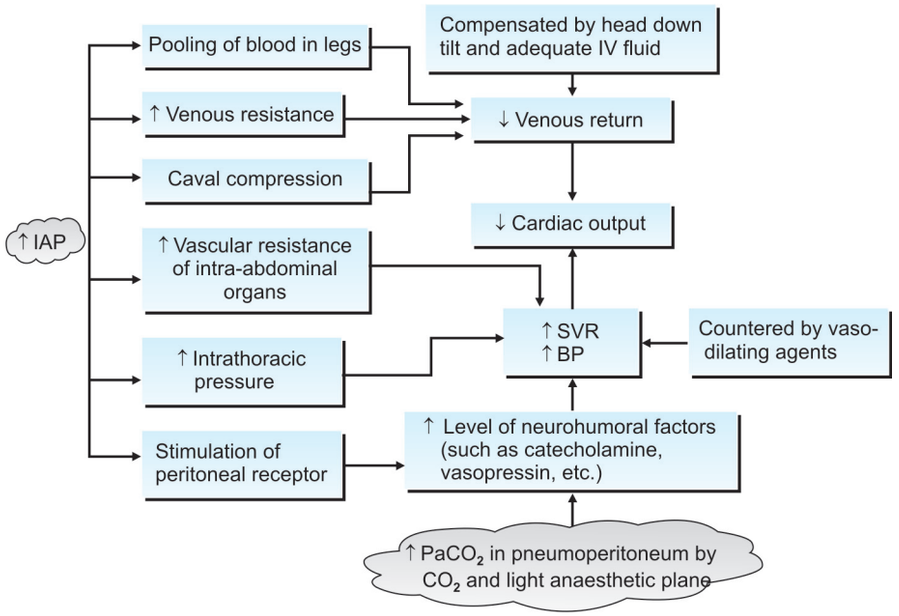


Fig. 36.1: Increased IAP due to pneumoperitoneum patients's position

(mechanical factors) and (ii) release of neurohumoral factors such as catecholamines, prostaglandins, renin-angiotensin and vasopressin, etc. due to mechanical stimulation of peritoneal receptor caused by stretching due to pneumoperitoneum. Within physiological limits, a normal heart tolerate this increase in afterload and ↓CO. But, patients with cardiac disease cannot tolerate this ↑afterload and ↓CO. The ↑SVR in pneumoperitoneum is also due to the reflexly increased sympathetic activity in response to the reduced cardiac output. This is proved by the fact that SVR decreases in Trendelenburg position which tries to increase the venous return and CO and increases in head up position, which tries to decrease the venous return and CO. The increased SVR or afterload can be corrected by vasodilating agents like isoflurane, nitroglycerine, nitroprusside, nicardipine and α_2 agonist (clonidine or dexmedetomidine), etc.

The magnitude of the cardiovascular response due to pneumoperitoneum is directly proportional to the insufflation pressure. So to avoid any cardiovascular response, IAP should be kept below 12 mm Hg. On the otherhand, most of the anaesthetic agents depress the myocardium and further reduce the cardiac output. Head up tilt further detoriates these parameters (↑SVR ,↓CO).

Increased intra-abdominal pressure (IAP) also results in venous stasis in lower limbs which predisposes to the development of thromboembolic complications. Increased IAP decreases renal plasma flow, GFR and urine output. ↑IAP also leads to decreased blood flow to the intra-abdominal organs except adrenal gland. Mesenteric, intestinal mucosa and splenic blood flow is also decreased. Thus, the intestinal mucosal ischaemia results in decreased intestinal mucosal pH and may delay the return of normal bowel function.

Haemodynamic changes due to pneumoperitoneum are well tolerated in healthy patients as suggested by the normal arterial O_2 saturation and normal plasma lactate level, observed during laparoscopic procedures. But this tolerance might be different in patients with impaired cardiac function, anaemia or hypovolaemia. Therefore, IV nitroglycerine, IV nicardipine or IV dobutamine is used to manage the haemodynamic changes (↑SVR, ↑MAP, ↓CO), induced by ↑IAP in selected patients with heart disease. In these patients preoperative preload is also augmented by the judicious use of IV fluid that offsets the haemodynamic effect of pneumoperitonium, i.e. reduction of preload and subsequent reduction of cardiac output.

Steps to prevent haemodynamic changes

Several steps can be taken during laparoscopic surgery to prevent the haemodynamic changes caused mainly by pneumoperitoneum and head down or head up position of patient. These are as follows.

i. Premedication with α_2 adrenergic agonist such as clonidine or dexmedetomidine (more selective α_2 agonist).
ii. Use of anaesthetic agents having least haemodynamic effects, such as fentanyl / alfentanil / sufentanil, isoflurane / sevoflurane, vecuronium, etc.
iii. Maintenance of proper plane of anaesthesia.
iv. Increasing the circulating blood volume by infusing 7 to 8 ml/kg of crystalloid solution before inducing the pneumoperitoneum.
v. Considering the gasless laparoscopy.
vi. Slow insufflation of CO_2 for pneumoperitonium (rate 1 lit/min) which will allow adequate time for compensation.
vii. Maintaining low intra-abdominal pressure (10 mm Hg).
viii. Head up tilt after insufflation.
ix. Considering the vasodilating drugs like nitroglycerine, nicardipine nintroprusside, etc. for prevention of haemodynamic changes associated with pneumoperitonium, i.e. ↑SVR.

PROBLEMS DURING LAPAROSCOPY

Problems Due to Hypercarbia

Mild hypercarbia (P_aCO_2 is between 45 to 50 mm Hg) have little impact on the haemodynamic system. Increasing $PaCO_2$ from 55 to70 mm Hg has a direct myocardial depressant and vasodilating effect. At cellular level, it has a depressant effect

on myocardial contractility and a stimulant effect on myocardial irritability and arrhythmicity. Hypercarbia also decreases the responsiveness of blood vessels to catecholamines. It also causes vasodilatation especially on the venous side leading to peripheral pooling of blood, decreased venous return and decreased cardiac output. Exception exists in the pulmonary vessels which undergo vasoconstriction in response to ↑$PaCO_2$. However, the effect of ↑$PaCO_2$ on pulmonary vessels is due to indirect acidosis rather than direct hypercarbia. But the local effect of $PaCO_2$ on pulmonary vessels is over shadowed by its systemic effects or the effects of ↑$PaCO_2$ on the central nervous system. Hence, the net effect of CVS in response to ↑$PaCO_2$ usually are (after an initial increase) the decrease in cardiac output, ↓stroke volume, ↓heart rate, ↓force of myocardial contraction and increase in blood pressure, ↑central venous pressure, vasoconstriction of pulmonary vessels and increase in peripheral vascular resistance and cardiac arrhythmias. Respiratory acidosis also increases sympathetic outflow resulting cardiac arrhythmia, especially in the presence of halogenated anaesthetic agents such as halothane, isoflurane and sevoflurane. Among these halothane is the most notoreius. Bradycardia and other cardiac arrhythmias may also occur from increased vagal reflexes and it is due to the peritoneal stretching during insufflation of peritoneal cavity.

In summary gas insufflation into the peritoneal cavity which is followed by stretching of the peritoneum which is followed by raised intra-abdominal pressure and altered patient's position all together can cause a range of clinical responses. These are:

i. *Sympathetic response:* Hypertension, tachycardia, ↑SVR. These are treated by increasing the dose of volatiles, short acting opioids (fentanyl, sufentanil, remifentanil), vasodilators and/or betablocker.
ii. CVS response: CVS depression with fall in cardiac output leadint to hypotension, tachycardia or bradycardia. This is treated by fluids, vasodilators, and/or inotrops.
iii. *Vagal response:* Asystole, sinus bradycardia, nodal rhythm, hypotension etc. This can be treated by vagolytics.

Problems Related to Patient's Position

For laparoscopic surgeries patient is positioned with a head down (for pelvic or infra-mesocolic surgery) or head up (for supramesocolic surgery) tilt and it may be added with lithotomy position. These altered positions of patients working synergistically with the ↑IAP are responsible for the development of different pathophysiological changes during laparoscopy. The changes are also influenced by: (i) extent of the tilt, (ii) intravascular volume status, (iii) the patient's age, (iv) anaesthetic drugs administered, (v) associated cardiac disease and (vi) type of ventilation techniques. The changes in respiratory system and CVS due to head down position is same as that due to ↑IAP, but only in exaggerated form. On the other-hand, the changes in respiratory and cardiovascular system due to head up position is opposite to the changes due to ↑IAP and favours improved pulmonary dynamics.

In head down position the FRC, total lung volume, FVC and the compliance of lung decreases which facilitate the development of atelectasis, intrapulmonary shunt, hypoxia and hypercarbia. In head down tilt, there is also increase in central blood volume and decrease in vital capacity and all of these are due to the diminution of diaphragmatic excursion. Thus, the changes due to head down position is unfavourable for respiratory system. In healthy patient these changes in respiratory system are minimally seen, but are more marked in obese and elderly patient. In the contrary, changes due to head up position is favourable for the respiratory system.

When head down tilt does not increase more than 15°, then shift in blood volume is too small to induce any clinically significant haemodynamic changes. In normal healthy subject, isolated increased hydrostatic pressure associated with head down position results in increased venous return, ↑CVP and ↑CO (whereas isolated ↑IAP due to pneumoperitoneum causes ↑CVP ↓CO). So, during laparoscopic surgery, Trendelenburg position and pneumoperitonium producing (↑IAP) together causes ↑↑CVP, ↑↑PCWP and ↓↑CO. These changes are tolerated well by healthy patient, but not by patients with low cardiopulmonary reserve. Isolated reverse Trendelenburg position decreases the preload, CVP, MAP and CO, i.e. ↓preload, ↓CVP, ↓MAP, ↓CO (↑IAP also causes ↓preload though CVP paradoxically increases, ↑MAP, ↓CO). So during laparoscopic surgery anti Trendelenburg position with pneumoperitoneum together causes : ↓↓preload, ↓↑CVP, ↓↑MAP, ↓↓CO. The steeper will be the tilt, the greater will be the fall in CO.

If there is intraoperative hypoxia during laparoscopic surgery, the causes may be:

i. Hypoventilations due to pneumoperitoneum, head down position, inadequate ventilation during IPPV, etc.
ii. Ventilation – perfusion mismatch due to reduced FRC, atelectasis, endobronchial intubation, extraperitoneal gas insufflation, bowel distension, pulmonary aspiration and rarely pneumothorax.
iii. Reduced cardiac output due to IVC compression, arrhythmias, haemorrhage, myocardial depression, venous gas embolism, extraperitoneal gas.

So, the patient should be tilted very slowly and progressively, avoiding sudden respiratory and haemodynamic changes. The position of ET tube should be checked after every change in position of patient. Mask ventilation may inflate the stomach. So, it should be aspirated by a ryle's tube before introduction of trocar and cannula to prevent gastric perforation.

CONTRAINDICATION OF LAPAROSCOPIC SURGERY

There is no absolute contraindication for laparoscopic surgery. Therefore, all the contraindications to laparoscopic surgery are relative. For example, when the physiological effects arising from the CO_2 insufflation into the abdominal cavity under pressure is combined with the effects arising from the variations in positioning of patients, then it has a major impact on cardiopulmonary function, particularly in ASA grade III and IV and is contraindicated. But, the recent report of 'gas less laparoscopy' using an abdominal wall lifting device may obviate the requirement of pneumoperitoneum and allow safe laparoscopy for these ASA grade III and IV patients. Successful laparoscopic procedures also have been now carried out on patients who are anticoagulated, morbidly obese or pregnant which are previously contraindicated. Even the different literatures now confirms that LC (laparoscopy cholecystectomy) can be safely be performed in all the trimesters of pregnancy with no increase in fetal and maternal morbidity. The available datas suggest that the efficacy and safety during LC in pregnancy can be increased by using the open Hasson technique for instrumentation. This safety also can be increased by:

i. Limiting the IAP during pneumoperitoneum in pregnancy.
ii. Ensuring adequate maternal oxygenation and normocapnia by proper ventilation.
iii. Using appropriate maternal and foetal monitoring.
iv. Using active antithromboembolism measures.
v. Preventing aortocaval compression by tilting the patient on left side.

Acute cholecystitis, despite concerns about the technical difficulties due to associated oedema, inflammation and necrosis, etc. is no longer considered as contraindication to the laparoscopy which was taken as contraindication previously. Any previous intra-abdominal surgery was initially taken as contraindication for laparoscopic surgery, but they are now considered safe in experienced hand. There is considerable controversy regarding the appropriateness of laparoscopic surgery for the treatment of known malignant disease. For example, laparoscopic cholecystectomy in known gallbladder malignancy is controversial. Fit and young patients tolerates the physiological changes well and definitely are not contraindicated. But the elderly patients of ASA III and IV status with cardiac and pulmonary disease have more marked and deleterious responses to laparoscopy but still they are not contraindicated. Contrary, they should be thoroughly reviewed and their medical condition is optimised preoperatively and should have a surgeon well experienced in this procedure.

COMPLICATIONS OF LAPAROSCOPIC SURGERIES

Surgical Complications

Unusual and unexpected vascular trauma and haemorrhagic shock is responsible for 30% of major complications of endoscopic on laparoscopic surgery. Blood vessels of the anterior abdominal wall, or peritoneal cavity or retroperitoneal space may be punctured by the Verres needle or trocar and canula. Near the level of umbilicus, both the medial vessels (superficial and inferior epigastric) and lateral vessels (superficial and deep circumflex iliac) are at the increased risk of injury. But, we will have to keep in mind that blood loss in the anterior abdominal wall and retroperitoneal space may be considerable in amount before detection than the blood loss into the peritoneal cavity before detection. Retroperitoneal haematoma can develop insidiously and result in significant amount of blood loss without major intraperitoneal effusion, leading to delayed diagnosis. Other than injury of blood vessels, another important complications of endoscopic surgery is trauma to the abdominal visceral which may lead to peritonitis, subdiaphragmatic abscess formation and septic shock. Accidental fulguration by electrocautery has also been associated with bowel burns and bowel gas explosions (Fact file- II).

Examples of other complications resulting from endoscopic surgeries are: hepatic and splenic rupture, avulsions of of band arising from previous adhesions, omental disruption, or herniation at trocar insertion site, etc. To avoid the above mentioned injuries caused by blind Verres needle or trocar insertions, 'Hasson' minilaparotomy technique has also been advocated for creation of pneumoperitoneum. In this technique a minilaparotomy incision is primarily made, through which a trocar is inserted under direct visual guidance to create pneumoperitoneum.

FACT FILE- II

i. Laparoscopic surgery provides lots of benefits which include : Less trauma, less pain, quick recovery, less pulmonary complications, less hospital stay, less cost, etc.
ii. Pneumoperitoneum causes cardiorespiratory changes. $PaCO_2$ increases due to absorption of CO_2 through peritoneal cavity when CO_2 is used for pneumoperitoneum.
iii. In sick patients (ASA III and IV) these cardiorespiratory changes due to IAP and head down tilt is further accentuated by $\uparrow PaCO_2$.
iv. Hence, better knowledge of pathophysiology of these haemodynamic changes allow successful anaesthetic management of sick patients by optimising preload and use of vasodilating agents.
v. Gasless laparoscopy is theoretically helpful, but technically is very difficult.
vi. Alternative to CO_2, other inert gases such as argon, helium, N_2O do not seem to reduce the haemodynamic changes.
vii. The death rate in laparoscopic surgery is 0·1 to 1 per 1000 cases. The incidence of both visceral injury and haemorrhagic complications is 2 to 5 per 1000 cases. This is favourable when compared with open surgery.
viii. No anaesthetic technique is superior to other. But GA with controlled ventilation is safest for operative laparoscopy.

It is very important to mention that all the above mentioned complications of endoscopic procedure are surgery related. But anaesthesiologist must be aware of all these surgical complications and also the timing of their occurrence. Because they should be prepared to respond promptly to these adverse situations.

Respiratory Complications

The use of pressurised gas during pneumoperitoneum introduces the possibility of extravasation of used gas along the tissue planes, resulting in subcutaneous or retroperitoneal emphysema. This may prolong the surgery or cause its abandonment. Subcutaneous emphysema occurs when the tip of the Veress needle does not enter the peritoneal cavity before the insufflation of gas. This produces the insufflating gas to accumulate in between the fascias sheath and the peritoneum or in the subcutaneous tissue plane of anterior abdominal wall. The incidence of this complication is near about 0.4% to 2% and is the most common. If the insufflating gas is CO_2 then the extraperitoneal accumulation of this gas may cause quick absorption of it than the intraperitoneal insufflation and may be the cause of sudden rise in $PaCO_2$ and $ETCO_2$ tension.

If the pressure used to inflate the peritoneal cavity by gas is too high, then this gas may be forced out through the occasionally present congenital foramina (patent pleuroperitoneal canal) in the diaphragm causing pneumothorax, pneumopericardium or pneumomediastinum. These complications occur primarily on the right side and usually also is reduced within 30 to 60 minutes of desufflation. The insufflated gas from peritoneal cavity also may track around the aortic and oesophageal hiatuses of the diaphragm into the mediastinum and then may rupture into the pleural space. Commonly, these weak points or defects in the diaphragm occur at the pleuroperitoneal hiatus or foramen of Bochdalek. Sometimes, these complications remain undiagnosed and pneumomediastinum or pneumothorax may become life threatening. The subcutaneous emphysema over the chest wall, neck and face should also alert the anaesthetist regarding the possibility of these dreadend complications. The intraoperative diagnosis of these complications can be confirmed by the presence of increased airway pressure, haemodynamic instability and O_2 desaturation. If the patient is haemodynamically unstable and there is clinical evidence of pneumothorax, then abdominal insufflation should be stopped immediately. The diagnosis of pneumothorax should be confirmed by chest radiograph and immediate decompression of thorax should be done by putting a tube in the pleural cavity. Once the chest decompression is in a satisfactory position, then the abdomen can be insufflated again by gas and the procedure can be continued, if the patient remains stable.

Gas embolism is the most feared complication of endoscopic surgery which may lead to hypoxemia, pulmonary hypertension, pulmonary oedema and cardiovascular collapse. The causes of gas embolism are : (i) the Veeres needle or trocar cannula may directly be into a vessel, or (ii) the gas may be forced into the vessels through open sinuses of the surgical site by high intra-abdominal pressure. Unlike air embolism, in CO_2 embolism there is no bronchoconstriction, but only the end tidal CO_2 tension may increase transiently.

Sometimes inadvertently endotracheal intubation may be converted to endobronchial intubation by the cephalad shift of the diaphragm along with the intrathoracic organ due to ↑IAP due to intraperitoneal insufflation and head down position of the patient. So, the ET tracheal tube should be firmly taped and its cuff should lie well above the carnia. Therefore, it should be rechecked after pneumoperitonium and after any further change in the patient's position. Increased intra-abdominal pressure decreases the risk of regurgitation (by increasing the lower oesopahgeal sphincteric tone) and head down position further reduces the risk of aspiration of these regurgitated material into lungs. Still preoperative administration of H_2 receptor blockers is recommended, since the risk of regurgitation and aspiration persists in high-risk patients.

Cardiovascular Complications

There is high incidence of cardiac arrhythmias during the laparoscopic surgeries. Hypercapnia is the major cause of it. Other precipitating factors of cardiac arrhythmia are hypoxia, haemodynamic changes and vagal reflexes (resulting from the sudden stretching of peritoneum due to pneumoperitoneum). In light plane of anaesthesia this intense vagal stimulation may cause severe bradycardia, cardiac arrhythmias and even asystole. 27% incidence of vagal stimulation have been reported in spontaneously breathing patients under halothane. This incidence may be reduced to 5% in mechanically ventilated patients and when peritoneal insufflation done with N_2O rather than CO_2. Therefore, mechanical ventilation and adequate depth of anaesthesia by the use of isoflurane/sevoflurane etc. is recommended to reduce the incidence of cardiac arrhythmia during laprascopic surgery. Arrhythmias may be the first sign of gas embolism. The cardiac arrhythmias occurring during the early part of CO_2 insufflation (when $PaCO_2$ is at normal level) is mainly due to the vagal stimulation, caused by the rapid haemodynamic changes and rapid rise of IAP. So, these arrhythmias are quickly treated by stoppage of insufflation, injection of atropine (for bradycardia) and deepening of anaesthesia only after recovery of heart rate from bradycardia.

Nerve Injury

Sometimes nerve injury is a potential complication during laparoscopic surgery in head down and lithotomy position. The commonly inflicted nerves are brachial plexus and common peroneal. The nerves of

brachial plexus are commonly injured due to the over extension of arm. So, prevention of over extension of arm and cautious use of shoulder braces can reduces the incidence of brachial plexus injury. Common peroneal nerve is highly vulnerable during prolonged lithotomy position and so care should be taken during the positioning of patient in lithotomy position. Lower extremity compartment syndrome is also reported after prolonged lithotomy position.

ALTERNATIVES TO CO_2 PNEUMOPERITONEUM

Besides CO_2, pneumoperitoneum can also be produced by using air, O_2, N_2O and N_2. But, CO_2 is generally preferred and at present it is the most commonly used gas for laparoscopy This is because of its greater solubility in blood (so the risk of gas embolism is reduced), rapid elimination by the lungs, ready availability, low cost and noninflammability during electrocautery which is part and parcel of laparoscopic surgery. N_2O also can be used for insufflation of peritoneal cavity during laparoscopy surgery to produce pneumoperitoneum, but it is inflammable during electrocautery. Another advantage of N_2O to produce pneumoperitoneum is that it does not increase the size of CO_2 bubbles in blood. Other alternative approach for pneumoperitoneum in laparoscopy is the use of inert gases or even gasless laparoscopy.

Inert Gases

Among the inert gases, only argon and helium have been used to cause pneumoperitoneum, instead of CO_2 during laparoscopy. The only advantage of inert gases is that it avoids the increase in $PaCO_2$, secondary to CO_2 absorption through peritoneum. But the inert gases cannot avoid the pulmonary and haemodynamic changes due to ↑IAP. On the contrary, the main disadvantage of the use of inert gases is their low blood solubility and decreased safety in the event of gas embolism.

Gasless Laparoscopy

Peritoneal cavity can also be expanded by elevating the abdominal wall by using a fan retractor instead of using any gas. Thus, it avoids the haemodynamic and respiratory changes due to the increased IAP and the use of CO_2, specially in patients with cardiorespiratory compromised. But, gasless laparoscopy compromises surgical exposure and increases the technical difficulty. Therefore, combining the abdominal wall lifting with fan retractor and low pressure CO_2 pneumoperitoneum (5 mm Hg) might improve the surgical exposure and will reduce the bad effecct of high pressure CO_2 pneumoperitoneum on RS and CVS. The other advantages of gasless laparoscopy is that it is associated with the less incidence of PONV and less incidence of metastasis of malignancy at the site of laparoscopic part.

LAPAROSCOPY DURING PREGNANCY AND CHILDREN

The most common surgeries that are performed by laparoscopy during pregnancy are appendisectomy and cholecystectomy. During laparoscopic surgery in pregnancy the important points that should be kept in mind are the following:

i. Any abdominal surgery during (endoscopic or not) pregnancy increases the risk of miscarriage and premature labour and this is maximum before 12th week of pregnancy and after 24th week of pregnancy. So, the laparoscopy performed between 12 and 23 weeks of pregnancy has the minimum risk for miscarriage and preterm labour and provides adequate intra-abdominal working space for endoscopy.
ii. Laparoscopy has the special risk of directly hitting and damaging the gravid uterus. This can be avoided by the alternative sites of entry for the verres needles and trocar cannula.
iii. Open laparoscopy can be used to avoid damaging the uterus.
iv. Pneumoperitoneum produced by CO_2 can induce significant foetal acidosis. So, maternal $PaCO_2$ should always be monitored closely and maintained at normal levels. Hence, the mechanical ventilation should be adjusted correctly to maintain a physiological maternal alkalosis.
v. Tocolytics should be used routinely during laparoscopy to arrest preterm labour.
vi. Foetal monitoring is must during laparoscopy by transvaginal USG.
vii. IAP during pneumoperitoneum in the state of pregnancy should be limited between 8 and 10 mm Hg. Gasless laparoscopy is an alternative to avoid the potential side effects of CO_2 pneumoperitonium and elevated IAP during pregnancy. Operation in a left lateral position is a safeguard against the supine hypotension which is often found during pregnancy.
viii. Laparoscopy during pregnancy under epidural anaesthesia reduces the hazards of anaesthetic drugs on foetus and the course of pregnancy.

The diagnosis of acute appendicitis continues to be a great problem for clinicians, despite the significant advances in surgery over the past century. In 20% of patients with appendicitis, the diagnosis is missed clinically. On the other hand, the appendix is normal in 15 to 40% of cases when they are undergoing emergency surgery for suspected appendicitis. Now, more and more laparoscopy guided surgery is performed in children and the most common indications of these is appendisectomy. But, datas concerning the haemodynamic changes and ventilatory tolerance produced by pneumoperitonium in children is inadequate. Due to the increased ratio of peritoneal surface area to body weight, the absorption of CO_2 in CO_2 – pneumoperitoneum is intense and faster in children. But, during brief laparoscopy, $ETCO_2$ tension rises slightly and no increase in ventilation is required.

In a recent randomised study, it is seen that the laparoscopic appendisectomy does not improve the postoperative recovery and analgesia in children. The laparoscopic appendisectomy technique is associated with longer duration of surgery, but shorter hospital stay and no difference in terms of time to return to normal activity compared with conventional open surgery.

ANAESTHETIC PROCEDURE

Any standard anaesthetic technique such as LA, RA or GA adapted for laparoscopic surgery does not play any major role in patient's outcome. But, GA with endotracheal intubation and controlled ventilation is considered as the safest technique for long laparoscopic surgical procedures. During pneumoperitoneum CO_2 which is absorbed through the peritoneum increases $PaCO_2$ and thus makes the tracheal intubation and artificial ventilation necessary. General anaesthesia and artificial ventilation is also chosen, because under LA or RA patients feel great discomfort which is due to the creation of pneumoperitoneum and the extent of the changes of the position of patient necessary for the procedures.

In general, the local or regional anaesthetic technique is not recommended for upper abdominal and long laparoscopic surgeries. The choice of agents for induction and maintenance of GA are not important, except that the cardio-depressant agents should be avoided. There is higher incidence of PONV after laparoscopic, surgery especially following gynaecological procedures. So, an antiemetic agent should be given prophylactically in all the cases of laparoscopic surgeries. As the pneumoperitoneum needs increment of minute ventilation by 15 to 25%, so it can be achieved by increasing the respiratory rate rather than the tidal volume which avoids much alveolar inflation and reduces the risk of pneumothorax (by rupturing the emphysematous bullae). This principle is more applicable for COPD and emphysematous patients. Whatever may be the technique of ventilation, $ETCO_2$ tension should be maintained at approximately 35 mm Hg. The N_2O used for maintenance of anaesthesia is not contraindicated for any laparoscopic surgery, but it is better to avoid in laparoscopic intestinal and colonic surgery. IAP should be monitored closely and is not allowed to exceed maximally above 15 mm Hg in any condition. Theoretical profound muscle relaxation is not necessary for laparoscopic surgery, but inadequate muscle relaxation may intensely increase IAP without adequate pneumoperitoneum and reduces working space. Reversely, adequate muscle relaxation provides adequate working space without much increase of IAP.

The use of LMA as an alternative to ET tube in laparoscopic surgeries has both the advantages and disadvantages. The advantages of LMA are: less laryngeal irritation, less postoperative cough, easy to insert, etc. which are discussed in appropriate chapters. The disadvantages of LMA in laparoscopic surgery are: (i) It cannot protect the airway from aspiration of gastric contents and (ii) controlled ventilation is sometimes difficult when the airway pressure exceeds 20 cm of H_2O due to decreased thoracopulmonary compliance due to pneumoperitoneum. So, the use of LMA for laparoscopic surgery is limited only to the healthy and thin patients for spontaneous or controlled ventilation. GA with spontaneous respiration without LMA or intubation should be used only for short procedures with low IAP and slight degrees of tilt.

Laparoscopic surgeries performed under local anaesthesia requires very short, precise and gentle surgical procedure such as tubal ligation, some diagnostic procedures, some investigation during infertility management, etc. Laparoscopic surgery done under LA provides several advantages. These are: fewer haemodynamic changes, early diagnosis of complication, early recovery, reduced PONV and avoidance of complications of GA. But the success of endoscopy under LA depends on the relaxed and co-operative patient, trained OT staff, skilled surgeon, and as low as possible increased IAP. During laparoscopy under local anaesthesia patients usually suffer from discomfort due to pneumoperitoneum and so necessitiate IV sedation. But, sedation and pneumoperitoneum both usually produce O_2 desaturation and so care should be taken. Regional anaesthesia (spinal and epidural) for laparoscopic surgeries share the same advantages and disadvantages like LA, but it may be applied for surgical procedures which are longer than that can be done under LA but shorter than that which need GA. Whereas very long surgical cases should be done under GA, rather than RA. The RA provides better muscle relaxation and so less sedation is needed (than LA), without major impairment of ventilation. The surgical stress related to metabolic responses are also reduced in RA which is a great advantage of it than GA. The haemodynamic effects of pneumoperitoneum under RA is still being studied. So, the patient's co-operation, experienced surgeons, less increase in IAP and moderate head up or head down tilt are the key factors for the success of laparoscopic surgeries under regional anaesthesia (RA).

37 Laser Surgery and Anaesthesia

INTRODUCTION AND PHYSICS

The full form of the word laser is Light Amplification by Stimulated Emission of Radiation. In simple form, it can be said that laser provides a huge quantity of energy in the form of light or photon particles which can be transferred very rapidly to a remote and a very specific location to destroy the tissue by heat and vaporization. Actually, visual light is an electromagnetic wave with combined electrical and magnetic properties. It propagates at a speed of 299792458 meter/second. Thus ordinary light is a form of radiant energy that spans in the mid-range of whole spectrum of electromagnetic wave. It is released as photons and travels as a wave. This was the explanation of Maxwell about light in 1864. The wavelength of visible light ranges between 385 to 760 nanometer. The light below this wavelength is called the ultraviolet rays and the light above this wavelength is called the infrared rays. Subsequently Max Plank had said that if a light only of blue in colour and of certain wavelength falls on a specific metal, then it emits some electrons from the metal at a rate which is proportional to the brightness of the light. After that in 1905, Einstein, by his quantum mechanics explained that electromagnetic radiation or wave of normal light which consists of photons have properties of both the particle (mass) and the energy (wave). Einstein also said that emission of electron from a specific metal as a result of this fall of blue light is independent of the number of photons, present in the falling light. Energy is the key factor for emission of electron from metal i.e. only photons of high energy with high frequency wave can provide this energy which is necessary to stimulate this electron emission from metal. Lower energy photons, even arriving in large numbers at a given time can not emit electrons from this specific metal. These findings results in the development of laser.

The electrons usually encircle the nucleus of an atom in many orbits and each orbit has a specific energy level with fixed number of electrons. If an electron moves from one orbit to another, i.e. from higher to lower or lower to higher orbit, then it absorbs or emits an amount of energy which is exactly equal to the difference in energy between the two adjacent orbits. When an energy or a photon falls from outside on an atom, then the electron of lower energy orbit, absorbs it and jumps to the outer next higher energy orbit. This phenomenon is called the stimulated absorption and the new state of this atom is called the stimulated state. Similarly, when an electron from higher energy orbit enters into the next inner lower energy orbit, then it emits some energy or photon. This phenomenon is called the spontaneous emission and the new state of this atom is called the emission state. A third situation, predicted by Einstein in 1917 is the stimulated emission which is a combination of previously mentioned both the states of a atom. Here, if a photon or energy of a particular wavelength colloids with an atom which is ready from previously for a spontaneous emission (i.e. having an electron already in the higher energy orbit and ready to enter in lower energy orbit with emission of energy or photon) then two photons or energy waves will come out of this atom (one that is falling on the atom and the other by the mechanism of spontaneous emission). Thus, the emitted two photons will have the identical wavelength, phase and directions. This phenomenon is called the stimulated emission.

The energy differences among the different orbits are specific to different atoms. Thus, the emission and absorption spectra of energy of an atom is very specific, like fingerprint for this atom and hence is used for atom's chemical identification. Normally, in the thermodynamic equilibrium state, the electrons of an atom usually lie in the orbit of lowest available energy. So, the key for formation of laser is to pump up the electrons to the higher energy orbit (stimulated state) where they will wait for an external photon to collide and start a chain reaction (or amplification) of stimulated emission, i.e. when one photon will collide with an stimulated atom, then two photons will come out, which again falls on another atom lying in already stimulated state. Thus 4 photons will come out which again fall on another stimulated atom and this type of chain reaction will go on repeatedly. The technology for previous pumping up of electron from lower energy orbit to higher energy orbit in an atom of a material (which is known as the laser medium) and to achieve stimulated state of an atom was introduced in 1958. Then later, a method was also developed by placing the laser

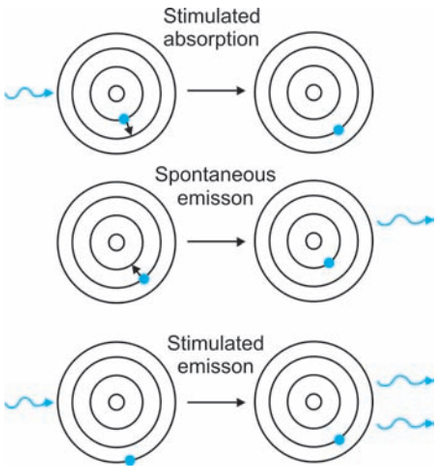


Fig. 37.1: Interaction of photon with electron
Stimulated absorption: Here a photon strikes an electron and transfers its energy to this electron. This transferred energy pushes the electron into a higher oribt.
Spontaneous emission: Here an electron is pushed from higher energy orbit to lower energy orbit. Thus it losses some energy which is emitted as photon.
Stimulated emission: Here, an incoming photon interact with an electron that is already pushed in a high energy orbit before by some energy, with the result that two photons or energy particles leave the electron and it is pushed back in the lower orbit.

medium between two parallel reflecting mirrors, so that stimulated emitting photons could traverse the medium by repeatedly striking the more and more atom of this laser medium which are already in the stimulated state and emitting more and more photon and thus maximising the number of stimulated emission (Fig. 37.1).

Now, this amplified photons or light energy that is radiated by the mechanism of stimulated emission (laser light) differs from the ordinary light in that the laser light consists of photons that have very well defined and narrowband of wavelength. Whereas, the ordinary light consists of photons of wide wavelength and less defined. Laser light has no dispersion. It is confined and propagated as a very narrow beam. Whereas, the ordinary light spread out in all directions from the point of its source. All the waves of photons (or energy) of Laser light always remain in the same phase, whereas the waves of ordinary light remain in different phases. This property of Laser is called the coherent, i.e. all the peaks of the wave of the energy or photon move synchronously at the same direction and same amplitude. Another property of laser is that it is monochromatic, i.e. all the waves of same wavelength. Thus these three characteristics allow the Laser: (i) To generate intense light beam, (ii) To send such light beam efficiently and accurately at distance places through lenses and (iii) to deliver intense energy on a small target site.

So, to produce Laser, we need three things: (i) The Laser medium containing the atoms whose electrons could be capable of creating the Laser light, (ii) An energy source to pump and excite—(stimulate) the electrons of the atom of Laser medium from lower energy orbit to higher energy orbit and (iii) Two resonating mirrors to amplify the amount of liberated photons and to create the chain reaction. In a laser tube, the application of an energy source on a lasing medium back and fourth between the carefully aligned mirrors and are focussed into a high intensity beam. Three types of laser medium are used practically. These are : (i) Gaseous laser medium, for example CO_2, argon, krypton, helium, neon, etc, (ii) Liquid laser medium such as some dyes and semiconductors, and (iii) Solid laser medium such as chromium, neodymium, holmium and synthetic crystals known as YAG (Yttrium Aluminium Garnet). According to the mode of delivery of light beam laser also can be classified into intermittent, short, long or continuous. Gas laser produces either a continuous or intermittent pulsed beam. But, solid laser always produces intermittent pulsed beam. The continuous wave of CO_2 laser produces radiation, having a wavelength of 10 µm. It is strongly absorbed by water and damages tissue surfaces up to the depth of 200 µm. For this reason the CO_2 laser is suitable for removing any superficial lesions, for example removal of a small growth from the vocal cords or larynx. For energy source, which is used to pump and excite the electrons from lower energy orbit to higher energy orbit in the atoms of a laser medium, usually the xenon flash lamp (for solid laser medium) or high electrical power (for gaseous laser medium) is used. As lasers mediums are not very efficient in converting electrical energy into light energy, so they require a large power supply (e.g. a laser with 10 W output requires in excess of 1000 w of current) (Table 37.1).

Table 37.1: Different types of laser and their wavelength and colour

Laser type	*Colour*	*Wavelength (nm)*
Argon	Blue / green	488-515
CO_2	Far-infrared	10,600
Helium-neon	Red	633
Dye	Blue to red	360-670
Ruby	Red	694
Nd-YAG	Near infrared	1064

After emission of Laser, usually a light guide is used which directs the laser beam to the surgical site. But, now the development of fiber-optic bundles provide a convenient, flexible way to deliver the laser light to a distant surgical site. At the end of this light guide or the fibre-optic bundle, there is a lens which focuses the laser light to a minimum size (sometimes the spot size is 30 µm or 0.03 mm), creating a very high density of power or energy over a small area. In operating microscpe, the laser light is focussed on the tissue by the lenses of microscope.

CLINICAL APPLICATION AND BIOLOGICAL EFFECTS OF LASER

So long, we have learnt that laser is nothing but a intensly amplified number of photon particles or energy, directed at a very small pinpoint area. Actually, it does not increase the energy of a particular photon, but simply places or concentrated the more photons or energy at a given place and time than the ordinary light sources. This high density of power or energy, delivered at the

very small target site, produces enormous heat at the rate of many thousand calories per second (approximately 2500 cal/sec). This causes rapid vaporization of any tissue or material, except metals. So, to remove tissues (by heat and vaporization) laser is used as a scalpel, allowing highly precised microsurgery, to perform in a confined or difficult to reach sites. Laser also causes electrocoagulation. So, laser surgery is relatively dry, providing a near instantaneously sealed small blood vessels and lymphatics, even in the presence of clotting abnormalities. In summary, the advantages of using laser include: Less bleeding, ability to coagulate small blood vessels, maintenance of sterile operating conditions, less tissue handling and reaction, increased precision of dissection and preservation of surrounding normal tissues (Fig. 37.2).

Normally water is the main constituent of tissues, and a living tissue is a complex aqueous solution, containing varieties of molecules. Absorption of laser energy in this water of living tissue (mechanism of action of laser on tissues) depends on the wavelength of this laser light. The larger will be the wavelength, the more will be the absorption of laser light in the water and more will be the production of heat for vapourisation of the tissues. CO_2 laser (10600 nm wavelength) is completely absorbed by water. So, after falling of CO_2 laser on tissues it can not penetrate or pass,

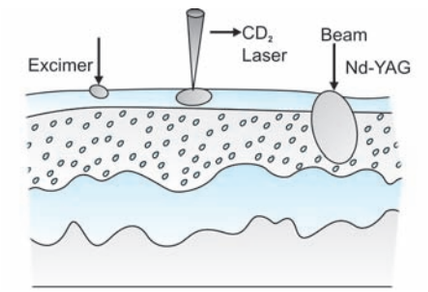


Fig. 37.2: Laser beam of different wavelength causes different patterns of tissue destruction. The actual tissue destruction by laser light depends on both the laser parameters and tissue factors. The laser parameters are: power density, duration, and wavelength. The tissue factors are: Absorption, scatter, thermal conductivity and local circulation

except for a few superficial cell layers of the tissue. Thus, only these surface tissues or cell layers are heated and vapourised with surprisingly little damage to the underlying cells or tissues. Excimer laser is of greater wavelength than CO_2 laser and so has an extremely precise effect on the very superficial cells than CO_2. The Nd-YAG laser is of short pulsed, high powered glass laser which can be transmitted by fibreoptic bundle. The wavelength of YAG laser is 1064 nm and is so less absorbed by water. It is absorbed preferentially by the haemoglobin and pigmented tissues and has deep penetrating effect. So, it can pass through the cornea and is useful in treating the detached retinas. The Nd-YAG laser beam diffuses several millimeters through a tissue which is 100 to 1000 times greater than CO_2 laser. As Nd-YAG laser disseminates widely, so it does not cause heat and vaporisation of tissues, but produces thermal coagulation. Some lasers such as ruby laser has wavelength of 694 nm (very small). So it is also poorly absorbed by tissues except by the cells containing dark pigments. The argon (wavelength 514,488 nm) and krupton (wavelength 476,521,568 nm) gas lasers is transmitted through water though they have large wavelength (so pass through cornea), but intensly absorbed by Hb. It provides the ability to penetrate the skin or occular structures and selectively coagulate the vascular or pigmented regions (also useful in treating detached retinas) (Fact file-I).

FACT FILE - I

Laser light striking the tissue surface may be :

i. Reflected

Reflection of laser rays from the shiny surfaces may damage the eyes of any person in the vicinity.

ii. Transmitted

Laser light which is transmitted through superficial tissues to the deeper layers of variable depth is partially determined by the wavelength.

iii. Scattered

After striking the tissue surface, some laser light scatters. Shorter wavelength induces greater scattering.

iv. Absorbed

After falling most of the laser rays are absorbed by the tissues. This produces the clinical effect by converting the absorbed light into heat. Organic tissues contain various substances capable of absorbing light. Each substances has a particular absorption spectrum which is determined by its chemical structure. Laser light which has the frequencies close to the absorption spectrum of the tissue will be most effective for that tissue.

HAZARDS OR RISKS OF LASER

There are four main risks or hazards of laser surgery. These are:

i. Atmospheric pollution,
ii. Perforation of great vessels or structures,
iii. Gas embolism,
iv. Energy transfer at wrong location,
v. Fire.

Atmospheric Pollution

An important problem during laser surgery is the pollution of enviornment of OT. This is due to the excessive smoke produced during vapourisation of tissues. The plumes of smoke and fine particles, produced during the vapourisation of tissues by laser energy may be transported and deposited in the distant tissues, especially during laryngeal surgery. Here, the smoke and fine particles can be deposited in the alveoli, causing bronchitis, increased tracheo-bronchial secretion, interstitial pneumonia, inflammation and reduced mucociliary clearance, etc. CO_2 laser produces smoke maximally, whereas Nd-YAG laser (contact probe) produces much less. However, the effective method of preventing this dissemination of smoke is immediate sucking of it from the surgical site. Many OT personals may find the odour of this smoke very objectionable and complain of headache, nausea vomiting and irritation due to inhalation of this smoke (Fig. 37.3).

Perforation of Great Vessels or Structures

Sometimes the desired depth of tissue penetration by laser beam cannot be controlled. Thus, it may cause perforation of

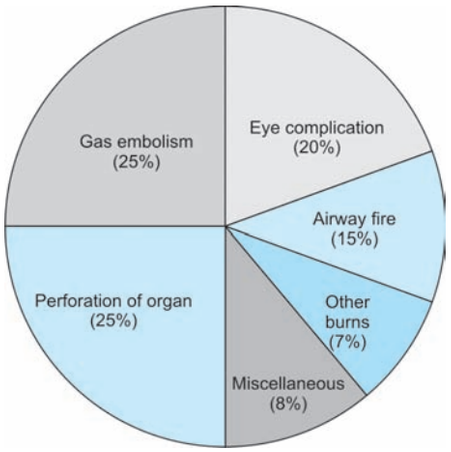


Fig. 37.3: Type and percentage of laser injury

the structure (if it is hollow) or may cause damage to the other tissues and great vessels underneath the said tissue. Vessels greater than 5 mm are not coagulable by laser energy and may cause profuse bleeding. With Nd-YAG laser, it is impossible immediately to assess the depth of injury, until the necrosis of tissues becomes maximal, several days after the laser surgery.

Gas Embolism

The tip of the contact probe of Nd-YAG laser contains a gas as coolant. During hysteroscopic surgery by Nd-YAG laser, if this coolant gas of the probe accidentally leaks and inflates the uterine cavity, then fatal gas embolism may occur. So, the liquid coolant in the laser probe is strongly recommended during the hysteroscopic surgery. If a coolant gas has to be used, then CO_2 is preferred because it produces less damage following embolisation than either N_2 or air. Venous gas embolism has also been reported during section of tumour by Nd-YAG laser in the trachea and during various types of laparoscopic and endoscopic procedures by it.

Energy Transfer at Wrong Location

The misdirected laser energy may perforate the hollow viscous or the large blood vessels, situated by the side of the operative site. For example, laser-induced pneumothorax has been reported following a laryngeal procedure. Similarly pressing the laser control trigger at the wrong time and at wrong site also can precipitate tragic scenarioes including ignition of surgical drapes or burning of a ET tube during airway surgery.

Fire

Laser light can ignite plastic, rubber or any other inflammable materials except metal. So, during the laser therapy of any lesion within airway or at any other site of body a careful consideration should to be given to the fire. This is discussed in more details below.

LASER SURGERY OF LARYNX AND FIRE OF ET TUBE

An important complication during airway surgery by laser is ET tube fire or the anaesthetic gas mixture is catching fire by itself. Laser induced ignition of ET tube or its cuff is responsible for most of the perioperative complications (40%) of laryngeal laser surgery. This is followed by postoperative laryngeal web (20%) and laser related facial burns (10%). Fire during laryngeal laser surgery is due to (i) the proximity of ET tube to surgical sites around the larynx where laser is used, (ii) the use of high energy, delivered by laser light during laryngeal laser surgery and also (iii) the presence of other hydrocarbon materials including plastic, rubber, other PVC material and even tissue except ET tube which can catch fire and burn easily, especially in an O_2 enriched atmosphere.

The CO_2 laser beam can penetrate an endotracheal tube and ignite fire, which would then be supported by O_2 and N_2O gas mixture present within the tube. Usually most fires are located on the outer surface of ET tube causing local thermal tissue destruction. But some times fire can catch the inner-side of tube, without recognition from outside, and produces a blow torch like flame. This is due to the flow of O_2 enriched gas mixture through the tube. In such situation ventilation further blows the hot smoke and toxic products of combustion in the fashion of blow torch like flame down to the pulmonary parenchyma, causing serious lung damage. Again the perforation of ET tube or the puncture of cuff by laser beam causes O_2 enriched gas to flood the operative site and increases the chance of a devastating fire.

So, the fire due to laser can be the result from the following :

i. Direct ignition of ET tube by laser
ii. Indirect ignition of ET tube from reflected laser light
iii. Incandescent particles of tissue, blown from the surgical site.
iv. Ignition of cottonoids or gauze pieces by laser.

So, to reduce the incidence of fire of ET tube, two things can be done.

i. Reduction of inflammability of ET tube by different methods.
ii. Removal of inflammable ET tube from the airway by using Venturijet ventilation by a metallic canula or apneoic anaesthesia technique with intermittent ventilation.

Reduction of the Inflammability of ET tube

The inflammability of ET tube can be reduced by changing the material by which it is made or by adopting some procedures which will prevent the catching of fire of conventional inflammable tube made of PVC, red rubber or silicon. The ideal properties of a laser safe ET tube which will not catch fire should be the following:

i. Noninflammable
ii. Malleable
iii. Thin walled
iv. Disposable
v. Soft, pliable, low pressure cuff
vi. Inexpensive
vii. Electrically nonconductive
viii. Impervious to multiple wavelength of laser beam (Fact file-II)

FACT FILE- II

Thin plastic endotracheal tube cuff is extremely susceptible to laser energy. Simple puncture of the cuff by misdirected laser beam is more common than combustion. Then this unrecognized cuff puncture may lead to enrichment of the area, surrounding surgical site and ET tube, with O_2. This increases the likelihood of catastrophic airway fire. Practically, the laser resistant ET tube cuff which maintain its mechanical properties necessary to minimise the tracheal trauma is not available. Sometimes, it is recommended to fill the cuff with coloured saline which clearly identify the puncture and also helps off the fire. The cuff should be placed as far distal as possible in the trachea from the laser surgical site. Surgeon should completely cover the visible part of the cuff with moist cotton plugs during the laser surgery. The cotton tails attached to the plugs should be replaced by uninsulated wire.

Only metal ET tube is 100% resistant to fire caused by laser energy. But the ET tubes which are made up of only metal have many disadvantages because it can not maintain the mechanical property of conventionally used PVC and red rubber tube. So, ET-tube made up of materials other than metal and conventionally used materials is tried which are less inflammable. But like PVC and red rubber ET-tube they also provide fuel for potential airway fire during microlaryngeal laser surgery though with less incidence and less severity. So, the different types of endotracheal tubes made up of different materials are used and different methods are also employed to prevent fire during administration of anaesthesia in laser surgery. These are:

i. Red rubber endotracheal tube, protected usually by adhesive aluminium or copper foil—most widely used.
ii. Polyvinyl chloride (PVC) endotracheal tube—most susceptible to fire. It can also be protected like above.
iii. Silicon endotracheal tube—less inflammable with laser beam. It also can be protected like above.
iv. Norton (metal) endotracheal tube.
v. Oswal – Hunton (metal) endotracheal tube – enormous cost. So it is rarely used.
vi. Xomed laser shield endotracheal tube
vii. Mallinckrodt laser – Flex endotracheal tube

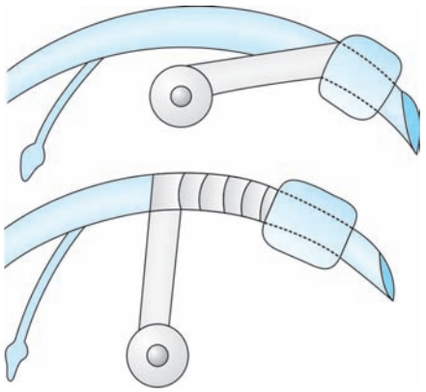


Fig. 37.4: The method of wrapping of ET tube by metal foil

viii. Bivona 'Foam Cuff' laser endotracheal tube.

Red rubber and PVC endotracheal tube

Red rubber and PVC endotracheal tubes are highly inflammable to laser energy. But this high inflammability can be reduced by adapting different methods. Among these the most popular approach is by wrapping the red rubber or PVC endotracheal tube with metallized foil or tape. Three types of foil or tape have been used : aluminium foil, copper foil and plastic tape thinly coated with metal on one side. All these foils and tapes have adhesive coating on one side. These tape and foil are widely available from retail electronics, arts and crafts, or building supplying shops. Lead foil is similar in appearance with adhesive coating on one side, but is very toxic and should never be used in the airway (Fig. 37.4).

These tapes though give protection to the shaft of the tube from laser energy but does not provide any protection to the cuff from fire as the cuff is not included within the wrapping. If the wrapping of endotracheal tube is the chosen method for laser protection, then the technique for wrapping is also important in ensuring the protection from both the ignition of fire and foil or tape induced mucosal abrasions. It is often helpful to first sparingly paint the tube with a medical adhesive such as benzoin. Then, one end of the tape should be cut and wrapping is begun by aliging the cut end

FACT FILE - III

Laser resistant ET tubes are usually bulkier and more rigid than conventional tubes. So, they are more liable to produce mucosal abrasions and requires particular care. Surgeons must be particular that laser energy should not reflect from the smooth metal surfaces of any surgical instrument or metal ET tube and is directed at other sensitive structures.

of the tape with the junction of the tube and the proximal end of the cuff. After that wrapping is done in a spiral fashion with 30 to 50% overlapping between the layers. The wrapping of ET tube with metal foil or metal coating tape should also include the inflation pilot tube and should be continued until just short of the pilot balloon, with care taken not to wrinkle the tape at any point which may cause abrasions of the tracheal mucosa (Fact file-III).

Norton Tube

It is a spirally winded stainless steel endotracheal tube without any cuff. Sometimes separate cuff may be placed at the distal end of this tube. The exterior of the tube has a matte or sand blasted finish. This decreases the reflection of laser beam and hence the incidence of fire is caused by reflected laser beam. The tube has a rough exterior and is of thick walled. The roughness of the exterior of the tube can cause damage to the mucosal surface of airway. The wall thickness is also considered as a disadvantage, since a smaller calibre tube (with further reduction of inner diameter) is usually selected in laryngeal laser surgery. This is because it will allow the surgeon a better exposure. The ET-tube large external diameter (thick) and its stiffness or rigidity (as made of metal especially which are not spirally winded) make the surgical exposure and the positioning of an operating laryngoscope difficult. The norton tube also may not be airtight into the trachea and it is due to the absence of cuff. This could cause contamination of the surgical field with back flowed anaesthetic gases which have a high concentration of O_2 and thus increases the chances of combustion

of tissues by laser energy. During the use of this type of metal ET tube ventilation of patient may also be impaired by the leak at the site of larynx and it is due to the absence of cuff of the tube. Norton tube is more or less similar to Oswal-Hunton ET tube, so the later is not discussed further.

Laser-Flex endotracheal tube

It is made up of flexible stainless steel with a plastic adapter at the proximal end. It has two PVC cuffs on the distal end. The two cuffs can be inflated via two separate pilot tubes. The proximal cuff, when filled with saline, shields the distal cuff from the unintentinal laser beam contact. Therefore, the proximal water filled cuff allows for a tracheal seal and also protects the distal cuff.

Xomed Laser Shield Endotracheal Tube

It is a fabricated ET tube made up of a non-reflective silicone elastomer with an outer layer coated by finely divided aluminium powder. This aluminized powder layer also extends over the inflatable cuff. It is designed to offer protection from CO_2 laser at a power settings below 25 W and at focal diameters of less than 0.8 mm in the pulsed mode only. The tube can, however, be penetrated and perforated by CO_2 laser, if sufficient energy is used. The cuff of this ET-tube is very thin and is easily punctured by CO_2 laser. Penetration and ignition of the xomed tube by laser required higher energy than either red rubber or the PVC tubes. However, the prohibitive cost and the possibility of silica ash (if set on fire) which causes extensive damage to the lungs than the PVC or red rubber ET-tube (if they caught fire) are points against the use of xomed tube (Fact file-IV).

FACT FILE - IV

It has been found that during laser resection of tumour, carbon monoxide is evolved in the smoke. Patients undergoing laser resection of an airway tumour by venturi jet ventilation can absorb this carbon monoxide through lungs. This CO may result in false overestimation of arterial O_2 saturation in pulse oximetry. Jet ventilation without ET tube usually provides adequate ventilation without introducing large obstacles or inflammable material at the surgical field. This is a great advantage. But the potential disadvantages of it include : barotrauma, pneumothorax, gastric distension, only dependence on IV anaesthetic agents, applicable only for compliant lungs.

Bivona 'foam cuff' laser endotracheal tube

This ET tube features a metal aluminium spiral tube in core which is covered with silicone from outside and a cuff made of foam. The 'foam cuff' consists of polymethane sponge with a silicone envelope. The tube is inserted initially after aspirating all the air out of the foam cuff and it is squeezed. Then once the tube is inserted, the pilot tube is simply left open to the air. The cuff inflates automatically without air having to be injected. Inflation of the foam cuff with saline solution is however recommended for CO_2 laser surgery. The pilot tube runs along the outside of the wall of the main tube and is marked in black, so that it can be positioned away from the laser beam. A distinct advantages of this ET tube is that the foam cuff will still remain inflated even when it gets struck by the laser beam. This feature allows continued IPPV and also causes separation of anaesthetic gases enriched with O_2 from the surgical site which catch fire.

Type of Ventilation when ET-tube is not used for Reduction of Incidence of Fire

A. Venturi jet ventilation by metallic cannula

This is a very simplest form of ventilation avoiding reducing the use of ET tube and thus subsequently reducing the risk of fire altogether. This procedure involves the use of a high pressure jet of O_2 and subsequently the entertainment of it by atmospheric air. The metallic injector or canula for O_2 jet is placed into the lumen of a rigid laryngoscope or bronchoscope, which are placed in larynx and are open at both ends and permits entrainment of O_2 with air during inspiration and escape of CO_2 during expiration while the patient is in muscle relaxant. This system is safe and reduces the chance of barotrauma producing pneumothorax. Intravenous anaesthesia is usually emplyed to ensure an adequate depth of anaesthesia during venturi jet ventilation as only the O_2 and air without any gaseous anaesthetic mixture is used for ventilation. In such situation the depth of anaesthesia is very important, because it prevents the patient from moving and coughing during the surgical procedures using laser. So, a suitable muscle relaxant should be used and the depth of neuromuscular transmission is monitored with a nerve stimulator.

B. Apnoeic anaesthesia technique with intermittent ventilation

The need for an alternative technique of ventilation for laryngeal laser surgery was felt because of the shortcomings (mentioned later) of the conventional technique of ventilation by ET tube and the venturi jet ventilation by metallic cannula. Thus, the apnoeic anaesthetic technique with intermittent ventilation provides a good alternative as it allows the intermittent withdrawl and insertion of ET tube and permits unhindered surgery by laser in the interval. In this procedure the muscle relaxant must be used to maintain the adequate depth of anaesthesia. The withdrawal of endotracheal tube connotes the apnoeic phase. Laser surgery is done in the apnoea period in between two ventilatory spells through ET tube by reinserting it. Such an approach totally eliminates the risks of airway fire, barotrauma and other complications associated with endotracheal tube and eliminates the disadvantages of jet ventilation by metallic cannula (as enriched O_2 enviornment around the surgical site causes fire), besides providing a clear and unobstructed view of the laser site to the surgeon. But hypoxia, hypercarbia during apnoeic phase and their associated complications are the inherent dangers of this technique. However the risks are largely held in check by the alertness of concerned anaesthetist, judicial use of monitors and their interpretations, along with in depth understanding of the physiology of respiration.

In this type of anaesthesia, the ET tube is removed intermittently and surgery is done after removal of the tube. Then, again ET tube is reinserted and ventilation is resumed when SPO_2 falls. This insertion and removal of ET tube is done in cyclical manner. Before removing the tube N_2O is switched off and the patient is ventilated with 100% O_2 with isoflurane mixture in order to achieve a high PaO_2, although an SPO_2 is of 100%. Sevoflurane is not generally used in this procedure, because it is very short acting and the adequate depth of anaesthesia cannot be maintained for the desired period. Halothane is also not used as it is phasing out due to its propensity causing arrhythmia. Supplemental doses of thiopentone and muscle relaxant are given when required. After induction, intubation, and placement of operating bronchoscope or microlaryngoscope as a first step of this apnoeic anaesthetic technique, the endotracheal tube is gently withdrawn without disturbing the position of microlaryngoscope. This marks the begining of the 1st apnoea phase. The surgeon now starts excising the lesion with laser which is now clearly visible and accessible to him, because of no hinderance by the ET tube or metallic cannula for O_2 jet. Also there is no risk of fire, since there is no combustible material and O_2 rich anaesthetic mixture at the surgical site. The endotracheal tube is reintroduced after the apnoeic phase through the suspension of laryngoscope and ventilation is resumed when there is:

i. Sliding down of SPO_2 to 93% (allowing for an after drop to 90%)
ii. Apnoeic period beyond 7 minutes.
iii. Any severe arrhythmias or obvious ST segment changes
iv. Extremes of HR and BP
v. Compulsory stoppage of surgery at intervals to allow the laserised area to cool and also to allow the suction and evacuation for clearing off the excessive smoke and charred tissue that accumulates.
vi. Completion of the laser excision.

At the end of first and subsequent apnoeic phase, ET tube is further reintroduced. Thus resumption of ventilation is done with 100% O_2 and hyperventilation is performed for first few seconds in order to correct the arterial desaturation and to wash off the accumulated CO_2. This is followed by ventilation of patient with O_2 and isoflurane mixture till SPO_2 reaches 100% and ET CO_2 comes down to 30 mm of Hg. The ET tube is then again withdrawn and the next episode of apnoea and surgery begins. Thus these cycles of ventilation – apnoea – ventilation continues till the surgeon achieves a satisfactory clearance of the disease. Towards the end of surgery isoflurane is switched off. Satisfactory SPO_2 and ET CO_2 level is achieved with ventilation. Patient should receive steroid as prophylaxis against postoperative laryngeal oedema. The microlaryngoscope is removed and the patient is intubated with normal size conventional oral cuffed endotracheal tube. Then neuromuscular block is reversed by neostigmine with atropine sulphate and the patient is extubated (Fact file- V).

No ET tube is safe for laser except metal. ET tubes of all materials except metal are infact quite vulnerable to fire and the vulnerability of different types of tubes (red rubber, PVC, silicone) depends on the type of laser. For CO_2 laser PVC tube is most vulnerable and then red rubber and silicone tube. But red rubber tube produces more toxic combustion products than PVC tubes. Silicone tube is most resistant to ignition than the other two varities but produces copious white silica ash if it catch fire, suggesting the potential for late development of silicosis. For Nd-YAG laser PVC tube is resistant (*in vitro*) as it is transparent. But during practical use any coating of mucuous and blood on PVC tube will absorb laser energy and does not make it safe, catching fire.

AIRWAY FIRE PROTOCOL

The incedence of ET tube fire during the laser assisted airway surgery is estimated to be in the range of 0.14 to 1.5%. During laser surgeries surgeons also should take the responsibility to prevent fire. They should set the laser power as low as possible (10 to 15w) and use the noncontinuous mode. They must always use wet gauzes to protect the nontarget tissue in the surgical field and the cuff of ET tube. Between the repeated pulses of laser, sufficient time should be allowed to disperse the heat. Nitrous oxide and oxygen mixture is known to support the combustion. So, the FiO_2 should be kept as low as possible as the patient's O_2 saturation of haemoglobin permits (usually between 0.25 to 0.3). Some anaesthetists avoid the use of

FACT FILE - V

As ET tubes of any material such as PVC or red rubber or silicone (except metal) are not resistant to laser so protection of tube from fire by laser should be given at first. Initially, the protection of tube by wrapping it with moistened muslin or dental acrylic was tried. But problem is that when the muslin is dried, it becomes highly inflammable by the laser. On the other hand, the dental acrylic makes the tube hard and rough (outer surface) and may cause trauma to the mucuous surface of larynx. So, the best approach to the problem of fire by laser is by wrapping the nonmetallic tube (PVC, red rubber and silicone) with metallised foil tape. The metallised foil tapes, which are in use are of aluminium and copper with adhesive on one side. But these metallised foil tapes do not provide protection to the cuff of the tube and is not 100% resistant to all types of laser. So, now Mercel laser guard tape (approved by FDA) consisting of an adhesive metal foil laminated on a synthetic sponge surface is used and provides protection against most of the lasers. But it can not protect the cuff. There is another ET tube (FDA approved) which uses integral laser resistant metal coating during the manufacture of the tube.

Laser resistant cuff that will maintain the mechanical properties and also will minimise the tracheal trauma are not yet available. The air filled ET tube cuff is highly susceptible to misdirected laser. Simple puncture is more common than fire of the cuff. Unrecognised cuff puncture causes leaking and enrichment of the ventilating O_2 around the surgical site and hence more likelihood of airway fire. So, to prevent the cuff injury, it should be placed in the trachea as distal as possible from the surgical site and the visible portion should be moistened by cotton pledgets continuously by surgeon. Many authors recommend filling of the cuff with saline, coloured with methylene blue which will help to detect the rupture of cuff.

N_2O and use air / O_2 mixture. Altenatively, helium / O_2 mixture can be used.

Whatever the type of ET tube is used, the cuff should be inflated with sterile saline to which methylene blue may be added. This is because the methylene blue will help to detect the cuff rupture easily by a misdirected laser beam. Also the cuff should be placed as far distally as possible, so that it is out of the line of target of laser. Though sudden airway fire and explosion usually incapacitate all the operating room staff temporarily, still surgeon and anasthetist must act quickly, decisively and in a very coordinated fashion. Usually surgeon detects the fire first. So he should stop the laser as soon as he will detect the fire and inform the anaesthetist immediately. Anaesthetist immediately stops ventilation, disconnects the circuit from the anaesthetic machine and extubates. Before extubation pharynx should be flushed with water. So, as a source of water a 50 ml syringe, filled with cold saline, should always be immediately available. These manoeuvres will remove the flame and stop the flow of O_2 enriched gas to the burning site. After extubation the flaming tube should be diped into a bucket of water which should always be available in OT during laser surgery. Then, ventilation should be done with 100% O_2 by mask. After that direct laryngoscopy and rigid bronchoscopy should be performed to assess the damage and to remove all the debris. If the fire is of interior blow torch type, then fibre-optic assessment of distal bronchial damage (if available) and gentle bronchial lavage is necessary. If the airway damage is severe and artificial ventilation is needed for proper management of complication then patient should be reintubated for ventilator management or tracheostomy should be done.

Pulmonary damage due to heat or smoke inhalation also necessitates prolonged intubation and mechanical ventilation. Pulmonary damage from heat and/or smoke inhalation should be assessed by taking repeated arterial blood gas samples and repeated chest radiographs. Late complications from airway fire include the formation of granulation tissue or stenosis in the larynx and/or trachea. So a brief course of high dose of steroids may be helpful. Fortunately, in most of the cases small fire involves exterior of the tube and does not cause appreciable damage of the local tissue. In case of difficult airway, leading to difficult intubation during induction of anaesthesia the tube should not be removed immediately. Because there is further fear of difficult reintubation or failed intubation and hypoxia. Here, all the above mentioned steps should be taken immediately to stop the fire and the patient is not extubated. Instead, the tube and trachea should be flushed with water. After flushing and extinguishing the fire, a tube exchanger is inserted through the lumen of the previous tube and the burn tube is removed. Then another ET tube is inserted over the tube exchanger.

LASER SAFETY PROTOCOL

In every hospital where laser is used for different surgical procedure should have a laser safety protocol. This protocol is described below:

i. A designated trained laser safety officer must be present continuously in OT when a laser machine is in use. An indicator light must be displayed outside the operation theatre when the laser is in play.
ii. Laser light is usually reflected off from the mirror like shiny exterior smooth surfaces metal instruments and metal ET tube. So, all the surgical metal instrument and tube used during laser surgery should have matt exterior surfaces, rather than shiny.
iii. The eye is the most susceptible part of body for injury by laser. So, all the operating room personnel must use safety glasses. These should have side shields. It will protect the lateral aspect of eye. If an anaesthetised patient is scheduled to recive laser therapy close to the eyes, then a protective metallic eye cover with matt finish should be applied. Otherwise, the eye should be taped closed and covered with moist swabs.
iv. Damage to the skin by laser beam can also occur. But it depends on the type of laser in use. The OT personnels do not normally need to protect against skin damage. Because they will be able to move away from the path of an misdirected laser beam. But the anaesthetised patients must have all the exposed skin covered with drapes, except the surgical site because they cannot move. The drapes should be made of absorbable material and not plastic which is potentially highly combustible. Plastic drape is much more combustible than canvas type drapes. So, it should be avoided. Tissues adjacent to the surgical site should be protected with moistened gauzes or swabs.
v. Some fluids used for skin preparation during surgery also are in flammable. So, these should not be used during laser surgery.
vi. Efficient smoke evacuation system must be maintained close to the surgical site.
vii. During the laryngeal laser surgery conventional ET tube made of PVC or red rubber should be avoided if possible in fear of fire and ventilation is maintained by venturi principle. If in any circumstances the use of an ET tube can not be avoided then specially prepared non-flammable laser tubes are used or tracheal tube protector such as metal foil or metalised tape can be wrapped around the conventional tubes which are discussed before.
viii. All the airway fire protocols should be maintained.

38 Anaesthesia for ENT Surgery

INTRODUCTION

The patients who have undergone ear, nose and throat (ENT) surgery are usually young and healthy adult. But the patients approached for laryngeal operation or throat surgeries are usually older. Previously most of the operatins in ENT department were done as indoor cases. But, now-a-days many ENT operations are performed as day cases under LA or under fast track GA. Thereby, the need for in-patient admission for ENT surgery is reduced and also the workload on the ENT anaesthetic department has been lowered.

Children and young adults are apprehensive. So, if they are chosen for ENT surgeries under LA, they require extensive reassurance and exhaustive counselling or they need GA. Some of them may have an atopic history which influences the anaesthetic technique, if GA is required. Older patients for laryngeal operations usually have hypertension, IHD (ischaemic heart disease) and other co-existing diseases. So, they require proper perioperative care as most laryngeal operations are done under GA.

During ENT operations under GA, two things should be taken in mind by an anaesthetist. These are smooth anaesthesia and clear airway. Because most of the ENT operations are now done under microscope. So, a very smooth and deep anaesthesia is needed which will help to avoid coughing, straining, bucking, etc. that occurs under light anaesthesia and causes venous congestion and increases bleeding and spoils the goal of microsurgery under a high powerful microscope. Operations on nose and throat but not ears involve the airway, and both the surgeon and the anaesthetist work on this airway, fighting with each other and causing complete or partial obstruction of airway. Complete airway obstruction is a life threatening condition. Partial obstruction of the airway may lead to hypoxaemia and hypercapnia. So, maintenance of clear airway by an anaesthetist is very crucial for ENT surgeries. Patient's eye should be protected from corneal abrasions in all ENT procedures.

GENERAL PRINCIPLE

An anaesthetist, during preparation of the patients for ENT operations under GA will be concerned with the following particular problems.

1. The provision for satisfactory pulmonary ventilation while permitting adequate surgical access for the nose and throat surgeries, because the airway is shared by both the surgeon and the anaesthetist in such surgeries.
2. The prevention of aspiration of blood, pus or other materials into the lungs during nose and throat surgeries.
3. The provision of good operating conditions for microsurgery of the ear and larynx.
4. Care of patients undergoing major surgery of the head and neck.
5. Maintenance of the airway in upper respiratory tract obstruction – partial or complete.

Sharing of Airway

Problems arise when the airway is shared by both the anaesthetist and the surgeon. But, these are usually solved by the following ways. For nasal operations, the problem is solved by the passage of an oral endotracheal tube. Surgeon usually approaches the nose from the patient's right hand side. So, it will be helpful to shift the endotracheal (ET) tube to the left side of the patient's mouth.

For oral operations, e.g. tonsillectomy, where the surgeon uses mouthgag and tongue blade, the airway problem is solved by an anaesthetist by the use of nasotracheal tube which will give a clear oral surgical field to the surgeon without compromising the airway. But sometimes, nasal intubation is difficult, due to the presence of some nasal obstruction or is undesirable in small children or if postnasal space is required during surgery, then in that situation, adequate surgical exposure and an unobstructed airway can also be provided by an anaesthetist by the presence of an oral endotracheal tube with the use of Doughty's modifications of Boyle-Davis gag. In this modification, the ET tube lies comfortably within the slot of the tongue plate of Boyle-Davis gag and does not obstruct the surgeon's view. However, sometimes the ET-tube is also compressed by the tongue plate of Boyle-Davis gag which is detected during IPPV by the decrease in compliance of lungs and the increase in inflation pressure or in spontaneously breathing patients by decreased movement of the reservoir bag.

This difficulty can be corrected by using a long metallic special connector with larger portion of it inside the tube. This will prevent the compression and subsequently the obstruction of the tube.

Prevention of Aspiration

In oral, laryngeal and nasal surgery, not only the restoration of airway, but also the protection of airway from aspiration during anaesthesia (if intubated or non-intubated) and the quick restoration of the postoperative protective laryngeal reflexes after extubation should be in the forefront of an anaesthetist's mind.

Although, a cuffed ET-tube provides a larger protection from aspiration, still it is possible for blood to collect in a pool above the cuff and may enter the lungs when the cuff is deflated, either deliberately at the end of the operation for extubation or accidentaly anytime. Therefore, it is an usual practise to insert a well lubricated gauze pack into the pharynx or around the laryngeal inlet above the cuff of ET-tube before the nasal or oral operations is started.

For quick restoration of the postoperative protective laryngeal reflexes, the following measures are usually taken. It is generally agreed that preoperative medications with long acting opiate drugs has a depressant effect on laryngeal protective reflexes. So, better it should not be used where a quick return of reflexes are desired. But the use of narcotics is not absolutely contraindicated. It depends on an anaesthetist's judgement. For example, the newer short acting opioids like fentanyl and its congeners, especially remifentanil can be used safely. Again local anaesthetic agents applied topically either in the form of spray or gel may reduce the integrity of the laryngeal protective reflexes and should be avoided. However, this is also not absolutely contraindicated. On the whole, the conduct of GA should obviously be designed in such a fashion that it will ensure rapid return of the swallowing and cough reflexes (i.e. protective laryngeal reflexes) at the end of the each ENT surgical procedure. There is little objective evidence of the superiority of any particular anaesthetic technique in this respect. So, an anaesthetist must apply his or her own judgement and assessment of the preferable method, but ensure that the depth of anaesthesia will not be very light intraoperatively causing cough, ↑BP ↑HR, increased bleeding at operative site, etc; which is very troublesome specially during microsurgery.

Postoperatively, the likelihood of aspiration is also reduced if the patient is placed in the lateral position with head tilted slightly down. At the end of every ENT surgery the pharynx should be sucked out completely under direct vision and there should be evidence that the reflex activity of larynx has returned before the ET-tube is removed. The partial incompetence of the laryngeal closure reflex may persist for two hours after extubation, even after the relatively short duration of anaesthesia. So, the practice of maintaining the lateral position and avoiding the fluid intake for 2 hours postoperatively is important. It should also be borne in mind that a progressive impairment of protective laryngeal reflexes occur with advancement of age.

PREOPERATIVE EVALUATION AND AIRWAY ASSESSMENT

Since, anaesthesia in ENT surgeries is very challenging, so the proper preoperative evaluation and the proper airway assessment of every patient by proper history, clinical examination and investigation is very vital.

History

1. Many preparations of antihistamines and certain other medications which are used rampantly in patients suffering from common cold may contain aspirin. So, a special attention should be given to the platelet function tests and coagulation profiles preoperatively in these patients.
2. Polyps and other causes of nasal obstructions, for which the patients come for surgery, may make the ventilation by mask very difficult. Hence, clinical examination for the above causes and airway assessment for obstruction in these patients is mandatory.
3. Stridor is a common ENT problem. So, it requires direct laryngoscopy or bronchoscopy for preoperative airway evaluation of patient. Age of onset, cause, and positions of patients that make the stridor better or worse should be evaluated well. Along with the stridor some other symptoms such as wheeze, cyanosis, chest retraction, nasal flare, etc; which indicate some form of airway obstruction should also be carefully noted preoperatively.
4. Patients with longstanding history of stridor, haemoptysis or hoarseness of voice are usually booked for diagnosis by endoscopy or are booked for major surgery (when diagnosis is confirmed beforehand and it is usually malignancy). These patients are usually elderly with significant comorbidity. For example, COPD, CVS disorders, anaemia, alcoholism, smoking, etc, are commonly associated problems with these patients. So, the assessment of all the risks in these group of patients, preoperatively, is very important for better perioperative management.
5. Endocarditis from recurrent streptococcal bacteraemia due to infected tonsil or due to other infected focus in body such as in ear, throat or nose is not uncommon in patient especially children scheduled for ENT surgeries with cardiac vulvular disease. So, during anaesthesia of ENT surgery anaesthetist should be careful about it.
6. Prolonged preoperative airway obstruction, presented for ENT surgery, specially in children, causes chronic hypoxaemia, hypercarbia which may lead to corpulmonale. So, all these should be taken into consideration before anaesthesia. Along with corpulmonale right ventricular hypertrophy, cardiomegaly,

pulmonary artery hypertension, ventricular dysfunction, and cardiac arrhythmia are some possible complications of these patients who are suffering from chronic airway obstruction. So, proper evaluation of these patients by an anaesthetist before being put up for ENT surgery is vital.

7. Enlarged tongue or tonsil and/or adenoid make a patient more prone to the obstructed sleep apnoea syndrome (OSA). These syndrome consists of periods of absent nasal and oral airflow during sleep, despite continuing respiratory effort. This is at least partly due to the backward movement of tongue and pharyngeal wall collapse (glossoptosis) secondary to the interference of the normal coordinated contraction of pharyngeal and hypopharyngeal muscles. These OSA patient are at increased risk of airway obstruction specially duing induction and recovery phase of anaesthesia. So, vigorous clinical monitoring, use of different airway devices (nasopharyngeal or Guedel) or carrying out induction and recovery in sitting or lateral position etc. may minimise the risk of OSA syndrome and can reduce the complications due to airway obstruction.
8. Most patients who are sheduled for ENT surgeries such as tonsillectomy, adenoidectomy, or maringotomy with tube insertion, etc, are usually present with chronic URTI, especially children. But, here postponement of surgery due to chronic URTI is not recommended, since removal of the infected focus is important to resolve this chronic URTI.

Airway Assessment

Before bringing the patient to OT, an anaesthetist must try to ensure whether problems will precipitate or not from the airway. Preoperative airway assessment should start from the history of airway diseases – such as abscess, tumour, infection, trauma, the presence of postirradiation or postsurgical scarring, or any postoperative difficulty of airway from record of previous anaesthesia, etc. After history, proper assessment of airway is next done by physical examination of patient. The physical examination include: (i) general appearance of the patient-gross deformities of head and neck, obesity, etc, (ii) observation of type of patient breathing – stridor, mouth breathing, wheezing, etc. (iii) inspection of mouth and chin – extent of opening of mouth, loose teeth, size of tonsil, size and mobility of tongue, micrognathia, Mallampati score, etc. (iv) inspection of nose – nasal obstruction, mucosal congestion, deviated nasal septum, etc. (v) inspection of neck and larynx – short neck, position of trachea, mobility of cervical spine, mobility of atlanto occipital joint, thyromental distance, goitar, etc. Indirect laryngoscopy can be carried out before surgery for extra information of the airway. If it is needed, the help of CT scan and MRI may be taken for the proper assessment of airway. If there is any substantial doubt about the airway, one has to consider special technique for intubation such as awake intubation, intubation for accessory devices fibre optic intubation or performing a tracheostomy under local anaesthesia before induction of anaesthesia.

PREOPERATIVE MEDICATION

Narcotics or Opioids

The disadvantages of opioids as premedicant in ENT surgeries have already been mentioned in previous discussion. These disadvantages of opioid are also compounded by the fact that operation on the middle and inner ear may themselves be associated with nausea and vomiting which may be exaggerated by these narcotics or opioids used during premedication. Keeping all these in mind, it is still justified to use narcotic analgesics where it is necessary such as to relieve severe pain preoperatively, to maintain an intraoperative stable haemodynamic condition and for preparation of a major ENT surgery such as for malignancy.

Sedatives and Tranquillisers

Among the sedatives and tranquillisers benzodiazepines are the most widely used drugs which are very effective in relieving anxiety when given by mouth, preoperatively. They produce both the sedative and amnestic effect. The commonly used benzodiazepines are diazepam, lorazepam, alprazolam and midazolam. In children, trimeprazine and promethazine are also very popular drugs as premedicants. It provides sedative, antiemetic, antisialogogue and amnestic effects.

It is always worthy by re-emphasizing that frequent pre-anaesthetic visits to an anthetist's clinic by patient and his relatives and are associated with a reduced incidence of nervousness and apprehension. Thus, it also reduces the dose of preoperative sedatives.

Anticholinergic

Although, there are some objections to the routine use of atropine before anaesthesia, but ENT surgeons find it very helpful to have a dry mucous membrane when they are operating on the nose and throat. This may only be achieved by the use of atropine or glycopyrrolate preoperatively by IV route. But before induction and institution of an IV route in case of children IM route is the only option. If atropine is contraindicated or tachycardia is not desired, then glycopyrrolate is the best alternative or perhaps is the first choice. It should be given IM at least 30 minutes preoperatively. IV administration of atropine or glycopyrrolate at the time of induction is not seen to be so effective.

Antiemetic

Although, there may be an increased incidence of nausea and vomiting after aural operations, still it is questionable whether routine use of antiemetic drugs is justifiable or not. This is because many

patients may be subjected to unnecessary antiemetic therapy. Therefore, it may be thought reasonable to prescribe them only when a patient complains spontaneously of previous postoperative vomiting, although there is no drug that can gurantee success. Drugs which are successful in the treatment of motion sickness are likely to be successful antiemetic after operation on ear such as cyclizine and prochlorperazine (stemetil).

ANAESTHETIC AGENTS

Inducing Agents

Any of the inducing agents that are used for induction of anaesthesia in other discipline of surgery can be used for ENT surgeries. So, it does not need any special discussions.

Muscle Relaxants

ET-intubation is needed for most of the ENT surgeries where GA is applied. But this should be performed with the background in mind of obstructed airway and possibilities of difficult intubation. So, obviously suxamethonium is the choice to facilitate intubation where possible difficulty of it is anticipated. But the choice of relaxants for the next part of the operation after intubation and reversal from suxamethonium is influenced by the expected duration of that part of operation. For shorter procedures, supplementary doses of suxamethonium may be given by intermittent bolus doses or by infusion. If operation is longer than 30 minutes duration, then a non-deporizating relaxant is preferable. On the other hand, muscular relaxation is not an absolute prerequisite for ENT surgeries. So, anaesthesia can be maintained by volatile anaesthetics and spontaneous ventilation after intubation.

Nitrous Oxide

Like other surgeries, N_2O also plays an integral part in the anaesthetic gas mixture used for the majority of ENT operations. But, in middle ear surgery its use has definite disadvantages. Since, N_2O is 34 times more soluble than nitrogen in blood, so during N_2O anaesthesia, N_2 molecules leaving from air cavities in the body are replaced by greater number of molecules of N_2O. Therefore, if the cavity is not distensible (e.g. middle ear), then there will be a constant rise in pressure in it; which may reach maximum after 30 to 40 minutes of the onset of inhalation of N_2O. When N_2O is withdrawn, it takes also a similar time for the pressure to return to normal. Hence, during certain types of tympanoplasty, variation of pressures of this magnitude may cause the instability of graft (dislodgement of graft). So if N_2O is used , it should be turned off some 30 to 40 minutes before the expected completion of surgery.

Alternatively, N_2O should be omitted altogether and anaesthesia should be maintained with volatile agents, O_2 and air (which should be used in place of O_2/N_2O gas mixtures). However, recently, surgical techniques have been improved and modified over the years, so that an increase in middle air pressure has no longer any importance and does not influence the result of surgical procedure. It is, therefore, no longer necessary to turn off the N_2O before the end of surgical and anaesthetic procedure.

Halothane and Other Volatile Anaesthetic Agents in ENT Surgeries

Like other surgeries halothane is also the most commonly used volatile anaesthetic agent in ENT surgeries, both during controlled and spontaneous ventilation. Whereas most ENT surgeons wish to use adrenaline as topical or locals injectable forms for vasoconstriction which makes the field dry. But it is well-established that adrenaline in the presence of halothane may induce different cardiac arrhythmias, even ventricular fibrillation. So, to balance between the use and the non-use of adrenaline, the present dictum is that adrenaline can be used safely with halothane, provided there are limits to its concentration and dose used in a given period, and hypoxia and hypercarbia are avoided, or the two drugs should never be used simultaneously i.e. when adrenaline is used halothane should be turned off. Alternatively the surgeon should be aware of the properties of other vasoconstrictors such as octapressin, ornithine-8-vasopressin (POR-8), etc, which are more compatible with halothane. Otherwise, other volatile anaesthetic agents such as sevoflurane, isoflurane, etc. are better choice than halothane in the presence of adrenaline as they maintain a good haemodynamic stability and there is less chance of arrhythmia.

Anaesthetic Circuits

The anaesthetist must keep himself out of the surgeon's way during the ENT surgeries. So, it could be inconvenient to use equipment with an expiratory valve close to the patient which may need frequent adjustment. Hence, this would preclude the use of Mapleson-A circuit, Ruben valve or a miniature ventilator. So, it indicates the use of circle system in adult or T-piece arrangement in children. However, the Bain anaesthetic circuit which is a co-axial system with the expiratory valve on the bag mount, is particularly useful in these conditions.

Induced Hypotension

Most of the ENT surgeries are performed with the help of microscope. So, it is argued that even a small amount of blood would be magnified under the operating microscope and this will make the microsurgery difficult and does not allow the surgeon to take the necessary decision for a successful outcome. Hence, in order to minimise the bleeding (especially during microscopic surgery) it has long been advocated that one should induce deliberate hypotension, aiming at mean arterial blood pressure around 50 to 55 mm of Hg. This can be

achieved by using drugs such as sodium nitropruside, nitroglycerine, hydralazine, betablockers etc. On the otherhand, induced hypotension has a potentially harmful effect on the cochlear blood flow during otological surgery. Autoregulation is also lost during controlled hypotension.

Experienced practitioners have used hypotensive techniques for many years with impressive safety. But, even when adequate precautions are taken, still controlled hypotension is not free of complications. These complications, however uncommon, may become major problems involving the heart and CNS. So, the goal of induced hypotension should be diminished bleeding, rather than an absolutely bloodless field. Again newer reports say that there is no correlation between the blood pressure and quality (i.e. dryness) of the operative field. So, individual anaesthetics and surgeons vary in their views and their desirabilities.

An anaesthetist should not practise unnecessarily the hypotensive technique on his patients and also the surgical colleagues should not force to practise it against the anaesthetists will. For those anaesthetists who are unwilling or insufficiently experienced to use the hypotensive method, a modified hypotensive technique can be achieved. This is based on the clear airway, controlled ventilation with halothane, absence of straining, use of topical vasoconstrictors and moderate degree (15°) of head-up tilt. Another best way to reduce the surgical bleeding during microscopic surgery is (usually) to combine the use of opioids with isoflurane or sevoflurane in a N_2O/O_2 or air/O_2 gas mixture. This is titrated to maintain a systolic blood pressure at around 90 mm of Hg. The total intravenous anaesthesia with propofol as the main agent can also be used. The advantages of using propofol for ear operations are its lower incidence of postoperative nausea and vomiting, the reduction of blood pressure without a compensatory increase in heart rate, the preservation of autoregulation of inner ear blood flow during controlled hypotension and its excellent recovery profile.

Blood Loss

Blood loss in most ENT operations is small, with obvious exception for major head and neck surgeries especially for malignancy. For example, in majority of adenotonsillectomy operation in children the blood loss is less than 10% of the estimated total blood volume of the body. Sometimes, up to 20% of the estimated total blood volume of the body may be lost during operation. So, in such circumstances if postoperative haemorrhage (if occur) is added to this loss, then blood transfusion should be given to this patient. An experienced anaesthetist usually can estimate the amount of intraoperative blood loss by visual impression. But, if there is any doubt, then it is a simple matter to get some estimation of blood loss by weighing swab and measuring of the contents of suction bottle.

Laryngeal Mask Airway (LMA)

Now, instead of ET-tube, the LMA has been used for many types of ENT surgeries. But to justify its use, the anaesthetist must be able to explain that it has some advantages over the traditional use of an endotracheal tube for that particular case. After the introduction of a flexible reinforced version, LMA is now gradually becoming very popular in ENT surgery. This fexible reinforced version has many advantages in comparison to standard classic LMA. These advantages which make the flexible reinforced LMA more useful in ENT surgeries are: (i) it is more resistant to kinking and obstruction caused by oropharyngeal instruments (e.g. mouth gag), (ii) it is less likely to be displaced during movement of head and neck, (iii) it can be connected to a breathing system at any angle.

Gradually, LMA itself is becoming an important anaesthetic tool in ENT surgery because it can be inserted blindly without the need of muscle relaxant in a spontaneously ventilating patient where there is any chance of difficulty or failed intubation. Another advantage of LMA over ET-tube during ENT surgery is that coughing which increases the risk of rebleedding or displacement of grafts after ear surgery can be avoided. This is because LMA is better tolerated and associated with less coughing in comparison to ET-tube. Another advantage of LMA over ET-tube is that in case of an expected prolonged recovery, following a major surgery of head and neck, the trachea can be extubated in deep plane of anaesthesia and then a LMA can be inserted further to maintain the patient's airway during the prolonged recovery period. This technique will also help to reduce the incidence of postoperative coughing and subsequently bleeding.

INDIVIDUAL SURGERY

Tonsillectomy

The age of most of the patients scheduled for tonsillectomy operation are less than 15 years and most of these children attend hospital on the day of surgery. During routine preoperative anaesthetic evaluation of these patients, special emphasis is given on checking for loose tooth, recent ingestion of aspirin and determination of coagulation profile. As discussed before, the use of premedication is also debatable in tonsillectomy operation, because some anaesthetists like them and some do not. If premedication is given, it is administered most conveniently to the younger child as syrup of trimeprazine (1.5 mg/Kg) or promethazine (1 mg/Kg) or diazepam (0.2 mg/Kg) and atropine (0.02 mg/Kg) orally.

The aims of different techniques of anaesthesia for elective tonsillectomy are:

1. To provide deep anaesthesia that prevents reflex tachycardia arising from surgical stimuli in light plane of anaesthesia and cardiac arrhythmias. This is because one of the important intraoperative complication in tonsillectomy

is arrhythmias which is caused by the increased levels of endogenous epinephrine from light general anaesthesia and sensitization of myocardium to this catecholamine.

2. To provide adequate muscle relaxation which will allow easy placement of mouth gag.
3. To prevent bucking, coughing or straining.
4. Rapid recovery to consciousness and also rapid return of protective airway reflexes.

Most of the children who are presented for tonsillectomy surgery are younger enough and allow an IV induction of anaesthesia. But in some children with poor venous access, inhalation induction may be preferred followed by IV access. Oral or nasal intubation is facilitated by succinylcholine or performed under deep inhalational anesthesia.

Anaesthesia for tonsillectomy is usually maintained by using N_2O, non-depolarising muscle relaxants and narcotics with or without volatile anaesthetic agents. A topical spray of 4% lignocaine on tonsillar operative area or infiltration of 2% lignocaine at surgical site will help to decrease the general anaesthetic requirements, the incidence of arrhythmias, and postoperative stridor and laryngospasm. Blood loss should be replaced, if it exceeds 10% of the circulating blood volume.

Tracheal extubation is performed with the patient's head slightly down in a lateral position, and after complete suction which ensures that the pharynx and larynx is free from blood secretions and tissue debris. Extubation may be done either under deep anaesthesia or when the patient is fully awake. When 'extubation is done under deep anaesthesia' to prevent cough, vomiting, laryngospasm, etc. then the anaesthetist must continue to take the responsibility of protecting the airway after extubation too. Commonly trachea is extubated in the operating room when the patient is awake and protective airway reflexes have come back. It results in some cough and laryngospasm which usually do not interfere with the surgical closure of tonsillar bed. Sometimes IV lignocaine (1 mg/Kg) may be used to decrease this laryngospasm after extubation.

After extubation, patient should be observed for any bleeding and for any airway obstruction in recovery room for at least 90 minutes in tonsillar position (i.e. on one side, with the head slightly down). This is because it will allow the blood or secretions to drain out rather than to flow back into the larynx through vocal cords. Then the pharynx should be rechecked directly for bleeding before discharge from the recovery room.

The incidence of nausea and vomiting can be as high as 70% during the first 24 hours after tonsillectomy. Although, post-operative bleeding is the most serious complication, but persistant vomiting and poor oral intake are the most common cause for readmission after discharge. To reduce the incidence of post tonsillectomy (postoperative) vomiting, it is important to modify some anaesthetic techniques and also to develop some recovery protocol, such as avoidance of narcotics as postoperative analgesic, emptying of stomach from blood by suction, administration of antiemetic regimen, proper hydration and never force early oral food or fluid intake, etc.

Use of LMA in tonsillectomy is very difficult because Boyle-Davis gag cannot be placed in position if LMA is used and obstruction to the airway occurs more frequently. Also LMA cannot protect the larynx from regurgitation and aspiration of stomach content during operation. It also cannot protect from aspiration of blood coming from operating site.

Adenoidectomy

The adenoidectomy surgery is usually combined with tonsillectomy or examination under anaesthesia (EUA) of ear (for paediatric group of patient). In the absence of tonsillectomy operation the adenoidectomy surgery is usually performed as a day case procedure. For this surgery oral tracheal intubation is must and is performed under deep inhalation anaesthesia or is facilitated by the use of succinylcholine. Nasal intubation is not done for adenoidectomy as it obliterates the surgical space. After intubation, Boyle-Davis gag is inserted into the oral cavity and adenoid is curetted. Then nasopharynx or post-nasal space is tightly packed by gauzes to achieve haemostasis for 3 minutes. After removal of the pack when proper haemostasis is achieved (if haemostasis is not achieved, nasopharynx should be packed again), then only the patient is extubated and is turned to tonsillar position.

Peritonsillar Abscess

It is usually drained and/or decompressed by giving incision or doing needle aspiration under local anaesthesia. General anaesthesia with intubation is only applied in paediatric age group of patients or uncooperative patients. In peritonsillar abscess the risks of GA includes difficult intubation, because the respiratory tract is already partially obstructed due to inflammation, oedema and abscess itself. Intubation may cause further obstruction because difficult intubation produces further oedema, traumatic rupture of the abscess and subsequent spilling of pus into an unprotected airway before intubation. On the other hand, difficult intubation in peritonsillar abscess may be due to distorted anatomy, oedema and trismus. If difficult intubation is anticipated, then the following three methods can be adopted: (i) Awake intubation under local block, (ii) Intubation with inhalational anaesthesia with spontaneous respiration, (iii) Elective tracheostomy. Sometimes, planning of intubation and GA for drainage of a peritonsillar abscess may include the preoperative partial decompression of abscess by needle aspiration. It will help to minimize the risk of rupture of abscess and aspiration of pus during subsequent intubation.

Bleeding Tonsil after Tonsillectomy

The management of bleeding tonsil after tonsillectomy is a great challenge to an anaesthetist. The incidence of this post operative bleeding that actually requires re-surgery is near about 0.3% and usually occurs within 6 hours of primary surgery. The problems which an anaesthetist faces during handling of such patients are unsuspected hypovolaemia, full stomach (due to blood or food) and airway obstruction by blood. So, before sending the patient to the OT, the following things should be done: (i) blood loss should be assessed which is usually underestimated, (ii) no premedication should be given, (iii) coagulation profile should be checked, (iv) blood should be grouped, cross matched and kept ready for transfusion, (v) patient should be properly hydrated by IV fluids.

By nasogastric tube blood should be sucked from stomach before reinduction of anaesthesia. Rapid sequence induction with cricoid pressure and head slightly down in lateral tilted position is followed to prevent the aspiration of blood which is continuously oozing out. During induction and intubation of GA, an assistant must be available who will continuously suck blood from the pharynx. Like elective tonsillectomy, extubation should also be done when the patient is fully awake and the protective airway reflexes have returned.

ANAESTHESIA FOR MINOR SURGERY SUCH AS ENDOSCOPY AND MICROSURGERY OF LARYNX

Endoscopy of upper airway includes: laryngoscopy for any diagnostic or operative purposes, on larynx, microlaryngoscopy which means laryngoscopy aided by an operating microscope, oesophagoscopy, bronchoscopy, etc. Any laryngeal endoscopic procedure may or may not be accompanied by laser surgery. Patients presenting for laryngeal endoscope surgery are often evaluated preoperatively for stridor, hoarseness of voice, haemoptysis, etc with which the patients are usually presented. The possible causes of these symptoms are foreign body aspiration, papillomatosis, trauma, tracheal stenosis, vocal cord dysfunctions, etc. which have tremendous implication on subsequent intubation and GA.

The operating microscope has revolutionized the treatment of operative laryngeal disorder. At the same time, a wide variety of anaesthetic techniques have also come up for microlaryngeal and endoscopic surgery. But the common aims of all these anaesthetic techniques are: (i) to provide the surgeon a clear, immobile view, (ii) to provide the adequate space for work to surgeon, (iii) to provide good ventilation and oxygenation for patient, (iv) to protect the trachea from aspiration and, (v) rapid awakening with quick return of the protective airway reflexes.

Patients coming for microlaryngoscopy (endoscopy) or microsurgery of larynx have varieties of upper airway pathology which extends from a minimum to severe one, for examples, a small lesion on vocal cord (carcinoma *in situ*, polyp, etc.), or a large potentially obstructive lesion above the glottis (such as papillomatosis) or a large friable subglottic tumour that will completely obstruct the glottic opening. So, according to the pathology, preoperative decision about tracheal intubation or different modes of ventilation and anaesthetic management is taken on.

Only light premedication by benzodiazepines is desirable or advisable for rapid reawakening from the brief endoscopic or microsurgical procedures. Antisialagogue is must to facilitate the drying up of oral secretions. Small dose of narcotics may also be helpful. If there is any doubt about the airway (regarding intubation or ventilation) preoperatively, then direct laryngoscopic examination should be performed (after topical laryngeal block) in the awake patient to assess the difficulty of any mask ventilation or intubation.

As previously said, although varieties of anaesthetic techniques have been developed to satisfy the requirements of adequate pulmonary ventilation and oxygenation and unimpeded surgical view for microlaryngeal surgery, but a few among them are used practically. The most popular anaesthetic technique among them is the use of Coplan's microlaryngoscopy tube (a type of ET-tube). It is a narrow (5 mm ID), long tube (31 cm) and constructed of soft plastic with a 10 ml cuff volume (high volume low pressure cuff). The Coplan's tube can be passed either orally or nasally. The small diameter of this tube does not impede the surgeon's view and allows good access to the larynx.

Of all the pathological conditions of larynx asking for microsurgery, in 95% of cases the pathlogy is situated on the anterior 2/3rd of vocal cord or the anterior commissure. Only in 5% cases the pathology involves the posterior 2/3 of vocal cord or the posterior commissure. Hence, this small tube does not obscure the anterior commissure. Posterior commissure can be inspected by moving the tube aside. Adequate ventilation and oxygenation can be maintained in adults by controlled ventilation through this small endotracheal tube, and the cuff of the tube also protects the trachea from contamination by blood or tissue debris. This narrow ET-tube also allows a variety of general anaesthesia regimens even for an indefinite period of surgery. At the end of surgical procedure the pharynx and larynx is cleared by suction under direct vision, muscle relaxants are antagonised and tracheal extubation is performed in lateral position. Oxygen is administered to minimise the risk of hypoxaemia if laryngeal stridor occurs (Fact file-I).

Another method of anaesthesia for microlaryngeal surgery is jet ventilation by metal canulla using venturi entrainment effect of air.This method provides both anaesthesia and ventilation without the use of an endotracheal tube. This venturi injector technique to achieve artificial ventilation was first used in bronchoscopy and was then subsequently adopted for

FACT FILE - I

The anaesthetic goal for endoscopy include: (i) adequate ventilation and oxygenation during surgical manipulation of airway, (ii) profound muscle paralysis to provide good relaxation of masseter muscle for introduction of suspension laryngoscope, (iii) an immobile surgical field, and (iv) a good cardiovascular stability during the period of rapidly varying surgical stimulation. Several methods have been successfully used during endoscopy to provide adequate vantilation and oxygenation. But, most commonly the patients are intubated by a small diameter ET-tube such as 4 to 6 mm of ID. However, unfortunately the ET-tubes of these sizes are designed for paediatric group of patients. Therefore, they tend to be too short for adult trachea. Hence, a special type of ET-tube called microlaryngeal tracheal tube (MLT) is commonly used whose size varies from 4 to 6 mm ID. The other characteristics of this tube are : the same length as an adult tube, has high volume low pressure cuff, and more stiffer (less prone to compression) than a regular tracheal tube. The advantages of intubation for endoscopy or microlaryngosurgery are: better ventilation and oxygenation, protection from pulmonary aspiration, ability to administer inhalational anaesthetics, provide unlimited time for surgery, continuous monitoring of $ETCO_2$.

Insome cases, the intubation may interfere the surgeon's performance such as when the lesion involves the posterior commissure of vocal cord. In such circumstances, a simple alternative is insufflation of high flows of O_2 through a small catheter placed in the trachea. These patients are usually not paralysed by neuromuscular blocker. This is because, though oxygenation is maintained for brief periods in patients with good lung function, but it is inadequate for longer periods unless the patient is allowed to breathe spontaneously.

Another possibility for ventilation and oxygenation for endoscopy and microlaryngeal surgery is the intermitted—apnoea technique in which alternate apnoea and ventilation with 100% O_2 by face mask or tracheal tube is performed. In this technique full muscle relaxant is used and the surgeon acts during the apnoeic period.

An another sophisticated technique for endoscopy or microlaryngosurgery involves jet ventilator by connecting a jet ventilator to the side effect of the laryngoscope. During inspiration O_2 under high pressure is directed through the glottic opening and entrains room into the lungs by venturi effect. Expiration is passive and patients are kept under spontaneous respiration. Therefore, it is crucial to monitor the movement of patient's chest wall (as there is no breathing bag) and to allow the sufficient time for expiration to avoid air trapping and barotrauma.

A variation of this above mentioned technique is high frequency jet ventilation where muscle relaxont is used. It utilises a small cannula or tube in the trachea, through which gas is injected 100 to 300 times per minute. In this technique, capnography will tend to greatly underestimate the $PaCO_2$. This is due to constant dilution of alveolar gases by O_2. In all the above mentioned technique such as insufflation by high flow of O_2, intermittent apnoea, jet ventilation, and high frequency jet ventilation (except standard anaesthetic technique using Coplan's microlaryngoscopy tube (MLT) or stand and (ET-tube) need continuous intravenous anaesthetic.

laryngeal (diagnostic and short therapeutic) procedures. In this procedure a thin 16 G cannula is introduced into the trachea either by the oral, nasal or transtracheal route through the cricothyroid membrane, just below the cricoid cartilage. Intermittent jet of O_2 down the cannula will entrain sufficient amount of air through the glottis to provide adequate pulmonary ventilation. With lungs of average compliance, this is true even if the glottis tends to close reflexly or becomes partially obstructed during inspiration. If the glottis is open (by muscle relaxant), additional air will be entrained and a given tidal volume will be achieved more quickly. In this method, it is not easy to measure the tidal volume directly, but rough clinical assessment of tidal volume by observation of chest movement can be made. If there is some degree of glottic obstruction then a longer expiratory phase will be observed. The failure to allow adequate deflation of lungs increases the risk of pneumothorax. This method is also applicable in children. But for paediatric group of patient it is essential to use smaller bore cannula and lower inflating pressure.

Similar anaesthetic technique using ventilating laryngoscope also have been described. Here, the cannula is incorporated into the blade of laryngoscope. So, the surgeon has an unobstructed view of the larynx. As the jet of O_2 is applied above the vocal cords, so it is difficult to control the direction of gas flow. Hence, alignment of the laryngoscope blade with the tracheal axis is essential. Also the vocal cords need to be relaxed fully and any pathological condition in the airway must not be so large as to obstruct the airflow into the trachea. It has also been observed that blood and biopsy material may be blown into the lungs by this jet ventilation technique.

Another method of ventilation for microlaryngeal surgery is the apnoeic oxygenation technique when a period of ventilation is followed by a period of apnoea when the ET-tube is taken out and it is again followed by intubation and ventilation, thus repeatating this cycle again and again. It is found that ventilation of lungs by 100% O_2 (not jet) by ET-tube can provide adequate oxygenation in apnoeic patient (i.e. when ventilation is not done) for certain period of time after the elimination of body N_2. But the limiting time factor for apnoea from clinical point of view is the rate of rise of arterial PCO_2. This may be reduced slightly by using higher flow rates of gas, such as 10 lit/min. In practise it is not advisable to prolong the procedure for more than 10 minutes. So, it is a suitable method for brief therapeutic and diagnostic microlaryngeal surgical procedure (It is further discussed in LASER Chapter).

Good muscle relaxation is an essential part of anaesthetic management for the microsurgery of larynx. So, succinylcholine infusion is useful for short cases. If the procedure is expected to exceed at least 30 minutes, then non-depolarising neuromuscular blocking drugs such as vecuronium, mivacurium or atracurium are also used.

Technique of Anaesthesia

Use of the injector technique (jet ventilation) or a small endotracheal tube allows a surgeon more time for leisurely examination of the larynx and microsurgery which is not possible by apnoeic oxygenation technique. In addition, many things such as teaching and photography may be done without being pressed for time

by the above two techniques. Anaesthesia is provided by an intravenous inducing agent. This is followed by suxamethonium and the chosen technique and equipment which is then put in place. A few minutes of preoxygenation before induction of anaesthesia helps to provide a favourable alveolar-arterial O_2 tension gradient. Further suxamethonium is given when it is required to maintain apnoea. During jet ventilation, if jets of O_2 only are used for ventilation, then it is important to give supplementary doses of IV induction agent (e.g. propofol). Otherwise, the patient may awake during the procedure and experiences the terror of being paralysed but awake (feeling of drowning) and may also hear remarks of OT personnels.

In children, microlaryngoscopy is performed by using spontaneous respiration via an oral tracheal tube which is one size smaller than that is used normally. The larynx should be sprayed with measured quantity of lignocaine in an attempt to prevent postoperative laryngospasm.

Major Surgery of Larynx

Major surgeries of larynx in ENT department includes laryngectomy, hemimandibulectomy, laryngoesophagectomy, etc. and these are done for malignancy of larynx. Airway obstruction by tumour is the major anesthetic problems in this group of surgery. Alcohol, smoking and old age are the aetiological factors of laryngeal malignancy which may also influence the course of anaesthesia. So, anaesthetist has to frequently face the patients who are elderly, having bronchitis, emphysema and chronic cardiovascular diseases, etc. If the tumour interferes with proper eating, then weight loss, malnutrition, anaemia, dehydration and electrolyte imbalance can also be significant and a anaesthetist has to face all rhese problems. So, these patients are properly evaluated and treated as representing difficult ET-intubation and with potential problems in airway management preoperatively. Respiratory functions should be assessed preoperatively by pulmonary function test. But this is difficult to measure accurately if there is any airway obstruction. Chest physiotherapy should always be prescribed as it aids the clearance of secretions pre and post operatively. These operations are often prolonged and associated with considerable blood loss, necessitating generous pre-operative provisions of compatible blood.

If the patients are scheduled for tracheostomy, then respiratory obstruction is suspected. So, narcotic and sedative premedications should be avoided. All the patients should have preoperative assessment of airway by flexible nasal or oral endoscope to know the magnitude of obstruction of larynx which have a great implication during induction and intubation. If there is a possibility of complete mechanical obstruction and failed intubation after muscular paralysis, then an inhalational technique should be used for intubation. If the inhalational technique results in possibility of severe obstruction, then an awake intubation should also be tried. Laryngoscopy and intubation sometimes become difficult if preoperative radiotherapy has done, because it reduces the mobility of the floor of the mouth due to fibrosis.

If respiratory obstruction is suspected, IV inducing agent should be given very slowly till consciousness is lost. Then patient's lung should be inflated using face mask and bag. If it is possible, it will indicate that patient will not go to the "not to ventilate and not to intubate condition", then only succinylcholine is given to facilitate intubation. If not, anaesthesia is deepened slowly with halothane, isoflurane or sevoflurane and intubation is tried preserving spontaneous respiration. All these volatile anaesthetic agents dilate the bronchi, depress the airway reflexes and permit the use of higher concentration of O_2.

Induced hypotension is often used to reduce the blood loss during surgical dissection of neck tissue. But, it is not without risk in debilitated patients and it may be unnecessary and dangerous too in these group of patients. Therefore, alternatively deep halothane anaesthesia and 10° to 15° tilt (head up) is sufficient to produce moderate hypotension and diminish the intraoperative blood loss, instead of restoring deliberate induced hypotension.

Intraoperative surgical manipulation of the carotid sinus during the dissection of the tissue of neck may elicit a vagal reflex that causes bradycardia, hypotension, arrhythmia or even cardiac arrest. If this is persistent, then the infiltration of this carotid sinus with local anaesthetic agent or IV atropine may be an effective treatment. Trauma to the right stellate ganglion and cervical autonomic nervous system during laryngeal surgery can prolong the QT interval and lower the threshold for ventricular fibrilation. But its incidence is low. Like neurosurgery, opened neck veins may also create the possibility of air emboli during major laryngeal surgery.

When the larynx and trachea has been dissected free to divide the trachea, then it is important to check whether a second sterile cuffed tracheostomy tube, catheter mount and a compatible connector which will attach the tracheostomy tube with anaesthetic machine are included in the surgical instruments trolly or not. Before division of trachea, patient is ventilated with 100% O_2 for two minutes. Then, the previous ET-tube is withdrawn from the larynx, trachea is divided and a second tracheal tube is rapidly placed through the opened end of trachea. After this the second tracheal tube is connected to the anaesthetic circuit and secured firmly. This tube should be positioned carefully within the shortened trachea to prevent inadvertent one-lung anaesthesia. The previous oral ET tube, having been withdrawn above the incision, is left in place until the new airway is secured. In cases of difficulty, it can be remanipulated into the trachea, so that the cuff lies distal to the incision.

At the end of surgery, patient should be reversed from the neuromuscular

block completely and the tracheal tube is changed for tracheostomy tube. When a patient with previous tracheostomy presents for anaesthesia, a cuffed tube should be inserted before induction of anaesthesia and anaesthesia is maintained through this tracheostomy route.

ANAESTHESIA FOR NASAL SURGERIES

All the Operations on nose have one common feature, i.e they involve surgery on a very vascular structure. In 1942, Moffatt had first described the method of topical anaesthesia for nasal surgeries using cocaine. Cocaine is a first discovered local anaesthetic agent with intense vesoconstrictive properties. There are three advantages of this local anaesthetic method for nasal surgeries by cocaine with vasoconstrictive property. These are: (i) minimal patient's discomfort from pain during operation, (ii) shrinkage of blood vessels of mucuous membrane, and (iii) blood less surgical field. Cocaine is known to have sympathomimetic side effects and sensitizes the organs to epinephrine by blocking its reuptake at the synaptic level. Major cardiovascular complications (VT, VF, MI, etc.) are reported even after the use of topical cocaine, especially when it is combined with the use topical epinephrine or with the use of halothane. So, this lead to the question whether cocaine still has a role in nasal surgery or not. Because sudies have shown that lignocaine with epinephrine and/or oxymetazoline are good effective alternatives to cocaine.

Still, if one wants to use cocaine, the dose will be 4% solution or less (without the addition of epinephrine) with a maximum dose of 1.5 mg/Kg or a total dose of 160 mg. Now, most of the nasal operations are done under local anaesthesia using various local anaesthetics (lignocaine or bupivacaine) mixed with some vasoconstrictor (adrenaline). When epinephrine is used, the maximum concentration of it should not exceed 1:1,00,000 or 10 µg/ml. Lower concentration is also acceptable, because no difference were found in the degree of vasoconstriction with the use of epinephrine at concentration as low as 1:4,00,000 (2.5 µg/ml). Concentration and total dose of epinephrine should be kept as low as possible, because it is known that the combined use of volatile anaesthetic agents during GA (especially halothane) and epinephrine can induce cardiac arrhythmias.

By blocking the sphenopalatine ganglion, most of the sensory supply to the nose, (including the anterior ethmoidal nerve) can be blocked. But only the columella is not affected by this method and requires a separate injection. Indications and contraindication of LA and/or GA for nasal and ear surgeries are like ophthalmic anaesthesia and are discussed in details in 'opthalmic anaesthesia' Chapter (Fact file -II).

Nasal surgical procedures such as septoplasty, removal of polyp, reduction of fractured nasal bones, etc, are often carried out safely under local anaesthesia by using infiltration of tissue by local anaesthetic agents combined with or without sedations. However, potentially serious complications may arise, if the patient moves during endoscopic sinus surgery. These serious complications may include: entering the intracranial space, blindness due to entry into the orbital cavity, damage to the internal carotid artery, etc. So, paralysis of patients is advised when the risk of complications from movement is high. Thus, GA is recommended for these type of endoscopic surgeries, where chances of movement is high such as in paediatric and psychiatric group of patients. GA for these endoscopic nasal surgery has been revolutionised by the introduction of LMA. In the presence of nasal packing, difficulty in maintaining airway is almost completely eliminated by leaving LMA in place postoperatively, until the patient himself rejects it spontaneously in the recovery room.

General anaesthesia for nasal surgeries may be maintained by using either spontaneous or controlled ventilation. During GA and surgery whatever tube is used (ET or LMA), pharynx should be packed with gauze, so that blood, pus or debris does not contaminate the larynx and at the time of extubation may not lead to coughing and/or laryngospasm. After surgery, the packs are removed, the pharynx is cleared and the patient is turned in lateral tonsilar position. It is more safe to extubate the patient while completely awake. Sometimes, after nasal surgery but before extubation, blood may collect at the back of the softpalate. Therefore, in the immediate postoperative period following extubation, these clots may dislodge from its site and fall into the glottis leading to complete airway obstruction. This clot is called the 'coroner's clot'. So, thorough suctioning before extubation, and reduction of bleeding by using topically applied vasoconstrictive drugs and head up position by 15 to 20° which provide a mild degree of hypotension will help to reduce the incidence of this problem.

FACT FILE - II

Most nasal surgeries can be performed satisfactorily under local anaesthesia with or without sedation. The nasal septum and the lateral wall of the nose get their sensory innervation by anterior ethmoidal and sphenopalatine nerves. Both these nerves can be blocked by topical application of LA agent by packing the nose with gauze or cotton soaked with local anaesthetic agent. This topical anaesthetic agent should be allowed to remain in place for atleast 10 minutes before surgery. Somtimes, in addition to this topical application, local infiltration of LA agent in the submucosal level is often required. This is mainly found, particularly if scar tissue is present from prior surgery. The use of epinephrine containing LA solution or cocaine solution (usually a 4% or 10% solution) will shrink the nasal mucosa and reduce the intraoperative blood loss. The disadvantasge of cocaine is that it is very rapidly absorbed and may cause detrimental cardiovascular effects. GA is needed for nasal surgeries when the topical or local infiltration block is inaqdequate producing discomfort, or paediatric and psychiatric patients are met.

ANAESTHESIA FOR EAR SURGERIES

The ear gets its sensory supply by four nerves: These are: (i) the auriculotemporal nerve, (ii) the great auricular nerve, (iii) the auricular branch of the vagus nerve, and (iv) the tympanic nerve (Fig. 38.1). The auriculotemporal nerve is the branch of the mandibular division of trigeminal nerve. It supplies the external auditory meatus. It can be blocked by giving 3 ml of local anaesthetic agent into the anterior wall of the external auditory meatus. The greater auricular nerve is the branch of the cervical plexus. It supplies the middle and lower aspect of auricle and a part of the external auditory meatus. The auricular branch of the vagus nerve supply the concha and the external auditory meatus. These two nerves, i.e. the great auricular and the auricular branch of the vagus can be blocked by giving 3 ml of local anaesthetic agent posterior to the external auditory meatus. The tympanic nerve is the branch of the glossopharyngeal nerve and supplies the tympanic cavity. It can be blocked by instillation of 4% lignocaine into the middle ear.

Ear surgeries can be performed both under local anaesthesia and GA. Operations such as premeatal operations, stapedectomy and uncomplicated middle ear surgeries (of less than 2 hours duration etc,) are all usaully performed under LA. GA is needed only when the patient is non cooperative or for paediatric age group. When surgery is performed under local anaesthesia, then usually the surgeon injects the local anaesthetic agent. But both the surgeon and the anaesthetist must keep track on the total amount of the local anaesthetic agent used in order to prevent toxic blood concentration of it. If the patient is very anxious, then a benzodiazepine premedication is often given. A small dose of IV fentanyl (0.5 to 1 µg/Kg) or a small dose of IV propofol (0.3 to 0.5 mg/Kg) can be given just before the injection of local anaesthetic agent. For many anxious patients, carefully titrated sedation (by propofol 0.5 to 0.7 mg/Kg IV, followed by an propofol infusion with or without midazolam at the dose of 0.02 to

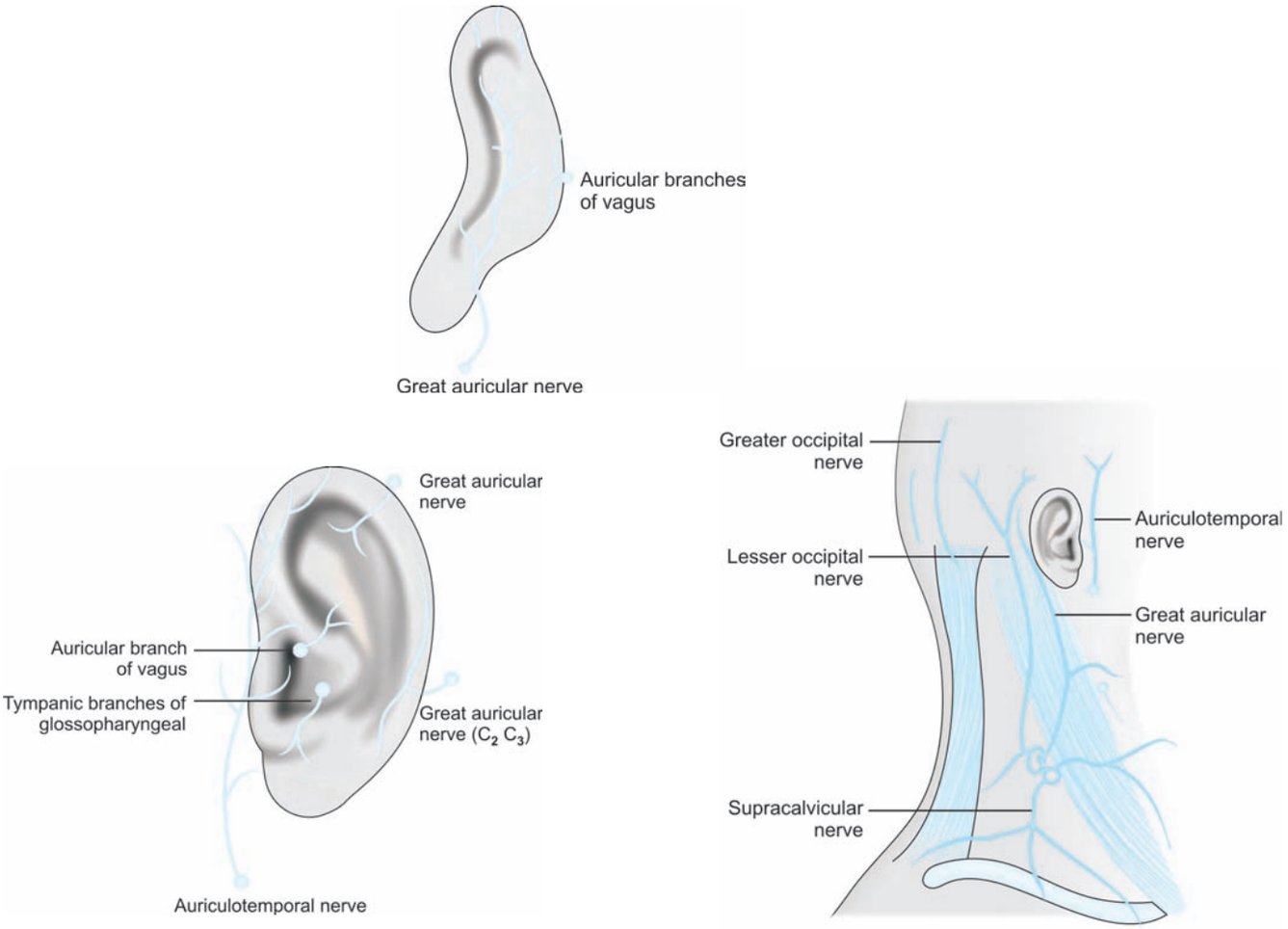


Fig. 38.1: Sensory supply of nerves: (i) Auriculotemporal nerve, (ii) Auricular nerve, (iii) Auricular branch of the vagus nerve (iv) Tympanic nerve

0.04 mg/Kg/min) have also been helpful. By this carefully titrated awake sedation, patients become calm, cooperative, and can gossip with the surgeon during operation under local anaesthesia. Full sedation should be avoided, because it will cause the patient to be uncooperative and may cause airway problems. Though the cases are selected for LA, but still the preoperative workup of patient by anaesthesiologist should be the same as for the GA. Due to high incidence of PONV, antiemetics should be used routinely during ear surgeries. Addition of epinephrine to the local anesthetic agent increases the duration of it and causes vasoconstriction and thereby decreases the bleeding. Safe dose of epinephrine is 0.05 to 0.1 mg and can be repeated after 20 minutes.

Ear surgeries under GA are done only for the paediatric, uncoopearative and anxious group of patients and for procedures such as tympanoplasty and mastoidectomy in adult. The things that should be kept in mind during ear surgery under GA are: (i) the possibility of facial nerve injury, (ii) the effect of N_2O in middle ear surgery, (iii) the extremes of head position, (iv) the possibility of air emboli, (v) blood loss and control of bleeding during microsurgery of ear.

During surgery under GA with muscle relaxant, monitoring of evoked facial EMG activity may assist in the preservation of the function of facial nerve. Facial nerve also can be monitored by using a nerve stimulator during GA. Its function also can easily be monitored, if deep muscle relaxation is avoided or at least 30% of the muscle response (as measured by a twitch monitor by TOF) is preserved. However, many studies revealed that despite significant neuromuscular block, as measured by no response state on the stimulation of ulnar nerve, facial nerve activity could still be detected on elctrical stimulation.

Middle ear, like other cavities (e.g. sinuses) of the body is a closed air containing space which is connected to the environment by eustachian tube (whereas sinuses are connected with environment through ostium). During N_2O anaesthesia, N_2O enters the cavity 34 times rapidly than N_2 exits the cavity (as N_2O is 34 times more soluble in blood than N_2, blood gas coefficient of N_2 being 0·013 and N_2O 0.46). This results in the increase in volume and pressure of air in the middle ear. As a result, there is bulging of ear drum and lifting of the tympanic membrane which causes disruption of the graft in tympanoplasty surgery. Normally, when the middle ear pressure rises between 200 to 300 mm of H_2O, automatic venting of air occurs through the eustachian tube. But, when the eustachian tube remains blocked due to inflamation or oedema, then venting of air can not occur and the middle ear pressure rises, causing problems. In eustachian tube block, the middle ear pressure can rise upto 375 mm of H_2O within 30 minutes of the starting of N_2O inhalation. In addition, after discontinuation of N_2O, the gas is rapidly absorbed in blood than N_2 which enters in the cavity, causing marked reduction of the volume and negative pressure in the middle ear. Sometimes, this negative pressure in the middle ear becomes so great that it causes serious otitis, disarticulation of stapes and impaired hearing, etc.

Finally, it can be concluded that fluctuation of middle ear pressure during N_2O anaesthesia causes problems (is also a cause for PONV) only in susceptible persons i.e those with the previous eustachian tube block due to otologic surgery, acute or chronic otitis media, sinusitis, URTI, adenoids etc. There is also no evidence of interference in graft placement or outcome of surgical procedure in type 1 tympanoplasty if N_2O is used in less than 50% concentration. But it is better to avoid possibilities of complications. So anaesthetist should limit the concentration of N_2O to 50% and discontinue N_2O 15 to 20 minutes before the closure of the middle ear. The subsequent decrease of middle ear cavity pressure to the subatmospheric level can be avoided by flushing the middle ear cavity with air prior to closure of the tympanic membrane. During ear surgery under GA, an anaesthetist should be careful about the extreme positions of neck, such as extreme extension or rotation which may cause injury to the cervical spine, brachial plexus, etc. Patients with limited carotid artery supply to the brain are especially vulnerable to further decrease in flow from exaggerated neck position. Also, in patients with Down syndrome or with rheumatoid arthrosis extreme rotation of the neck should be avoided because of the risk of $C_1 - C_2$ sublaxation.

Control of bleeding during microsurgery of ear under GA can be done by maintaining 10 to 15 degree head up tilt position which will increase the venous drainage and will decrease the venous bleeding. Thus they will create a relatively dry operative field and help in microsurgery of ear. Infiltration of operative area by local anaesthetic agent mixed with adrenaline is also helpful for controlling the bleeding and helps in post-operative analgesia. But, the total dose of adrenaline should be limited to 0.1 mg (20 ml of 1:200000 solution in which 1 ml contain 5 µg adrenaline) which can be repeated after 20 minutes. This is also a safe practice in a well ventilated patient who is given halothane anaesthesia. Isoflurane and sevoflurane does not sensitize the myocardium to catecholamines to the same extent as does the halothane and hence are more safe. Topical application of epinephrine in the ear is also helpful to reduce bleeding from operating site and to make a dry operative field. But higher concentrations of adrenaline like 1:50,000 need not provide any additional vasoconstrictive effects.

LMA is used in major ear surgery but the anaesthetist must be aware that if the airway is lost during the procedure, as a result of movement of the head, then the operation may have to be abandoned.

39 Anaesthesia for Geriatric Patients

INTRODUCTION

There is no precise definition of the term, named elderly, geriatric or aged. There is also no specific clinical marker for geriatric group of population (in the society) from which we can stamp that the patient is elderly. This is because ageing is a continuous process. So the determination of age at which people are considered elderly also remains arbitrary. But, still it is generally agreed for administrative and epidemiological purposes that patients aged more than 65 years are considered as geriatric or elderly. However, some specific classifications of geriatric population are : persons between 65 to 74 years of age are called as 'elderly', persons between 75 to 84 years of age are called 'aged' and those above 85 years of age are called 'very old'.

Age itself is an independent factor for increased morbidity and mortality in a society. It is also an important independent factor for a number of diseases, injuries, hospitalisation and adverse drug reactions which occur predominantly in this age group of patients. It itself has also been shown to be an independent predictor for perioperative outcome. As all over the world, the geriatric population is now on the rise, so India is also not lagging behind of the fact that more and more number of geriatric patients are coming for surgey in this country also. So, the anaesthesiologists are now going to encounter more and more number of elderly patients in OT. Therefore, it is mandatory to understand precisely the pathophysiological changes which occur with age and to evaluate its affect on anaesthetic risk. Thus, equipped with proper knowledge an anaesthesiologist will be in a better position to take a good perioperative care of the geriatric group of patients.

The speciality of geriatric cases such as geriatric medicine have, therefore, become increasingly important and is gradually now developing in recent years in all the countries. Geriatric medicine is not concerned merely with prolonging the lives of elderly. But it is much more concerned with the keeping old people young. Similarly, surgery on the elderly should comprise not only the possibilities of treating an illness by operation, but also include an assessment of the patient's ability to withstand the surgery and benefit from it. The modern development in anaesthesia has made surgical proecedures which was previously deemed unfit due to age, now feasible. But this must not obscure the dangers of postoperative period that will throw an additional strain on the cardiovascular and respiratory systems which the aged patient may not be able to sustain. On the other hand, the general view is that all the surgeries in the very old are 'unwarranted interference' and cannot be justified, especially if it does not improve the quality of life and bring comfort for the remaining months or years of the patient's life.

Ageing is defined as the a progressive physiological process that produces measurable changes in the structure and function of tissues and organs. Till now mechanism of ageing is not yet clearly understood. But it is postulated that decreased cellular energy production due to the deterioration of mitochondrial function (mainly in cardiac and neural tissues) plays a fundamental role in the age-related decline of tissue or organ functions. Ageing is a natural, inevitable and biological phenomenon of every cellular structure. However, the onset and the rate of progress of age varies with every individual, depending on few known and many unknown variables. The biological age (decrease of production of cellular energy with passing of time) of a person is not indentical with the chronological age.

Ageing appears to be a universal phenomenon which is characterized by degenerative changes, involving both the structure and functions of tissues. It is not a linear progress as it was earlier thought of. The decrements of function of tissues due to ageing in most organs are now believed to be relatively subtle upto the middle past of adult life and then the progress is faster after seventies. The elderly persons who maintain a greater average functional capacity than others is referred to as physiologically youngs and when the function declines early they are often referred to as physiologically old. In healthy geriatric patients the maximum organ function is higher than the basal level at all ages. The difference between these two (maximum level of organ function and basal level of organ function) is the functional reserve of the organ system. The functional reserve of organs is able to meet the additional demands of cardiac output, CO_2 elimination or protein synthesis imposed by trauma, surgery or disease.

PHYSIOLOGICAL AND PATHOLOGICAL CHANGES ASSOCIATED WITH AGEING

Perhaps chronological ageing only wrinkles the skin. But worry, doubt, fear, anxiety and self distrust, etc, wrinkle the soul (biological aging) as chronological age progresses. With the current continuation of the decline in fertility and increase in life expectancy, the current population of the world will be aged much faster in the next half century than the previous one. For example, the total population of the elderly persons of the world is supposed to grow 3.5 times in 75 years, from 2.5 billion in 1950 to 8.46 billion in 2025 (projected). The world population of 60 years old and above will increase 6-fold from 201 million (in 1950) to 1·2 billion in 2025 (projected). In this period the fastest growing age group will be 80 years and above. Most astonishingly this population will increase from 13 million (in 1950) to 137 million in 2025. We are concerned with the fact that in many developed countries 2/3 of the hospital beds are occupied by the aged of which 50% need surgery. As the age advances, the physiological functions of the body get compromised. Degenerative changes in all the tissues are more common, but history is always not reliable. So, hospital notes sometimes become formidable. With this, the body's mechanism of drug handling gets altered, leading to ever increasing problems to anaesthesiologist during the administration of anaesthesia. So, it will be worthwhile to recapitulate the physiological changes and the altered mechanism of drug handling in this elderly age group of patients (Fig. 39.1).

Cardiovascular Function

The geriatric surgical group of patients have the higher incidences (50 to 60%) of overt and /or subclinical cardiovascular diseases. The coronary disease has been found even in completely symptom-free octogenarian. More than half of all the mortality in this geriatric population is due to this cardiovascular disorders. With the increased age the ventricular compliance gradually decreases and it is due to the gradual increase in ventricular wall thickness, myocardial fibrosis and valvular calcification. Thus, due to increased stiffness of cardiac chambers (reduction of compliance) haemodynamic function of an elderly heart runs within a narrow range of end-diastolic pressure and subsequent end-diastolic volume. Hence, they become volume dependent (preload) and easily become volume intolerant.

With increased age the elastic fibres of blood vessels show thickening and fragmentation. This along with the progressive arteriosclerotic changes in the arterial wall make the arterial tree narrow and less distensible. So, this causes the rise in systolic BP (due to non distensibility), pulse pressure and impaired vascular compensation for blood loss (as vessels fails to contract properly). With increased age the narrowing and the stiffness of the wall of the blood vessels also causes ↑SVR and ↑diastolic pressure. This increase in SVR and diastolic pressure causes increased impedence to the ejection of stroke volume and elevated systolic pressure associated with that given stroke volume. Thus, this increase in afterload further increases the ventricular work load which again increases the wall thickness and stiffness of ventricle with further decrease in diastolic ventricular filling and cardiac output (a viscious cycle). Due to the impedence of ejection, cardiac index (CI) also progressively decreases with age (linear relationship). Age imposes a ceiling on the increase of cardiac output as a person grows from childhood. It becomes maximum at the middle of the life, then it decreases approximately 1% per year starting from the middle of adulthood.

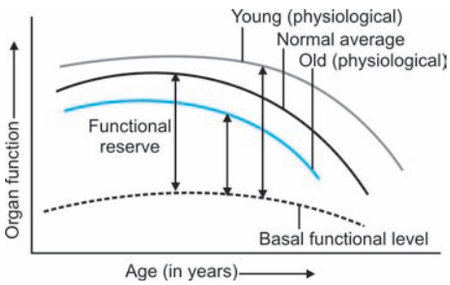


Fig. 39.1: When there is lesser rate of decline of functional reserve, then this geriatric person is called 'physiological young'. Contrary, when there is greater rate of decline of functional reserve, then this geriatric person is called 'physiological old'. They have significant different functional reserve. Functional reserve is the difference between the maximum (unbroken lines red for average, blue for young and green for old) and the basal level of function (broken red line)

As age advances, so due to the decrease in ventricular end-diastolic volume (due to stiffness and hypertrophy of wall) the ventricular diastolic filling and subsequent CO now depends on atrial contraction. Hence, the loss of sinus rhythm or the atrial 'kick' (e.g. atrial flutter and fibrillation) produces severly compromised CO in elderly patients. In the elderly persons the haemodynamic insufficiency due to diastolic ventricular dysfunction is more common than the young adults. In children and young adults the CO increases by tachycardia and β-adrenergic agonistic action. But, in the elderly or aged persons during demand, the CO can only be increased by increasing the left ventricular end-diastolic volume in response to augmented preload (by IV fluid or by prolonged filling time by reduction of heart rate) which compensate for slow heart rate (as the HR decreases with age). This increase in cardiac output is associated with little enhancement of ejection fraction. Here the mechanical compensatory mechanism predominates over heart rate caused by adrenoceptor activation or baroreflex activity. So due to limited reflex mediated ability to increase the heart rate, hypotension can be frequent and severe during both intraoperative and postoperative period in the older surgical patients. Thus, Frank-Sterling principle with increased O_2 demand works in elderly heart.

Only loss of arterial elasticity (not narrowing due to atherosclerosis) causes

reduction of diastolic BP and increase in systolic BP and widens the pulse pressure, while narrowing of the arterial wall with loss of elasticity causes both ↑systolic, ↑diastolic pressure. Reduction of diastolic BP decreases coronary artery perfusion and narrowing of coronary artery due to atherosclerosis in aging process further decreases the coronary flow. So, hypotension is usually badly tolerated by the aged persons. Due to same reasons, blood flow to the kidneys and brain is also reduced with age with impaired autoregulation. The physiological response to cardiovascular disturbance may be also blunted with advanced age, due to reduced baroreceptor sensitivity and impaired autonomic function. Atrial fibrillation is common in older people.

Pulmonary Function

With advancing age, there are also changes both in the chest wall and the lung parenchyma. In the lung parenchyma, the quality of elastin deteriorates with age (but quantity of elastic tissue does not decrease). This results in progressive loss of lung recoiling effect and decrease in tethering property of it which are normally helpful for the patency of small airways and homogeneous distribution of inspired gases. Thus, the lungs become more compliant (due to loss of recoiling or elastic property) and the patency of airways is impaired. But, due to increased rigidity of chest wall the compliance of it (i.e. chest wall) is reduced and, therefore, the total pulmonary compliance decreases.

The breakdown of alveolar septa (due to reduction of tethering property) with increasing age also causes the merging of small alveoli into a large alveoli and reduces the total alveolar gas exchanging surface area. So, the lung becomes emphysematous and dead space (anatomic and alveolar) increases. As the lungs become emphysematous and the recoiling property is lost, so the residual volume of lung increases at the expense of expiratory reserve volume. At the same time FRC increases at the expense of vital capacity (↓VC) also. Closing volume and closing capacity both increase gradually overlapping FRC. So, airway closure occurs at increasing lung volumes with increasing age. Even small airways close during tidal volume. This critical relationship between CV and FRC is more marked in the supine and lithotomy with head down position and gradually increases the mismatch of ventilation/perfusion ratios. The alveolar – arterial O_2 gradient widens with age which indicates inadequate oxygenation.

The anatomical dead space also increases as the diameter of larynx and trachea increases with age. So, a large ET-tube is needed for older patients. Calcification, fibrosis and osteoarthritic changes of the chest wall also reduces the movement and compliance of it. This results in decreased FEV_1 and tidal volume. Thus V_D/V_T ratio increases with age, causing VQ mismatch, arterial hypoxaemia and reduction of CO_2 elimination. Ronchi are fairly common in the elderly patients without underlying pulmonary disease, but crepitations are usually a sign of incipient pneumonia or CHF (Fig. 39.2).

It is advisable whenever possible to have a preoperative chest X-ray in all the elderly patients. Atelectasis, pulmonary embolism and chest infection are all more common in the elderly patients. The later in part is due to the ineffective mucociliary activity for advanced age. P_AO_2 and P_aO_2 decrease with age (P_AO_2 = 100 − age / 4 mm of Hg). The geriatric persons also have the markedly decreased ventilatory response to hypercapnia and hypoxia. The elderly has further increased incidence of sleep apnoea which make them more susceptible to hypoxaemia in recovery room.

Renal Function

Like all other organs, kidney also becomes aged with time. So, among all the geriatric patients who undergo surgery, 30% have kidney dysfunction. Also acute renal failure is responsible for 1/5th of the total perioperative death in geriatric population. The prevalence of renal disease among the geriatric group of patient not only increases the perioperative risk of acute renal insufficiency or failure in them, but also affects the duration of action (pharmacokinetic) of many anaesthetic and adjuvant drugs. With ageing the renal tissue mass is atrophied, the total number of nephrons decrease, fatty tissue accumulates and interstitial renal fibrosis occurs. About 20% of renal tissue mass is lost by the eighth decade and more than one third of glomeruli with their tubule disappear.

The renal plasma flow (RPF) decreases (10% per decade) along with the decrease of GFR. This decrease of renal blood flow is about one-half of that of the young adults. The rate of decrease of GFR is 7 to 8 ml/min/1.7 m^2/day. This decrease of GFR and RPF is more sharp than decrease of renal tissue mass. This is because renal vasculature is compromised preferentially with age. The active tubular secretion and reabsorption of drugs and other solutes is also reduced with age. Thus, the elimination

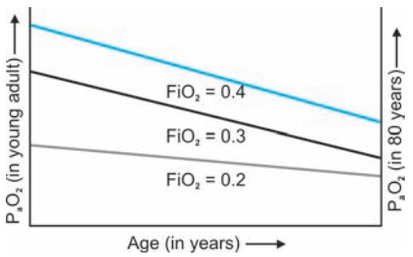


Fig. 39.2: The decrease of arterial O_2 tension with age at different inspired O_2 concentration (FiO_2)

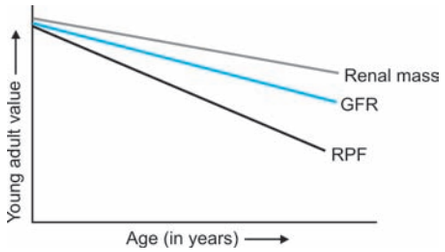


Fig. 39.3: The effect of age on renal function such as RPF (renal plasma flow), GFR and renal mass in man

half-life of virtually every anaesthetic drug is prolonged in elderly patients, especially in those with pre-existing renal dysfunction (Fig. 39.3).

Excretion of free water load is also markedly delayed in elderly people. Creatinine clearance also declines, but the serum creatinine level does not rise as creatinine load on the kidney also decreases due to the reduction of skeletal muscle mass with increasing age. So, a modest rise in serum creatinine level in elderly persons may represent a significant renal impairment. Tubular functions is also impaired with reduced renal concentrating ability and reduced free water clearance. Fluid balance in elderly patient is more critical, as responses to both the fluid loading and dehydration are impaired. Although renal function detoriates with advancing age, still the residual function is sufficient to avoid gross uraemia if demands are basal. The other changes in renal function in geriatric patients are: ↓responsiveness to ADH, ↓absorption of filtered glucose, ↓ability to conserve Na^+ and to concentrate urine and functional hypoaldosteronism. In older age the reduction of lean body mass decreases the total body stores of K^+ and thus predisposes to hypokalaemia. Therefore, due to the limited renal functional reserve, geriatric patients require meticulous calculation and monitoring of fluid and electrolyte balance during the perioperative period. But no fluid replacement protocol is appropriate for this group of patient. Acute renal failure is usually responsible for at least approximately one-fifth of the perioperative mortality in elderly surgical patients. This age related changes in renal function has important pharmacokinetic consequences causing prolonged elimination half-life of anaesthetic drugs and its metabolites which require renal route for their clearance.

Hepatic Function

With advancement of age the size of hepatic tissue, hepatic blood flow and hepatic function decreases. This loss of hepatic function is quantitative and not qualitative (i.e. the quality of hepatocellular enzymatic function does not decline). This is because normally as much as 40 to 50% of the total hepatic tissue may involute by the age of 80 years. Thus, there is progressive redistribution of perfusion away from the hepatic splanchnic vascular bed to the other organs due to atrophy of it. Hence, this quantitative loss of hepatic tissue plays a major role in the age related decline of anaesthetic drug clearance. The duration of clinical effect of anaesthetic agents may be further prolonged if their primary or secondary metaboites take the renal route for elimination instead of the drug itself. On the other hand, as the quality of hepatocellular function does not decline, so the microsomal and non-microsomal enzyme activity of hepatic cells appear to be well preserved. But, the hepatic synthesis of plasma cholinesterase is deficient in many elderly men. The hepatic capacity for protein synthesis significantly reduced by the eighth decade of life. But still this reduction of protein synthesis can meet the requirements for normal coagulation due to previous huge reserve. Due to the present limited hepatic functional reserve the elderly persons produce many postoperative complications and so require supportive therapy and intensive care.

Nervous System (Central, Peripheral, Autonomic)

With increased age, the brain also has undergone definite structural and functional changes. Age reduces the brain size and weight. The average weight of brain of an 80-year-old person is approximately 20% less than that of an 30 year old person. The very rapid decrease of brain tissue occurs after the 6th decade of life. At the same time, there is also a compensatory increase in CSF volume. So, aging produces a low pressure hydrocephalus. Normally, the supportive glial cells constitute about almost ½ of the total brain mass and reduction of brain size reflects not the atrophy of glial cells, but the reduction of the number of neurons. The average rate of neuronal loss in brain tissue is 55,000 per day. However, among the neurons those responsible for the synthesis of neurotransmitters undergo the greatest degree of age related attrition. With increased age, the intelligence does not decline. The storage, integration and consequently the processing of information which is responsible for language skills, aesthetic skill and personality remains also intact. However, on the other hand the short-term memory, visual reaction time and auditory reaction time, etc, that require rapid retrieval of information and immediate processing gradually decreases. With ageing the cerebrovascular diseases are common and confusion is more likely during both the pre and postoperative period. In elderly, the autoregulation of cerebral blood flow (perfusion) in response to change in arterial blood pressure is still maintained. Therefore, ageing is not associated with inadequate cerebral perfusion with the change of BP. If there is any decrease in cerebral blood flow, then it is the consequence of cerebral atrophy. But this reduced cerebral blood flow is not the cause of cerebral atrophy. The cerebral vasoconstriction response to hyperventilation remains intact in elderly persons like young brain tissue (Table 39.1).

The intrinsic mechanism that couple cerebral electrical activity, cerebral metabolism and cerebral blood flow remain similarly intact with increased age. In aging brain, there is generalised depletion of neurotransmitters such as dopamine, norepinephrine (NE), epinephrine (E), tyrosine, serotonine, etc, and simultaneous increase in activity of enzymes such as MAO and COMT which are responsible for breakdown of these neurotransmitters. One of the example of this deficiency of neurotransmitter is Alzheimer's disease, where there is deficiency of acetylcholine in cerebral cortex. The affinity of these neurotransmitters to their receptors is also

Table 39.1: Summary of anatomic and functional changes due to ageing

System	*Anatomic changes*	*Functional changes*
1. Body composition	↓Skeletal muscle mass	↑Drug effect
	↓Lean tissue	↓Metabolism and heat production
	↓Relative	↓Resting cardiac output
2. CVS	↓β-adrenergic responsiveness	↓Cardiac and arterial compliance
	↓Vascular elasticity	↓Maximal heart rate and CO
	↓Ventricular hypertrophy	↓Pulse pressure
3. Nervous system	↓Neuronal tissue mass	↓Neural plasticity
	↓Central neurotransmitter acitivity Deafferenation	↓Anaesthetic requirement
		Impaired (↓↑) autonomic homeostasis
4. Pulmonary system	↑Thoracic stiffness	↓Vital capacity, ↑RV
	↓Lung recoil	↑Work of breathing
	↓Alveolar surface area	↓Efficiency of gas exchange
5. Blood and immune system	Thymic involution	↓Immune competence
	Reabsorption of bone marrow	↓Hematopoietic reserve
6. Renal/hepatic system	↓Tissue mass	↓Drug clearance
	↓Vascularity and perfusion	↓Ability to withstand salt and water loads
		↓GFR, ↓Plasma flow

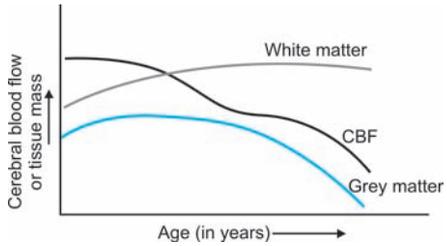


Fig. 39.4: The relation between the increased age and brain tissue mass and CBF (cerebral blood flow)

diminished and it is due to the reduction of number of receptors. In ageing brain, the upregulation (increase in number of receptor sites in response to reduction in neurotransmitter activity) is less vigorous than in the young population. The CNS 'plasticity' (the ability to reroute the neural pathways) to compensate the neural injuries is less marked and less complete in aged person than young. Therefore, recovery from neural injury (e.g. stroke, accident, etc) in geriatric patient is slow and incomplete.

In the elderly persons at peripheral nervous system there is also reduction of both the velocity and the amplitude of the electrical transmission of impulses through both the afferent (sensory) and efferent (motor) pathways. In old age the degenerative changes in sensory receptors also occur and the threshold for perception of snsory stimulus such as touch, pain, temperature, smell, vision, hearing etc. increases. Hence, impairment of cortical transmission thus delays the onset of voluntary motor activity. But skeletal muscles do not undergo any change with age except man, as enzymatic machinary within it remains intact. With increased age, the number and density of motor end plate also decreases. To compensate this, there is both the thickening and the spread of the existing post-junctional membrane beyond the usual areas of motor end plate, and increase in the number of cholinergic receptors at the end plates and surrounding areas. However, the sensitivity to non-depolarising relaxants does not decrease significantly with age. Alternatively the sensitivity to succinylcholine is increased in some elderly. It is due to the reduced plasma cholinesterase enzyme concentrations and not due to the changes at neuromuscular junction itself with age.

With increased age the plasma levels of NE increases gradually, though there is attrition of neurons in the sympathoadrenal pathways. But, clinically the increased effect of NE is not always found due to the reduction of the autonomic end-organ responsiveness with age. There is significant impairment of the ability of β-adrenergic agonist to stimulate β-receptors, causing less positive inotropic and chronotropic actions. The probable mechanism of reduction in action of β-adrenergic agonists are attrition of receptors, reduced affinity of neurotransmitter towards the receptors and impairment of adenylcyclase activation due to decreased cell membrane fluidity. The autonomic reflexes maintaining the cardiovascular homeostasis also decreases progressively with age. So, BP is less well maintained in a steady state level in adverse situations (i.e. in hypotension or hypertension) in elders than the young. Hence, the anaesthetic agents (such as β-blockers, etc.) and the techniques (spinal or epidural) that block the sympathetic system causes more hypotension in an elder than a young (Fig. 39.4).

Haemopoietic Function

Age has little effect on RBC, WBC and platelet count. The hypercoagulability of blood and thrombosis in vessels is not directly related to ageing. The age actually indirectly enhances the platelet mediated haemostasis. The common observation of ecchymotic lesions on the skin of the extremities of many elderly individuals is the result of age related increase in the fragility of cutaneous blood vessels. The volume of bone marrow and also the mass and volume of spleen, responsible for haemopoiesis, reduces in size with age. So, anaemia cannot be corrected easily in elderly patients, though clinically significant anaemia is not the physiological process of aging. Although, the volume of bone marrow, spleen and other haemopoietic reserved tissues are reduced with age, but the effect of aging is rarely enough to alter the day to day haemostasis or the acute

haematologic responses to accidental injury or mild stress. With age anatomical involution of thymus occurs (that begins at young adulthood) and causes a decrease in the immune responsiveness in elderly. With the quantitative age related change in thymic mass, there is also progressive change of thymic composition. Thus, both these quantitative and qualitative changes of thymus play a central role in reduction of the adaptive immune system, primarily the T-lymphocyte mediated responses. So, elderly are particularly predisposed to streptococcal pneumonia, meningitis and septicaemia. Infection or sepsis is notoriously occult in geriatric surgical patients. It is the second only cause after cardiac failure of perioperative morbidity and mortality. Erythropoietin levels are generally normal, but may be depressed easily by infection.

Body Composition, Drug Distribution and Metabolism

After 60 years of age, the body weight decreases rapidly and the body composition also changes. Throughout the whole path extending from young adulthood through middle age to the old age, a person generally gain 12 Kg of adipose tissue, but lose about 8 Kg of skeletal muscle mass. When this loss of muscle mass and atrophy of central organs is combined with the loss of subcutaneous fat, then it produces a significant fall in total body weight in aged men. The age-related changes in body composition are universal, progressive and irreversible. This change is due to the steady increase in the ratio of lipid to aquous tissues (i.e. lipid fraction increases and water fraction decreases), and results in the increase in lipid fraction of total body mass which acts as reservoir for anaesthetic and other lipid soluble drugs. This total body fat increment is more profound in woman than man. Thus, the significant reduction of intracellular and interstitial water reflects the attrition of metabolically active tissues. Diminished thirst, poor diet and the use of diuretics to treat the age related hypertension also make the intracellular and interstitial dehydration a more common finding during the preoperative examination of elderly patients.

Glucose intolerance is almost universal among the elderly patients. The cause of glucose intolerence at this age is due to the insulin antagonism and impairment of insulin function, but is not due to the decreased insulin secretion. The reduction of lean body mass that provides the storage for carbohydrate is also an explanation for the carbohydrate intolerence. So, the loss of skeletal muscle mass is also associated with the progressive impairment of ability to handle an intravenous glucose challenge.

In elderly the basal resting metabolism is reduced by 10 to 15% and it is in parallel with the reduction of lean tissue mass. So, the rate of production of body heat gradually declines. Simultaneously, there is also age-related impairment of thermosensitivity and also the impairment of autonomic thermoregulation which in combination increase the risk of inadvertant hypothermia, especially in cold enviornment in OT. The Intraoperative decrease in core body temperature is almost 1°C per hour which is about twice that observed in young adults under similar circumstances. So, core body temperature of geriatric patients frequently fall during intra-and postoperative period (Table 39.2).

In a similar manner to the reduction of intracellular and interstitial water volume, the plasma volume which is a major determinant of β-phase (molecular aspect of drug distribution from plasma to other compartment) of pharmacokinetics of drugs is also reduced. So, the doses of

Table 39.2: Effects of aging on pharmacology of anaesthesia related drugs

	Drugs		*Pharmacology*
1.	Inducing agents		
	Propofol		↑drug effect
	Thiopentone		↓dose requirement
	Cause	(i) CNS changes	
		(ii) decreased volume of distribution	
2.	Benzodiazepines		
	Diazepam		↓dose requirement
	Midazolam		↑drug effect
	Cause	(i) CNS changes	
		(ii) ↓liver and renal mass	
		(iii) ↓blood flow of liver and kidney	
3.	Opiates		↑drug effect
	Morphine		↓dose requirement
	Fentanyl		
	Cause	↓volume of distribution	
		↓hepatic and renal blood flow CNS changes	
4.	Volatile anaesthetics		
	Halothane		↑drug effect
	Sevoflurane		↓dose requirement
	Isoflurane		
	Cause	CNS changes	
5.	Muscle relaxants		↓dose requirement
	Succinylcholine		
	Cause	↓plasma cholinesterase	
	Nondepolarizing agent		↓dose requirement ↑drug effect
	Cause	Neurogenic atrophy decreased renal and hepatic function	

drugs based on body weight shows higher concentration than expected in blood in older one and explain increased sensitivity to drugs in elders.

Most of the drugs which are used in anaesthesia are metabolised in liver (small amount is metabolised in extra hepatic tissue) before elimination and very small amount is eliminated in intact form through bile or urine. Therefore, with age as the hepatic blood flow and hepatic mass is reduced, so the clearance of drugs also declines. Thus, there is a growing interest in replacing the pharmacokinetic parameters which are derived from the multicompartmental models by a more complex but realistic analysis such as context-sensitive pharmacokinetics. This context sensitive pharmacokinetics of anaesthetic drug definitely show the difference between the elderly and younger populations. MAC is the minimum alveolar concentration (in volumes percent) of an volatile anaesthetic agent at 1 atmospheric pressure that prevents the movement of 50% of population to a standard given stimulus. For inhalational agents, the anaesthetic requirement is typically quantified by MAC. Whereas for intravenous agents, anaesthetic requirement is typically quantified by ED_{50} which is required to abolish reponse to a given standard stimulus in 50% of subjects. With increasing age, MAC or ED_{50} requirement decreases progressively with increased sensitivity to many anaesthetic agents, especially the CNS depressant drugs. MAC decreases steadily with age (4 to 5% per decade after 40 years for example, the MAC of isoflurane is approximately 0.92 at 80 years of age).

Diazepam have elimination half-life of 20 hours at 20 years of age and 85 hours in 80 years of age. The plasma concentration of midazolam required to prevent response to verbal command in an 80 years old person is only 25% of that required in a 40 year old, proving increased sensitivity of brain to benzodiazepine. MAC decreases with age, proving increased sensitivity of inhalatinal agent in elderly. MAC values of halothane are 0.84, 0.76 and 0.64 at 25, 42 and 81 years of age respectively. While MAC values of isoflurane are 1.28, 1.15 and 1.05 at 26, 44 and 64 years of age respectively. Therefore, the incidence of awareness during anaesthesia is a rare occurrence in the elderly. Plasma proteins are often reduced, resulting in reduced protein binding of drugs and its metabolites. Thereby there is every chance of increasing the free anaesthetic drug levels and its possible toxic effects. About 15 to 20% decrease in plasma albumin concentration leads to decreased binding and increased bioavailability of intravenous induction agents. Study has shown that there is 44% decrease in thiopentone requirement in elderly persons compared to a young adult as up to 80% of this drug is albumin bound. On the other hand, the brain sensitivity to thiopentone does not reduce with age. This also explains the increased response of thiopentone in geriatric patients. Though, propofol has a decreased (15 to 30%) dose requirement in elderly patient, still the rapid clear headed recovery is not observed in them. Inspite of the increased incidence of hypotension and apnoea the propofol is not contraindicated in elderly patients, if not judiciously administered. The cardiovascular stimulatory effects of ketamine are retained in the elderly age group of patients. Thus, this effect makes this agent very useful in high risk patients, but with cautious use in ischaemic heart disease. Ketamine's hallucinogenic effects are not more marked in the elderly.

Regional anaesthesia provides a desirable alternative to GA as maintenance of intraoperative consciousness in former permits prompt recognition of angina pectoris and acute changes in cerebral function, during intraoperative period. RA is associated with less postoperative confusion compared to patients rceiving GA. Apart from decreased operative blood loss, lowered incidence of postoperative deep vein thrombosis in RA following hip surgery has been observed in elderly patients and it is a great advantage. Another advantage of RA over general anaesthesia in elderly patients is less respiratory problems in postoperative period. Limb and plexus nerve blocks are also ideal for surgery performed on extremity in elderly. Still in patients with severe cardiovascular disease, GA is a better alternative. One review had concluded that RA may reduce mortality in one month but RA and GA appear to produce comparable results for long-term mortality. Like most other drugs, the dose requirements for RA are significantly less in elderly. The level of subarachnoid analgesia is usually two segments higher in elderly patients which may even be unpredictable due to higher specific gravity of CSF in this age group. There is also decreased segmental dose requirement of local anaesthetic agent during epidural analgesia in elderly. This may reflect the decreased volume of epidural space in elderly patients due to arterio sclerotic changes of vertebral column. Though hypotension is more frequent, postspinal headache is less in geriatric group of patients.

ANAESTHETIC MANAGEMENT AND PERIOPERATIVE RISK OF GERIATRIC PATIENTS

For anaesthetic management of elderly patients, there is no specific technique or specific anaesthetic agent which can reduce the perioperative risk or mortality in this group of patients. There is no difference in outcome between the GA and RA when they are applied correctly on elderly for the same surgery. Though regional anaesthesia has many advantages over general anaesthesia, but hypotension is more commonly seen in elderly patients undergoing spinal/epidural anaesthesia. This is due to the impaired autonomic function and reduced compliance of arterial tree in geriatric group of patients. Conversely, the rates of intravenous fluid administration that would be modest for young adults

may precipitate congestive heart failure and pulmonary oedema in elderly patients. GA may be the best for those who require precise control of blood pressure and heart rate. RA for hip fracture may reduce mortality at 1 month, but regional and general anaesthesia appear to produce comparable results for long term mortality. The overall perioperative morbidity and mortality rate is same between healthy, fit, octogenarians and young adults, undergoing similar surgical procedures. Only very debilitated and sickly older patients are particularly prone to perioperative complications.

The three major risk factors that appear to determine the mortality rates for geriatric patients are: (i) the operative site, (ii) the need to perform surgery on an emergency basis, and (iii) the physical status of patient at the time of surgery. When elderly patients are undergone emergency surgery, then mortality rate rises many fold. It is due to (i) the inadequate preoperative evaluation and preparation of elderly patient and (ii) the nature of surgical lesion and its acute consequences, such as haemorrhage, dehydration, ischaemia, acidosis, etc. on already critically reduced organ's reserve. Infection and sepsis are two major important causes of death in elderly patients, despite vigorous IV antibiotic therapy. This is due to age related reduction of immune response. Operative site is also an important determining factor of mortality rate for elderly patients. Superficial surgery as for example cataract surgery, skin biopsy, superficial excision, etc, under local anaesthesia has much lesser risk than a surgical entry into any major body cavity. Mortality risk for herniorrhaphy, transurethral prostetectomy, etc, is in between the above mentioned two categories of surgery. The preoperative physical status of elderly patients clearly correlates well with the perioperative mortality.

Age was previously misunderstood as a factor of increased mortality. But, now it has been properly evaluated that age related disease, causing poor physical status is the most important determinant of mortality rate and not the age itself. For example, one half of the elderly surgical patients have hypertension which have widespread effects on multiple organs, causing decreased reserve and thus increase the risk of anaesthesia, despite continuing therapy. The significant portions of geriatric patients also have coronary artery, metabolic (most common is diabetes mellitus), pulmonary, renal and hepatic diseases with ill effects on multiple organs and reduce the reserve in every systems. Preoperative malnutrition or hypoalbuminemia or the development of negative protein balance may also have predictive value on the rate of surgical and anaesthetic mortality for elderly patients. The metabolic response of elderly patients to tissues injury is sluggish. The ability to ambulate properly after surgery are also the fundamental determinants of uncomplicated surgical recovery. But, these can not be achieved in older adults simply by giving injection of growth hormone or increasing the parenteral protein replacement.

Though, there is no specific or best anaesthetic agent or technique for the elderly patients, still a satisfactory and uncomplicated anaesthetic course can be carried out by: (i) a proper and good preoperative evaluation and preparation of patient, (ii) a proper anaesthetic plan, and (iii) vigilant monitoring to suit the physical status of the patient with the type and site of surgery. In old age, the arm – brain circulation time is increased and dose requiements for induction agents are drastically reduced. So, during induction of anaesthetic drugs should be titrated very slowly against the effect. Due to the loss of functional reserve of all the organs, anaestheitc agents which have cardio deperssant effects and reduces cardiac output (e.g. volatile anaesthetic and others) should be used very cautiously. Regional anaesthesia (causing pharmalogical sympathectomy) is also less well tolerated in elderly patients who have already reduced circulating blood volume due to age related physiological changes. From the begining of young adulthood the MAC (for inhalational agents) and ED_{50} value (equivalent to MAC for non-inhalational agents) decline linearly with increasing age. Typically, an 80-year-old patient requires only 2/3 to 3/4 of the anaesthetic dose which is needed to produce similar effects in a young adult. This reduction in MAC and ED_{50} with age probably reflects the fundamental neurophysiological changes in the brain (reduced neuron density and reduced concentration of brain neurotransmitter) due to aging. The amount of anaesthetic requirement may be a quantifiable measure of the functional reserve of the central nervous system. The reduction of requirement of IV anaesthetic agents (due to $\downarrow ED_{50}$) is similar to that observed for inhalational agents (due to $\downarrow$MAC). This is simply due to the result of higher than expected initial plasma concentration of these drugs, during the early phases of their redistribution from plasma to body tissues. This may be again due to the exaggerated age related early or alpha phase of pharmacokinetic changes rather than pharmacodynamic changes. The classic two or three compartment models used for pharmacokinetic analysis of IV anaesthetic agents is also less predictable for elder subjects. Dosage of opioids and benzodiazepines should be reduced due to age related changes in pharmacokinetics and pharmacodynamics of these drugs, for example, increased sensitivity of cerebral cortex (pharmacokinetic) and reduced elimination (pharmacodynamic) of fentanil etc. As remifentanyl, atracurium and cisatracurium do not depend on organ based elimination, so their clinical effects in elderly patients are prompt and predictable.

The dose of nondepolarizing muscle relaxants is same or slightly increased in elders than youngers. But their duration of actions is prolonged due to the decreased rate of clearance. These pharmacodynamic change reflects the quality and quantity of

cholinoreceptor dynamics at the neuromuscular junction, but not the skeletal muscle mass itself. The cholinoreceptor upregulation appears to offset the declining prejunctional acetylcholine mobilization.

Though the dose of anticholinesterase to reverse the effect of muscle relaxant is same in elderly and younger patients, but the incidence of arrhythmias produced by these drugs is higher in elderly, especially who have cardiovascular disease. For any given level of pre-existing neuromuscular blockade, the choice of reversal agent is determined by the speed and the completeness of recovery of neuromuscular transmission, but not by the patient's age. In elderly the action of all the drugs become prolonged if they require hepatic or renal biotransformation for their elimination. Elderly patients due to the loss of muscle mass and impaired thermoregulations are more prone to perioperative hypothermia. So, body heat should be conserved aggressively by fluid warmer or body warming devices, whenever possible, to avoid the cardiovascular and metabolic stress due to shivering with already diminished reserve.

Though the function of central nervous system return quickly and completely after general anaesthesia, still neurological examination shows abnormality upto 60 minutes after recovery. The residual central nervous system dysfunction in subtle form after general anaesthesia is unique for the geriatric population. In 25% cases there is memory deficit and impaired spatial and verbal cognition even upto 7 days postoperatively. All these are due to the increased volume of distribution, reduced drug clearance, delayed transfer of drugs among compartments and the combination of these factors. For the older patients postoperative delirium, disorientation and acute brain syndrome are common and it is due to the disorder of metabolic states such as the hyper and hypoglycaemia, hypoxia, hypercarbia, fluid and electrolyte imbalance, prolonged anaesthetic effects, etc. It also may be the expression of subclinical age related neurological disease.

Intraoperative gross central nervous system injury can happen from cerebral embolism, haemorrhage or ischaemia. Such injuries are distinguishable from residual central nervous system dysfunction or residual anaesthetic effect by their severity, focal nature and the absence of conspicuous improvement in the first few hours after anaesthesia. Reduced responsiveness of protective airway reflexes in elderly patients need routine protection against regurgitation and aspiration of gastric contents. All the elderly patients should be administered O_2 postoperatively to compensate for the inevitable decrease in oxygenation due to loss of body reserve.

40 Obesity and Anaesthesia

INTRODUCTION

The obesity is defined as an abnormal growth of adipose tissue. It may be due to enlargement of fat cells in size (hypertrophic obesity) or due to increase in fat cells in number (hyperplastic obesity) or even a combination of both. It is the consequence of an interaction between the environmental forces and the individual genetic substrate. The genes which are responsible for fat metabolism enhance the storage of fat without causing obesity where food is limited and cause an increased risk of obesity when food is abundant and energy expenditure is less or reduced.

The term 'obesity' is derived from the Latin word 'obesus' which means 'fattened by eating'. This is due to the excessive net energy intake in excess of net energy expenditure. The excess energy intake is laid down on various parts of the body as fat, resulting in obesity. Modern life-styles and better standards of living have been in the way of contributing increased prevalence of obesity. So, obesity is a chronic disease that is gradually becoming widespread and is posing a serious risk in the development of non-insulin dependent diabetes mellitus, hypertension, ischaemic heart diseases, peripheral vascular disease, gallstones, osteoarthritis, etc. which cause increased risk for anaesthesia and mortality. Hence, undernutrition and malnutrition are the problems of developing countries, while obesity is the bane of developed countries.

The total body fat and its distribution in a person are affected by his or her gender, age, degree of physical activity and number of drugs used. In both men and women, body fat increases with age. In lean young healthy men, the body fat is usually less than 20% of his body weight and may rise with age to more than 25%. In young women, body fat stores may be below 30% and increases gradually to more than 35% in older women. At all ages after puberty women accumulate more fat than men. Sometimes, the term obesity is frequently used synonymously with overweight from the aspect of risk factors. But, the term 'overweight' means an excess average weight for a given sex, height and age. Overweight is usually due to obesity, but can arise from other causes also such as abnormal muscle development or fluid retention (Fact file- I).

The regional fat maldistribution also has a profound influence on health risks. For example, only increased deposits of visceral or abdominal fat correlate well with the risks for heart disease, diabetes and hypertension. For estimating or measuring the total or regional body fat, there are several techniques which are listed in the table. Among these, the dual energy X-ray absorptiometry provides the best method for assessment of total body fat, but not the regional body fat. The regional body fat can only be measured accurately by MRI or CT-scan. But for practical purposes, waist circumference or sagittal diameter of it is the most useful parameter for estimation of regional fat in body. The ratio of waist circumference to hip circumference is also widely used to measure or estimate the regional fat distribution, but is not so accurate. For estimation of total body fat X-ray absorptiometry, CT-scan, MRI, etc. are highly accurate, but such measurements may not be clinically feasible. (Table 40.1) Body weight, though, is not an accurate measurement of excess body fat, still it is a widely used index of obesity. In epidemiological studies, it is conventional to accept deviation of +2 SD (Standard Deviation) from the median weight for that height as the cutoff point for obesity. So, overweight or obesity can be defined from the tables of height and weight. On the other hand, the ideal body weight (Broca index) can also be estimated from the height (cm) by deduction of 100 from it. For example, if a person's height is 160 cm, then his ideal body weight should be 160 – 100 = 60 Kg. A person is said to be obese when his or her actual body weight exceeds this ideal body weight by more than 20%. However, the most widely used formula for relating height and weight in a person is the body mass index (BMI) which is calculated by Weight (Kg)/Height^2 (meter) [i.e. BMI = Mass (Kg)/[Height (m)]^2. A BMI between 20-25 Kg/m^2 is considered usually as a good weight for most individual. A BMI of 25 to 30 Kg/m^2 is considered as overweight, but with low risk for associated serious medical complications. Those with BMI of >30 Kg/m^2, > 35 Kg/m^2 and >55 Kg/m^2 are respectively considered as obese, morbidly obese and supermorbidly obese. Weight gain confers increased health risk even if the BMI does not excees 25 Kg/m^2.

FACT FILE- I

There are four processes which are involved in the regulation of food intake. These are : (i) olfactory and gastatory factors which can stimulate or inhibit the intake of food according to its appetizing property, (ii) release of gastrointestinal hormones such as cholecystokinin and gastrin releasing peptide, (iii) gastrointestinal distension, and (iv) activation of thermogenic component of effarent sympathetic nervous system. All these factors work together to induce safety after ingestion of food and also do not produce new arousal for seeking food till the next blood glucose level dips.

Excessive nutrient is stored in the body as fat. To maintain the normal body fat, dietary nutrients should be oxidized in the proportion by which they are taken through diet. Among the ingested carbohydrate, fat and protein, the intake of carbohydrate approximates the body stores of it. While intake of fat and protein constitutes a small fraction of the stored quantities of these nutrients. Therefore, as the daily intake of carbohydrate nearly equals the body store of it, so carbohydrate store is more vulnerable to the changes in the dietary carbohydrate than fat or protein. The respiratory quotent (RQ) of fat (0.7) is less than that of carbohydrate (1). Hence, if the percentage of dietary fat increases, the RQ should be declined to maintain the body weight stable. But if RQ does not decline (which normally occurs in obese patient) the body continues to oxidize the carbohydrate store and must replace these by eating more food to obtain carbohydrate or synthesise endogenous glucose from protein stores. This adjustment strongly depends on the genetic determinants.

If the carbohydrate oxidation is reduced or not available, the oxidation of fat increases to provide for nutrient needs and lower the RQ. If the body is unable to reduce the carbohydrate oxidation, the compensatory mechanism is increased foods intake to provide needed carbohydrate with increasing fat storage and obesity.

Estimated total energy need = BMR × Activity factor

(For low or sedentary activity the activity factor is 1.3, for intermediate activity such as regular exercise the activity factor is 1.5, and for high activity the activity factor is 1.7.)

Estimation of basal metabolic rate (BMR):

For women:

15 to 30 years = (LBW × 0.0621 + 2.0357) × 240 kcal/day
30 to 60 years = (LBW × 0.0342 + 3.5377) × 240 kcal/day

For men:

15 to 30 years = (LBW × 0.063 + 2.8957) × 240 kcal/day
30 to 60 years = (LBW × 0.0484 + 3.6534) × 240 kcal/day
LBW = Lean body weight
Daily energy requirement (calculated)
At rest : 2000 kcal (8.4 MJ)
Light work : 2700 kcal (11.3 MJ)
Heavy work : 3500 kcal (14.6 MJ)

Table 40.1: Methods of estimating body fat and its distribution

Method	*Accuracy*	*Ease of use*	*Estimation of regional fat*
Weight and height	High	Easy	No
Circumferences	Moderate	Easy	Yes
Skinfold	Low	Easy	Yes
Density			
Immersion	High	Moderate	No
Plethysmograph	High	Difficult	No
Ultrasound	Moderate	Moderate	Yes
Potassium isotope	High	Difficult	No
Heavy water	High	Moderate	No
Bioelectric impedance	High	Easy	No
Total body electrical conductivity	High	Moderate	No
Computed tomography	High	Difficult	Yes
MRI	Difficult	High	Yes
Neutron activation	Difficult	High	No

In a woman, a weight gain of more than 5 Kg is associated with an increased risks of diabetes and heart disease. In men any weight gain after age of 25 years appears to carry increased health risks (Table 40.2).

The another method of assessing the total body fat is measurement of skin fold thickness. It is a rapid and noninvasive method and several varieties of callipers are available for this purpose. The measurement is taken at the four sites of body such as at midtriceps, biceps, subscapular and suprailiac regions and the sum of the measurements should be less than 40 mm in boys and 50 mm in girls. Unfortunately, any standards of the subcutaneous fat for determination of obesity do not exist for comparison. Further, in extreme obesity, measurements of subcutaneous fat may be impossible. The another main drawback of skinfold measurements for assessing total body fat is their poor repeatability (Fig. 40.1).

It is now also recognised that in addition to the amount of excess fat present in an obese individual, the anatomical distribution of this fat has an important bearing

Table 40.2: Body mass index according to weight

Weight	*BMI [Wt (Kg) / Height^2 (m^2)]*
Underweight	< 18.5
Normal	18.5-24.9
Overweight	25-29.9
Obese	30-39.9
Extremely obese	> 40

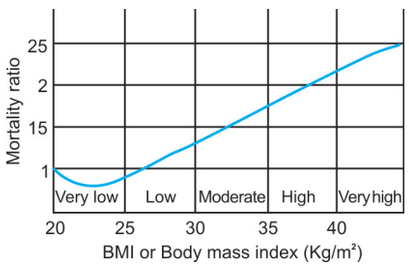


Fig. 40.1: The relationship between the BMI and overall mortality rate. At BMI greater than 20 Kg/m^2 but less than 25 Kg/m^2 there is decrease in mortality

on the health risk. Central or android type of distribution of fat, which is more common in men, manifests as abdominal obesity. In contrast, peripheral or gynecoid type of distribution of fat, which is more common in females, manifests as deposition of fat mainly around the hips, buttocks and thighs. The central adipose tissue is more metabolically active than the fat deposited in the periphery. Here the obese individuals who have a more central distribution of body fat tend to suffer more from metabolic complication such as dyslipidaemias, glucose intolerance, diabetes mellitus, ischaemic heart disease, heart failure and stroke, etc. As abdominal fat is more easily mobilised, men also tend to lose weight more readily than women.

When triglycerides are deposited in fat cells, then the cells initially increase in size, until a maximum limit is reached, at which point the cells divide. Moderate degrees of obesity (BMI < 40 Kg/m^2) are likely to result from an increase in the size of fat cells, whereas extreme obesity (BMI > 40 Kg/m^2) is likely to result from the proliferation of fat cells from the adipocytes (Fact File- II).

Fat Cells and Obesity

The fat cells not only store the fat, but also secrete some enzymes named lipoprotein lipase which hydrolyses the triglycerides of VLDL and chylomicrons. They also produce some complements like D_2, C3b, cytokines, etc (such as angiotensinogen, leptin, lactate) and metabolise glucose to provide glycerol-3-phosphate for synthesis of triglyceride. Fat cells also synthesise long chain fatty acids when there is abundancy of diet (Table 40.3).

FACT FILE - II

There are three known predictors which control the future weight gain. These are: (i) Low metabolic rate, (ii) High RQ indicating high carbohydrate oxidation and the need to eat more to replace this carbohydrate, and (iii) Insulin resistance. The regulation of food intake is controlled by feedback system with afferent and efferent signals. Factors that increase hunger include decrease in blood glucose level, an increase in gastric contractions or abdominal uneasiness. These peripheral signals are integrated by neurotransmitters in the brain to regulate food intake. Several neurotransmitters increase or decrease the food intake. In addition, some neurotransmitters are specific modulators for the intake of specific food such as fat, carbohydrate and protein. Thus decrease or increase of intake of carbohydrate, fat and protein occur as a major response to specific neurotransmitter which are controlled by the genetic code of this individual.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH OBESITY

Obesity is associated with certain physiological changes that have important anaesthetic implications. This is because obese individuals handle drugs differently than their normal counterparts as the pharmacokinetic and pharmacodynamic of drugs are changed in obese patients. So, understanding of these physiological and pharmacological changes is necessary for the proper management of anaesthesia on obese patients presenting for surgery either to reduce the obesity (gastric bypass, vertical banded gastroplasty, uvulopalatopharyngoplasty, liposuction) or presenting for surgery for other diseases.

Cardiovascular System

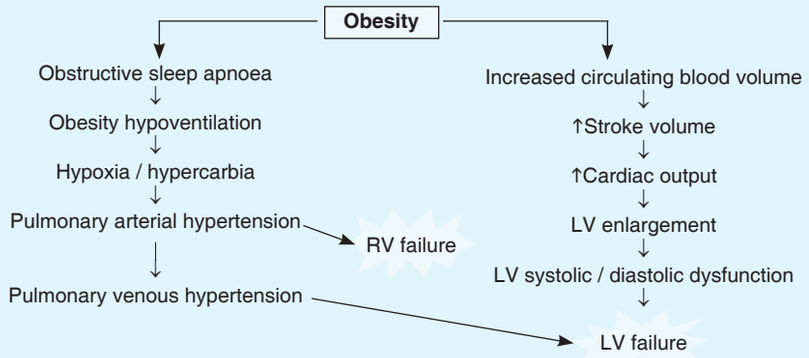
Obesity is associated with increased work load on the heart. This is due to the developement of hypertension and/or hypervolaemia. Obesity is also associated with increase in absolute blood volume, although this is lower than normal value in relation to body mass (occasionally 45 ml/Kg). Increased extracellular fluid volume resulting in hypervolaemia and increased cardiac output is estimated to increase by 0.1 L/min for each Kg of weight gain. Each Kg of fat contains extra 3000 metres of blood vessels. Mild to moderate degree of systemic hypertension is seen in 50 to 60%, of obese patients while severe hypertension is present in 5 to 10% of obese patients (mechanism being unclear). The probable hypotheses are: (i) obesity is associated with hyperinsulinaemia and increased insulin resistance which enhance Na^+ reabsorption from the renal tubules, (ii) obesity causes increased sympathetic outflow, promoting arterial vasoconstriction and (iii) enhancement of pressure activity (or sensitivity) of nonepinephrine and angiotensin II in obesity. Obesity is also associated with an increased risk of sudden death, and this is probably due to sudden cardiac arrhythmia. It is also associated with an increased risk of artherosclerosis probably due to abnormal lipid profile. The abnormal lipid profile in obesity includes decreased level of HDL cholesterol, and increased level of LDL cholesterol. Obesity is also associated with pulmonary hypertension which is probably due to chronic arterial hypoxaemia and increased pulmonary blood volume. Therefore all these factors such as hypertension, ↑cardiac workload, atherosclerosis, hyperinsulinaemia, diabetes, etc. which are common in obese individuals, compound the likely development of ischaemic heart disease. (IHD) (Table 40.4).

Table 40.3: Some specific causes of weight gain

A.	Genetic
	Pradder-Willi syndrome, Laurence-Biedl syndrome, etc.
B.	Endocrine factors
	Hypothyroidism, insulinoma, Cushing's syndrome.
C.	Drugs used
	Phenothiazines, tricyclic antidepressants, sulphonyl urea, oral contraceptive, glucocorticoids, antiepileptic (valproate).

With obesity, there is increase in the volume of epicardial fat but no myocardial fatty infiltration. So, obesity is not directly responsible for the myocardial weakness and heart failure but indirectly responsible for all these ailments. Hence, obesity-induced cardiomyopathy is mainly due to hypertension, IHD, hypervolaemia, ventricular dysfunction and these are responsible for heart failure. LV

Table 40.4: Obesity induced cardiomyopathy and association of obesity with congestive heart failure



hypertrophy and its dysfunction demonstrated, by echocardiography, is characteristic of obesity. Obesity induced changes in cardiovascular system reduce its reserve and limits its exercise tolerance. Morbidly obese patients tolerate exercise poorly. This is because increase in cardiac output necessary for exercise is achieved only by increasing the heart rate without an increase in stroke volume or ejection fraction, i.e. increased myocardial contractility in oberity due to cardiomyopathy. On changing position from sitting to supine, obesity is also associated with higher increase in PCWP and mean pulmonary artery pressure.

Respiratory System

Moderate obesity in the absence of underlying pulmonary disease has little effect on respiratory function. Whereas in severely obese individuals, obstructive sleep apnoea (OSA) syndrome is a potentially serious problem. This is because increased BMI is associated with an exponential decrease in respiratory compliance. In extreme cases the compliance can fall up to 30% of the predicted value. The reason for this decrease in respiratory compliance is due to twofold accumulation of fat in and around the chest wall leading to reduction of chest wall compliance and due to increased pulmonary blood volume resulting in decrease in lung compliance and splinting of diaphragm. The reduction of this total respiratory compliance (chest wall and lungs) is in turn associated with a decrease in FRC and encroachment on closing volume which causes impairment of gas exchange. Therefore, the increase in intrapulmonary shunt and increase in alveolar-to-arterial oxygen tension difference which are evident as arterial hypoxaemia is more worsened during induction of anaesthesia of an obese person. So always a high inspired O_2 concentration is required during the induction of anaesthesia and whole perioperative period to combat this arterial hypoxaemia. Reduced FRC can be increased by administering PEEP or large sustained manual inflation. But, the use of PEEP does improve this arterial O_2 tension (P_aO_2) at the expense of cardiac output and oxygen delivery to tissues (Fact file -III).

FACT FILE- III

Obesity also imposes a restrictive ventilation defect. This is due to the extra weight, added to the thoracic cage and the abdominal wall impeding motion of the diaphragm, especially in supine position. This results in decrease of functional residual capacity (FRC), expiratory reserve volume (ERV) and total lung capacity. FRC declines exponentially with increasing BMI. FRC may be decreased to such a point that small airway closure occurs within the tidal volume resulting in a ventilation-perfusion mismatch (shunt and arterial hypoxaemia). Further, induction of anaesthesia in an obese individual results in 50% decrease in FRC as compared to 20% decrease in a non-obese individual.

Sleep Apnoea

Sleep apnoea is defined as an intermittent cessation of airflow to lungs through the nose and mouth during sleep. By convention an apnoea of at least 10 second duration is considered important. But, in most patients these sleep apnoeas are of 20 to 30 seconds duration and also may be as long as 2 to 3 minutes.

The sleep apnoea which is a type of respiratory dysfunction is a serious consequence of obesity. The cessation of breathing during apnoea may be either due to occlusion of airway (obstructive sleep apnoea or OSA) or absence of respiratory effort (central sleep apnoea), or a combination of these two factors (mixed sleep apnoea). Approximately, 5% of morbidly obese patients present with features of OSA (obstructive sleep apnoea) characterised by episodes of apnoea or hypopnoea during sleep. Failure to recognise and appropriately treat these conditions may lead to sometimes serious cardiovascular complications and increased mortality rate.

Hypopnoea is defined as 50% reduction in airflow which is sufficient to cause a decrease in arterial O_2 saturation. More than 10 to 15 apnoeas per hour or more than 30 apnoeas per night is significant in OSA. It is also important to say that clinical sequelae of OSA such as hypoxaemia, hypercarbia, systemic and pulmonary hypertension, cardiac arrhythmias, right ventricular failure and polycythaemia are more important than the frequency and duration of apnoea. All such patients usually always show some evidences of sustained daytime hypoxaemia in addition to the nocturnal ventilatory disturbance, usually as a result of reduced ventilatory drive and/or diffuse airway obstruction. Most of these patients are obese and sleepy and are, therfore, said to have the Pickwickian syndrome.

Apnoea occurs when the pharyngeal airway collapses (obstructive) due to relaxation of muscles during sleep and / or there is no central drive (central) for respiration. Both these mechanisms are also responsible

for apnoea during anaesthesia in obese patients. In an obese individual local fat accumulation in the tracheopharyngeal area or compression of pharynx by the superficial fat masses of neck also predisposes to airway collapse. (In nonobese patient with OSA the adenotonsillar hypertrophy, craniofacial skeletal abnormalities such as retrognathia and macroglossia, etc. are taken as responsible for airway closure during sleep). Normally, the patency of pharyngeal airway is maintained by the action of dilator pharyngeal muscles. During sleep the tone of there muscles is reduced and airway becomes narrowed causing turbulent flow and snoring (a high frequency vibration of the palatal and pharyngeal soft tissues) and obstruction. The resulting hypoxia and hypercarbia from this airway obstruction causes arousal of the individual which in turn again restores the upper airway tone. The individual then falls asleep again and the cycle is repeated. The predisposing factors for sleep apnoea during anaesthesia of an obese patient are degree of obesity (BMI > 30), middle age, male and anaesthetic drugs depressing the respiratory centre and muscle tone (Fig. 40.2).

Disturbed sleep at night in OSA patients leads to day time somnolence and inability to concentrate the mind. Obese individuals with OSA gradually develop features of chronic hypoxia and hypercarbia in the form of polycythaemia, pulmonary hypertension right heart failure and respiratory acidosis. An extreme form of OSA is the obesity hypoventilation syndrome (OHS) which initially results in the desensitisation of respiratory centres to hypercarbia (limited to sleep) manifesting as central apnoeic events (apnoea without respiratory efforts). Eventually, patients with OHS present with type II respiratory failure with increasing dependence on hypoxic drive for maintaining ventilation.

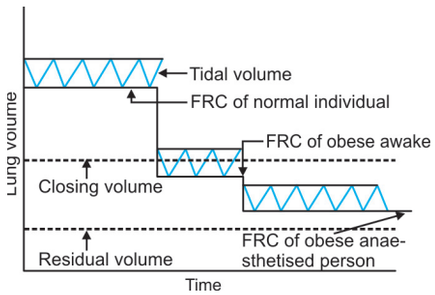


Fig. 40.2: The effect of severe obesity on FRC during awake and anaesthetised condition which result in small airway closure, ventilation perfusion mismatch and impaired arterial oxygenation

Anaesthetic management of a patient with the history of obstructive sleep apnoea poses significant risks. These patients are highly sensitive to all the anaesthetic drugs, causing upper airway obstruction or apnoea, even in minimum doses. So, sedatives (benzodiazepine) or opioids should be used very cautiously in the perioperative period. Upper airway abnormalities due to decreased anatomical space (due to accumulation of fat), accomodating the large tongue and displacing it anteriorly, causes great difficulty in exposure of glottic opening during direct laryngoscopy. When awake, these patients compensate for the compromising airway anatomy by increasing their craniocervical anagulation which increases the space between the mandible and the cervical spine and elongates the tongue and soft tissues of neck. This postural compensation is lost when these patients are rendered unconscious or paralysed. So, all the anaesthetic drugs should be titrated to get their just desired effect and preferably short acting agents such as sevoflurane, propofol, remifentanil should be used. N_2O should be avoided in the presence of coexisting pulmonary hypertension. Neuromuscular blocking drugs characterised by rapid spontaneous recovery should be selected. Tracheal extubation is not considered, until patients are fully conscious with intact airway reflexes. Oxygen consumption is increased by the metabolically active adipose tissue and the workload of in obese subjects supporting muscle. So, oxygen desaturation occurs rapidly in the obese apnoeic patients.

Others

Very frequently obesity is associated with glucose intolerance and diabetes. This is due to increased resistance of insulin by the presence of increased adipose tissue. So, hyperinsulinaemia is a uniform feature and its level is directly related to the degree of obesity. Thus, NIDDM commonly coexists in obese individuals. Reversely, NIDDM is almost non existant in an individual with a BMI below 22 Kg/m^2. Still, in obese patients with NIDDM the catabolic response to surgery may necessitate the use of exogenous insulin during the perioperative period.

Obese patients are also more prone to gall bladder and biliary tract diseases due to the increased excretion of cholesterol through hepatobiliary system. The amount of cholesterol synthesised in the body per day is increased by about 20 mg for each Kg increment of adipose tissue. So that a 10 Kg increase in adipose tissue mass increases the daily cholesterol production and excretion by an amount comparable to the cholesterol present in one egg. On the other hand, obesity is usually associated with abnormal liver function tests and fatty liver infiltration. So, volatile anaesthetic agents should be used cautiously.

The incidence of deep vein thrombosis is almost double in obese patients than in an nonobaese. This is due to the effects of polycythemia, increased abdominal presure and prolonged immobilisation.

Obesity also increases the gastric volumes, raises the intra-abdominal pressure and increases the incidence of hiatus hernia which pose a significant risk of aspiration.

INFLUENCE OF OBESITY ON DRUG PHARMACOKINETIC

The pharmacokinetic of drugs used in the anaesthesia practice is changed due to the pathophysiological changes associated with obesity. The volume of distribution of drugs in obese individual is influenced by the increase in blood volume and cardiac

output, decrease in total body water content (fat contains less water) and the lipid solubility of drug. Despite the occasional presence of liver dysfunction, hepatic clearance of drugs is not usually altered in obese individuals. Renal clearance of drugs is increased due to the increased renal blood flow and GFR in obese. For a desired concentration of drugs in plasma, two factors operate. One is the increased plasma volume in obesity which decreases the drug concentration in plasma and the other is the less blood flow in adipose tissue which increases the plasma drug concentration. So, the actual plasma concentration for a given bolus inducing dose of a drug is difficult to predict. It would, therefore, be wise to calculate the initial loading dose of a drug on the basis of 'ideal body weight' (lean body mass) than the present actual body weight. Subsequently, the further doses should be adjusted according to the pharmacological response of patient to the initial dose. Repeated injection or infusion of drugs, particularly the lipophilic group, could result in a cumulative effect and hence a prolonged response. It is due to the gradual storage of drugs (mainly lipophilic) into depot fat and later its subsequent release from it into systemic circulation as the plasma concentration of drug declines. It should be kept in mind that just as the increased fat depot in obesity increases the storage of drugs, but poor total blood supply to adipose tissues also limits the delivery of drugs to it. So, multiple factors playing on the pharmacokinetics of a drug make the calculations of its plasma concentration composite and difficult.

ANAESTHETIC MANAGEMENT OF OBESE PATIENT

Regional Anaesthesia vs General Anaesthesia

Bony landmarks are likely to be obscured in obese patients. So, spinal and epidural anaesthesia is technically very difficult in such group of patients. As compared to a nonobese individual, in obese the requirement of local anaesthetic agents for spinal and epidural anaesthesia is 20% lower. This is due to the reduced volume of epidural space because of fatty infiltration and vascular engorgement of it. But the advantages of regional technique over general anaesthesia in obese individual include the avoidance of difficulties related to securing the airway, perioperative hypoxaemia, ventilation and pulmonary complications. Regional anaesthetic techniques also provide good postoperative pain relief and hence use of drugs such as opioids that may depress respiration can be avoided.

Preoperative Assessment

A detailed preoperative assessment of an obese patient is routinely performed before induction of anaesthesia which includes mainly the air passage, respiratory system and cardiovascular system. Difficulties in mask ventilation and tracheal intubation should always be anticipated in obese patients and this is because of the unique anatomical features in them such as big-fat face and cheeks, short neck, large tongue, restricted mouth opening, little airway space due to excessive palatal and pharyngeal soft tissue, high and anterior larynx, limitations of movement of cervical spine, and restriction of atlanto-occipital flexion and extension due to accumulation of fat in neck etc. A BMI of 45 is associated with 13% risk of difficult intubation. Though inspection of previous anaesthetic records might provide some evidence of previous difficulties, but one should bear in mind that an uneventful previous anaesthesia may not be relevant any longer in this present case and it is due to the further accumulation of fat and weight gain during this interval. Preoperatively, airway is assessed clinically by different measurements and scoring systems, and by investigation such as X-ray, MRI of soft tissues, CT-scan, etc. and also by referral to an otolaryngologist for direct and indirect laryngoscopy which helps in a more complete evaluation of airway. It is also useful to assess the airway in both erect and supine positions (Table 40.5).

With airway assessment, the venous access and the risk of aspiration also should be assessed. If any difficult intubation is anticipated in any clinical scoring system or in radiological investigations then the possibilities of awake intubation, fiberoptic aided intubation, cricothyroid puncture with jet ventilation, tracheostomy and provision of postoperative ventilation should always be kept in mind and make ready. In addition to the airway assessment, preoperative assessment of patient should also include the full blood count, chest X-ray, supine and upright blood gases, lung function tests and overnight oximetry according to the merits and demerits of each case. Patients with symptoms, suggestive of OSA should also be evaluated by polysomnography and their condition is optimised with preoperative noninvasive ventilation such as CPAP and BIPAP. The possibility of other endocrine disorders associated with obesity (such as thyroid) or mistaken for obesity (such as Cushing's disease where diureal variations in plasma

Table 40.5: Medical and surgical complications associated with obesity

CVS	Systemic hypertension
	Ischaemic heart disease
	Cardiomegaly
	Congestive heart failure
	Deep vein thrombosis
	Peripheral vascular diseases
	Pulmonary hypertension
	Pulmonary embolism
	Cerebrovascular accident
	Sudden death
Respiratory system	Obstructive sleep apnoea
	Restrictive lung disease
	Hypoventilation syndrome
GI system	Gall stones
	Fatty liver
	Inguinal hernia
	Hiatus hernia
Endocrine	Diabetes mellitus
	Hypothyroidism
	Cushing's syndrome

cortisol and the concentration of urinary free cortisol is abnormal) should also be considered and is evaluated if necessary.

Like respiratory system, cardiovascular system also should be evaluated properly before anaesthesia of an obese patient. The severity of impairment of CVS may be underestimated by clinical evaluation only. So, echocardiogram may be frequently asked for to get information about the left ventricular function and other associated abnormalities (e.g. ventricular hypertrophy, cardiomegaly, cardiomyopathy etc). But echocardiography may be technically difficult in an obese patient and it is due to inability to obtain a proper acoustic window because of fat. Rapid weight gain, preoperatively, due to oedema may indicate worsening cardiac failure and it can be mistaken for obesity. In such circumstances cardiac performance may deteriorate quickly following induction and tracheal intubation or due to many other reasons during anaesthesia. So, an anaesthesiologist must always be prepared with a selection of inotropes, vasodilators and other drugs. Preoperative ECG is mandatory for obese patients. Overlying excessive adipose tissue may result in low voltage complexes in ECG, masking any ventricular hypertrophy that might be present.

Premedication

In obese patients the opiates and sedative drugs as premedication should be used very cautiously and in a titrating doses. This is because with the same degree of sedation there is more chance of airway obstruction in obese than nonobese patients. But, the degree of central repiratory depression is same for the same doses of drug in both the obese and nonobese patients. Premedication in obese patients should be given orally or IV. The intramuscular route for delivery of drugs in obese patients is associated with unpredictable pharmacokinetics and frequently the drug is deposited mainly into subcutaneous fat. So, this route should be avoided especially in obese patients. Antisialogogue should be used routinely in obese patients as there is more chance of difficult intubation and increased secretions make it more difficult. The obese patients are traditionally presumed to be at the increased risk for pulmonary aspiration (probably due to increased intra-abdominal pressure, delayed gastric emptying and increased incidence of hiatus hernia) during the induction of anaesthesia and intubation. But there is no supporting evidence for this notion. So, perhaps a group of anaesthetists thought that the greater risk of pulmonary aspiration is potentially related to the technical difficulty during tracheal intubation. So, as prophylaxis a combination of H_2 receptor blocker (ranitidine 150 mg) or proton pump inhibitor (omeprazol) and a prokinetic agent (metoclopramide 10 mg) should be administered orally 12 hours and 2 hours before surgery to reduce the risk of aspiration. In addition, some anaesthesiologists also advocate administering 30 ml of 0.3 M sodium citrate orally just before induction of anaesthesia. The advantages and disadvantages of administration of sodium citrate just before induction and intubation is discussed earlier.

The morbidly obese patients are more likely to develop deep vein thrombosis. Because they are likely to be less ambulent in the postoperative period. So, a low dose of subcutaneous heparin should be given as prophylaxis in the preoperative period and continued into the post operative period, until the patient is fully mobile. Other measures like pneumatic leggings, a graded compression stockings are also useful in reducing the incidence of deep vein thrombosis in obese patients.

Induction of Anaesthesia

Induction of anaesthesia is very tricky in an obese patient. Always an experienced assistant or a second anaesthetist should be available during induction, apprehending difficult intubation, ventilation and other airway related problems. On the other hand, tracheal intubation and IPPV is very essential for oxygenation in the morbidly obese patients as spontaneous respiration is very difficult and sometimes becomes impossible too. Intubation may be warranted for all, except the briefest procedures due to the risk of aspiration. IPPV is often necessary, because there is increased work of breathing and tendency to hypoventilation in spontaneous respiration. The choices among the awake intubation, intubation under inhalational anaesthesia or intubation after muscle paralysis depends on the experience of anaesthesiologist and his preoperative evaluation regarding the anticipated difficulties of intubation. Some authors recommend awake intubation when the actual body weight is >175% of average body weight. Presence of features suggesting significant OSA may also indicate the possible difficulties with bag and mask ventilation.

Another approach for intubation in obese patient is by direct laryngoscopy under topical and infiltration anaesthesia. If laryngeal structures can not be visualized, then fibreoptic intubation is probably a safe option. Blind nasal intubation with spontaneous ventilation can also be tried, but practically it is very difficult (not practised frequently) and trouble-some as nasal bleeding might cause further deterioration of an already difficult airway.

Apart from different techniques of intubation, rapid sequence induction and intubation using succinylcholine following an adequate period of preoxygenation and deep sedation is essential. The low FRC associated with obesity means that there is rapid decrease in arterial oxygen tension during direct laryngoscopy and tracheal intubation. The risk of quick arterial oxygen desaturation emphasizes the importance of maximising the oxygen content in the lungs before initiating direct laryngoscopy and also emphasizes the importance of monitoring of the arterial oxygen saturation continuously by pulse oximetry.

The anaesthetist should be well prepared with a full range of aids for tracheal intubation such as short-handled laryngoscope, polio blade, McCoy laryngoscope, gum elastic boogies, LMA, etc, anticipating difficult intubation. Equipment for emergency cricothyrotomy should also be kept ready and capnograph must be available to confirm the correct placement of ET tube. The obese patient will require ventilation with high inspired O_2 fraction and the addition of PEEP to maintain adequate arterial oxygen tension.

Maintenance of Anaesthesia

There is nothing special for maintenance of anaesthesia in obese patients. Use of sevoflurane and propofol during intraoperative period helps in rapid recovery from anaesthesia in such group of patients. Though, it is often stated that obese individuals awake slowly from GA than nonobese individuals, but the same does not happen in actual practice if short acting agents are used in very titrating doses. N_2O is frequently used for maintenance of anaesthesia in obese patients, because of its rapid elimination and quick recovery. But the frequent need for increased oxygen concentration in the inspired anaesthetic gas mixture may sometimes limit the usefulness of N_2O. Controlled ventilation using a large tidal volume is often used in an attempt to improve the oxygenation in obese individual, but the adverse effects of it on cardiac output and subsequently less tissue oxygen delivery must be borne in mind.

For noninvasive blood pressure monitoring, the width of sphygmomanometer cuff should be 20% greater than the diameter of arm. Invasive blood pressure monitoring may be required, if necessary. An arterial line allows accurate monitoring of arterial blood pressure and frequent blood gas analysis. Central venous pressure monitoring is desirable, as it helps in better assessment of cardiac functions in obese patients. Obese patients with cardiac failure may benefit from the use of a pulmonary artery catheter. The fluid balance may be difficult to assess clinically and increased blood loss is common in obese patients due to difficult surgical conditions.

Postoperative Care

The incidence of postoperative mortality of obese patients is twice than that of the nonobese patients. Pulmonary atelectasis is common and lung capacities remain in decreased state for at least 5 days after abdominal surgery in obese patients. So, to optimise the FRC and closing capacity ratio, ideally the obese patients are recovered in a head up or semisitting position (since this position is best for respiratory mechanics) and extubation is done when the reflexes are recovered fully. Postoperative ventilation is sometimes required in obese patients who are suffering from co-existing cardiorespiratory diseases and especially in those who have undergone prolonged surgery. It is mandatory that obese patients should be monitored intensively for hypoxaemia, especially with the history of OSA syndrome and humidified oxygen should be given regularly during postoperative period. Obese patients with the history of OSA syndrome may also benefit from nocturnal nasal CPAP. The episodes of OSA are most frequent during rapid eye movement (REM) sleep. But the incidence of it is relatively low in the initial postoperative period, and is common between the third to fifth postoperative nights. The hazards of OSA may, therefore, be worst a few days after surgery. This has great implications for the duration of postoperative monitoring by oximetry and oxygen therapy. The maximum decrease in P_aO_2 occurs typically at second and third days postoperatively. Regular physiotherapy should be administered postoperatively for obese patients.

41 Ophthalmic Anaesthesia

ANATOMY

Osteology

Our eyeballs lie in two bony cavities, called orbits. It is situated in the sagittal plane of skull and on either side of the root of the nose. Each orbit is pyramid in shaped, with base lying anteriorly and apex posteriorly at the optic canal. The shape of each of the orbit is also like a truncated pear and is made up of seven bones. Optic canal forms the stalk of this pear. The orbit develops around the eyeball. So, nearly one millimeter behind the anterior margin of the orbit lies the widest diameter of the cavity that corresponds with the equator of the eye ball. The seven bones that take part in the formation of bony orbit are: frontal, maxilla, zygomatic, lacrimal, ethmoid, palatine and sphenoid. Each orbital cavity has a roof, a floor, a medial wall and a lateral wall of the orbit. All the walls are directed forwards, laterally and slightly downwards, diverging anteriorly. The roof, floor and lateral wall are more or less triangular, but the medial wall is oblong.

The medial wall of each orbit lies in the sagittal plane of the head, and is parallel with the medial wall of the contralateral orbit. The lateral wall of each orbit forms a 90^{o} angle with the lateral wall of the contralateral orbit. The medial and lateral walls of each orbit make a 45° angle posteriorly with each other. The apex of the orbit, including the optic foramen lies in the same sagittal plane as the medial wall of the orbit. The anterior end of the medial wall lies about 20 mm in front of the lateral wall. The globe occupies the frontal half of each orbit, and projects anteriorly beyond the anterior margin of it. When the eye is in primary gaze, then the visual axis lies in the sagittal plane. The anatomical axis of each orbit diverges from the visual axis by 23 degrees.

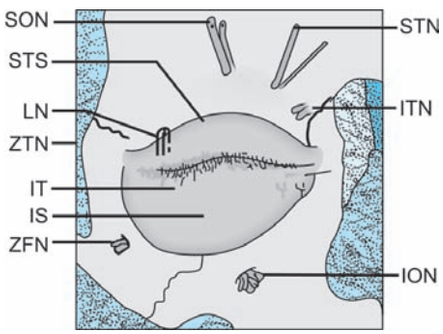
The orbit lies beneath the anterior cranial fossa and above the maxillary sinus. The medial wall of the orbit separates it from the ethmoidal sinuses and the middle meatus of the nose. The lateral wall separates the orbit from the middle cranial fossa posteriorly and from the muscular temporal fossa anteriorly. The anterior margin of each orbit is known as the orbital rim. It forms a protective buttress for all the vital structures held within the orbit and comprises of three robust bones such as zygomatic, frontal and maxillary. The orbital rim forms the rounded rectangular base of the pear shaped orbital pyramid which tapers posteriorly to form a tight apex and made up of the greater and lesser wings of the sphenoid bones. The greatest diameter of the orbit is the part which is situated immediately inside the rim. The volume of an adult orbit is about 30 ml, while that of an average sized globe is 6.5 ml. The typical dimensions of an orbit at the rim are 35 mm vertically and 40 mm horizontally. The depth of an orbit measured from the inferior orbital rim to the optic foramen ranges from 42 to 54 mm. The lateral orbital rim lies 12 to 18 mm behind the cornea, allowing exposure of the globe at its equater. Medially, the orbital margin breaks its continuity at the lacrimal fossa.

The orbital rim or the anterior orbital margin of the orbit consists of superior, lateral, inferior and medial parts. The superior orbital margin is formed entirely by the orbital arch of the frontal bone. It is sharp at its lateral two-third and rounded at its medial one-third. At the junction of these two parts of superior orbital margin lies a notch, called the supraorbital notch through which passes the supraorbital nerves and vessels. Sometimes, this notch is converted into a foramen, or into a canal by a periosteal ligament which ossifies in about 20% of cases. Another small foramen, named supraciliary canal is also found near the supraorbital notch. It transmits a nutrient artery and a branch of supraorbital nerve to the frontal sinus. About 6 mm medial to the supraorbital notch, there is another notch called the Notch of Arnold which transmits the medial branches of the supraorbital nerve and vessels. Just medial to it (i.e. 10 mm medial to the supraorbital notch,) lies the supratrochlear notch which transmits the supratrochlear nerves and vessel. The lateral orbital margin is formed by the zygomatic process of the frontal bone above and the frontal process of the zygomatic bone below. It is the strongest portion of the orbital outlet. There is a tubercle, called the zygomatic or the molar tubercle which is situated just outside the orbital margin, below the fronto-zygomatic suture. The inferior orbital margin is formed by the zygomatic bone laterally and the maxillary bone medially, usually in equal parts. The suture between the two is frequently

marked by a tubercle which can be felt on palpation. The infraorbital foramen lies about 4 mm below this tubercle and transmits the intraorbital nerves and vessels. The medial orbital margin is formed by the frontal bone above and the frontal process of the maxilla below. The medial margin of the orbit is indistinct in its lower part. In this indistinct part it presents a double countour, forming lacrimal fossa for the lacrimal sac. The anterior margin of the lacrimal fossa or the anterior lacrimal crest lies on the frontal process of the maxilla and the posterior margin of the lacrimal fossa or the posterior lacrimal crest lies on the lacrimal bone. At the junction of the medial and superior margins, a tubercle is present which is called the lacrimal tubercle. The orbital septum is attached to the entire medial orbital margin (Fig. 41.1).

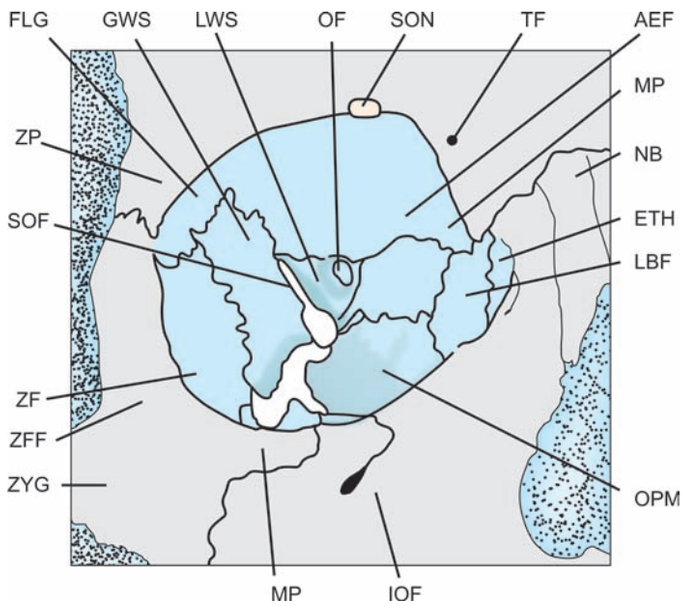
The roof of the orbit is formed anteriorly by the orbital plate of frontal bone and posteriorly by the thick lesser wing of sphenoid bone. The fossa for the lacrimal gland is located on the roof, anteriorly and laterally. The trochlear fossa is a small dimple which is located on the roof, 5 mm behind the rim on the medial side and lodges the cartilaginous trochlear pully, through which passes the tendon of superior oblique muscle. The roof of the orbit is separated from the lateral wall, anteriorly by the zygomatico frontal suture and posteriorly by the supraorbital fissure. The roof of the orbit is separated from the medial wall by the sutures which are situated between the orbital plate of the frontal bone above and ethmoid, lacrimal and maxilla below (from posterior to anterior). In the fronto-ethmoidal sutures there are foramina through which passes the anterior and posterior ethmoidal vessels and nerves. Superior to the roof of the orbit and in the anterior cranial fossa lies the frontal lobe of the brain. Inferior to the roof of the orbit lies the frontal nerve, levator palpebrae superioris muscle, superior rectus muscle, superior oblique muscle, supra-orbital artery, trochlear nerve and lacrimal gland. Optic foramen lies at the apex of the roof. A prominent tubercle on the sphenoidal part of the roof gives origin to the extrinsic muscles of the eye ball (Fig. 41.2).

The floor of the orbit is formed by three bones: zygomatic bone laterally, maxillary bone medially and a small portion of palatine bone posteriorly. The infraorbital fissure (posteriorly) and its canal (anteriorly) extend forwards from the apex to the floor. This canal which transmits infraorbital vessels and nerves finally exits at the infraorbital foramen. It is situated 1 cm inferior to the midpopint of the inferior orbital rim. The nasolacrimal canal which is 12 mm in length lies in the maxillary bone. It commences anteromedially from the orbital floor and passes vertically and slightly lateral to the nasal cavity. It passes the nasolacrimal duct and drains tears from conjunctival sac to the inferior meatus of the nose. In the extreme anteromedial angle of the floor and just behind the inferior orbital margin and lateral to the nasolacrimal canal, there lies a fossa which gives origin to the inferior oblique muscle. Superiorly, the floor is related to the inferior rectus muscle, inferior oblique muscle and the nerve to inferior oblique. Inferiorly the floor is related to the maxillary antrum and the palatine air cells. Anteriorly the floor and the



SON – Supraorbital nerve and artery, STS – Superior tarsal plate and septum, LN – Lacrimal nerve and artery, ZTN – Zygomaticotemporal nerve and artery, IT – Inferior tarsal plate, IS – Inferior septum, ZFN – Zygomaticofacial nerve and artery, STN – Supratrochlear nerve and artery, ITN – Infratrochlear nerve and artery, ION – Infraorbital nerve and artery.

Fig. 41.1: Dissection of the orbit from front. Orbicularis oculi muscle has been removed



OF – Optic foramen, LWS – Lesser wing of sphenoid, GWS – Greater wing of sphenoid, FLG – Fossa for lacrimal gland, ZP – Zygomatic process, SOF – Superior orbital fissure, ZF – Zygomatic foramen, ZFF – Zygomatic facial foramen, ZYG – Zygomatic bone, MP – Maxillary process, IOF – Inferior orbital foramen, OPM – Orbital plate of maxilla, LBF – Lacrimal bone and fossa, ETH – Ethmoid bone, NB – Nasal bone, AEF – Anterior ethmoidal foramen, TF – Trochlear foramen, SON – Supraorbital notch.

Fig. 41.2: The right orbit

lateral wall are continuous with each other while posteriorly the floor is separated from the lateral wall by the inferior orbital fissure (Fig. 41.3).

The medial wall of the orbit is more or less quadrangular in shape and comprises of four bones: most anteriorly the frontal process of the maxilla, followed by the lacrimal, ethmoid and the lesser wing of sphenoid (from anterior to posterior). The lacrimal fossa which measures about 15 mm × 5 mm and houses the lacrimal sac is situated on the medial wall of the orbit and is bounded by the anterior and the posterior lacrimal crests. The anterior lacrimal crest is formed by the frontal process of the maxilla and the posterior lacrimal crest is formed by the lacrimal bone. Besides the lacrimal sac, the fossa also lodges the lacrimal fascia, the areolar tissue containing the plexus of veins and some fibres of the orbicularis oculi muscle which is known as the Horner's muscle. The lacrimal fossa which contains the nasolacrimal sac continues below with the nasolacrimal canal and contains the nasolacrimal duct. The anterior lacrimal crest extends inferiorly to join with the lower orbital margin and forms an elevation called the lacrimal tubercle. The posterior lacrimal crest extends superiorly to join with the superior rim. In the medial wall, the anterior and posterior ethmoidal foramina traverse the suture line between the ethmoidal bone and the orbital plate of the frontal bone. The ethmoidal bone is the thinnest and the weakest part of the orbit and is called the lamina papyracea. The two medial walls of the orbit are almost parallel. The medial wall of the orbit is related medially to the anterior, middle and posterior ethmoidal sinuses, middle meatus of the nose and the sphenoidal air sinuses. The superior oblique muscle, the medial rectus muscle, the nasociliary nerve and the terminal part of the ophthalmic artery run over the lateral surface of the medial wall (Fig. 41.4).

The lateral wall of the orbit is made up of the zygomatic bone (anterior 1/3) and the greater wing of the sphenoid bone (posterior 2/3). The superior and inferior orbital fissures separate the posterior portion of the lateral wall of the orbit from the roof and the floor of it, respectively. It is triangular in shape with the base lying anteriorly. The greater wing of the sphenoid separates the superior and inferior orbital fissures. A prominence, called the lateral orbital tubercle of Whitnall is situated 4 mm behind the midpoint of the lateral orbital margin and 10 mm below the zygomaticofrontal suture. This tubercle of Whitenall gives attachment to the (i) lateral palpebral raphe, (ii) lateral horn of the tendon of levator palpebrae superioris, (iii) lateral end of the suspensory ligament of Lockwood and (iv) lateral check ligament of the lateral rectus muscle (Fig. 41.5).

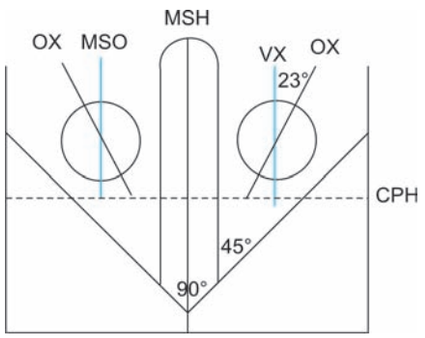


Fig. 41.3: Planes of the head and orbital region
OX – Orbital axis, VX – Visual axis, MSH – Midsagittal plane of the head, CPH – Coronal plane of the head, MSO – Midsagittal plane of the orbit

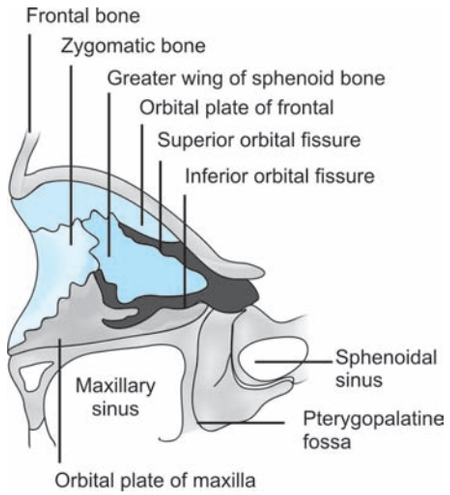
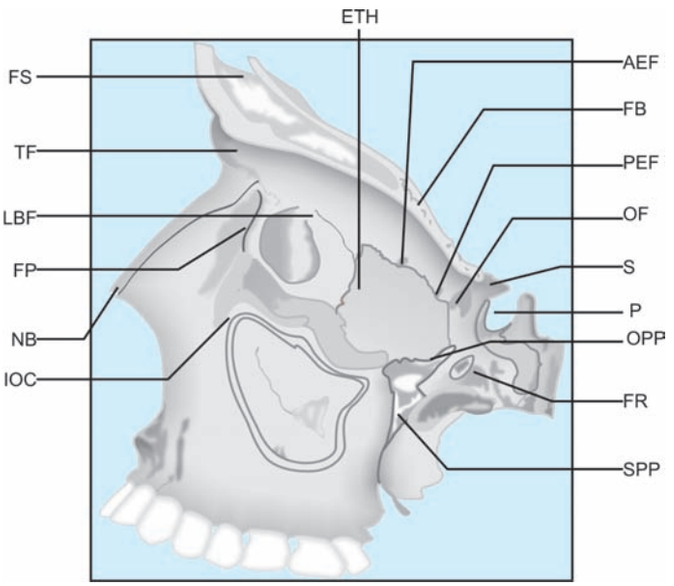


Fig. 41.5: The lateral wall of the right orbit



FS – Frontal sinus, ETH – Ethmoid bone, AEF – Anterior ethmoidal foramen, FB – Frontal bone, PEF – Posterior ethmoidal foramen, OF – Optic foramen, S – Sphenoid, P – Pituitary, OPP – Orbital process of palatine, FR – Foramen of rotundum, SPP – Sphenoid process of palatine, IOC – Infraorbital canal, NB – Nasal bone, FP – Frontal process, LBF – Lacrimal bone and fossa, TF – Trochlear foramen

Fig. 41.4: Medial wall of the orbit

The zygomatic bone of the lateral wall has two minute foramina for the zygomaticofacial and zygomaticotemporal nerves on their way to innervate the fascial skin. There is a small bony projection on the inferior margin of the superior orbital fissure which is called the spinal recti lateralis. It provides origin to a part of the lateral rectus muscle and the common tendinous ring of Zinn. The lateral wall is related laterally to the temporal fossa anteriorly and middle cramial fossa posteriorly. Medially the lateral wall is related to the lateral rectus muscle, lacrimal nerve and vessels, zygomatic nerve and a communication between the zygomatic and the lacrimal nerves (Fig. 41.6A).

The superior orbital fissure is a gap which is situated between the greater and the lesser wings of the sphenoid bone. It lies between the roof and the lateral wall of the orbit. The frontal bone forms the lateral boundary of the fissure. It is comma or retort-shaped because it is wider at the medial end and narrower at the lateral end. At the junction of these two parts of superior orbital fissure lies the spine which gives origin to the lateral rectus muscle. Its medial end is separated from the optic foramen by the posterior root of the lesser wing of the sphenoid bone. The anterolateral part of this fissure is closed by duramater, so that no structure can pass through it. However, its posteromedial part communicates with the middle cranial fossa, allowing the passage of the nerves and vessels for the eyeball. The annulus tendineus communis, spans over the superior orbital fissure and divides the fissure into three parts : (i) the upper or lateral part transmit the trochlear, frontal and lacrimal nerves and the superior ophthalmic vein, (ii) the middle part transmits the superior divisions of the oculomotor nerve, the nasociliary nerve, the sympathetic root of the ciliary ganglion, the inferior division of the oculomotor nerve and the abducent nerve. It is also called the oculomotor foramen, (iii) the inferior part transmits only the ophthalmic vein (Fig. 41.6B).

The inferior orbital fissure lies between the lateral wall and the floor of the orbit. It connects the orbital cavity with the inferotemporal fossa in front and the pterygopalatine fossa behind. It is bounded anteriorly by the maxilla, and posteriorly by the greater wing of the sphenoid bone. It is separated from the posterior end of the superior orbital fissure by a bridge of bone extending from the greater wing of the sphenoid. Both the fissures are covered by a periorbital membrane and the Muller's muscle. The inferior orbital fissure transmits the infraorbital nerve, the zygomatic nerve, the branches from the pterygo palatine ganglion and a communication between the inferior ophthalmic vein and the pterygoid venous plexus (Fig. 41.7).

The optic foramen is actually a canal which is formed by the union of the two roots of the lesser wing of sphenoid with its body. The optic canal starting from the optic foramen is a communication between the apex of the orbit and the middle cranial fossa. The canal is about 10 mm in length and about 5 mm in breadth. The optic canal transmits the optic nerve and along with it the meninges, the ophthalmic artery and few twigs of the sympathetic plexus along the artery. At this optic canal the duramater splits into two layers − the inner layer forms the sheath of the optic nerve, while the outer layer continues with the periosteum. The common tendinous ring is also attached to the infraoptic tubercle which is an elevation present inferolateral to the optic foramen. The posterior ethmoidal air sinuses are situated just medial to the optic canal.

The anterior and posterior ethmoidal foramen and its canals are situated at the junction of the roof and the medial wall of the orbit and form a communication between the orbit and the anterior cranial fossa. The anterior ethmoidal canal transmits the anterior ethmoidal nerve

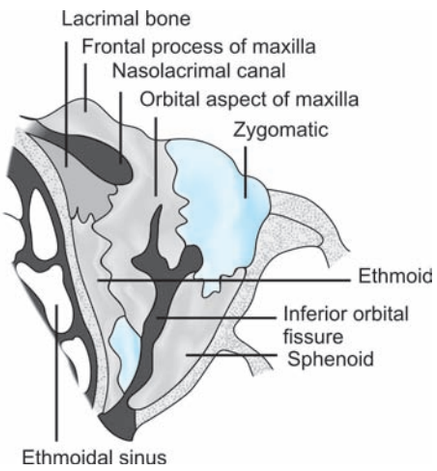


Fig. 41.6A: The floor of the right orbit

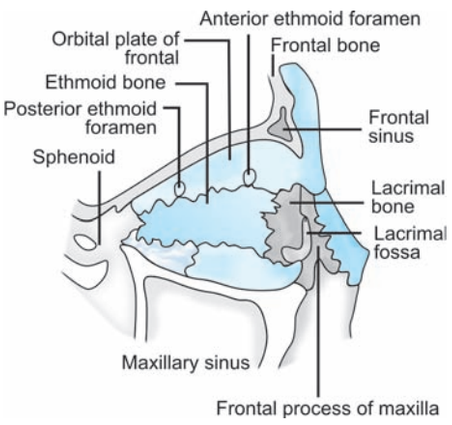


Fig. 41.6B: The medial wall of the right orbit

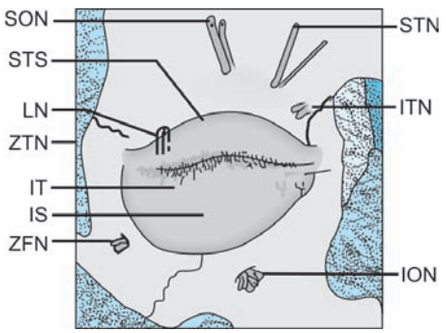


Fig. 41.7: The apex of orbit, fissures, vessels and nerves

and vessels, while the posterior ethmoidal canal transmits the posterior ethmoidal vessels and nerve.

ORBITAL CONNECTIVE TISSUE

Orbital Periosteum

The periosteum of the orbit is known as the periorbita and it lines the bones of the orbit loosely. It can easily be stripped off from the underlying orbital bones. It is thickened along the anterior orbital margin and is called the arcus marginalis. Along the anterior orbital margin it blends with the periosteum of the facial bone and with the orbital septum circumferentially. Posteriorly at the orbital apex, the periorbita is continuous through the optic canal with the pericranium and also with the dural sheath of the optic nerve (Fig. 41.8).

Here, it provides origin to the four rectus muscles from a common tendon. Anteriorly, it encloses the lacrimal sac in its fossa and passes down with the nasolacrimal duct to become continuous with the periosteum of the inferior meatus of nasal cavity. It forms a dense membrane covering the superior orbital fissure. The fine lamelle of the periorbita divide the orbital fat into many lobules and form a coverings for the nerves and vessels. The orbital septum is a weak membranous sheet which is attached to the anterior margin of the orbit and is continuous with the facial periosteum and the periorbita of the orbit. It defines the antomical anterior border of the orbit. On the nasal side it is attached with both the anterior and the posterior lacrimal crests. Its central attachments are in the upper and lower eyelids and lie deep to the orbicularis oculi muscle (Fig. 41.9).

Tenon's Capsule

Tenon's capsule or the bulbar fascia is a thin fibrous membranous structure which envelops the eyeball from the limbus to the optic nerve. It extends from the corneal limbus anteriorly to the optic nerve posteriorly where it blends with the meninges of the optic nerve. Posteriorly it is in contact with the orbital fat and is pierced by the ciliary nerves with their accompanying arteries. Anteriorly it merges with the sub-conjunctival connective tissue and is pierced by the tendons of six extra-ocular muscles (the four rectus muscles pierce the tenon's capsule behind the equator, while the two oblique muscles pierce it anterior to the equator) prior to their insertion on the sclera. At the site of the insertion of the tendons of extraocular muscles, the Tenon's capsule sends tubular reflection around these tendors so as to clothe them like a glove and allows unrestricted control of the movement of muscles within this capsule. The globe rotates around its centre point within the smooth inner lining of this Tenon's capsule. However, this movement is possible due to the great mobility of the anterior part of the optic nerve. The tubular reflections of the medial and lateral rectus muscles from Tenon's capsule send expansions to the neighbouring structures. The lateral expansion from the reflection of lateral rectus is attached to the Whitnall's tubercle and is called the lateral check ligament, while that of the medial rectus to the lacrimal crest is called the medial check ligament. These expansions are quite strong and limit the action of the respective muscles. Therefore, they are known as the check ligaments. The expansion from the reflection sheath of the superior rectus is attached to the levator palpebrae superioris through a band and that of the inferior rectus is inserted between the tarsal plate and the orbicularis of the lower lid. The expansions from the reflection sheaths of the superior oblique and inferior oblique muscles are attached to the trochlea and the lateral part of the floor of the orbit, respectively. The expansions of the fascial sheaths of the inferior rectus and the inferior oblique muscles also extend posteriorly and are joined by the expansions from the lateral and medial rectus muscles to form a sling on which the eyeball rests. It provides an effective support to the eyeball and is so known as the suspensory ligament of Lockwood. All these fibrous expansions from the reflection covering of the muscles are attached to the conjunctiva, thereby preventing its folding during their action. The intermuscular septa between the adjacent margins of the four rectus muscles which divide the orbital space into intraconal and extraconal area are well-developed in the anterior part of the orbit. They merge with the Tenon's capsule in this area.

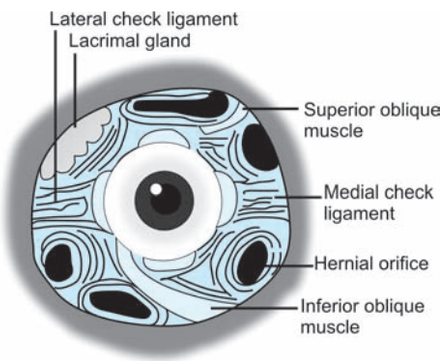


Fig. 41.8: The connective tissue diaphragm of orbit with the hernial orifices. It is situated just anterior to the globe of equator. The eyelids and orbital septum are removed

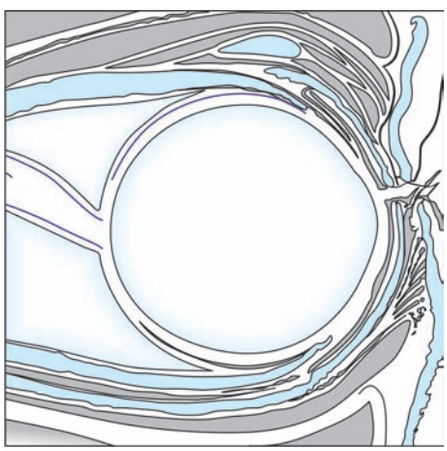


Fig. 41.9: The display of connective tissue (white lines) around the structures in the orbit

Diffuse Connective Tissue System

The diffuse connective tissue system of the orbit is divided into two parts: (i) The

clearly defined supporting connective tissue system of anterior orbit and (ii) the diffuse ill defined connective tissue system of the posterior orbit.

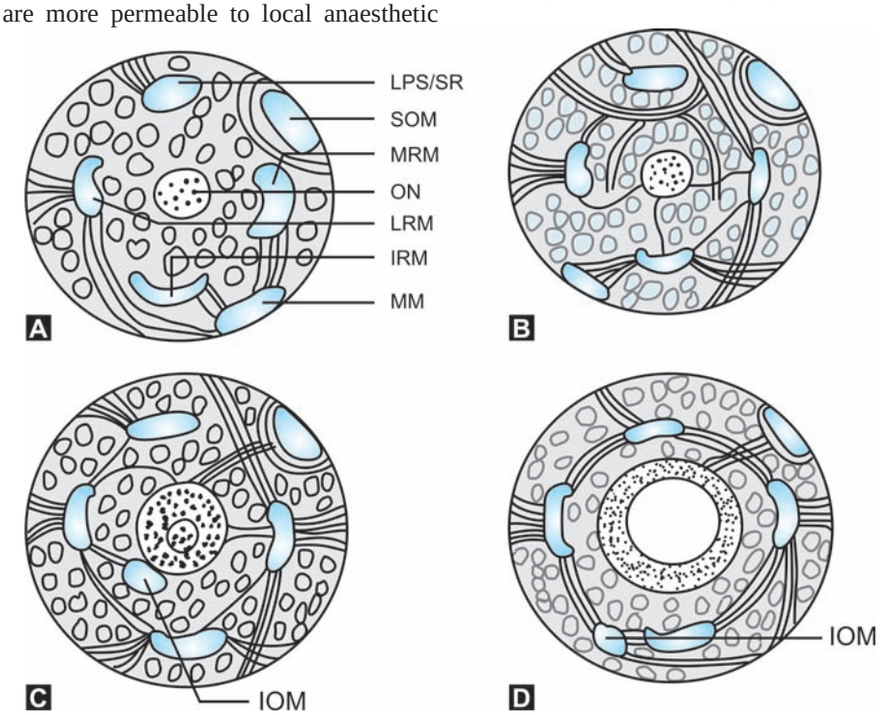
The clearly defined supporting connective tissue system in anterior orbit consists of a diaphragm which extends out from the Tenon's capsule and the globe to the periorbita just behind the orbital margin. Condensation of these tissues above and below the globe form the suspensory ligaments which are known as the Ligaments of Whitnall and Lockwood, respectively. They support the globe and limit its displacement. Several sheets of connective tissue also fan out from the respective muscle sheaths which is formed by the reflection of Tenon's capsule to attach to the periorbita at the sides of the orbit. In case of the medial and lateral rectus muscle, these are called the medial and lateral check ligaments which are considered to act as a servo-mechanism of the eyeball. The intermuscular septa, between the adjacent margins of the four rectus muscles are well-developed in the anterior part of the orbit. They merge anteriorly with the Tenon's capsule in this area.

The diffuse ill-defined connective tissue system of the posterior orbit is derived from the fascial sheath of the extraocular muscles. It radiates out from the fascial sheath of rectus muscles to the periorbita and encloses all the structures, including the nerves and vessles of the orbit. Adipose tissue lies between these radiations. Unlike the anterior orbit, posteriorly the intermuscular septa are less well-developed, particularly in the inferotemporal quadrant of the orbit where almost none exists. Of the rectus muscles, only the medial rectus is significantly separated from the adjacent bony orbital wall by a fat compartment. The connective tissue around the medial rectus muscle exhibits connections or extensions to the orbital floor and roof. At the level of the equator, a condensation of connective tissue of the medial rectus extends nasally to the medial orbital wall. This is called the medial check ligament. The medial compartment opens anteriorly above and below the medial check ligament as two hernial orifices in the connective tissue diaphragm that surrounds the globe. Thus local anaesthetic agent, deposited in the medial orbital compartment by injection will spread through these orificies to the orbital spetum into the upper and lower eyelids. This spread of local anaesthetic agent in the upper and lower eyelids is in this tissue plane which is deep to the orbicularis oculi muscle and where lies the fine terminal motor branches of the 7th cranial nerve. So they are readily blocked (Figs 41.10A to D).

The quality of these connective tissues among the different individuals varies. The quality deteriorates with increasing age and thus the weaker connective tissues are more permeable to local anaesthetic agents injected into the mid-orbit. So, the critical concentrations of drug to block the oculomotor nerve near the apex are more easily attained in the elderly as compared to young adults. Similarly, orbital haemorrhage in the elderly which drains in the anterior orbit, causing black eye, may be of less important than a similar bleeding in younger patients, in whom more firm tissues may trap blood and result in a dramatic loss of vision from the unrelieved building up of pressure (Fig. 41.11).

SPACES IN THE ORBIT

Surgically, there are four spaces in the orbit which are of immense importance to the anaesthetist. These spaces are: (i) subperiosteal, (ii) peripheral, (iii)



LPS – Levator palpebrae superioris, SR – Superior rectus, SOM – Superior oblique muscles, MRM – Medial rectus muscle, ON – Optic nerve, LRM – Lateral rectus muscle, IRM – Inferior rectus muscle, MM – Muller's muscle.

Figs 41.10A to D: Schematic diagram shows extraocular muscles and the connective tissue system, in different coronal sections of the orbit.
A. Coronal section at the apex of the orbit,
B. Coronal section of the orbit at the posterior pole of the globe,
C. Coronal section of the orbit, midway between the posterior pole and the equator of the globe,
D. Coronal section at the equator of the globe.

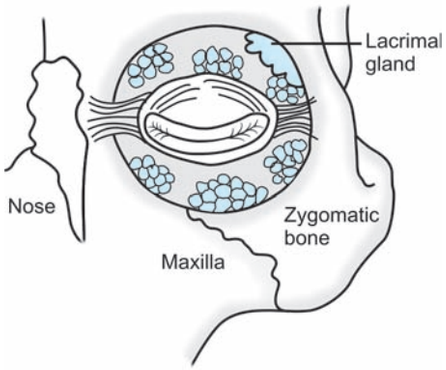


Fig. 41.11: The pads of orbital fat, coming out of different apertures of the connective tissue system of the left orbit

central and (iv) sub-Tenon's space. Each space is self-contained and an inflammatory process may remain confined in it for a considerable period.

Subperiosteal Space

This space lies between the bones of the orbit and the periorbita (periosteum). It is an uneven potential space, which is obliterated at sutures. Periosteum is detachable in most parts, except its firm attachment at the sutures margins, roof and fissures.

Peripheral Orbital Space

It is the space between the periorbita and the extraocular muscles with their fascial expansions among them, forming more or less a continuous circular septum. This space is limited anteriorly by the check ligaments and posteriorly by the approximation of the common tendinous ring and the periosteum, at the optic foramen. This peripheral space contains lacrimal gland, branches of the trigeminal (frontal, lacrimal, infraorbital and nasociliary) and trochlear nerves, lacrimal and infraorbital vessels and the ophthalmic vein. Collection of fluid in this space may extend through the orbital septum and lead to oedema of the eyelids.

Central Space

It is a cone-shaped area enclosed by the four rectus muscles, and their fascial expansions in between them. Anteriorly the space is limited by the posterior aspect of the eyeball, laterally by the muscles and their fascial sheaths and posteriorly by the common tendinous origin of the extraocular muscles at the apex of the orbit. It contains the optic nerve and its meningeal coverings, superior and inferior divisions of the oculomotor nerve, abducent nerve, ophthalmic artery, superior ophthalmic vein and nasociliary nerve. The last three passes to the peripheral surgical space, after piercing the medial aspect of the space. The presence of any tumour or fluid in this space usually results in proptosis (Fig. 41.12).

Sub-Tenon's Space

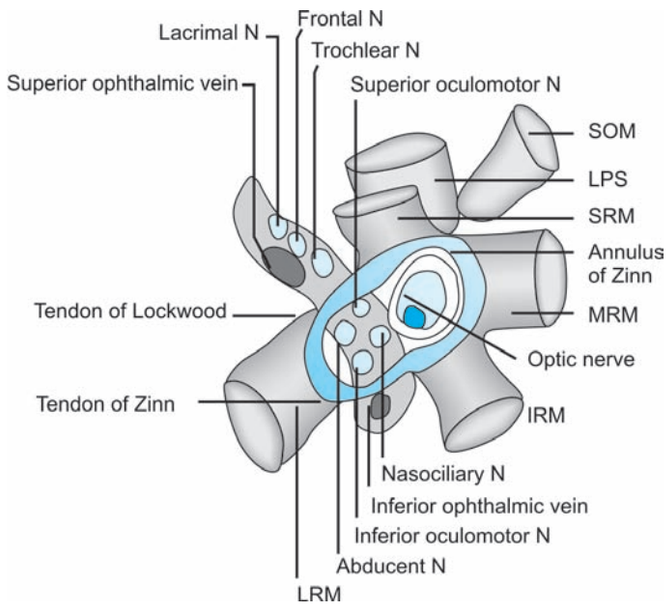
It lies between the Tenon's capsule and the sclera and forms a potential space around the globe. It contains insertions of the tendons of the extraocular muscles, some nerves and vessels piercing the eyeball and some loose reticular tissues.

SKELETAL MUSCLES OF THE PERIORBIT AND ORBIT

Orbicularis Oculi Muscle

The orbicularis oculi muscle is situated around the anterior margin of the orbit and intimately attached to the deep surface of the skin. It is responsible for the closure of the eyelid, including the automatic and reflex blinking action. It is innervated by the facial nerve (VII cranial nerve), entering from the deep surface of the muscle. It is divided into three parts : orbital part, preseptal part and pretarsal part. The last two parts together are called the palpebral part.

The orbital part of this muscle originates from the medial third of the upper and lower orbital margins, medial palpebral ligaments, maxillary process of the frontal bones and the frontal process of the maxilla. These fibres of muscle are arranged in a concentric manner around the anterior orbital margin and cover



SOM – Superior oblique muscle, LPS – Levator palpebrae superioris,
SRM and IRM – Superior and inferior rectus muscle,
MRM and LRM – Medial and lateral rectus muscle.

Fig. 41.12: The apex of orbit with the annulus of Zinn

the lids. It intermixes with the brow muscle and the frontalis. This orbital part of the orbicularis oculi muscle helps in the firm closure of the eyelid.

The palpebral part (preseptal and pretarsal) originates from the medial palpebral ligament and the adjacent bone and forms the lateral palpebral raphe by merging with the septum orbitale to get attached to the Whitnall's tubercle. The pretarsal part contributes to form more or less the entire thickness of the eyelid margin. The follicles of the eyelashes, glands of Moll and meibomian ducts traverse the pretarsal part of this muscle. The palpebral part of the orbicularis oculi muscle helps in smooth and gentle closure of the eyelids during blinking.

The third part of the orbicularis oculi muscle which is known as pars lacrimalis is attached to the posterior lacrimal crest and the lacrimal fascia. It helps in dilatation of the lacrimal sac and thus facilitates the drainage of tear by tear-pump mechanism.

Extraocular Muscles

These extraocular muscles are involved in the movement of eyeball and its adnexa. They may be divided into three broad groups:

i. Extrinsic muscles of the eyeball,
ii. Muscles of the lid,
iii. Non-striated muscles of the lid.

Extrinsic muscles of the eyeball

These muscles are comprised of four recti and the superior and inferior obliques. These four recti with their average 40 to 42 mm of length have a common origin from a tendinous ring (annulus of Zinn) which is attached to the sphenoid bone at the apex of the orbit. The ring encircles the optic foramen and the medial end of the superior orbital fissure. This annulus ring forms the apex of the interconal space whose base is Tenon's capsule covering the posterior surface of the globe. The interconal space is now no longer considered as a closed compartment which was originally thought. But, because of its intimate relationship with the optic, oculomotor, sensory and autonomic nerves, this intraconal space is important for understanding and mastering the orbital regional anaesthesia. The four rectus muscles of orbit run forwards after their origin from the tendinous ring close to the optic foramen and are then inserted into the sclera, anterior to the equator of the globe. Their muscle belly is replaced before their insertion by a tendon near the globe. The superior and inferior oblique muscles are inserted obliquely in the postero-superior and postero-inferior quadrant of globe, respectively and is almost lateral to the mid vertical plane.

The superior rectus muscle

It takes origin from the upper part of the annulus of Zinn, from the lateral side of the optic foramen and the optic nerve sheath. It is inserted into the sclera, 7.7 mm behind the limbus by a tendon. At the origin this muscle is related inferiorly to the dural sheath and the optic nerve, superiorly to the levator muscle and the frontal nerve, medially to the medial rectus and laterally to the lateral rectus, lacrimal artery and nerve. The levator palpebrae superioris remains above the superior rectus muscle throughout its course. Between the superior rectus and the optic nerve lie the orbital fat, the ophthalmic artery and the nasociliary nerve. In the later part of the course, the tendon of the superior oblique muscle runs between the superior rectus and the globe. The superior rectus muscle is supplied by the superior division of the oculomotor nerve which enters the muscle from its undersurface at the junction of its middle and posterior-third (Fig. 41.13).

The inferior rectus muscle

It arises from the lower part of the annulus of Zinn. It is shortest of all the rectus muscles of orbit. It passes forwards along the floor of the orbit and is inserted into the sclera, approximately 6.5 mm away from the limbus. The optic nerve, orbital fat, the inferior divisions of the oculomotor nerve and the eyeball lie above the inferior rectus muscle. The floor of the orbit, maxillary sinus and the infra orbital vessels and nerves lie below it. The nerve to the inferior oblique and the lateral rectus form the lateral relations of this muscle. The inferior oblique muscle crosses the orbit below the inferior rectus and fibrous the sheaths of these two muscles blend at the crossing. The inferior rectus is also attached to the lower lid by a fascial expansion of its sheath. It is supplied by a branch from the inferior division of the oculomotor nerve which enters the muscle from bulbar surface.

The medial rectus muscle

It takes origin from the medial part of the annulus of Zinn and the sheath of the optic nerve. It is the strongest and the thickest of all the extrinsic muscles of the eyeball. It runs forwards and medially along the medial orbital wall and is inserted into the sclera, 5.5 mm behind the limbus. The superior oblique muscle lies above the medial rectus. The ophthalmic artery and its branches, the ethmoidal nerve and the infratrochlear nerve are present between these two muscles. The floor of the orbit lies below the medial rectus muscle. The orbital plate of the ethmoid bone and the ethmoidal air cells are placed medial to this muscle, while central orbital fat lies laterally. The medial rectus muscle is supplied by a branch from the inferior division of the oculomotor nerve from its lateral surface.

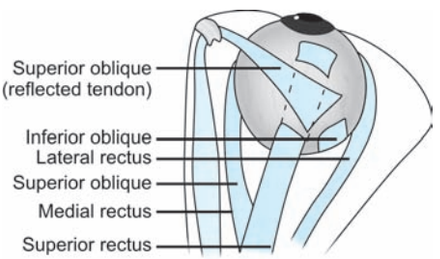


Fig. 41.13: Extraocular muscles of the eyeball

The lateral rectus muscle

It arises from the lateral part of the annulus of Zinn. Then the muscle runs forwards and laterally between the eyeball and the lateral orbital wall. It is inserted into the sclera, 6.5 mm behind the limbus. The lacrimal gland, the lacrimal nerve and the lacrimal artery lie above this lateral rectus muscle. The floor of the orbit and the tendon of the inferior oblique form the lower relations of this muscle. Laterally, it lies directly on the periosteum. It is supplied by the 6th cranial nerve which enters the muscle from its medial aspect.

The superior oblique muscle

It takes origin from the periosteum of the body of sphenoid bone, just above and medial to the optic foramen. It is the longest and thinnest of all the extrinsic muscles of the eyeball. After origin, it runs forwards between the roof and the medial wall of the orbit, and between the superior and medial rectus. Then behind the anterior orbital margin it becomes a rounded tendon which passes through a pulley called the trochlea After that the superior oblique muscle runs downwards, backwards and laterally at an angle of about 55°, underneath the superior rectus muscle and fans out before its insertion on the posterior superior quadrant of the sclera. The superior oblique muscle has two distinct parts. A direct muscular part which is 40 mm in length and extends from its orign to the trochlea, and a tendinous reflected part which is 20 mm in length and runs from the trochlea to its insertion. It is supplied by the trochlear nerve.

The inferior oblique muscle

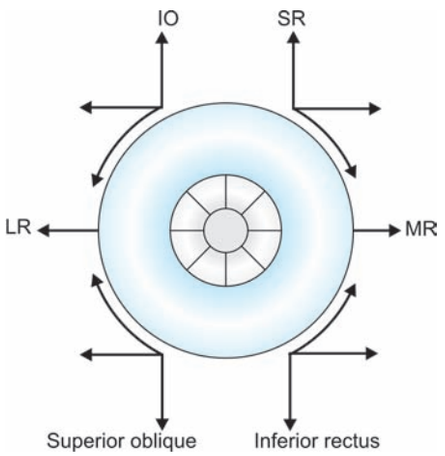
It is the only extrinsic muscle of the eyeball which does not take origin from the annulus of Zinn. It arises from a rough area (small depression) on the orbital plate of maxilla, just lateral to the lacrimal fossa. Then, it runs backwards and laterally, passing between the inferior rectus and the floor of the orbit and curves around the eyeball to lie underneath the lower border of the lateral rectus. It is inserted on the posterolateral quadrant of sclera, underneath the lateral rectus muscle. The muscle is innervated by inferior division of oculomotor nerve (Fig. 41.14).

Muscles of the lids

The levator palpebrae superioris and the superior palpebral muscles elevate the upper eyelid. The tendinous palpebral expansion of the inferior rectus and the inferior palpebral muscle retract the lower eyelid. The orbicularis oculi helps in the closure of eyelids.

The levator palpebrae superioris (LPS)

It takes origin from the under surface of the lesser wing of the sphenoid bone, just superior and slightly medial to the superior rectus muscle. The thin, flat belly of this muscle runs forward under the roof of the orbit and lies on the superior rectus muscle. These two muscles have a common fascial sheath. In the region of the superior fornix, it forms an expanded aponeurosis with an anterior and a posterior lamella which fans out and occupies the whole breadth of the upper part of the orbit. It is here, where its direction is changed from horizontal to nearly vertical, moulding itself on the eyeball and the upper eyelid. The anterior lamella has multiple diffuse terminal attachments which is described below. While the posterior lamella which is known as the sympathetic muscle of Muller is inserted on the superior border of the tarsal plate.



MR = Medial rectus, LR = Lateral rectus
SR = Superior rectus, IR = Inferior rectus
IO = Inferior oblique, SO = Superior oblique

Fig. 41.14: Actions of extraocular muscles of right eye

The insertion of the anterior lamella has been divided into the following parts:

i. The bulk of the fibres passes through the muscle fibres of the orbicularis oculi and get inserted into the skin of the upper eyelid, at and below the upper palpebral sulcus.
ii. Some fibres are attached to the front and lower parts of the tarsal plate.
iii. The fascial sheath of the muscle is also attached to the conjunction of the superior fornix.
iv. The two horns of the levator aponeurosis get attached to the orbital bones, at the midpoint of the lateral and medial orbital margin. The lateral horn is stronger than the medial horn. The lateral horn divides the lacrimal gland into orbital and palpebral portions, and supports the gland against the orbital roof. The medial horn is attached to the frontolacrimal suture medial to the palpebral ligament.

The roof of the orbit, the trochlear and the frontal nerves and the supraorbital vessels lie above this levator palpebrae superioris muscle. The trochlear nerve crosses the levator near its origin from lateral to medial side. Similarly, the frontal nerve crosses it obliquely from lateral to medial. The superior rectus muscle and the eyeball lies below this muscle. The muscle is supplied by the superior division of the oculomotor nerve. The sympathetic fibres carrying through the oculomotor nerve supply the nonstriated superior and inferior palpebral muscles along the respective divisions of the oculomotor nerve.

Non-striated muscles of the orbit

A group of the nonstriated muscles of the orbit almost completely envelop the eyeball. It has superior, inferior and medial palpebral parts. The superior palpebral part

of this muscle is also known as the superior palpebral muscle of Muller. This muscle arises from the inferior aspect of LPS at the level of superior fornix in the form of a wide band and runs a near vertical course to be inserted on the upper edge of the superior tarsal plate. The inferior palpebral part is also known as the inferior palpebral muscle of Muller and passes from the bulbar surface of the inferior rectus muscle to the lower margin of the lower tarsal plate. The fibres of these muscles spread out mostly as a fascia, lying between the inferior rectus and the inferior oblique muscle. These muscles are innervated by the sympathetic nerve. The superior palpebral muscle elevates the upper lid and the inferior palpebral muscle retracts the lower lid. So, the irritation of sympathetic nerve results in the retraction of both the eyelids.

NERVES OF THE EYE, ORBIT AND PERIORBIT

The cranial nerve II (optic), III (oculomotor), IV (trochlear), V (trigeminal), VI (abducent), and VII (facial) are responsible for the sight, motor function, sensation and autonomic control of the ocular region of the face. So they are called the nerves of the eye, orbit and periorbit.

Optic Nerve

Strictly speaking, the optic nerve is not a cranial nerve, rather it is an extension of the brain. Because, unlike of the other cranial nerves, it carries meningeal coverings over it from the cranial cavity. The outer meningeal covering of the optic nerve is nothing but the extension of dura, and blends anteriorly with the sclera (Fig. 41.15).

The middle and inner coverings of the optic nerve are also continuation of the arachnoid and the pia matar. Like the meninges, the subdural and the subarachnoid space also separate the three sheaths of the optic nerve from each other. From the optic chiasma to retina the total length

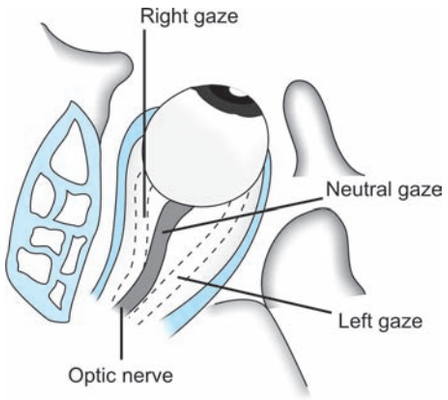


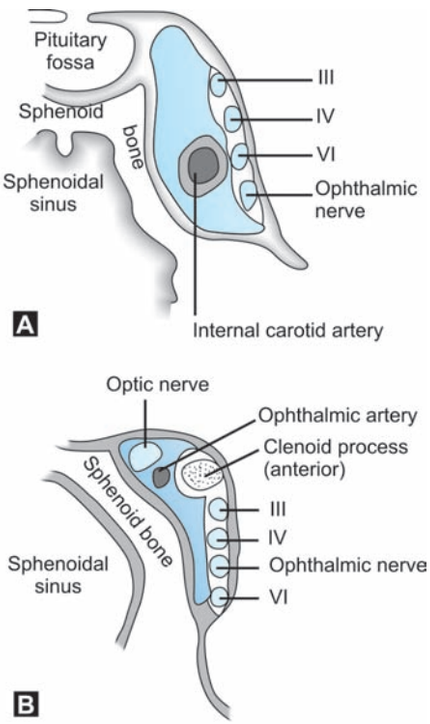
Fig. 41.15: Schematic diagram of the transverse section of the orbit, showing different positions of the optic nerve, during neutral, right and left gaze

of an optic nerve is approximately 5 cm. Anatomically, the optic nerve is divided into four parts: intracranial, intracanalicular, intraorbital and intraocular. The intracranial portion of the optic nerve extends from the optic chiasma to the cranial end of the optic canal and is approximately 1 cm in length (Figs 41.16A and B).

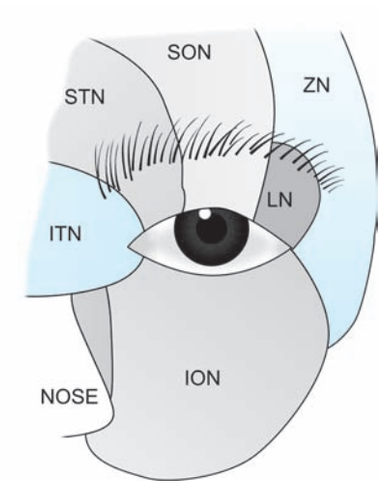
The anterior cerebral artery and the frontal lobe of the brain lie superior to it. As the optic nerve emerges from the cavernous sinus, the internal carotid artery lies lateral to it. The intracanalicular portion of the optic nerve is only 5 to 6 mm in length and lies in the optic canal. As the dural sheath is tightly adhered to the periosteum of the canal, so this portion of the optic nerve is completely rigid. The intraorbital portion of the optic nerve extends from the optic foramen to the posterior surface of the eyeball, 3 mm on the nasal side. It is 3 cm in length. But the distance from the foramen to the eyeball is only 2.5 cm. So, this portion of the optic nerve is loose, lax and tortuous. This tortuosity of the optic nerve permits free movement of the globe in all positions, without detrimenting its function. The dural sheath of the optic nerve fuses anteriorly with the sclera and posteriorly with the periorbita (periosteum) at the optic foramen. The CSF flows freely within this dural sheath around the optic nerve and is in continuity with the CSF of the midbrain. In primary gaze position, the intraorbital portion of the optic nerve is closer to the medial than the lateral rectus muscle and assumes a tortuous course between the posterior pole of the globe and the optic foramen. In abduction and upward gaze, the optic nerve becomes straight. In abduction and downward gaze the optic nerve takes on a S-shaped curve. The intraocular part of the optic nerve is only 1 mm in long, representing the thickness of the sclera where the nerve enters near the posterior pole of the globe (3 mm to the nasal side) (Fig. 41.17).

Motor Nerves to Extraocular Muscles

The three cranial nerves such as the oculomotor (III), trochlear (IV), and abducent (VI) nerves supply the motor functions of the extraocular muscles of the eyeball. The trochlear nerve supplies the superior oblique muscle, and the abducent supplies the lateral rectus muscle. The remaining

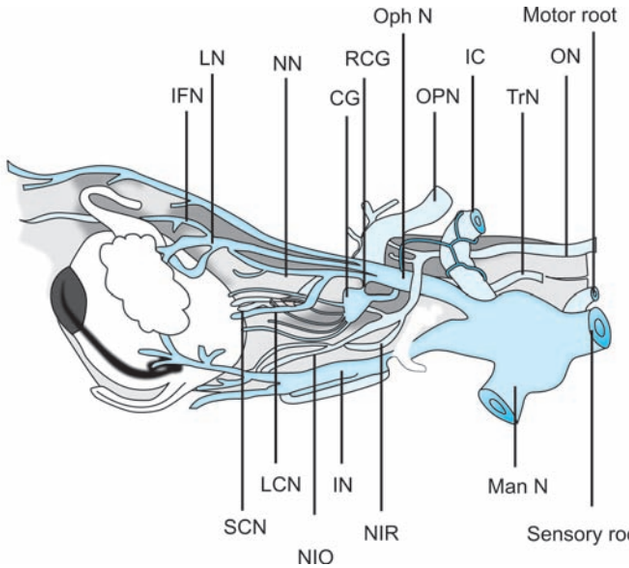


Figs 41.16A and B: The cavernous sinus and different other nerves and arteries. **A.** The coronal section at the level of pituitary fossa. **B.** The coronal section at the level of anterior clenoid process



SON – Supraorbital nerve, ZN – Zygomatic nerve, LN – Lacrimal nerve, ION – Infraorbital nerve, ITN – Infratrochlear nerve, STN – Supratrochlear nerve.

Fig. 41.17: The cutaneous nerve supply of the periorbital region



IFN – Infratrochlear nerve, LN – Lacrimal nerve, NN – Nasociliary nerve, CG – Ciliary ganglion, RCG – Ramus to ciliary ganglion, Oph N – Ophthalmic nerve, OPN – Optic nerve, IC – Internal carotid artery, ON – Oculomotor nerve, Man N – Mandibular nerve, NIR – Nerve to inferior rectus, IN – Infraorbital nerve, NIO – Nerve to inferior oblique, LCN – Long ciliary nerve, SCN – Short ciliary nerves.

Fig. 41.18: Nerves within the orbit

four extraocular muscles and the levator palpebrae superioris are supplied by the oculomotor nerve. The oculomotor nerve also carries the parasympathetic fibres for the sphincter muscles of the iris and the ciliary muscles. The dilator muscles of the iris is supplied by the sympathetic fibres carried by the nasociliary nerve. The motor nerve to the four rectus muscles and the inferior oblique muscle enter their respective muscle bellies from within the muscle cone. Whereas, the trochlear nerve remains outside the cone and enters its supplying muscle, named the superior oblique through its superolateral edge. This anatomic difference explains the cause of delayed onset of akinesia of this muscle, following a small volume of intraconal local anaesthetic injection.

Oculomotor nerve

It supplies all the extraocular muscles, except the superior oblique and the lateral rectus. It also supplies the parasympathetic fibres to the sphincter pupillae and ciliary muscles which are intraocular. So, the functional components of oculomotor nerve are:

i. Somatic efferent for the movement of the eyeball,
ii. General visceral efferent for accomodation and contraction of the pupil (these fibres come from Edinger-Westphal nucleus),
iii. General somatic afferent for the proprioceptive impulses from the muscles of the eyeball (Fig. 41.18).

The oculomotor nerve emerges from the interpeduncular sulcus on the ventral surface of the brainstem by 15 to 20 rootlets which then quickly coalesce into a single trunk. It then passes between the posterior cerebral and superior cerebellar arteries and traverses through the lateral wall of cavernous sinus but above the trochlear nerve. It divides here into superior and inferior branches, and then these two divisioins enter into the intraconal space of the orbit through the intermediate part (oculomotor foramen) of the superior orbital fissure. The nasociliary nerve and the sympathetic twig to the ciliary ganglion lie between these two divisions of the oculomotor nerve, and the abducent nerve lies lateral to them. The superior division of oculomotor nerve runs lateral to the optic nerve and supplies the superior rectus and the LPS muscle. The inferior division of the oculomotor nerve divides again mainly into three branches such as (i) the nerve to medial rectus, (ii) the nerve to inferior rectus, and (iii) the nerve to inferior oblique. The nerve to medial rectus passes inferior to the optic nerve. The nerve to inferior rectus passes downwards and enters the muscle from its upper aspect. The nerve to inferior oblique passes in between the inferior rectus and the lateral rectus and supplies the muscle from its posterior border. It also gives a thick branch to the ciliary ganglion. This branch carries the preganglionic parasympathetic fibres to the ciliary muscles and the sphincter pupillae.

Trochlear nerve

This 4th cranial nerve is the longest and the thinnest of all the cranial nerves. It first exits from the dorsum of the brain stem. Then it winds around the brain stem and traverses along the lateral wall of the

cavernous sinus inferior to the oculomotor nerve. After that it, enters the orbit through the superior orbital fissure, outside of the annulus of Zinn. In the orbit it passes forward near the roof and supplies the superior oblique muscle from its orbital surface. As the motor supply of the superior oblique muscle is from the outside of the cone of rectus muscles, so there may be some retained activity of the superior oblique muscle (intortion), following a small volume of intraconal local anaesthetic injection. The functional components of the trochlear nerve are: (i) the somatic efferent for the movement of eyeball and (ii) the somatic afferent for the proprioceptive impulses from the superior oblique muscle. At the cavernous sinus the fibres carrying the proprioceptive impulses leave the trochlear nerve and join the ophthalmic division of the trigeminal nerve. These fibres relay into the mesencephalic nucleus of the trigeminal nerve.

Abducent nerve

The abducent nerve is designated as the 6th cranial nerve and supplies the lateral rectus muscle only. It emerges from the CNS at the groove which is situated between the medulla and the pons (pontomedullary junction). Then, it ascends on the brainstem and makes a sharp bend over the petrous part of the temporal bone. After that it enters the cavernous sinus where it lies between the internal carotid artery medially and the trigeminal ganglion laterally. In the laterval wall of the cavernous sinus the nerve lies inferior to the oculomotor and trochlear nerves, but internal carotid artery lies superomedial to it. During the intracavernous course, the abducent nerve is joined by some branches from the sympathetic nerve which supplies the dilator pupillae. Then, the abducent nerve enters the intraconal space of the orbit through the superior orbital fissure but within the common tendinous ring, lying inferolateral to the oculomotor and the nasociliary nerve. It supplies only the lateral rectus muscle from its ocular surface (Fig. 41.19).

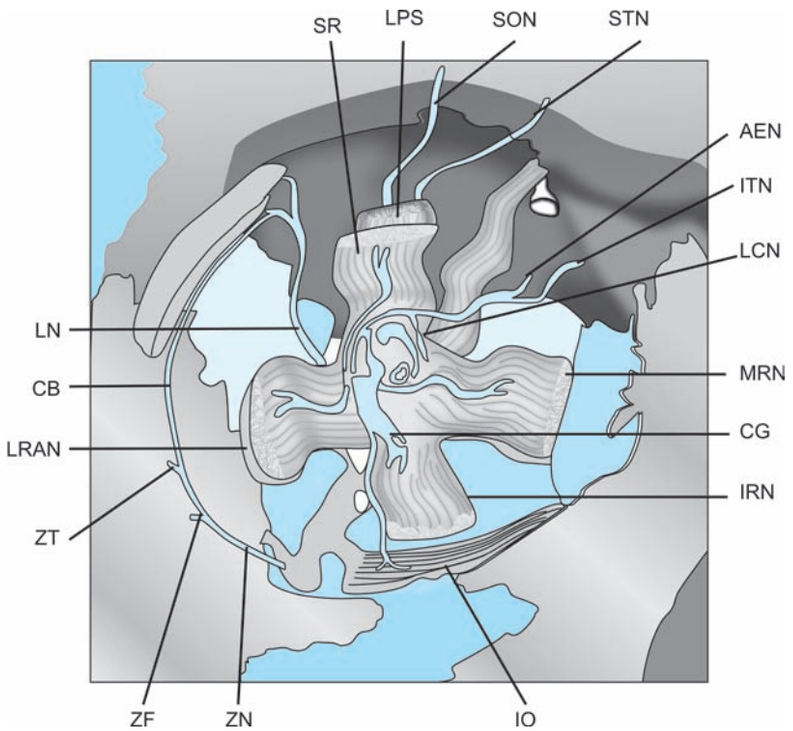
Trigeminal Nerve

The trigeminal nerve is the 5th and the largest cranial nerve. It is the nerve of the 1st brachial arch. The functional components of the trigeminal nerve are: (i) general somatic afferent which carries the sensation from the eyeball, lacrimal gland, conjunctiva, whole of the face, anterior half of the scalp, the auricle and the oral and nasal cavities, (ii) efferent fibres carrying motor to the muscles of mastication, tensor veli palatini, tensor tympani, the mylohyoid and the anterior belly of digastric muscle.

It arises from the ventral surface of the pons by two roots: a small motor root and a larger sensory root. These two roots then run forwards towards a notch at the upper margin of the petrous part of the temporal bone. After crossing the superior border of the petrous bone, the two roots then enter the middle cranial fossa to join the trigeminal ganglion. This trigeminal Gasserian ganglion is the sensory ganglion of trigeminal nerve. The sensory fibres are relayed and rearranged within this ganglion and gives emergence to the ophthalmic nerve, maxillary nerve and mandibular branche (only sensory part of the mandibular nerve) to form the mandibular nerve. The motor root passes inferior to the ganglion, and joins with mandibular branches to form the mandibular nerve.

Ophthalmic nerve

It is completely a sensory and is the smallest division of the trigeminal nerve. It supplies the eyeball, lacrimal gland,



SR – Superior rectus, LPS – Levator palpebrae superioris, SON – Superior orbital nerve, AEN – Anterior ethmoidal nerve, ITN – Infratrochlear nerve, LCN – Long ciliary nerve, MRN – Medial rectus and nerve, CG – Ciliary ganglion, IRN – Inferior rectus and nerve, IO – Inferior oblique, ZN – Zygomatic nerve, ZF – Zygomatico facial nerve, ZT – Zygomaticotemporal nerve, LRAN – Lateral rectus and abducent nerve, CB – Communicating branch, LN – Lacrimal nerve

Fig. 41.19: Orbital nerves from the front

conjunctiva, eyelids, forehead, scalp, nasal mucosa and the skin of the nose. After arising from the trigeminal ganglion, it runs forwards through the lateral wall of the cavernous sinus but below the oculomotor and the trochlear nerve. In the front of the cavernous sinus, the ophthalmic nerve then divides into three branches such as the lacrimal, frontal, nasociliary nerve which pass separately through the superior orbital fissure. The lacrimal and frontal nerves pass outside of the annulus of Zinn and the nasociliary nerve passes through the annulus of Zinn of superior orbital fissure (Fig. 41.20).

The lacrimal nerve enters the orbit as the lateral most structure through the surperior orbital fissure. Then, it runs forwards along the upper border of the lateral rectus muscle to enter the posterior border of the lacrimal gland. Besides supplying the secretomotor fibres to the lacrimal gland, it also innervates the most lateral part of the skin of the upper eyelid and adjacent conjunctiva. The lacrimal nerve also receives a branch from the zygomatico-temporal nerve. This branch carries the post-ganglionic parasympathetic fibres which are secretomotor to the lacrimal gland. The origin of this preganglionic parasympathetic fibres is in the lacrimatory nucleus which is situated in the lower part of the pons. The fibres arising from this nucleus first run through the nervous intermedius part of the facial nerve. Then, they run through the greater petrosal branch of the facial nerve and joins with the deep petrosal nerve to form the nerve of the pterygoid canal. Here the fibres make connection with the post-ganglionic fibres in the pterygopalatine ganglion. Then the postganglionic fibres arising from the pterygopalatine ganglion enter the maxillary nerve and passes through its zygomatic branch and then its zygomaticotemporal branch to join the lacrimal nerve.

The frontal nerve which is a branch of the ophthalmic division of the trigeminal nerve enters the orbit through the supraorbital fissure above the anular tendon and traverses between the LPS and the periosteum. At the midway between the apex and the anterior margin of the orbit, it divides into two branches: supraorbital and supratrochlear. The supratrochlear nerve runs anteromedially above the trochlea and supplies the skin of the upper medial part of the upper eyelid, medial conjunctiva and the skin of the scalp. The supraorbital nerve passes forwards and emerges at the front of the orbit, either through the supraorbital foramen (20%) or notch (80%). It provides sensation to the rest of the forehead, anterior 2/3 of the scalp, the skin of the upper central part of the eyelid and the adjacent conjunctiva. Thus, the peripheral conjunctival sensation is mediated via the lacrimal and the frontal nerves, both of which do not course through the intraconal space. So, incomplete conjunctival anaesthesia may result from a small volume of intraconal local anaesthetic injection.

The nasociliary branch of the ophthalmic division of trigeminal nerve passes through the annulus of Zinn. Then, it enters the intraconal space and sends a communicating branch to the ciliary ganglion. As it passes over the optic nerve, the long ciliary nerves (3 or 4 in number) are given off from it. These long ciliary nerves accompany the short ciliary nerves and then pierce the sclera close to the optic nerve. In addition to the afferent sensation from the iris, ciliary body, cornea and the central bulbur conjunctiva, these nerves also carry the sympathetic motor fibres to the dilator pupillae muscle. After passing over the optic nerve, the nasociliary nerve runs along the medial orbital wall in close relationship with the ophthalmic artery. Here, it gives off the anterior and posterior ethmoidal branches which pass through their respective foramina on the medial orbital wall and supply the mucosa of the ethmoidal sinuses and the nasal cavity. The most anterior division of the nasociliary nerve is the infra- trochlear nerve. It runs along the superior border of the medial rectus muscle and penetrates the orbital septum to innervate the skin of the side of the nose, the medial side of the skin of the lower

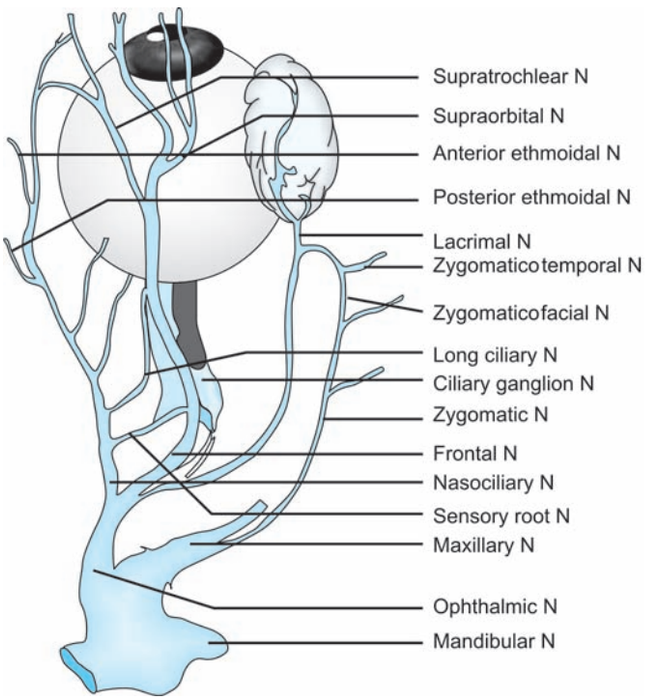


Fig. 41.20: Nerve supply of the orbit

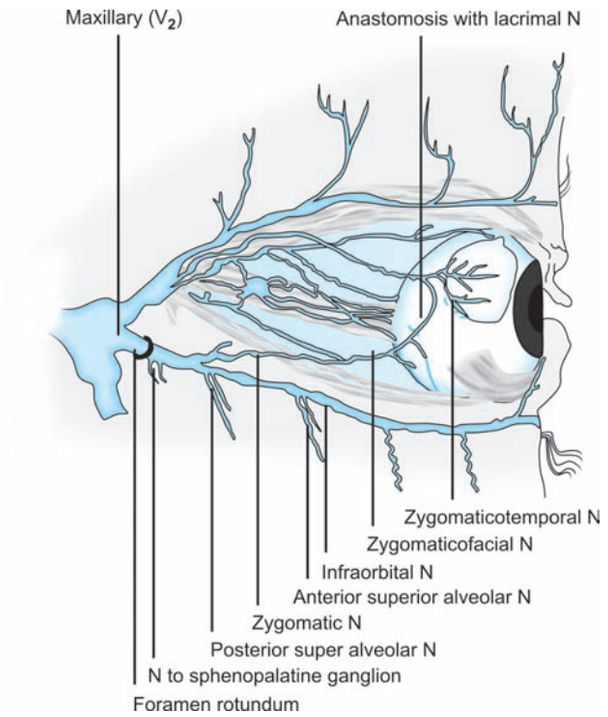


Fig. 41.21: Nerves of the orbit

eyelid, the adjacent conjunctiva and also the lacrimal sac (Fig. 41.21).

Maxillary nerve

The maxillary nerve is the second division of the trigeminal nerve. It is completely a sensory nerve supplying the middle portion of face, anterior temporal region, lower eyelid and the upperlip. It also supplies the sensation to the upper gums and teeth, the mucous membrane of upper mouth, nasopharynx and the maxillary sinuses. After emerging from the trigeminal ganglia, it runs forwards through the lateral wall of the cavernous sinus. Then, it exits from the cranial cavity through the foramen rotundum and enters the pterygopalatine fossa. Here, it sends branches to the pterygopalatine ganglion. After crossing the pterygopalatine fossa, the maxillary nerve enters the orbit through the infraorbital fissure, where it is known as the infraorbital nerve. Passing anteriorly, this nerve lies in the infraorbital groove. Then, it descends through the infraorbital canal to reach the front of the face at the infraorbital foramen which is situated 1 cm below the midpoint of the infraorbital rim. The infraorbital nerve supplies the skin of the lower eyelid, nose, upperlip and the central part of the face. In the pterygopalatine fossa the maxillary nerve gives off its zygomatic branch. This branch then enters the orbit through the infraorbital fissure and divides into zygomatico-facial and zygomatico-temporal nerves. The former exits through a foramen which bears the same name and supplies the skin overlying the malar bone. The later also travels a short distance along the lateral orbital wall. Then, it exits through a foramen, bearing the same name and innervates the skin of the anterior temporal region.

The preganglionic parasympathetic secretomotor fibres to the lacrimal gland emerge from the brainstem with the facial nerve. Then, it is transferred to the trigeminal nerve by a complex pathway and travels through the maxillary nerve. It relays in another peripheral ganglion of the parasympathetic system, named the sphenopalatine ganglion. This ganglion lies in the pterygopalatine fossa. From the ganglion, the postganglionic parasympathetic fibres reach the lacrimal gland, via the interconnections between the zygomatico-temporal and the lacrimal nerve.

There is a great anatomical proximity of the central and peripheral orbital nerves, with their shared innervating adipose tissue compartments and the skin. This explains easily the widespread area of the peripheral sensory block, associated with the intraorbital regional anaesthesia. The spread of to intraorbital regional anaesthetic block the frontal nerve complex in the superior orbit and the maxillary nerve complex in the inferior orbit results in a unilateral loss of sensation, which extends from near the occiput above to the upper lip below, and from the mid-line of the nose to the anterior temporal region laterally, including anaesthesia of the mucosa of the upper mouth and teeth and the nasal cavity. So, patients usually experience unilateral nasal stiffness or nasal block, andfeel that their nose is running.

Mandibular nerve

The detailed anatomy of the mandibular nerve has no direct importance to an ophthalmic anaesthetist. So, it will not be discussed here in detail.

Facial Nerve

It is the VII cranial nerve and is the nerve for the 2nd brachial arch. The functional components of facial nerve are:

i. Efferent fibres for all the facial muscles of face,
ii. General visceral parasympathetic efferent fibres for the submandibular and sublingual salivery glands and also for the lacrimal, nasal, palatine and the pharyngeal glands,
iii. Special visceral afferent fibres for taste sensations from the presulcal area of the tongue (anterior 2/3) and palate,

iv. General somatic afferent fibres from the concha of the auricle.

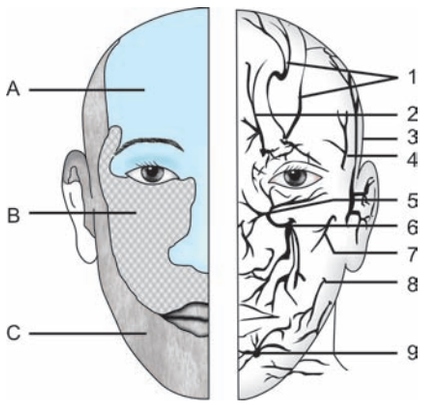
Among all the functional components of the facial nerve, only the efferent component for the the facial muscles is of the main interest to an ophthalmic anaesthetist (Fig. 41.22).

Facial nerve originates in the pons. Then, it exits from the base of the skull at the stylomastoid foramen in close proximity to the glossopharyngeal, vagus and spinal accessory nerves which are emerging from the jugular foramen. Here, the whole branchiomotor component of the facial nerve comes out, except the fibres going to the stapedius muscle. The landmark of the stylomastoid foramen is 2 cm deep and medial to the anterior border of the mastoid process. So, block of the facial nerve at this level results in a complete hemifacial akinesia and spread of injected local anaesthetic agent to the other adjacent major cranial nerves. After its exits from the stylomastoid foramen, the facial nerve first crosses the styloid process of the temporal bone. Then it passes under the external auditory meatus and enters the substance of the parotid gland through its posterior border. At this level, the facial nerve supplies the occipitalis, auricularis posterior and superior (through its posterior auricular branch), stylohyoid and the posterior belly of diagastric muscles. Inside the parotid gland the facial nerve divides first into two main divisions and then subsequently into several branches such as temporal, zygomatic, buccal, mandibular and cervical. However, the pattern of this break-up and distribution of the branches of the facial nerve within the parotid gland varies greatly between individuals. The temporal branch supplies the intrinsic muscles on the lateral surface of the auricle and the auricularis anterior, auricularis superior, frontalis, orbicularis oculi, and corrugator muscles. The zygomatic branch supplies the orbicularis oculi. The buccal branch supplies buccinator, small muscles of the nose, levator anguli oris, levator labi superioris and zygomaticus major. The mandibular branch supplies the depressor anguli oris, depressor labi inferioris and mentalis muscle. The cervical branch supplies only the platysma muscle (Table 41.1).

The fibres carrying the secretomotor and special sense (taste) component of the facial nerve are discussed in table. The effarent or motor components of the facial nerve, which hold the interest of an ophthalmic anaesthetist are the upper branches of the facial nerve such as the temporal and the zygomatic branches. This is because they innervate the forehead and the eyebrow musculature (frontalis) and the three components of the orbicularis oculi. It is also important to remember that all the facial muscles which are supplied by the facial nerve are innervated from their deep surface. So, block of the peripheral distribution of the terminal fibres of the facial nerve depends on the block technique. This is because if local anaesthetic drugs are injected superficial to the facial muscles, then they may not spread to their deep surface effectively. So, this will frequently cause poor abolition of their muscles action. Usually, the orbital rim, the zygomatic arch, the mastoid process and the temporomandibular joint form the important bony landmarks which are used for the peripheral facial nerve blocks (Fig. 41.23).

APPLIED ANATOMY

The matrix of the connective tissues of orbit supports the different structures of it, allows the dynamic function of the



A-Ophthalmic division
B-Maxillary division
C-Mandibular division
} of the Vth Cranial N

Fig. 41.22: Sensory nerve supply of the face. 1. Supraorbital N, 2. Supratrochlear N, 3. Auriculotemporal N, 4. Zygomaticotemporal N, 5. Infratrochlear N, 6. Infraorbital N, 7. Zygomaticofacial N, 8. Buccal N, 9. Mental N

Table 41.1: Fibres carrying the secretomoter and special sense (taste) component of facial nerve

Secretomotor

- Facial nerve → Chorda tympani N → lingual N → Submandibular ganglion (relay here) → Post-ganglionic fibre → Supply → Submaxillary and sublingual salivery gland.
- Greater superficial petrosal N → along nerve of pterygoid canal → pterygopalatine ganglion (relay here) → Post-ganglionic fibres run.
  - Along palatine nerve to the glands of the palate
  - Along zygomatic nerve → Along zygomaticotemporal N → Along communication with lacrimal N → Lacrimal N → Lacrimal gland

Taste

- From anterior 2/3 of tongue and gums except the papillae vallatae → along lingual nerve → along chorda tympani nerve → along facial N → to geniculate ganglion → from here axon starts.
- From palate → along palatine nerves → through pterygopalatine ganglion (no relay) → along nerve of the pterigoid canal → along greater superficial petrosal nerve → to geniculate ganglion → from here axon statrs.

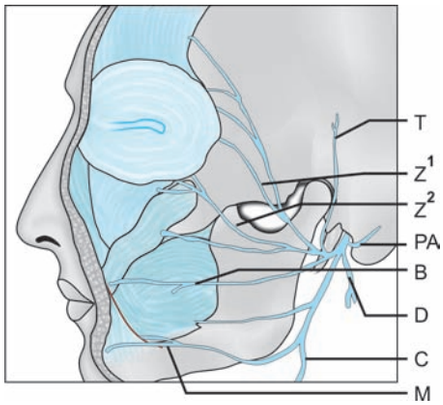


Fig. 41.23: The branches of the facial nerve. T–Temporal branch, Z^1 and Z^2-Upper and lower zygomatic branch, PA-Posterior auricular branch, B-Buccal branch, D-Branch to posterior belly of digastric and stylohyoid, C-Cervical branch, M – Mandibular branch

eye-ball and limits the spread of the locally injected anaesthetic agents. The sensory anaesthesia of globe and conjunction results from the conduction blockade of intraorbital part of the ophthalmic branch of trigeminal nerve. On the other hand, globe akinesia is achieved by the conduction blockade of the intraorbital portions of the cranial nerves, such as III (oculomotor), IV (trochlear) and VI (abducent) nerves.

The branches of oculomotor nerve enters the muscle bellies of the four rectus muscles from their conal surfaces, 1 to 1.5 cm anterior from the apex of the orbit . The local anaesthetic agents have to reach at least 5 to 10 mm exposed segment of these motor nerves in the posterior intraconal space to produce sensory block and akinesia of the muscles supplied by them. So, when the local anaesthetic agent is injected intraconally, it achieves the motor block more easily with a small volume than when an extraconal method is used. The motor branch of the oculomotor nerve which supplies the inferior oblique runs a long intraconal course. Therefore, it is most easily blocked by the intraconal injection. On the other hand, the trochlear nerve which runs a short intraorbital, but long extraconal course before entering the muscle at its superolateral edge, is most resistant to intraconal local anaesthetic injection.

The autonomic and the sensory nerves have a longer course within the orbit from their point of entry at the apex to the globe and their supplying structures than the motor nerves. So, the local anaesthetic agents have a greater access to these sensory and autonomic nerves and produce a faster block than their motor component. The corneal and perilimbal sensation is mediated through the nasociliary nerve which lies within the cone of muscles. So, the intraconal injection effectively produces anaesthesia of the cornea and the conjunctiva immediately surrounding it. The lacrimal, frontal and infraorbital nerves, suppling the peripheral conjunctiva, run outside the muscle cone. So, surgical pain may be experienced in this area, following a solely intraconal block.

BLOOD VESSELS OF THE EYE AND THE ORBIT

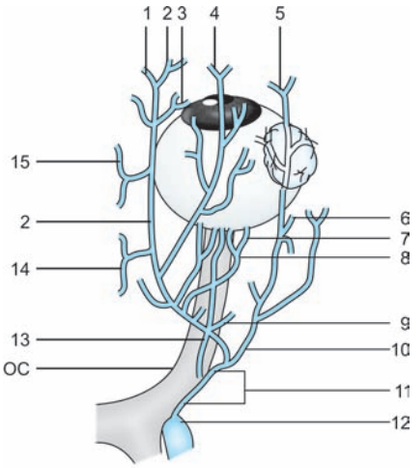
Generally, in the body arteries and veins travel together. But, in the orbit the arteries and veins behave differently. They run independently according to their anatomical distribution. The veins of the orbit do not accompany their corresponding arterial system, but rather take their own course and direction. The arteries of the orbit radiate from the apex towards their target organs, and perforate the connective tissue septa while passing from one compartment to the next. However, the veins run circularly and are confined to the connective tissue septa, without perforating it. In general, the arteries are located centrally in the intraconal space at the apex of the orbit, and superiorly at the anterior part of the orbit. Whereas veins are located peripherally, mainly outside of the intraconal area. The posterior part of the intraconal area has a high arterial density with addition of some venous drainage system from the retina. Considering the arteries and veins as a common entity, the posterior orbit on the lateral side has the greatest vascular constellation, whereas in the anterior orbit most of the vessels are found medially.

Arteries

There is much variability between the individuals, regarding the anatomical layout of the orbital arterial system. The orbital arterial system predominantly consists of the ophthalmic artery which is the branch of internal carotid artery. There are also variations of contributions in supplying the orbital arterial system from the external carotid artery.

The ophthalmic artery arises from the internal carotid artery when this vessel emerges from the root of the cavernous sinus, medial to the anterior clinoid process. Then, the ophthalmic artery enters the orbit through the optic canal, infero-lateral to the optic nerve and both of them lie in a common sheath of dura. In the orbit it pierces out the duramater, winds around the lateral side of the optic nerve and then passes forward and medially above it but below the ciliary ganglion (in 80%) between the superior ophthalmic vein in front and the nasociliary nerve behind. In 20% cases the ophthalmic artery does not pass above, rather lies underneath the optic nerve which is a more vulnerable position of it for injury by needle, directed towards the orbital apex during the local block (Fig. 41.24).

When the ophthalmic artery lies below the optic nerve, it gives off the first branch, called the central retinal artery. It pierces the dural sheath of the optic nerve, usually from its inferomedial aspect and 1 to 2.5 cm posterior to the globe, to reach the centre of the optic nerve. This tiny vital artery then runs forward within the core of the optic nerve and emerges at the optic disc where it divides into multiple retinal arteries supplying the retina. When the ophthalmic artery turns round and reach above the optic nerve, then it gives off the second branch, named the lacrimal artery. The lacrimal artery passes forward along



1. Dorsal nasal artery, 2. Supratrochlear artery, 3. Medial palpebral artery, 4. Supraorbital artery, 5. Lateral palpebral branch, 6. Zygomatic branch, 7. Long and short posterior arteries, 8. Muscular branch of lacrimal artery, 9. Muscular branches of ophthalmic artery, 10. Lacrimal artery, 11. Ophthalmic artery, 12. Internal carotid artery, OC-Optic canal, 13. Central retinal artery, 14. Posterior ethmoidal artery, 15. Anterior ethmoidal artery.

Fig. 41.24: Arterial supply to the orbit

the upper border of the lateral rectus muscle and terminates as superior and inferior lateral palpebral arteries for each eyelid. These superior and inferior lateral palpebral arteries anastomose with the medial superior and inferior palpebral arteries. In its course, the lacrimal artery gives of multiple branches such as the muscular, zygomatic and recurrent meningeal arteries and branches to the lacrimal gland. The recurrent meningeal branch passes back through the superior orbital fissure, and anastomoses with the middle meningeal artery.

When the ophthalmic artery turns nasally above the optic nerve, it gives off some muscular branches to the rectus muscles, and the long and short posterior ciliary arteries. These long and short posterior ciliary arteries enter the globe after piercing sclera in association with the long and short ciliary nerves, close to the optic nerve. The long posterior ciliary arteries usually are two in number. They course forward within the globe, deep to the sclera and supply the anterior part of the uveal tract. The multiple short posterior ciliary arteries also pierce the sclera like the long posterior ciliary artery, and supply the choroidal coat of the eye and the ciliary body. The anterior ciliary arteries arise from the different muscular arterial branches, and enter the globe close to the limbus. They supply the anterior parts of the uveal tract.

The ophthalmic artery then reaches the medial wall of the orbit and passes forward along the this wall between the medial rectus and the superior oblique muscles. At the medial end of the upper eyelid the ophthalmic artery divides into two terminal branches, the supratrochlear (sometimes called the frontal artery) and the dorsal nasal artery. After the ciliary arteries are given off when the ophthalmic artery touches the medial wall of the orbit, it gives off a branch, named the supraorbital artery. This branch courses forward with the nerves of the same name. After the supraorbital artery, the ophthalmic artery while passing along the medial wall of the orbit gives off the following branches: posterior ethmoidal artery, anterior ethmoidal artery, and the superior and inferior medial palpebral artery. The ethmoidal arteries, as they exit through their respective foramina, anchor the ophthalmic artery to the medial wall of the orbit.

During regional anaesthesia any needle should not be introduced into this posterior 1.5 cm of the orbital apex. This is because large vessels are located there which may be the potential sources of any vision-threatening bleeding. These areas also contain vital structures, such as the optic nerve and the extraocular muscle's origins which are tightly packed there and may be subjected to serious damage due to bleeding or direct injury from the needle tip. There are, however, three adipose tissue compartments in the anterior and midorbital area, which are relatively avascular and are so preferred sites for local anaesthetic injection. These compartments are : inferotemporal, superotemporal and medial. The superotemporal space extends from the sagittal plane of the lateral limbus close to the roof and about 3 cm behind the orbital rim. In the medial space the needle entry point should be at the extreme medial end of the palpebral fissure on the nasal side of the caruncle. The needle should be directed upto the maximum distance of 2.5 cm in the transverse plane and 5 degrees medial to the direct sagittal plane. The superonasal quadrant should be avoided as an injection site, because it contains the end arteries of the ophthalmic artery, large venous connections between the facial angular vein and the superior orbital vein, and the trochlear mechanism of the superior oblique muscle. The transconjunctival injection is less likely to produce significant ecchymosis in comparison to the transcutaneous route.

Veins

The two principal veins that drain blood from the eyeball and other orbital structures are: the superior ophthalmic vein and the inferior ophthalmic vein. Among these two, the former is the most constant structure. The superior ophthalmic vein is formed by the confluence of major tributaries of the superior orbital vein, supratrochlear vein and the angular facial vein. The angular facial vein descends lateral to the nose, with the angular artery. It is subcutaneous and is often visible as a blue ridge, until it pierces the orbicularis oculi muscle. This vein complicates the surgical approaches to the lacrimal sac. It (the angular vein) is continuous with the facial vein and communicates freely with the cavernous sinus through the superior ophthalmic vein. After its formation, the superior ophthalmic vein runs backward along the medial boarder of the superior rectus muscle from where it enters the intraconal space. In the conal space, it runs further backward and laterally in a hammock-like structure of the connective tissue septa which is suspended under the superior rectus muscle, between it and the optic nerve. It again exits the intraconal space at the

lateral border of the superior rectus muscle. Here, it runs backward in the direction of the superior orbital fissure, through which it gains access to the cavernous sinus above the annulus. During its course, it accompanies the ophthalmic artery and receives tributaries that corresponds with the branches of the accompanying artery.

The inferior ophthalmic vein which is also called the inferior orbital vein begins at the floor of the orbit and collects the blood from the inferior orbital muscles, lacrimal sac and eyelids. It drains in the cavernous sinus either directly or after joining with the superior ophthalmic vein. It communicates with the pterygoid venous plexus through the inferior orbital fissure.

Other veins of the orbit and globe are: vortex vein, central retinal vein, middle ophthalmic vein and medial ophthalmic vein. The vortex veins are usually four or more in number. The superomedial vortex veins drain into the first part of the superior ophthalmic vein, while the superolateral vortex veins enter its third part. The inferior vortex veins join to form the inferior venous plexus. The central retinal vein leaves the optic sheath and joins the network of venules from the sheath. It drains usually in the superior ophthalmic vein. The middle ophthalmic vein arises near the lateral side of the medial rectus. It drains in the inferior venous network and joins the confluence of the superior ophthalmic vein with the cavernous sinus.

REGIONAL VERSUS GENERAL ANAESTHESIA

The term regional anaesthesia (RA) signifies the conduction block of a specific nerve or a group of nerves of a region by local anaesthetic agents. Whereas, the term local anaesthesia should be restricted to the technique of infiltration of local anaesthetic agent in a area of local tissue, resulting in blockade of only the nerve endings. On the other hand, topical anaesthesia implies to the action of local anaesthetic agents, when it is applied on the surface of epithelial tissues. After the discovery of cocaine as a local anaesthetic agent, the topical and regional anaesthesia became the cornerstone of many ophthalmic surgery. But, cocaine had many complications and in few cases was only taken as an alternative to GA which was at that time also not so improved and had a high mortality rate. After cocaine, many other local anesthetic agents were also discovered. These had no such problems like cocaine and hence established the local anaesthesia as first choice over GA in ophthalmology up to 1950. During that period with firm establishment of RA in ophthalmic surgeries as first choice, some ophthalmic surgeons still preferred GA, even though it was not so improved during those years. The causes behind their perference to GA over RA are : (i) Some surgeons did not believe in RA as local anaesthetic agents had just been developed, (ii) Some surgeons were not mentally prepared to wait for the local anaesthetic agent to act. (iii) Some surgeons thought that postoperative results were better with GA than RA, and (iv) Simply, some surgeons did not like to operate on a conscious patient.

Then, between 1950 and 1960 a swing back to GA from RA for most of the ophthalmic surgeries had again occurred. This is because improved drugs, machines and techniques for GA became available. During that period surgeons were also comfortable to perform surgeries under GA, as ophthalmic surgical techniques were not so improved matching with RA and surgical complication rates were high under RA. But, in the last part of that century and over the last two decades RA has been again supplanting GA for many ophthalmic surgical procedures. This is because surgical techniques were improved with the help of modern surgical equipments of higher technology. Thus, the average surgical time for cataract extraction and other complicated surgical procedures has markedly decreased and this may be one of the causes for preferring RA over GA, recently. This surgical improvement, in combination with the efficient scheduling of operation time and the predominant use of out-patient surgical facilities have made a high volume of patients-turnover possible. So, this form of practice again dictates itself to RA techniques, prohibiting GA for most of the ophthalmic surgeries, except in certain special cases.

Stress is a common and almost unavoidable factor during the perioperative period of ophthalmic surgeries performed under RA. It is associated with the release of catecholamines, cortisol and glucose in the circulation, and this is evidenced by the signs of tachycardia, hypertension and elevated blood glucose level. The increased plasma level of catecholamines in patients undergoing ophthalmic surgery under RA resulted primarily from the endogenous sources and sometimes secondarily (less important) from the exogenous sources. It is found that as an exogenous source 10 ml of local anaesthetic solution containing 1:2,00,000 epinephrine (5 µg/ml) causes no untoward clinical effect. It is also found that entry of a patient into the operating area for block or RA is the most significant stress factor, than the performance of block itself. So, for the perioperative management of a patient who is scheduled for ophthalmic surgery under RA adequate counselling during the first meeting with him is extremely important for successful attenuation of stress. This can be performed efficiently by repeated reassurance, preoperative visit with the anaesthetist, booklet, video, tape, etc. Many patients appreciate music as a distraction, before giving block. The simple act of having a staff member holding the hand of a patient during RA and surgery has a considerable calming effect. In extreme cases, judicious use of benzodiazepine (midazolam) orally or intravenously may be useful to reduce the stress response. But in an ambulatory setting the use of preoperative sedative medications

should be such that it allows the patients to be discharged promptly after completion of surgery (Table 41.2).

For a small percentage of elderly patients who are benefited from preoperative sedation, fine judgement is required to select the correct drug and dosage of sedative agent which are to produce only a calming effect, but remains alert and cooperative without respiratory depression. The advantages of RA over GA can be negated rapidly with the excessive use of sedation. The combination of RA with heavy sedation may produce a less satisfactory outcome than either methods on their own.

The time spent by an anaesthetist for establishing a good rapport with the patient is more effective in removing anxiety than depending on the pharmacological methods. To perform RA efficiently and successfully, the anaesthetist must have certain personality traits and good communication skills. This enables him to gain the patients' trust rapidly. This will also educate the patients, regarding the experiences that they have to face during operation. Thus property treated and prepared patients scheduled for ophthalmic surgery under RA will have a minimal anxiety and have a low incidence of perioperative complications. Sometimes, absence of such a skill in an anaesthetist may force him to take the decision in favour of GA.

Table 41.2: Respective advantages of regional and general anaesthesia. Advantage of one type of anaesthesia is a disadvantage for the other and vice versa

Regional anaesthesia (RA)

- Simple technique,
- Early recovery,
- Less hospital stay,
- Early discharge,
- Quick turnover,
- Less expensive,
- Better postoperative analgesia,
- Avoidance of oculocardiac reflex,
- No loss of control of patient,
- Less physiological change,
- Absence of respiratory depression,
- Full mental status retained,
- No risk of malignant hyperthermia.

General anaesthesia (GA)

- Complete control of patient,
- Risk of globe perforation is nil,
- Risk of intraorbital haemorrhage is nil,
- Risks of myotoxicity, nerve injury are nil,
- Risk of allergy to local anaesthetic agent is nil,
- Applicable to all ages,
- Preferable for teaching of surgery methods for trainees.

There is also a widespread of opinion that patients do better under RA than GA. But, scientifically it is very hard to prove, except in some specific cases. Multiple, major retrospective and prospective non-randomized studies have failed to favour one method of anaesthesia over the other. On the other hand, cataract surgeries which constitutes the main bulk of ophthalmic surgeries are more frequently performed on elderly patients. The more elderly a patient, the higher is the intrinsic risk of death. This should be added to the risk of death which is associated with the clinical intervention. The elderly patients are associated with multiple systemic diseases such as hypertension, coronary arterial disease, COPD, diabetes mellitus, obesity, etc. These are also added to the operative risk and presents an additional challenges to the operating team. It is also demonstrated that complication rate correlates well with the number of the associated diseases, rather than the age of the patient.

All the patients scheduled for ophthalmic surgery under GA or RA require proper preoperative assessment and preparation. They also need an open discussion regarding the risks and complications of anaesthesia and surgery which is based on a thorough history and physical examination. The whole system requires cooperation among the patients, their relatives, their family doctors, surgeons and the anaesthetists. A list of medications, currently taken by the patients is also required. Because it ensures that essential therapy can be continued through the time of surgery and potential drug interaction can also be anticipated. Necessary preoperative laboratory and radiological investigations should be done only when these are indicated, and appropriate for that particular patient or according to the ASA guidelines. Whatever is the method of anaesthesia regional or general, every effort should be made to have the patients in the best possible medical condition prior to surgery. Most ophthalmic surgeries are nonemergency. Therefore, the date of surgery should usually be postponed, until the medical status of each patient becomes optimal.

The decision of whether general or regional anaesthesia should be selected, is based on the consensus among the team members who are involved in the surgery including the patient. The choice of anaesthetic technique is usually predicted by the team's previous experience for that type of surgery on a particular group of patient (Table 41.3).

Whether RA or GA, the skill of application of the technique is more important for patient's morbidity and mortality than any academic discussion of the merits or demerits of the this two anaesthetic technique RA and GA. However, a high standard peri operative monitoring and anaesthetic skill must be maintained for both forms of anaesthesia. Usually, it is a common practice to select sick patients for RA, because they are unfit for GA. But it should be kept in mind that RA should be an alternative to GA for the more fit and healthy patients, and RA should always not be considered as an alternative means of anaesthesia for operating on unfit patients. This is because unfit patients do not co-operate well even under RA for prolonged periods. Thus, the tragedy is that the patients who are unfit for GA cannot be selected under RA, and vice-versa.

Before selecting the patients for GA, few things can be tried or followed which may help to perform surgery under RA instead of GA. For example in the management of patients with mild to moderate degrees of senile dementia or mental

Table 41.3: Contraindication to regional and general anaesthesia with decreasing order of importance from absolute at the top of the table. Contraindication of RA is indication to GA and vice versa

Regional anaesthesia (RA)
Refusal of informed consent by the patient
Surgeon preference for GA
Surgery for open eye injury
Prolonged surgery (more than 2 hours)
Children up to the age of early teens
Unsuitable psychological status
Psychiatric disorders
Uncooperative patient
Mental retardation
Senile dementia
Communication barrier
Language
Deafness
Head tremor or movement
Parkinsonism
Tardive dyskinesia
Inability to lie flat
Severe arthritis
Respiratory diseases
Cardiac diseases
Claustrophobia
Previous complication from RA
High myopia
Inexperience of anaesthetist on RA
True allergy to local anaesthetic agent
Patients on anticoagulants
Needle phobia
Intractable cough
General anaesthesia (GA)
Refusal of informed consent by the patient
Severe medical condition, ASA III or IV
History of difficult airway
History of serious adverse effect from previous GA History of malignant hyperthermia
Muscle diseases
Dystrophia myotonica
Myasthenia gravis
Haemoglobinopathies
COPD
History of porphyria
History of atypical pseudocholinesterase

retardation who are presented for ophthalmic surgeries under RA, a family member can hold hands with the patient and give verbal support in the operating room. It also acts in the same fashion in the presence of a language barrier, where communication with the patient becomes impossible which results in the choice of general anaesthesia. In such situations a family member can be recruited to interpret the language. When a patient with slight tremor of head is scheduled for ophthalmic surgery under RA, then Intravenous sedation in titrable doses can control the Parkinsonian head tremors effectively. Incomplete block can be best managed by further supplementation of drug. Because operation in the presence of partial regional anaesthesia or block failure puts the patients in a severe unpleasant and stressful experience. Use of IV sedation which is not up to the level of GA and is used to cover the block failure or partial block is hazardous and inappropriate. In such situations, full GA with all precautions and monitoring should be the real answer.

In the past, when the ophthalmic surgeries were performed under conventional GA then it was the traditional domain of an anaesthetist, while local regional block was the domain of an ophthalmologist. The ophthalmologists were also considerably reluctant to permit anaesthetists to perform the orbital regional anaesthesia. This is because, they believed that only the physicians of their own discipline had the necessary elaborate anatomical and technical knowledge to avoid serious complications during regional block. But, for the last two decades a change has been under way due to many reported or unreported deaths during RA by ophthalmologists. So, at present in many developed and under-developed countries idea to improve the patient care by increasing the involvement of an anaesthetist, including administration of regional block by them, has been given official sanction. The various commonly used methods of RA for ophthalmic surgeries are all completely blind procedures. So, multiple serious complications have been reported, following RA by efficient persons of both the disciplines. It does not depend on the person of any particular discipline who is administering the block. On the other hand, there is an obivious added disadvantage when acts both as an ophthalmic surgeon together with giving a complete attention to the patient's medical condition during surgery under RA, especially in the absence of an anaesthetist who can continuously monitor the patient. He can never give his undivided attention to the general condition of the patient which an anaesthetist can. Moreover, in the event of an emergency and serious cardiopulmonary complications, anaesthetists are more familiar with them and can perform better and more efficient cardiopulmonary resuscitative measures than their surgical colleagues. There is also no inherent reason why an anaesthetist who is proficient in various regional anaesthesia ouside the orbit should not become efficient in ophthalmic cases, too.

TECHNIQUE OF ORBITAL REGIONAL ANAESTHESIA

History

The history of anaesthesia for ophthalmic surgery dates back to over 2500 years from present date. The earliest authentic writings on this subject were those of Susruta who was an ancient Indian surgeon. He first described cataract surgery by couching, around 600 BC. Couching is nothing but pushing back the lens in the vitreous cavity by a blunt pressure on the eyeball. He also outlined the use of inhalational anaesthesia for this method but the name of the inhalational agent was not known and also described aseptic techniques. Later, Egyptian and Assyrian surgeons described the use of carotid compression to produce transient unconsciousness by cerebral ischaemia under which couching was performed. In the first century of AD, Dioscorides produced a soporific sponge from an extract of mandrate, boiled in wine and was used to produce unconsciousness.

After that twelve hundred years had passed without any advancement in the science of ophthalmic surgery and anaesthesia. Then, in the 13th century, a Spanish alchemist described a liquid which was produced by the mixture of sulphuric acid and alcohol to make the patient unconscious after inhalation of this liquid. He called this mixture as 'sweet vitriol'. But, in 1730, this substance was renamed as ether. However, during this period nobody except this alchemist knew the anaesthetic property of this compound. In 1818, Faraday discovered its anaesthetic effects accidentally. Up to that period, all the ophthalmic surgeries, mainly the cataract were done under GA produced by excessive consumption of alcohol, opium, etc.

In 1855, Gaedcke first extracted crude alkaloid from the leaves of cocoa plant. Then, 5 years later, it was purified and named as cocaine by Neiman. He noted that cocaine numbed the nerves of the tongue and deprived it from the feeling of taste. 25 years later, in 1884, Koller in collaboration with Sigmund Freud first used cocaine as a topical anaesthetic agent for minor surgery only of the conjunctiva. News of this discovery rapidly spread across the whole world. Then, in New York city an ophthalmologist named Dr Herman Knapp used cocaine in all the type of ophthalmic surgery by injecting if in the orbital cavity and published his work in December of the same year. This publication also inlcuded his own work on retrobulbar injection of cocaine. He had done this for painless enucleation of an eyeball. But, subsequently serious toxic effects and death were experienced by the other surgeon with the use of cocaine which was injected in large doses for nerve blocks, particularly in general surgery. This dettered the other ophthalmologists from using cocaine for regional anaesthesia in ophthalmic surgeries, until well up to the twentieth century. But, topical anaesthesia using cocaine continued, apparently successfully, for minor conjunction surgical procedures and all other ophthalmic surgeries were done under G.A.

During the early part of the twentieth century adrenaline (in 1901) and procaine (in 1905) were discovered. After that, various and much safer regional anaesthetic techniques were developed in general surgery which was accomplished with larger doses of local anaesthetic agents other than cocaine. But, unfortunately this was not introduced into the ophthalmological practice for many years. Then, in 1914, Van Lint first reported his classical facial nerve block technique, using procaine. This removed the problem of suddenly high rise of IOP by forceful contraction of the orbicularis oculi muscle, during ophthalmic surgery. This akinesia of facial muscles were commonly used as an adjuvent to the topical anaesthesia for corneal and conjunctival surgeries and was in routine practice until 1930. Later, retrobulbar techniques in conjunction with facial nerve block for ophthalmic regional anaesthesia using procaine became wide spread instead of topical. Although, this retrobulbar block using cocaine as the local anaesthetic agent was first done in 1884 by Knapp, but he failed to popularize this method, until 1930.

From 1934 to 1964, Atkinson published many articles on regional anaesthesia for ophthalmic surgery. At this time, hyaluronidase was not available. He used only procaine and adrenaline. In 1936, he convinced all the opthalmologists that for best results the injection should be given within the muscle cone and just posterior to the globe. Atkinson also advocated that the inferotemporal quadrant is relativley avascular and the safe route for needle introduction into the orbit for regional block. During his period, many other persons like Lowenstein, Swan, Gifford, O'Brien, etc. also worked on the retrobulbar block by using procaine with different size, length and position of the needle and also with different volumes of the drugs. Then, came the peribulbar method which was also described long ago, in 1914 by Allen. But, this technique did not come into common ophthalmic practice, until 1986.

The whole scenario of this ophthalmic regional anaesthesia practice was changed dramatically after the lignocaine was synthesized by Lofgren and Lundqvist in 1943 and after the introduction of hyaluronidase around 1956. Lignocaine was first used clinically after its synthesis by Gordh in 1947. Then with the intorduction of mepivacaine in 1957 and its chemical modification such as bupivacaine in 1963, the stage was rightly set for dependable clinical ophthalmic regional anaesthesia practice to cover a wide range of ophthalmic surgical procedures and to provide greatly improved postoperative analgesia.

Practical Management and Patient Preparation

An anaesthetist who is totally devoting his practice on ophthalmic anaesthesia should have a thorough knowledge regarding the anatomy of orbit and eyeball, the physiology of eye and the pharmacology of the ocular and local anaesthetic drugs. It will enormously help him to prevent any criticism and opposition from any ophthalmologist during any complication which may occur of the fine of administration of RA. The anaesthetist who also wants to engage himself in this type of work is always encouraged to meet and observe some highly specialised ophthalmic centres which are operated by qualified personnel with wide experience and vast knowledge on this subject. The goal of each such practitioner is to build up an experimental database by himself from which later increasingly good judgement may result.

During ophthalmic operation, the required anaesthetic technique (RA or GA) is mainly dictated by the type of surgery, the surgeon's particular preference to the type of anaesthesia for that surgery and the wishes of the patient. So, a good understanding between the anaesthetist and the ophthalmologist's preference to the type

of anaesthesia for this surgery is essential. For example, some surgeons quarrel for complete akinesia, while some surgeons do not during cataract extraction. Again, it is not necessary or desirable in all the cases. Achievement of complete akinesia demands a higher volume of injected local anaesthetic agent, which may increase the intraorbital and subsequently the intraoccur pressure. This may also be of great disadvantage to some surgeons. Again, most surgeons may prefer globe hypotony. But, some surgeons may not prefer it and there may be certain situations where this becomes undesirable.

On the other hand, ophthalmic surgeons who are operating under regional anaesthesia must know how to deal with an awake patient on the operating table. It is unwise for an ophthalmic surgeon to ask repeatedly whether the patient is feeling pain or not. If the achievement of complete motor akinesia is used as the yard stick of block effectiveness, then pain will not be experienced. This is because motor fibres are blocked only after the block of sensory fibres. In such situations, appreciation of touch and tissue movement by the patient (proprioceptive sensation) may be interpreted wrongly as pain in the nervous patients. If the local anaesthesia is not adequate, then it is usually not difficult to recognise it by an anaesthetist. But if it is not i.e. when the block is very good then it is a bad practise to take suggesstion from the patient. Again, it will make the patient feel that the surgeon does not have the required confidence on the surgery and anaesthesia. The surgeon who knows better and trusts a carefully selected anaesthetic team by himself should start the operation without any confusion. At the same time, he should be aware of any significant non-verbal responses due to pain on the part of the patient.

Most of the patients presenting for ophthalmic surgery are at the extremes of age. Again, majority of eye surgeries consist of cataract extraction and are performed as day-cases under local anaesthesia. As most patients are elderly, they have many serious systemic diseases. So, preoperative assessement and preparation of the patient undergoing ophthalmic surgery under regional anaesthesia is same as that of general anaesthesia. On the other hand, in many centres, patients undergoing cataract extraction under RA do not warrant routine investigations. But, more stress is given on the psychological aspect of the patient for preoperative preparation. All the patients should receive a careful explanation of the procedure, that lies ahead on the day of surgery.

Whatever may be the type of surgery and anaesthesia (even topical) an informed consent from the patient is mandatory. During the period of preanaesthetic examination, preparation and taking consent, the patients should be given the opportunity to ask questions and receive answers. Premedication may or may not be indicated. Care should be taken during application of sedative premedication on very elderly patients. Oral sedation may produce pleasure in some patients, but some may complain of vertigo and dislike it. But as a whole, the use of short acting oral benzodiazepines as premedication is beneficial for most of the patients.

The preoperative fasting protocol for regional anaesthetist is similar to that of general anaesthesia. Clear fluid may be given 3 hours before sending the patient to the anaesthsia room. But, some clinics or hospitals maintain their own fasting protocol for regional anaesthesia. They do not routinely make starve such patients and provide a light meal 2 to 3 hours before operation, thinking that it is less disruptive for the elderly population and also facilitates better diabetic control. Regular medications should be continued up to and also on the day of surgery, including anti-hypertensives, anti-diabetics, anti-coagulants, anti-inflamatory, anti-asthamatic drugs, etc. Prophylactic antibiotic are generally not considered necessary for patients with cardiac lesions, undergoing routine anterior chamber (cataract) surgery. In patients receiving anticoagulant therapy, INR should be kept less than 2.5. Whenever required, the anticoagulant therapy should be adjusted to reduce the INR to less than 2.5. If this is considered inappropriate, e.g. in patients with artificial heart valve, then the relative risks of GA must be considered. An alternative option is to use the subtenon's approach or just topical anaesthesia.

Preoperatively, the axial length of the eyeball should always be measured in all cases. In severe myopic patients (axial length > 26 mm) the globe often has a long anteroposterior diameter (sausage-shaped eye ball). This increases the likelihood of globe perforation during regional anaesthesia which is diagnosed by sudden pain during injection, loss of vision, poor red reflex or vitreous hemorrhage. So, where axial length is greater than 26 mm, then single medial canthus injection, subtenon's approach, topical anaesthesia or GA should be considered. Hearing aids and dentures are left in place during RA.

It is a very good practice to set up a venous line routinely for all patients. Though, it is not a part of a planned routine intravenous therapy, but will be helpful in the event of an unplanned emergency intervention, calling for intravenous therapy. Good record keeping of every patient is essential. This includes medical history, health status of the patient, type and length of the surgical procedure, surgical complications, anaesthetic procedure and patient's reaction to it, etc. Anaesthetic record will include : used anaesthetic drugs, its volume and concentration, sites of injection, increased intraorbital pressure due to injection, decompression procedures, etc. Parameters of all the vital signs should also be measured and recorded. A foolproof system of checking of all the drugs and equipments in the anaesthetic room and operating theatre is essential. It will help to avoid dangerous errors and damage to the patients, particularly during emergency. It will also help in smooth and safe functioning of the whole

unit in operating suit. Personal or self-confidence of an anaesthetist is also acquired with repeated use of different regional anaesthetic techniques and tackling their complications. This in-turn will help the patients to be more stable, reassured and less dependent on sedative premedicant drugs.

History of claustrophobia is also very important. Because, many patients undergoing ophthalmic surgery are bothered to some degree with surgical drapes which encroach on their face. In such circumstances, alternative draping techniques or light intravenous sedation will be helpful. In extreme situations, general anaesthesia is indicated.

No patient should be left unattended in anaesthesia room and OT. Engagement of all the patients with light conversation by both the anaesthetist and the surgeon during both administration of anaesthesia and surgery is considered a good practice. Patients should be encouraged to express any difficulties on their part. By doing so, they act as their own monitor and are more reliable than any electronic gadget. While a surgeon is working with a particular patient, then conversation with a staff or an the anaesthetist or with another surgeon regarding other patients is inappropriate. This is because it is thought that this patient is not getting proper attention.

Most of the patients undergoing ophthalmic surgery are elderly. They are frequently suffering from arthritis, spondylytis, kyphosis, osteoporosis, etc, which are sometimes painful. So, it is frequently impossible for them to accomodate on the operating table for prolonged period-which have little or no head rest. Hence, intraoperative posture of a patient is very important. Ophthalmic surgeons usually prefer the patient's head in a horizontal plane under the microscope. But, the peculiar ophthalmic table with little or no head rest make it difficult for elderly patients to accomodate their head in this horizontal plane. This can be achieved by the necessary number of pillows under the occiput on the OT table.

Types of Surgeries which can be Undertaken Under RA

Usually, the type of surgery is not an important factor for selection of regional or general anaesthesia. Any type of surgery, except a few, can be performed under any type of anaesthesia. But most of the ophthalmic surgeries are performed under RA, except a few where intraorbital injection is contraindicated or topical cornea-conjunctival anaesthesia is not appropriate, or RA cannot be provided due to the patients health factors such as ASA III and ASA IV group of patients, The RA is also not applicable for ophthalmic surgeries in paediatric, psychiatric, cerebral palsy group of patients, etc. whose long list are given in table. The long list of surgeries which can be performed safely using regional anaesthesia are: cataract extraction with or without intraocular lens implantation, corneal transplantations, trabeculectomy, strabismus repair, lid surgeries, oculoplastic surgeries, vitreo-retinal surgeries, etc. But the main limitation of regional anaesthesia is its fixed time frame. Duration of operations extending beyond 2 to 2.5 hours tend to be rather difficult under RA. This difficulty is more applicable for conscious elderly patients who have cervical spondylosis or increased frequency of micturition due to enlarged prostate, or any other cause for which he is unable to lie supine for prolonged period. For regional anaesthesia a wide range of local anaesthetic drugs are now available, with which the duration of safe therapeutic time-window usually can be predictably planned. For example, 10 ml of 2% lignocaine with 1:2,00,000 adrenaline and 7.5 turbidity units of hyaluronidase per ml will produce a dependable 60 to 90 minutes of therapeutic time-window for complete akinesia. For surgical procedures lasting for 2 to 3 hours, such as vitro-retinal surgeries, long acting agents like bupivacaine or etidocaine should be the agent of choice. Because, both of these agents produce a therapeutic time-window of about 2 to 3 hours.

Retrobulbar or Intraconal Block

'Retrobulbar' or 'intraconal' are two clinically interchangeable word, because both usually signify the same space. But the 'retrobulbar' is a more vague term, as it indicates any space with in the orbit but behind the globe (or bulb) and may not be within the geometric confines of the four rectus muscles. Whereas the term intraconal block exactly signifies that the needle tip and the injection placement is within that space which is confined by the four rectus muscles. On the other hand, when the needle tip is placed and the local anaesthetic agent is deposited within the orbit, but not within the geometric confines of the cone of the rectus muscles, then it is called the peribulbar or periconal or periocular block. The peribulbar block may be posterior or anterior to the equator of the globe. When the peribulbar block is placed posterior to the equator of the globe, then it is called the posterior peribulbar or periconal block and when the peribulbar block is placed anterior to the equator of the globe, then it is called the anterior peribulbar block. The intraconal area is always posterior to the globe. So, there is no need to mention the word 'posterior' during its use. On the contrary, during the use of the name 'peribulbar' we can fix the word posterior with it, as there is also a peribulbar space anterior to the equator of the globe (Fig. 41.25).

During the intraconal or retrobulbar block, a straight needle with different lengths and sizes (discussed later), mounted on a syringe containing the chosen anaesthetic mixture is introduced within the orbit either transconjunctivally or transcutaneously. This site of introduction is through the inferotemporal quadrant of the orbit which commences at the junction of the lateral third and medial two-thirds of the inferior orbital rim. The safety of the retrobulbar block mainly depends on the proximity of the needle tip to the orbital wall at the

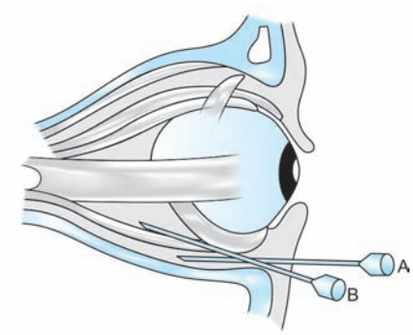


Fig. 41.25: Transcutaneous approach of intraconal block through inferotemporal space. In position A, the path of the needle is followed close to the orbital floor until the equator of globe is crossed. Then, in position B of the needle the angle of direction is changed upward and medially and is advanced to enter the intraconal space, posterior to globe

time of first entry and until the globe equator is passed. Initially, the inferotemporal orbital rim is palpated by the finger and its relationship to the globe is noted, including the orientation of the equator of the globe to the lateral orbital rim.

When the transconjunctival route is chosen for the retrobulbar block through the inferotemporal quadrant, then the tip of the needle enters the orbit just behind the inferior tarsal plate at the lower orbital rim. But, if transcutaneous route is used, then the lower lid is not retracted and the needle entry point would be inferior to the lower tarsal plate. The needle runs first parallel and close to the orbital floor with slight medial direction. In this direction when the needle crosses the equator of the globe, the angle of direction of the needle tip is adjusted upwards, medially and posteriorly as if the tip enters the cone of the muscles posterior to the globe. After crossing the equator for this direction the needle tip should be aimed at an imaginary point behind the globe on the axis formed by the central pupil and the macula in primary gaze position. During the advancement of the needle in the retrobulbar space, great care should be taken to avoid crossing the mid-sagittal plane of the globe. During either transconjunctival or transcutaneous route the tip of the needle should always run inferior to the lower border of the lateral rectus muscle, till it crosses the equator. During advancement of the needle the globe should be observed continuously to detect any rotation or movement that may indicate fixation of the needle in the sclera (Fig. 41.26).

The needle then enters the intraconal space by piercing the intermuscular septum, just inferior to the lower border of the lateral rectus muscle. During the advancement of needle the continuous observation of the relationship between the shaft and hub junction of the needle and the plane of the iris usually establishes an appropriate depth of insertion of the needle within the orbit.

The inferotemporal space for retrobulbar or peribulbar block is chosen for three reasons because :

i. It is relatively most avascular. The other two low vascular areas are superotemporal and medial compartment.
ii. The lateral orbital rim is set back from the line of the equator of the globe at the inferotemporal region.
iii. The space between the globe and the orbital rim for placement of the needle in deeper orbital structures is widest here.

To avoid trauma to the inferior oblique muscle or its motor nerve the inferotemporal needle placement should be lateral to the sagital plane of the lateral limbus. During injection the deposition of local anaesthetic agents directly into any of the extraocular muscles should be diligently avoided. Otherwise, direct muscle injury from the needle prick and myotoxicity from the local anaesthetic agent may result in a prolonged diplopia which may even become permanent.

Following negative aspiration test of blood the injection is performed, confirming the absence of abnormal resistance or the presence of atypical discomfort. If anyone is suspected, then the needle tip should be relocated. While injecting the drug, monitoring should be done visually and / or digitally for the increasing intraorbital volume and the intraconal pressure. The 3 to 4 ml of local anaesthetic mixture is injected very slowly over 2 minutes. Proper placement of the needle is indicated by bulging of the superior orbital sulcus which is accompanied by the filling out of upper eyelid crease and some degree of ptosis with proptosis. After injection is completed, the needle is withdrawn and a check for the bleeding is made. If there is any bleeding or sudden abnormal increase in the intraorbital pressure, then immediate digital compression over the eyeball should be instituted to minimize any potential complication from high intraorbital pressure which has built up in the orbit. During introduction of the needle, no attempt is made to contact with the bone of the orbital floor. This is because the tip of the needle may enter the infraorbital canal or fissure resulting in unpleasant infraorbital nerve paresthesia (Fig. 41.27).

Following injection, a period of gentle message or decompression by 'pinky' for about 2 to 5 minutes is done. Then, the effectiveness of the block is assessed by checking the globe movements, superior

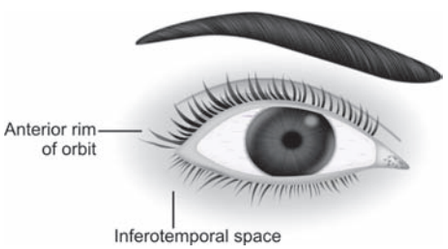


Fig. 41.26: The inferotemporal space which is wide and recommended for needle entry site for regional block

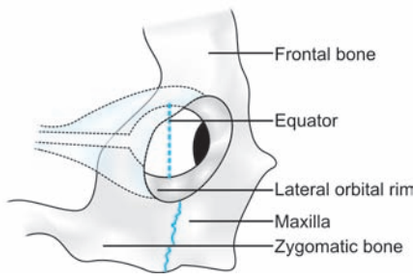


Fig. 41.27: The lateral orbital rim which is set back in line with the globe of equator. Thus, it makes the inferotemporal approach the route of choice for regional block

levator activity and orbicularis oculi function. If there is any ineffective block, then it can be completed by supplementation. The supplementing injections are : medial periconal injection and/or superotemporal periconal injection (which are discussed later).

The complications of retrobulbar intraconal block are:

i. Globe perforation (0.1 to 7%),
ii. Intravascular injection,
iii. Intraorbital haemorrhage (1%),
iv. Penetration and injection within the optic nerve sheath (0.3%) with resulting optic nerve damage, subarachnoid spread of local anaesthetic agent, brain stem paresis and cardiopulmonary arrest.

So, retrobulbar intraconal block for ocular surgeries is not recommended any more.

Peribulbar or Periconal or Periocular Block

In this method of ophthalmic regional anaesthesia, local anaesthetic agents are deposited outside the cone of the rectus muscles, but within the orbit and posterior to globe. So, it may be called as the posterior peribulbar block. When the local anaesthetic agents are deposited anterior to the equator of the globe and obviously outside the cone of the muscles, then it is called the anterior peribulbar block (Fig. 41.28).

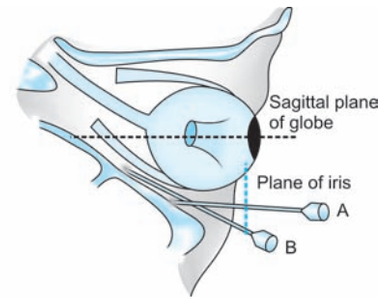


Fig. 41.28: Transcutaneous approach of periconal block through inferotemporal space. A 24 G 24 mm needle enters the orbit close to the bone (A). The needle then passes backwards in sagittal plane parallel to the orbital floor (B). It crosses the equation of globe up to a depth when the needle hub junction reach the plane of iris. This technique is equally applicable for transconjunctival route

The peribulbar or periconal block was first described as early as in 1914 by Allen. But it came into common practice only in 1986. Davis and Mandel first published papers on this method of peribulbar block. They used two routes : one below and one above the globe. Both the routes were chosen at the inferior and superior orbital margins respectively through the inferotemporal and the superotemporal quadrant of the orbit up to 3.5 cm, where near about 10 ml of the local anaesthetic solution was injected. Through both the routes the needles were directed to the floor or the roof of the orbit respectively, but not to the axis joining the centre of the pupil and the macula. Then, Bloomberg did more work on the peribulbar block. He entered the orbit only through the inferotemporal route, and the needle was directed to the floor of the orbit. In this method, there was a controversy regarding the failure rate and incidence of subsequent supplemental block. In some studies only 5% patients required supplemental upper superotemporal quadrant injection to achieve complete globe akinesia, while many studies reported up to 50% failure rate.

At that time, many other techniques of peribulbar block were also tried using many routes (inferotemporal, superotemporal, medial periconal, etc.) at a time in different permutation and combination, using needle of different lengths and sizes. They have a wide variation in results. Among all the combinations, three-needle-technique is the best, requiring only 5% supplemetation through the medial periconal route. This three-needle-technique consists of (i) preliminary subcutaneous or subpalpebral conjunctival (lower) infiltration of local anaesthetic agent which is followed by (ii) a second infratemporal intraconal injection and (iii) lastly a superotemporal periconal injection. But, whichever peribulbar technique is used, it is important to note that there is insufficient space between the lateral rectus and the lateral wall and the inferior rectus and the inferior wall of the orbit. So, true periconal block is very difficult or may be theoretical in inferotemporal quadrant.

After the introduction of the periconal block, many variations of this technique have developed which have already been discussed. But, the difference between the peribulbar and the retrobulbar block is that in peribulbar block the onset of akinesia is considerably slower, the volume requirement is greater and the supplementation rate is higher. In both the retrobulbar and peribulbar block the young patients are more resistant to total akinesia and analgesia of the globe and peribulbar tissue than the elderly. This is because the more dense connective tissues in the young patients hinder the access of the anaesthetic solution to the sensory and motor nerves, which are situated both in the intraconal and periconal spaces.

There are three main routes for peribulbar block :

i. Inferotemporal (most commonly used),
ii. Medial periconal,
iii. Superotemporal.

Types of needles

There are volume of discussion regarding the types of needles used for regional anaesthesia in ophthmology. But, the traditional teaching favours the use of dull tipped, intermediate size (gauge) needle. It has the advantage of pushing the blood vessels aside, rather than traumatizing them and the tissue planes are more accurately felt. There is also a common believe among the ophthalmologists, though it is not true, that it is more difficult to penetrate the globe and the optic nerve sheath with a blunt or dull tipped needle. But, multiple studies have shown that penetration or perforation of the eyeball by a dull needle (if it occurs) causes more serious damage than when a fine or sharp (i.e. of higher gauge) needle is used. Thus, it questions the arguments which advocate the use of blunt needles. Any needle, blunt or sharp, advanced blindly within the orbit has the potential of causing serious complications such as

globe perforation, optic nerve injury, and retrobulbar haemorrhage. Therefore, any serious practitioner of ophthalmic regional anaesthesia must keep a thorough knowledge of the anatomy and the contents of the orbit, rather than choosing the blunt or sharp needle. It is also found that pain and tactile discrimination is progresively reduced by decreasing the needle width, i.e, increasing the gauge (size). This is because, the increased resistance caused by a blunt needle is no more appreciated here due to the increased preload at the tip of the fine needle.

Special attention should also be paid to the length of any needle which enters beyond the orbital rim. However, at any circumstance, the intraorbital distance of 31 mm as measured from the orbital rim should never be exceeded. During the medial direction of the needle which advances from the inferotemporal entry point should be such that the mid sagittal plane of the eyeball should never be crossed. All the needles placed periconally or intraconally should be oriented tangentially with the bevelled opening facing towards the globe.

The force required to inject the local anaesthetic agent at a given rate through a given needle, mounted on a larger syringe, is more than a smaller syringe. This is because, a larger syringe has a greater plunger cross-sectinal area than a smaller one. So, a change in resistance while injecting 10 ml of the drug is more easily felt by the injecting finger when smaller size syringes are used. Here the fingers serve as a transducer. It relays information to the sensory cortex of an anaesthesiologist. The ability to detect the change in resistance during injection, (more or less easily), is very important for the avoidance of complications.

Facial Nerve Block

Before the era of retrobulbar and peribulbar block, the techniques of combining the corneoconjunctival topical anaesthesia with transcutaneous 7th cranial nerve block was in vogue. The facial nerve block causes the paralysis of orbicularis oculi muscle and prevents the squeezing or movements of the eyelids. During that period various methods of 7th cranial nerve block were introduced by Van Lint, Wright, O'Brien, Atkinson, Nabath & Rehman and Spaeth, etc. But, among these Van Lint is the most distal and Nabath-Rehman is the most proximal site of block for the facial nerve after its emergence from the base of the skull at the stylomastoid foramen. In Van Lint block the local anaesthetic drug is injected directly deep to the orbicularis oculi muscle and close to the bone at the lateral angle of the eye.

Before the days of hyaluronidase and the development of decompression devices, a small volume retrobular block with facial nerve paralysis at the stylomastoid foramen was the only choice for most of the ophthalmic surgeries under regional anaesthesia. But, with the discovery of hyaluronidase and the decompression devices the peribulbar block allows the injection of a large amount of local anaesthetic agent into the orbit. It has been observed that an effective spread of this adequate amount of local anaesthetic agent from the orbit through the orbital septum causes akinesia of the orbicularis oculi muscle, which makes the block of the 7th cranial nerve at the stylomastoid foramen unnecessary. The local anaesthetic drug spreads out from the orbit with the help of hyaluronidase into the deep plane of the orbicularis oculi muscle and abolishes the activity of lid closure by conduction blockade of the terminal divisions of 7th cranial nerve, entering from the muscle's deep surface. Thus, in the technique of peribulbar block using hyaluronidase and large amount of local anaesthetic agent in vast majority of cases sufficient blockade of the lid closure muscular activity is achieved. Hence, the painful transcutaneous 7th cranial nerve block through the sensitive facial skin is avoided and found to be unnecessary. So, the historical and traditional concept of globe akinesia and anaesthesia by retrobulbar injection and orbicularis muscle akinesia by direct separate intervention of the 7th cranial nerve after its emergence from the skull is not needed now. In an occassional patient who exhibits strong recruitment of the more peripheral fibres of the orbicularis oculi muscle and / or exibits excessive use of brow musculature, then only supplemental transcutaneous blocking of the orbicularis oculi by Van Lint method may be necessary.

Combined Retrobulbar (Intraconal) and Peribulbar (Periconal) Method

Multiple distinct techniques of injection for regional anaesthesia of orbit were studied. From this it was determined that a method of combining an initial intraconal (best through inferotemporal route) injection with a secondary periconal (best medialpericonal) injection is the most suited for the rapid turnover in day case ophthalmic practice. Alternatively, a technique with solely periconal placement of the local anaesthetic agent may be a more prudent practice for the relatively inexperienced practitoner.

This combined method consists of a preliminary injection of the local anaesthetic mixture, diluted with balanced salt solution, at subjunctional or subcutaneous level by a 30 G needle to anaesthetize the local area. It is followed by two full strength local anaesthetic injections in retrobulbar and peribulbar space. The first is an inferotemporal intraconal injection and the second is a medial periconal injection. The rational behind this three-needle – technique is to provide effective (i.e low supplementation rate) and safe (low complication rate) local anaesthesia and akinesia according to the requirements. This method is virtually pain-free. As a result preoperative and intraoperative sedation are usually not necessary, except a good rapport and assurance to the patient. This no-sedation approach avoids the problem of patients falling into a deep sleep during surgery and awakening precipitously with potential detrimental effects on the surgery in hand.

Inferolateral Periconal Block

This is the most commonly used technique for peribulbar or periconal block. Sometimes, it is supplemented with medial and / or superotemporal periconal block. This is because a single inferolateral injection is often inadequate and may not be predictable for complete anaesthesia and akinesia of globe.

After proper examination of the patient, an IV line is accessed and monitoring is started as a standard rule. If mild sedation is indicated, then it is administered by midazolam (0.5 to 1.5 mg) and /or fentanyl (50 µg) or sufentanil (150 µg). Topical local anaesthetic drops are instiled to anaesthetize the palpebral conjunctiva. For this purpose, 1% amethocaine or 2% xylocaine is sufficient, but it may cloud the cornea. So, 0.4% oxybuprocaine or 0.5% proxymetacaine may be a better alternative. This topical anaesthesia of the conjunctiva is only necessary for the transconjunctival route of the inferotemporal periconal block. The junction of the medial 2/3rd and lateral 1/3rd of the inferior orbital rim is palpated with the nondominant hand and a groove is felt at the junction of the maxilla and the zygoma. Just lateral to this point and 1 mm above the orbital rim a standard hypodermic needle (25G, 25 mm), mounted on a 10 ml syringe is inserted and passed slowly backwards perpendicular to all the planes. Needle entry can be either subcutaneous or transconjunctival (by retraction of the lower lid). If the needle tip touches the bone, it is redirected slightly superomedially to follow the orbital floor once more, i.e at a 10 degree angle with the transverse plane. The needle is advanced till its tip reaches the level of the posterior pole of the globe (i.e. until the hub reaches the plane of the iris).

The globe should be observed carefully for any sign of rotation during needle insertion into the orbit, indicating scleral contact. In such situation every temptation to wriggle the needle to confirm scleral engagement should be avoided. Because, this may increase the risk of haemorrhage if perforation of globe occurs. After proper positioning of the needle and aspiration, 6 to 8 ml of the local anaesthetic agent is injected slowly and at the same time the globe should be palpated with the other hand to assess the tension. If the globe becomes tensed or proptosed or the upper eye lid droops, then the injection should be stopped. Because, this likely indicates the retrobulbar injection, requiring much smaller volume of local anaesthetic agent. After completion of the injection the needle is slowly withdrawn and a small volume of the local anaesthetic solution is deposited under the orbicularis oculi muscle of the lower lid when the needle is withdrawn. Then, digital massage or a compression device (Hanon's Balloon) should be applied to dissipate the local anaesthetic solution within the orbital tissue, which quickly normalises the IOP. The block is assessed after 5 to 10 minutes and a second injection is repeated if a greater degree of akinesia and analgesia is required. In modern ophthalmic practice a completely akinetic eye is less often required and a second injection doubles the risk of complication. So, the required extent of the block should be discussed with the surgeon beforehand.

The larger volumes of local anaesthetic drugs which is required for peribulbar block tend to cause proptosis and a temporary increase in IOP. However, in the intact globe this has no significance. But, it becomes problematic when the globe is opened for surgery. After the dissipation of the drug in the surrounding orbital tissue with the passing of time, the raised IOP usually disappears. Alternatively, digital massage by the fingers or application of the Hanon's Balloon on the eyeball helps in dissipation of the drug. The Hanon's Balloon is a type of tamponade which is applied on the eyeball at a set pressure of 25 mm of Hg. This compresses the eyeball and transiently increases the IOP further. During compression, the volume of blood and aqueous in the eye is reduced. After release of the tamponade, the 'empty' eye becomes hypotonic and remains so for about 15 minutes, until the blood and aqueous volumes are re-established.

Medial Periconal Block

Here, the injection of local anaesthetic agent is administered into the fat compartment which is situated on the nasal side of the medial rectus muscle. This block has distinct advantages due to the relative avascularity of this region and the peculiar arrangement of the connective tissue in this area. Local anaesthetic mixture, injected into this area spreads to the orbital apex posteriorly, but its spread is restricted laterally by the intraconal compartment. Subsequently, the drug spreads anteriorly through the two hernial orifices which are situated above and below the medial check ligament of the connective tissue diaphragm that surrounds the globe just near its equator. The drug also passes through the orbital septum into the upper and lower eyelid in the tissue plane deep to the orbicularis oculi muscle. Here, the fine terminal motor branches of the 7th cranial nerve are readily blocked. Superiorly the access of local anaesthetic agent to the motor nerve supply of the superior oblique, superior rectus and levator complex is also facilitated. The injection of the local anaesthetic agent in this space also promotes the spread of the drug to the lacrimal and frontal nerves and the peripheral conjunctiva. Thus, it effectivley abolishes the intraoperative discomfort which is sometimes observed in the low-volume, solely intraconal technique.

The entry point of the needle for the medial periconal block is the small depression immediately medial to the caruncle. Caruncle is the specialized portion of the conjunctiva which occupies the extreme medial end of the palpebral fissure. Caruncle lies medial to the sagittal plane of the medial equator of the globe in almost all patients. So, there is no chance of perforation of the sclera by a needle when it enters

through this point. The needle should be passed in the transverse plane, directed towards the midline of the skull at the occiput. The medial compartment is 5 to 10 mm wide anteriorly at the equator of the globe, and 3 to 5 mm wide at the posterior surface of the eye. Then, it rapidly becomes narrower as the medial rectus muscle reaches its bony origin posteriorly. The needle must avoid the penetration of the medial rectus muscle, because injection of local anaesthetic agent directly into the muscle could result in myotoxicity with resultant prolonged paralysis or paresis. If there is any doubt, then the needle tip should hit the periosteum of the medial wall of the orbit, and withdrawn slightly to redirect with a lesser medial inclination. This allows the needle tip to be free in the fatty tissue the medial compartment. If the above mentioned guidelines are obeyed, then the entry of needle in the medial rectus muscle directly will not occur.

After proper placement of the needle volume of 2 to 4 ml of the drug is injected into this space. This volume of drug depends on the degree of supplementation block required, aiming at not to impede the desired goal of intraocular hypotomy. The residual activity of the extraocular musculature which persists even after the initial inferotemporal intraconal block is effectively abolished within 3 to 5 minutes in most cases, following the medial compartmental block.

Though, this compartment is relatively avascular but it contains a portion of the superior ophthalmic vein, the anterior ethmoidal artery, and the supra and infra trochlear arteries. But, they lie above the needle entry point. These vessels are traumatized if the needle enters through the supero-nasal quadrant of the orbit. In such situation the incidence of bleeding by a 30G and 31 mm needle is negligible and always minor in nature. As a whole, the medial periconal block is an effective and safe method of supplementation of the primary inferotemporal block. It is painless because, the needle entry point which is innervated by the nasociliary nerve, lies inside the cone of the muscles and is relatively well-blocked by the previous inferotemporal intraconal injection.

Supero-temporal Periconal Block

It mainly affects the superior rectus and the levator palpebrae superioris muscle. Even after the primary inferotemporal block, sometimes the acitvities of these muscles are retained. The explanation of this failure is that the injection of local anaesthetic agent through the inferotemporal region does not reach in sufficient quantities to the branches of the oculomotor nerve which supplies these muscles. Such a situation may arise, because the connective tissue hammock for the superior ophthalmic vein is usually well-developed in some individuals. This is partially permeable to the LA agent and prevents it from accessing the nerve in the central core of this compartment. So, by the superotemporal block the access of local anaesthetic to the nerve, supplying the muscle, like superior rectus and levator palpebrae superioris from above is possible.

The point of entry of needle for this block is the superior orbital rim and 3 to 4 mm lateral to the sagittal plane of the lateral limbus. Thus, this relatively avascular area lies between lacrimal vessels on the temporal side and the supra-orbital vessels on the medial side. The needle is inserted tangentially from above the globe which is directly towards the roof of the orbit with the eye to be blocked held closed. After making the first bony contact with the orbital roof, the needle is redirected 5 degree medially. Then, it is inserted posteriorly till the depth of 31 mm from the superior orbital rim is reached. Following negative aspiration test the 3 to 4 ml of local anaesthetic solution is injected in this position with the aim of not increasing the intraorbital pressure excessively. This superotemporal supplemental block is needed only in 5 to 10% cases (Fig. 41.29).

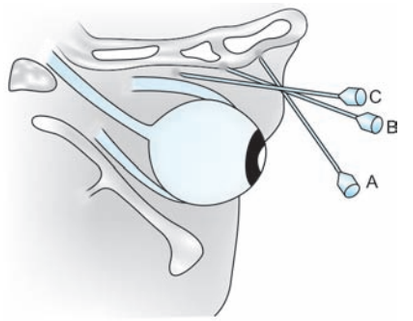


Fig. 41.29: The supero temporal periconal block.The needle is inserted through the superotemporal route and is aimed up towards the roof of the orbit A. Then the needle tip walks along the periorbit of the orbit in a curved line fashion, until the needle tip is at a depth of 24 to 30 mm. At this point injection is made with usual precautions. It is seuperotemporal block

RECENT REGIONAL ANAESTHETIC TECHNIQUES FOR OPHTHALMIC SURGERIES

The large incision cataract surgery, constituting the main bulk of all the ophthalmic operations done in the past, required complete extra ocular muscular paralysis (or akinesia) including orbicularis occuli to avoid the loss of globe contents by muscular contraction during surgery. But the recent small-incision, closed-system surgical technique for cataract extraction does not require complete akinesia or extra occur muscular paralysis. Rather, it may require only surface anaesthesia which is solely confined to the anterior part of the eyeball. So, the concept of alternative non a kinetic methods of regional anaesthesia for cataract extraction surgery has been introduced.

These are:

i. Subconjunctival injection of the local anaesthetic agent,
ii. Sub-Tenon's block,
iii. Topical corne-conjunctival anaesthesia.

But these newer methods of RA are not universally applicable to all the patients for cataract surgery. This is because of the different patient's temperament, different

lens pathology and personal variations of surgical skill.

Subconjunctival Block

In this subconjunctival block (first technique) a small amount of the local anaesthetic agent is injected under the conjunctiva near the superior limbus and this technique is used mainly for the anterior segmental surgery. This technique is also combined with the intracameral injection of a preservative free lignocaine (xylocard). But, in these subconjunctival and topical corneoconjunctival techniques (described below) which is combined with or without intracameral injections of LA agent, anaesthesia is not as complete as with the standard intraorbital blocks. The iris and the ciliary body retain their sensation and akinesia is not a feature. So, many ophthalmologists do not prefer this technique. Because, avoidance of intraconal or periconal block for fear of complications allows exposure to the greater risk of performing intraocular surgery in the presence of extraocular muscle activity.

Sub-Tenon's Block

The sub-Tenon's block was first introduced by Swan in 1956 and was then used extensively after 1960. At that time he suggested that the Sub-Tenon's block produced better iris and anterior segment anaesthesia than a subconjunctival injection. But, the eyeball mobility is usually retained which depends on the volume of LA drug. Subsequently this technique gained popularity as an easy, safe and effective alternative to the retro and peribulbar anaesthesia. It has the advantages of avoiding a needle blindly into the orbit and so has no appreciable risks of the complications which are discussed later.

This technique involves the dissection of a space beneath the Tenon's capsule and passing a blunt curved cannula (Southampton's cannula) into this space beyond the equator of eyeball to deposit the local anaesthetic agent there. It effectively blocks the ciliary ganglion with the long and short ciliary nerves. If larger volumes of local anaesthetic agent is deposited more posteriorly, then it may block the motor nerves and the extraconal branches of the ophthalmic and maxillary nerves. Thus, this large volume of local anaesthetic agent produces complete anaesthesia of the eyeball. During this procedure first the conjunctiva is anaesthetised by topical anaesthesia. This is followed by a small incision on the conjunctiva at the inferolateral quadrant of the globe which is then dissected up to the plane between the sclera and Tenon's capsule. Here the Tenon's capsule is recognised by the white, avascular structure, easily distinguished from the vascular sclera. Then, a blunt curved Southampton's canula is passed backwards beyond the equator through this incision and 3 to 5 ml of the local anaesthetic solution is deposited there. If the canula is placed subconjunctivally, then an attempt to push in the local anaesthetic agent shall immediately make it apparent by chemosis. Following the deposition of local anaesthetic solution beneath the Tenon's capsule by the canula, the LA agent spreads mainly into the anterior intraconal space and produces anaesthesia. The degree of akinesia of the extraocular muscles produced by this subtenon's injection is proportional to the volume of local anaesthetic solution. The peripheral orbital anaesthesia, such as peripheral conjunctiva, lids, etc, is usually incomplete by this to be of block. So, supplemental local anaesthetic injection may sometimes be necessary to achieve the patient comfort or to complete the surgery. Intravenous sedation is often used during surgery, following this method of anaesthesia. Sub-Tenon's block can be used safely in patients where the axial length of globe is more than 26 mm and intraorbital block is more risky. It is also the block of choice in anticoagulated patients, since any bleeding point can be canterized directly. It may be more easily performed by the surgeon, though it is now being increasingly performed by the anaesthesiologist too.

Topical Anaesthesia

Throughout the whole 19th century and the first few decades of the twentieth century, cocaine was the only available local anaesthetic agent. At that period, it was only used in retrobulbar injection and in different general surgeries. But due to its high toxicity, cocaine was abandoned from retrobulbar injection. Then, it was used solely for topical corneo-conjunctival anaesthesia, albeit without the advantages of modern surgical technology which was not developed during that period. However, history is repeating itself. So, after cocaine many good local anaesthetic agents have been developed with more development of sophisticated technology for cataract extraction by very small sclerocorneal incision. Therefore, now reintroduced by Fichman topical anaesthesia by newer local anaesthetic agents is again being commonly used for cataract extraction. For cataract surgery under topical corneo-conjunctival anaesthesia, critical selection of subjects is important and there must be a continuous and open dialogue between the surgeon and the patient throughout the operation. This is because as the eyeball of the patient is not paralysed, so surgeons have to verbally guide the position of the eyeball of patient continuously. This topical corneoconjunctival anaesthesia is most applicable for only cataract extraction by phacoemulsification with or without foldable lens in a very cooperative patients. For topical corneo-conjunctival anaesthesia, the most commonly used drugs are 0.5% bupivacaine and 2% lignocaine.They are very effective, but may sting initially and cloud the cornea. So the newly developed local anaesthetic agents, such as 0.4% oxyprocaine and 0.5% proxymetacaine are considered superior. This topical method cannot be used in patients with language barrier, deafness, dementia and obviously

in children. Dense or trauma-induced cataracts, small pupils failing to dilate, macular degeneration, etc. cannot be managed with this type of topical corneo-conjunctival anaesthesia alone. They are best managed with the other forms of intraorbital regional anaesthesia.

The clear advantages of topical corneo-conjunctival anaesthesia are :

i. Appeal for no-needle procedure,
ii. Avoidance of complications caused by intraorbital injection,
iii. Early visual rehabilitation, especially in patients with only one-sighted eye,
iv. Suitability for patients on anticoagulant medication,
v. The patient's ability to look at any direction directed by the surgeon, which facilitates the surgery also etc.

Junior surgeons still do not prefer this technique and are happier to perform surgery under akinetic block-anaesthesia as they are less experienced regarding the use of topical conrea conjuctional anaesthesia. Patients having cataract surgery under topical corneo-conjunctival anaesthesia require more psychological preparation and oral anxiolytic premedication. The topical agent best suited for this method is 2% lignocaine without preservative. Unlike cataract extraction under intraorbital regional anaesthesia, there is no reduction of optic nerve function in topical anaesthesia. Hence, an awareness of the brightness of the microscope light may be distrubing enough to some patients.This problem can usually be overcome by starting with reduced illumination of the microscope and bringing it up gradually. The iris and ciliary muscles retain their sensation. So, intraoperative use of intracameral miotic agents may precipitate discomfort from ciliary muscle spasm. This can also be prevented by intracameral injection of the local anaesthetic agent, or by avoiding the touching of iris by operating instruments (Table 41.4).

RECENT GUIDELINES FOR ANAESTHETIST IN OPHTHALMIC SURGERY

In 1993, the Royal College of Anaesthetists and the College of Ophthalmologists published certain guidelines on the roles and responsibilities of the anaesthesiologists during ophthalmic surgery under local and topical anaesthesia. The guide line said that the presence of an anaesthesiologist is mandatory to monitor the patient's general condition throughout the operation and to give resuscitation as and when required. In addition, it was also recommended that the anaesthesiologist should be whole responsible for providing sedation when necessary, administering local anaesthesia or block and providing IV access. These recommendations are also applied to simple infiltration anaesthesia for extraocular surgery.

In 2001, these above guidelines were updated with further certain recommendations. These are :

i. Local anaesthesia can also be administered by appropriately trained staff.
ii. Surgeons may administer topical, subconjunctival or sub-Tenons anaesthesia, but an anaesthetist must be present.
iii. An anaesthetist must be available when surgery is performed under retro or peribulbal anaesthesia.
iv. An anaesthetist must be pressent and have sole responsibility if sedation is required.

Table 41.4: Qualities in a surgeon required to select topical anaesthesia

1.	Senior surgeons.
2.	Vast experiences regarding scleral tunnel and intracapsular phacoemulsification.
3.	Good communication skill with the patient.
4.	Appropriate mental makeup to perform the surgery under topical anaesthesia.
5.	Willingness to talk continuously with their patients during the procedures, are most suited for this anaesthetic technique.

SPECIFIC SURGICAL PROCEDURES AND MODIFICATION OF REGIONAL ANAESTHESIA

Today, though most of the ophthalmic surgeries are performed under regional anaesthesia and follow a generalised rule, still some specific ophthalmic surgical procedures may need certain modifications of this regional anaesthetic technique according to their necessity.

For example, secondary intraocular lens implantation in aphakic patients require more surgical time than the standard cataract extraction and intraocular lens implantation procedure. So, it warrants for the selection of more long-acting local anaesthetic agents.

Trabeculectomy usually needs complete akinesia and sensory anaesthesia of the globe. So, topical anaesthesia has no place in such type of surgery. For trabeculectomy operation intraconal or periconal block is the idea RA. But sub-Tenon's block may be an alternative to the intraconal and periconal anaesthesia for trabeculectomy. If there is presence of any bleb of previous trabeculectomy operation, then no external pressure for intraorbital decompression after retro or peribulbar block should be used. Cataract surgery may be combined with trabeculectomy or trabeculectomy may be designed alone to reduce the intraocular pressure in glaucoma. But, in the management of only glaucoma by trabeculectomy the orbital decompression devices are after interconal block best omitted. During surgery of glaucoma instead of intra operative control of 10p the normal intraocular pressure is usually achieved by: careful preoperative control of higher intraocular pressure (by acetazolamide and/or topical β-blocker), perioperative induction of osmotic diuresis with mannitol, using low volume of local anaesthetic agents for intraorbital block incorporating hyaluronidase in the anaesthetic mixture and allowing sufficient time (at least 15 minutes) to pass between the

completion of block and the commencement of surgery.

The strabismus (squint) surgery usually requires full akinesia and deep sensory anaesthesia of the globe by intraorbital intraconal and/or periconal block. But, many other methods of RA have also been described including sub Tenon's, topical, or non-akinetic periconal block for squint surgery.

For refractive keratoplasty procedures, including Excimer laser keratectomy, topical surface anaesthesia by 2% lignocaine is sufficient. But, these surgical procedures are associated with moderate postoperative discomfort or pain for 24 to 36 hours. So this can be postoperatively managed by conjunctival instillations of topical NSAID preparation combined with the use of bandage contact lens.

For corneal grafting the regional anaesthetic technique requires a dependable therapeutic time window of 1 to 2 hours with full akinesia and sensory anaesthesia of the eyeball including both the lids. So, intraconal and/or periconal block with a large volume of long-acting anaesthetic agents is the choice for this type of surgery. Large volume of anaesthetic agents result in an increased intraorbital and subsequently increased intraocular pressure. This can be reduced by preoperative induction of osmotic diuresis by mannitol. An orbital decompression device is also used to reduce the intraoccular pressure. By the use of hyaluronidase and by giving sufficient time between the completion of block and the commencement of surgery, ocular hypotony can be produced.

Epikeratophakia and keratomileusis require a long therapeutic window of 2 to 2.5 hours with full globe akinesia and sensory anaesthesia, including both the eyelid. In both these cases, the moderately potent systemic analgesics are also required postoperatively for about 48 hours. So, appropriate agents should be used with proper postoperative care. During RA the anaesthesiologist should avoid production of conjunctival chemosis, if possible.

Photocoagulation is done with argon laser and it is very painful in an unanaesthetized eye. At the same time the slight globe movement may momentarily expose the relatively healthy part of the retina to iatrogenic injury. So, complete akinetic orbital regional anaesthesia is required for patient's safety and also for surgeon's comfort. Hence, intraconal and /or periconal block is used for this type of surgery. But, some surgeons prefer sub-Tenon's technique also.

Oculoplastic surgeries are also commonly performed under regional anaesthesia and the principles are same as those for other ophthalmic regional anaesthesia in general. However, in oculoplastic surgeries higher concentration of adrenaline is used with the mixture of local anaesthetic agent to reduce bleeding.

For vitreoretinal surgery under regional anaesthesia a more prolonged therapeutic time window is necessary. So, intraconal and/or periconal block by a sufficient amount of long actinglocal anaesthetic agent is advocated. Adrenaline is also usually used to prolong the duration of action of the local anaesthetic agent and to reduce the blood concentration of it, as the large amount of drug is used. The duration of the planned surgery in itself may dictate in favour of general anaesthesia or a combined regional anaesthesia and intravenous sedation technique in the interest of patient's comfort.

COMPLICATIONS OF ORBITAL REGIONAL ANAESTHESIA

The complications of orbital regional anaesthesia may be acute or delayed in onset. Again, it may be systemic or is only confined to the orbit and its contents. The complications of this orbital regional anaesthesia may also range from a trivial one to something serious, such as the death of a patient of drugs. The orbital regional anaesthetic complications are sometimes directly related to the local anaesthetic drugs or may be due to the technique of administeration. The orbital regional anaesthesia, sometimes, indirectly invites the complications resulting from sedative or narcotic drugs and from general anaesthesia but only if they are combined with the previous one in case of inadequate or failed block. In many centres, patients usually receive sedative or narcotic drugs to facilitate the incomplete regional anaesthetic technique, or inadequate psychological preparation of the patient. But, sedatives or narcotics are often unnecessary. Because intravenous medications are only rarely required, if the patients are psychologically properly prepared and regional anaesthesia is adequate. Thus, the side effects and complications related to the use and misuse of these sedatives, narcotics, or general anaesthetic drugs are minimized. The most appropriate management of an inadequate block is supplementation of it by further injection of local anaesthetic agent, rather than the suppression of reflex reactivity with systemic medications such as sedatives or narcotics.

In the past and before the firm establishment of peribulbar technique for better ophthalmic RA with the help of hyaluronidase, the desired goal of complete global and adnexal anaesthesia with akinesia and concurrent global hypotony is achieved only by a two-injection method which is described below and had become the traditionally accepted technique. This two injection method was combining the deposition of a small volume of local anaesthetic agent near the apex of the orbit (retrobulbar) with the block of 7th cranial nerve at some point along its extracranial path. But recently, the introduction of hyaluronidase, peribulbar block and orbital decompression devices allow a larger volume of local anaesthetic drug to be injected into the orbital cavity for complete block. This avoids the necessity to block the 7th cranial nerve, because an adequate volume of drug spreads through the orbital septum to paralyse the orbicularis oculi.

Table 41.5 Complications of ophthalmic regional anaesthesia

1. Globe perforation

   Causes trauma to the retina or chroid. Diagnosed by hypotomy of globe, intravitrol haemorrhage, retinal detachment, retinal tear at the point of perforation, loss of vision, etc.

2. Venous haemorrhage

   Caused by puncture of any orbital vein. Diagnosed by retrobulbar haematoma which progresses less slowly than arterial haemorrhage. Haematoma produces proptosis, tight globe subconjunctival haemorrhage ecchymosis, etc.

3. Arterial haemorrhage

   Caused by puncture of any orbital artery. Produces same picture like venous haemorrhage but very rapidly progressing (acute).

4. Optic nerve injury

   Caused by direct needle injury to the nerve or ischaemic compression by haematoma. Diagnosed by optic atrophy, optic nerve head swelling, visual field defects, permanent loss of vision, etc.

5. Intravessel injection

   Caused by direct injection of LA agent in vein or artery. Produces increased systemic levels of local anaesthetic or cerebral levels of local anaesthetic. Diagnosed by dizziness, drowsiness, confusion, twitching, convulsion, unconsciousness, hypotension, bradycardia, apnoea, coma, cardiac arrest.

6. Deposition of LA agent in subarachnoid space

   Caused by needle penetration of optic nerve sheath and direct spread of LA agent in the central CSF. Diagnosed by vertigo, deafness, aphasia, facial palsy shivering, convulsion, hemiplegia, paraplegia, quadriplegsia, loss of consciousness, apnoea, hypotension, bradycardia, cardiac arrest.

7. Oculocardiac reflex

   Caused by dull or blunt needle and rapid injection of drug in a fixed orbital space. Diagnosed by bradycardia, hypotension, loss of consciousness and cardiac arrest.

However, as larger volume of drugs are used, it is easy to understand the mechanisms causing complications in ophthalmic RA.

Safe regional anaesthesia can be accomplished by both the intraconal and periconal techniques. But, serious complications can arise from both the techniques, if carried out incorrectly. So, it cannot be said that one is better than the other. Although, there are definite description of both the intraconal and periconal techniques for orbital RA, but recently multiple exhaustive studies have failed to find out any evidence of a closed 'cone', consisting of the four rectus muscles and their interconnecting intermuscular septa, thus creating a distinct cone like compartments in the posterior part of globe. So, it can be concluded that the concept of discrete intraconal and periconal compartments are erroneous (Table 41.5).

The advancement of needle by an anaesthetist within the confines of the orbital cavity for regional ophthalmic anaesthesia is essentially a blind procedure. So, it has the potential of serious complications. Therfore, the perception of changes of tissue planes during the advancement of needle is very important for safe regional anaesthesia. But, it is an acquired skill which requires experience and continuous practice to reduce the rate of complications. The traditional teaching of placing an inferotemporal needle intraconally with the globe elevated and adducted i.e. 'up and in' position (Atkinson technique) has largely been abandoned now. Because, in this position the optic nerve is brought easily closer to the needle tip and the macular area is further exposed to the damage. So, optic nerve sheath penetration, optic nerve trauma and globe penetration by the needle may result in this position of the globe more frequently. Further, the posterior pole of the globe is more endangered, particularly in the ovoid shaped globes of myopic patients in such 'up and in' position. But, many of the serious complications can be avoided by having the patients eyes directed in the primary gaze position during the needle placement and subsequent injecton. However this has been substantiated by CT-scanning and MRI.

Special attention should also be paid to the length and direction of the needle which enters the orbital cavity beyond the rim. Longer needles which is more than 31 mm may reach the orbital apex where the vessels are numerous and of larger lumen. Again, at the apex the optic nerve and vessels are less mobile. So, the retrobulbar hemorrhage or optic nerve trauma may result more frequently, if the needle tip approaches more towards the apex. Thus, while it is possible to get a beautiful block with a small volume of drug of it is injected at the apex of the orbit, but the risks increase many-fold. So, a distance of 31 mm within the orbit as measured from the orbital rim should never be crossed. Also, a needle which is advanced from the inferotemporal entry site should not be allowed to pass the mid-sagittal plane of the eyeball. All the needles used for intraconal and / or periconal injection should also be directed obliquely to the globe with the bevelled opening facing the eyeball. This tangential or oblique alignment of needle is most easily achieved through the transcutaneous route by putting a finger between the globe and the inferior orbital rim over the lower eye-lid than the transconjunctival route. This is because the finger pushes the globe upwards and makes more room for the needle in the inferotemporal quadrant. The finger also helps to assess the size of the globe, the distance of the equator from the inferior orbital rim, and guide the direction of the needle tangentially. If a tangentially aligned needle touches the sclera, still globe penetration is less likely to occur than when a needle approaches at

an acute angle. Having placed the needle at a desired depth, if there is an increased resistance which is more than expected during pushing the drug, then it is imperative to reposition the tip of the needle first, rather than inject against this resistance.

Blocking of the main trunk of the facial nerve after its exit from the stylomastoid foramen may be associated with the unilateral blocking of vagus, glossopharyngeal and spinal accessary nerve which are also coming out from the base of the skull near the stylomastoid foramen, causing difficulty in swallowing and respiratory distress. So, for facial nerve block at the stylomastoid foramen it is wise not to go deeper than the recommended 12 mm depth from the skin and to avoid hyaluronidase. Thus, bilateral facial nerve block at the stylomastoid foramen should never be allowed. Another vital structure near the stylomastoid foramen is the internal carotid artery which can also be injured by the deeper placement of needle.

There is a communication or continuation of the subarachnoid space of the optic nerve with that of the chiasma and the subarachnoid space, which surrounds the pons and the mid-brain. The dural sheath at the apex of the orbit and along the optic nerve is not impervious to local anaesthetic agents. So, the local anaesthetic agents deposited in the orbital cavity can easily diffuse into the subarachnoid space which surround the optic nerve. This is evidenced by the incidence of temporary ipsilateral amaurosis (loss of vision, especially that occurring without apparent lesion of the eye), following intraorbital block. Studies of cortical visual evoked potential also indicate temporary suppression of the optic nerve conduction which is greater with intraconal blockade, than with the periconal block. All these points favour the theory of absorption of local anaesthetic agents in the CSF bathing the optic nerve and extension of it to the CNS with the brainstem anaesthesia following intraorbital block. This was explained and was first published in mid 1980's, although there was previous knowledge of this meningeal pathway. About 4 to 5% of patients undergoing cataract extraction under regional anaesthesia generate emergency calls for an anaesthetist. Among these, the direct cerebral spread of local anaesthetic agent from the orbit is very important. The effect of spread of the local anaesthetic agent in the CNS during the intraconal or periconal block depends on the amount of drug entering the CNS and the specific area of CNS to which it has spread. Usually, the patient describes the symptoms about 2 to 3 minutes after the intraorbital injection. Frequently, the peak is reached at about 10 to 15 minutes and resolves over 1 to 2 hours. The clinical picture of the spread of local anaesthetic agent in the CNS is protean and produces signs and symptoms which vary from mild confusion to marked shivering or convulsions. The clinical pictures may also show the bilateral brainstem nerve palsies, including hemi or para or even quadriplegia and with or without loss of consciousness. In extreme cases, the clinical picture shows apnoea with marked cardiovascular instabilty. As this is a potential complication which may occur in any intraorbital block, so patients should not be covered with drapes for surgery until 20 minutes have passed after completion of block. Otherwise, identification and corrective treatment may be dangerously delayed and serious sequelae including death could obviously result. Central spread of the local anaesthetic agent should be suspected, if there is onset of any of the following signs and symptoms, such as : mental confusion, signs of extraocular paresis or amaurosis of the contralateral eye, shivering, convulsion, nausea or vomitting, dysphagia, sudden changes in the vital cardiovascular signs, dyspnoea or respiratory depression, etc. Treatment of this serious complication includes : ventilatory support with oxygen, intravenous fluid, pharmacological circulatory support with vagolytics and vasopressors and anticonvulsants with close vital sign monitoring. The traditional Atkinson's technique with elevated and adducted globe during inferotemporal needle placement increases the chances of cerebral spread of local anaesthetic agent. Because, this position places the optic nerve with its subarachnoid space in close ploximity to the advancing needle. On the other hand, 'down and out' position of the globe advocated by some anaesthetist, where the optic nerve is less vulnerable has the disadvantage of bringing the approaching inferotemporal needle into the field of vision of the patient. So this may be frightening to the patient. However, the 'down and in' position of the globe which places the anterior part of the optic nerve in a safer position in the intraconal space and the needle is away from the field of vision of the patient, is more acceptable to avoid this complication. Whatever may be the reason, the avoidance of deep penetration of the orbit by needle during any technique, is the key factor for both to prevent the cerebral spread of LA agent and avoid other serious complications of regional anaesthesia. Maximum penetration of the needle from the orbital rim should not be more than 31 mm. Modern regional anaesthetic techniques avoid deep orbital placement of the needle and instead advocate accurate site of injection at the limited orbital depth, using increased volume of drug in order to achieve the critical blocking concentration at the apex.

The true incidence of scleral penetration (entry wound only) and perforation (entrance and exit wound) are not known, because most of the cases are not reported. So, the reported incidence ranges from none in a series of 3000 peribulbar (periconal) anaesthesia to 1 in a series of 10,000 combined peri and intraconal anaesthesia to 3 in a series of 3000 intraconal block. But, it is definite that the incidence is higher in both myopic patients and intraconal block. Myopic patients with posterior staphyloma are particularly at higher risk.

Patients presenting for retinal detachment and radial keratotomy also have higher propensity of scleral perforation due to large globe, like myopes. Recessed eyes, tight lower eyelids, small orbital cavity, etc. are more challenging situations and are at an increased risk of scleral penetration. In such situations, periconal needle placement may be safer than intraconal placement of the needle. When someone does not believe in the difference between the periconal and intraconal block, they just try to direct the needle tip towards the orbital floor during the placement of needle through inferotemporal route and roof during the superotemporal route to avoid this complication. A safe pre-requisite to perform the regional anaesthesia of the orbit is to know the exact axial length of the eyeball prior to block. This warns one about the higher risks in larger than average sizes of eyes. In cataract surgery the precise axial length of the eyeball is usually available from biometry which is done to calculate the power of the intraocular lens. But, in other than cataract procedures where axial length is not precisely known, then close attention to the dioptre power of the patient's spectacles or contact lenses will provide valuable clues to the globe dimensions. USG of patients with suspected straphyloma and high myopia is also effective in reducing this complication rates. In such situations, it is prudent to perform periconal method and/or intraconal injection (if it is absolutely necessary) with patient's gaze directed downard and outward or to opt for general anaesthesia. Penetration or perforation of eyeball caused by thick blunt needles, though incidence is low, results in more serious and permanent damage than when such injuries result from the use of fine disposable ones. Fine disposable needles which are less painful for the patient have been proved to be relatively safe than the blunt needles in respect to the postpenetration management. More than 50% of all the iatrogenic globe perforations go unsuspected at the time of their occurrence. The event of perforation may be suspected if there is hypotomy, vitreous haemorrhage, poor red reflex, etc. Patients may complain of marked pain during the occurrence of perforation, particularly if the local anaesthetic agent is injected intraocularly. Fundoscopy confirms the diagnosis. Globe perforation involving only retinal tears with minimum blood in vitreous can be managed with laser photocoagulation, cryotherapy or sometimes by close observation only. When much blood is present in the vitreous cavity, then emergency vitrectomy may be indicated. Without surgical intervention, this severe vitreous haemorrhage frequently leads to proliferative vitreoretinopathy and subsequent detachment of the retina, where prompt surgical treatment is indicated. Actually, the appropriate management of scleral penetration and perforation is complex (Table 41.6).

Intraorbital bleeding is another common complication of ophthalmic regional anaesthesia. It may be manifested as retrobulbar haemorrhage, peribulbar hemorrhage, subconjunctival haemorrhage, lid ecchymoses, etc. Retrobulbar or peribulbar haemorrhage varies in severity. It may be small enough and go unrecognized or is severe enough which results in a loss of vision due to tamponade of the small nutrient vessels of the optic nerve. This explains those cases of profound visual loss where the findings of retinal vascular occlusion were not seen but late optic atrophy had developed. Loss of vision may also occur due to tamponade of the central retinal artery from massive retrobulbar or peribulbar haemorrhage. Some retrobulbar haemorrhage are of venous origin and spread slowly. Whereas, arterial haemorrhage produces rapid and tight orbital swelling, marked proptosis, immobility of the globe, massive blood staining of the lids and conjunctiva, etc. Due to the increased intraorbital pressure from arterial bleeding, serious impairment of the vascular supply to the retina and globe may result. Anterior orbital hemorrhage, subconjunctival bleeding and lid ecchymoses are also the most disconcerning sequelae of the intraconal or periconal anaesthesia. These commonly cause the patient and his family to make complain. Nevertheless, even if bruising occurs, then the patients and the accompanying person should be informed. In such circumstances reassurance should be given to them that the surgical outcome will not be affected at all and the bruising will clear away spontaneously within a few days. The anterior orbit has less vessels than the posterior orbit. Three anterior orbital locations are relatively avascular. These are inferotemporal, superotemporal and the nasal side of the medial rectus muscle. So,

Table 41.6: What we shall do and what we shall not?

1. When we shall use inferotemporal route for intraorbital block, we must maintain the primary gaze position of the eyeball or at least the 'down and out' or the 'down and in' position of the eyeball. 'Up and in' or Atkinson position should not be used during inferotemporal route for fear of optic nerve injury.
2. Needles more than 31 mm approaching the orbital apex should not be used. The length of the needle should always be below 31 mm and better if it be 24 to 27 mm.
3. The axial length of the eyeball should always be measured or known before introducing any needle in the orbit. So, don't fail to measure or check the axial length of eyeball.
4. Always avascular injection sites should be used. So, vascular superonasal quadrant should be avoided.
5. Extra precaution should always be taken for patients having staphyloma, scleral buckle, coloboma, etc. Failure to take history of previous surgical intervention (scleral buckling which increases the axial length of eyeball) or to check for any global anomalies may cause serious disaster.
6. During practice of regional anaesthesia in ophthalmology, everybody must execute his highest knowledge in orbital anatomy. Don't attempt any regional block in ophthalmology without proper anatomical knowledge.
7. We should always try to avoid direct injection into the extraocular muscles.
8. We will always use time honoured regional technique with well-thought volume and concentration of local anaesthetic agent. We will not use unnecessary newer technique and unnecessary higher volume and concentration of local anaesthetic agent.

by using fine needles and confining the needle prick within these three locations and not going beyond 31 mm from the orbital rim posteriorly, we can reduce the incidence and severity of the intraorbital bleeding. If it occurs, it may be minimized by constant vigilence for any sign of bleeding immediately following needle withdrawl and by rapid application of digital pressure with a gauge pad, applied to the closed lids. Other management of retrobulbar haemorrhage are osmotic diuresis and lateral canthotomy, which allows drainage of the blood and decompression of the orbit. So, surgeons should be informed immediately and the pulsation of the central retinal artery should be assessed. The superonasal area should be avoided for needle insertion, because the complex trochlear mechanism of the superior oblique muscles is located there.

Prolonged malfunction of the extraocular muscle may also sometimes occur after the regional anaesthesia of the orbit. Among these the diplopia and ptosis are common which may last for 24 to 48 hours postoperatively, when long-acting local anaesthetic agents have been used in higher concentration and in large volume. When these persist for long period and fail to recover, it may give evidence of toxic changes of the muscles by local anaesthetic agents. Where the recovery is delayed for more than 6 weeks, 25% of the change becomes permanent. It is indeed pathetic, when a patient who has come for a perfect optical result, ends up with devastating diplopia because the eyes are misaligned. Local anaesthetic agents containing hyaluronidase and/or adrenaline may be more myotoxic than plain local anaesthetic solutions. Higher concentration of local anaesthetic agents is more likely to result in a more intense myotoxicity. Another common cause of prolonged malfunction of the extraocular muscle is direct intramuscular injection of the local anaesthetic agent of any concentration.

Ptosis is also a very common complication after ophthalmic RA. This postoperative ptosis is of multifactorial origin.

Table 41.7: Some factors responsible for muscle damage and ptosis

1. Pressure applied to the globe and upper lid,
2. Oedema of the eyelid,
3. Traction on the superior rectus muscle complex,
4. Pressure exerted by the lid speculum,
5. Prolonged postoperative patching.

Among these, the injection of local anaesthetic agent directly into the levator palpebrae superioris muscle plays an important role. The toxic damage of the muscle fibres from local anaesthetic agent which is not injected directly into the muscle may also account for many cases of transient and permanent ptosis (Table 41.7).

Most postoperative ptosis also occurs in patients in whom the levator aponeurotic apparatus was already pathological beforehand and the RA only serves to accelerate the preexisting condition. The preexisting degenerative conditions of the aponeurosis of the levator palpebrae superioris which usually accelerate the postanaesthetic ptosis include : disinsertion in the tarsal plate, dehiscence and rarefaction of the aponeurosis. Many of these lids with the above mentioned pathologies would have become ptotic, even if surgery and RA had not been performed. The RA has just accelerated the pathological process. A low incidence of postoperative ptosis is seen in surgeries which are done under general anaesthesia than with local anaesthesia. Surgical correction of such postoperative ptosis is done when there is only interference with the vision. But, it should be delyed for 6 months, until a self correction of certain limit occurs and a stable state has been reached. So, it is very prudent and should be a routine practice to check the positions of the eyelid margins above the central cornea before embarking on sugery and is documented with photography, if needed. Patients also should be informed beforehand about the possbility of ptosis which may be temporary or permanent after surgery. Written consent for surgery acknowledging this complication of ptosis should also be taken.

Exposure of anaesthetized cornea and subsequently its abrasion are also very common complications of ophthalmic regional anaesthesia. Abrasion is seen as a dull nonreflective patch or as a positive area by fluorescein staining. So, care must be taken to protect the cornea by occlusive dressing, during the whole perioperative period. An occlusive dressing should be used after anaesthesia to seal the eyelids shut, until their full function and reflexes have recovered. The time of recovery will depend on the duration of action of the chosen anaesthetic drug. On the other hand, a prolonged patch can provide a moist atmosphere beneath the gauge as an ideal culture medium for organism to grow. That's why some experienced surgeons do not use patch over the eye postoperatively, especially after small wound phacoemulsification cataract extraction with foldable intraocular lens implantation under solely topical anaesthesia. But, the safety of this decision from the point of view of risks of superficial corneal damage would depend on the degree of the recovery from anaesthesia. After recovery from anaesthesia, corneal abrasion (if it occurs) is manifested as pain, foreign body sensation, tearing, conjunctivitis and photophobia. Pain is also made worse by blinking. Management of corneal abrasion consists of covering the eye with an antibiotic eye ointment. But, topical applications of anaesthetic drops and steroids over the cornea to reduce pain is contraindicated, because they impair the healing of wound.

OCULOCARDIAC REFLEX (OCR)

OCR is a trigeminovagal reflex which is manifested by cardiac arrhythmias such as bradycardia, nodal rhythm, ectopic beats, ventricular fibrillation, asystole, etc. in response to vagal stimulation. Although the most common manifestation of this reflex is sinus bradycardia, but virtually

any cardiac dysrhythmia such as nodal, junctional, atrial or any serious ventricular arrhythmia may occur. This oculocardiac reflex was first described by Aschner and Dagini by two simultaneous but independent reports in 1908. The impulses for OCR usually arise from the stretch and pressure receptors which are present throughout the globe and orbit. The afferent pathway of the reflex first goes through the long and short ciliary nerves to the ciliary ganglion. Then, it passes to the gasserian ganglion along the ophthalmic division of the trigeminal nerve (the 5th cranial nerve). Ultimately, these afferent pathways terminate at the main trigeminal sensory nucleus which is situated on the floor of the 4th ventricle. The efferent pathway comes down by the vagus nerve and ends at the cardiovascular centre, respiratory centre and vomiting centre, causing negative ionotropic effects, negative chronotropic effects, conduction defects, vomiting, sinus arrest and/or respiratory arrest. So, the term 'Oculocardiac Reflex' should be changed to 'Oculomedullary Reflex', consisting of oculocardiac, oculorespiratory and oculoemetic reflexes.

The OCR may be triggered by many factors such as pressure on the eyeball, traction on the extraocular muscles, orbital haematoma or many other. Traction on the medial rectus produces more marked effects than the traction on other muscles. The reflex seems to be most active in children. So, the OCR occurs most often during strabismus surgery in children. But it may also occur occasionally during retinal surgery or at the time of injection of the intraorbital block. The reported incidence of OCR varies considerably from 30 to 90%. Because, it depends on the intensity of observation and the definition of arrhythmias. Transient cardiac arrest may occur as frequently as 1 in 2000 cases of strabismus surgery. The force and the type of stimulus usually influence the incidence of OCR. The more acute, stronger and sustained will be the stimulus and the more sensitive will be the patient, the more likely is the OCR to occur. Therefore, ECG should always be monitored continuously during ophthalmic surgery. The OCR ceases when the stimulus (from pressure or traction) ends. So the surgeon and the anaesthesiologist should not hesitate to communicate each other during any procedure involving the possibility of an OCR.

Intramuscular atropine or glycopyrrolate as premedication are not very effective in preventing the oculocardiac reflex, compared to the intravenous administration. Atropine in the dose of 0.02 mg/Kg through IV prior to surgery will reduce the incidence of OCR by 5 to 15%. Intravenous glycopyrrolate in the dose of 0.01 mg/Kg, is preferred than atropine as it causes less tachycardia. Hypercarbia increases the sensitivity to the reflex, and an anaesthetic technique such as controlled ventilation rather than spontaneous ventilation might be preferred.

The first step of treating OCR is to stop the production of stimulus by surgeon, before the arrhythmia progresses to sinus arrest. Fortunately, the repeated and sustained stimulation usually causes the OCR to become fatigue. If arrhythmias persist, then treatment with atropine (20 µg/Kg IV) and injection of local anaesthetic agent into the eye muscle may be necessary. If the patient still remains sensitive to the manipulations of the extraocular muscles, then the anaesthesiologist should check the adequacy of the depth of general anaesthesia, the existence of normocarbia and the gentleness of surgical manipulation. If the dysrhythmia is fast or ventricular in origin, then surgery should be stopped immediately. Then, we should wait for the return of normal rhythm before giving atropine, otherwise may provoke ventricular tachycardia or fibrillation.

INTRAOCULAR PRESSURE (IOP) AND ANAESTHESIA

IOP is the result of a dynamic balance between the production of aqueous humour by ciliary body in the posterior chamber and its eventual elimination by the episcleral venous system via the spaces of Fontana and the canal of Schlemm at the iridocorneal angle. So, the most important factors which influence on IOP are: the production and movement of aqueous humour, the changes in choroidal blood volume, the central venous pressure and the extraocular muscle tone. The normal IOP is approximately 15 to 20 mm of Hg.

The ciliary body lies behind the root of the iris and consists of two parts. The posterior muscular part is called the pars plana. The muscle in this part has three important functions. The most important of which is to relax the suspensory ligament of the lens. Thus, the lens becomes more spherical and allows accomodation of near vision. Secondly, it exerts tension on the scleral spur. This widens the spaces in the trabecular meshwork and thus facilitates the drainage of aqueous humour. A third and minor action of this muscle is as dilator of the iris. The pars plana is the favoured site for the sclerotomies through which insertion of instruments into the eye is done during vitreoretinal surgery. The anterior part of the ciliary body is thrown into about 70 folds and is called the pars plicata. Here, the stroma is highly vascular and is richly supplied by fenestrated capillaries. It is from these folds that the aqueous humour is secreted. The aqueous humour is produced at a rate of about 2 µl/minute.

After secretion the aqueous humour circulates freely from posterior chamber to the anterior chamber around the free margin of the iris. If there is any increase in venous pressure, or decrease in the cross-sectional area of the spaces of Fontana, then there is increase in the resistance to outflow of aqueous humour which increases IOP. Mydriatic drugs relax the ciliary muscles and close the iridocorneal angle at Fontana's spaces. Thereby, they increase the IOP. Coughing, straining and Valsalva manouevers significantly increase the CVP. Thus, they decrease the

outflow of aqueous humour from the Schlemm's canal into the episcleral venous system and increases the IOP.

The uveal tract is the intermediate vascular coat of the globe lying between the sclera and retina. It consists of the choroid, ciliary body and iris. The choroid coat is present in the posterior 5/6th of the eyeball and is juxtaposed to the sclera. It extends forward up to the ora serrata of the retina. It is chocolate-brown in colour and is highly vascular. Choroid is being fed by the branches of the short posterior ciliary arteries and is drained by a venous network which ultimately converges into four or five vortex veins. The vortex veins pierce the sclera 5 to 8 mm posterior to the equator of the globe. One of the these is located at the lateral border of the inferior rectus muscle and 5 mm posterior to the equator. It may be the source of intraorbital bleeding during the inferotemporal needle placement. The choroid is responsible for the nutirtion of the outer layer of retina. The inner layer of retina receives its blood supply from the central retinal artery. The vascularity of the choroid layer increases with systemic venous congestion, arterial hypertension, hypoxia and hypercarbia. The sclera and the choroid are loosely adherent and separated by a potential suprachoroidal space which may fill with blood during an expulsive or suprachoroidal hemorrhage. This is a dreaded surgical complication.

The choroidal blood flow or its volume affects the IOP significantly. But, it is usually autoregulated over a wide range of systemic systolic pressure to keep the IOP stable. The sudden increase in systolic blood pressure causes a transient increase in choroidal blood volume and the IOP. Hypotension (systolic blood pressure < 90 mm of Hg) reduces the choroidal volume and subsequently decreases the IOP. During an open eye surgery IOP usually remains lower than normal. But a sudden increase in the choroidal blood volume can force the vitreous gel forward into the anterior chamber and also cause the prolapse of iris. Any cause which increases the CVP increases the choroidal blood volume and its pressure and thus elevates the IOP. Choroidal circulation, choroidal pressure and subsequently IOP is also sensitive to the changes of partial pressure of oxygen. So, hypoxia increases the choroidal circulation and its volume by vasodilatation and increases the IOP. Respiratory acidosis and hypercarbia also increases the choroidal blood flow by vasodilatation and, therefore, elevates the IOP. Hypocarbia decreases IOP through vasoconstriction of the choroidal blood vessels, and decrease in the formation of aqueous humour through reduced carbonic anhydrase activity. The IOP is also controlled by CNS through the neurovascularly mediated responses and extraocular muscle tone. These are usually depressed by barbiturates, volatile inhaled anaesthetics and nondepolarizing muscle relaxants. It is also found that IOP is more directly related to CVP than the arterial pressure. So, a slight head up tilt during the intraocular surgery reduces the IOP due to any cause. External pressure on the eyeball initially increases the IOP. But, this increased IOP promotes increased outflow of aqueous humour and thus returns IOP towards normal (Fig. 41.30).

In general, the most anaesthetic agents except ketamine and succinylcholine relax the extraocular muscle tone, depress the CNS, improve the outflow of aqueous humour, lower the venous and arterial pressure and thus reduce the IOP. Inducing agents such as thiopentone and propofol also lower IOP by depressing the CNS and improving the outflow of aqueous humour. Antisialagogues such as atropine and glycopyrrolate, given as premedication through IV or in route have no significant effect IOP. However, when these drugs are applied topically on the eye, they cause mydriasis and increase IOP. But, neostigmine and atropine combination which are used to reverse the nondepolarizing muscle relaxants do not increase the IOP. On the other hand, laryngoscopy and intubation or extubation elevate the IOP. However, the mechanism of it is not clear, but is probably related to the sympathetic cardiovascular responses to tracheal intubation or extubation. Several attempts have been advocated to attenuate the IOP response, related to the laryngoscopy and intubation or extubation. These are: pretreatment with IV lignocaine, narcotics and β-blockers. Oral administration of any centrally acting antihypertensive drug, such as, clondine in the dose of 5 µg/Kg of body weight and given 2 hours before induction of anaesthesia will blunt the IOP response to intubation. Benzodiazepines, administered intravenously, reduce the IOP but not when administered orally. On the other hand, narcotics do not decrease the IOP, even in glaucoma. The effect of ketamine on IOP is controversial. Early studies show an increase in IOP after an

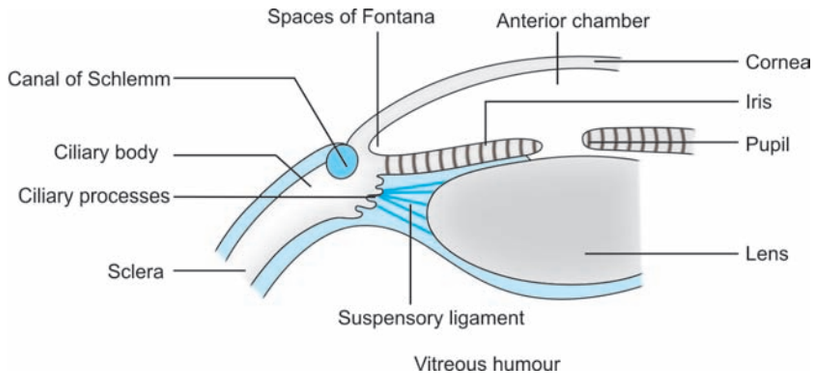


Fig. 41.30: Circulation of aqueous humour

IV administration of ketamine. But when ketamine is used after premedication with BDZ, then IOP does not elevate.

All the nondepolarizing muscle relaxants lower the IOP. But, succinylcholine causes a significant and transient rise in IOP, though the mechanism is not clear. It is definite that an increased IOP by succinylcholine is not due to mere fasciculations of the extraocular muscles as sectioning of recti do not prevent the increase in IOP. So, it may be due to the direct effect of succinylcholine on the choroidal blood volume or on the formation of the aqueous humor.

During retinal surgery the ophthalmologists, sometimes, inject gases into the vitreal cavity to tamponade the retina. The gases commonly used for this purpose are C_3F_8 (carbonoctofluorine) and SF_6 (sulphur hexafluride). They are inert, very insoluble in water and poorly diffusible. N_2O is 117 times more diffusible than SF_6 and so it enters into the gas bubble very rapidly. If administration of N_2O is continued after injection of C_3F_8 or SF_6 gas into the vitreal cavity, then the size of the injected gas bubble rapidly increases and becomes about three times of its original size. Thus, IOP increases from normal 15 to 30 mm of Hg. This may result in occlusion of the retinal artery and loss of vision. Both, the bubble size and the IOP will then decrease and become normal within 15 minutes of discontinuation of N_2O by 90 % elimination from the lungs. This rapid and wide variation in bubble size during general anaesthesia by N_2O may adversely affect the result of the surgery. This outcome is more affected, if hypotension occurs during general anaesthesia. So, administration of N_2O should be discontinued at least 20 minutes before the institution of an intravitreal injection of C_3F_8 or SF_6 gases. Bubble size and IOP would then remain stable. So, some anaesthetists avoid N_2O altogether, when intravitreal injection of gas is planned. SF_6 gas remains in the vitreal cavity for at least 10 days. Other gases remain in the vitreal cavity for as long as 20 to 30 days. So, N_2O should always be avoided in any patient returning for retinal resurgery within 3 to 4 weeks of undergoing intravitreal injection of gases. Patients with intravitreal gas bubbles may also risk ocular damage during air travel. This is because, if patients having intraocular air volumes of only 0.25 cc, were subjected to pressures simulating that inside a commercial aeroplane, there would be an average rise of IOP by 40 mm of Hg. This will again decrease to lower than normal, after return to preflight pressures.

FACTORS AFFECTING THE IOP

These are analogus to the factors affecting ICP (intracranial pressure). The factors which affect the IOP are:

i. Head up or down position.
ii. Volume of aqueous humour determined by the balance of production and drainage.
iii. The tone of extraocular muscles.
iv. Choroidal blood volume, determined by the balance of arterial flow and venous drainage.
v. Mannitol and acetazolamide: Mannitol in the dose of 0.5 gm/Kg IV reduces the IOP by withdrawing fluid from the vitreous. Acetazolamide in the dose of 500 mg orally or IV reduces the IOP by reducing the production of aqueous by the ciliary body.
vi. Anaesthetic factors.

Anaesthetic factors increasing IOP

i. External compression on the globe by face mask which is applied tightly.
ii. Laryngoscopy – through pressure response or from straining in an inadequately relaxed patient.
iii. Suxamethonium – through its effect on extraocular muscles.
iv. Large volume of local anaesthetics placed in the orbit. The effect here is also transient. The ↑IOP can be reduced by different decompression method.

Anaesthetic factors decreasing IOP

i. Inducing agents like thiopentone and propofol. They act by reducing the arterial and venous pressure.
ii. All non-depolarizing muscle relaxants. They act by reducing the extraocular muscle tone.
iii. Head up tilt (> 15°) by assisting venous drainage.
iv. Hypocapnia by reducing the choroidal blood volume by vasoconstriction of choidal vessels.

RETINOPATHY OF PREMATURITY (ROP)

As the neonatal care has been improved due to the advancement of technology, so more and more premature infants now survive. Therefore, the incidence of retinopathy of prematurity is gradually increasing. It has a complex cause with many aetiologies. Previously, it was thought that the ROP was only associated with hyperoxic conditions during neonatal care. But, the full-term non-hyperoxic neonates and infants can also have this condition just like premature infants who have never had O_2 therapy. So, it is decided that ROP may also be associated with factors such as hypoxia, hypocarbia, hypercarbia, sepsis, apnoea, etc., other than hypoxia. The ROP still occurs, despite the efforts in the neonatal intensive care unit to control and monitor the O_2 delivery. ROP also occurs even when the capillary PO_2 is kept between 35 to 40 mm of Hg and P_aO_2 is maintained between 50 to 70 mm of Hg in premature infants. So, the problem for the anaesthetists who is giving general anaesthesia to a premature infant is to balance the risk between the hypoxic damage and prolonged exposure to high O_2 concentration, causing ROP. Although, there is no convincing evidence that ROP has always occured solely because of high O_2 concentration, given during anaesthesia, still prolonged exposure to high intraoperative concentration of O_2 is best avoided during the period of retinal immaturity, i.e. until

8 months of age. P_aO_2 is maintained between 60 to 90 mm of Hg by keeping SPO_2 in pulse – oximetry between 90 to 95%.

GENERAL ANAESTHESIA FOR OPHTHALMIC SURGERY

The list of indications of GA for ophthalmic surgery has been tabled before. The main aim of GA in ophthalmic surgery is to minimise the increase in IOP and keep the patient motionless, while maintaining cardiovascular stability. But, deep anaesthesia should be avoided as the main population in ophthalmic surgery is likely to be elderly with several co-morbidities. GA is provided, unless there are overwhelming risks. Then, the patients and their attendants are informed about the risks and GA is provided only if they accept them. Always a risk-benefit ratio has to be calculated, keeping in mind that ophthalmic surgeries are not life-saving. The preoperative assessment and preparation for GA in the patients scheduled for ophthalmic surgeries follow the same guidelines as GA for other sugeries.

A Standard Technique of General Anaesthesia which is usually Followed for Ophthalmic Surgeries

i. IV induction by propofol or thiopentone. Ketamine is used only if properly indicated.
ii. Non-depolarizing muscle relaxants are preferred. Succinylchoilne can be used only if it is properly indicated.
iii. Airway is maintained by ET tube or LMA.
iv. Ventilation is maintained by IPPV or spontaneous ventilation.
v. Maintenance of anaesthesia is by O_2 with air/N_2O/propofol infusion by TCI/volatile inhalational agents. N_2O should be avoided in vitreoretinal surgeries, especially if SF_6 or C_3F_8 gases are used.
vi. Analgesia is provided with fentanyl/alfentanyl/sufentanyl/remifentany, etcl.
vii. Use of glycopyrrolate as antisialagogue is preferred in ophthalmic surgeries. It reduces the volume of saliva which often produces cough, laryngospasm, etc.
viii. Airway should be secured properly as access to the airway is limited by the surgical drapes, instrument trolleys, and other equipments overlying in this area. Most importantly, there prevails a low threshold for moving every one out of the way to inspect the airway when some problem is suspected.
ix. Which is the better or safe for ophthalmic surgeries – an ET tube or a LMA? This is a potent question which is often asked. Unless contraindicated, the LMA is ideal for ophthalmic surgeries as it avoides laryngoscopy with the consequent adverse effects of it on IOP. It produces minimal stimulation once is *in situ* and permits a lighter anaesthesia. The quality of emergence is also superior, ET-tude and very smooth in case of LMA. 10% Lignocaine is usually sprayed in the larynx during endotracheal intubation. But unfortunately, its effect is very short-lived and so may no longer be effective during extubation. Extubation of ET-tube in a deep plane or administration of a bolus dose of IV lignocaine (1 mg/Kg BW) or propofol (0.5 mg/Kg BW/min) just before extubation are some of the methods which are often opted for smooth extubation. It is better not to lighten the plane of anaesthesia before completion of surgery and the removal of the typical stick-drapes used in ophthalmic surgeries. If a peribulbar block is not used, drape removal may well be the most stimulating part of the procedure. During extubation emergence hypertension and a concomitant rise in IOP can be managed by the use of IV lignocaine and / or β-blocker.
x. Choice between the IPPV and spontaneous ventilation is another important question in ophthalmic surgeries. For minor and extraocular surgeries the spontaneous ventilation is acceptable. Controlled ventilation or IPPV has a number of advantages in intraocular and other major ophthalmic surgeries. It allows a more precise control of CO_2, reducing the IOP and desensitizing the oculomedullary reflex. It also allows the benefits of a balanced anaesthesia technique. IPPV by LMA is also uneventful. But, high pressure (> 15 cm of H_2O) with risk of gastric insufflation should be avoided. CO_2 waveform should always be monitored. Any change in the waveform usually heralds a change in ventilation, before it is clinically apparent (malpositioned LMA, inadequate muscle relaxation, etc.). Nerve stimulators should be routinely used for ophthalmic surgeries, because coughing and gagging are less well tolerated by ophthalmic surgeons, than their colleagues of other surgical streams.
xi. If local block is used as a supplement to GA, it should be administered only after induction. However, since the principal benefit of a local block is the avoidance of GA. But when it is used in addition to GA. Then the risk-benefit ratio is now altered. So, it may no longer be justified now. But, many anaesthesiologists still use a local block in addtion to GA, especially in ophthalmic surgeries, because it allows a very good control of patients even with lesser anaesthestic drugs and most importantly it provides better postoperative analgesia.

42 Kidney and Anaesthesia

INTRODUCTION

The kidneys are a pair of essential excretory organ which form urine, eliminate nitrogenous waste products from blood produced during protein metabolism, and maintain the electrolyte and water balance of the body. In it the fluid that resembles plasma is ultra-filtered through capillaries of glomeruli and is collected in the Bowman's capsule. It then passes down the renal tubule and its volume is reduced by the reabsorption of water. The composition of this glomerular filtrate while passing through the renal tubule is also altered by the process of tubular reabsorption and secretion of different solutes to form finally the urine whose composition may vary according to the circumstances. Many homeostatic mechanisms also try to alter the compositions of plasma or ECF by changing the composition of urine. In addition, the kidneys also secrete the renin for autoregulation of renal blood flow and blood pressure, erythroprotein for maturation of red blood cells and 1,25, hydroxycholecalciferol for the control of calcium metabolism which may modify the action of parathyroid hormone. Thus, the kidneys also subserve the function of endocrine organs. The other endocrine part of kidney include the interstitial tissue of the medulla. These cells are called the 'type I medullary interstitial cells'. They secret prostaglandin, predominantly PGE_2. The PGE_2 is also secreted by the cells of collecting duct. Prostacyclin (PGI_2) and other prostaglandins are also secreted by the afferent arterioles and glomeruli.

STRUCTURE OF KIDNEY

Structure of kidney can be studied under two headings – macroscopic and microscopic.

Macroscopic Structure

On coronal section, macroscopically the kidney presents two parts – inner renal sinus and outer renal substance itself. The outer renal substance itself again consists of two parts such as inner medulla and outer cortex.

Medulla

In coronal section the medulla presents 8 to 18 striated, pale and conical masses which are called the renal pyramids. Each pyramid has a base directed to the cortex and an apex projected into the renal sinus. This apex of renal pyramid projected in the renal sinus is called the renal papilla. Each renal papilla of renal pyramid is perforated by 16 to 20 ducts of Bellini. The renal sinus which receives renal papilla is called the calyx minor. As a rule only one calyx minor receives 1 to 3 renal papillae. Each renal pyramid, capped with the adjoining renal cortex on its outer surface forms the lobe of the kidney. There are many striations on the pyramids which are due to the following factors:

i. Loops of Henle (LOH) with their descending and ascending limbs: These long renal tubules are derived from the glomeruli which are situated in the cortex but near the medulla (juxta – medullary glomeruli) and are plunged into the substance of the pyramids. The longest loops even extended close to the renal papilla. The shortest loops which are derived from the most superficial cortical nephrons does not extend upto the medulla or if extend it reaches only close to the basal zone of the pyramid. This U shaped long loops of Henle of justa medullary glomeruli with the vasa recta act as counter current osmotic multiplier system and are responsible for maintaining the graded osmolarity of the interstitial fluid of renal pyramids or parenchyma. The apex of this pyramid is hypertoic, whereas the body is isotonic and the base of the pyramid is hypotonic to the plasma.
ii. Collecting tubules and ducts of Bellini from base to the apex the pyramids are traversed by the collecting tubules and ducts of bellini. When the collecting ducts and the ducts of Bellini pass through the hypertonic apical zone of pyramid, the urine becomes concentrated and hypertonic and is collected in the minor calyces.
iii. Arteriolae recti and venae recti: These vessels are also called the vasa recta. Arteriolae recti are the wide bored straight vessels, derived from the efferent glomerular arterioles of juxta medullary glomeruli and descend by the side of the loop of Henle. Then they break up into many straight capillaries which are arranged longitudinally and surround

the loops of Henle and finally return to the arcuate veins by the ascending venae recti. The descending and ascending vasa recta are so close to each other and the blood flow through them is so sluggish that they exchange osmolarity amongest themself and do not disturb the osmolarity (hyper) of the renal pyramid or parenchyma. This is explained by the fact that arteriolae recti (descending vasa recta) are only permeable to solutes, but not water. On the otherhand, venae recti (ascending vasa recta) is only permeable to water and not solutes. So, it drains away the water and maintains the gradient of osmolarity in the interstitium of medulla. Thus, the blood vessels of the pyramids act as counter current osmotic exchanger (Fig. 42.1).

Cortex

The outer portion of the renal substancesituated above the renal medulla is called the renal cortex. This renal cortex is granular in appearance (not striated) and consists of cortical arches and renal columns.

Cortical arches are the area of cortex which intervene between the bases of the pyramids and the surface of the kidney. Each cortical arch again consists of numerous cortical rays and smooth parts in between them. Each ray is a narrow conical mass like small pyramid. The apex of each ray is directed to the surface of kidney and the base is continuous with the striations of the pyramid. Each cortical ray is occupied by collecting tubules and the commencement of duct of Bellini. The interlobular blood vessels pass outwards along the each side of these cortical rays. The convoluted plain part of the cortex is the area which intervene between the adjacent cortical rays. These are occupied by the nephrons which consist of renal corpuscles and renal tubules with different convoluted parts of it. The renal corpuscles and tubules are arranged into 13 or more superimposed layers. The nephrons situated in the superficial portions of the cortex is called the cortical nephrons and their glomeruli are called the cortical glomeruli. The renal tubules of these cortical nephron and the capillaries around them remain confined within the cortex. On the other hand, the nephrons which are situated in the cortex, but close to the medulla are called the juxta medullary nephrons and their glomeruli are called the juxta medullary glomeruli. Their corresponding loop of Henle are long and extend into the pyramid of medulla with the straight capillaries (vasa recta) around them.

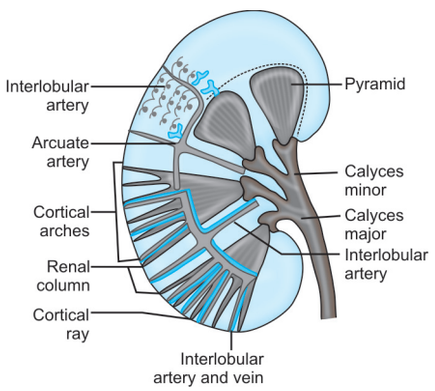


Fig. 42.1: Macroscopic structure of kidney in coronal section

Renal columns of the cortex are the areas which intervene between the adjacent cortical arches. These also extend into the medulla between the two pyramids. It contains nil or few renal corpuscles and is traversed mainly by the interlobar blood vessels.

Blood supply of kidney

Each kidney is supplied by a renal artery which is a branch of abdominal aorta. Each renal artery after its origin from the aorta reaches the hilum of respective kidney and divides into anterior and posterior trunk. The anterior trunk again subdivides into four segmental arteries and the posterior trunk continues as a separate segmental artery (i.e. there are 5 segmental arteries). These segmental arteries again divide into lobar branches which further divides into interlobar branches of arteries. These interlobar arteries then pierce the substance of kidney and run through the renal columns between the adjacent pyramids. At the junction of the cortex and the medulla these interlobar arteries divide dichotomously into arcuate arteries which run as an arch over the base of the pyramids. These arcuate arteries do not anastomose with one another. From these arcuate arteries numerous interlobular arteries arise and runs outward towards the surface of the kidney through cortex by the sides of the cortical rays. Then the extreme terminal branches of the interlobular arteries ramify beneath the renal capsule to form a subcapsular plexus (Fig. 42.2).

Each interlobular artery when it runs through the cortex by the side of the cortical rays gives origin to a number of afferent glomerular arterioles from its sides at different directions. Each afferent glomerular arteriole then forms a glomerular capillary plexus in the Bowman's capsule of cortical glomeruli. Efferent glomerular arterioles arise from these cortical glomerular capillary plexus and are somewhat narrower in diameter than their corresponding afferent arterioles. Efferent arterioles after their origin from the glomeruli of superficial zone of cortex breaks up into peritubular plexus around their corresponding renal tubules. They are usually confined within the cortex. The efferent arterioles arising from the glomeruli which are situated in the superficial part of the renal cortex do not go deep into the medulla and do not take part in the counter current multiplier system. Blood from the cortical peritubular arterial plexus then empties into the interlobular veins which again drain into the arcuate vein and finally drains into the inferior vena cava after passing successively through the arcuate, interlobar, lobar, and renal veins which correspnds with the arteries.

About 15% of the afferent glomerular arterioles arising from the base of the interlobular arteries form glomerular capillary plexus in the juxta medullary glomeruli. These glomeruli are larger and lesser in function than the superficial cortical glomeruli. The diameter of efferent arteriole

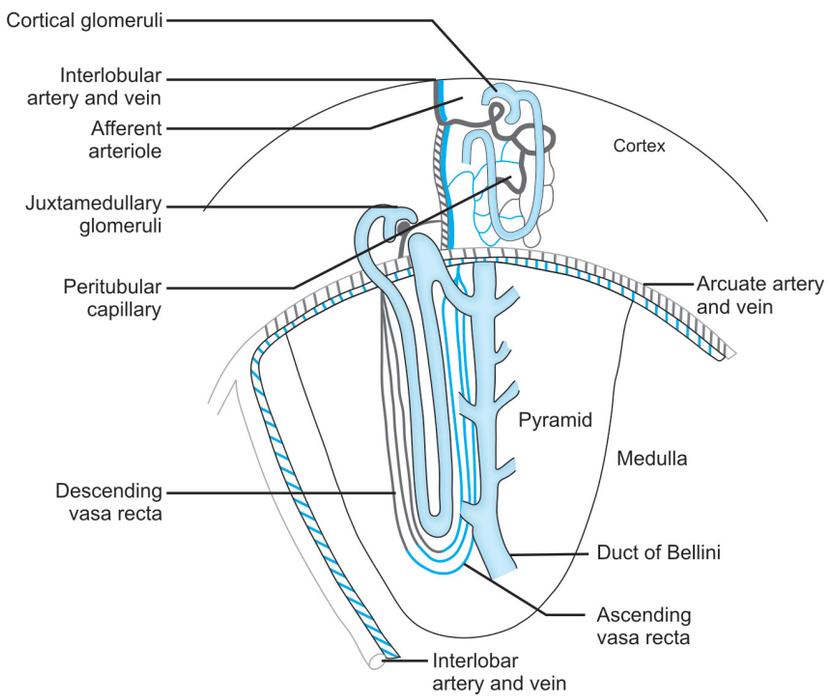


Fig. 42.2: Microscopic structure of kidney

arising from these juxtamedullary glomerular plexus is either equal or slightly larger than their corresponding afferent arteriole and goes deep straight into the renal pyramids. These straight arterioles which are a continuation of the efferent arterioles of the juxtamedullary glomeruli divide further into 20 or more straight branches (vasa recta) and later breaks up into capillary plexus (peritubular capillaries) around the renal tubule which also arise from the corresponding juxtamedullary glomeruli and goes deep into the renal medulla. These capillary plexuses then return to the arcuate veins at the corticomedullary junction by forming some straight veins. These straight arterioles which arise from these efferent arteriole of juxtamedullary glomeruli are called the descending vasa recta. The straight venules arising from the peritubular plexus, drain into the arcuate veins are called the ascending vasa recta. In the medulla these straight vessels and their divisions run parallel to one another and with the renal tubules. Thus, these straight vascular pattern with the renal tubules arising from the juxtamedullary glomeruli form the structural basis of the counter current multiplier system of the renal pyramid. This is because the endothelial linings of the glomeruli capillary plexus, cortical peritubular capillaries and the ascending vasa rectae are fenestrated, but the endothelial lining of descending vasa recta are not fenestrated and lined by continuous endothelial cells.

Nerve supply of kidney

The kidneys are supplied by both the sympathetic and parasympathetic nerves. The efferent sympathetic preganglionic innervation of kidney comes from the lower three thoracic and upper one or two lumbar segment of the spinal cord. The post ganglionic efferent sympathetic fibres are then derived from the sympathetic chain and passes through the coeliac and renal plexus. The sympathetic fibres are distributed primarily to the afferent and efferent arterioles, the proximal and the distal tubules, and the juxtaglomerular cells. In addition, the sympathetic fibres also deeply enter the renal parenchyma and supply the thick ascending limb of LOH. The afferent sympathetic fibres carrying the nociceptive pain sensation from kidney also run parallel to the efferent sympathetic fibres and enter the lower thoracic and upper lumbar segment of spinal cord, through their respective dorsal nerve roots. Other renal afferent sympathetic fibres presumably mediate a reflex, called renorenal reflex which causes decrease in efferent nerve activity and subsequently increase in the excretion of Na^+ and water in one kidney, in response to the increase in ureteral pressure in another kidney.

Both the kidneys also get the parasympathetic innervation through the vagus nerve, but its function is uncertain.

Microscopic Structure

The kidney is composed of numerous nephrons. These nephrons consists of closely packed glomeruli and their tortuous uriniferous tubules which are held together by connecting tissue stroma. This glomeruli and their uriniferous tubules consists of physiologically two parts such as secreting part which is developed from the matanephros and the collecting part which is developed from the ureteric bud. The secreting part includes the nephron consisting of renal corpuscles (glomerulus) and renal tubules and the collecting part includes the collecting tubules and ducts of Bellini.

Nephrons

The total number of nephrons in each human kidney is near about 1 to 1.3 million and forms the structural and functional unit of it. The size of each kidney is determined largely by the number of nephrons, they contain. The length of each nephron varies between 5 to 5.5 cm and consists of two parts – (i) renal corpuscles (or glomerulus) for filtration, and (ii) renal tubules for selective reabsorption and secretion. The nephrons are classified

under two broad groups – cortical nephrons (85%) and juxtamedullary nephrons (15%). The cortical nephrons are primarily responsible for the absorption of Na^+ and juxtamedullary nephrons are primarily responsible for reabsorption of water by counter current mechanism.

Renal corpuscles (glomerulus)

Renal corpuscles are also called as the Malpighian body and consists of a plexus of capillaries (called glomerular capillary plexus) and a Bowman's capsule into which this capillary plexus invaginates. The renal corpuscles are 200 µm in diameter. They are mainly located in the cortical arches and a few in the renal columns.

Glomerular capillary plexus

It is a lobulated tuft of capillary plexus and is formed by an afferent and slightly narrower efferent arteriole. This tuft of capillary plexus projects into the Bowman's capsule and is invested by the visceral layer of the latter. About 50 intercommunicating lobules are present in each glomerular capillary plexus and each lobule consists of few capillary loops which are virtually suspended in the capsular space by a mesentry, derived from the visceral layer of Bowman's capsule. This mesentry for capillary loop contains some mesangial cells which are phagocytic and contractile in nature. This mesentry also contains some acellular matrix. The contractility of these mesangial cells is due to their cytoplasmic content of some myosin like filaments and angiotensin II receptors at their surface. This suggests they have immense role in the control of blood flow through the glomerular capillary loop. They also take part in the regulation of glomerular filtration, in the secretion of various substances and also take up immune complexes. These mesangial cells are involved in the production of glomerular disease.

The afferent and efferent glomerular arterioles are approximated to each other and form the vascular pole of the nephron. The ascending limb of the loop of Henle returns to this vascular pole of the corresponding mother nephron (this happens in case of juxtamedullary nephron only, in case of cortical nephron the distal convoluted tubule comes in close contact with the vascular pole) in close contact with the afferent glomerular arteriole. Usually, the efferent arteriole is somewhat narrower than the afferent one, So it increases the hydrostatic pressure of the glomerular capillary plexus to the extent of about 60 mm of Hg and help in filtration.

Bowman's capsule

It is nothing but the dilated, blind, upper end of the renal tubule in which the glomerular tuft of capillaries invaginate. Thus, Bowman's capsule consists of a parietal layer, a visceral layer in which glomerular plexus invaginates and a capsular space which is filled with glomerular filtrate. The parietal layer of Bowman's capsule is made by a single continuous layer of flattened epithelium, resting on a basement membrane. The visceral layer is made up of a discontinuous large polyhedral cells resting on a basement membrane. These large polyhedral cells are called the 'podocytes'. From the cell body of this podocyte numerous major processes pass outwards parallel to the basement membrane. Then each major process gives rise to a number of minor processes which are attached to the basement membrane by expanded foot plates of pedicles. These foot plates or the minor processes overlap on one another to form a diaphragm with numerous slits. Therefore, when viewed from the capsular space, the podocyte cells present stellate appearance (Fig. 42.3).

Thus, the structures intervening between the blood of glomerular capillaries and the intracapsular space of Bowman's capsule are the following from within outwards:

i. Fenestrated flattened endothelial layer of capillaries with numerous pores. The pore size is about 160°A.
ii. A continuous, but porous basement membrane upon which rests the capillary endothelium. The thickness of this basement membrane is about 0.33 µm. It is formed by the interlacement of fine reticular fibres which are held together by some amorphous materials. Average pore size of the basement membrane is about 110°A.
iii. Fenestrated layer of podocytes with its processes and foot plates. The pores within this layer are arranged like zip fastener between the cell processes or foot plates. The diameter of pores in this layer is about 70°A.

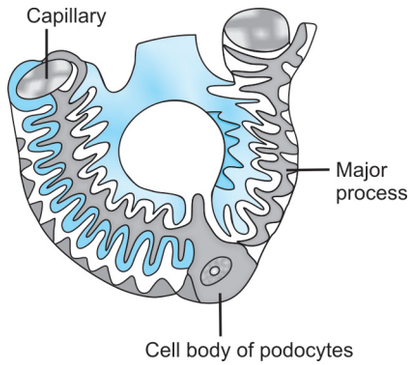


Fig. 42.3: The podocytes or glomerular epithelial cells lining the visceral layer of Bowman's capsule

The glomerular basement membrane which is situated between the capillary endothelium and the podocytes acts as a true membrane for ultrafilter. It allows the filtration of water with simple solutes of low molecular weight which are present in plasma. Therefore, the glomerular filtrate consists essentially of true plasma minus macromolecules of proteins, droplets of lipid and blood cells. Constituents of plasma which are of 68,000 molecular weight or above are held back by this basement membrane. It is also postulated that filtration through the structures intervening between the blood of glomerular capillaries and the Bowman's capsular space is governed by the electrostatic force. As for example, the matrix of the basement membrane which acts as the filtration barrier is negatively charged due to the presence of acidic glycoproteins and this opposes the passage of negatively charged molecules such as albumin (Fig. 42.4).

The diameter of each renal corpuscles (glomerulus) is about 0.2 mm and the total filtration surface area of the glomeruli of both kidneys averages about 1·5 sq.meters. The net glomerular filtration pressure in each renal corpuscles is equal to the glomerular blood pressure (60 mm of Hg) minus colloid osmotic pressure of plasma (32 mm of Hg) and Bowman capsular hydrostatic pressure (18 mm of Hg). Therefore, the net filtration pressure of human kidney comes to about 10 mm of Hg (60 − 32 − 18 = 10). Colloidal osmotic pressure of the ultra filtrate in Bowman's capsule is not taken into account for the calculation of net filtration pressure as there is no protein.

About 1700 litres of blood circulate through all the glomeruli of both the kidneys in 24 hours. Therefore, with a net filtration pressure of about 10 mm of Hg, about 170 litres of ultra filtrate are collected into the Bowman's capsular space in 24 hours. After abundant reabsorption of this filtrate by the renal tubules only about 1.5 litres of urine is formed in 24 hours. When such values are considered in minutes, then it is found that out of 650 ml normal plasma flow through both kidneys per minute, the glomerular filtration rate comes to about only 125 ml/minute. Therefore, filtration coefficient at the filtration pressure of 1 mm of Hg is 12.5 ml.

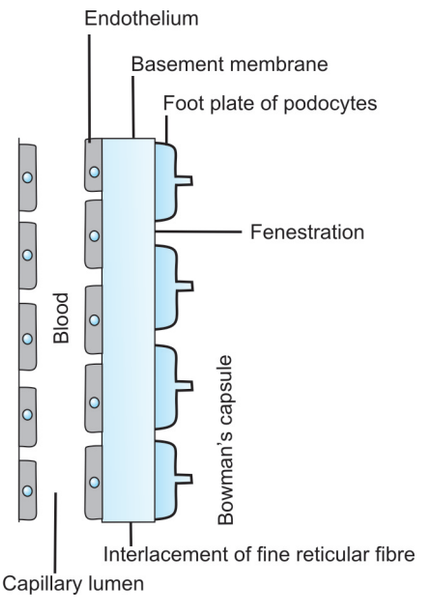


Fig. 42.4: The structures intervening between the blood of glomerular capillaries and the intracapsular space of Bowman's capsule

Renal Tubules

Bowman's capsule is continuous distally as a thin tubular structure which is called the renal tubule. Each renal tubule consist of the following parts such as proximal convoluted tubule, loop of Henle with descending and ascending limbs (or descending loop of Henle, loop of Henle, ascending loop of Henle), distal convoluted tubule and collecting tubule.

Proximal convoluted tubule (PT)

Each proximal convoluted tubule is about 69 µm in diameter and lined by a single layer of truncated columnar epithelial cells, resting on a basement membrane. The nucleus of each of these of these cells is basal in position and the cytoplasm is acidophilic. The luminal surface of each of these cells presents a brush border due to the presence of numerous microvilli. This brush border is rich in alkaline phophatase which helps in active absorption of glucose from the glomerular filtrate. The basal zone of these tubular epithelial cell presents numerous cytoplasmic infoldings. The mitochondrias in each cell are arranged radially at the basal zone in between these cytoplasmic infoldings. Close to the apical zone near the luminal surface the tubular cells are connected to one another by tight junction, but rest of the lateral surfaces of the cells are separated by intercellular clefts. The cytoplasm of the tubular cells contain acid phosphatase (in membrane bound lysosomes) which help in the hydrolysis of low molecular weight proteins into amino acid, when the former is absorbed directly from the glomerular filtrate through the tubular cells by pinocytosis. The cytoplasm of tubular cells also contains a number of enzymes like cytochrome oxidase, succinic dehydrogenase, acid phosphatase, glucose-6-phosphatase etc. which suggests active transport of some ions and small molecules from the tubular lumen in to the peritubular capillary plexus against concentration gradients through these cells (Fact file -I).

The proximal tubules allow active reabsorption of sodium (Na^+) and then subsequent reabsorption of potassium (K^+), chloride (Cl^-), calcium (Ca^{2+}), bicarbonate (HCO_3^-), phosphate, glucose, and amino acids etc. along with the absorption of Na^+. Here, water is absorbed passively as a solvent of the solute along the osmotic gradients through the specialized water channel present on the opieal surface of tubular cells which is composed of membrane protein called aquapronin-I. So, it is known as the obligatory reabsorption of water. Thus about 60 to 70% of the glomerular filtrate is absorbed from the

FACT FILE - I

Regulation of Na^+ reabsorption:

In the renal tubule, the reabsorption of Na^+ plays a major role in the reabsorption and secretion of other ions such as H^+, K^+, Cl^-, SO_4^{2-}, PO_4^{2-}, HCO_3^-, glucose, amino acids, organic acids and other substances across the walls of the tubule. For this, various pumps, cotransporter, antitransporter (or exchanger), channels, etc. are involved. At the capillary side Na^+ is actively pumped out of the tubular cell by Na^+-K^+ ATPase system, which extrudes 3 Na^+ in exchange of 2 K^+. Then, subsequently Na+ moves from the tubular lumen into the tubular epithelial cell by cotransporter or antiporter system in PT, thick portion of the ascending limb of LOH, DT and CD. The tubular cells are connected by tight junctions at their luminal end, but there is space between the cells along the rest of their lateral border. Much of the Na^+ is actively transported into these spaces through the cell and then into the capillary. The remaining portion of Na^+ is transported through the capillary side of tubular cells and then in the capillary blood. Principally Na^+ is reabsorbed at the luminal surface of tubular cells by Na^+-H^+ antitransporter at PT, Na^+-K^+-Cl^- cotransporter at thick ascending limb of LOH, Na^+-Cl^- cotransporter at DT and ENaC (sodium channel) in CD. This ENaC or Na^+ channel is the site of action of alsosterone and homeostatic adjustment in Na^+ balance.

proximal tubules. During absorption and passing through the PT although the volume of the filtrate is reduced, but the fluid remains isotonic to the blood or plasma. After absorption from the tubular lumen into the cell, the absorption of Na^+ then actively takes place at the basal zone of the columnar cells of PT by the active $Na^+ – K^+$ ATPase pump which is present on the capillary side of cell membrane. The energy of this action is derived from the ATP of the mitochondria of the proximal tubular cell. As a result more sodium with water, as a solvent, rush passively into the cytoplasm of the proximal tubular columnar cells from the tubular lumen to replenish the loss within the cell (Fig. 42.5).

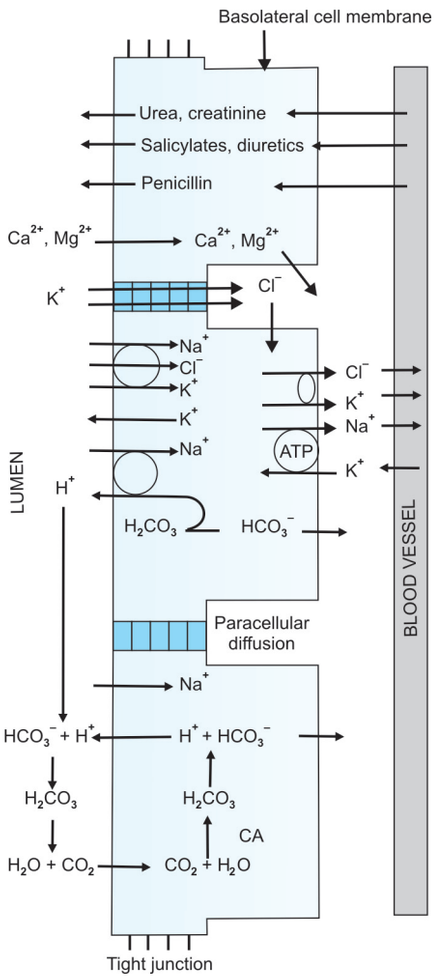


Fig. 42.5: Mechanism of secretion and absorption in proximal tubular cells

The fluid entering the proximal tubule from Bowman's capsule has a composition similar to that of plasma except for the absence of protein. But, as the proximal tubule is considered to be the bulk reabsorber of the glomerular filtrate, so it is responsible for reducing the volume of glomerular filtrate by approximately 65%. The 70% of sodium and chloride, 90% of calcium bicarbonate and magnesium, and 100% of glucose, phosphate, and amino acids all are reabsorbed with in proximal convoluted tubules. The main ion to be reabsorbed in PT is Na^+, on which the reabsorption of other ions depend.

Sodium is reabsorbed through the proximal tubular cells both by passively and actively. Passive reabsorption of sodium through the luminal surface of the tubular cells occur by two gradients: chemical and electrical. In chemical gradient reabsorption process the intracellular Na^+ concentration in the proximal tubular cells is 30 $m.molL^{-1}$ which is considerably less than the concentration of Na^+ in the tubular fluid which is about 140 m.mol/L and creates a chemical gradient for the reabsorption of it. Therefore, the Na^+ travels down the chemical gradient from the tubular lumen into the tubular cell. In electrical passive reabsorption process the electrical potential difference between the tubular cells and the lumen acts which is −70 mV. This creates an electrical gradient for the positively charged sodium ions to travel from the lumen into the cell.

It is already stated that after entry of Na^+ into the cell by passive chemical or electrical gradient, it is actively pumped out of the proximal tubular cell through their basal surfaces into the capillaries by Na^+-K^+-ATPase pump. But, in the proximal tubule this reabsorption of Na^+ is facilitated by angiotensin II and norepinephrine, while fenoldopam and dopamine inhibits it. Thus, Na^+-K^+-ATPase system situated at the capillary side of the cell membrane of proximal tubular cells provides energy indirectly for reabsorption of most of other solutes through the luminal end of these cell membrane. The net loss of intracellular +ve charges due to the absorption of Na^+ from the proximal tubular cells into the capillary blood also favours the absorption of other cations such as K^+, Ca^{2+}, Mg^{2+}, etc. from the tubular lumen into the proximal tubular cells. At the luminal side of the cell membrane of proximal tubular cells, the reabsorption of Na^+ is coupled with the secretion of H^+ by counter or antitransporter system. This secretion of H^+ into the proximal tubular lumen again helps in 90% reabsorption of filtered HCO_3^- from the lumen into the cell. Chloride (Cl^-) is also absorbed actively from the PT cells into the capillary blood by the K^+-Cl^- cotransporter system situated at the capillary side of the cell membrane of proximal tubular cells. As a result further absorption of Cl^- from the lumen in the proximal tubular cells is occurred passively following its concentration gradient. But unlike other solutes, Cl^- also traverses through the tight junction between the two adjacent proximal tubular cells. Most of the other substances also first traverse through the luminar side of the proximal tubular cells and then cross the cell membrane at the basolateral side to enter the renal interstitium, before entering the peritubular capillaries.

Other than reabsorption, proximal tubule is also capable of secreting some cations and anions. These cations are cimetidine, creatinine, quinidine, etc.; and anions are urea, salicylate, penicillin, ketoacids, diuretics, etc. But they share the same pumping mechanisms and one interfere the secretion of other. These pumps also play major role, in the excretion of many circulating toxins and X-ray dyes (Fact file-II).

Loop of Henle (LOH)

The LOH is the part of nephron which is situated next to the proximal tubule. It consists of three parts such as the thin descending limb, the thin ascending limb and the thick

FACT FILE - II

Regulation of K^+ reabsorption and excretion:

Maximum portion of the filtered K^+ of the glomerular filtrate is reabsorbed in PT, though some K^+ is secreted in this portion of the renal tubule. But the net result is maximum absorption. The thin descending limb of LOH is not permeable to K^+, whereas the thin ascending limb of LOH is permeable to K^+ like Na^+. In this thin descending and ascending limb of LOH, there is no Na^+-K^+-ATPase pump. So, in this portion of renal tubule, reabsorption or secretion of K^+ depends on the concentration gradient between the interstitium and tubular fluid. The thick ascending limb of LOH also absorbs and secrets K^+, but the net effect is more absorption than secretion. As a whole, in the absence of any complicating factors or diseases, the amount of reabsorption of K^+ is equal to the amount of K^+ filtered and the amount of K^+ secreted is approximately equal to the amount of K^+ intake. Thus, the K^+ balance of the body is maintained. The rate of K^+ secretion is parallel to the rate of flow of the tubular fluid through the distal portion of the nephron. Because with rapid flow, there is less opportunity for the tubular K^+ concentration to rise to a value that stops further secretion. In the collecing duct (CD), Na^+ is reabsorbed and K^+ is secreted, but there is no fixed one for one exchange and also much of the K^+ movement is passive. As Na^+ is reabsorbed in association with secretion of H^+, so there is competition of secretion between K^+ and H^+ for absorption of Na^+. Secretion of K^+ is decreased when the quantity of Na^+ reaching the distal tubule is reduced or when secretion of H^+ is increased.

ascending limb. The thick ascending limb is again divided into two parts – medullary portion and cortical portion. The nephron situated in the renal cortex (cortical nephron) have small LOH and does not contain the thin ascending limb. Contrary the nephrons situated in cortex near the medulla (juxtamedullary nephron) have the long LOH which goes deeps in to the medulla and contains the medullary and cortical portion of thick ascending limb of LOH. The LOH of juxta medullary nephron maintains a hypertonic medullary interstitium by counter current multipler mechanism. Among the parts of LOH, only the thick ascending part is metabolically active to absorb different solutes and has Na^+-K^+-ATPase pump. Contrary, the other parts of LOH are not metabolically active and only reabsorb Na^+

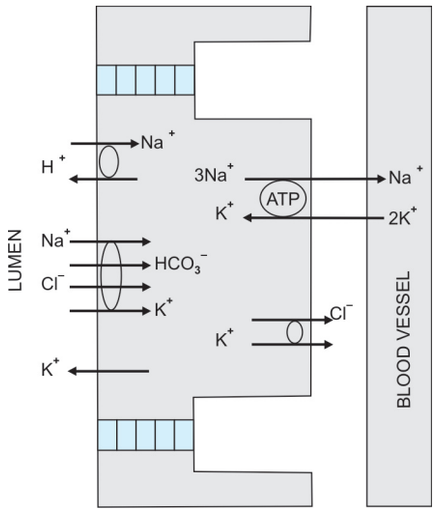


Fig. 42.6: Mechanism of secretion and reabsorption in the thick ascending limb of Henle (LOH)

or water passively, according to the concentration or osmotic gradient between the tubular fluid and interstitial tissue of kidney. The thin decending limb is permeable to H_2O and impermeable to Na^+, therefore it reabsorbs H_2O but not Na^+. Whereas the thin ascending limb is impermeable to H_2O and permeable to Na^+. Therefore it reabsorbs Na^+ but not water (Fig. 42.6).

The thick ascending part of LOH is impermeable to water, because water channel aquaporin is not expressed in this segment, but Na^+, K^+, HCO_3^- and Cl^- are reabsorbed. The reabsorption of K^+, HCO_3^- and Cl^- are coupled with reabsorption of Na^+ which still results from the Na^+-K^+-ATPase activity on the capillary side of the tubular cell membrane. The water impermeable thick ascending limb of LOH is also called the diluting segment of nephron. This is because as the Na^+ and other solutes are reabsorbed from this segment of tubular lumen, then only water remains in this part of tubule and reduce the osmolality of tubular fluid. Like the cells of the proximal tubule as the Na^+ is reabsorbed actively into the capillary blood through the cell membrane of capillary side by ATPase activity, then the Na^+ from the lumen is further absorbed through the cell membrane of the luminal side. This is coupled with the secretion of H^+ into the lumen by the Na^+-H^+ antiporter systemwhich helps in the absorption of Na^+ and exeretion of H^+. Another important symporter system which is present on the luminar side of cell membrane couples the reabsorption of K^+, Cl^- and HCO_3^- along with the reabsorption of Na^+ across the luminal side of cell. This is the major site of action of loop diuretics which inhibit the reabsorption of Na^+ along with the water at the thick ascending limb of loop of Henle. As the concentration of K^+ in the tubular lumen of this segment is much lower than Na^+ and Cl^- concentration so there is need for K^+ to be recycled in this segment. It means K^+ should be secreted in the tubular lumen and reabsorbed. Ca^{2+} and Mg^{2+} are also reabsrobed from this thick ascending limb of LOH. At this segment of renal tubule the reabsorption of Ca^{2+} is controlled by PTH (parathyroid hormone). The fluid leaving the thick ascending limb of LOH is hypotonic whose osmolality varies between 100 to 200 m.mol/L. On the otherhand, the interstitium surrounding the tip of LOH is hypertonic. Therefore a couter current multiplier mechanism is established between the tubular fluid in LOH and the interstitium of kidney which increase gradually with the increase of the depth of medulla from cortex. This couter current mechanism includes the collecting tubules, LOH and their capillaries. This LOH accounts for another 15% absorption of glomerular filtrate.

Distal (convoluted) tubules

This portion of the renal tubule lies next to the cortical portion of thick ascending limb of LOH. The tubular cells in this portion are tightly attached with each other and maintains a relative impermeability to both water and Na^+. The distal tubule receives hypo osmolar fluid from the thick ascending portion of LOH and slightly modifies its composition (Fig. 42.7).

This segment has less capacity for Na^+ reabsorption than the segment before it, but

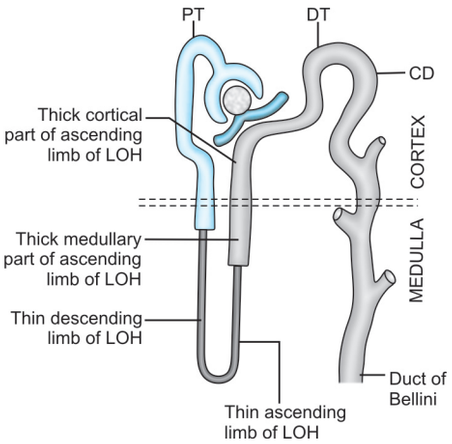


Fig. 42.7: Nephron
PT = Proximal tubule, LOH = Loop of Henle, DT = Distal tubule, CD = Collecting duct

it shows considerable capacity to adapt it in the face of incerased Na^+ load from the earlier part of nephron. This portion of the renal tubule accounts for about 5% reabsorption of glomerular filtrate. This reabsorption include Na^+, K^+, Cl^-, Ca^{2+} etc. Like other parts of nephron the reabsorption of Na^+ in this part is also associated with Na^+-K^+-ATPase activity on the capillary side of the tubular cells. But on the luminal side of te tubular cells Na^+ is absorbed from the lumen by the concentration gradient created by the absorption of it in the capillary blood by Na^+ - K^+ ATPase system, and Cl^- is reabsorbed by the Na^+- Cl^- cotransporter system. Na^+ reabsorption in this segment is directly proportional to the amount of Na^+ delivered in this part of tubule from the LOH. In this portion of renal tubule the reabsorption of Na^+ and Ca^{2+} is controlled by aldosterone and parathyroid hormone (PTH), respectively (Fact file - III).

Collecting tubule (CT) or duct

This portion of the renal tubule also can be divided into cortical and medullary portion which normally accounts for the reabsorption of last 13 to 13.5% of glomerular filtrate, and finally form and modify the composition of urine.

The cortical portion of CT has two types of cells – principal cells (P cells) and intercalated cells (I cells). The P cells primarily reabsorb Na^+ and secret K^+ with the help of aldosterone, whereas I cells are responsible for the acid-base regulations. Aldosterone enhances the Na^+-K^+-ATPase activity on the capillary end of the P cells in this part of nephron and increase the active reabsorption of Na^+ at the capillary side and passive reabsorption of it at the luminal side of tubular cell with subsequent indirect secretion of K^+ in the tubular lumen. Aldosterone also enhances the H^+ secreting ATPase acitivity on the luminal border of I cells and increases the secretion of H^+. Unlike PT, secretion of H^+ in this part of renal tubule is independent of reabsorption of Na^+. Because in this part of renal tubule most of the H^+ is secreted actively by an ATPase driven proton pump, where aldosterone acts and increases or decreases its secretion. So, hyperaldosteronism is associated with alkalosis. These I cells are like the parietal cells of stomach and contains abundant carbonic anhydrase (CA) enzyme which also helps in the formation of H^+. These I cells additionally also have a luminal H^+-K^+-ATPase pump which secretes H^+ in the exchange of absorption of K^+. As these I cells help in the regulation of acid base balance, they also have anion exchange protein (such as Cl^--HCO_3^- exchanger) which are capable of preventing the reabsorption of HCO_3^- in exchange of Cl^- in response to large alkaline loads. With Cl^- the Na^+ and water is also absorbed, but the absorption of water is in excess than Na^+ and makes the tubular fluid from hypoosmolar to iso-osmolar (Fig. 42.8).

FACT FILE - III

Reabsorption and excretion of HCO_3^- :
The amount of reabsorption and secretion of HCO_3^- is proportional to the amount of filtration in Bowman's capsule and the acid-base status of the individual. The concentration of HCO_3^- in the plasma and consequently in the glomerular filtrate is normally about 24 m.mol/L. The process of reabsorption of HCO_3^- does not involve any direct transport system in the tubular cells. Because HCO_3^- is not permeable to cell membrane. For absorption of HCO_3^- most of the secreted H^+ reacts with HCO_3^- to form H_2CO_3. Then this H_2CO_3 breaks down to form CO_2 and H_2O. In most of the tubular cells (except the distal tubule and collecting tubule) there is presence of carbonic anhydrase (CA) in luminal border. Thus this CA facilitates the formation of CO_2 and H_2O. Then the CO_2 as it diffuses readily across all the biological cell membrane and so enters the tubular cells. In the cell, CO_2 again reacts with H_2O to form H_2CO_3 which further breaks down to yield HCO_3^- and H^+. Then this HCO_3^- passes to the blood and H^+ goes to the lumen. This is the mechanism by which HCO_3^- is absorbed. For each mole of HCO_3^- removed from the tubular fluid, one mole of HCO_3^- diffuses from the tubular cells into the blood but these two HCO_3^- ions are not the same.
In acidosis, when the plasma HCO_3^- concentration is low, then all the filtered HCO_3^- is reabsorbed through tubule by the use of secreted H^+ ion. The excess of H^+ ion after neutralisation of HCO_3^- is excreted through urine and the urine becomes acidic. The excess of H^+ also react with NH_3 and form NH_4^+ which is excreted through urine. But, in alkalosis when the plasma HCO_3^- concentration is high above the normal level, then some filtered HCO_3^- appears in the urine after neutralisation of all the H^+ and the urine becomes alkaline. The normal HCO_3^- level in plasma is 24 to 27 m.mol/L.

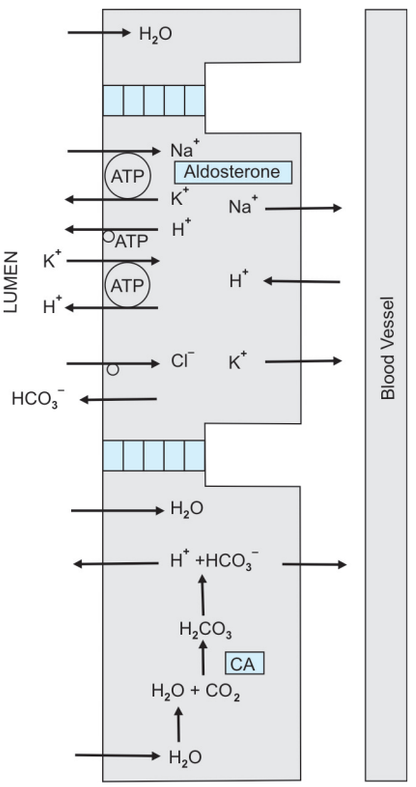


Fig. 42.8: Mechanism of secretion and reabsorption of the cortical portion of collecting tubule (CT)

The medullary portion of CT runs down through the hypertonic interstitium of medulla and joins with other CT to form the duct of Bellini which empties at the tip of the pyramid. This medullary portion of CT is the principal site of action of ADH or arginine vasopressin (AVP). Therefore, permeability of water in this portion of CT is entirely dependent on the presence of ADH. This ADH acts through V receptors which are situated on the special water channel called aquaporin 2. These V receptors are also responsible for increase the vascular resistance. Dehydration increases ADH secretion and increases the permeability of luminal surface of this portion of CT to water. As a result more and more water is reabsorbed and concentrated urine is formed whose osmolality varies upto 1400 m.osm/L. On the Contrary, proper hydration inhibits the secretion of ADH and permeability of this portion of CT to water is lost. This results in non absorption of water and diluted urine whose osmolality varies between 100 to 200 m.osm/L. In the absence of ADH (diabetes insipidus) the osmolality of urine may come down to 30 m.osm/L. This medullary portion of CT also contains P and I cells. Like cortical portion P cells here also regulate the reabsorption of Na^+ by the help of aldosterone and I cells regulate the acid base balance by secreting H^+ in the form of titrable acids of phosphates ($H_2PO_4^-$) and ammonium ions (NH_4^+).

Urea contributes to the establishment of osmotic gradient in the medullary interstitial tissues. Thus, it helps to form a concentrated urine in the collecting duct. The mechanism is like that the fluid entering the distal tubule is hypoosmolal (100 m.osm/L). In the collecting tubule the osmolality of the tubular fluid returns to that of plasma (300 m.osm/L) due to absorption of water by ADH. But unlike the contents of PT, the solute component of DT largely consist of urea, creatinine and other excreted compounds. In the presence of ADH water moves out of the CT and the tubular fluid becomes hypertonic and the urea becomes highly concentrated. In the presence of ADH, the innermost part of medullary CT becomes permeable to urea also. Thus, urea then diffuses out deeply into the medullary interstitium and subsequently the amount of urea in the urine varies with the amount of urea filtered. This in turn varies with the dietary intake of protein. Therefore, high protein diet increases the ability of the kidney to concentrate the urine (Table 42.1).

Table 42.1: Functional divisions of nephron

A. Glomerulus	:	Ultrafiltration
B. Proximal tubule		
Absorption	:	Water, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphates, urea, uric acid, glucose, protein, amino acid
Secretion	:	Ammonia products, some anions and cations
C. Loop of Henle		
Absorption	:	Water, sodium, potassium, chloride, calcium, magnesium.
Secretion	:	Nil
D. Distal tubule		
Absorption	:	Water, sodium, potasium, chloride, bicarbonate, calcium.
Secretion	:	Hydrogen ion, potassium, calcium.
E. Collecting duct		
Absorption	:	Water, sodium, potassium, chloride, bicarbonate.
Secretion	:	Hydrogen ion, potassium, ammonia products.
F. Juxtaglomerular apparatus	:	Secretion of renin

Juxtaglomerular apparatus or complex (JGA)

The renal tubule after making a sharp bend at the loop of Henle ascends upwards and reaches again near to its mother glomerulus from which the renal tubule arises. Here, the renal tubule rests between its afferent and efferent arterioles, forming juxta glomerulus apparatus. Thus, the JGA is formed by the afferent arteriole, efferent arteriole, renal tubule (thick ascending limb of LOH or distal tubule) and the intervening tissue resting between them. In this junction or JGA, the smooth muscle cells of afferent arterioles are modified and called the juxtaglomerular (JG) cells. The epithelial cells of renal tubule in this junction are also modified and are called the macula densa cells. The specialised mesangial cells, entangled between the afferent arteriole, efferent arteriole and renal tubules also takes part in the formation of JGA and are called the Lacis cells. Thus, the JGA is consisted of: granular juxtaglomerular cells of afferent arteriole, macula densa cells of thick ascending limb of LOH or distal tubule, and agranular interstitial cells of Lacis. The JGA is thought to be related with some way in control of circulating blood volume, BP, renal blood flow, salt balance, and erythropoiesis (Fig. 42.9).

The JG cells are deeply innervated by the sympathetic nervous system and contain baroreceptors. This responds to the changes of pressure of afferent arteriole and regulate the blood flow through glomerulus and subsequently GFR. These JG cells also contain an enzyme, named renin. The secretion of this renin is determined by the degree of stretching of the afferent arteriole, Na^+ concentration of macula densa cells and β-adrenergic stimulation. After the release of renin in response to hypotension, it acts on a special circulating protein in the blood stream, named angiotensinogen

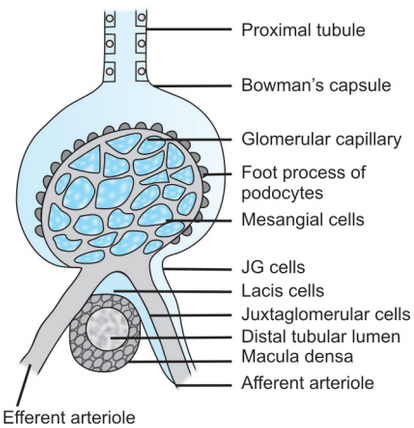


Fig. 42.9: Juxtaglomerular apparatus

which is synthesized by the liver. By the action of renin, angiotensinogen is converted to inert angiotensin I (decapeptide) which is then rapidly converted to angiotensin II (octapeptide) in the lungs by the angiotensin converting enzyme (ACE). This angiotensin II plays a major role in the secretion of aldosterone, control of BP, blood flow in the kidney and formation of volume of urine. Angiotensin II is also formed locally in the kidney and there is the presence of angotensin II receptors which controls the absorption of Na^+ through renal tubules other than aldosterone. Except kidneys and lungs there are also other extrarenal sites where renin and angiotensin II are synthesized locally. These are vascular endothelium, brain tissue and adrenal gland. Angiotensin II modulates the tone of afferent and efferent arterioles and subsequently maintain the GFR. It is also known that under hypoxic state or following haemorrhage, a hormone named erythropoietin is formed in the blood by the interaction of renal erythropoietin factor (REF) with the plasma globulin. This erythropoietin stimutes the process of erythropoiesis. This REF is secreted by JG cells.

The cells of macula densa appear to have chemoreceptor function. It senses the concentration of NaCl in the tubular lumen of thick ascending limb of LOH or distal tubule and regulate the secretion of aldosterone from adrenal gland which in turn regulate the reabsorption of Na^+. The function of Lacis cells is still unknown. (Fact files- IV, V, VI, and VII)

RENAL CIRCULATION OR BLOOD FLOW (RBF)

Both the kidneys receive 20 to 25% of the total cardiac output as their blood supply. This results in total 1 to 1.5 L/min of blood flow through both the kidneys. There is much discrepancy regarding the flow of blood, delivery of O_2 and the consumption of O_2 between the renal cortex and medulla. Approximately, 80% of the total blood flow of each kidney goes to the cortical nephron in superficial cortex and only 15% reach the juxtamedullary nephron in juxtamedullary cortex. The medulla receives only the remaining 5% of the total renal blood flow. The average O_2 tension in medulla is about 10 to 15 mm of Hg. Whereas the O_2 tension in renal cortex is 50 mm of Hg. This indicates that renal cortex has high blood flow, but extracts little O_2 than medulla. This is because cortex is metabolically less active than medulla as it is concerned mainly for filtration function. Whereas, the renal medulla is metabolically more active than cortex as it is mainly concerned for reabsorption of more solute and water to maintain high osmotic gradient of interstitium and to concentrate the urine respectively (Table 42.2).

Table 42.2: Distribution of RBF between the medulla and cortex

	Medulla	*Cortex*
Blood flow (ml/min/gm)	0.05	5
% of RBF	5	95
PO_2 (mm of Hg)	10	50
O_2 extraction ratio	0.8	0·2

FACT FILE- IV

Excretion of water through urine:

Every day normally about 150 to 180 L of fluid is ultra-filtered through all the glomeruli of both the kidneys. But the average daily urine formation varies between 1 to 1.5 L. In adverse situation this volume of urine may come down to 500 ml or may go upto 23 L (diabetes insipidus). On the other hand the same load of solute is excreted in 24 hours within this varying volume of urine with the varying osmolality which varies from 1400 m.osm/L to 30 m.osm/L. Normally among this ultra-filtrate, 87% of water is reabsorbed mandatarily. The reabsorption of remaining 23% varies without affecting the excretion of total solute. When the urine is concentrated the water is reabsorbed in excess of solute. On the otherhand, when it is diluted water is lost in excess of solute. The key regulator of this water absorption and excretion is ADH (vasopressin) which acts on the collecting duct.

In the PT, water moves out of the tubule along with the osmotic gradient which is set up by the active transport of solutes and thus isotonicity is maintained. Therefore, the tubular fluid passing at the end of PT is isotonic or iso-osmotic. About 65% of the filtered water and 65% of the filtered solute is absorbed in the PT. In the thin descending and ascending limb of LOH, there is no system of pump for active transport of Na^+. The thin descending limb of LOH is permeable to water, whereas the thin ascending limb of LOH is permeable to Na^+only. On the other hand, there is graded increase in the osmolality of interstitium of renal medulla from outer cortex to the tip of pyramid. Therefore, the fluid flowing down the descending limb of LOH gradually becomes hypertonic as water moves out of this part of renal tubule into the hypertonic interstitium. Then this hypertonic fluid gradually becomes hypotonic as it flows up the thin ascending limb of LOH, because in this portion only Na^+ moves out, leaving water in the tubule.

In the thick ascending part of the limb of LOH active Na^+ transport system is present and is also impermeable to water. Therefore, fluid passing up the thick ascending limb of LOH gradually becomes more dilute and when it reaches the top it becomes maximum hypotonic in relation to plasma. During passing through loop of Henle (LOH), 15% of filtered water is removed. So, approximately next 20% of the filtered water enters the distal tubule (DT). DT is less permeable to water, but more permeable to solutes. So, continuous removal of solute in excess of water from DT further dilutes the fluid in this segment of nephron. 5% of filtered water is removed in this segment.

The collecting duct (CD) has two portion - cortical and medullary. The cortical portion of the CD receives hypotonic fluid from DT. Vasopressin or ADH secreting from the posterior pituitary acts on this portion of renal tubule i.e. CD. In the presence of enough vasopressin maximum antidiuretics occurs. Therefore, maximum amount of water moves out of hypotonic fluid in cortical portion of collecting duct and enters into the interstitium of cortex. Thus here the tubular fluid becomes isotonic. In this fashion 10% of filtered fluid is removed in the cortical portion of CD. Next, isotonic fluid enters the medullary portion of CD. Here, additional 3.5% or more of the filtrate is reabsorbed in the hypertonic interstitium of medulla and produce concentrated urine. In human being, the osmolality of urine may reach 1400m.osm/L which is 5 times greater than that of plasma with total 99.5% of filtered water being absorbed.

In the absence of ADH or vasopressin (AVP), CD is impermeable to water. The fluid in CD, therefore, remains hypotonic and large amount of tubular fluid flow into the renal pelvis. In human being in such circumstances, the urine osmolality may be as low as 30 m.osm/L.

FACT FILE - V

Excretion of H^+ and acidification of urine :

The cells of the proximal tubule, thick ascending limb of LOH, distal tubule and the collecting duct secrete H^+, like the cells of gastric gland. This secretion of H^+ primarily involves the Na^+-H^+ antiporter system situated on the luminal side of cell membrane of the tubular cells. This Na^+-H^+ antiporter system acts as secondary to Na^+-K^+ ATPase system on the capillary end of tubular cells which lowers the intracellular Na^+ concentration and subsequent entry of Na^+ from the tubular lumen coupled with extrusion of H^+. This H^+ comes from the intracellular dissociation of H_2CO_3 which is formed by the reaction of CO_2 and H_2O. The HCO_3^- formed from dissociation of H_2CO_3 diffuses back into the interstitial fluid. Thus for each H^+ secreted one Na^+ and one HCO_3^- enter the interstitial fluid and is preserved in body.

In respiratory acidosis, there is more CO_2 in the body, which produces more H_2CO_3, and more H^+ and HCO_3^-. This means more H^+ is excreted through urine and urine becomes acidic. The excess HCO_3^- produced from excess CO_2 is preserved in body and produce compensatory metabolic alkalosis. In respiratory alkalosis the reverse is occurred. There is less CO_2 due to more washout through lungs. This leads to less H_2CO_3 and subsequently less H^+ and HCO_3^- which leads to less excretion of H^+ and urine becomes alkaline (metabolic acidosis). In metabolic acidosis there is more formation of H^+ in the body. So, there is more excretion of H^+ through urine and urine becomes acidic. Subsequently, due to more H^+ there is more consumption of HCO_3^- and more formation of CO_2 and H_2O. This excess CO_2 is excreted through lungs (compensatory metabolic alkalosis). on the contrary, in metabolic alkalosis (e.g. vomiting) the reverse is occurred. There is less H^+ or more HCO_3^- in the body. Therefore, the body tries to preserve the H^+ and less excretion of it. Thus, urine becomes alkaline. Due to less H^+ there is less consumption of HCO_3^- and less formation of CO_2. This causes less excretion of CO_2 through lungs (compensatory respiratory acidosis).

The amount of H^+ secreted in the tubular fluid depends upon the pH of it. If the pH of tubular fluid is 4.5 i.e. an H^+concentration in it is 1000 times more than plasma, then secretion of H^+ stops. Thus, the pH of urine which goes upto maximum is 4.5. This is normally reached in the collecting ducts. If there is no buffer in the renal tubules which neutralise the H^+, then pH will rise rapidly and the secretion of H^+ will stop. There are three important buffer in tubular fluid which remove the free H^+ and permits more H^+ to be secreted. These are HCO_3^- forming CO_2 and H_2O, HPO_4^{2-} forming $H_2PO_4^-$ and NH_3 forming NH_4^+. Among these HCO_3^- is most important which maximum neutralises the H^+. This is because the concentration of HCO_3^- in plasma and subsequently in glomerular filtrate is normally about 24 mEq/L, whereas that of phosphate is only 1.5 mEq/L. The secreted H^+ reacts with diabasic phosphate (HPO_4^{2-}) to form monobasic phosphate ($H_2PO_4^-$). This happens to the greatest extent in the distal tubules and collecting ducts. Because it is here that the phosphate which escapes proximal reabsorption is greatly concentrated by the reabsorption of water. The reaction of H^+ and NH_3 occurs maximally in the proximal and distal tubules.

Each H^+ that reacts with the above mentioned buffer such as $H_2PO_4^-$ and NH_3 constitutes or called the titrable acidity of urine. Because this is measured by determining the amount of alkali which is needed to change the urinary pH to 7.4 which is the pH of glomerular filtrate or plasma. But it does not measure the HCO_3^- part, because it is converted to CO_2 and H_2O. It measures the other two fractions of acid secreted.

FACT FILE - VI

Secretion of ammonia:

Multiple reactions in the renal tubular cells produce NH_4^+. Among these the principal reaction is conversion of glutamine to glutamate with one molecule of NH_4^+. This reaction is catalysed by glutaminase which is abundant in renal tubular cells. Glutamate is again converted to α-ketoglutamate by the help of enzyme glutamic dehydrogenase, when more NH_4^+ is produced. Subsequently, metabolism of α-ketoglutamate utilises $2H^+$ and makes free $2HCO_3^-$. In the tubular cells NH_4^+ remains in equilibrium with NH_3 and H^+. pK value of this equilibrium is 9. So in acidosis this equilibrium shifts towards NH_3 and therefore more NH_3 is produced from NH_4^+. Then this NH_3 enters the tubular fluid, because NH_3 is lipid soluble and diffuses across the cell membrane down its concentration gradient. In the tubular fluid it reacts with H^+ and form NH_4^+ which remains in the urine. Thus, excretion of NH_4^+ causes further removal of H^+ from tubular fluid and consequently further enhancement of secretion of H^+.

$$\text{Glutamine} \xrightarrow{\text{Glutaminase}} \text{Glutamate} + NH_4^+$$

$$\text{Glutamate} \xrightarrow[\text{dehydrogenase}]{\text{Glutamic}} \alpha\text{-ketoglutamate} + NH_4^+$$

$$NH_4^+ \rightleftharpoons NH_3 + H^+$$

FACT FILE - VII

The medullary concentration of solutes and osmolality (1400 m.osm/L) is very high. This is because (i) the ascending limb of loop of Henle (LOH) actively reabsorbs Na^+ and Cl^-, but not water into the interstitium of medulla and (ii) large amount of urea enter the deeper part of medulla from the collecting duct. This is because the cortical and the outer medullary part of the collecting duct are the sites of passive diffusion of water, but impermeable to urea. So, the urea gradually becomes concentrated in the collecting duct of deeper medulla, which is permeable to it and moves passively down its concentration gradient. Again the high concentration of urea, Na^+ and Cl^- in the deeper medulla are not washed out, because blood flow in this portion (medulla) is low and the configuration of capillaries (vasa recta) allows countercurrent exchange. Thus all these factors cause the gradual increase of tonicity from outer cortex to medulla.

On the contrary, the renal medulla has little blood flow (to maintain osmotic gradient) and extracts large amount of O_2 (due to high metabolic acitivity) than cortex. Therefore, severe hypoxia and necrosis could develop first in the medulla, sparing the cortex during compromised circulation. Thus, in conclusion we can say that kidney is such an organ where O_2 consumption is primarily determined by the blood flow, but not by the metabolic activity or O_2 demand. Whereas, in other organs the blood flow is primarily determined by the O_2 demand and the subsequent consumption of it by this tissue which again depends on its metabolic activity. In adverse condition the sympathoadrenal response tries to redistribute the flow of blood from the cortex to the medullary area by cortical vasoconstriction, mediated by the increased level of catecholamines and angiotensin II.

When the mean systemic arterial pressure (MAP) is 100 mm of Hg, then the glomerular capillary pressure at the afferent arteriole is about 40 mm of Hg. This pressure further drops to only 1 to 2 mm of Hg at the efferent end of arteriole after the blood flows through the glomerular capillaries. Then, it drops much at the peritubular capillaries and comes down to about

10 mm of Hg. Therefore, the glomerular capillary pressure gradient which is similar to the pressure of afferent arteriole is about 40% of the mean systemic blood pressure.

Regulation of Renal Blood Flow (RBF)

The renal blood flow is regulated by some very complex mechanisms which are interplayed by several factors such as autoregulation (intrinsic), tuboglomerular feed back (reflex), hormones and nerves.

Intrinsic autoregulation of RBF

The RBF usually remain autoregulated between the mean systemic arterial pressure of 80 to 200 mm of Hg. This is due to the changes in renal vascular resistance in response to the changes of pressure within this value and keeps the RBF relatively constant. This type of autoregulation is also seen in other organs such as brain, liver, heart, etc., and several factors contribute to it. This autoregulation is also present in denervated, isolated, perfused and transplanted kidney, but it can be prevented by administration of drugs which paralyses the vascular smooth muscles. Thus, it indicates that this autoregulation is an intrinsic myogenic response of afferent arterioles (vasoconstriction and dilatation) to the changes in blood pressure which keeps the RBF constant. This intrinsic myogenic response to regulate the RBF is nothing but the direct contractile response of the smooth muscles of the afferent arteriole to stretch, mediated by the baroreceptors. Nitric oxide (NO) may also be involved in this intrinsic autoregulation of RBF. The RBF is generally decreased or autoregulation fails when the MAP falls below the 80 mm of Hg. Outside this limit the autoregulation of RBF becomes pressure dependent i.e. when the pressure increases, RBF decreases and vice versa. Glomerular capillary pressure and subsequently the filtration pressure gradient comes down to zero and filtration ceases when the MAP falls to 40 to 50 mm of Hg (Fact file - VIII).

FACT FILE - VIII

The release of renin from juxtaglomerular apparatus is controlled by several mechanisms. A reduction in renal artery perfusion pressure stimulate the baroreceptors in afferent arterioles. Then, subsequent stimulation of sympathetic nerve and increasd circulating catecholamines act on α and β adrenergic receptors on the afferent arteriole which produces vasoconstriction and simultaneously causes release of renin. The cells of medulla densa also sense the increased concentration of Na^+ in the tubular fluid and triggers the release of renin from the afferent arteriole in hypotension. Thus, this tubuloglomerular reflex appears to play a role in modulating GFR, during normal and abnormal renal function through feed back loop. Hence, renin secretion is stimulated by actual hypovolaemia (haemorrhage, duresis, Na^+ loss etc.) and relative hypovolaemia or decreased perfusion (heart failure, IPPV, sepsis etc.).

Regulation by tubuloglomerular feedback mechanism

This tubuloglomerular feedback reflex is very important to maintain the renal circulation and subsequently the GFR, over a wide range of variation of perfusion pressure. Although, the mechanism of this reflex is very poorly understood, but still the macula densa cell is thought to be responsible for controlling this reflex by changing the tone of afferent arteriole and subsequently the RBF with pressure gradient of glomerular capillary. This tubuloglomerular reflex is nothing but the changes of RBF and GFR with the changes of flow of fluid through the renal tubules, mainly the thick ascending limb of LOH and distal tubule. Increase in tubular flow through the thick ascending limb of LOH or DT reduces the RBF and GFR, whereas decrease in tubular flow increase the RBF and GFR. Thus, it is completely a compensatory mechanism.

During hypotension when the thick ascending limb of LOH becomes ischaemic, then reabsorption of NaCl through this part of renal tubule ceases and delivery of NaCl to macula densa cells is increased. This causes increased release of renin and angiotensin II from afferent arteriole and triggers the arteriolar constriction and decreased GFR. During overhydration the reverse occurs. Thus, the tubuloglomerular reflex mechanism induces the oliguria, conserve intravascular volume and protects the organism from dehydration. Another probable mechanism of tubuloglomerular reflex is local release of adenosine. It inhibits the release of renin and dilate the afferent glomerular arteriole. In dehydration the release of adenosin is inhibited and the secretion of renin is increased which causes constriction of afferent arteriole and decrease of GFR. In overhydration the opposite occurs and GFR is increased.

Hormonal regulation

For this type of autoregulation two important hormones, named renin and angiotensin II come into play for action. During any circumstances such as in hypotension, surgical stress, trauma, severe sepsis, etc.; there is stimulation of sympathetic system and secretion of these two hormones (first renin and then conversion of renin to angiotensin) which causes the afferent arteriolar constriction and reduces the RBF with reduction of GFR. Thus, they preserve the ECF volume. Both the afferent and efferent arterioles are constricted, but as because the efferent arterioles are smaller, so its resistance becomes greater than that of the afferent arterioles and minimum GFR, therefore, tends to be preserved. This autoregulation can also be carried out by adrenal catecholamines such as epinephrine, norepinephrine and by aldosterone. Angiotensin induced secretion of vasoconstrictive prostaglandin F_2 is also responsible for this autoregulation. Inhibition of synthesis of PGF_2 by NSAID can thus block this autoregulation (Fact file-IX).

Renal synthesis of some vasodilating prostaglandins such as PGE_2, PGI_2, etc. is also an important protective mechanism during the period of systemic hypotension and renal ischaemia. Another local hormone, named ANP (arterial natriuretic peptide) is secreted from the arterial

FACT FILE- IX

Two mutually dependent but opposing neuro hormonal system is present in the kidney which control the BP, intravascular volume and concentration of salt with water homeostasis, by a complex set of interactions. Among these the renin - angiotensin II - aldosterone - ADH system acts against the hypovolaemia and hypotensin by promoting vasoconstriction (renin and angiotensin) and salt and water retention (aldosterone and ADH). On the otherhand, the another system including bradykinins, some prostaglandins and ANP protect against hypervolaemia and hypertension by producing vasodilatation and excretion of salt and water.

myocytes. It is a direct smooth muscle dilator and antagonise the vasoconstrictive action of epinephrine, norepinephrine and angiotensin II. It preferentially constricts the efferent arterioles and dilates the afferent arterioles. It, thus, effectively increases the GFR and protects the kidney during hypotension. ANP also inhibits the release of aldosterone, induced by renin and angiotensin II and its (aldosterone) action on renal tubules (Fig. 42.10).

Neuronal regulation

Sympathetic system innervates the juxtaglomerular cells through β_1-receptors. It also innervates the general renal vasculature with afferent and efferent arterioles through the α_1 and α_2-receptors. Both these receptors mediate vasoconstriction and is responsible for the stress induced reduction in GFR. The action of sympathetic nerves on juxtaglomerular cells is also mediated by the β_1-receptors and causes increased secretion of renin. The proximal and distal tubules and the thick ascending limb of LOH are thickly innervated by sympathetic nerves. Here, α_1-receptor is responsible for reabsorption of Na^+ in proximal tubules. Whereas, α_2-receptors inhibits the reabsorption of Na^+ and promotes the excretion of H_2O. There is also D_1 and D_2 receptor in kidney. Activation of D_1 receptor directly dilates the afferent arterioles. Whereas, the activation of D_2 receptors, situated on the presynaptic membrane of postganglionic neurone inhibit the release of norepinephrine and indirectly dilates the afferent arterioles. Thus, dopamine (acting on both D_1 and D_2 receptors) and fenoldepam (acting only on D_1 receptor) cause the dilatation of afferent glomerular arteriole and increases the GFR (Fact file- X).

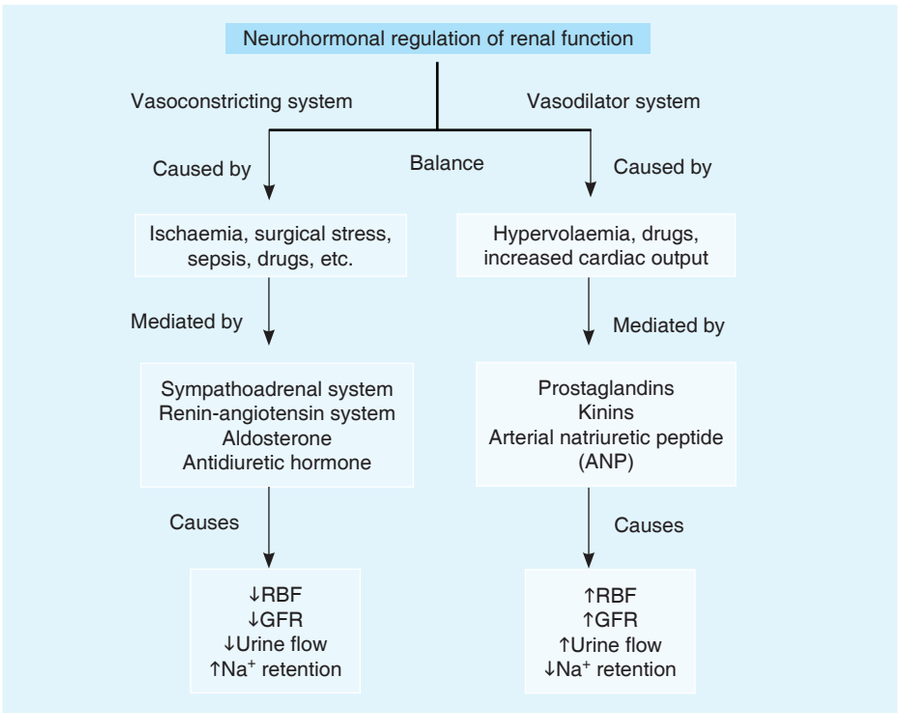


Fig. 42.10: Neurohormonal regulation of renal function

Measurement of RBF

Renal blood flow can be measured by indicator dilution technique, radiolabeled tracers, doppler USG, electromagnetic procedure, or by some other types of flowmeter. It can also be measured by applying the Fick principle. For Fick principle, a nontoxic substance which is completely cleared by the kidney and not metabolised or stored or produced by body or kidney and does not itself affect the RBF is used. By Fick method, first renal plasma flow (RPF) is measured, and then from it renal blood flow (RBF) is calculated. This is because the kidney ultra-filters the plasma and RPF is equal to the amount of substance excreted per unit of time divided by the renal arteriovenous concentration difference of that substance. Therefore, the RPF = UV/A − RV. Here, U is the urinary concentration of substance which is used to measure the RBF, V is the urinary flow rate, A is the arterial plasma concentration of that substance and

FACT FILE - X

Mild adrenergic stimulation (initial stage of humoral and neural autoregulation) causes activation of α-receptor and produce only preferential glomerular efferent arteriolar constriction. This preserves the filtration fraction and GFR, still in the face of hypotension and decreased RBF. This α-adrenergic stimulation occurs through renin-angiotensin system. Therefore, the importance of this protective mechanism is lost and GFR is reduced if ACE inhibitor is used in patients with hypotension, renal insufficiency and renal artery stenosis. Contrary, severe α-adrenergic stimulation (late stage of hormonal and neural autoregulation) causes predominant constriction of afferent arteriole and decreases GFR with RBF. This can be opposed by α-adrenergic blockade.

RV is the renal venous plasma concentration of that substance.

RPF is measured by using PAH (para amino hippuric acid) through IV route. PAH is used to measure RPF, because it is physiologically inert, nontoxic, filtered completely at the glomerulus, secreted through renal tubule, and eliminated completely from the plasma by single passage through kidney. When PAH is infused at low doses, 90% of it is removed by a single circulation through kidney. It is, therefore, become easy to calculate the RPF by dividing the amount of PAH in urine by the plasma PAH level, ignoring its level in renal venous blood. Peripheral venous plasma can be used for plasma PAH level, because its (PAH) concentration is essentially identical to that in arterial plasma, reaching the kidney. Thus, the value obtained is called the effective renal plasma flow (ERPF) which does not need to measure the renal venous plasma PAH level. Therefore, ERPF = UV/P_{PAH}, where P_{PAH} is plasma PAH level. This also indicates the clearance of PAH like the clearance of insulin and creatine. In human, the average ERPF value is 700 ml/min.

Example:

Urinary concentration of PAH (U) is 14.4 mg/ml
Urine output (V) is 1 ml/minute
Plasma concentration of PAH is 0.02 mg/ml
Therefore, ERPF = 14.4 × 1/0.02 = 720 ml/min
This ERPF can be converted to actual RPF
This can be done by: ERPF / excretion ratio of PAH = 720 / 0.9 (excretion ratio of PAH is 0.9) = 800 ml/minute
Therefore, the actual RPF = 800 ml/minute
RBF is calculated from RPF from the following formula:
RBF = RPF ÷ (1 − Haematocrit value)
= 800 ÷ (1 − 0.45) [Normal haematocrit value is 45%]
= 800 ÷ 0.55
= 1454.5 ml/minute

Therefore, renal blood flow (RBF) is 1454.5 ml/minute.

GLOMERULAR FILTRATION

Usually, both the kidney receive total blood flow of 1.2 to 1.3 L/min which is about 25% of the total cardiac output. But, out of this only 125 ml/min or 7.5 L/hour or 180 L/day of fluid is filtered by the glomerulus and only 1 to 2 L/day of urine is formed. Therefore, 99% or more of glomerular filtrate is reabsorbed in renal tubules. It is estimated that to clear the nitrogenous waste products, produced during metabolism throughout the whole day, at least 400 to 500 ml of urine per day is required to be formed mandatorily. For reabsorption of glomerular filtrate in renal tubules the counter current multiplier exchanger system is a critical component which help the kidney's ability to excrete or conserve the salt and water. The Na^+ and water reabsorption by kidney depend on the hypertonicity of the medullary interstitium which again depends on the maintenance of normal renal blood flow. The major hormonal influences determining the conservation or loss of filtered Na^+ and water are aldosterone, ADH, ANP and the renal prostaglandin. At the filtration rate of 125 ml/min, the kidney filter an amount of fluid which is 4 times of the total body water, 15 times of the ECF volume and 60 times of the plasma volume per day.

Like the capillary of other parts of body, the filtration in glomerular capillary is also governed by four forces opposing to each other. These four forces are: glomerular capillary hydrostatic pressure (C_H), glomerular capillary oncotic pressure (C_{ON}), hydrostatic pressure in Bowman's capsule (B_H) and oncotic pressure in Bowman's capsule (B_{ON}). Therefore, the effective glomerular filtration pressure is: $(C_H - B_H) - (C_{ON} - B_{ON})$ and GFR = $K_f [(C_H - B_H) - (C_{ON} - B_{ON})]$, where K_f is the glomerular ultrafiltration coefficient. The K_f depends mainly on 4 factors. These factors are the permeability of glomerular capillary, charge of the filtrate substances, size of the filtration pore and size of the capillary bed. Therefore, GFR depends upon on these above mentioned factors which determine the filtration coefficient and the hydrostatic and oncotic pressure of the glomerular capillary and Bowman's capsular fluid (Table 42.3).

Capillary permeability is different at the different parts of our body. Permeability of glomerular capillary is 40 to 50 times more than that of the skeletal muscle. Substances with molecular diameter of smaller than 4 nm are freely filtered out through the glomerular capillary. Whereas substances with molecular diameter of greater than 8 nm are not at all filtered out. Therefore, filtration of substances with molecular diameter between 4 to 8 nm is inversely proportional to their molecular size.

GFR also depends on the charge of the filtered substances. Glomerular capillary itself is negatively charged and it is due to the presence of sialoprotein (a special type of protein). So, the –ve charge of the capillary bed repel the –ve charged

Table 42.3: Factors affecting the GFR

A.	**Changes in hydrostatic pressure of glomerular capillary**
	Changes in systemic blood pressure
	Contraction of afferent or efferent arteriole
B.	**Changes in oncotic pressure of glomerular capillary**
	Hypoprotinaemia
	Dehydration
C.	**Changes in hydrostatic pressure of Bowman's capsule**
	Obstruction in urinary passage
D.	**Changes in oncotic pressure of Bowman's capsule**
	Oncotic pressure in Bowman's capsule is negligible as the ultrafiltrate does not contain any protein or very minimum amount.
E.	**Changes in permeability coefficient**
	Changes in surface area for effective filtration
	Changes in permeability of glomerular capillary
F.	**Changes in renal blood flow**

substances in blood and reduces their filtration. Hence, filtration of −ve charged substances of 4 nm molecular diameter is more or less half than that of neutral charged substances of the same molecular diameter. On the contrary, filtration of the +ve charged substance of 7 nm molecular diameter is greater than the neutral and −ve charged substances of the same molecular diameter. This probably explains why the normally −ve charged albumin with molecular diameter of 6 to 7 nm has concentration in glomerular filtrate of only 0.1 to 0.2% of its plasma concentration. This is far less than the expected higher concentration in glomerular filtrate calculated on the basis of the molecular diameter alone. The total amount of protein in the urine is usually less than 100 mg/day. However, most of this is not filtered, but comes from the shed tubular cells. In nephritis the −ve charge of the glomerular capillary bed is lost and then albuminuria can occur without any increase in the size of the pores of the filtration membrane.

The sizes of the pores on the filtration membrane of capillary bed depend on the contraction of mesangial cell. The increase in contraction of these mesangial cells decrease the size of the pores and K_f. Many agents such as angiotensin II, epinephrine, norepinephrine, vasopressin, thromboxane A_2, PGF_2, leukotrines, etc., also induce contraction of the mesangial cells and decrease filtration. Whereas ANP, dopamine, PGE_2, etc., relax these cells and increase the size of pores with increased filtration.

The hydrostatic and oncotic pressure of the glomerular capillary blood and Bowman's capsular fluid also alter the GFR. Afferent glomerular arterioles are short and arise directly from the interlobular arteries. Further, in the downstream the efferent arterioles also have relatively high resistance. Therefore, the hydrostatic pressure of glomerular capillary is much higher than that of the capillaries inother part of the body. This glomerular capillary hydrostatic pressure which is the main filtration pressure is opposed by the hydrostatic pressure in Bowman's capsule. This is further opposed by the oncotic pressure gradient across the glomerular capillary bed i.e. $C_{ON} - B_{ON}$. Usually B_{ON} is negligible as there is no protein in the capsular filtrate. So, the equation of GFR can be rewritten as:

$$GFR = K_f [(C_H - B_H) - C_{ON}]$$

The net filtration pressure at the afferent end of glomerular capillary is 16 mm of Hg. But it gradually falls to zero and a filtration equilibrium is reached at the effarent end of glomerular capillary. This is due to the gradual leaving of fluid and other solute, except protein from the capillary bed and, therefore, gradual increase in oncotic pressure of capillary blood due to increased concentration of serum protein passes through the glomerular capillary. Due to the autoregulation, change in renal vascular resistance tries to stabilize the filtration pressure. But, when the MAP drops below this autoregulatory range, then GFR falls sharply. The GFR is maintained when the efferent arteriolar constriction is greater than that of the afferent arteriole, but constriction of both the arterioles decrease the GFR (Table 42.4).

Table 42.4: Net filtration pressure at the afferent and effarent end of the glomerular capillary

Net filtration pressure = $C_H - B_H - C_{ON}$
C_H = Hydrostatic pressure in glomerular capillary, B_H = Plasma oncotic pressure in glomerular capillary, C_{ON} = Hydrostatic pressure in Bowman's capsule

	Afferent end (mm of Hg)	*Effarent end (mm of Hg)*
CH	45	44
BH	−10	−10
CON	−25	−34
Net filtration pressure	10	0

Measurement of GFR

The normal value of GFR varies between 120 to 130 ml/minute. It is usualy about 20% of RPF. GFR is usually measured by inulin or creatinine. Creatinine is a break down product of phosphocreatine which normally present in muscle. Whereas inulin is a fructose polysaccharide with molecular weight of 5200. The measurement of GFR by inulin or creatinine is also called inulin or creatinine clearance, respectively. Inulin is completely filtered by glomerular capillary but it is neither secreted, nor reabsorbed by renal tubules. Therefore, the use of inulin gives very accurate result of GFR (or inulin clearance). Whereas, the use of creatinine to measure GFR (creatinine clearance) tends to overestimate the result, because though it is completely filtered but small amount of it is secreted through renal tubule. In addition, determination of plasma creatinine is inaccurate at low creatinine level. This is because the method used to estimate plasma creatinine also measures the small amount of other plasma constituents such as chromogens. In spite of this, creatinine clearance is frequently measured in patients to estimate the GFR accurately. This is because it is more practical, easy and the value matches quite well with the value of GFR, measured by inulin. This is also true, because although $U_{CR} \times V$ is high as a result of tubular secretion, but the value of P_{CR} is also high as a result of nonspecific chromogens. Therefore, the two errors cancel each other. Hence, the measurement of endogenous creatinine clearance is a worthwhile index of renal function. The creatinine clearance (C_{CR}) is measured by the following formula:

$$C_{CR} = U_{CR} \times V / P_{CR}$$

U_{CR} = creatinine concentration in urine, V = urinary flow rate, P_{CR} = creatinine concentration in plasma.

Example

U_{CR} = 35 mg/ml, V = 0.9 ml/minute, P_{CR} = 0.25 mg/ml

Therefore, $C_{CR} = 35 \times 0.9 / 0.25 = 126$ ml/minute

The ratio of GFR to RPF is called the filtration fraction and is usually 20%.

ASSESSMENT OF RENAL FUNCTIONS

Generally the kidney performs three principal functions in the body. These are: (i) excretion of potentially toxic and non-toxic metabolic end products, (ii) regulation of water and electrolyte balance and (iii) production of hormones. Direct assessment of all these renal functions are practically impossible and also simultaneously direct on-line evaluation of these renal functions are limited. Most of the renal functions are, therefore, assessed indirectly. Furthermore, these assessments of renal function are not simple and are very expensive. On the otherhand, the readily available tests fail to accurately reflect the status of kidney in large percentage of patients, especially the elderly, malnourished and dehydrated individuals.

Kidneys perform their functions through glomerulus and renal tubules. So, renal functions are divided into glomerular and tubular functions. But this classification is arbitary, because in any renal diseases both these functions are impaired simultaneously. On the contrary, fortunately any standard test performed for renal functions evaluate both the glomerular and tubular functions. Furthermore, it is also important to remember that most of the renal function tests are insensitive to detect the early renal dysfunction. Therefore, the subsequent serial results are more helpful than a single result (Table 42.5).

Table 42.5: Tests used to evaluate renal function

Glomerular function
Blood urea nitrogen (BUN) [Normal value: 10 - 20 mg/dl]
Plasma creatinine [Normal value: 0.5-1.5 mg/dl]
GFR or creatinine clearance [Normal value: 120 - 130 ml/min
Proteinuria [Normal value: < 100 mg/day]
Renal tubular function
Urine osmolality [Normal value: 30-140 m.Osm/L]
Urine specific gravity [Normal value: 1.003 - 1.030]
Excretion of Na^+ through urine [Normal value: < 40 m.mol/L]
Renal glycosuria
Cellular cast
Urinary lysozyme

The most common tests for renal function are urine analysis, measurement of blood urea nitrogen (BUN) in plasma, estimation of serum creatinine level, creatinine clearance, etc. Many other intravenous tests, urography, renal ultrasound, renal MRI, renal CT and renal biopsy etc. may also be performed to diagnose the renal pathology, responsible for renal dysfunction.

Urine analysis

Information from urine analysis should be interpreted very cautiously to assess the renal function, because there are many flaws. The urine analysis includes: the measurement of urine output, the measurement of urinary osmolality and specific gravity, and the microscopical examination.

The estimation of urine output is an indirect parameter for assessment of renal function. This is because many prerenal factors directly and profoundly affect the urine output without the presence of any renal dysfunction. For example, oliguria due to severe systemic hypotension and subsequently reduced renal perfusion without any renal parenchymal dysfunction or any obstruction at any where on the passage of urine on one hand and polyuria due to central diabetes insipidus without any impairment of renal function on the otherside, make it obvious that urine output does not always specifically reflect the renal function. This is more true intraoperatively when the several other factors such as increased secretion of ADH, aldosterone, catecholamines, angiotensin, etc., due to stress affect decrease the output of urine with normal renal function.

Still, the measurement of urine output as a primary indicator of renal function is important in certain situations, where anuria can develop due to some parenchymal diseases of kidney or due to impaired renal blood flow for any cause that may lead to renal dysfunction. The evidence of formation of urine, regardless of its amount, suggest that there is adequate blood flow to the kidney. The intraoperative oliguria does not always indicate impaired renal function and if is not due to impaired renal function, it does not correlate (if the cause is prerenal) with increased BUN and creatinine level or decreased creatinine clearance. The level of nitrogenous waste in blood depends on its production and its clearance through kidney. On the other hand, the renal clearance depends on renal blood flow and glomerular filtration. In the circumstances of reduced renal blood flow, kidney concentrate the glomerular ultra-filtrate, so that at maximal concentration at least 400 to 500 ml of urine can be excreted which is required to clear the daily obligatory nitrogenous waste (Table 42.6).

Table 42.6: Difference in urinary indices of patients with oliguria due to prerenal, renal and physiological causes

Indices	*Renal causes*	*Prerenal causes*	*Physiological causes*
Urinary osmolality (m.osm/kg)	200-300	> 450	> 700
Urine / plasma osmolality	< 1.5	> 2	> 2.5
Urinary Na^+ concentration (m.mol/L)	> 40	< 20	< 10
Fractional Na^+ excretion (%)	> 1	< 1	< 0.5
Urine and plasma creatinine ratio	< 20	> 40	> 60
Specific gravity of urine	1.010-1.015	> 1.015	> 1.024
Urine and plasma urea ratio	> 3 (rarely > 10)	> 20	> 100

During analysis of urine, the measurement of specific gravity and osmolality of urine are also used as parameter to assess the renal function. This indicates the tubular function only, i.e. concentration capacity. In specific gravity the mass of 1 ml of urine is compared to the mass of 1 ml of distilled water. Whereas, in osmolality the number of osmotically active particles in solution is measured. Usually, the osmolality force governs the movement of fluid throughout the body and also in kidney. Therefore, the measurement of osmolality of urine is more superior than the measurement of specific gravity as a test of renal function. In poor renal perfusion due to reduced circulation (prerenal azotemia), kidneys try to concentrate the urine. Therefore, its osmolality and specific gravity may go up above 500 m.osmol/kg of H_2O and 1.03, respectively. Whereas, in acute tubular necrosis (renal tubular dysfunction) urine osmolality and specific gravity may go below 350 m.osmol/kg of H_2O and 1.01, respectively. Thus, it makes an important guide line to differentiate the causes of low urine output due to renal from prerenal causes. Still, the measurement of osmolality and specific gravity of urine is nonspecific for diagnosis of renal dysfunction. Because there are many other factors which affect the osmolality and specific gravity of urine, other than renal dysfunction. These are the presence of protein, glucose, mannitol, dextrose, antibiotics in urine and use of diuretics, etc.

Haematuria which is defined as more than 2 RBC per high power field of centrifused urine indicates glomerular diseases, or trauma to the kidney, ureter, lower urinary tract, etc. If urine test is positive for blood, but there is no RBC, it indicates the presence of free haemoglobin in urine (haemoglobinuria). Urine normally may contain hyaline or granular cast, but presence of cellular cast confirms pathological condition of kidney. Trace proteinuria may be a normal finding. Whereas 3 to 4+ proteinuria suggests glomerular disease as proteins are not prevented from filtration. Patient without renal disease may excrete upto 100 mg of protein per day, but greater amount may be present after heavy exercise or after prolonged standing. Massive proteinuria with protein content above 500 to 700 mg/day is always abnormal and indicates severe glomerular damage. However, proteinuria may also be due to: (i) failure of tubular reabsorption of small amount of protein that is normally filtered, (ii) abnormally increased concentration of normal plasma protein, (iii) the presence of abnormal plasma proteins which are excreted through urine. Pyuria indicates infection at any level of genitourinary system.

Measurement of urinary pH may assist in the diagnosis of some acids base disturbances in body, but determination of pH from a single sample of urine has no value. Presence of glycosuria without hyperglycaemia suggests proximal tubular damage. Normal urinary lysozyme level is less than 1.9 mg/ml. Urinary level of it above 5 mg/ml indicates significant renal tubular disease (Table 42.7).

Estimation of BUN

Like urine analysis, estimation of BUN (blood urea nitrogen) is a commonly performed test to asses the renal function. The level of BUN greater than 50 to 60 mg/dl indicates the renal disease, unless proved otherwise. But abnormalities in the level of BUN indicates the renal dysfunction which is already advanced. As urea is filtered and then partially reabsorbed and secreted, so BUN level is not a sensitive index of GFR or renal dysfunction. The level of BUN is also elevated during low circulatory states such as congestive heart failure, dehydration, etc. This is due to the increased reabsorption of filtered urea for renal hypoperfusion. The reabsorption of urea is greater, approximately 60% of the filtered load, when urinay flow is low and only about 40% when this flow is high. There are other multiple nonrenal conditions where BUN level is increased. These are: high protein diet, GI bleeding, large haematoma, increased tissue breakdown in high catabolic state of body such as sepsis, high fever, starvation, steroid therapy (due to increased protein catabolism), etc. On the otherhand, the BUN level may remain within normal range despite significant reduction of GFR, if there is liver disease which causes decreased synthesis of urea.

Table 42.7: Factors that influence the result of renal function

- Variable protein intake
- Dehydration
- Degree of catabolism
- GI bleeding
- Skeletal muscle mass
- Advanced age
- Timing of measurement of urine volume

Estimation of plasma creatinine

Like BUN, plasma creatinine level is also measured to assess the renal function (mainly GFR). In a normal individual, daily a constant amount of creatinine is produced in body from creatine – phosphate, present in muscle. It is excreted by filtration through kidney. Therefore, a muscular individual may have high plasma creatinine level, though GFR is normal. On the otherhand, an individual with low muscular mass may have normal creatinine value, despite significant reduction of GFR. Thus, like BUN increased plasma creatinine level is also a late sign of renal dysfunction. This is because GFR must often be reduced as much as 50% before the elevation of creatinine concentration reach the abnormal level. Further, this is more true for individual with reduced muscle mass who has already low creatinine value. As creatinine is a product of skeletal muscle's protein catabolism, so it is formed at lower rate in elderly and women than young and male persons. Consequently, plasma creatinine level does not accurately reflect the magnitude of loss of nephron. Because creatinine production is directly proportional to the

muscle mass and indirectly proportional to the nephron loss. Therefore, many chronically ill, wasted, elderly patients may have palsma creatine value in normal range, though there is reduced renal concentrating ability and GFR.

Measurement of creatinine clearance

The excretion of creatinine from plasma by glomeruli measure or reflect the ability of glomeruli to filter it. This is called the creatinine clearance. It gives the more useful result than the only plasma creatinine value to quantify the renal reserve. From the only plasma creatinine level (without measuring the urinary concentration of it which is needed to measure the creatinine clearance rate as described before) the creatinine clearance can also be measured with reasonable accuracy by the following formula:

Creatinine clearance = [(140 – Age) × Body weight in kg] ÷ [72 × Plasma creatinine value]

But, the precise measurement of creatinine clearance (using the formula $C_{CR} = U_{CR} \times V/P_{CR}$) require collection of urine samples for a fixed time say 24 hours or 2 hours. 24 hours urine collection gives more accurate results than the 2 hours collection. This is because the changing hydration of a patient invalidates the result calculated from the short term collection of urine volume (2 hours) which varies greatly. On the otherhand, for a patient with acute renal failure a test that requires 24 hours collection of urine is often impractical. Creatinine clearance may also be used to differentiate the prerenal azotaemia from acute tubular necrosis (ATN) or renal azotaemia. In the postoperative period, a creatinine clearance value which is < 25 ml/minute, measuring over 2 hours appears to be a good and early predictor of impaired renal function (Fact file - XI).

FACT FILE - XI

Creatinine (anhydride of creatine) is mostly formed from the breakdown of creatine phosphate which is present in the muscle. This process is not catalysed by any enzymes and is irreversible. It is formed within the muscle itself. So, liver diseases do not affect the blood creatinine level. It is considered as a waste product and serves practically no function in the body. It is a no-threshold substance and is filtered completely by glomeruli. A small amount of creatinine is also secreted by the tubular cells in the urine. Its excretion is not related to exogenous food protein. The normal plasma value of creatinine is 0.7 to 2 mg/dl. This level is very constant and is considered to be pathological when its value increases above 2 mg/dl. Usually about 1.2 to 2 gm of creatinine is excreted in 24 hours urine. This amount is remarkably constant for a particular individual. It is related to muscle bulk and is higher in muscular persons. Creatinine excretion increases in fevers, starvation, carbohydrate free diet and in diabetes mellitus.

Creatinine represents the waste products of creatine metabolism. It arises in the body (muscle) from creatine during the spontaneous breakdown of creatine phosphate. Therefore, creatinine level increases during excessive muscle dstruction releasing creatine or due to failure of creatine being properly phosphorylated. So, creatinine excretion is independent of exogenous food protein and is considered as in index of endogenous protein metabolism. Due to any inborn metabolic disorders creatine does not convert to creatinine and appears in urine. This is known as creatinuria. Usually a small amount of creatine is excreted through urine along with creatinine. But it gradually diappears as the maturity advances.

Miscellaneous tests

Except the above mentioned tests, there are other tests which may be used to take an overview about the renal functions. Among these, some are not so reliable but only few are very promising. For example, the urine-plasma creatinine ratio and the urine-plasma urea ratio or index were initially introduced as a very promising methods for evaluation of patients with suspected acute tubular necrosis or renal dysfunction. But subsequently these tests show the lack of reliability and have more prognostic than diagnostic value.

The concentrating capacity of renal tubules also can be assessed by measuring the urinary Na^+ concentration and fractional excretion of Na^+ (FENa). If these two values go above 40 mEq/L and 1 respectively, it indicates acute tubular necrosis. On the contrary in hypotension ADH induced increased Na^+ reabsorption leads to a decrease in urinary Na^+ concentration < 20 m.Eq/L and FENa < 1 in prerenal azotemia which indicates the fallacy of this test. Some other tests of tubular function such as concentrating ability, ability to excrete water load and ability to excrete acid through kidney are valuable in some circumstances.

More accurate measurement of GFR is now most easily undertaken by ascertaining the clearance of ^{51}Cr-labelled EDTA. This has largely replaced the estimation of inulin and creatinine clearance in clinical practice.

ANAESTHESIA AND RENAL FUNCTION

Anaesthesia and any surgery have enormous impact on renal function. This can be caused directly or indirectly by affecting the renal physiology due to the changes in the levels of different hormones, electrolytes, body water, cardiac output, RBF, pH, etc. In general, the anaesthesia results in decrease in RBF and subsequently results in deterioration of renal function due to the decreased GFR. The likely mechanism of this deterioration of renal function induced by anaesthesia includes the loss of renal autoregulation, increased neurohormonal factors (ADH, vasopressin, renin, angiotensin) and increased neuroendocrine response. This inturn decrease the excretion of nitrogenous wastes, electrolytes, H^+, anaesthetic and other drugs, and conservation of body fluid etc. Decreased excretion of anaesthetic and other drugs lead to prolongation of their effect. On the other hand, anaesthetic agents also affect the renal function directly. This is mainly applicable for volatile anaesthetic agents such as methoxyflurane which produces many nephrotoxic metabolites in our body after its administration. IV anaesthetic agents have minimal direct effects on kidney. They deteriorates the renal function indirectly by reducing the RBF. Among

the anaesthetic agents which are mostly concerned about the renal function are: IV anaesthetic agents, inhalational agents, muscle relaxants and its reversal.

Intravenous Anaesthetic Agents

In patients with impaired renal functions, the CNS depressant effect of intravenous anaesthetic agents are exaggerated. This is because they are mostly protein (albumin) bound and in renal dysfunction as the level of albumin is reduced, so most of the drug remains in unbound free form and theri actions are enaggenated . In addition, the renal dysfunction is frequently associated with acidosis which increases the unionized form of drug, as their pK value acts usually at the physiological range of plasma. The unionized form of the drug is more lipid soluble. Therefore it causes higher drug concentration in CNS. Hence, the thiopentone which remains as 15% unbound free and un-ionized form in normal individual, increases to 30% in chronic renal failure. Therefore, the induction and maintenance dose of thiopentone should be reduced in uraemic patients. On the other hand, as the metabolism of thiopentone in liver remains unchanged in renal dysfunction patient, so the amount of it which is necessary to produce and maintain anaesthesia is reduced. The same consideration is also true for the methohexitone, although metabolism of it plays a slight greater role in termination of its therapeutic effect than thiopentone. On the other hand, the reversal of effect of ultra-short acting barbiturate such as thiopentone will depend only on redistribution and hepatic metabolism, but very little or nil on the elimination through kidney. Therefore, the recovery from thiopentone in a renal dysfunction patient is not affected.

However, it is surprising that in a renal dysfunction patient the pharmacodynamics and pharmacokinetics of a new I V anaesthetic agent such as propofol do not change and is very safe to use. Ketamine should be avoided in renal failure patient. Because it causes exaggerated reaction to coexisting hypertension and tachycardia in renal failure patient, where they are already present. However, ketamine is reported to minimally affect the renal function directly. It also tries to preserve the renal function during haemorrhage and hypovolaemia. For benodiazepines the increased free fraction of these drugs due to decreased protein binding also increases its CNS sensitivity. Further, due to impairment of excretion caused by renal dysfunction there is accumulation of active metabolites of some long acting BZD such as diazepam lorazapam, oxazepam, etc. and prolongs their clinical effect.

For narcotics the same is true as barbiturates and BZDs. As the protein binding capacity is reduced in renal dysfunctional patient, the unbound level of morphine and its active metabolites such as morphine-6-glucoronite (non toxic) in plasma increases and predisposes the patient to more and prolonged respiratory depression. Meperidine (pethidine) has a toxic metabolite, named normeperidine (norpethidine). So, it is not recommended for use by repeated bolus doses or through infusion in renal failure patient due to gradual accumulation of these toxic metabolites which are excreted through kidney. The pharmacogenetic and pharmacodynamic effects of alfentanil and fentanyl are appeared to be unaffected by the renal dysfunction. Further, fentanyl has short half-life and its metabolites are inactive. So, these agents are good choice in patient with renal disease.

Drugs with antidopaminergic activity such as metoclopramide, phenothiazines, etc., may impair the renal response of dopamine when it is used as protection for kidney. Use of analgesic drug such as ketorolac inhibits the synthesis of which have renal vasodialating property prostaglandin of renal origin. This is especially important in patients with high level of angiotensin II and norepinephrine which causes renal vasoconstriction. Thus, it attenuates the renal protective response and decreases GFR, producing or enaggerating renal dysfunction. ACE inhibitors also block the protective effect of angiotensin II and causes additional reduction in GFR during anaesthesia. Thus, it potentiates the detrimental effect of anaesthetic agent on renal perfusion.

Volatile Anaesthetic Agents

Indirectly the volatile anaesthetic agents affect the renal function by eliminating the renal autoregulation and reducing the RBF and GFR, with decreased urine output. All these haemodynamic changes, produced by volatile anaesthetic agents are dose dependent and can be attenuated by adequate preoperative hydration which probably helps to maintain the better renal perfusion.

On the otherhand, the volatile anaesthetic agents also directly affect the renal functions by their nephrotoxic metabolites which are formed by liver and excreted through kidney. Though 99% of volatile anaesthetic agents are excreted out through the lungs, still to some extent all the inhaled anaesthetics are biotransformed to nephrotoxic metabolites during their metabolism in liver. Impaired renal function does not alter the pharmacodynamics and pharmacokinetic effect of any volatile anaesthetic agents, but the agents affect the function of kidney. So, from the point of view of selecting a volatile anaesthetic agent one should be careful regarding the effect of agent on kidney which may make further detorioration of its function than the effect of renal dysfunction on the haemodynamic and pharmacodynamic effect of the agent.

All the modern volatile anaesthetic agents such as methoxyflurane, enflurane, halothane, isoflurane, sevoflurane and desflurane are halogenated compounds, containing mainly fluorine. These fluorinated volatile anaesthetic compounds produce inorganic fluorides as their metabolites which are nephrotoxic. These inorganic fluoride induced nephrotoxicity depends on the type of volatile agent used and the duration of their exposure. The threshold

level of nephrotoxicity of these inorganic fluorides are 50 M/L. The amount of inorganic fluoride below these level does not produce nephrotoxicity. In impaired renal function methoxyflurane is absolutely contraindicated, because it is extensively biotransformed into inorganic fluoride and oxalic acid due to its metabolism in the liver. This inorganic fluoride induced nephrotoxicity caused by volatile agents includes an inability to concentrate the urine in response to ADH, leading to polyuria, hypernatraemia and increased serum osmolality. Other halogenated volatile agents are metabolised in body duirng their use to inorganic fluoride, but their levels are below the threshold level. For example, after 3 to 4 hours of use of enflurane, the inorganic fluoride level in plasma is 20 ± 5 μM/L. Again obesity is associated with production of higher level of inorganic fluorides following enflurane anaesthesia. Whereas the plasma fluoride level after the use of isoflurane and halothane increases to only 3 to 4 μM/L and 1 to 2 μM/L respectively. Therefore, the use of isoflurane and halothane is a better alternative in renal failure patient. Recently introduced volatile anaesthetic agent is desflurane. It is highly volatile and boiling point is 19°C (near the room temperature). But it is very stable in sodalime and also resists degradation by liver. So, the mean inorganic fluoride concentration after 1 hour exposure of desflurane at the dose of 1 MAC is only 1 μM/L or less. On the other hand, sevoflurane is very unstable in sodalime which decomposes it. It is also biotransformed in liver. So after prolonged exposure of sevoflurane, the level of nephrotoxic inorganic fluoride may reach upto 50 μM/L, but still there is no report of gross change of renal function in humans, after its prolonged use.

Muscle Relaxant

The level of plasma cholinesterase is reduced in severe renal dysfunction patient, but the value is rarely so low to cause prolonged action of succinylcholine. Therefore, it can be used without difficulty in patient with decreased or absent renal function. Succinylcholine is metabolised by plasma cholinesterase to nontoxic succinic acid and choline. The metabolic precursor of these two compounds is succinylmonocholine which is excreted through kidney. Hence, prolonged use of succinylcholine by infusions or repeated bolus doses should be avoided in patient with renal failure. The use of succinylcholine is associated with the transient rise of plasma K^+ level to 0.5 to 0.7 mEq/L. This rise may be as great as 5 to 7 mEq/L in burn, trauma or neurologically injured patient. In renal failure patient the level of plasma K^+ also remains high. Hence, the use of succinylcholine in renal failure patient with this high level of plasma K^+ can cause cardiovascular collapse. So, the use of succinylcholine in severe renal failure patient is inadvisable, unless the patient undergone dialysis within 24 hours prior to anaesthesia and surgery. Still succinylcholine is the agent of choice for rapid sequence induction and intubation for difficult airway (as its onset of action is not delayed and duration of action is not prolonged in renal dysfunction patient), if the plasma K^+ level permits. In majority of patients with renal failure, a single dose of succinylcholine is considered safe, provided the serum K^+ level is below 5 mEq/L.

The two nondepolarising muscle relaxants such as atracurium and its derivative cisatracurium are broken down in plasma by enzymatic ester hydrolysis and by nonenzymatic alkaline degradation (Hofmann elimination) to their inactive products. Therefore, they are not dependent on renal excretion for their termination of action. Hence, the indices of these two muscle relaxants such as onset, duration and recovery are same in patient with normal and with severely impaired renal function. So, they appear to be the neuromuscular blocking agent of choice for renal failure patients. Severe renal dysfunction does not prolong the neuromuscular blocking effect of these two agents, even when is given by constant infusion over several days. Laudanosine is one of the important metabolic end products of atracurium and cisatracurium which may cause convulsion. This laudanosine is excreted through kidney. But fortunately the risk of convulsion from accumulation of laudanosine in renal failure patient after continuous infusion in ICU has not been reported.

Vecuronium is another nondepolarising muscle relaxant which is 70 to 80% metabolised in liver and the remaining 20 to 30% is excreted as mother compound through kidney. Hence, in patients with renal failure the normal intubation and maintenance doses should be reduced and the intermittent dosing interval should be increased. One of the metabolites of vecuronium is 3-desacetyl vecuronium which is pharmacologically active. Hence, continuous infusions of vecuronium is not recommended in renal failure patient in fear of accumulation of its active metabolites.

Another short acting nondepolarising muscle relaxant is mivacurium which is metabolised by plasma cholinesterase, but slowly than succinylcholine. Therefore, as the level of plasma cholinesterase is reduced in impaired renal function or after dialysis, so the duration of action of it is prolonged by another 10 to 15 minutes. But the use of this drug in renal failure patient is not a contraindication. This agent can be used cautiously with lower doses. The clearance of rocuronium is not changed in renal failure patient, but the elimination half-life is increased. This is due to the increase in volume of distribution in renal dysfunction. Therefore, there is somewhat longer duration of action of rocuronium in renal failure.

Other long acting non-depolarising muscle relaxants such as pancuronium, doxacurium, pipercuronium, etc.; show reduced clearance, increased elimination half-life and prolonged duration of action in patients with renal disease. Therefore, if

possible these agents should be avoided or can be used with lower doses and longer dosing interval. Use of any neuromuscular agent in presence of renal dysfunction should be monitored by nerve stimulator.

The anticholinesterases such as neostigmine, edrophonium and physostigmine are excreted mainly through kidney. Among these the 50% of neostigmine and 70% of edrophonium and physostigmine are excreted unchanged by urine. So, in renal dysfunction their actions are prolonged, but this is matched with the prolonged action of neuromuscular blocking agents.

Anaesthetic Procedure

Before operation it is not always possible to become certain whether the patient has any renal disease or not. The best way to know the presence or absence of renal disease is past medical history. The physical findings are often minimum until renal disease is far advanced. This is because until approximately 50% of renal function is lost, the laboratory results remain within normal limits, except the creatine clearance. Patient with this 50% loss of renal function are said to have decreased renal reserve and their anaestheitc management is same as that of the patients with normal renal functions (Table 42.8).

For renal dysfunction two terms are used – renal insufficiency and renal failure. The renal insufficiency is characterised by mild anaemia, mild azotaemia, slight decrease of urine concentration ability. During anaesthesia of this category of patients, attention is paid to avoid the conditions which may further deteriorate the renal function. On the other hand, the renal failure is said to be present when patients have hypocalcaemia, hypernatraemia, hyperphosphataemia, hyperchloraemia, hyperkalaemia, progressive anaemia and loss of urinary, concentrating or diluting, ability. In these renal failure group of patients the plasma creatinine value and creatinine clearance vary between 3.5 to 4 mg/dl and 15 to 20 ml/minute, respectively. They are also unable to adapt to the rapid changes in fluid balance. Hence, they run the risk of becoming acutely hypovolaemic or fluid overload and the clinical condition of these patients are uncertain. The aim of anaesthetic management of these category of patients is directed at avoiding the deterioration of renal function which will cause them to become grossly uraemic and require haemodialysis. Drugs which are excreted through kidney should completely be avoided or if is required at all, they should be given very cautiously in decreased doses or at prolonged intervals.

If the patients lack the significant medical history focussing on renal disease and its function, then the routine preoperative blood tests and urine analysis for screening is sufficient for early identification of renal disease or its dysfunction. In screening, if renal dysfunction is thought to be present, then the more precise methods of assessing the degree of deterioration of renal function are necessary. Therefore, the laboratory tests useful for preoperative evaluation of renal functions are as follows: urine analysis (including output, appearance, pH, specific gravity, protein content etc.), blood tests (includig Hb%, coagulation profile, electrolytes, pH, BUN, creatinine etc.), ECG, chest X-ray etc. If necessary, other renal function tests such as creatinine clearance and GFR should also be measured. Among these many are described before and those which are not described before are mentioned below.

Table 42.8 : Manifestations of renal dysfunction

- Hyperkalaemia
- Hyponatraemia
- Hypocalcaemia
- Hyperchloraemia
- Hyperphosphataemia
- Metabolic acidosis
- Anaemia
- Coagulopathies
- Unpredictable intravascular fluid volume status
- Hypertension
- Congestive heart failure

Haematocrit

Anaemia is a common finding for renal diseases and severity of it depends on the depth of renal dysfunction. It is due to the decreased production of erythropoietin (erythropoiesis stimulating factor). The Haematocrit value running between 25 to 30% is appeared to be well tolerated and does not always need blood transfusion, because it is associated with unnecessary several disadvantages such as volume overload, hyperkalaemia, viral infections, etc. If this haematocrit value is thought not to be justified for the proposed surgery or is poorly tolerated due to some systemic diseases such as cardiac disease, then blood transfusion should not be withheld (Table 42.9).

Coagulation profile

Haemorrhagic episodes remains the major risk factor contributing to the morbidity and mortality, associated with anaemia in renal dysfunction patient. Prothrombin time (PT) and partial thromboplastin time (PTT) remains usually normal in such patient, though they have increased tendency to bleed. Hence, the bleeding time

Table 42.9: Treatment of coagulopathy due to renal failure

Drug	*Dose*	*Onset of action*	*Peak effect*	*Duration of action*
Cryoprecipitate	10-15 units IV over 15-30 minutes	< 1 - 2 hours	6 - 12 hours	12 - 24 hours
Desmopressin	0.3-0.6 µg/kg IV or SC	< 1 - 2 hours	2 - 4 hours	4 - 8 hours
Estrogen	0.6 mg/kg/day	6 hours	6 - 7 days	15 days

(BT) is the best screening test for this group of patient that correlates well with the tendency to bleed in renal dysfunction patient. The treatment of uraemic bleeding usually includes the adminstration of cryoprecipitate plasma which provides factor VIII or administration of desmopressin (1-desamino-8-D-arginine vasopressin or DDAVP). The DDAVP is an analogue of ADH and increases the circulating level of factor VIII. Thus, it decreases the bleeding. The maximal effect of desmopressin is found within 2 to 4 hours after administration and lasts for 6 to 8 hours. It acts by increasing or changing the platelet membrane receptor binding capacity with the factor VIII and making a more active complex. Although, cryoprecipitate plasma and desmopressin can correct BT and the surgical procedure can be performed without excessive bleeding in renal failure patient, but the effects of both these drugs lasts only for few hours. Therefore, if prolonged effect is desired then conjugated oestrogen may be given in the dose of 0.6 mg/kg/day through IV. Repeated daily administration of oestrogen for 5 days decreases BT within 6 hours and this lasts for 15 days. Administration of erythropoietin also decreases the BT. It probably acts by increasing the erythropoiesis which acts like blood transfusion.

Electrolytes and acid-base status

As a preoperative checkup, the plasma Na^+, K^+, HCO_3^-, pH, BUN and creatinine level of a patient suffering from renal dysfunction should be checked routinely. If plasma Na^+ level is <125 m.mol/L, K^+ level is > 5.5 m.mol/L and both are associated with hypoalbuminaemia and acidosis, then the patient should be put under haemodialysis to control all these parameters, before induction of anaesthesia. Among these the plasma K^+ concentration is most important. So, if dialysis is performed 24 hours before surgery, still plasma K^+ level should be checked just before induction of anaesthesia. This is because plasma K^+ level is changed very rapidly than that of other electrolytes. In emergency circumstances, if dialysis can not be instituted immediately before anaesthesia and surgery, then the plasma K^+ level can be controlled by administration of IV glucose with insulin. Hyperventilation after induction and intubation may also decrease the plasma K^+ level by about 0.5 m.mol/L for every 10 mm of Hg reduction of P_aCO_2 level. Renal dysfunction is also associated with acidosis (low HCO_3^- level). Control of this acidosis by IV administration of bicarbonate also control the plasma K^+ level. But to control this acidosis and hyperkalaemia, bicarbonate should be infused very slowly, keeping in mind that rapid administration of it may precipitate overt symptoms of hypocalcaemia. If serum bicarbonate level is very low, i.e. between 12 to 15 m.mol/L then anion gap acidosis, for example ketoacidosis, should be thought. In renal dysfunction as the GFR is reduced, so the filtration of glucose is also reduced. Therefore, control of plasma glucose level, especially in diabetic patient is very difficult. Furthermore, an increase in plasma glucose level causes increase in plasma K^+ level. If plasma BUN level goes > 100 mg/dl, then dialysis should be performed 12 to 24 hours before any anaesthesia and surgery. It will help to remove the waste products and excess fluid. It will also help to control the K^+ and Na^+ level and acidosis (Table 42.10).

ECG and Chest X-ray

Renal dysfunction is associated with electrolytes imbalance, mainly K^+ and Na^+. Therefore, ECG in patients with renal failure often reveals conduction abnormalities and arrhythmias. Hence, continuous perioperative ECG monitoring is mandatory during anaesthesia of a renal failure patient.

Preanaesthetic chest radiograph also should always be obtained in patient suffering from renal dysfunction. Because renal failure is commonly associated with pulmonary infection, congestion, oedema, pleural or pericardial effusion, etc.

Premedication

For premedication before any anaesthesia and surgery in a renal dysfunction patient benzodiazepines are the most commonly used agents for sedation and anxiolysis. But caution must be exercised by reducing the dose and avoiding the repeated administration, as they may cause the excessive and prolonged sedation. Other premedicant such as H_2 blocker (ranitidine) or proton pump inhibitor (omeprazole) and prokinetic agent (metoclopramide) may be used safely in renal dysfunction patient, but their dose should be reduced appropriately. On the otherhand, use of these agents is mandatory in renal dysfunction patients,

Table 42.10: Management of hyperkalaemia

Type of treatment	*Dose*	*Onset of action*	*Mechanism of action*	*Side effects*
Sodium bicarbonate	50 - 100m.mol IV	Short	Shifting of K^+ into cells	Na^+ overload
Glucose & insulin	50 ml of 50% glucose solution with 10 unit soluble insulin	6-8 hours	Shifting of K^+ into cells	Hypo or hyperglycaemia
Calcium gluconate	10 - 20 ml of 10% solution IV	Short	Directly antagonize the effects of K^+ on the heart	Arrhythmia
Dialysis	–	According to severity of renal dysfunction	Directly remove K^+ from the body	Require vascular access
Ion exchange	–	- Do -	- Do -	Na^+ overload

because gastric emptying time is delayed in uraemia. Patients who are already under chronic steroid therapy should receive steroid preoperatively and in higher doses than previous one. This is because the long term use of steroid impair the stress response and therefore higher doses are needed. The dose of anticholinergic agents such as atropine and glycopyrrolate also should be reduced accordingly as they are partially excreted through urine.

Monitoring

Routine monitoring devices which are used in other patients should also be applied here to the renal dysfunction patient. Among these the ECG is very important to detect conduction abnormalities and arrhythmias which are commonly associated with hyperkalaemia, found in renal failure. BP cuff should not be used on the same extremity in which arterio venous fistula for dialysis is performed. This is because the fistula can be blocked by thrombosis during inflation of cuff. Special monitoring such as intra-arterial BP monitoring, CVP monitoring, pulmonary arterial pressure monitoring, etc. are needed according to the severity of renal dysfunction. A peripheral nerve stimulator may also be useful to avoid excessive dose of muscle relaxant with prolonged neuromuscular blockade.

Induction of anaesthesia

The commonly used inducing agents such as thiopentone and propofol has hypotensive effect which may be exaggerated in patients suffering from renal dysfunction. So, an anaesthetist must be careful about it and the incidence of severe hypotension can be reduced by reducing the dose of the above mentioned inducing agents and maintaining the adequate intravascular volume status prior to induction. In this regard, ketamine is safe and the agent of choice in severly ill patient, provided there is no hypertension which is commonly associated with renal dysfunction. The Rapid sequence induction and intubation is preferred in severe renal failure patient, because of the delayed gastric emptying and the risk of aspiration. If succinylcholine is contraindicated due to hyperkalaemia, a quick acting nondepolarising muscle relaxant that does not depend on the kidney for its clearance may be used. But, unfortunately, such ideal agent is not, available. Therefore, atracurium, cistracurium, rocuronium, mivacuronium, etc; are the better choice. Laryngoscopy should be brief, because prolonged apnoea and hypoxia may lead to respiratory acidosis which may aggravate the existing hyperkalaemia. After intubation slight hyperventilation is preferred, because it can correct acidosis and subsequent hyperkalaemia if these are present.

Maintenance of anaesthesia

After induction and intubation, general anaesthesia is maintained by N_2O and volatile anaesthetic agents. Among the volatile anaesthetic agents methoxyflurane, enflurane are contraindicated and sevoflurane is best avoided in patients with impaired renal function, the cause of which is discussed before. Therefore, isoflrane and halothane is the agent of choice as volatile anaesthetic agent. Opioids such as fentanyl, sufentanil and remifentanil can be used safely in conjugation with volatile anaesthetic agents. During maintenance of anaesthesia slight hyperventilation is better, the reason of which is also discussed before. On the otherhand, excessive hyperventilation is not desirable which is more applicable in anaemic patients only. This is because respiratory alkalosis, resulting from hyperventilation may shift the O_2 dissociation curve to the left and thus affect the O_2 unloading to the tissue. During artificial mechanical ventilation, intrathoracic pressure should be maintained at optimim level by appropriately adjusting the respiratory rate, tidal volume and I:E ratio. Otherwise, increased intrathoracic pressure may decrease the cardiac output and further deteriorates the renal function by decreasing the perfusion in kidney. The intraoperative severe hypertension can be controlled by infusion of nitroglycerine and nitroprusside. Cyanide toxicity following prolonged infusion of nitroprusside is unlikely in patient suffering from renal failure. This is due to decreased excretion of thiosulfate through kidney which facilitates the conversion of cyanide to thiocyanate.

During maintenance of general anaesthesia, intraoperative monitoring of renal function is important. This can be performed by measuring the urine output. Oliguria or anuria should be recognised promptly and treated immediately which may thus avoid the development of acute renal failure. If there is any suspicion of acute renal failure, then rapid infusion of 500 ml of normal saline as bolus and a small dose of frusemide (0.1 to 0.2 mg/kg), if intravascular volume is adequate, is effective. Still, if the urine output does not increase, then the intravascular volume status and cardiac output are monitored by invasive monitoring such as CVP and PWAP. Once the filling pressure is optimised by IV fluid and the urine output does not increase by frusemide, then dopamine in the dose of 1 to 2 µg/kg/minute is used to increase the renal blood flow and urine output. Sometimes, severe hypotension refractory to adequate intravascular volume repletion may occur in severe renal failure and dialysis patient which is due to autonomic dysfunction. This is generally treated by increasing the dose of dopamine (5 µg/Kg/minute) which increases the cardiac function and renal blood flow or by noradrenaline (Fig. 42.11).

Postoperative care

The Postoperative care of a patient suffering from renal dysfunction is similar to that of other patients, except some special points. Hyper or hypokalaemia usually occur during the first 24 hours of postoperative period in renal failure patient which depends on the severity of failure. So, electrolytes level should be checked

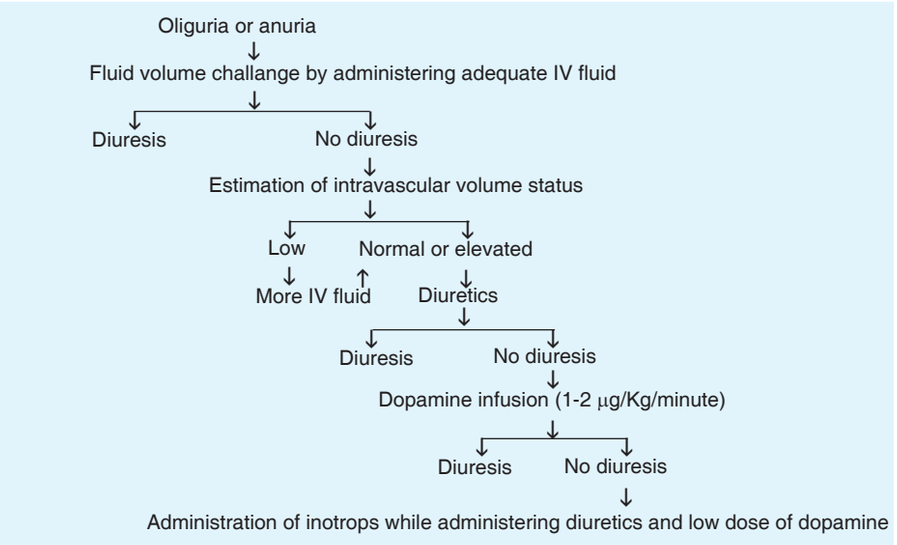


Fig. 42.11: Management of oliguria in renal dysfunction

routinely in recovery room and measures should be taken accordingly. Continuous ECG monitoring is essential for the detection of any conduction abnormalities and arrhythmias which is common due to electrolyte disturbances during the first 24 hours of postoperative period in a renal dysfunction patient. PCA using fentanyl is the best method of postoperative analgesia for patients with impaired renal function. Regional analgesic technique is very helpful for postoperative analgesia, if coagulation profile remains within normal limit. If a patient with history of impaired renal function shows skeletal muscular weakness, then partial reversal of the action of muscle relaxant should be thought. So, neuromuscular conduction should be monitored by nerve stimulator and if necessary additional dose of anticholinesterase with anticholinergic agent can be administered. Postoperative renal failure patient may suffer from hypertension or hypotension. So, blood pressure should be monitored closely and the recovery room sister is informed regarding the site of AV fistula used for dialysis to avoid the inadvertent placement of BP cuff on the same extremity.

43 Orthopaedic Anaesthesia

INTRODUCTION

It is very interesting to mention that only this subspeciality of anaesthesia experiences a large varieties of anaesthetic techniques or procedures such as GA, RA, combination of GA and RA, different types of nerve block, IV regional anaesthesia, only sedation, monitored anaesthetic care, etc, which the other specialities of anaesthesia do not. Also the orthopaedic anaesthesia encompasses a great range of patients extending from a child with congenital skeletal deformities requiring surgery and anaesthesia to an young adult with multiple trauma or fracture to a very old person with multiorgan problems coming with fractured neck femur etc. The degree of surgical complexity also vary from minor surgical manipulation of a joint which has limited mobility due to scars, fibrosis or adhesions, etc. to minor finger surgery to hemipelvectomy. There is also huge advancement in orthopaedic surgical technique which is gradually making it lesser to lesser invasive procedure and this is due to the development of CT scan, MRI, and computer. This causes only the overnight stays or the same day discharge of patient. Otherwise, they were kept admitted for many days after surgery which was done before. All these have great implication on anaesthesia. The other pecularities of orthopaedic surgeries that anaesthetists have to face are: (i) the different positions of the patient to facilitate the surgery which has many implications on on patients and subsequently on anaesthesia, (ii) the use of tourniquate which has many complications, though has many advantages, (iii) the use of orthopaedic cement and its bad consequences, (iv) the venous, fat and air embolism which are very common for orthopaedic surgery, (v) the amount of blood loss which may vary from few drops to 2 litres and blood transfusion related complications. So, different types of techniques are adapted to reduce the blood loss during major orthopaedic surgery such as induced hypotension, haemodilution, cell saver technique, etc. which have their own intrinsic complication and have to tackle by the anaesthetist. It is also very interesting that some orthopaedic surgeries are very short and some are very long and complex in nature requiring extensive monitoring such as intra arterial pressure monitoring, central venous pressure monitoring, transoesophageal echo cardiography, etc. Therefore, the rate of perioperative morbidity and mortality in orthopaedic surgeries vary greatly and is different from other surgical discipline (Table 43.1).

Some patients seeking orthopaedic surgery also have rheumatoid arthrities, alkylosing spondylits, etc. which affect the cervical, thoracic and lumbar spinal vertebrae with the other bony joints of the body.

Table 43.1: Causes of atlantoaxial instability

- Down's syndrome
- Adult rheumatoid arthritis
- Juvenile rheumatoid arthritis
- Ankylosing spondyitis
- Fractured cervical spine
- Morquio disease (mucopolysaccharidosis)

These patients may also have instability of cervical spine or atlantoaxial joint and can make the airway management difficult. In rheumatoid arthritis the damage of atlantoaxial joint is developed from the erosion of ligaments by rheumatoid involvement of the bursae around the odontoid process of C_2 vertebra. So, iatrogenic acute subluxation of joint between C_1 and C_2 vertebra may occur by the flexion of neck during intubation and it may result in cord compression or sudden death. Hence, during anaesthetic management of these type of patients previous diagnosis of this type of ailment is essential and all the precaution should be taken which must prevent flexion of the neck and maintain the stability of cervical spine. Therefore, orthopaedic anaesthesia sometimes demands a high degree of skilled airway management facility requiring fibreoptic laryngoscope, flexible bronchoscope, intubating LMA and all the other accessories to offset the movement of cervical spine during intubation.

Ankylosing spondylitis is more common in men than women and involves the ossification of ligaments of joints at their attachment to the bone. Progressive ankylosis also involves the cartilages of joint and intervertebral disc with diminution of spaces. Thus the vertebral column gradually becomes fused, making lumbar epidural or spinal anaesthesia difficult or impossible. Due to ankylosing spondylities sometimes the positioning of patient also becomes very painful while he is awake for central neuroaxial block. Similarly, there is also some choice between

the axillary and the interscalene route of brachial plexus block for regional anaesthesia of upper extremity when the patient is suffering from severe ankylosis of shoulder joint. The difficulty of positioning the patient or extremities may also arise from fractures, joint deformities, or unstable vertebrae which influence the mode of anaesthesia. Sometimes, it is very helpful to exercise the position preoperatively while the patient is awake.

Arthritis and ankylosis affecting the temperomandibular joint may also restrict the opening of mouth and can cause visualization of larynx difficult. These diseases may also affect the cricoarytenoid joint and may leave the vocal cord with limited mobility and restricted glottic opening. All these may produce difficulty of tracheal intubation. On the otherhand, as both the rheumatoid arthiritis and ankylosis spondylities are systemic disease, hence they may also affect the different organs or systems of body other than bones and joints causing different diseases. These are cardiac valvular lesions, ischaemic heart disease, pericarditis, pulmonary interstitial fibrosis, etc. However, these patients also have an impaired immune system, wasted musculature and underlying hypermetabolism which will contribute to an increased rate of postoperative infections and other complications (Table 43.2).

Many patients admitted for orthopaedic surgeries have the history of corticosteroid therapy in the past. Therefore, it has become routine for many anaesthetist to administer a large dose of glucocorticoids on the day of surgery with the aim to avoid the risk of acute adrenal insufficiency. But many anaesthetist oppose this view and their arguments are that: (i) The acute adrenal insufficiency causing unwanted hypotension is rare and can be better treated after it occurs than taking prophylactic measures. (ii) Preoperative large dose of corticosteroid may impair wound healing and immune function. Thus, it causes more harm to patient than good. (iii) The previous history of steroid therapy does not always predict the occurance of adrenocortical deficiency and thus it is impossible to select the patient who should receive the prophylactic steroid therapy without previous testing of adrenal response. (iv) The daily dose of corticosteroid is sufficient unless the severity of surgical stress warrants larger doses.

Table 43.2: Systemic manifestations of rheumatoid arthritis

CVS	Pericardial effusion, conduction defects, myocarditis, valvular defects, coronary arteritis, etc.
Respiratory system	Interstitial pulmonary fibrosis, pleural effusion, etc.
Others	Anaemia, thrombocytopaenia, adrenal insufficiency, impaired immune system, etc.

Some Specific Problems Related to Orthopaedic Surgeries and Anaesthesia

As discussed previously, the orthopaedic surgeries have some specific problems which are not found in other subspecialities of surgical discipline. So, the anaesthetists have to face these problems only or more frequently during orthopaedic anaesthesia. These problems are: tourniquet, bone cement, embolism, DVT, blood loss, and position of patient.

Tourniquet

It is frequently used in orthopaedic surgeries around the upper and lower extrimities to reduce or eliminate the intraoperative blood loss and to provide a clear surgical field. Though it is very useful, but is not completely devoid of problems, because it produces many changes in body such as haemodynamic, metabolic, embolic, pain, neurological damage, etc which are detrimental to patients. When the tourniquet is applied and inflated above the systolic pressure to get the blood less dry surgical field, then the distal tissue is cut off from its O_2 supply. So, within 8 to 10 minutes of application of tourniquet the partial pressure of O_2 in the mitochondria of the cells of ischaemic tissue falls to zero and anaerobic metabolism begins. Thus the stored NAD and creatine phosphate in the cell of ischaemic tissue decreases and is completely depleted within 60 minutes. Hence, the pH of tissue distal to the tourniquet rapidly falls < 6. Thereafter, the developed cellular hypoxia and acidosis cause the release of myoglobin, intracellular enzymes and K^+ from the muscle cells into the circulation. Subsequently the endothelial integrity of blood vessels is also lost. This is due to the release of thromboxane and tissue oedema supervens. Gradually after that the ischaemic portion of extremities becomes cool and approaches the room temperature.

Application of tourniquet is also associated with some haemodynamic changes in body. This is due to the exsanguination of limb before the application and inflation of tourniquet which causes a sudden shift of large volume of blood from the peripheral compartment to the central compartment. But usually in healthy adult patient this suddn shifting of huge amount of blood from peripheral compartment to central compartment does not produce any significant haemodynamic effect except a small increase in central venous and arterial pressure. However, in patient with poor ventricular compliance and with extensive vericose vein where tourniquet is applied over this limb may experience a considerable increase in pulmonary artery pressure. Also the bilateral application of tourniquet at a time and exsanguination of both the limbs before its application may cause the shift of a greater amount of blood with higher rise of CVP and systemic blood pressure that may not be sometimes tolerated in healthy patients causing failure. For the proper function of the tourniquet the inflation pressure within it should be raised to about 50 to 100 mm of Hg above the present mean arterial blood pressure which is needed to block the arterial flow. Then BP of a patient may increase after surgical incision or due to any cause

during intraoperative period. Therefore, the BP measured during preinduction preparation of patient is not always a reliable guide to set the pressure of the tourniquet during intraoperative period. Hence, the tourniquet pressure should be changed according to the intraoperative blood pressure of the patient. The time of application of tourniquet and the periodic pressure within it should be noted on the anaesthetic record. Like all the other medical devices, the pneumatic tourniquet also requires regular preoperative periodic check up and calibration.

For the proper functioning of tourniquet, the width of the cuff of it should be more than the half of the diameter of the limb. Because it will improve the transmission of cuff pressure to the deeper tissue and occludes the artery better. For the good functioning of tourniquet it should also be placed over a smoothly applied cotton padding around the limb. This will prevent the damage of underlying skin caused by tourniquet. It will have to be kept in mind that antiseptic solution used to prepare the skin of surgical site should not spread under the tourniquet. Otherwise it may cause chemical burn to the skin.

Within 30 minutes of inflating the tourniquet the conduction of impulses through the nerve (affarent and effarent) also ceases and it may also contribute to anaesthesia at the surgical site other than the action of anaesthetic agents on CNS. Due to tourniquet as the extremity is isolated from the central circulation and becomes cool, so it also reduces the sensation. The neurological and vascular problems arise when the tourniquet is inflated for prolonged period (> 2 hours) or when the excessive inflation pressure is applied. After the speculated time or when the surgery is over, then the tourniquet is deflated and the ischaemic limb is again reperfused from itself with the reduction of central venous pressure and arterial blood pressure. Sometimes this reduction of systemic BP becomes excessive and may result in cardiac arrest. The other contributing factors for this cardiac arrest associated with tourniquet may be the excessive blood loss from the surgical site or the circulatory effects of metabolites (e.g. thromboxane) from the ischaemic limb after the deflation of tourniquet. Washout of the accumulated metabolic wastes from the ischaemic limb into general circulation also increases P_aCO_2, $ETCO_2$, serum lactate and serum K^+ level. These metabolites can increase the minute ventilation in spontaneously ventilated patient.

Some patients receiving spinal, epidural, IV regional or brachial plexus block feel pain at the site of tourniquet before the level of anaesthesia recedes from the site of tourniquet where it is applied (tested by the pin prick). This pain occurs inconsistantly and comes at intervals. Similarly some patients undergoing GA also feel pain after inflation of tourniquet. This tourniquet pain is reflected by the sudden unexplained intraoperative hypertension after one hour of the application of tourniquet. The mechanism of this tourniquet's pain is not exactly known. Still the probable explanation is that it is the unmyelinated, slow conducting fine sympathetic C nerve fibres which are relatively resistant to the local anaesthetic agent and carry this pain sensation. However this is an explanation only for RA. The explanation in GA is given below. But this argument is sometimes contradicted by the following observation that tourniquet pain from lower extrimity is still experienced despite blockade up to the level of T_4 spinal segment and stellate ganglion block cannot ameliorate this pain from the upper extremity.

The management of intraoperative hypertension due to this pain from tourniquet during GA is very difficult. This is because attempts to relieve this pain with IV narcotics and increasing the dose of inhaled anaesthetics are not always successful. This pain can only be relieved by deflating the tourniquet for 10 to 15 minutes and then reinflating it. Thus this correlates well the relief of pain with the correction of cellular acidosis and also explains the another mechanism of this tourniquet pain in GA. The uncontrolled intraoperative hypertension due to tourniquet pain which cannot be managed by increasing the dose of narcotics and inhaled anaesthetics can usually be managed by vasodilator agents such as IV nitroprusside, nitroglycerine, or nifedipine, etc. The tourniquet pain under spinal or epidural anaesthesia sometimes becomes so severe that patient may need supplemental analgesia or light GA, despite the regional block is adequate for surgical incision.

Now, after multiple studies it is also observed that the tourniquet pain is mainly related to the quality or intensity of neural block than the level of the block. This is confirmed by the observation that tourniquate pain also can be relieved during continuous regional block by increasing the density of block by increasing the concentration of local anaesthetic agent or by adding some opioids with LA agent or by adding bicarbonate to LA agent which increases the fraction of the drug present as free base. It is also found that hypobaric and isobaric spinal technique result in lower incidence of tourniquet pain than the hyperbaric technique, even when the drugs, dose, and dermatome levels are same.

Bone (methacrylate) cement

Chemically the bone cement is a complex polymethylmethacrylate compound and is frequently used in joint arthroplasty. It acts only by helping strong binding between the metal prosthetic device and the cancellous or medullary part of the patient's bone. It also acts as a space filler which improve the fitting of implanted prosthetic device in the marrow cavity of the bone. However, the quality of interface between the cement and the bone is improved, if there is no layer of blood covering the bone surface when the cement is applied. So, some anaesthetists use hypotensive anaesthesia during the use of cement. But it has some disadvantages which are described below and are not routinely used.

Mixing of the solid methylmethacrylate polymer powder with the liquid methylmethacrylate monomer produces this polymethylmethacrylate compound which is known as cement. This is an exothermic reaction and leads to hardening and expansion of the cement substance. During preparation and hardening of this bone cement a strong pungent vapour is given off which produces some air pollution in operating theatre. This exothermic reaction also may cause some risk of thermal injury to the patient's tissues.

The major concern regarding the use of bone cement during joint arthroplasty is the pulmonary and cardiovascular responses of the patient. These responses are increased pulmonary vascular resistance, development of pulmonary hypertension, reduced cardiac output, hypotension, cardiac arrhythmias, and even cardiac arrest. These cardiovascular responses of patient during the use of bone cement may be due to the indirect and/or direct effect of cement. However, the indirect effect is more important than the direct effect of cement. The indirect effect of cement is due to the embolization of bone marrow into the right side of the heart and direct effect is due to the toxic effect of cement itself. In the indirect effect as the cement improves the fitting between the prosthetic device and the walls of the marrow cavity, it increases the intramedullary pressure, because during curing of cement in the marrow cavity it expands in volume. Thus, it forces out the remaining bone marrow contents or substances into the bloodstream and produces catastrophic pulmonary embolism of bone-marrow with the above mentioned complications. It is proved by the transoesophageal echocardiography (TEE) which shows the continuous raining of echogenic substances (pieces of bone marrow) in the right side of the heart after the application of cement. Sometimes, few large emboli may be observed in the right side of the heart, obstructing completely the right ventricular outflow tract and leading to acute right sided heart failure, reduced cardiac output, hypotension and cardiac arrest. Small emboli of bone marrow travers the right ventricle and embolises in the lung. These may increase the pulmonary artery pressure and intrapulmonary shunt. In patients with patent foramen ovale these emboli may pass into the systemic circulation through this foramen and cause systemic embolic manifestation such as infarction, stroke, etc. This is also proved by the fact that insertion of the stem of femoral prosthesis into the marrow cavity of femur increases the intramedullary pressure > 1 atmosphere and produces more entry of the medullary contents into the bloodstream than the only act of cementing of the acetabular prosthesis which is shown by echocardiography. It is also found that the emboli during prosthesis of hip is larger in size than the other joint arthroplasties such as knee. In patients undergoing total knee replacement surgery this reaction is not seen until the tourniquet is deflated which also prove the above explanation. However, this entry of bone marrow contents into the circulation is not so severe during other orthopaedic surgeries using bone cement such as surgeries on the proximal humerous. Also these reactions are not as common or as severe in prothesis where cement is not used. This increase in intramedullary pressure by bone cement not only causes the embolisation of the bone marrow contents, but also causes the embolisation of fat and air into the femoral venous channels.

The direct toxic effect of bone cement on the cardiovascular system of patient is due to the vasodilating and decreased systemic vascular resistance effect of the monomer component of the cement. It also release thromboplastin which trigger the aggregation of platelet and, the formation of microthrombus in the lungs. Thus it causes cardiovascular instability.

Therefore, the clinical symptoms of bone cement implantation is due to the embolic manifestation in lungs and direct toxic effect on CVS, all of which include pulmonary hypertension, hypoxia, hypotension, decreased cardiac output, cardiac arrhythmias and even cardiac arrest. As most of the hypotension after the use of cement results from the impaired left ventricular filling which is due to the pulmonary embolism and increased PVR, so the previous existing hypovolaemia will further impair the left ventricular filling and aggravate the hypotension leading to cardiac arrest. Hence, the management of the cardiovascular response of bone cement includes: increase in FiO_2, maintenance of euvolaemia before the use of cement, continuous monitoring of BP, and the use of vasopressor if necessary. The other measures which also can prevent the cardiovascular responses of cement during the joint arthroplasty are: the use of a plug previously into the marrow cavity of the femoral shaft that will limit the distal spread of cement in the femur, waiting for cement to become more viscus before its insertion, making a vent hole in the distal femur which will decrease the intramedullary pressure, vacuum drainage of marrow substances from the proximal femur during riming, performing a high pressure lavage in the distal femoral shaft which will remove the debris, or adopting some procedures where cement is not necessary.

Another major drawback of the use of bone cement during arthroplastic surgery is the delayed gradual loosening of prosthesis and it is due to the breakage of cement in small pieces over the years into the marrow cavity. In cementless arthroplastic surgeries, the natural bone grows slowly and fits the implants tightly. So, cementless arthroplasty last longer and advantageous for younger and active group of patients where healthy active bone will be formed, though the full recovery is slow and prolonged. Therefore, the bone cement for arthroplastic surgery is preferred where the chance of active healthy bone formation is less such as older (> 80 years) and less active patients who are suffering from osteoporosis or other diseases.

Hence, the use of bone cement depends on the patient's status, surgical technique, and the type of joint to be replaced. In modern practice, the articular surface is made up of plastic, ceramic, or metal.

Fat embolism

It means the appearance of fat globules in the bloodstream. The incidence of fat embolism is as much as 90% for the victims of major trauma. But the majority of cases remains subclinical and are only detected by the active investigations of serum or urine for the evidence of macroscopic fat globules. An association between the age and the incidence of fat embolism may be seen. Its incidence is low in the very young group of patient and much higher in the very old subject. When the fat embolism is manifested clinically, then it is known as the fat embolic syndrome (FES). However, the incidence of FES is rare (1 to 2%), but is fatal with high mortality rate (10 to 20%) when it occurs. It classically presents as the triad of pulmonary symptoms, CNS symptoms and cutaneous symptoms such as dyspnoea, confusions and cutaneous petechiae. But, the clinical diagnosis of FES is based on the major or minor criteria described in the (Table 43.3). It usually appears within 72 hours following the major orthopaedic surgeries or trauma. This syndrome can also be seen following parenteral feeding with lipid infusion or during liposuction. A full blown FES has cutaneous, CNS, pulmonary, and haemodynamic manifestations with less clincal effects on the other organs, depending on the site of embolic events.

Table 43.3: Diagnostic criteria of fat embolism

Major criteria	*Minor criteria*
PaO_2 < 60 mm of Hg	Tachycardia (HR >120/m
↑ PVR	Fat in urine
↑ Pulmonary artery pressure	Fat in sputum
Pulmonary oedema	Emboli in fundoscopic examination
Petechiae	Thrombocytopenia

Till now two theories of fat embolism have been advanced for its pathogenesis. Among them, the most widely accepted theory for the aetiology of fat embolism is the mechanical tissue trauma which forces out the fat globules, (released by the disruption of fat cells), into the circulation through tear in medullary vessels. This is proved by the fact that malignancy of long bones causes higher incidence of fat or marrow embolism. This is because the enlarged venous sinuses caused by malignant tumour permit greater access of fat globules into the circulation. Another alternative theory of fat embolism is that the circulating fat globules in the vessels result from the aggregation of the increased circulating free fatty acid (FFA) molecule due to the changes in the fatty acid metabolism for tramuma or surgery.

Regardless of the theories and the sources of fat globules in circulation, the clinical manifestation of fat embolism which is known as FES are due to the result of the deposition of fat particles at different organs and as well as the activation of some enzymes (particularly lipase) that lead to the capillary damage, endothelial leakage and release of many vasoactive substances such as prostaglandins, amines, etc. All these lead to the cutaneous manifestation (petechiae, mainly over neck, back, chest, trunk), pulmonary manifestation (ARDS), CNS manifestation (confusion, agitation, stupor, coma), CVS manifestation (due to pulmonary manifestation caused by fat embolism in pulmonary vasculature), ophthalmic manifestation (retinal exudate due to capillary leakage which is seen by fundoscopic examination as cotton wool), etc. It must also be considered that for systemic manifestation of fat embolism there must be a patent foramen ovale or intrapulmonary shunt which bypass the pulmonary filtration system and contribute the passage of fat globules directly into the systemic circulation.

The first step of diagnosis for early FES is a high index of suspicion. So, during anaesthesia for patients with higher risk and increased chances of incidence of FES attention should be focussed on the early signs and symptoms of FES and on the alterations of the normal physiology which indicate that fat embolism is occuring. The signs of pulmonary fat embolism during GA include ↓$ETCO_2$, ↑P_aCO_2, ↑pulmonary arterial pressure, ↓cardiac output, hypotension, etc. which are like the pulmonary embolism of bone marrow substance during the use of cement in arthroplasty. For diagnosis of cutaneous involvement of FES petechiae can be obvious. It can be further confirmed by retinal fundoscopic examination if cotton wool exudates are found. The clinical diagnosis of pulmonary involvement of FES may range from mild hypoxia with normal chest findings to mild hypoxia with wheezing, crepitations, secretions, etc. to full blown picture of ARDS. The diagnosis of cardiovascular involvement of FES depends on the stage of evolution. An early CVS finding in FES is only nonspecific tachycardia and right heart ECG changes which may pass later to severe hypotension, cyanosis, and left ventricular failure. Later DIC can result. Fat embolism to the specific parts of brain can cause seizure activity and predict serious FES. Coma can evolve from ischaemia, hypoxia and embolism to the key areas of brain stem.

There is no specific laboratory test which absolutely confirm the diagnosis of FES. The serum lipase activity may be elevated in majority of cases of FES, but bears no relationship to the severity of disease process. A large number of cases of fat embolsim will detect the fat globules in sputum, serum, or urine. But this test is too sensitive to use as an indicator of serious FES. Different coagulation abnormalities as the part of DIC may be present. There is general agreement that an unexplained low P_aO_2 (< 60 mm of Hg) which is not linked to other pathology is highly suggestive of FES. Patients with A-a O_2 tension gradients greater than 100 mm of Hg represent a high

probability of severe FES. It is also reported that bronchial lavage has both diagnostic and therapeutic value in FES.

The first step of the treatment of clinically manifested fat embolism (FES) is to minimise the factors which contribute to this process such as the decreased manipulation of fractures, decreased reaming of medullary canal, increased immobilisation of fractured long bones, etc. The second step of treatment of this disease process is supportive which are designed to decrease the impact of changes due to fat emboli. This includes the support of pulmonary and cardiovascular system according to necessary. Support of the pulmonary system will be the key factor for the survival of patient with severe FES. The principal objective of this support is adequate oxygenation of the tissues particularly the CVS, CNS, and other end organs. This is accomplished by the optimum support of cardiac output and adjustment of ventilation to achieve the best possible O_2 delivery to the tissues with the lowest possible FiO_2 to avoid injury of the pulmonary parenchyma from high FiO_2 for prolonged period (O_2 toxicity). This mandates the optimum PEEP, adequate cardiac output, proper patient's sedation and supportive mechanical ventilation. The defect of coagulation system must be treated based on the accurate assessment of the step of defects. For example the thrombocytopenia is treated by platelets. Decreased labile clotting factor or factor V (this factor is necessary for conversion of prothrombin into thrombin and is used up during clotting) is managed by fresh frozen plasma. Decreased fibrin level is maintained by pooled cryoprecipitate. The clinical situation where the laboratory results have long return intervals also can be managed by thromboelastogram and sonoclot devices which can provide accurate information and direct therapy. As the pathology of FES mainly involves the inflammatory reaction to the lungs and other tissues, so it is rational to use high doses of steroid for their profound anti-inflammatory property and to decrease the release of tissue activating factor from cellular injury (vasoactive substances). Previously for the management of FES, ethyl alcohol was used with the aim to decrease the activity of lipase. But now its use is abandoned as it had no effect. Similarly, the dextran and heparin was used previously to consolidate the fat. But recently these treatments are also ineffective and abandoned. Further they may contribute to the instability of coagulation system.

Deep venous thrombosis (DVT)

Pulmonary embolism (PE) originating from the clots of deep venous system by the process of thrombosis (deep venous thrombosis or DVT) may be the leading cause of morbidity and mortality following trauma or orthopaedic surgeries on the pelvis and lower extremities. The incidence of DVT is usually determined by a number of factors. These are: advanced age (> 60 years), prolonged bed rest or immobility, obesity, use of pneumatic tourniquet, prolonged surgery (> 30 minutes), surgery on pelvis or lower extremities, prior history of DVT or PE, malignancy, etc. Decreased fibrinolysis or release of plasminogen activating factors secondary to the inflated tourniquet are also the cause of tourniquet related DVT.

The risk of DVT and embolism from immobilisation of patient increases with the duration of immobilisation. The risk of DVT and embolism from upper extremity is very uncommon and is only related to trauma but not to surgeries. The use of oral contraceptive pill among the young woman patients also doubles the normal low incidence rate of DVT. The incidence of DVT in lower extremity (e.g. knee) following orthopaedic surgery using tourniquet and without any prophylactic measures varies between 40 to 60% which is demonstrated by venogram. This incidence is more high in pelvic fracture and this is due to the direct trauma of pelvic venous structure. Whereas the incidence of clinically significant PE following hip surgery is only 20 to 30%, among which only 1 to 2% becomes fatal. Although the clinical detection of DVT most often occurs between the 3rd and 5th day of surgery, but many clots are present in subclinical stage from earlier. This can only be detected by radiolabelled fibrinogen immediately after the surgical procedure. The likely major pathophysiological mechanism of DVT include the venous stasis and decreased fibrinolytic activity leading to hyper coagulable state which is further influenced by hormone related to pain or surgical stress. These facts comprise the triad of DVT which include : the change in constitutions of blood, the change in vessel wall and the change in flow of blood. Therefore, the prophylaxis of DVT acts at any of these steps.

Like fat embolism, the diagnosis of DVT is also triggered by the high index of suspicion in patients of high risked group. The first step of diagnosis of DVT is clinical examination. But, unfortunately the diagnosis of DVT by clinical examination alone may frequently overlook the presence of thrombosis which is sufficient to cause embolization and morbidity. So, the other more accurate methods of diagnosis are gradually evolved. The gold standard for diagnosis of DVT is the contrast venogram. This is only performed by cannulation of the distal vein on the involved limb and then the injection of contrast dye into that canulated vein to get the radiological picture of that venous system. This contrast venogram has very high detection and very low false negative rate. But its invasive nature, high cost, patient's discomfort, difficulty during cannulation and sometimes the chance of contrast media to cause thromboembolic disease itself leads to the search of ultrasound technique for diagnosis of DVT. The ultrasound technique diagnose the presence of thrombi in the venous system noninvasively by detecting the altered flow of blood in the venous system. Unfortunately, however, in ultrasound technique the false negative rate is very high. This is because of the

absence of a preoperative baseline study to compare with the postoperative picture and if the study is not performed by the same specialist pre and postoperatively, and also especially if the patient is obese.

Next, the radioactive fibrinogen study for the diagnosis of DVT also has high false negative and false positive rate. Another technique for diagnosis of DVT such as impedence plethysmography has also high detection but low false negative rate. But technically it is not very simple for clinical application. Therefore, in specialised centre performing major orthopaedic surgeries and when the suspicion is very high, then the combined approach of clinical examination, ultrasonography and venography is usually performed.

The prophylaxis for DVT is certainly more appealing than the treatment of it and its sequelae such as PE, cerebral embolism, coronary embolism, etc. This is because the institution of postoperative therapy in an established case of DVT by full dose of heparin may increase the bleeding at surgical site and therefore the morbidity by formation of haematoma at the operative site and at the spinal or epidural level. The treatment of an established case of DVT also increases the chance of postoperative infection, the length of hospitalisation, the cost, etc. Therefore, the prophylaxis of DVT has immense importance than its treatment. The prophylaxis of DVT is performed by interfering with the steps that lead to thromboembolic manifestation. These include : physical measures, antithrombotic drugs, and some modification of surgical and anaesthetic techniques. Among the physical measures the compressive elastic stocking or the intermittent compressive pneumatic stocking are most effective. This is because they more readily simulate the normal muscular contraction which helps in venous pumping from the lower extrimity. These should be applied prior to the surgical preparation and during the surgical procedure. The old electrical stimulation and contraction of the calf muscle for prophylaxix of DVT is proved to be no more effective than the simple intermittent compression of the muscle. In the postoperative period the most effective prophylactic physical measure of DVT is ambulation, if possible after orthopaedic surgery.

Many antithrombotic drugs that interact with the coagulation cascade have been used for the prophylaxis of DVT. These drugs are : various concentration of high molecular weight dextran, antiplatelet agent, aspirin, coumarin, heparin, and recently LMWH (low molecular weight heparin). Dextran acts by decreasing the platelet activity and interfering with the fibrin deposition. Despite its initial enthusiastic report, dextran is used now very rarely for the prevention of DVT and not at all for its treatment. Aspirin acts by preventing the adhesion of platelet to the injured vessel wall. It is given orally or rectally. It is not so effective in preventing the formation of thrombus, because the concentration of aspirin necessary to achieve the antiplatelet activity for antithyrombotic effect increases the intraoperative blood loss and causes the higher incidence of wound haematoma formation post operatively. However, among the antiplatelet agents only the dipyridamole is used as prophylaxis for DVT. It acts in the same way as aspirin or other prostaglandin synthetase inhibitor and has the same disadvantage like aspirin which is discussed above.

Coumarin (warfarin) is the most commonly used drug for the prophylaxis of DVT in high risk patients. It is usually used at the evening following surgery or at the next morning. The therapeutic end point of administration of coumarin (warfarin) is increasing the PT by 50% over the control value. The use of coumarin preoperatively is abandoned now, because it also increases the intraoperative bleeding. When DVT occurs inspite of the use of coumarin, then heparin is started as an acute course. Later coumarin is reinstated for maintenance.

Heparin acts by activating the plasma antithrombin III. At low concentration of heparin, factor Xa mediated conversion of prothrombin to thrombin is selectively affected (antithrombin activity). The anticoagulant action of heparin is exerted mainly by the inhibition of factor Xa as well as inhibition of thrombin (IIa) mediated conversion of fibrinogen to fibrin. For the treatment of DVT or pulmonary and systemic embolism such as cerebral embolism, coronary embolism, etc, the full anticoagulating dose of heparin is used. But this is too dangerous for prophylaxis of DVT, because of the fear of excessive bleeding, formation of haematoma, and other of haemorrhagic events elsewhere in the body. So, the idea of low dose of heparin has been evolved. It is administered in the dose of 5000 unit 8 hourly through subcutaneous route which only interfere the formation of clot at the site of injured vessel. In the majority of cases PT or PTT is not prolonged. But, as the result is not absolutely guaranteed, so it may rise concern in spinal and epidural block and most anaesthetist feel that evaluation of PT/PTT is mandatory prior to performing any central neuroaxial block, even in a patient receiving low dose SC heparin as prophylaxis.

Refined heparin preparations containing only the smaller molecules of it, called LMWH, has less effect on the platelet function than standard heparin. So, it has the same antithrombotic quality but less direct effect on coagulation and give the effective DVT prophylaxis with the decreased risk of postoperative bleeding and haematoma formation. The PT/PTT is also not prolonged by LMWH. Therefore, unless the patient pose any exceptionally high risk which demand the anticoagulant treatment preoperatively, all these anticoagulants should be started few hours after surgery only to prevent the excessive intraoperative surgical bleeding and prophylaxis of DVT.

Though it is generally agreed that preoperative full anticoagulation or fibrinolytic

therapy provide an unacceptable risk for spinal or epidural haematoma formation following regional anaesthesia, but still there is some controversy regarding the danger of patients who is receiving the low dose of anticoagulation preparation as prophylaxis preoperativley and undergoing regional anaesthesia – spinal and epidural. However, it is agreed that placement of spinal or epidural needle or catheter should generally not be undertaken 8 to 10 hours after administration of minidose of unfractioned heparin through SC route or within 12 to 24 hours of LMWH. Concomitant use of antiplatelet agent with heparin may further increase the risk of spinal or epidural haematoma formation. It is also interesting to mention that regional anaesthesia with continuous postoperative analgesia can mask the signs and symptoms of an expanding haematoma resulting cord compression (back pain, muscular weakness, etc.) and thus delaying the diagnosis and treatment.

It is an established fact that there is less incidence of DVT among the patients who are undergoing orthopaedic surgeries of pelvis or lower extremities under spinal or epidural anaesthesia compared to GA. There is also more reduction of incidence of DVT when the regional anaesthetic technique is extended postoperatively as continuous epidural infusion for postoperative analgesia. However, the method of detection of DVT must be the same with either venogram or radio labelled fibrinogen uptake. The probable theories about the decrease in thromboembolic manifestation associated with regional anaesthesia is that it improves the blood flow in microcirculation due to the effect of sympathectomy, as venous stasis is the known cause of DVT. Another probable threory is that pain or stress response inhibit fibrinolysis and thus regional anaesthesia is associated with this increase in fibrinolytic activity and reduction of the incidence of DVT. Some works have also established that there is an increase in DVT when blood loss is higher. Therefore, as regional anaesthesia is known to decrease the blood loss, this also causes the decrease in incidence of DVT.

Blood loss

Major orthopaedic surgeries are associated with significant amount of bloos loss. But the blood loss during orthopaedic surgeries is somewhat different from the blood loss in other specialities of surgery. This is because in major orthopaedic surgery the large amount of blood is lost from the raw bone and muscle surfaces which limits the surgeon's ability to control it directly and allows much of the shed blood to escape the method of retrive by suction catheter and gauze sponges, and it also continues after the closure of surgical wound. It is also proved by the radio isotope studied that the actual amount of blood loss in major orthopaedic surgery is 50% higher than the amount which is estimated clinically. Thus, the surgeons and anaesthetists always underestimate the blood loss during major orthopaedic surgeries. There are also many factors which increase the loss of blood during orthopaedic surgeries. These are: previous surgeries, large area of raw bones, proximal site of operation where tourniquet cannot be applied, presence of infection at the operative site, previous radiation at the operative site, surgeon's technique, etc. The reduction of blood loss during orthopaedic surgeries has many benefits to the patient. It reduces the exposure of patient to donated blood (homologus banked blood) and transmission of fatat viral disease such as hapatitis, HIV, and protozoal disease such as malaria, etc. The use of donated blood may have other harmful effects which can also be reduced by decreasing the blood loss. The intra operative decrease in blood loss also causes the reduction in postoperative infections, improved surgical results, better binding of cement to the bone, etc.

There are different methods by which the intraoperative blood loss and/or donation of homologus banked blood during orthopaedic surgeries can be reduced. These may begin with the use of tourniquet, preservation of normothermia, intraoperative haemodilution etc, and end with the predonation of autologus blood, induced hypotension, conduction anaesthesia, use of cell saver, progressive use of erythropoietin, use of antifibrinolytic agent, etc. In practice, the combination of several of these modalities is most effective in reducing the blood loss and subsequently reducing the incidense of homologus blood transfusion. Cell savers are expensive and have certain risks. So, they are used selectively in the operating room for major spinal surgery. Antifibrinolytic drugs such as tranexamic acid and aprotinin, and postoperative cell salvage are probably best used when the expected blood loss exceeds 2 litres. But it is warranted in minor procedure due to the risks of aprotinin. It acts by inhibiting the fibrinolytic pathway and intrinsic coagulation pathway by decreasing the activation of plasminogen. Thus it reduces the intraoperative blood loss. However, it is usually reserved for high risk cases (coagulopathies) or revision arthroplasty or bilateral hip arthroplasty. This is becaue it has high propensity to produce immunological sensitization. However, the use of aprotinin does no increase the incidence of DVT or PE.

A pneumatic tourniquet placed proximal to the site of surgery on extremities and inflated to occlude the arterial blood flow at the operative site eliminates the intraoperative blood loss. But, the significant loss of blood will occur postoperatively when the tourniquet is removed. So, some surgeons routinely deflate or remove the tourniquet before closing the wound to control the postoperative bleeding. The another method for the reduction of intraoperative blood loss is avoidance of hypothermia. This is based on the finding that mild hypothermia (35°C) is associated with an average increase of 500 ml of blood loss during single total hip arthroplasty.

Haemodilution and maintenance of normal blood volume with normal blood

pressure of a patient by administering cell free fluids such as saline, starch solution, albumin solution, etc. is also a common method of managing the blood loss and reducing the use of banked blood (homologous transfusions). When the patient's haemoglobin concentration falls between 6 to 7 gm/dl, then the anaesthesiologists must determine whether patient's risk due to inadequate oxygenation caused by anaemia will justify the transfusion of blood on not.

The transfusion of banked blood can be replaced by more safer autologous transfusion. This can be arranged by collecting the blood from surgical field or donating by patient and preserving preoperatively. This autologous transfusion of blood will remove the adverse effects of homologus transfusion for which the intraoperative reduction of blood loss is attempted. Recently much attention has been directed at the using of synthetic erythropoietein factor to increase the red cell mass of patient preoperatively. It is used in the dose of 600 IU/Kg subcutaneously weekly beginning 3 weeks before surgery. It increases the red cell mass by enhancing the production of it by stimulating the division and maturation of megaloblast in bone marrow. Therefore, it increases the number of collected autologous blood unit and reduces the amount of homologous blood transfusion.

During orthopaedic surgeries under regional or general anaesthesia intraoperative blood loss from raw oozing surfaces also can be reduced by the induced hypotension. This can be achieved by high spinal or epidural anaesthesia or by using Na-nitroprusside and nitroglycerine during GA and maintaining the BP at lower level such as MAP at 50 to 60 mm of Hg. But many patients scheduled for orthopaedic surgeries are old enough and may present relative contraindications to this type of hypotensive anaesthesia. The high regional anaesthesia produces patient's discomfort and it can be ameliorated by combining it with GA. Now, it is suggested that the combination of high level spinal or epidural anaesthesia with GA is safer and may be applied as a method of reducing blood loss during orthopaedic surgeries.

Positioning of patient

For different orthopaedic surgeries different position of the patient is needed. Further, different positioning places the patients at the risk of varieties of injury, but mainly nerves by compressions. Therefore, an anaesthetist must be aware of it and almost try to prevent their occurances. An awake patient will not tolerate this compressive nerve injury for long time, because pain and restlessness caused by the ischaemia of nerve will trigger the patient to correct its position spontaneously. But, in the sedated or anaesthetised patient this is not possible. So, different nerves and other structures such as blood vessels, skin, muscles, etc, are more liable to injury during anaesthesia. If a patient incurs nerve injury during anaesthesia and surgery, then the anaesthetist will be held responsible for it, whether the injury is related to the position, surgery, or other causes (Fig. 43.1).

The principal means of brachial plexus injury under GA is stretching. This is because of the hypermobility of upper extremity, the long course of nerves in the plexus, the extreme mobility of neck, and some points of fixation of this plexus of nerves during formation. When the patient's arm is constantly held for long time in excessive abducted position with flexion and rotation of neck to the contralateral side, then it puts the brachial plexus under stretching and subsequent ischaemia. Here the head of the humerus acts as a pivotal point against which the stretching of nerves occur. In another circumstances if the humerus is allowed to fall posteriorly against the trunk in supine position then it also causes the excessive stretching of nerves in the brachial plexus and injury. When the patient is kept in lateral position, then the brachial plexus is also at risk for both the dependent and the non dependent limb with more risk to the first one. This is because in dependent limb the plexus is compressed between two bony structures, i.e. the rib cage and the head of the humerus. So, in order to avoid this compression injury of brachial plexus the weight of the patient's thorax must be kept off the humerus and a roll of foam or towel of proper size should be placed in the axilla. The vascular integrity of dependent arm should also be checked by pulse oximeter. But it does not always guarantee the integrity of brachial plexus. In prone position, there is more danger to the ipsilateral brachial plexus, if the head is rotated toward the contralateral side, placing the brachial plexus under stretch at its origin. In the postoperative period the diagnosis of brachial plexus injury is first suspected, if the patient has unusual pain in the neck and the upper arm on the first postoperatvie day. This pain may be accompanied by numbness and loss of motor function. It can affect the entire brachial plexus (C_5 to T_1), but commonly it involves only the upper roots (C_5 to C_7, Erb's palsy) with the involvement of upper arm and forearm, and less commonly the lower roots (C_8 to T_1) with the involvement of hand (Fig. 43.2).

Just immediately above the elbow the ulnar nerve is situated very superficially in the olecranon notch. So, direct compression at this place can render the ulnar nerve ischaemic and after prolonged ischaemia

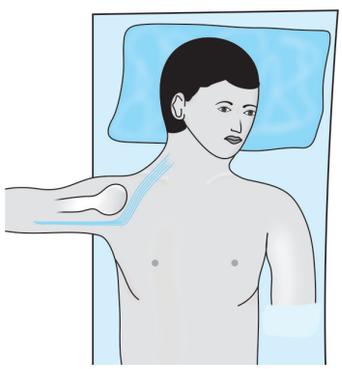


Fig. 43.1: Stretching of brachial plexus due to excessive abduction of arm and flexion and rotation of neck

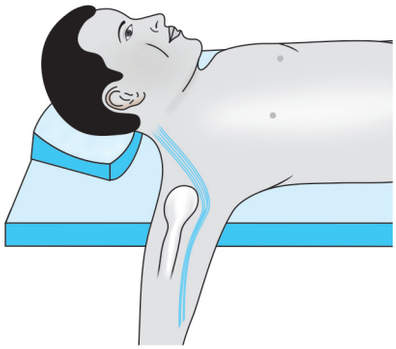


Fig. 43.2: Stretching of brachial plexus due to hanging of hand below the table

neuropraxia can occur. For a patient under GA the ulnar nerve is highly susceptible to injury at this site in supine posture by the edge of the table. So it must be always positioned such that direct compression of the ulnar nerve does not occur. The ulnar nerve injury may be detected in the post-operative period as a weak grip strength of hand. By specific examination it is found that the weakness is localised only to the ulnar function of the hand. Depending on how high the lesion is, there may be weakness of the wrist flexors also. The intrinsic muscles of the hand supplied by ulnar nerve will be weak and finger dexterity will be poor. Abduction and opposition of the 5th finger may be weak. There may be sensory deficit over the ulnar fingers and palm. In complete lesion of nerve there is no regeneration. So, there is wasting and contracture of the the intrinsic muscles, resulting in claw hand (Fig. 43.3).

The saphenous nerve is very superficial at the region of the upper part of the leg. So, this nerve is also more susceptible to injury at this site by compressions when the patient is positioned in lithotomy position by some devices like the picture for knee immobilization during arthroscopy. The compression injury of the saphenous nerve produces only the sensory loss over the distribution of this nerve on leg and foot. The saphenous nerve of the dependent leg is also at risk from pressure injury when the patient is kept in lateral position for prolonged period (Fig. 43.4).

Normally, in supine position the sciatic nerve is protected from compressisn injury by the muscles of the buttock. However, in supine position especially in thin and malnourshied patients or due to any position of buttock in normal individual over the edge of a positioning device can result in compression injury of the sciatic nerve. The incorrect application of the lateral position of patient also can put the sciatic nerve of dependent side liable to injury by the edge of the table, or by any positioning devices or other irregular surfaces due to direct compressions over the lateral gluteal surfaces. Intramuscular injection in the buttock should be performed in the superior and medial location to minimise the possibility of intraneural injection of the sciatic nerve, as it emerges from the pyriformis. Trauma to the branches of sciatic nerve is also possible. For example the common peroneal nerve is very superficial and liable to direct pressure injury as it sweeps around the head of the fibula just below the joint line of knee. This occurs in dependent leg when the patient is kept for prolonged period in lateral position or during lithotomy position when the leg is kept medial to the stand which is erected to hold the leg in hanging position (Fig. 43.5).

When the sciatic nerve injury occurs, then all the muscles below the knee will be paralyzed or becomes weak and numbmess of the anterolateral part of the calf and foot, except the spahenous area will also occur. When the injury of common peroneal nerve occurs, then the loss of dorsiflexion of the ankle (foot drop) is accompanied by the anterolateral numbness of the calf and the medial planter side of the foot. Deep peroneal injury also involves foot drop and numbness of the dorsum of foot. Posteriar tibial nerve injury results in numbness of the plantar surface of the foot, toes and the lateral edge of foot, combined with weakened plantar flexion.

Of all the positions chosen for orthopaedic surgery, the prone position is the lest physiological for the patient under anaesthesia. The prone position brings a hot of challenges to an anaesthetist depending on the types of surgery and anaesthesia selected. GA presents different issues from RA and LA with or without sedation. There is definite problem for ventilation and excessive surgical bleeding in prone position. In addition to the risk of injury to nerve, the prone position may also precipitate the risk of injury to the muscle and skin also. The direct prolonged contact of bed with the body during prone position is sometimes associated with isolated lesion by pressure of different terminal branches of the facial nerve, bracial plexus, femoral and

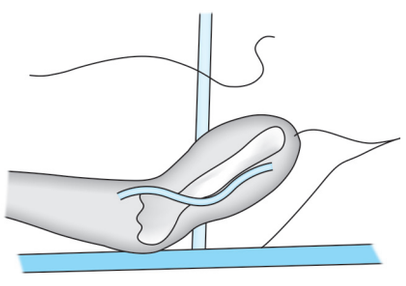


Fig. 43.3: Compression of radial nerve

Fig. 43.4: Compression of saphenous nerve on the medial side of the leg below knee by iron stand

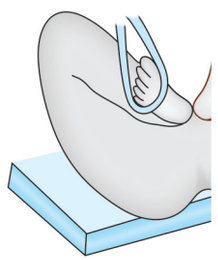


Fig. 43.5: Compression of common peroneal nerve over the head of fibula

other nerves. Different positioning devices that facilitate the prone position also can injure the different nerves or their branches. Curved frames that allows the abdomen to hang freely may also place direct pressure on the lower abdomen. But care should be taken to avoid direct pressure to the ilioinguinal and illiohypogastric nerve in the region of iliac crest (Table 43.4).

The use of tourniquet is also a risk factor for nerve injury. So, the size of the cuff, proper placement of it, padding and the duration of cuff inflation are the all important consideration. Inflation of tourniquet for more than 2 hours increases the risk of ischaemic injury to the underlying muscle and nerve. However, the nerve of upper extrimity is more sensitive to injury by tourniquet than that of lower extrimity.

When the fractured table is used for some orthopaedic surgeries with the patient in supine position, then all the risks of injury arising from supine position will persist and the other extra risks for this type of table also will be added. The purpose of the fractured OT table is to immobilize the patient's lower extremities and also to allow some rotation and traction of leg which will facilitate the surgery. After anaesthesia the patient is shifted from a regular bed to the fractured table. The trunk and hips are placed in supine position and the legs hang freely, supported by the heels. Longitudinal traction is applied and counter traction is indirectly imposed at a fixed postplaced between the patient's leg. Thus potential injury of lower extremities can occur from traction and counter traction or due to other positions caused by the fractured table. The post is placed at the perineum. So the external genitalia, especially of male are at increased risk of injury from compression by the post.

Table 43.4: Problems faced by anaesthetist during prone position of patient

Airway	Dislodgement of ET tube
	Kinking of ET tube
Nerves	Stretching or compression of brachial plexus
	Compression of ulnar nerve
	Compression of common peroneal nerve
	Gross hyperextension or hyperflexion of neck
	External pressure on eyes
	Excessive rotation of neck
Others	Kinking or obstruction of blood vessels
	Excessive lordosis

INDIVIDUAL ORTHOPAEDIC SURGERY

Total Hip Replacement (THR) or Arthroplasty

Most of the patients who are advised for THR surgery are usually suffered from osteoarthiritis, rheumatoid arthiritis, avascular necrosis of the bones of hip joint, etc., and it is for these diseases they are advised for such surgery. Osteoarthiritis is a degenerative process and affects not only the hip joint for which the patient is put for surgery, but also affects the articular surfaces of the bones of other joints. But among all the joints, the hip and knee are mostly affected. Bones of the vertebral column are also affected by osteoarthiritis. So, making different positions of the patient during THR surgeries and also positioning of neck during intubations is very difficult which is important to an anaesthetist. This is because excessive movement of vertebrae due to positioning or intubation can cause nerve root compression or disc prolapse.

Unlike osteoarthiritis, rheumatoid arthiritis is an immune mediated disease and affects the synovial membrane of joints instead of the articular surfaces. It affects multiple joints including hip, knee, vertebrae, shoulder, and some small joints of hands and legs. It becomes a concern to an anaesthetist when it involves the cervical vertebra and temperomandibular joint. When cervical vertebrae are involved, it causes sublaxation of atlantoaxial joint. Atlantoaxial sublaxation is important to an anaesthetist because during the flexion of neck for intubation the odontoid process may protrude into the foramen magnum and can compress the spinal cord or brainstem causing serious injury or death. Rheumatoid arthritis is also a concern to an anaesthetist because it may produce difficulty in intubation due to involvement of temperomandibular joint. Sublaxation of the atlantoaxial joint can be diagnosed radiologically. So, during preoperative evolution all the patients suffering from severe rheumatoid arthiritis and getting steroid or methotrexate as medication must have the lateral radiograph of neck in both the position of flexion and extension. If the atlantoaxial instability exceeds 5 mm, then intubation should be performed by awake fibreoptic laryngoscope or other techniques with out any movement of the neck. Rheumatoid arthirits also have the systemic involvement affecting the immune, haematology, pulmonary and cardiovascular system, which have immense implications on anaesthesia. Sometimes, patients with rheumatoid arthritis suffer from severe deformities which make the insertion of invasive catheters and even gaining an intravenous line a challenge.

The surgical procedure of THR involves the prosthetic replacement of acetabulum and the femoral head. It includes the procedures such as: (i) Reaming of acetabulum and insertion of prosthetic acetabular cap with or without cement, (ii) Dislocation and removal of femoral head, and (iii) Reaming of femur and insertion of prosthetic femoral head into the shaft with or without cement. The anaesthetic consideration of THR involves the general principles of orthopaedic surgeries which are discussed under the heading of 'introduction' and 'specific problems related to orthopaedic surgery'. Among these the three potential life threatening complications of THR are: Intra and postoperative haemorrhage, bone cement implantation syndrome and DVT.

THR is a major surgical procedure and takes 2 to 3 hours as intraoperative time. The expected perioperative blood

loss during THR is 1 to 1·5 litre and the position of patient to facilitate the surgery is lateral (more common) or supine. To maintain the lateral position of patient an anaesthetist must discuss with surgeron regarding the proper placement of anterior pelvic brace. Because if it is placed too far caudally it will exert much pressure on the femoral triangle of the dependent leg of patient causing venous or arterial obstruction. On the other hand, if it is placed too far cranially, it will also press the patient's abdomen too forcefully and can limit the movement of diaphragm causing impairment of respiration. THR surgery is particularly amenable to RA with slight sedation or full GA. But the technique may be influenced by the patient's wishes and its medical status. In RA, postdural puncture headache is very rare with 25G needle as the procedure involves mainly the older age group of patients.

As THR is a major surgery and may involve many complication, so intraoperative monitoring of patient by invasive arterial line, transoesophageal echocardiography, $ETCO_2$, etc may be considered. These are more applicable for revision arthroplasty after prior surgery, or bilateral hip arthroplasty, or very sick patient. But, unless, the patient is at particular risk due to severe illness, then intraoperative monitoring by measuring BP with an arm cuff and measuring urine output with a bladder catheter is usually sufficient for cardiovascular system. Embolic phenomenon most frequently occurs during the insertion of femoral prosthesis or at the end of surgery when the hip is relocated. This is because during relocation of leg emboli formed by the contents of bone marrow are dislodged from the previously obstructed femoral vein. More emboli occur in patient when cement is used for THR than when it is not used. Therefore, uncemented THR is preferred for patient at higher risk of FES. The measures taken to avoid the embolic manifestations include omitting cement, high pressure wash out of femoral canal to remove debris (potential microemboli), and drilling a venting hole in the distal part of the femur to relieve intramedullary pressure. Increased pulmonary artery pressure at the time of cementing the femoral prosthesis is the usual finding during THR surgery. So, many anaesthetists increase the FiO_2 prior to cementing. Careful maintenance of blood volume at the time of the placement of prosthesis and hip relocation attenuates the chance of decrease in BP due to bone marrow emboli. Severe hypotension during THR reflects large emboli in pulmonary artery causing large increase in PVR, decreased cardiac output and resultant right heart failure or severe reaction from cement. So, immediate inotropic support is recommended. As DVT is prevalent after THR, so all the measures to prevent this complication should be taken when managing THR. This is already discussed before and among these regional anaesthesia is important. So, THR should better be performed under spinal or epidural block.

Blood loss in THR is expected to be large and may increase to about 2 litres or above in case of revision of prior arthroplasty. It depends on many factors such as the surgical technique used, the skill of surgeon, and the type of prosthesis chosen, etc. This losses of blood can be reduced by deliberately inducing controlled hypotension. So, a combination of RA (like continuous lumbar epidural or single shot spinal with or without narcotic) with anaesthetic level upto T_4 and light GA could be employed. With mean arterial pressure maintaining at 50 to 60 mm of Hg the intraoperative blood loss can be reduced to less than 300 to 500 ml. Thus, by providing dry surgical field, controlled hypotension also improves the result of THR using cement and make short the duration of surgery. If deliberate hypotension is contraindicated due to any reason, then deliberate haemodilution and/or preoperative preservation of autologuous blood unit can prevent the intraoperative transfusion of banked blood. Preoperative administrations of recombinant human erythropoietin represents an another alternative for perioperative allogenic blood transfusion. Maintenance of normal body temperature is also an another mean to reduce the intraoperative blood loss. Preoperative insertion of epidural catheter and diluted local anaesthetic solution with or without opiates greatly facilitates the postoperative pain management in THR. This may extend for 48 to 72 hours.

Total hip replacement of both the sides at the same time is a longer and more invasive procedure than THR of one side. So, they are associated with more haemodynamic changes particularly if cement is used. Therefore, in such situation consideration should be given to direct arterial pressure monitoring, access to large bore venous system for quick transfusion, and other full haemodynamic monitoring, especially in elderly frail patient. The amount of blood loss may go above 2 litres. It can safely be performed in one anaesthetic sitting if there is no significant PE of bone marrow contents after insertion of the first femoral component. Monitoring of pulmonary artery pressure may indicate pulmonary embolization by a rise in pulmonary artery pressure and fall in cardiac output. The normal pulmonary artery pressure is 200 dyne × s × cm^{-5}. If it rises above normal, then the plan for surgery of contralateral side should be postponed. Recently, synthetic prosthetic system is available which does not require cement and therefore cementless hip arthroplasty of both sides at one sitting does not require monitoring of pulmonary artery pressure.

Hip Fracture

Usually there are two types of hip fracture: Intracapsular and extracapsular. Intracapsular fracture is again of two types — subcapital and transcervical, and extracapsular fracture is again of three types — base of the femoral neck, intertrochanteric, and subtrochanteric. In general, the intracapsular fracture is associated with less amount

of blood loss (400 ml) than the extracapsular fracture (800 ml). Most patients coming with hip fracture for surgery and anaesthesia are aged, frail and suffering from many concomitant systemic diseases such as osteoporosis, IHD, COPD, hypertension, diabetes mellitus, cerebral vascular diseases, psychiatric disorders, etc. In such group of patients the common cause of hip fracture is indirect trauma due to fall. But, occassionally young patients may also present with hip fracture and this is mainly due to direct accidental trauma. The patients presenting with hip fracture are often severly dehydrated. This is because of occult blood loss, use of diuretics in case of hypertensive patient, inadequate oral intake in psychiatric patients, delayed rescue after accident and trauma, etc. They also present with a false normal or borderline normal haematocrit value and it is due to dehydration and haemoconcentration or actual anaemia due to occult blood loss. It is also very important to know the cause of fall or cause of accident which may be stroke, MI, cardiac arrhythmia, etc. resulting in hip fracture. Because all these have imanse effect on anaesthesia (Fig. 43.6).

Generally, the operative decision for hip fracture is taken in the hope of getting the older patient out of the bed as much as quick possible in order to reduce the bad effects of prolonged staying in bed. These bad effects due to prolonged staying in bed include the bed sore, pneumonia, thromboembolic manifestation, etc. However, emergency surgery for hip fracture is not undertaken and is usually performed after one or two days, during which period the patient is treated for the concomitant diseases and is also prepared for surgery. However, more delay in surgery does not increase the mortality, but increase only the morbidity which are mainly related to the lungs and skin. Sometimes, during preoperative evaluation the examination of mental status of patient is very important. This is because: dementia patients are not suitable for RA, mental illness is associated with delayed recovery and increased mortality, they cannot be communicated during perioperative period, and others which are discussed in the chapter 'Psychiatric diseases and anaesthesia'. The hip fractured patients are more likely to be hypoxaemic than expected for their age. This may probably due to the result of occult fat embolism. Many studies have reported that the rate of mortality following hip fracture may vary from 10 to 15% during admission in hospital and 20 to 25% at the end of 1 year. The significant predicting factor for this mortality include : old age > 85 years, pulmonary complications, infection, depressed mental function, etc.

The choice between GA and RA for fractured hip surgery is also extensively studied and is tilted towards the later like other orthopaedic surgeries. This is because RA is associated with decreased thromboembolic manifestation, induced hypotension facilitating surgery, reduced blood loss, postoperative analgesia, more prompt return to the preoperative mental state, lower mortality rate in the early postoperative period, etc. However, in recent studies it is found that the mortality rates after 1 to 2 months following RA or GA is more or less same. There is also a general impression that RA is less associated with postoperative confusion and mental impairment than GA but it is only in the absence of previous psychiatric disease and if excessive sedation are not used perioperatively. However, recent studies do not confirm it and shows that both the type of anaesthesia (general and regional) produce the same postoperative confusion and mental impairment. The postoperative confusion correlates best with the presence of preoperative confusion, presence of preoperative hypoxaemia, and the use of drugs with anticholinergic effects, but not on the mode of anaesthesia. The mode of anaesthesia in fractured hip also depends on the type of surgery which varies from close reduction with surface traction to open reduction with different types of internal fixation such as cannulated screw fixation, intramedullary Gamma nail, extramedullary sliding screw and plates, etc. according to the site of fracture, degree of displacement, patient's status, etc.

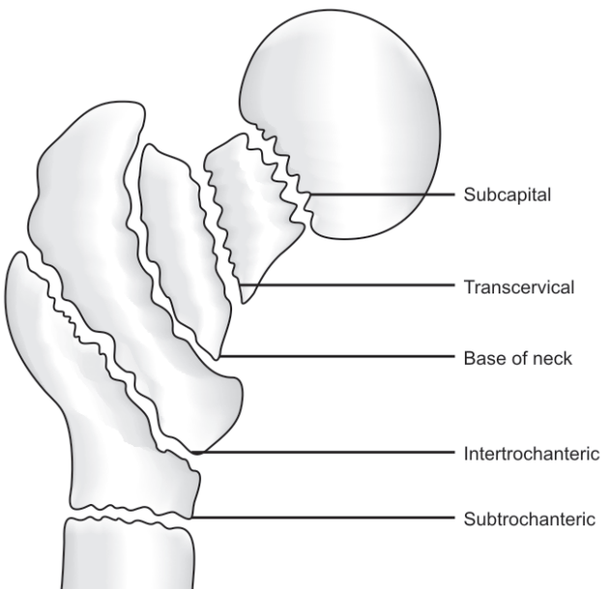


Fig. 43.6: This figure shows different types of fracture of the head of femur

Total Knee Arthroplasty (TKA)

The anaesthetic consideration of TKA is more or less similar to THR surgery. RA offers several advantages to the patients

undergoing such surgery and therefore is preferred. The usual position of the patient for TKA is supine and tourniquet is commonly used to reduce the blood loss. So, there is more chance of DVT and other thromboembolic manifestation than THR, and the prophylactic measures do not seem to reduce the incidence of these problems. When the TKA using cement is performed under tourniquet then the syndrome of ↑PVR, ↓CO, systemic hypotension, etc. which are usually found after the use of cement is delayed until the tourniquet is deflated at the end of surgery. Otherwise, when tourniquet is not used this syndrome may begin immediately after the insertion of prosthesis. The patient may suffer from the combined effects of embolism arising from cement, blood clot, fat or marrow debris and blood loss. This can be diagnosed by TEE showing emboli in RV, increased pulmonary artery pressure, hypotension, and hypoxaemia. Large emboli greater than 5 mm produces fatal consequences and is more commonly associated with tourniquet. So, the vital signs of patient should be monitored continuously in the perioperative period especially after insertion of prosthesis or deflation of tourniquet when bone cement is used and the patient is treated with O_2, fluid, pressure agents as required. Sick patients or with cardiovascular diseases who might not be able to compensate adequately for these events during TKA should be monitored extensively by invasive method and ventilators should be kept ready at hand.

Recently, many studies are showing their result that the complication rate and initial recovery of knee movement is better when TKA is performed without tourniquet. The expected blood loss in single TKA is about 1 to 1·5 litres. The use of tourniquet reduces this intraoperative blood loss, but may be the same after deflation of tourniquet. Deliberate hypotension reduces the perioperative blood loss, but may increase the incidence of PE.

The surgical insult caused by single TKA is usually tolerated by most of the healthy patients who do not have serious pulmonary and cardiovascular diseases. On the other hand, bilateral TKA in one sitting is associated with double amount of blood loss, requiring subsequent blood transfusion, and double the risk of PE. Therefore, the decision of TKA in both legs in one sitting will depend on the patient's health status, invasiveness of monitoring and the outcome of surgery of one leg. It is better to stage the bilateral TKA procedure into two when performed in one sitting, so that the second part does not begin until it is seen that there is no complication after the first phase of TKA procedure.

Postoperative pain following TKA is more severe than THR. Therefore, effective postoperative analgesia is essential for early physical rehabilitation after TKA. This will in turn prevent the joint adhesions and increases the movement. Non-cooperative patients will not do exercise even with good postoperative analgesia. So, there should be a balance between the pain control and the cooperative patient willing to do exercise. The preoperative placement of epidural catheter is the best way for postoperative pain management and physiotherapy. For this 0·2% ropivacaine infusion at the rate of 10 ml/Hour will provide good analgesia with minimum motor blockade. Alternatively, placement of an indwelling catheter in femoral sheath may be performed for postoperative analgesia. Through this catheter 0·2% ropivacaine or 0·25% bupivacaine can be used continuously at the rate of 5 to 10 ml/hour for good analgesia with minimum motor block.

Knee Arthroscopy

The surgeries of knee joint that can be done through arthroscopy include menisectomy, ligament repairs, replacement of cruciate ligaments, removal of loose foreign bodies, etc. The typical patients undergoing knee arthroscopic surgeries are young healthy adult, usually atheletes. However, it is also performed on aged persons with multiple medical problems. All forms of anaesthesia as an outpatient basis is suitable for knee arthroscopic surgery. So, it may vary from GA to spinal anaesthesia using fine pencil point needle to combined spinal epidural anaesthesia to femoral block. Less invasive and least prolonged procedure also can be performed with the intraarticular injection of local anaesthetic solution. Absorption of local anaesthetic (LA) agent from joint surface is slow and addition of epinephrine in this local anaesthetic solution will further decrease its absorption. Therefore, blood concentration of LA agent will be always minimum and 30 ml of 0·5% bupivacaine with or without epinephrine is safe. If blood less field is required for arthroscopic surgery then tourniquet should be applied and mode of anaesthesia also should be changed accordingly.

Closed Treatment of Fracture, Joint Manipulation and Reduction of Dislocation

The management of these group of patients are more or less similar. As the procedures are very brief, so GA is often preferred to regional techniques. The later is chosen for elderly patients with multiple medical problems and full stomach. For example, reduction of Colles's fracture in an elderly patient can be achieved by intravenous regional anaesthesia or brachial plexus block. If GA is chosen then violent fasciculation by succinylcholine which may disturb some fractures should be avoided. Whatever may be the type of anaesthesia profound muscle relaxation is mandatory. This will allow the surgeon to distinguish between the limitation of joint movement due to anatomical cause or muscle guarding. Thus, short acting IV anaesthetics and small dose of succinylcholine is effective. If surgical lesions permit then intra-articular injection of LA may provide some postoperative analgesia after joint manipulation.

44 Anaesthesia for Surgeries of the Genitourinary Tract

INTRODUCTION

About 15 to 20% of all anaesthetic procedures are undergone for genitourinary tract surgeries. With a drastic revolution in technology and introduction of fibreoptic instrumentation, complicated urological procedures have become common. Patients undergoing genitourinary tract surgeries are usually elderly, with multiple, coexisting medical disorders, thus making anaesthesia more challenging. The commonly used lithotomy position, the approach through the transurethral route, the extracorporeal shock waves used in lithotripsy and other radical methods make the procedures more complicated. Proper and meticulous preoperative evaluation of the patient, understanding the surgical procedure, being acquainted with the surgical skill and estimating the approximate time of surgery – helps the anaesthesiologist to formulate the best anaesthetic plan.

The anaesthetic plan for all genitourinary tract surgeries partly depends on the innervation of the area (Table 44.1).

Motor suply of the bladder is by the parasympathetic nerves. Sensation of fullness and stretching of the bladder is carried by the afferent parasympathetic fibres. Sympathetic fibres carry the pain, touch and temperature sensations. Pain from the ureter and kidney is felt in the low back area, flanks, scrotal, labial and ilioinguinal areas, i.e. along the innervation of the 10th thoracic nerve mainly, but also extending to the second lumbar regions. Nerves from the lumbosacral area innervates the prostate.

Some important genitourinary procedures shall be discussed now, to help further understanding of the subject.

CYSTOSCOPY

One of the most commonly performed genitourinary procedure is cystoscopy. Introduction of the flexible fibreoptic scope have made this procedure very easy to perform.

Indications

Urinary obstruction, haematuria and recurrent urinary obstruction are most common indications for cystoscopy. Bladder tumour biopsies and resection, renal stones extraction and placement of ureteric stents are also done through a cystoscope. Retrograde pyelograms are also performed through a cystoscope.

Position

The most commonly used position for genitourinary procedures is the lithotomy position, which may be accompanied by the trendelenburg (head-down) position. Improper positioning of the patient may cause severe iatrogenic complcations. The patient lies supine and straps, holders, stirrups or supports hold the legs in position. These supports should be padded to prevent nerve injuries. The legs should hang freely. Pressure of the straps on the lateral part of the leg causes injury to the common peroneal nerve, with loss of dorsiflexion of the foot. Pressure of the straps medially on the leg injuries the saphenous nerve, causing numbness along the medial calf. The obturator and the femoral nerves may be damaged by too much flexion of the thigh. Extreme flexion of the thigh may also damage the sciatic nerve. Prolonged lithotomy position often presents with a compartment syndrome of the inferior extremities, with rhabdomyolysis.

Table 44.1: Level of regional anaesthesia required for surgeries of different structures of the genitourinary tract

Urethra		S2 - S4
Bladder	Dome	T11 - L2
	Lower tract	S2 - S4
Ureter		T10
Prostate		T11 - L2 and S2-S4

Various physiological changes are associated with the lithotomy position, which makes the work of the anaesthesiologist more demanding. Congestive cardiac failure is often exaggerated, as raising of the legs increase venous return and blood pressure though cardiac output remains almost unchanged. Lowering of the legs similarly decreases the venous return and the blood pressure. This hypotension is further increased by regional or general anaesthesia, due to vasodilatation. So blood pressure measurement and monitoring is essential before and after positioning of the patient in the lithotomy position. Lung atelectasis and hypoxia is common as functional residual capacity decreases, which is further aggravated by the trendelenburg position.

Anaesthesia

Age of the patient, gender and indication for cystoscopy decides on the plan

of anaesthesia. Cystoscopy in children is always performed under general anaesthesia. Short urethra in females allows the procedure to be performed under topical anaesthesia, with viscous lidocaine, with or without sedation, but only for diagnostic purposes. All cystoscopies for therapeutic or operative purposes are preferred under general anaesthesia. In males, cystoscopies for diagnostic as well as operative purposes are done under general or regional anaesthesia.

General anaesthesia is preferred by most anaesthesiologists for cystoscopy, due to the short duration of the procedure (about 18-20 minutes). Patients are usually very apprehensive and so they too prefer general anaesthesia. LMA (laryngeal mask airway) is usually used. Oxygen saturation is closely monitored in all patients.

Regional anaesthesia may also be opted. Either spinal or epidural anaesthesia may be preferred, though most anaesthesiologists like spinal anaesthesia, as epidural anaesthesia takes 20 minutes to provide satisfactory blockade whereas spinal anaesthesia takes just 4-5 minutes. All cystoscopies can be done with a sensory block up to T10. Most anaesthesiologists believe that the sensory block by the hyperbaric local anaesthetic agent, used for regional block should be well "fixed", before putting the patient in lithotomy position, as that may raise the level of the sensory block. But, there is no substantial evidence to prove this.

Obturator reflex is not abolished by regional anaesthesia. Muscle paralysis in general anaesthesia is needed to block the obturator reflex (electrocautery of the lateral bladder wall stimulates the obturator nerve, which causes external rotation and adduction of the though).

TRANSURETHRAL PROSTATECTOMY (TURP)

Transurethral prostatectomy is the most commonly adopted operative procedure for either benign or malignant hypertrophy of the prostate, in elderly men. Prostatic enlargement leads to urinary bladder neck obstruction.

Indications

The patients present with recurrent urinary infections, persistent haematuria or even impaired renal function. TURP is preferred in patients with a prostate gland volume less that 45-50 ml. Larger volumes require alternative aproaches like suprapubic prostatectomy or perineal prostatectomy. TURP is also the procedure of choice in patients with prostatic carcinoma and helps to relieve the urinary obstruction.

Position

The usual lithotomy position.

Anaesthesia

Most patients are elderly and have coexisting pulmonary, cardiac or renal diseases. No wonder TURP carries a 0.5-7% mortatity rate, even today. Preoperative evaluation and optimising of the patient presenting for TURP is of utmost importance to an anaesthesiologist (Table 44.2).

Spinal anaesthesia is the choice of most anaesthesiologists, though other forms of regional anaesthesia like epidural block may be opted for too. Block up to T10 sensory level is enough to make the patient, surgeon and anaesthesiologist comfortable. Regional anaesthesia is contraindicated only when there is possibility of lumbar metastasis of prostatic cancer and then GA is preferred (Table 44.3).

TURP Procedure

A cystoscope, more precisely a resectoscope is introduced, which has a cutting and coagulating wire loop. By passing a cutting current through this loop, hypertrophic prostatic tissue is resected and removed from the medial and the lateral lobes, under continuous irrigation and direct visualisation. Continuous irrigation is used to distend the bladder, remove the resected materials and clear the field of surgery.

Complications

Here are some of the major complications in TURP:

i. TURP syndrome
ii. Bladder perforation
iii. Haemorrhage
iv. Bacteraemia and septicaemia
v. Coagulopathy – DIC (Disseminated intravascular coagulopathy)
vi Hypothermia
vii. Rarely death due to myucardial infarction, renal failure or pulmonary oedema.

TURP Syndrome

The prostate has a network of large venous sinuses, which open up during

Table 44.2: Comparison of regional anaesthesia over GA in TURP

1. Regional anaesthesia does not mask the signs and symptoms of TURP syndrome, unlike GA
2. Regional anaesthesia does not mask the signs and symptoms of bladder perforation, unlike GA
3. Regional anaesthesia decreases the incidence of postoperative venous thrombosis.
4. Reversal and recovery from general anaesthesia is delayed due to hyponatraemia, caused by TURP syndrome.
5. GA is preferred in cases of lumbar metastasis of prostate cancer.

Table 44.3: Essential intraoperative and early postoperative monitoring in patients of TURP

1. Mental status: Any alteration detects early signs of TURP and bladder perforation.
2. Arterial oxygen saturation: A decrease detects fluid overload.
3. Temperature: To detect hypothermia.
4. ECG: To detect ischaemic changes.
5. Blood chemistry: Haemodilution may decrease the haematocrit values.
6. Blood loss: Larger prostatic volume (> 45 ml) and longer operative procedures (> 1.5 hours) may require blood transfusion, as controlling prostatic bleeding is often difficult. So blood should be cross-matched and arranged.

transurethral resection and cause absorption of the irrigating fluid into the systemic circulation.This results in a set of manifestations, commonly referred to as the TURP syndrome, which may become evident intraoperatively or in the early postoperative period. If not treated instantaneously and with utmost care, fatality is not uncommon. The amount of irrigating fluid absorbed depend a number of factors, listed below (Table 44.4).

The irrigating fluid should be nonelectrolytic because electrolyte solutions disperse the electrocautery current, passing through the loop of wire. Visibility is best with water, but can cause severe water intoxication on absorption. Water also causes lysis of red blood cells due to its hypotonicity. Water irrigation is used only for resection of bladder tumours. To increase the osmolality of the irrigating fluid mannitol, glycine, sorbitol, urea, etc. have been added to it, but one has to be careful. These solutes and their metabolites should be nontoxic and easily excretable (Table 44.5).

Hyponatraemia occurs due to intravascular absorption of any non-electrolytic irrigating fluid, due to its hypotonicity. The CNS symptoms of TURP syndrome are usually due to hyponatraemia, which causes metabolic encephalopathy, which in turn is caused by cerebral oedema. Clinical manifestations of hyponatraemia appear only when the serum sodium concentration falls below 120 mEq/L (Table 44.6).

Glycine is commonly added to the irrigating fluid for TURP, to increase its osmolality to plasma level. Hyperglycinemia due to intravascular absorption of this irrigating fluid, is also responsible for most of the CNS symptoms. Visual disturbances like transient blindness has been reported, but the vision usually returns back to normal within 24 hours. Normal plasma glycine level is about 12-15 mg/L and may increase to 900-1000 mg/L after TURP. CNS symptoms of glycine is because it is an inhibitory neurotransmitter in the CNS. It also acts on the retinal receptors to cause transient blindness. Glycine also causes cerebral oedema.

Ammonia is a metabolic product of glycine degradation. Hyperammonaemia causes seizure and coma in TURP patients, by increasing the concentration of neurotransmitter in the brain. Normal ammonia level in blood is 5-50 µmol/L and may exceed 100-150 µmol/L in TURP patients.

Dextrose or sorbitol in irrigating fluid may cause hyperglycaemia (Table 44.7).

Mannitol does not undergo metabolism in the body. It causes osmotic diuresis, increases fluid overload and may cause congestive cardiac failure or pulmonary oedema.

The absorption of the irrigating fluid may be intravascular or extravascular. Intravascular absorption occurs when the hydrostatic pressure of the irrigating fluid (the height of the irrigating fluid above the open venous channels of the prostate) is more than the pressure inside the venous sinusoids of the prostate. Extravascular absorption of the irrigating fluid occurs only when the prostatic capsule is perforated during surgery and it effects the haemostasis. Extravascular diffusion of the irrigating fluid along with excretion through the kidney, decreases the severity of complications due to intravascular absorption (Table 44.8).

Treatment of the TURP syndrome

The treatment of TURP syndrome depends on the early detection and severity of symptoms. Patients should be closely

Table 44.4: Factors on which absorption of irrigating fluid depends

1.	Duration of the surgical procedure.
2.	Type, nature and amount of fluid used for irrigation.
3.	Hydrostatic pressure of the irrigating fluid.
4.	Number, size and pressure in the venous channels opened up in the prostate.
5.	Skill of the surgeon.

Table 44.5: Common irrigating fluids used in TURP

Plain water
Glycine solution (1.5% - 230 mOsm/L)
Mixture of sorbitol (2.7%) and mannitol (0.54% - 195 mOsm/L)
Sorbitol solution (3.3%)
Mannitol solution (3%)
Dextrose solution (2.5 - 4%)
Urea solution (1%)

Table 44.6: Characteristics of an ideal irrigating fluid in TURP

1.	It should be isotonic.
2.	It should be nonhaemolytic.
3.	It should be nontoxic.
4.	It should be nonelectrolytic.
5.	It shouldnot be easily metabolised.
6.	It should allow clear visibility.
7.	It should not affect the osmolality.
8.	It should be rapidly metabolised.
9.	It should be an osmotic diuretic.

Table 44.7: Major physiological changes in TURP syndrome

Circulatory fluid overload
Water intoxication
Hypo-osmolality and hypotonicity
Haemolysis
Solute toxi
Hyponatraemia – from all irrigating fluid
Hyperglycinaemia – from glycine solution
Hyperammonaemia – from glycine solution
Hyperglycaemia – from sorbitol or dextrose solution
Intravascular fluid volume-expansion from mannitol solution

Table 44.8: Common clinical manifestations of TURP syndrome

1.	CNS manifestations - Restlessness, confusion, anxiety, agitation, nausea, disorientation, visual disturbance, seizure and coma.
2.	CVS manifestations - Increased CVP, bradycardia, anginal pain, ischaemic changes in ECG, hypotension, congestive cardiac failure, cyanosis, arrhythmia, etc.
3	Respiratory symptom - Dyspnoea, pulmonary congestion and pulmonary oedema.

monitored. Investigations should be done immediately to evaluate the severity of TURP syndrome. Blood glucose, blood urea, serum creatinine, ECG, glycine and ammonia levels and electrolytes should be evaluated. Hyponatraemia should be corrected to prevent the CNS manifestations with hypertonic saline solution, in patients with normal renal function. In patients with renal failure, dialysis should be started. Hyponatraemia creates acute hypotonia and our aim should be to shift fluid from the intracellular compartment to the extracellular compartment. This helps to decrease cerebral oedema. But one should be careful that rapid correction of hyponatraemia may cause circulatory overload, cerebral haemorrhage or cerebral demyelination. The rate at which hypertonic saline solution is given should not be more than 100 ml/hour and the amount of hypertonic saline solution repuired depends on the level of hyponatraemia. Seizures may be corrected with diazepam (2 to 5 mg), midazolam (2 to 4 mg), thiopental (75 to 100 mg), phenytion (10 to 20 mg/kg) slow IV (at the rate of 50 mg/min). Lasix may be given to correct fluid overload. Transient blindness may evaluated by an ophthalmologist but is usually self limiting. Hyperglycinemia and hyperammonemia doesnot resquire any specific treatment. Hypoxaemia should be avoided. Endotracheal intubation may be advised in very severe cases, mainly to avoid aspiration (Table 44.9).

The dreaded complications of TURP syndrome may be avoided by decreasing the resection time (to maximum 1 hour), by consultation with the surgeon. The procedure should be performed under spinal anaesthesia rather than GA, for early detection and management of symptoms. Hypotension due to spinal anaestiesia should not be corrected with large volume of hypotonic IV fluid, instead vasopressors should be used. 0.9% saline solution is considered best for IV infusion during TURP.

Table 44.9: Signs and symptoms of hyponatraemia

Serum sodium level	*Manifestations*
Below 120 mEq/L	Blood QRS complex, restlessness, disorientation.
Below 114 mEq/L	Nausea, vomting, elevated ST segment.
Below 100 mEq/L	Ventricular febrillation, seizure, coma.

Some other major complications of TURP are explained below.

(a) Bladder perforation

Bladder perforation may be caused by over distension of the bladder with irrigating fluid or by direct injury to the bladder wall by the resectoscope. In most cases the perforation in extraperitoneal and the patient complains of suprapubic, inguinal or periumbilical pain, accompained by nausea. Poor return of the irrigating fluid during the procedure signals extraperitoneal perforation of the bladder. Intraperitonal perforation of the bladder presents with hypotension, bradycardia and acute abdominal symptoms.

(b) Haemorrhage

Thromboplastins released from the prostate during TURP, into the circulation causes DIC (Disseminated intravascular coagulopathy). Diffuse uncontrollable bleeding is often seen in TURP and is tough to manage. Absorption of the irrigating fluid often causes dilutional thrombocytopaenia. Primary fibrinolysis caused by metastatic carcinoma of the prostate due to release of fibrinolytic enzymes from the cancer cells, causes coagulopathy and hence profuse haemorrhage. Laboratory tests confirm the diagnosis and the help of a haematologist is sought for. Heparin, replacement of clotting factors and platelets are used to treat DIC. Primary fibrinolysis is treated with E-aminocaproic acid 5 gm IV, repeated at a dose of 1 gm/hour IV.

(c) Septicaemia

The prostate is a site for bacterial colonisation and chronic infection. Opening up of the venous sinusoids and surgical procedure on the prostate, causes these bacteria to escape into the circulation, leading to bacteraemia and septicaema, or even septic shock may result if neglected. Fever, rigor and tachycardia are the common symptoms. Antibiotics like cephazolin, levofloxacin, gentamycin, etc. are preferred by most surgeons, prophylactically given before TURP, to avoid this complication.

(d) Hypothermia

Large volume of irrigating fluids and intravenous fluids (given to correct hypotension of spinal anaesthesia), given at room temperature, causes acute hypothermia. This often leads to rigor during the postoperative period. But this is best avoided as it may dislodge the clots formed and thus increase chances of acute postoperative haemorrhage. All fluids – whether irrigating or intravenous fluid – should be heated to body temperature to prevent hypothermia.

LITHOTRIPSY

Treatment of stones in the urinary tract has changed drastically in the past few years. The open surgical procedures have been replaced by noninvasive or lesser invasive surgical procedures, using cystoscopes – both rigid and flexible.

Indications

Stones in the urinary bladder and lower part of the ureters are removed by intracorporeal lithotripsy. Intracorporeal lithotripsy may be laser lithotripsy or electrohydraulic lithotripsy. Intracorporeal laser lithotripsy uses a Holmium-YAG laser. Stones in the upper part of the ureters and the kidney are removed by ESWL (Extracorporeal Shock Wave Lithotripsy) or percutaneous nephrolithotomy. Percutaneous nephrolithotomy is used to remove big

stones (more than 2 cm) and hard stones like cystine stones, uric acid stones and calcium oxalate monohydrate stones. It is similar to ureteroscopy, the approach is through a percutaneous sheath over the kidney, with the patient in the prone position.

Mechanism

ESWL comprises of a lithotriptor. The lithotriptor has a spark plug, which is the energy or shockwave generator; a reflector; a concentrator and either a fluoroscope or a ultrasonogram for viewing the stone. A water bath or a conducting gel attaches the generator to the patient. The spark plug produces energy waves repeatedly, which vaporise the water in the water bath, thus creating an external shock wave (sound waves) there. As the acoustic density of the tissue and water is same, these shock waves travel from the water bath into the tissue of the patient's body, without any damage to the tissue or loss of energy. As these extracorporeal shock waves meet a stone, the acoustic density changes (between the tissue and the stone) and energy is released. As these shock waves pass through the stone and leaves it to enter the tissue again, energy is again released. This double power breaks the stone into fragments and the small pieces are washed down the urinary tract. Ureteral stents placed preoperatively with the help of a cystoscope allows larger stones to pass through, without damaging the tissue.

There are three types of shock wave generators used in ESWL (Table 44.10).

In older electrohydrautic lithotriptors, the patient was submerged in a hot water bath on a hydraulic chair. The patient was so placed with the help of two image intensifiers, that an underwater spark plug (energy generator) was the first focus of an elliptical reflector, while the stone was the second focus. Modern lithotriptors generate energy using electromagnetic waves or from piezoelectric crystals. In electromagnetic generators, a metallic plate is placed in front of an electromagnet, the vibration of which produces shock waves. In piezoelectric lithotriptors electric current is passed through ceramic crystals and shock waves are produced when their external dimensions change. Both the electromagnetic and the piezoelectric generators are put in a case filled with water and a plastic membrane or conducting gel couples it to the patient. These newer lithotriptors have facilities for both ultrasonography and fluoroscopy, for localisation of the stones.

Table 44.10: Extracorporeal shock wave generators used in ESWL

Type	*Model*
Electrohydraulic generator	
– With tub	Dornier HM_3
– Tubless	Dornier MFL5000
Electromagnetic generator	Dornier DoLi, Compact Delta, Sigma, Siemens Lithostar, Storz Modulith.
Piezoelectric generator	Wolf Prezolith

Anaesthesia

Lithotripsy by older electrohydraulic lithotriptors using a water bath was painful. 1200-2400 high voltage shock waves were required to pass through. So regional or general anaesthesia was preferred. Newer lithotriptors use 1500-2500 low voltage shock waves, which can be performed even with light sedation.

Continuous epidural anaesthesia was the procedure of choice of most anaesthesiologists previously. Kidney is supplied by T10 to L2. So a T6 sensory block was sufficient for ESWL. Fentanyl was used epidurally for better analgesia. Light IV sedation was used and oxygen supplementation with a face mask or nasal catheter was given. During insertion of the epidural cannula and cathetor minimum air should be put in the epidural space (for testing the loss-of-resistance feeling) and foam tapes should be avoided for fixing of the cannula as both air and foam tapes cause release of energy, when the shock waves pass through them causing tissue damage.

Spinal anaesthesia was avoided because postdural puncture headache was common due to the sitting position of the patient in the hydraulic chair, after the spinal block. A loading volume 1200-1500 ml of lactated Ringers solution is given to the patient IV before hand, to prevent postural hypotension during positioning of the patient, after the regional anaesthesia. Further, 1500-2000 ml of lactated Ringers solution is given along with a diuretic intraoperatively, to increase urinary flow and wash out the stone fragments, clots and debris. Less and calculated fluid is given to patients with low cardiac reserve.

Diaphragmatic movement is not controlled in regional anaesthesia. The movement of the diaphragm during spontaneous respiration may move the stone in and away from the shock waves, thus prolonging the procedure. The patient may be asked to take shallow breaths but that is not always practical, especially when light sedation is administered to calm the patient. So general anaesthesia is prefered by some anaesthesiologists, especially when electrohydraulic lithotriptors with water bath is used. Endotracheal intubation with muscle relaxation is preferred but placing an anaesthetised patient on a hydraulic chair and raising and lowering him to submerge him in a water bath carries its own risks. Newer methods of ESWL require low voltage shock waves and can be done under sedation. Propofol infusion with midazolam and some opioid analgesic is often sufficient.

Monitoring is important in ESWL. ECG leads should be attached with some waterproof dressing. Oxygen saturation should be noted and temperature of the water bath maintained. Pulse and blood pressure monitoring is mandatory for each patient.

Complication

Placing a patient in a heated water bath causes vasodilatation and transient hypotension. The hydrostatic pressure of water

on the inferior extremity and abdomen, causes redistribution of the venous blood centrally. Thus preload is increased and CVP and PCWP raised. Stroke volume increases, cardiac output increases but heart rate remains the same. Subsequently systemic vascular resistance (SVR) rises and cardiac output falls. This increase in venous return can cause congestive cardiac failure in patients with poor cardiac reserve. Shock waves of ESWL can damage the parts of a permanent pacemaker or internal cardiac defibrillator, thus precipitating arythmia in these patients. If the shock waves are synchronised with the R wave of the ECG and the shock waves are generated during the ventricular refractory period (i.e. approximately 20 minutes after the R wave) of the cardiac cycle, arrhythmias may be avoided.

Hydrostatic pressure of water on the chest of the patient decreases the FRC, vital capacity and tidal volume. Thus work of respiration has to be increased. As all respiratory reserves are decreased, hypoxia is quite common.

Table 44.11: Other common surgeries of the genitourinary tract

Laparoscopic procedures	Pyeloplasty Partial nephrectomy
Nephrectomy	Renal cancer
Radical prostatectomy	For adenocarcinoma of prostrate
Cystatectomy	For bladder cancer
Orchiectomy	For testicular cancer
Renal transplantation	

Contraindications and Special Considerations

Pregnancy is a complete contraindication for ESWL. Coagulopathies and anticoagulant therapies are relative contraindications. Aortic aneurysms in the abdomen, especially with calcifications and orthopaedic prosthesis should be kept away from the path of the shock waves. Obesity is a problem for ESWL due to mechanical factors. The temperature of the water in the water bath may affect the body temperature. Lungs and intestine, should be kept away from the path of the shock waves, as air tissue interfaces can dissipate energy and cause tissue damage. Chronic infection and obstruction of the urinary tract below the stone is a contraindication for ESWL. Ecchymosis haematoma, blistering or bruising of the skin is common at the site of treatment. Development of a perinepheric haematoma has also been observed (Table 44.11).

Each has its own special consideration, positioning and complications.

45 Day Case Anaesthesia

INTRODUCTION

Day case anaesthesia in also termed as outpatient anaesthesia or ambulatory anaesthesia. Over the last few decades, day case surgery and according to the need of this surgery the day case ambulatory anaesthesia has grown up at an exponential rate. It is mainly due to the major development of sophisticated surgical equipment advocating more and more minimal invasive surgery and due to the development of newer ultrashort acting anaesthetic drugs which help in quick recovery. A day case or an out patient surgery and anaesthesia is one which is performed on a patient who is admitted only for investigation under anaesthesia or for minor examination under anaesthesia or for operation on a planned non resident basis and who nonetheless requires any overnight indoor facilities for recovery. Today, almost 60% of all the elective surgery and anaesthesia are performed at the outpatient surgical and anaesthesia setting in the form of GA, LA or MAc (monitored anaesthetic care). In USA and UK, over 80% of all the elective surgeries are performed as an outpatient basis and this is likely to increase more and more in near future in response to the economic pressures on the health care market.

For day case anaesthesia while the surgical procedure is same, but the anaesthesia and the nursing care are significantly different from if the same is performed at the in-patient setting. In the day case unit anaesthesiologists are mainly responsible for evaluating, screening, informing and preparing the patients, both by physiologically and psychologically. Specialized skills are required for day case or outpatient anaesthesia, because the patients are discharged to their home soon after their operation. So, at conclusion, we may say that to achieve a pain free ambulatory day case patient, it requires skillful patient selection, experienced anaesthetists and skilled surgeons working coordinately in a day case surgery and anaesthesia unit. The day case surgery and anaesthesia unit is also termed as the cost-effective quality care unit. This is because costs for anaesthesia and surgical procedures are much less in such setting than when the same procedure is performed at the in-patient setting without sacrificing quality. Costs in day case or out-patient anaesthesia unit can be minimised without sacrificing quality by (i) the proper preoperative screening, (ii) unnecessary cancellation of surgery, (iii) decreasing room turn over times, (iv) decreasing stays in post-anaesthesia care unit and (v) reducing unanticipated admission and staffing.

The cost of surgery and anaesthesia on an ambulatory basis has been estimated to be about 25 to 75% less than the similar inpatient procedure. Ambulatory day case surgery and anaesthesia also offers a wide variety of other advantages to all the parties involving patients, surgeons and insurance companies. Patients and their relatives experience less disruption to their personal lives and rapidly return to their daily activities. Patients are also able to recover at home in familiar surroundings. Thus, it provides an additional psychological benefit. There is also a reduced risk of complications such as wound infections (from other patients), deep venous thrombosis, pulmonary embolism, paralytic ileus and pneumonia (nosocomial), etc.

PATIENT SELECTION

Patient's selection for day case surgery and anaesthesia is the most important point, if the maximum use of resources and the smooth running of a unit is to be made. Proper preanaesthetic planning will minimize the unexpected cancellations or unnecessary postoperative admissions. It will also allow for easy access to in-patient services of the outpatient individual when necessary. The selection criteria of patients for day case anaesthesia and surgery should include: (i) the over all medical health of the patient (ASA physical status), (ii) age, (iii) social factors, (v) the surgical procedure, (vi) the limitations of surgical facility (vii) and the limitations of health care providers.

Normally the ASA I and II status patients (for example normal healthy patient with or without minor systemic disease, not interfering with the surgical and anaesthetic procedures or medical conditions that are well controlled by previous therapy such as hypertension or non-insulin dependent diabetes, etc), are included in this unit. But gradually the increasing numbers of medically stable ASA III patients are now included in outpatient surgical and anaesthesia unit due to the use of more and more local and topical anaesthesia and due to the more and more

use of minimally invasive (endoscopic) surgical procedures. Also it is important to notice that some ASA III patients do better in a day case enviornment rather than an in-patient enviornment e.g chemotherapy patients, stable diabetics, etc. But patients with significant cardiovascular or respiratory diseases, insulin dependent diabetes or those with gross obesity, etc., are not suitable for day case anaesthesia. Stable asthmatics are suitable for day case surgery and anaesthesia. Whereas frequent hospitalization, oral steroid therapy and poor control of symptoms of bronchial asthma would suggest unsuitability for day case unit. Stable epileptics on medications are suitable for day case surgery and anaesthesia, but propofol should be avoided if they have a driving license. Undiagnosed hypertensive disease and uncontrolled atrial fibrillation should be reevaluated on the day of surgery and anaesthesia.

Recently in USA, the patients of status of ASA IV are also inculded in day case surgery and anaesthesia. It is based on the findings that (i) there is no obvious relations between the ASA physical status and the rate of major morbidity or mortality after day case surgery and anaesthesia. (ii) It is also found that those with preexisting disease have the same complication rate as healthy patients. (iii) There is also no significant relation between the cause and the effect for pre-existing disease and the incidence of perioperative complications in the ambulatory patients. (iv) Major morbidity occurs less often in the ambulatory surgical population than in the age and gender matched population not having surgery. So, now a wide varieties of surgical procedures can be performed in an out patient basis (Table 45.1).

Duration of surgical procedure also has no impact on out patient surgical and anaesthesia unit as long as the post-operative physiological impairment of patient is at an acceptable level. There is great controversy on corelation between the duration of surgical procedure and anaesthesia with the recovery time. In one study, it is found that there is no correlation between the duration of anaesthesia and the recovery time. In another study, longer anaesthetic procedure is associated with longer recovery time and higher incidence of PONV, necessitating patient's readmission in hospital and overnight observation. So, the general rule is that operations lasting for more than 60 to 90 minutes and those associated with a risk of significant postoperative pain, haemorrhage, excessive fluid shifts and prolonged immobility should not be performed in day case unit. However, recently many oral, plastic, general, gynaecological and orthopaedic surgical procedures, lasting for 2 to 4 hours are now being routinely performed successfully in many ambulatory surgical and anaesthetic unit in USA.

Table 45.1: Common day case surgical procedures

General surgery	Superficial biopsy, abscess drainage, hernia repair, haemorrhoidectomy, laparoscopic cholecystectomy, varicose vein surgery, anal fistula repair, muscle biopsy.
Gynaecology	Superficial biopsy, dilatation and curettage, tubal ligation, polypectomy, hysteroscopy, Bartholin cystectomy.
Orthopaedics	Close reduction, biopsy, arthroscopy, anterior cruciate ligament repair, amputation, carpal tunnel release, excision of ganglion, removal of screw and plate.
Urology	Circumcision, orchidectomy, cystoscopy, lithotripsy, prostate biopsy, orchiopexy, urethral dilatation.
Ophthalmology	Cataract extraction, squint surgery, enucleation, ptosis surgery, chalazion excision, pterygium.
ENT	Tonsillectomy, adenoidectomy, tympanoplasty, rhinoplasty, polypectomy, myringotomy, mastoidectomy, removal of foreign body.
Plastic surgery	Cleft lip repair, skin graft, scar excision, basal cell cancer excision, mammoplasty.
Miscellaneous	Angioplasty, laser treatment, oesophageal dilatation, bone marrow aspiration, lumbar puncture.

Some ambulatory or day case surgical and anaesthetic centres question about the extremes of age (< 6 months and > 70 years) for selection of their patients. The cause is being: (i) the recovery of fine motor and cognitive functions are slower in older patients and (ii) the preterm infants who are less than 48 weeks of post-conceptual age are at a increased risk for apnoeic episodes after anaesthesia. But, the age alone should not be considered as a deterrent factor for the selection of patients for day case surgery and anaesthesia. Still, the infants less than 60 weeks post-conceptual age (gestational plus post natal age) should not be considered for day case surgery and anaesthesia and postanaesthetic apnoea monitoring for at least 12 to 24 hours has been recommended for them. Now, in many centres of developed countries there is no upper age limit for day case anaesthesia. Because there physiological fitness for surgery and anaesthesia is considered first rather than the chronological factor age. This is based on findings that there is no increase in morbidity with increasing age, when only the age factor is considered. However, special attention must be paid to the discharge criteria for that group of patient from day case unit, because recovery of fine motor function and cognitive skills following GA or sedation is slower in the elderly. Children are usually well suited for the ambulatory surgery and anaesthesia unit. This is because those who are treated on a same day basis have less psychological disturbances than those who are admitted on the day before and discharged on the day after surgery.

In some day care surgical and anaesthetic units severely obese patients are not selected. The upper limit of body mass index (BMI) for day case anaesthesia is 30 to 34 [BMI = weight (in kg)/height^2 in meter]. Moderate obesity in itself does not

preclude them from day case surgery and anaesthesia, but does cause unpredictable problems in terms of length of surgery and anaesthesia. BMI alone is not always considered as the ideal tool for assessing the fitness for day care surgery and anaesthesia. Obese patients in a day case unit should be scheduled for surgery at mid morning which will allow time for preoperative antacid therapy to work and will also allow adequate time for recovery. It will also have to remember that obesity may cause many problems to the surgeons or to the anaesthetist which will force them to treat these patients as indoor basis.

A limit is also set for the distance from the hospital to the patient's home during selection of patients for day case anaesthesia and surgery. A responsible adult must be present at home with the patient during the first 24 hours after day case surgery and anaesthesia. All the patients must be escorted to home during postoperative period by a responsible, and well-informed adult. All the patients should be adequately supervised during their recovery at home for a minimum period of 24 hours. Similarly all the patients must have suitable home conditions with adequate toilet facilities and a telephone should be readily available for advice during an emergency. The patient should also live within 1 hour's travelling distance from the hospital.

SURGICAL PROCEDURES

There is a long list of surgical procedures from different discipline of medicine which can be performed at a day case surgical and anaesthesia unit. But always it should be kept in mind that the procedures in which post-operative surgical and anaesthetic complications are likely to occur should be performed as an in-patient basis. The surgical procedures necessitating excessive fluid infusion or blood transfusion should be handled in the hospital's indoor patient setting. Operative procedures requiring prolonged immobilization and parenteral analgesic therapy are not ideally suited for the out-patient unit.

PREOPERATIVE VISIT, ASSESSMENT AND PREPARATION OF PATIENT FOR DAY CASE SURGERY AND ANAESTHESIA

It is already said that preoperative patient selection is the corner stone of running an outpatient anaesthesia and surgery unit. So for selection, preoperative visit of patient to the anaesthetic unit is important. Preoperative visit of patient to the anaesthetic unit has two parts: preoperative assessment and preoperative preparation. Preoperative preparation of patient again consists of pharmacological preparation, nonpharmacological preparation and preparation by information.

Preoperative Visit and Assessment

Preoperative assessment is the part of preoperative preparation of patient before coming to the out-patient anaesthetic unit on the day of surgery. The practice of not preparing the patients prior to the day of anaesthesia and surgery can result in unnecessary delays, last minute cancellation and inadequate patient management. So, the starting point of the day case anaesthetic process is the proper preoperative assessment of patient. Preoperative visit and assessment has also some public educative value, because anaesthetist may present different risks and complications of anaesthesia to the patient and its relatives related to the surgical procedure.

During the preoperative assessment of patient, the time required for taking history can be shortened by the use of pre-anaesthetic questionnaire. By that questionnaire information is usually obtained regarding the patients medical problems, previous operations, drug and family history, etc. and as well as it also provides a general review of the patient. The use of computerized questionnaire prior to pre-operative examination of patient by anaesthetist is more time saving and efficient. Modern computerized questionnaires are more accurate in listing positive and negative information and history than a physician's interview. This also can be used correctly to predict the need for preoperative laboratory testing. This approach has been shown to reduce the number of laboratory tests and result in considerable cost savings. In the near future, interactive screening process will almost certainly become available over the internet.

However, sometimes it is not always possible or practical to examine all the patients in the preanaesthetic unit regardless of their medical conditions prior to surgery. So, many day case institutions find alternative ways to achieve this same goals. Such alternative is, surgeons are asked to screen their own patients at their initial office visit prior to fixing the date of surgery. Patients who are of physical status like ASA I or II and who do not require laboratory testing or are not overly anxious about the surgery, can be seen by the anaesthesiologist on the day of anaesthesia and surgery. The preoperative laboratory investigation component should be tailored according to the patient's need, history, type of surgery and skills or preferences of the anaesthesiologist. Preoperative testing should also be based on the patient's age, history and examinations. The laboratory examinations should not be a lengthy screening procedures. Because it does not always provide benefit to the patient, anaesthetist, surgeon, hospital or society. Indiscriminate laboratory testing also produces a large number of false positive or random abnormal results and among them most of which are ignored by the anaesthesiologist. On the other hand, general physicians may treat these borderline or false positive abnormalities which can lead to patient's harm without any benefit. It is reported in a study that more than 60% of the routinely ordered preoperative laboratory investigation could be eliminated, if

these are tailored solely according to their correct indication. It is also known that only 0·2% of the abnormalities which are reported, might have influence on the perioperative anaesthetic care. Elimination of these unnecessary tests results in cost savings. It is also deplorable that some tests frequently ordered are not recommended at all, while others are not ordered though they are recommended. So, it is recommended that no laboratory tests are needed for active healthy male patients below the age of 40 without any history of previous medical disease and undergoing superficial outdoor surgical procedures such as biopsy, herniorrhaphy, circumcision, cataract, DCR, DCT, etc. For the female patients in this age group (i.e. childbearing age) only Hb or haematocrit estimation should be done. Estimation of haemoglobin or haematocrit value is also appropriate for children under the age of 5 years. Patients with an unexpected Hb concentration of less than 10 g/dl should undergo further evaluation prior to the elective out-patient surgery and anaesthesia, because low Hb concentration may be associated with many diseases that could influence the perioperative mortality and morbidity. Patients with chronic diseases such as diabetes, hypertension, COPD, etc. will require additional laboratory investigations according to the severity of diseases (Fact file- I).

FACT FILE - I

In summary, the following preoperative investigations for day case surgery and anaesthesia should be performed when appropriate. These are:

(i) Full blood count (FBC) only for patients with the possibility of anaemia e.g. bleeding piles, menorrhagia, child-bearing age, etc.

(ii) Sickle cell test in all patients of Afro-Caribbean origin.

(iii) Serum electrolytes and creatinine in patients on diuretics.

(iv) Blood sugar in patients who are diabetic.

(v) ECG in all male patients over the age of 40 years and women over 50 years and younger patients if they have a history of cardiac disease or signs of hypertension, dysrhythmias, diabetes etc.

(vi) X-rays only for patients with COPD, breathlessness, history of severe chest and cardiac disease or for all patients over 70 years of age. Very few day case surgery and anaesthesia patients need a preoperative chest radiograph.

After the preoperative visit in the anaesthetist's room, patients must visit the hospital's business office for financial interview, to familiarize himself and his party with the centre, and to complete all the paper works including the consent form which will effectively prepare the patient for out-patient surgery on the schedule day. This is because outpatients usually dislike to wait for long time before surgery.

Preoperative Preparations

Preoperative preparations have great impact on smooth functioning of an out patient surgical and anaesthetic departments. This is because, if the selected patients are not prepared properly, they might result in unexpected cancellation and great chaos. As for example, BP and blood sugar can go up in unprepared hypertensive and diabetic patient, leading to cancellation and so on so forth. Besides control of medical disorders from which the patient is suffering, the main aim of preoperative preparation in an out patient anaesthetic department is also the alleviation of anxiety of patient. Always a significant amount of anxiety is present among all the patients waiting for surgery. Hence the increased anxiety further increases the release of stress hormone and thus increases the anaesthetic requirement, resulting in prolonged recovery time. High level of anxiety can also be associated with other adverse outcomes such as increased incidence of tachycardia, increased BP, emesis, etc. Again, for day case anaesthesia surgical patients are not given any sedative premedications, because of the fear of prolonged recovery. So, to relieve anxiety patients must be prepared preoperatively by strong assurance. This is called non-pharmacological and informative methods of preanaesthetic preparation. The Pharmacological methods to relative anxiety are only applied when it is absolutely necessary. This excessive anxiety may later precipitate many behavioral problems in patients, especially paediatric group, after surgery. These behavioral problems are: aggression, regression, eating and sleeping disturbances, fears, angers, bed-wetting, increased dependency, etc. One of the key point to reduce this anxiety of a child is to allow the parents in anaesthesia room who will support their child during induction of anaesthesia. This will help in relieving the child's anxiety and producing smooth induction of anaesthesia. Similarly, the parents should be allowed to meet their child in the recovery room as soon as possible. It will also help to reduce the separation anxiety.

Non-pharmacological and informative method of preoperative preparation

An important and first step of non-pharmacological and informative method for preoperative preparation of patient is to visit this anaesthetist's room by patient and its relatives. The rationality behind the nonpharmacological preoperative preparation of patient is that information helps to build expectation and encourage cognitive control over the surgical events. A meeting among the anaesthetist, patient and his family is more effective to reduce anxiety than pre-operative benzodiazepines, barbiturates or any sedatives. Among the information only the perioperative events such as general plan for anaesthesia and surgery, benefits of relaxation, discussion of postoperative pain, hospital stay, etc, should be given. This type of preparation of patient by information will be beneficial, because this reduces uncertainty and subsequently anxiety. Patients may feel better having more control over the situation due to more clearly defined expectations. This will help in reducing the psychological stress factors which is associated with increased incidence of emesis. Information can be given in the form of

booklets or audiovisuals. Relaxation training is also given to reduce the anxiety and postoperative pain, successfully. These methods are economical and have no side effects which is the drawback of drugs or any medications. Patient's motivation and acceptance becomes high in non-pharmacological method than pharmacological one. Overall, a well-informed patient recovers faster and better and experiences less pain. Proper preoperative anaesthetic preparations should also include verbal and written instructions regarding arrival time, place of surgery, fasting instructions, postoperative advice, limitations of driving abilities after anaesthesia and the need for a responsible adult to escort and accompany the patient, while returning back to home.

Pharmacological method

For preoperative pharmacological preparation of patients, the use of drug as premedication for day case anaesthesia is controversial in outpatient anaesthetic unit. But this is not saying about the drugs which are taken preoperatively for medical disorders. The aim of premedications in out- patient anaesthetic department is like that of indoor patients i.e. anxiolysis, sedation, analgesia, amnesia, vagolysis, antiemesis and prevention of aspiration pneumonia. But problem is that the use of sedatives, hypnotics, analgesics, etc. prolongs the recovery time (some studies say) and causes more postoperative nausea and vomiting which are important concerns for out-patient anaesthesia. Also prolonged amnesia of the patient is not desired in the outpatient anaesthesia setting. But, recently many other studies have shown that the use of premedication does not delay the recovery and discharge of patients, although coordination and reaction times may be impaired for 6 to 12 hours. Hence, judicious use of preoperative medication can be extremely beneficial for some outpatients, without increasing morbidity. But, we will have to keep in mind that the choice of agents and timing of premedication for the outpatients requires different considerations than inpatients, with the special attention to specific needs of the patient and pharmacokinetics – pharmacodynamics of the used drug. So, in conclusion, it can be said that the proper choice of drug with its correct dose and timing, balanced with patient's need, actually facilitates the discharge of patient, reduce anaesthetic requirements and lesson the degree of postoperative emesis.

Among the sedatives and hypnotics, now barbiturates are not used as premedicant. This is because of their prolonged postoperative recovery time. So now, benzodiazepines and among them only short acting agents are the drug of choice. So, oral midazolam in the dose of 0.05 mg/kg with a little undiluted sweet fruit juice surpasses all and is used in out patient setting due to its short elimination half-life and lack of significant side effects. The rapid onset of action than other benzodiazepine and water solubility of midazolam offer a number of advantages for day case anaesthesia and surgery. This agent may also be given through IM 30 to 40 minutes before surgery or preferably IV before the induction. Midazolam (1 to 2 mg) given IV prior to the induction of GA reduces anxiety and increases amnesia without prolonging the recovery room stay. It may be associated with impaired postoperative psychomotor skills. Midazolam given orally has been reported to be highly effective for adults, as well as for children, although larger doses of it are required because of the first pass metabolism of midazolam by liver. Intranasal and rectal midazolam are also highly effective routes for administration of it, if the child tolerate them (Table 45.2).

Temazepam in the dose of 10 to 20 mg in adult has also been reported to be an important oral premedicant for out patient anaesthesia. Lorazepam, like diazepam due to its long duration of action is not in choice for day cases. If patient expresses severe anxiety in pre operative visit, then benzodiazepines can be given in a titrable fashion (in the evening at home and in the morning before leaving home). On the day of surgery after admission if severe anxiety is apparent in patient, then IV midazolam is the drug which is most often administered.

Table 45.2: Components of preoperative visit

Preoperative assessment
History
Physical examination
Laboratory investigation
Nonpharmacological preparation
Preparation by information
Counseling for stress and anxiety reduction
Counseling for reduction of pain
Pharmacological preparation
Anxiolysis
Amnesia
Antisialogogue
Antiemetic
Analgesia
Prevention for aspiration pneumonitis

For children, chloral hydrate (40 mg/Kg orally) is reported to increase the calmness and make asleep during induction of anaesthesia compared with midazolam (0·05 mg/Kg orally), alprazolam (0·005 mg/Kg P.O) and placebo. Injection ketamine (2 mg/Kg) given IM to uncooperative children also permit smooth inhalation induction by halothane or sevoflurane after 2 to 3 minutes of its administration. Although early recovery time is unaffected, but home discharge may be delayed by an average of 30 to 40 minutes.

Non selective α_2-agonist such as clonidine and highly selective α_2-agonist such as dexmedetomidine have also been proved to be useful adjunctives as premedication for outpatient anaesthesia. Because they cause sedation, potentiation of the effects of other anaesthetic agent and attenuation of the sympatho adrenal stimulation during intubation and surgery. In addition, dexmedetomidine also has analgesic and

anxiolytic property and reduce the plasma stress hormone level. But still the haemodynamic effects of these drugs limit their use as a primary anaesthetic agent and may prove to be valuable as adjunctive premedicants.

As premedication, opioid analgesics are not so much helpful to reduce the anxiety. This is because there are other better and specific drugs for this purpose, except when patients present with painful conditions. In these circumstances (i.e painful condition) preoperative opioid analgesics as premedicants are beneficial for acute control of pre-operative pain and anxiety, decreasing anaesthetic drug requirements and providing postoperative pain relief. But the drawback of opioid as premedicant is that it is associated with more PONV and slow gastric emptying time. Therefore, it should not be used in patients who are very obese, very old and fragile, and patients with COPD, etc.

PONV is the another common problem for day case anaesthesia. Because it can delay the discharge and may result in unplanned postoperative hospital readmission. So, its management should be started pre-operatively. There are multiple causes of PONV such as: age, gender, menstrual cycle, pregnancy, previous history of nausea and vomiting, anxiety, obesity, anaesthetic agents, type of surgery (laparoscopy, ear surgery, etc.), postoperative pain, movement, hypotension etc. The incidence of postoperative nausea and vomiting is very low in infants and gradually increases with adulthood. It is true that any one drug is not effective in preventing PONV in all conditions. So, a combination of two or three drugs is more successful. Droperidol, an active antagonist of dopamine receptor (D_2), is highly effective against PONV. But, full doses of droperidol as premedication may result in dyskinesia, restlessness and dysphoria which may persist up to 24 hours after surgery. So, these drawbacks limit the use of droperidol as a routine antiemetic premedicant for outpatinet anaesthesia. But, low doses of droperidol is as effective as higher doses in preventing PONV without delaying recovery. Thus, lowest effective dose (judged by anaesthetist) of droperidol is recommended as premedicant for prophylaxis of PONV.

Metoclopramide is another antidopaminergic antiemetic agent (i.e. block the dopamine receptor) which has also gastrokinetic effects and facilitates both the gastric and small bowel motility. It has some antagonistic effect on 5-HT_3 receptor also. It is postulated that metoclopramide is more effective in opioid induced vomiting and especially if it is given at the end of anaesthesia with or without any other antiemetics. But the drawback of metoclopramide is that it causes extrapyramidal side effects, drowsiness, drymouth or urinary retention.

Ondansetron, granisetron, tropisetron are other 5 HT_3 receptor antagonists. They are also effective in preventing nausea and vomiting both when administered alone or in combination with ranitidine and / or metoclopramide. Smaller doses (1 mg) of ondansetron also appear to be effective in prophylaxis of nausea and vomiting. It is especially effective in cytotoxic drug induced vomiting and has no extrapyramidal side effects like metoclopramide. Anticholinergic drugs, such as atropine and glycopyrolate are also used for premedication as they are antisialogogue and vagolytic agent. They also have central antiemetic effects. But some anaesthetists do not use them, because the modern intravenous and inhalational anaesthetic agents are not irritant to the airways and also the postoperative dry mouth is very unpleasant for the patients. They also do not like tachycardia, caused by atropine or glycopyrolate. When antihistamines are used as antiemetics, they act on the vomiting centre by inhibiting the histamine and vestibular pathways. They also cause drowsiness and prolongs recovery time. Extrapyramidal side effects are also commonly associated with these drugs. So antihistamines are not used routinely in out patients anaesthesia department. Benzodiazepines, especially lorazepam also have antiemetic properties. In paediatric population, lorazepam is as effective as droperidol in reducing postoperative nausea and vomiting.

Another important aspect of preoperative preparation of patient for day care anaesthesia is reduction of the risk of pulmonary aspiration. This can be achieved by reducing the volume and increasing the pH of gastric contents. The incidence of pulmonary aspiration in day care surgical patients is very low. It is only 1 in 40,000 and mortality rate is 0.00002. However several studies have found that 50 to 60% of day care patients would be defined as theoretically 'high risk' for aspiration pneumonitis by the traditional criteria where gastric volume is more than 25 ml, with pH less than 2.5, despite an overnight fast. It has also been suggested that all the patients receiving GA by mask or LMA should be protected against the pulmonary aspiration. So, the reduction of volume of gastric contents and increase of pH should be done and this can be achieved by fasting and medication (metoclopramide and H_2 blocker).

However, prolonged fasting does not guarantee an empty stomach (i.e. does not reduce the residual volume which is always present in the stomach) at the time of induction and so the risk of aspiration always persists. Again prolonged fasting (conventional fasting, i.e. 6 to 8 hours) causes moderate to severe hunger and thirst which may contribute significantly to the preoperative anxiety. On the other hand, half-life of clear fluid in stomach is about 11 minutes which justify that prolonged fasting is unnecessary. So, ingestion of 150 ml of water, tea, coffee, apple juice or orange juice (3 ml/kg) as late as 2 to 3 hours before anaesthesia and surgery has no significant effect on residual gastric volume and pH. Instead, it decreases gastric volume, thirst and hunger (especially

in children) and anxiety (mainly children's parents). There are also data to suggest that intake of oral fluids may dilute the already present concentrate gastric secretions and actually stimulate the gastric emptying. So, prolonged fasting causing discomfort to out-patients without any apparent benefit, is not recommended now.

Thus, the starvation instructions for out-patients will be like that: (i) morning lists – no solid food after midnight and free clear fluids up to 6.30 hours, (ii) afternoon lists–no solid food after 6.30 hours and free clear fluids up to 11.30 hour. Preoperative verbal and written instructions are important so that milky drinks are avoided. Only those patients, suspected or known to be at risk for delayed gastric emptying (e.g. diabetes, hiatus hernia, gastroesophageal reflux and gastric outlet obstruction, etc) should be considered for prolonged fasting. H_2 receptor antagonist such as ranitidine and its congeners are effective both in increasing the gastric pH and decreasing gastric volume by inhibiting the gastric acid secretion, though they have no influence on the volume and pH of gastric secretion which is already present in the stomach. Ranitidine is given either orally or parenterally with peak effects occuring within 2 hours. Compared to fasting without ranitidine, patients who receives coffee or orange juice with oral ranitidine, 2 to 3 hours prior to induction of anaesthesia has lower residual gastric volumes, higher pH values and decreased incidence of thirst. It has been suggested that all the patients who receive GA by mask should be protected by H_2 blocker from pulmonary injury by gastric acid component.

The use of metoclopramide in combination with an H_2 blocking drugs increase the gastric pH and decrease the residual gastric volume by increasing the gastric emptying time. However, the metoclopramide also offers an additional advantage by increasing the lower esophageal sphincter tone and thus reducing the chance of regurgitation and aspiration of gastric contents. Molar sodium citrate (0·3 M, 30 ml), a nonparticulate oral antacid is effective in directly raising the gastric pH (less effective than H_2 blocker), but it can increase the gastric volume. This drug can only be useful in combination with metoclopramide when prophylaxis against pulmonary aspiration is desired but only little time is available prior to the operation, as the onset of action of sodium citrate is immediate.

Actually, there is no evidence of any increase in regurgitation and aspiration in day case anaesthesia. So, the routine use of H_2 blocker, metoclopramide or molar sodium citrate is probably unnecessary. However, in those with a history of regurgitation ranitidine (300 mg orally) or omeprazol (40 mg orally) with metoclopramide is appropriate. The ASA task force on preoperative fasting has recommended no routine use of: gastric acid secretion blockers, antiemetics, antacids, gastrointestinal stimulants, anticholinergics or combinations of these medications for patients who have no apparent increased risk for pulmonary aspiration.

NSAIDs, e.g diclofenac 50 to 100 mg which is given orally or rectally or IM reach the peak effect after 1 to 2 hours of administration and are a useful adjunct to preoperative medication, with very few side effects. But the slow release oral preparations of it does not reach the plasma steady state concentrations, until after several doses and are thus not useful for early analgesia.

ORGANISATION OF DAY CASE ANAESTHESIA UNIT

The Day case anaesthesia unit is usually of three types.

i. An unit within the hospital main complex, but with separate OT, ward and staff.
ii. An unit with separate ward, but using the hospital's main OT complex. (No separate OT for day case surgeries and anaesthesia)
iii. An unit remote from the main hospital complex with separate building, OT, ward and staff.

Ideally, the day case surgical and anaesthesia units should have a separate building, but not be far away from the main hospital complex. It should be situated by the side of the in-patient department of the main hospital complex. The ward area of it should be near by of its own operation theatre, to reduce the transport time, particularly when the multiple short operative procedures are to be performed. This arrangements also enable the parents to accompany their children to the anaesthetic room when it is desired.

The ideal separate day case surgical and anaesthesia unit which is situated adjacent to the main hospital complex, must have an separate admission area, an anaesthetia room, an operating theatre, and a fully equipped recovery room. An admission area usually includes a reception area, examination and treatment room, a nurse's station, lavatory and discharge area. The anaesthestia room should be fully equipped too. It should be large enough to allow the free access of an anaesthetist around the patient's trolly to permit the use of local and general anaesthesia. There should be good arrangements for lighting, scavenging, piped gases, suction equipment, anaesthetic machine and all the types of standard monitoring equipment with all emergency drugs. The hazards and risks of general anaesthesia in a day case surgery and anaesthesia unit are not less than that of an in-patient surgery and anaesthesia unit. Indeed, they may be greater and the facilities should be like an in-patient anaesthestisa room. An operation theatre for day case surgery and anaesthesia unit should be of the same specification as the main in-patient's OT. There is always the possibility of a minor surgery, developing unexpectedly into a major operation and this demands that the theatre should be well equipped to deal with any eventuality. Like the main in-patient recovery unit,

the day case recovery room should also be well equipped and staffed properly, for the safe recovery of patients after general anaesthesia.

On the day of anaesthesia and surgery, patients should be admitted in the day case ward with adequate time for history taking and examination (if not done before). The results of prescribed investigaton should be available during preoperative examination and it is noted. Patients should receive an identity tag with the name and necessary information, printed on it. The surgeon should ensure that the indication for surgery is still present, as there may be a long gap between the first clinical examination and the day of surgery. The consent form should be signed, if not already done during the out patient appointment. The names should be entered in the nursing record and the operation site should be marked. A pregnancy test for women of vulnerable age should be performed, if there is any risk of pregnancy.

Technique of Anaesthesia

There is no any separate ideal or special technique for out-patient anaesthesia. General, local or regional anaesthesia which are generally used for indoor patients can be administered safely to day-case patients. But the choice of technique is tailored made and should be determined by the surgical requirements, anaesthetic consideration and the patient's physical status and preference. The ideal general anaesthetic technique for day cases should include rapid and smooth induction, followed by adequate intraoperative amnesia, analgesia and muscle relaxation i.e good surgical condition and good recovery without any side effects. Out-patient or day case anaesthesia delivery system requires the same basic care, safety, efficiency as an inpatient anaesthesia, including the same basic monitoring equipment such as ECG, BP, pulse oximeter, capnograph, temperature, etc. The EEG based monitoring the depth of anaesthesia helps to titrate the hypnotic and sedative effect of anaesthetic agents and thus reduces its dose and rapid recovery.

General anaesthesia

It is the widely choiced anaesthetic technique in outpatient or day case department by surgeons, anaesthetists and patients. For GA, there is no ideal or special separate anaesthetic technique for outpatients. But there is a vast array of pharmacologically active anaesthetic drugs. So when they are combined in a rational manner and carefully titrated, then they can produce the desired general anaesthetic condition for outpatients with an acceptable cost and recovery profile. The aim of GA in outpatient department is to deliver it safely with minimum side effects and rapid recovery. Forsurgical procedures under GA, lasting less than 15 minutes, and which do not require any IV administration of drugs or fluid (i.e. those can be done by only inhalational anaesthesia with spontaneous mask ventilation), then there is no need even for an intravenous line. This is because perioperative fasting even for periods of 10 to 15 hours do not usually result in hypoglycaemia in healthy individual who is more than 5 years old and adult. However, for longer periods or circumstances where the patient has been without oral intake for an excessive period of time (> 10 to 15 hours), an intravenous line is essential for maintenance of fluid balance and glucose haemostasis, as well as facilitating the administration of intravenous anaesthetic and emergency drugs during the perioperative period. But this dictum is not always followed in many developed countries. Therefore, any minor procedure even under topical or local block, IV line is procured with all standard monitoring.

The choice of an inducing agent for GA depends upon the requirement of patient and the preference of anaesthetist. But the aim of selecting any inducing agent in day case anaesthesia is it should ensure a rapid and smooth induction and good immediate recovery with minimal postoperative sequelae, and a rapid return to street fitness. Several agents such as propofol, thiopentone, methohexital, etomidate or any benzodiazepine have been used successfully for induction of anaesthesia in a surgical out patient unit. But propofol has replaced all, due to its favourable recovery profile for out-patients or day case anaesthesia. One of the main advantages of propofol is the ease and rapidity with which patients recover from its effects. Patients are clear–headed and have a lower incidence of PONV when propofol is used. Induction of anaesthesia with propofol is associated with a greater decrease in blood pressure and heart rate than with either thiopentone or methohexital. It is used in the elderly with the reduced dose. Pain on injection of propofol can be significant. But this may be reduced by the addition of lignocaine with propofol, using a large vein, or by cooling the propofol to 4°C.

Thiopentone is characterised by rapid induction without significant side effects. But psychomotor recovery is sometimes delayed and prolonged subjective feelings of tiredness and drowsiness by patients receiving thiopentone are drawbacks to its use in ambulatory anaesthesia. Methohexital is associated with slightly shorter awakening and recovery times than thiopentone. But pharmacokinetic property of it makes its administrations possible only by continuous infusion. Recovery of fine motor skills from methohexital is not complete until 8 to 10 hours is passed after induction. It may also cause pain on IV injection, involuntary muscle movements and hiccup. But the use of small doses of rapid acting opioids (fentanyl, sufentanil, remifentanil) can minimize the side effects of methohexitol without prolonging the recovery. Among the benzodiazepines, midazolam (0.2 to 0.4 mg/Kg, IV) only can be used as an inducing agent for day case anaesthesia (where propofol and thiopental is not indicated), but its onset of

action is slow and recovery is prolonged than propofol and thiopentone. Whereas the onset of action and recovery of midazolam is quicker than other benzodiazepines. Compared to propofol, recovery after flumazenil antagonized midazolam anaesthesia, is still significantly slower.

For day case anaesthesia inhalational induction by halothane or sevoflurane is also an alternative to intravenous induction where intravenous access is very difficult or contraindicated. Inhalational induction should not normally be used for patients with symptom of gastroesophageal reflux or where there is chance of gastric regurgitation and aspiration. In children, inhalational induction is a useful alternative to the standard intravenous induction techniques which is usually adapted in adult patients. But unfortunately, induction by inhalation is more time consuming and many children object to face mask due to apprehension and the pungent smell of the inhaled volatile anaesthetic agents. However, this problem can be reduced by the use of single breath induction technique. Traditionally, volatile anaesthetic agents are considered as superior than intravenous agents for maintenance of anaesthesia. But there is little or no basis for this justification. On the otherhand, combination of intravenous agents for induction and inhalation agents for maintenance of anaesthesia for very short procedures is associated with long recovery time than inhalation agents alone.

For the maintenance of anaesthesia, combination of O_2 and N_2O with minimum concentration of volatile anaesthetic agents is the most popular technique in a day case anaesthesia department. The extreme slow solubility of N_2O (0.46) causes rapid onset and also rapid recovery from its CNS effects and makes it a valuable adjunct for combination with other volatile or IV anaesthetic agents. Thus, it also reduces the requirement of other anaesthetic agents, and helps in early recovery. But, the use of N_2O for maintenance of anaesthesia has been shown to increase the risk of PONV (by increasing the pressure in the middle ear and thus stimulating the vestibular system) and this incidence is more when N_2O is combined with other volatile anaesthetic agents or opioid analgesics. However, minimum concentration of its use reduces the requirement of volatile or opioid agents and reduces the incidence of PONV. In many developed countries N_2O is not used now and it has become obsolete. But still the use of N_2O is standard practice in other developing nations.

For the maintenance of out-patient or day case anaesthesia, the three commonly used volatile anaesthetic agents are halothane, isoflurane and sevoflurane. Among these halothane and sevoflurane are also used for induction as both are non-irritant to the airway. But sevoflurane has the advantages of more rapid induction and recovery with minimal cardiovascular side effects than halothane. However, Sevoflurane causes more PONV than propofol, but less than the other volatile anaesthetic agents. Isofluranes is not used for induction as it is irritant to the airways, but recovery from isoflurane is faster than halothane and produces more stable CV effect than halothane. Ventricular arrhythmias are more likely to occur during halothane anaesthesia. Desflurane also provides stable CVS condition like isoflurane and helps in quick recovery as its solubility (0.42) is less than N_2O. But it possesses airway irritant property and may cause breath holding, laryngospasm, apnoea like isoflurane.

Opioid and nonopioid analgesics are frequently administered in the immediate pre-induction period and during the maintenance of general anaesthesia. They reduce the dose of sedative and hypnotic for induction and thus help in early recovery. Morphine and meperidine are not popular analgesic for outpatient anaesthesia. More potent, rapid, short acting, narcotic analgesics such as fentanyl (2 to 4 µg/kg), sufentanyl (0.25 to 0.5 µg/kg) and remifentanil are popular for day case anaesthesia and is used to attenuate effectively the CV responses to laryngoscopy and intubation. They are also useful supplements to the inhaled anaesthetics during the maintenance of anaesthesia. Some studies have demonstrated improved intraoperative conditions and a more rapid recovery from anaesthesia when fentanyl or one of its newer congeners were administered as a part of N_2O – narcotic – relaxant (balanced) technique. Remifentanil is an esterase – metabolised µ-opioid receptor agonist. Its biological halflife is only 3 to 5 minutes, regardless of the total dose and duration of infusion. It has no accumulation property even after prolonged infusion. So, remifentanil has become very useful in providing profound analgesia for day case surgery and anaesthesia without effecting recovery. However, its short duration of action is a definite disadvantage, if significant and prolonged postoperative analgesia is needed. The choice of opioid analgesic usually depends on the desired duration of effect. If a strong analgesic effect is needed for a brief period, then this is achieved by bolus administration of fentanyl, sufentanil, alfentanil or remifentanil. For a short surgical procedure the addition of fentanyl (50 to 100 µg) does not much affect the recovery from a propofol – N_2O and muscle relaxant combination technique without increasing PONV. In this circumstances alfentanil and remifentanil would have slight advantage. But, fentanyl is a better choice if analgesia is needed to maintain postoperatively. If the strong analgesic effect is needed by repeated bolus injections or a continuous infusion, then remifentanil, fentanyl or sufentanil are the best choice. If patients require moderate analgesia for 2 to 3 hours or more, an injection of morphine is a reasonable alternative to multiple bolus dose of fentanyl, sufentanil or remifentanil. The newer techniques, such as target controlled infusion (TCI) of propofol with or

without the ultrarapid acting opioid such as remifentanil or the use of sevoflurane may confer some advantages. But these have to be balanced against the cost of these agents. TCI of propofol is an intravenous technique for maintenance of intraoperative hypnosis. It takes into account the patient's weight (kg), and the desired drug concentration in blood (μg/ml). An initial target plasma concentration of 4 to 6 μg/ml of propofol is often set and then adjusted appropriately. Subsequently, the infusion rate is calculated by a computer within the pump.

Anaesthesia for day case surgery requires a variety of airway management techniques. This is because of the wide variety of surgical procedures which are performed in the day case surgery. In all this a clear airway is a fundamental requirement for safe anaesthesia. ET intubation causes higher incidence of airway related complications such as soar throat, croup, hoarseness, etc., and a greater morbidity during and after surgery. Thus, ET intubation is not essential or desirable for all outpatient general anaesthesia surgical procedures. For day case anaesthesia of small duration, simple face mask with Guedel airway is sufficient and is commonly used. Spontaneous ventilation via face mask does not result in significant hypercarbia or acidosis for brief procedures. Thus, by avoiding laryngoscopy and intubation, the amount of anaesthetic drugs administered is reduced and a faster recovery with fewer postoperative side effects may be anticipated. So, some anaesthetists have chosen not to intubate a selected group of low risks patients.

Instead of face mask and ET-tube (i.e. where face mask is not appropriate and ET intubation is not desired), LMA also can be used for both the adult and children. Longer procedures may necessitate the use of ET-tube. Thus it is suggested that LMA is superior than face mask for unobstructed spontaneous ventilation, but inferior to ET tube for the management of airway. It can be positioned without direct visualization of larynx and neuromuscular block. Patient is allowed to breath spontaneously throughout the procedure and anaesthesia is maintained continuously by volatile anaesthetic agents by attaching LMA with anaesthetic machine or by TIVA. Compared to anaesthesia with face mask and simple airway, the patients of the LMA group did not have any increased requirements of anaesthetic agents. The other advantages of LMA are: (i) it offers a hands free approach to air way management, allowing the anaesthetist to complete other tasks, (ii) there is decrease in haemodynamic changes during both induction and emergence, (iii) reduced work of breathing compared with the use of ET-tube and spontaneous respiration and (iv) if necessary controlled ventilation also can be performed, but up to a maximum airway pressure of 15-20 cm of H_2O. The disadvantage of LMA is it cannot protect the airway from gastric aspiration and hence it should not be used in patients with high risk of regurgitation, aspiration and upper airway bleeding. Another disadvantage of LMA is that when greater airway pressure is needed for ventilation then there is chance of gastric dilatation and subsequent regurgitation and aspiration of gastric contents.

Although few ambulatory or day case procedures require a secure airway by ET tube, but patients undergoing laparoscopy are often intubated. This is because gas insufflation and the head down position are believed to increase the risk of regurgitation and hypoventilation. But, in some units the patients undergoing small laparoscopic surgery are not intubated. These centres report that the spontaneous ventilation via face mask or LMA in the head down position does not result in significant hypercapnia or acidosis in non-obese patients and not it is associated with reflux of gastric contents. Thus, by avoiding laryngoscopy and intubation for laparoscopic surgery requiring brief period, the amount of anaesthetic drugs administered is decreased and there is a faster recovery with fewer and minor side effects.

For endotracheal intubation during day case anaesthesia, the choice of muscle relaxant depends on the anticipated duration of surgery. Many out-patient surgical and anaesthetic procedures that can be carried out by face mask and without intubation does not require any muscle relaxant. The conditions where face mask or LMA can not be used and intubation is needed, only then muscle relaxant is used to facilitate the tracheal intubation and to optimize the surgical condition. In addition, the use of muscle relaxant decreases the other anaesthetic requirements and shortens the recovery time. Before the introduction of atracuronium, mivacurium and vecuronium, the depolarizing agent succinylcholine was the most popular muscle relaxant for out-patient anaesthesia, both for intubation and maintenance, by infusion or repeated doses (only for short procedure). But as the succinylcholine causes a lot of problems such as hyperkalaemia, arrhythmia, malignant hyperpyrexia, severe muscle pain, etc. so it is now abandoned from the modern anaesthesia, except in certain few indicated cases for outpatient anaesthesia. Therefore, with the availability of many short acting non-depolarizing muscle relaxants such as atracurium, vecuronium and mivacuronium prompt reversal of neuromuscular blockade can be achieved after 15 to 30 minutes of brief surgical procedure. Atracuronium, vecuronium and mivacurium are each metabolized through distinctly different pathways. As atracurium and mivacurium release histamine it should not be used in certain cases. Mivacurium has the shortest duration of action and hence is the ideal for out-patient anaesthesia. But as it undergoes hydrolysis by plasma cholinesterase, so a small number of patients may suffer from prolonged muscle paralysis like succinylcholine and this is because of plasma cholinesterase deficiency. After the use of

recommended tracheal intubating dose of atracuronium or vecuronium, the duration of action (to 95% spontaneous recovery) is roughly 1 hour. Rocuronium may have a role in out-patient anaesthesia like succinylcholine as it has a more rapid onset of action than any of the other non-depolarizing muscle relaxants, providing intubating conditions within 30 to 60 seconds. However, it has a longer duration of action similar to that of vecuronium. Recently, the stereoisomer of atracurium, cisatracurium, has been introduced with similar duration of action to that of atracurium, but without the side effects of histamine release (Fact file- II).

Regional anaesthesia

Regional anaesthesia (spinal or epidural) offers many advantages over GA in day case surgical and anaesthesia unit, such as: (i) less nausea, vomiting, dizziness, lethargy, etc., (ii) no side effects of tracheal intubation, (iii) better postoperative analgesia, (iv) minimal post anaesthetic nursing care, (v) decreased recovery time. Still its use is limited in an out-patient anaesthesia unit due to the occurrance of an unacceptable incidence of post dural puncture headache (PDPH) and lignocaine induced TRI (transient radicular irritation). The actual lack of good alternative to lignocaine for short duration of action without the risk of TRI (incidence is 16 to 20%) has been the subject of recent controversy. Typically the pain of TRI begins within 24 hours after spinal anaesthesia and lasts for approximately 2 days. 5% hyperbaric lignocaine has the highest incidence of TRI. This is amenable to treatment by rest and oral analgesics. Bupivacaine is not associated with TRI. But it is not the first choised agent in a day case unit, because it is long acting. Now, there is an open debate that whether RA is truly safer than GA in out-patient or day case anaesthesia unit or not. Only caudal block may be useful in adult for day case anaesthesia without any debate.

During caudal block, the use of diluted solutions of LA agent (0.125% bupivacaine) with addition of preservative free opiates, ketamine 0.5 mg/kg or clomidine 1 μg/kg may prolong the analgesia for upto 24 hours without any loss of motor function. In caudal block, patient should also be warned about the ambulation difficulties. The caudal epidural anaesthesia is usually employed for anorectal, scrotal, penile, inguinal and some gynaecological surgeries involving lower part of vagina and perineum. This caudal epidural technique is associated with nil or fewer haemodynamic changes, no incidence of PDPH, no urinary retention and provide faster recovery when compared with spinal or lumbar epidural anaesthesia for the same procedures.

PDPH after spinal or epidural anaesthesia should always be differentiated from other causes of pain rather than regional anaesthesia. These are neurologic, vascular, musculoskeletal, metabolic, etc., such as migrane, rapid expansion of brain tumour, intracranial haemorrhage, withdrawal of caffeine, hypoglycaemia, etc. There are different treatment modalities which will relieve the symptoms of PDPH, rather than treating it which has been discussed earlier. Excessive water intake does not decrease the severity of PDPH as it does not increase the production of CSF. Intake of caffeine may sometimes treat mild PDPH. Activity of outpatients should not be limited with mild PDPH.

In children, a regional block is performed immediately after induction of GA. It can reduce the requirement of general anaesthetic drugs, provide postoperative analgesia and allow more rapid recovery due to lesser amount of anaesthetic drugs which are essential for day case anaesthesia. Caudal epidural anaesthesia is an effective technique for children undergoing surgical procedures on lower abdomen, perineum and lower extremity. Combined or individual ilioinguinal and iliohypogastric nerve block or caudal epidural anaesthesia reduce the pain following herniotomy and herniorrhaphy. Postcircumcision pain may be reduced by the block of dorsal nerve of penis or subcutaneous ring block of penis or topical local anaesthetic ointment, over the surgical site.

Peripheral nerve block is an first and excellent choice of anaesthesia for day case patients. For operations on the hand or arm brachial plexus block is the unique, but axillary approach of brachial plexus block is preferable to the supraclavicular approach, because of the risk of producing a pneumothorax which may become apparent only after discharge. The infraclavicular and axillary approaches for brachial plexus block are preferred for surgery on the elbow, forearm and hand. While the interscalene block is more commonly used for shoulder surgery. The coracoid technique for infraclavicular approach of brachial plexus block has been shown to be very effective. This technique avoids the important neurovascular structures in the neck and minimize the risk of pneumothorax. If brachial plexus block is used with GA, then the diluted solution of LA agent (0.25% bupivacaine) is used to minimise

FACT FILE- II

In summary, total intravenous anaesthesia with propofol is widely used for short out patient surgery and anaesthesia. Inhalation of O_2 enriched air will also allow omission of N_2O. Propofol induction with maintenance by isoflurane/sevoflurane is an alternative. Incremental fentanyl (2 to 4 μg/Kg) is often used in divided doses. Whenever possible LMA should be used avoiding intubation, muscle relaxants and reversal agents. LMA for gynaecological laparoscopy and armoured LMA for wisdom teeth extraction and many nasal operatoins can be used safely in many circumstances. Antiemetics are not indicated routinely, but should be reserved for treatment of any PONV or as prophylaxis in those with a history of PONV. Proper hydration reduces the postoperative morbidity such as thirst, dizziness, drowsiness, etc. It is found that a patient who receives 20 ml/Kg IV fluid instead of 2 ml/Kg has less postoperative morbidity. However, this postoperative morbidity also can be reduced by using heated humidifiers, heat and moisture exchangers, etc., which conserve heat and decrease the fluid loss.

the motor block. During the use of brachial plexus block without GA one must take into account the onset time of block during planning of the list. Otherwise it will make unnecessary delay and at the end of the day the list may remain incomplete. Peripheral nerve block is also useful for day case surgery on the legs.

The '3-in-1' block technique (obturator, femoral and lateral femoral cutaneous nerve block) is useful for any type of out-patient knee surgery (such as knee arthroscopy) with excellent postoperative analgesia and a high degree of patient acceptance. Popliteal sciatic nerve block may also be used successfully for surgical procedures on the lower leg and foot in 92% of patients where supplemental anaesthesia is required only in 5% of cases and general anaesthesia in 3% of cases. A nerve block at the level of ankle is also simple and effective for surgery on the foot at day case unit. There are other types of peripheral nerve block which can be used safely as day case anaesthesia.

Intravenous regional anaesthesia (Bier's block) may also be used successfully for upper and lower extremity surgery as day case procedure. This block is generally considered safe when performed by clinicians, who is familiar with this technique and with the safe doses. The most commonly used drug in Bier's block is 40 to 50 ml of 0.5% lignocaine, using a double tourniquet with cuff pressures of 250 mm of Hg or 100 mm of Hg above the systolic blood pressure. Ketorolac and clonidine can also be used with lignocaine which improve the quality of regional anaesthesia and analgesia. Intravenous regional anaesthesia of the leg requires a larger volume of solutions and higher cuff pressures, so it is not frequently used.

Local infiltration of operative site by diluted solutions of local anaesthetic agent is the simplest and safest technique of regional anaesthesia for day case patient. Out-patient arthroscopy of the knee is commonly performed under infiltration local anaesthesia. Different ophthalmic surgeries are also performed by peribulbar or retrobulbar block as day cases. Now cataract surgeries are also done under topical anaesthesia as day case surgery. Inguinal hernia repair can be performed by individual ilionguinal and iliohypogastric nerve block and local infiltration of the surgical site. A combination of local infiltration and intercostal nerve blocks can also be used for day case lithotripsy. There are many other surgical examples which are performed under RA, but cannot be listed fully here.

The injection of local anaesthetic agent is often associated with significant discomfort. So, the use of IV sedation and analgesics (conscious sedation) during the infiltration of local anaesthetic injection is popular. But with the local anaesthetic, only short acting sedative drugs will increase the tolerability. It also must be noted that sedation is a poor adjunct to an imperfect local anaesthetic block. However, judicious use of intermittent midazolam or propofol infusions (TCI 1 to 1.5 µg/ml) can provide good amnesia with few postoperative effects.

Regional anaesthesia is widely used in Europe and North America for day case surgery and anaesthesia. The timing and planning of RA in a day case unit are important. Because blocks take a longer time to wear off, compared with GA. 50, the discharge of patient may be delayed. For spinal block, 25 or 26 gauge pencil point needle and 0.25% heavy bupivacaine (1:1 diluted 0.5% heavy bupivacaine by sterile saline) is used. This gives a similar onset of anaesthesia with shorter discharge time (4 hours versus 6 hours). Epidurals (except caudal) are less suitable for day case anaesthesia. Usually RA is performed early on the day which will allow maximum time for recovery before the discharge and safe ambulation. However, sometimes it is reasonable to discharge the patients with still acting plexus blocks. This is applicable only to brachial, lumbar and sacral plexus block, but not to the spinal and epidural anaesthesia. This will allow the benefit of prolonged postoperative analgesia at home. In such circumstances patients need special instructions for care of the anaesthetized part of the body, so as to avoid the inadvertent damage. For example, this would include a sling for patients with brachial plexus blocks.

Recovery and Discharge

Before discharge proper recovery from anaesthesia (GA or RA) is an important aspect of day case anaesthesia. So, it should be assessed properly. If the assessment is not correct and patients is discharged without full recovery from anaesthesia, then catastrophy can occur. The assessment of patient's recovery from anaesthesia is divided into three phases: early, intermediate and late. Early recovery phase extends from the completion of surgery and the end of anaesthesia to the awakening and returning of the patient to orientation. Endotracheal tube is extubated in this phase and patient is monitored vigilantly. After that patient is transported to the PACU-1 (post-anaesthetic care unit) without unattended. During this early recovery phase in PACU-1, the patient may undergo many rapid physiological changes and so close observation of patient is important. This first post anaesthetic recovery unit should be provided with continuous monitoring of BP, heart rate, respiratory rate, temperature, ECG and SPO_2. In this phase, the patients especially the paediatric population are routinely given O_2. When the patient is sufficiently awake with stable vital signs and responsive to commands, then only he is signed out to the care of recovery room staff. Patients who have received monitored anaesthetic care or only intravenous sedation in minimum doses or regional anaesthesia may not always require supplemental O_2. Patient should be monitored in PACU-1 until he or she is completely

awake, oriented, vital signs are stable and adequate pain relief is achieved. Once the above criterias are achieved and the patient is able to maintain a semisitting position, then the patient is shifted to the second phase of post-anaesthetic care unit, i.e. PACU-II.

This intermediate recovery phase extends from the admission to discharge from the PACU-II. In this recovery phase, patient should be able to sit alone without any support. Gradually he starts to walk and takes oral fluids and should have minimum pain. This second phase of recovery involves lower nursing dependency and the patient is not attached to any monitoring system any more. Proper anaesthetic technique, high quality postoperative analgesic care and prophylaxis of PONV have major impact on the duration of this intermediate recovery phase. Prolonged intermediate recovery phase will fail to discharge the patient in time and will increase the cost of patient's hospital visit. At the end of this phase, patient will be able to walk unaided, tolerate oral fluids without vomiting, have minimal pain and is ready to be discharged from the hospital. Patient's family can participate in this last phase of recovery, when the criteria for 'home readiness' is achieved and patient is discharged.

The last and late recovery phase starts with the patient's return to the home and continues until the full functional recovery is achieved. Most anaesthesia related postoperative side effects such as pain, nausea, vomiting, dizziness, headache, myalgias, etc, usually resolve within first 24 hours after operation. In this period, the patient should be advised to refrain from activities such as driving a car, operating machines and drinking alcohol. However, recovery from surgery itself has the highest impact on the patient's full functional recovery. During discharge, a responsible person should be present to escort the patient to home and both the responsible person and the patient should be given the verbal and written discharge instructions. In some hospitals, patient's general practitioner is communicated over telephonic helpline and is made aware of the operation performed and the requirement for postoperative follow-up.

Discharge criteria

Following a general anaesthesia (GA), it is very difficult to determine when it is safe to discharge a patient from a day case unit. So, the accurate assessment of complete recovery of cognitive, sensory and psychomotor function is important. Because it will help in determining the appropriate time for discharge. Varieties of tests have been advised to assess the recovery from sensory, motor and cognitive function, but there is currently no standardised discharge criteria. The main principles on which basis the patients are discharged from day case unit are: they must have stable vital signs, there is there is no significant nausea vomiting and pain, they are fully oriented and are able to sit and walk unaided. Some tests which are used to assess the recovery of cognitive functions are: processing (mental arithmetic, reaction time); integration (critical fashion flicker test), memory (digit span), and learning (word lists). The test to assess the recovery of sensory functions are: stimulus detection, auditing perception, Maddox wing test. The tests to assess the recovery of psychomotor function are: choice reaction time, the post box test, the Triegger dot test, etc. Although these cognitive, sensory and psychomotor tests can provide adequate information which are sometimes useful in developing practical discharge criteria, but most of these tests are too complex and time consuming to use. So, some simple tests for memory and sensorimotor co-ordination appear to be the most useful indices of recovery. The Bender Gestalt Track Tracer Test is a very reliable, valid, objective, noninvasive, inexpensive test to assess the postoperative recovery that can be easily performed in less than 60 seconds.

The discharge criterias after spinal and epidural anaesthesia is different from GA. It should include the return of normal sensation, muscle strength and proprioception, as well as the return of functions of sympathetic nervous system. After regional anaesthesia, motor and sensory functions return before the return of function of sympathetic nervous system. So, some investigators suggest that patients can be safely discharged when the decrease between the two successive orthostatic mean arterial pressure (MAP) is less than 10% of preanaesthetic level which indicates return of sympathetic function. Prior to ambulation and discharge, patients should also have normal perianal (S_{4-5}) sensation, the ability to plantar flex the foot, and proprioception of the big toe which indicates the free of lowest spinal segment from the effect of local anaesthetic agent.

'Home discharge' criteria

1. Stable vital signs for more than 30 minutes.
2. After the operation there is no new signs and symptoms of complications.
3. No active bleeding.
4. No nausea or vomiting for more than 30 minutes.
5. Able to void.
6. Fully awake and no loss of orientation to person, time and place.
7. Minimal dizziness after sitting for more than 10 minutes.
8. Pain controllable with oral analgesics
9. Intact neurocirculatory function without evidence of swelling or impaired circulation after extremity surgery.
10. Able to eat and drink

Specific discharge criteria

A. *Spinal*

1. Full recovery of motor power and proprioception.
2. Passed urine.
3. Full recovery of autonomic nervous system.

B. *Brachial plexus block*

1. Some regression of motor block.
2. Understanding of protection of partially blocked limb.

C. *Lower limb block*

1. Some regression of motor block.
2. Adequate mobility demonstrated on crutches.
3. Understanding of protection of partially blocked limb.

Postoperative Analgesia

Pain control is an important factor in determining when a patient can be discharged after surgery and anaesthesia from an out-patient unit. So, the pain must be treated rapidly and effectively in order to minimize the delay of discharge. The excessive post-operative pain is usually due to surgery related causes but not due to anaesthetic causes. But the provision of good postoperative analgesia is primarily the responsibility of an anaesthetist. An anaesthetist can do a little for the number of patients requiring readmission for surgical complications, but can play a major role in reducing the readmissions, caused by pain and vomiting. The postoperative pain control should be started from pre or intraoperative period by supplementing any technique of anaesthesia with NSAID, short acting opioid analgesics and local/ regional block intraoperatively. Any type of NSAID can be used, but recently ketorolac is very useful for postoperative analgesia in day case surgery. It is a potent peripherally acting injectable analgesic associated with few CNS side effects. Caudal block, using 0.125% to 0.25% bupivacaine also provides excellent postoperative analgesia in herniorrhaphy, anal operations, perianal operation, hypospadious, circumcision, orchidopexy, etc. In caudal block, care should be taken that muscular strength should not be compromised. Other than caudal block, there are many other types of nerve block by which postoperative analgesic can be provided matching with the day case anaesthetic unit.

Postoperative admission

The reasons for not discharging the patient at time on the day of surgery and overnight admission are:

i. Unexpected surgical or anaesthetic complications, requiring more close postoperative observation.
ii. Unexpectedly more extensive surgery.
iii. Do not fulfil the discharge criteria before the scheduled closure of day case surgical and anaesthesia unit.
iv. Uncontrolled pain and / or PONV.
v. Inadequate social circumstances at the home of patient.

The overall incidence of complicated and not to be in discharged condition after a surgical procedure in a day case unit is 0.5 to 2%. Among these the gynaecology and urology department have the highest readmission rates. The surgical causes for postoperative readmission are three to five times greater than the anaesthetic causes. The most common anaesthetic causes for postoperative readmission are: inadequate recovery, nausea, vomiting, and pain. The anaesthesia related complications responsible for readmission are more frequent with GA than with local or RA with or without sedation. The surgical reasons for readmission include bleeding, extensive surgery, perforated viscus, etc. which needs further treatment.

46 Anaesthesia at Remote Location and for Radiodiagnosis or Radiotherapy

INTRODUCTION

Delivery of anaesthetic care for radiological diagnostic and therapeutic procedures in a room which is not originally designed for such a work and is located faraway from the main OT complex of hospital is called as the anaesthesia at remote location. The potential problems for an anaesthesiologist, providing good anaesthetic care for patients in such remote locations are: (i) poor physical layout of anaesthetic machine, monitoring equipment, gas supply, suction apparatus, emergency drugs, etc. and so subsequently providing poor facility for anaesthesia at remote area, (ii) unfamiliar or outdated anaesthetic equipment because those which are not usually used in main operation theatre are dumped at such remote area in most of the institutions, (iii) working with personnel who are less familiar with the anaesthetic aspects of patient's care and (iv) the remoteness from available intensive critical help. This lack of familiarity of nonanaesthetic personnel, combined with geographic remoteness from the main surgical and critical care suit, means less ancilliary help will be available to an anaesthesiologist when it is needed in emergency.

A few years ago, very few investigations in the radiology department require any form of anaesthesia. But, now due to the advent of many modern noninvasive radiodiagnostic and radiotherapeutic procedures and the development of fast track ambulatory outpatient anaesthesia; there is an increasing demand both by the patient and the radiologist for the use of anaesthesia in radiology department. Any form of anaesthesia i.e. from conscious sedation to deep sedation to GA with various levels of consciousness are used at such remote area. Among them the most common is conscious sedation and it is such a state that where a sedated patient can respond appropriately to verbal command and other stimuli. In conscious sedation the patient can maintain the patency of airway independently by himself and retain his own protective airway reflexes. Deep sedation is a state in which the patient is not easily aroused and the airway reflexes with patency are lost. The deep sedation is more akin to GA and deep sedation outside the OT is a challenge to an anaesthetist. This is because the environment of a radiological department creates a unique problem which will be discussed later. But instead of all these problems, an anaesthetist must attempt to provide service as good as the main OT without compromising the standards, safety and comforts of the patients.

The ASA standards required for basic anaesthetic monitoring at remote locations are:

i. A qualified anaesthetist must be present continuously.
ii. A Continuous source O_2 should always be available. During anaesthesia patient's oxygenation should be measured continuously by monitoring the inspired O_2 concentration (FIO_2) and SPO_2.
iii. Adequacy of ventilation should be evaluated continuously by clinical examination of patient and expired gas analysis for $ETCO_2$ tension.
iv. Disconnection alarms must be used with mechanical ventilators.
v. Circulatory status should always be evaluated by continuous display of ECG and by frequent determination of arterial blood pressure and heart rate.
vi. ET-tube positioning must be verified by frequent auscultation of chest with stethoscope or by continuous measurement of $ETCO_2$ tension.
vii. There should be readily available means to measure the patients temperature continuously.
viii. Have a complete arrangement for management of a situation like 'cardiac arrest' with CPR.
ix. There must have a suction apparatus and scavenging system.
x. There should be good illumination and a good communication system between the anaesthetist, radiologist, and assistant personale.

Indications for Anaesthesia in Radiology Department

The common indications for any time of anaesthesia (monitored anaesthetic care to conscious sedation to deep sedation to GA) for radiodiagnosis and radiotherapy at remote locations are:

i. Infants or uncooperative children.
ii. Older children or adults with psychological, behavioural or movement disorders.
iii. Many interventional procedures performed under CT or MRI

guidance, requiring analgesia, sedation or anaesthesia.

iv. For certain investigations in intubated patients who is already receiving intensive care or acute trauma victims in ICU.

HAZARDS IN RADIOLOGY DEPARTMENT AND GENERAL CONSIDERATIONS

The hazards which the anaesthetists have to face in the radiology department while providing their anaesthesia service can be divided into two main headings: (i) the environment and (ii) the adverse reactions resulting from contrast media.

Environmental Hazards

Poor visibility

The poor visibility due to darkness which is necessary for radiology unit makes difficulties for the anaesthetist. The radiological investigations are usually done under dark surroundings and the anaesthetist may then have problems in delivering good anaesthesia, by observing the patients and monitoring the anaesthetic machines in this dark vicinity. Again, when anaesthetist is asked to move away from the patient during X-ray exposure, then it adds further problems. This problem can be solved by only illuminating anaesthetic machines and monitoring devices and using audible alarm systems. So the use of a shaded angle lamp to illuminate the anaesthetic area and some part of the patient, while minimally interfering the radiologist's ability to see a picture clearly on the image intensifer is every helpful.

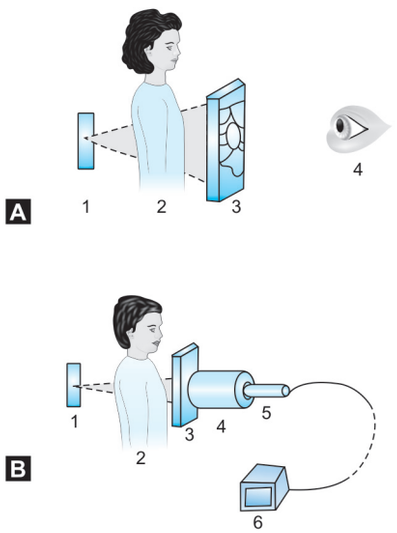
Electrical Hazards

Usually, in the radiology department high voltage apparatuses are used and they often cause malfunctioning of the sophisticated electronic gadgets, used for delivering anaesthesia and monitoring the patient. Unfortunately, it is also often necessary to use an earth lead, attached to the patient, in order to obtain a reasonably interfernce free electrical recording of an ECG. So, if there is any small leakage of current from any of the high voltage radiological equipment which surrounds the patient, then the danger of the patient through this earthing is clear, especially if a central IV line is present. The leakage of current of a few microamperes in these circumstances may precipitate cardiac arrhythmias. But recently, several monitors have been developed which can be used successfully without any outside interference by high voltage radiological equipments (Figs 46.1A and B).

Radiation hazards

X-ray is a form of electromagnetic radiation with wavelength varying between 100 and 0.1 m. This is usually generated by impinging a stream of electrons on certain metals.

The biological effects or hazards of this ionic radiation are caused by the ionisation of tissue cells. This ionization occurs when electrons travel through the tissues and causes physicochemical changes in the molecules of the cells. The two types of potentially harmful physicochemical changes due to ionization occur. These are: (i) somatic effects as for example causing skin burn, dermatitis, leukemia, etc. and (ii) genetic effects resulting in foetal abnormality due to the damage of gonadal cells. The maximum permissible limits of radiation dose for occupationally exposed persons is 50 mSV (milliSieverts) per year or 10 mSV × age for lifetime cumulative dose and 0.5 mSV per month for pregnant woman. So, an anaesthetist who is frequently called upon in the radiology department to anaesthetise the patients should beware of this radiation hazard and must avoid staying in the immediate vicinity during the radiological exposure.



Figs 46.1A and B: A. Simple screening by X-ray; 1 = Tube, 2 = Patient, 3 = Fluorescent screen, 4 = Radiologist, B. Screening with image intensifier and TV link; 1 = Tube, 2 = Patient, 3 = Fluorescent screen, 4 = Image intensifier, 5 = Camera, 6 = Monitor

The X-rays travel in straight line and the intensity of radiation diminishes in direct proportion to the square of the distance from the source. So, an anaesthetist should stand outside the direct line of radiation and as far away as possible from the source as circumstances permit. They also wear protective clothings such as lead apron, thyroid shield, etc. which are helpful in absorbing radiation and preventing exposure to it. Radiation exposure can also be reduced by employing moveable lead lined glass screens between the source of radiation and the anaesthetist and by many other innovative techniques such as allowing patient monitoring to be conducted away from the patient's immediate contact with the use of microphones and close circuit television, etc It is very important to mention that the greatest source of radiation is usually from the fluoroscopy and digital subtraction angiography. The chances of Ionising radiation from a CT scanner is relatively low, because here the X-rays are highly focused.

Space problem

Radiology rooms are so crowded with huge radiological equipments that little space is left for the anaesthetic persons, anaesthetic apparatuses and monitors. So, some compromise has to be made between

the radiological and anaesthetic equipments and the available space. So an anaesthetist should spend adequate time to be familiar with this new environment. Sometimes due to space crisis, access to the patient also becomes difficult and dangerous.

Patient movement

Sometimes during radiotherapy or radiological investigation, an anaesthetised patient moves away a distance of several feet from the anaesthetist and its machine and verities of patient's positions are used for radiological investigation. So, the anaesthetic circuits should be much long, flexible, light weight and tightly anchored to the patient to prevent disconnections during this movement. Therefore, Mapleson D or F anaesthetic circuit has been proved to be very successful and it is because of its length, simplicity and lightness in these circumstances. Further, its length may be easily adjusted to suit the varying distances of movement involved.

Miscellaneous

Truly speaking, anaesthetic equipments used in radiology department are often the oldest in the hospital as previously said. This is because older anaesthetic machines with features that do not meet with the recent standards are usually relegated from the main modern OT complex to the remote area such as radiology unit for anaesthesia. But the practice of using these obsolete equipments in remote locations such as in radiology unit should be condemned. The more tragedy is that It is again often disconnected and moved away to a corner of the radiology room when they are not in use for long period. Also modern monitoring equipments are not readily available in remote area.

So, an anaesthetist must be very vigilant in checking the anaesthetic machines before every use though it is once upon a time. Empty gas cylinders should be replaced, as soon as it becomes empty. All the anaesthetic and emergency drugs, spare laryngoscope, batteries, suction machine and other routine equipments for anaesthesia should be present and checked. Often the preparations of patients, scheduled for radiological investigation and therapy are inadequate for anaesthesia. Anaesthetic assistance is not up to the mark in remote area and the communication between the radiologist, radiotherapist and the anaesthetist is poor. Recovery rooms too are often nonexistent in such situation.

So, the modern radiology rooms have been designed and built by matching with the up-to-date anaesthetic requirements. These include: O_2 and anaesthetic gas supply through pipeline, wall mounted suction unit, properly placed modern anaesthetic machine with ventilator and monitor, and an anaesthetic supply cart fully equipped with all types of drugs, airway adjuncts, laryngoscope, syringes, etc. Within easy reach, the fully monitoring stack should be placed which can be viewed through a window from outside the scan room. Now, some modern scanners have close circuit television which images the patients in control room as they lie within the tube and allow the constant observation of continuing chest wall movement of patient.

ADVERSE REACTION RESULTING FROM THE INJECTION OF CONTRAST MEDIA

Though the quality of contrast media used for radiodiagnosis have considerably improved in recent years, still their injection may involve a definite morbidity and mortality. The radioopacity of the contrast media is due to its high atomic number which helps to absorb X-ray. The high atomic number of contrast media is due to its containing iodine (atomic number of iodine is 53). The example of oldest contrast media are meglumine, iothalamate, diatrizote, metrizoate, etc. These are toxic, ionized and hyperosmolar. The high osmolarity of these older contrast media is responsible for many of the bad haemodynamic responses. The osmolarity of these old contrast media is usually 4 to 5 times higher than that of the blood. Sometimes, it is as high as 8 times than that of the serum. So, occasionally gross hypervolaemia may result from injections of large amount of these older agents, resulting in depressed myocardial contracility and pulmonary oedema.

Hence, recently the nonionised, highly iodinated, water soluble contrast media which have much lower osmolarity are increasingly used, despite their cost. The examples of these newer agents are: iohexol, iopamidol, ipromide and ioversol. The use of these newer agents as contrast media is associated with much lower incidence and severity of adverse effects. They are typically used in the concentrations which are equivalent to 300 to 320 mg of iodine per ml. The volume of contrast media required for radio diagnosis varies with the preparation, type of investigation, age and the total body weight of patient. But it may be used maximally up to 150 ml. For example for CT of head of an adult 50 to 100 ml, for CT of whole body of an adult 100 to 150 ml, for aortography of an adult 100 ml, for urography 2 to 3 ml/kg, and for child 10+2 ml/kg is used.

The adverse effects encountered with these contrast media include: nausea and vomiting, hypertension, hypotension, bradycardia, bronchospasm, various arrhythmias, pulmonary oedema, and even ventricular fibrillation and cardiac arrest. Most organs or systems are affected, but the CVS and respiratory system are potentially at greatest risk. The adverse reactions usually occur within the first 5 to 10 minutes, following injection. So, it is advised to keep the patient under close observation for first 20 minutes, following injection. These iodine-containing contrast media occasionally also trigger allergic reactions (iodine sensitivity) and rarely anaphylaxis. These agents may cause renal failure in patients who are dehydrated or have impaired renal function. So, adequate hydration should be ensured in patients who have been starved

for prolonged period for GA. Lactic acidosis can be precipated in patients taking bigoanides (metformin) and so these oral hypoglycaemic agents should be stopped 48 hour before the administration of contrast media. DIC also can follow severe hypotensive shock after IV injection of contrast media. The incidence of these complications and severity of it depends on : (i) which agents are used, (ii) the type of investigations performed, (iii) the total dose and speed of injection, and (iv) the most importantly – patient susceptibility. Hypotension, induced by contrast media's reaction, can render the patient unconscious. Convulsions have been reported in patients with a history of epilepsy. Renal failure is a well-documented complication with the use of contrast media, particularly in patients with pre-existing renal disease.

Patients who have experience of previous reactions to contrast media have a higher incidence of potentially severe reactions (anaphylaxis), if they are exposed to these agents again. Pretesting appears to be of little value in the prediction of these reactions that are truly anaphylactic. The increased prevalence and severity of reaction caused by the contrast media can be reduced by pretreatment of patient with prednisolone and diphenhydramine. The mechanisms of these adverse drug reactions are often unclear. Some of these advase effects are immunologically based. But this is not universal. So the treatment of complications due to contrast media is directed at specific components of the patient's reaction. For example, the shock and hypotension is treated by fluid and vasopressor, bronchospasm by bonchodilator, bradycardia by atropine, anaphylaxis by steroid, O_2, adrenaline, etc.

PREANAESTHETIC MANAGEMENT OF PATIENTS UNDERGOING X-RAY INVESTIGATIONS UNDER GENERAL ANAESTHESIA

Preanaesthetic management consisting of assessment and preparations of the patients before any type of anaesthesia in radiology department are often neglected. This is because, unfortunately, many radiological studies have been wrongly regarded as minor procedures where anaesthesia and sedation is given with little importance. But clearly this is not the true, particularly in those patients who are of greater anaesthetic risk due to their age and coexisting medical conditions such as coronary artery disease, respiratory disease, diabetes, obesity, etc. Again unfortunately, the attitude such as 'he is only going for X-ray' prevails among all the staff of radiology department and is not correct for any patient who is going for X-ray under GA. Patients usually come in the morning on the day of investigation. They remain very much anxious because it may be his first experience of anaesthesia. Again huge radiological equipments and surroundings are frightening to them. Also the patient may be anxious about what the X-ray investigation may reveal and about the prospects of subsequent surgery. Anticipation of all these cause anxieties to patients and a brief explanation of the procedure before by the anaesthetist does much to allay the patient's fear, whilst establishing a rapport prior to anaesthesia.

Patients presenting in radiology department are frequently old. They have frequently cardiovascular diseases and because of the association with cigarette smoking also they have the respiratory problems. So, careful control of blood gases is required during cerebral and cardiac angiography. Precise manipulation of the depth of anaesthesia is needed for some radiological procedures which may finish suddenly, once satisfactory films have been taken after a prolonged trial. Yet the patient must be deeply anaesthetised during the injection of contrast media to avoid reflex movement. Such brief movements may be of little inconvenience to a surgeon. But it may easily ruin an X-ray film which may result in multiple X-ray exposure with the patient is repeatedly receiving unnecessary radiation and dangerously large doses of contrast media. So, if patient has to be managed in such circumstances, then a high standard preanaesthetic check up and investigations should be maintained. This includes full clinical examination and all the necessary investigations, including routine Hb%, blood film, urine, chest X-ray ECG and not infrequently pulmonary function tests, according to the patient's history and examination. A normal clotting time is preferable because of the danger of haemorrhage from a relatively large puncture on the wall of blood vessels, left by the radiologists needle, especially if the Seldinger technique is used.

For many arteriography procedures, a preoperative ECG is essential. This is because of the presence of generalised cardiovascular disease. Patients undergoing carotid angiography may present problems with a raised intracranial pressure due to trauma or the presence of a space occupying lesion for which radiography is done. In these patients vomiting, dehydration and consequent electrolyte disturbance due to ↑ICP indicate the need for serum electrolyte investigation. Renal failure patients, presenting for renal angiography require full investigations too. The paediatric patients undergoing any sorts of echocardiography under sedation or GA require a detailed examination and investigations of CVS prior to radiography.

INDIVIDUAL ANAESTHETIC MANAGEMENT IN RADIOLOGY DEPARTMENT

The common procedures for which anaesthetic department is called upon to anaesthetise the patients in radiology department are angiography, computed tomography (CT), magnetic resonance imaging (MRI), doppler and echocardiography and other non invasive procedures. Recently, many invasive radiological procedures are also done quite frequently. The patients are usually children or uncooperative adult who

are suffering from psychiatric diseases, cerebral palsy, down syndrome etc. Patients scheduled for elective scan are rarely normal. So, the indications for anaesthesia for scanning and the nature of the underlying pathology such as developmental delay, epilepsy, malignancy, psychiatric and movement disorders, etc, should be checked properly. Several 'syndromes' with their manifestations on RS and CVS are also not uncommon. The presence of pain and lengthy radiological procedures may also be an indication for anaesthesia in adult advised for radiological investigation. The patients those are brought from ICU for radiological investigation may be non cooperative and critically ill too.

The principal aim of anaesthesia during radio diagnostic or radiotherapeutic procedures is to keep the patient just motionless. So, radiological studies do not demand deep level of anaesthesia as surgical stimulus are not so intense. Therefore, all types of anaesthesia ranging from monitored anaesthetic care (MAC) to conscious sedation to GA may be applied. Most of the times conscious sedation is sufficient to alter the perception of pain and anxiety and keep the patient motionless, while maintaining protective airway reflexes and the ability to respond appropriately to verbal commands.

Benzodiazepines and opioids are frequently used for MAC or conscious sedation. Among the benzodiazepines, midazolam is mostly preferred due to its some definite advantages such as: (i) water solubility, (ii) minimum discomfort during intravenous injection, (iii) no adverse effects on cerebral metabolism and cerebral blood flow, (iv) shorter half-life and (v) lack of its active metabolites. In clinical doses, generally, the midazolam does not produce any significant cardiovascular depression.

Then among the opioids the commonly used opioid is fentanyl (1 to 2 µg/kg). But combination of midazolam and fentanyl can produce significant respiratory and cardiovascular depression. Higher doses of fentanyl can result in chest wall rigidity. Tachyphylaxis to propofol and ketamine have been reported.

Computer Tomography or CT Scanning

As the name implies, it provides a series of computer-integrated tomographic axial slices of different parts of our body. The CT produces a two-dimensional, cross-sectional, transverse images by rotating an X-ray beam around the area which is to be examined. A typical CT scan comprises 20 such transverse sections. It is usually used for the investigation of brain, thorax and abdomen. It has also proved to be valuable in studies of vascular malformation and tumour. Each image is produced by the computer integration of differences in the absorption coefficient of radiation between the different normal and abnormal tissues. The image of the structure under investigation is generated by X-ray and the brightness of each area is proportional to the radiation absorption value of that tissue which is later integrated by computer. Sometimes contrast medium is also used orally or through parenteral route in conjuction with CT scan to enhance the quality of image. In this situation such as when contrast medium is used orally and if GA is needed, then there is higher risk of aspiration. So, in such circumstances the patient should be always intubated (Fig. 46.2).

During CT scan the patient is moved slowly inside the dark tunnel and a gantry rotates around the whole body to cut the transverse slices of the image. Every cutting slice is produced by a single rotation of gantry and thus multiple series of slices are made by several rotation of gantry at interval of 7 mm. The interval of slices can be decreased or increased depending on the diagnostic information sought. The first generation scanners took 4 to 5 minutes for cutting every slice of image. But the newer generation takes only 2 to 4 seconds. The older CT machines scan the slices in a series of discrete steps. While the modern spiral CTs acquire only image data

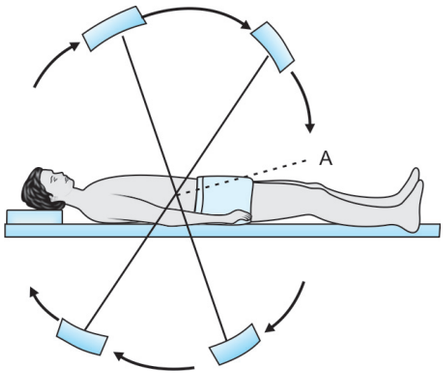


Fig. 46.2: Computer integrated tomography. A is the pivotal point of bar connecting tube and films

by a single continuous pass and later they constitute the image. In modern machines individual scan takes few seconds (2 to 4 sec) and a complete study may require only 5 to 10 minutes. Unlike MRI, in CT scanning the environment does not restrict the use of conventional type of anaesthetic equipment and monitoring. But the space is often limited. So, compact anaesthetic machines and monitors are more practical.

CT scan is a painless noninvasive procedure. So, it does not need any anaesthesia for adults. Only children, uncooperative individual and psychiatric patients need anaesthesia to keep them motionless. Sometimes, critical patients who are brought from ICU for CT scan needs supervision by anaesthetist. GA is usually not needed for them. Sedation is sometimes needed and is sufficient. Only light anaesthesia producing immobility and lack of awareness is required.

A variety of general anaesthetic technique can be used for CT scan by applying inhalation or intravenous agents with spontaneous or controlled ventilation. But the final choice should be determined by the equipment available and the patient's needs, e.g. only maintenance of clear airway, control of raised ICP, respiratory support etc. If there is any antecepated problem regarding clear airway due to falled back tongue under sedation and patient's head is inaccessible during CT scan, then

the airway can be cleared by LMA, provided the patient does not require IPPV or airway protection from aspiration. If intubation is needed for any cause, then every effort should be made to reduce the ICP (especially if the CT is being done for intracranial space occupying lesion) by hyperventilation causing hypocapnia and by avoiding the use of volatile anaesthetics agents.

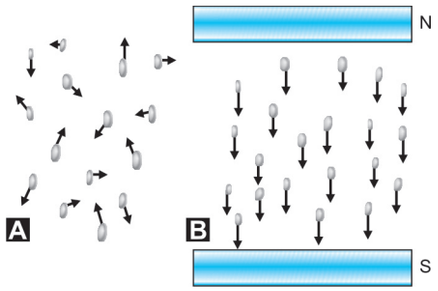
Anaesthetists may have to adopt their own techniques depending on whether the patient is elective or an emergency trauma victim with ongoing blood loss. These latter patients must be treated as if they have full stomach and therefore, sedation is not an option. These patients should be scanned in fully awake condition or be intubated following a rapid sequence induction and intubation, if general anaesthesia is needed. Before laryngoscope and intubation cervical spine (if fractured) should be stabilised. During extreme flexion of head (required for examination of posterior cranial fossa), kinking and disconnection of tube should be cared for.

Positioning and movement of the gantry during the radiological procedure may also cause kinking or disconnection of the anaesthetic circuit. Cannulas, catheters, drains and even ET tubes can be pulled out during the transfer or movement of patient through the scanner. The radiographer should be asked for how far the table will move. There should be always checking that IV lines and breathing circuit have not been snaged with other equipments. CT scanning generates the potentially harmful ionising radiation. So, it is preferable for the anaesthetist to monitor the patient from outside of the scan room. In this circumstance the patient can also be monitored visually through a lead glass window that is supplemented if necessary by closed circuit television. If the anaesthetist observes the patient from the control room, then the monitor's alarm should be a visual one that can be easily seen from the control room. But, if it is necessary for an anaesthetist to remain near the patient, then wearing of appropriate radiation protection gown is advisable. During scanning of thorax and abdomen to reduce the artefacts caused by respiratory movement, the patient may require brief periods of apnoea or breath holding. To achieve this, both the paralysed or spontaneously breathing patients should be ventilated manually and their lungs are held standstill in inspiration phase for few seconds. Patient of intensive care unit requiring CT scans should be managed like any inter-ICU transfer with full monitoring and ventilatory support during transfer.

MRI (Magnetic Resonance Imaging)

It is not based on ionising radiation. It depends on magnetic field and radiofrequency pulses for the production of images. In MRI machine, there is a large magnet in the form of a tube which is capable of accepting the whole length of a human body and creating a huge magnetic field around it. This magnet is approximately 2 metre in length and 500 kg in weight. Within this magnetic tube radiofrequency (RF) transmitting coils which transmit radiomagnetic waves are also incorporated, surrounding the patient. These transmitting coils also act as a receiver to detect the reflected radiofrequency waves from the patient and construct an image (Figs 46.3A and B).

MRI is based on the fact that some atoms which contain unpaired protons or neutrons in their nucleus and simultaneously unpaired electrons in their outer orbit have the potential to act as magnetic dipoles. This property of atom is possessed by the following paramagnetic elements such as ^{1}H, ^{13}C, ^{23}Na, etc. and therefore, they behave like tiny magnets. In this purpose hydrogen atoms of body which contain a single proton are particularly suitable for acting as a tiny magnet and produce an MRI image, since they are normally present in vast numbers in the body tissues. Normally, the hydrogen atoms (which is equivalent to a proton) of our body tissue are arranged in random haphazard fashion. But the use of strong external magnetic field will force a proportion of these atoms to align in a new magnetic axis (parrallel or antiparallel to the applied magnetic filed) from their previous random orientation. The power of external magnetic field used in MRI for clinical practice ranges from 0.15 to 1.5 Texla (1500 to 15000 Gauss) as compared with that of the earth's magnetic field which is only 0.5 Gauss. In addition to the large and costly magnet required for MRI, the machine also uses pulses of radio frequency waves. These radiofrequently waves are generated by RF transmitting coils that closely surround (incorporated in the magnetic tube) the patient. These radio-frequency waves are essential to excite and detect the magnetised aligned hydrogen protons. The pulsed radiofrequency wave displaces the nuclei or protons of hydrogen atom from their new parallel or antiparallel position which was produced by external strong magnetic force. Then again the nuclei or protons return to their previous parallel or antiparallel position produced by the external magnetic force immediately after the pulse ceases. At the same; time they release some energy from tissue as a radio signal which is detected by the same RF transmitting coils, used for transmission of radio frequently waves. Since the returned RF signal is proportional to the concentration of protons of tissue hydrogen atom, so



Figs 46.3A and B: Mechanism of MRI
A. Protons, behaving like tiny bar magnets are oriented randomly.
B. Alignment of protons when immersed in a strong external magnetic field.

it forms the basis for a digital record of the proton content of the tissues by a highly sophisticated computer. The computer creates cross-sestional or three dimensional images from this minute returned radiofrequency signal which is generated when the hydrogen nuclei are flipped in and out of the parallel or antiparallel alignment by a powerful magnetic field with high radiofrequency magnetic pulses. Then using a similar technique which is used in CT, the returning RF signal (captured by RF coils) is converted by computer of MRI into an analogue image presented on a cathode ray tube in varying shades of black and white.

The radio-signal received by RF transmitting coil during MRI scanning is of very low electrical intensity and so is easily subjected to interference from any electronic equipment or anaesthetic monitoring devices. For this reason, MRI scanning area is enclosed within the RF shield which is incorporated usually into the fabric of the MRI imaging suite. The prevention of interference of MRI scanning from anaesthetic monitors is usually made by using isolated power sources or battery, some filters and sometimes enclosing the anaesthetic monitor in its own small RF shield. The provisions for both safe anaesthesia and good MRI image requires specialised anaesthetic equipments and careful organization. Unlike CT, it is not possible to take simply the standard conventional anaesthetic machines and monitors to the MRI room.

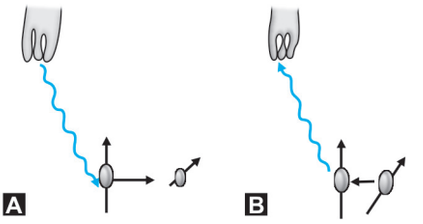
Anaesthetic procedure in an MRI suite creates several problems. Some arise from the effects of magnetic fields of MRI scanners on anaesthetic equipment and some from the effects of anaesthetic equipment on MRI scanner. The MRI image quality is superior to CT scan. It can differentiate clearly between the white and grey matter of brain which is not possible by CT scan. Again, unlike The CT scan which gives picture only in transverse section, MRI can display images in the transverse, sagittal, coronal and oblique planes. Unlike CT scan it is also capable of detecting diseases in the posterior fossa. MRI provides vascular picture without the need of intravenous contrast media. It requires very little patient preparation. As MRI is not an ionising radiation, so it does not produce biologically deleterious effects on patients and other personals present in this room and is non-invasive. MRI also permits evaluations of blood flow, CSF flow, contraction and relaxation of organs, etc. Calcium does not emit signals in the MRI. This lack of calcium signal, however, prevents MRI form detecting any pathological calcification in soft tissue tumour and pathological changes in cortical bone. Another disadvantage of MRI over CT scan is that a relatively long time is required to obtain images. Individual MRI scans may take up to 20 minutes and an entire examination may not take less than 1 hour. The other disadvantages of MRI are that very obese patient cannot be examined in this narrow magnetic tunnel and body surface absorb the RF energy causing increased body temperature. But it is usually unlikely that the patient's temperature will increase by more than 1°C (Figs 46.4A and B).

Anaesthesia and monitoring of patient in the MRI suite poses several unique problems. These are:

i. Need to exclude all the ferromagnetic components surrounding the patient.
ii. Limited patient's access and poor visibility of patient in the MRI tunnel.
iii. Low image quality of MRI due to disturbed radiofrequency (RF) waves caused by anaesthetic electric equipment.
iv. Interference and malfunctioning of anaesthetic monitoring equipment due to high magnetic field of MRI.

Patient acceptance of MRI is generally high. Most adults and small babies (recently well fed and wrapped) tolerate the procedure without sedation. Sedation may be required only in older children and in adults who cannot cooperate.

This sedation may be conscious sedation or deep sedation akin to GA. Conscious



Figs 46.4A and B: A. Effect of radiology pulse from an external coil which displaces magnetised proton from its axis with absorption of energy
B. Return of magnetised proton to its former axis with release of energy as radiofrequency pulse which can be registered by receiving coil and quantified

sedation can be defined as a medically controlled state of depressed consciousness which allow the protective reflexes of airway to be maintained and retains the patient's ability to maintain a patent airway independently. It also permits an appropriate response of the patient to physical stimulation or verbal command. Whereas deep sedation can be defined as a medically controlled state of depressed consciousness which may be accompanied by a partial or complete loss of protective airway reflexes, inability to maintain a patent airway independently and inability to respond purposefully to physical stimulation or verbal command. General anaesthesia (GA) is more or less close to deep sedation. GA is defined as a medically controlled state of unconsciousness accompanied by a loss of protective airway reflexes including the inability to maintain a patent airway independently and the inability to respond purposefully to physical stimulation or verbal command.

Sedation (usually for paediatric group) is usually ensured by chloral hydrate (50 mg/kg orally) or midazolam (0.3 to 0.5 mg/kg orally) or diazepam (0.1 mg/kg orally). For adult, sedation can be maintained by thiopentone or propofol. For each of these group of patients, the requirement of anaesthesia for MRI scan is only immobility.

In order to obtain high quality images, patients need to remain immobile within the confined space of magnetic core for at least 20 minutes. Complex scan may

take much longer time. So, though most patients tolerate the procedure without sedation, still a large number of patients, near about 3% of healthy adults are unable to do this without adjuvent sedation or general anaesthesia.

MRI scanner is very noisy and a patient has to lie for a long time on a thin table in a dark confined space made by tube wihtin this noise. This can cause claustrophobia or anxiety even in adults, necessitating sometimes sedation or anaesthesia. MRI has two implications on anaesthesia: (i) in-accessibility of an anaesthetised patient to an anaesthetist when the body enters totally into the scanner magnetic tunnel and (ii) malfunctioning of anaesthetic feromagnetic monitors in the strong magnetic field of MRI. Within the MRI tunnel, except conscious sedation, in deep sedation (only if it is needed) manual control of the airway of patient is impossible. So, tracheal intubation or laryngeal mask airway is essential to clear the airway of an anaesthetised patient from falling tongue. If the indication of scanning under GA is for suspected raised intracranial pressure or if GA is indicated in a patient with a potentially full stomach, then intubation with positive pressure ventilation is required. The effect of increasing the length of expiratory limb of the Ayre's T-piece has been studied on ventilation. Different studies have shown that with 10 metre long breathing circuit, there is only minimal decrease in tidal volume as a result of circuit compliance. So, it dictates that remote ventilation from outside the scanner room can be performed by using the long Bain circuit or Mapleson-D circuit when the patient is within the MRI room and the anaesthetic machine is outside the MRI room. Maintenance of anaesthesia by volatile anaesthetic agents or propofol infusion have both been employed. However, with the latter the dose requirement can be unpredictable, because infusion pump may malfunction near the strong magnetic field. The use of LMA is gaining popularity in MRI setting, where intubation is not absolutely indicated and is used for only better maintenance of airway. As there is no risk of ionic radiation in MRI, so the anaesthetist can observe the patient from both the ends of the tunnel and can take out the patient quickly if necessary. Due to intense magnetic field the anaesthetic monitoring equipments also do not work properly. Reversely, the ferromagnetic anaesthetic monitoring equipments distort the magnetic field sufficiently to degrade the image. It is also likely that the feromagnetic anaesthetic monitoring equipments are propelled towards the scanner machine and may cause a significant accident, if it makes contact with the patient or staff at a certain speed.

MRI room or suite can be laid out in two fashions for anaesthesia. If the majority of the anaesthetic equipment needs to be kept inside the radiology room, then the MRI compatible instrument should be used. But, usually most of the time, the anaesthetic machine and the monitoring equipments are kept outside the room and long MRI compatible (shielded or nonferromagnetic) anaesthetic circuits, ECG cables, SPO_2 cables, etc. are used and they lead to the patient from outside the room. The disadvantage of this approach includes the need for extra long monitoring leads, breathing tubes and other connections which frequently cause disconnection and leak.

Another common approach is to induce anaesthesia in the induction area adjacent to MRI suite outside the magnetic field using conventional anaesthetic equipments with the patient on a nonferomagnetic table or trolly, made of aluminium or stainless steel (MRI compatible). Then this table is transported with the patient after induction into the MRI room where maintenance of anaesthesia and monitoring are continued using MRI compatible anaesthetic machine and monitoring devices. Protable anaesthetic machine constructed of nonmagnetic material, aluminium gas cylinders and MRI compatible O_2 analyser also are used in MRI suite. Consideration also needs to be given to IV fluid stands, gas cylinders, ventilators, stethoscope, etc. Standard batteries of laryngoscope should be replaced with nonmagnetic lithium batteries if it is used in MRI suite. Laryngeal mask airways without metal spring in the pilot tube valve (armoured) should also be available. Heart rate and respiratory rate can be monitored with an oesophageal stethoscope. If the patient is allowed to breathe spontaneously, then the movement of the reservoir bag may be used as an index of ventilation. The metallic tubing connectors for noninvasive automated arterial pressure monitor should be replaced by nonmetalic connectors. But an extended length of the tubing from the BP cuff to the base unit is associated with some damping of the signal. Invasive monitoring is also possible. But in order to minimize damping the transducer must be kept as close to the patient as the magnetic field will allow. If transducer is kept within the 0.5 mT line, close to the patient then to avoid the damping of radiofrequency filter the use of will limit the interference (Fact file-I).

Patients fitted with a demand cardiac pacemaker should not be exposed to MRI. This is because induced electrical currents within the pacemaker by huge magnetic field may be mistaken for the natural activity of heart and may inhibit the pacemaker output, even in the absence of normal cardiac electrical activity. Other potential problems of the cardiac pacemaker due to MRI include (i) possible reed switch closure or damage, (ii) automatic switch over to an asynchronous mode and (iii) changes of programme, etc. Intracranial metallic vascular clips may be dislodged from the blood vessels due to magnetic induction of clips during the procedure of MRI. Malfunctioning of shunts, wire spiral of ET-tube, automatic implantable cardiac defibrilators and implanted biologic pumps are also other dangers. Metallic

FACT FILE- I

Specific problem and its solution during anaesthesia and monitoring of a patient in the MRI suite is like that:

i. Pulse oximeter must have the fibreoptic signal linking facilities between monitor and the sensor, RF filter and ECG locking device.

ii. ECG must have the RF filter and leads should be placed as close as possible to the centre of the magnetic field.

iii. Metal connection of the blood pressure cuff and pipes should be changed to plastic one for noninvasive monitoring of BP.

iv. Side stream capnography functions satisfactory in MRI unit but the length of the sampling tube may cause significant delay in signal transduction.

v. Precordial or oesophageal stethoscope does not function well. This is because of noise, created by scanner during its operation.

vi. Temperature probe should have RF filters for its proper functioning in MRI unit.

It is to be remembered that monitoring units which function satisfactorily in one MRI unit, produce problems in another MRI suite. This is due to differences in the RF and magnetic field strength employed by the two MRI system. Some centres permit the patient to breathe spontaneously during anaesthesia. But controlled ventilation by neuromuscular blockade is preferred. This is because it not only provides satisfactory gas exchange, but also avoid excessive head, neck, chest and abdominal movement that may interfere the imaging process.

objects such as scissors, stethoscope, BP instrument, cylinder opener, laryngoscope, etc, which are brought in the vicinity of the MRI magnet can literally fly into it and may cause severe injury to the patient and the bystanders.

Electric motors (e.g. in syringe infusion pump) may run erratically and administer wrong doses of drug to the patient. Also any information stored on magnetic media of credit card, bank cards, cassette tape, floppy disc, etc. will be erased by demagnetisation. The magnetic field decreases as distance from the scanner increases. Places beyond the 0.5 mT boundary line or outside of the scanning room can be considered safe. During scanning the noise level may sometimes reach 95 decibel So, ear plugs should be worn, even for anaesthetised patients to avoid the damage of cochlea. Devices, made from stainless steel which is not ferromagnetic can be taken into the scan room. Even weakly ferromagnetic objects such as metallic make up on face or tattoos, etc, can distort the image or be heated by the powerful magnetic field of the MRI machine to a point which can cause burns.

In complying with the minimum perianaesthetic monitoring standards, a balance must be made between the loss of MRI image quality due to electromagnetic interference from the different anaesthetic and monitoring equipments and degradation of the monitor signal quality as a result of the powerful magnetic field of MRI. There are several monitoring systems that are nonferromagnetic and, therefore, are compatible for use in the MRI room. Central capnography is not possible to use in MBI room, because within magnetic field sampling unit will tend to be overheated and would grossly distort the image. Side stream capnography should be used, but it necessitates a long sampling tube to keep the monitor beyond the MRI room or 0.5 mT line. ECG leads can cause the reduction of quality of both the monitor and scan signals. So, telemetric ECG is very useful in an attempt to circumvent this problem which is now available commercially. A liquid crystal display for cardiac monitoring should be used to avoid distortion of cathode ray tracing by the magnet of MRI machine. Recently, surgeries like laparotomies and craniotomies are being carried out with intermittent MRI picture to allow the accurate tomour resection. In such condition, scanners are horseshoe-shaped in design, like C arm with one side open to allow the access to the patient. Here, all the same precautions and principles are applied like the nonoperative MRI except titanium instruments are used.

Angiography

For angiography an arterial catheter is passed directly into the arterial lumen and a contrast medium is injected into the artery that produces image which is viewed by a conventional cut film radiography or by digital subtraction angiography. The arteries of viscera and lower extremities may be approached via the femoral artery, although arterial occlusive disease may require a translumbar approach to the aorta. It is an invasive technique, so the development of CT scan and MRI has now reduced the use of this type of invasive angiography. Also the advent of spiral and double helical CT scanner allows the whole vascular territories to be mapped out within 30 sec. Regarding the angiography MRI produces superior images than CT scanning, including three dimensional pictures and is also sensitive to the detection of flow.

Most of the angiographies are done under local anaesthesia with or without mild sedation. This is because the gaining of vascular access and the injection of contrast media in the vessels may result in the patient's discomfort. So, some patients may get benefit from the judicious administration of analgesics and sedatives. Indications for GA in angiography is same as for CT scan and MRI. The disadvantage of GA for angiography is it prolongs the time taken for investigation, and increase the cost and risk associated with anaesthesia. In GA the another disadvantage is that patient will not be able to react to untoward reactions due to radiocontrast medium, while under LA a conscious patient can describe symptoms and allow the procedure to be stopped immediately. Usually the patients undergoing arteriography to determine the extent of vascular occlusive disease have a higher incidence of serious comorbid conditions such as diabetes mellitus, coronary heart disease, hypertension, renal disease, etc. So, appropriate monitoring and precautions should be taken when applying sedation and

anaesthesia for angiography or CT or MRI scan in this group of patients.

Cerebral angiography

Cerebral angiography is usually done for the diagnosis of arteriovenous malformations, aneurysms or tumours, etc. in the brain where radio opaque contrast medium is given in the carotid artery and a plane or a digital X-ray is taken. It is mostly done under LA. The indications for GA in cerebral angiography are same as that of CT scan or MRI. But most of the patients scheduled for cerebral angiography have increased ICP. So, all the measures have to be taken to prevent the rise of ICP, if the patient requires GA. Smooth induction should be instituted, avoiding coughing, bucking, straining etc. and permitting BP to be well maintained. It is reasonable to employ a technique of controlled ventilation, avoiding the use of volatile anaesthetic agents as they increase the ICP. Hyperventilation produces hypocapnia and it is useful for reduction of ICP. So, during maintenance of anaesthesia reduction of P_aCO_2 by hyperventilation causes vasoconstriction of cerebral vessels resulting in slow cerebral circulation and increased transit time of contrast medium which will improve the delineation of small vascular lesions. The transient hypotension, bradycardia or asystole may occur during cerebral angiography due to contrast dye injection. Acute cerebral oedema has also been reported following injection of contrast media due to the hyperosmolarity of dye and also due to the changes in permeability of endothelium of blood-brain barrier. Other complications of cerebral angiography are haemorrhage which is due to the rupture of lesion or vessel and ischaemia which is due to thromboembolism or vasospasm.

Coronary angiography

Coronary vasculature is visualised by injecting the radioopaque contrast media into the ostium of any coronary artery. Thus, it helps in the determination of the anatomy of coronary artery, or the presence and location of any stenosis, or the detection of coronary vasospasm. Thus, information obtained from coronary angiography dictate further treatment, ranging from simple medical therapy for myocardial ischaemia to angioplasty during angiography to CABG. Though CT and MRI help in the diagnosis of coronary arterial disease, but still coronary angiography is the 'gold standard' method for the diagnosis of coronary arterial disease. During coronary angiography, some interventional procedure can also be performed to improve the coronary blood flow.

During coronary angiography local anaesthesia is provided at the site of the introduction of an arterial catheter which is either around the femoral artery or the brachial artery. Under local anaesthesia, coronary angiography is usually performed by passing a catheter via the femoral artery in a retrograde fashion to the aortic root. Then for the selective angiography injection of contrast medium is done into the ostia of each coronary artery. During coronary angiography, every patient should have an intravenous canula for administration of emergency medicines (if needed); analgesics or sedation. For analgesia, usually fentanyl and for sedation usually midazolam are helpful in reducing the discomfort during injection of contrast media and in maintaining the motionless supine position of patient during long procedures. Any benzodiazepines, given IV slowly, provides adequate sedation for most of the purposes. Sometimes fentanyl and midazolam is supplemented with propofol. Standard anaesthetic monitoring protocol is used during the whole procedure including continuous monitoring of SPO_2, heart rate, respiratory rate, ECG, arterial BP (by directly transduced from the arterial introducer), etc. The infusion of GTN should be readily available for administration, if the patient develops myocardial ischaemia. Supplemental O_2 should be administered to every patient via face mask or nasal cannula. Complications of coronary angiography are more common in patients with severe coronary artery disease and it includes arrhythmias, heart failure and strokes. Local bleeding and haematoma at the site of catheter introduction are the surgical complications. Arrhythmias are not uncommon which is both due to direct stimulation of myocardium by catheter and following injection of contrast media. Bradycardia is also common as the nonspecific ECG changes. Left heart failure is easily induced which is due to the rapid rise in left ventricular end diastolic volume and pressure, caused by the injection of contrast media in bolus. Myocardial infarction has been noted in 0.5% of patients during coronary angiography. Thorough proper pre-operative examination, correction of preexisting arrhythmias where possible, and good control of the serum electrolytes clearly minimizes the potential dangers, during coronary angiography.

Interventional transvascular coronary arterial procedure

Once the presence and location of any coronary arterial block or stenosis is confirmed, a variety of methods or interventional procedures can be employed to improve the myocardial blood flow directly. Heparin is used prior to any angiography and interventional therapeutic procedures. One of the methods or interventional coronary arterial procedure is the percutaneous transluminal coronary angioplasty (PTCA). Here, the stenosed or blocked area of coronary artery is traversed by a balloon-tipped catheter which is introduced through the femoral artery. The balloon is then inflated to dilate the area of stenosis and to remove the block which will increase the coronary blood flow. During balloon inflation, transient coronary artery occlusion can occur. So, patient's haemodynamic status must be closely monitored.

Other interventional coronary arterial procedures are: placement of coronary stents, removal of atheromatous plaque, extracorporeal circulation, etc. Extracorporeal circulation is usually established in patients who are not otherwise candidates for CABG surgery such as those with unacceptably poor ventricular function. It is performed via the femoral artery and vein following GA and systemic heparinisation. The coronary atherotomy may be performed using atherotomy catheter or excimer lasers. During all these procedures different types of ventricular arrhythmias can be precipitated and these haemodynamically unstable arrhythmias can be treated with lignocaine or cardio version. The rupture of coronary artery during these interventional transvascular coronary arterial procedure may result in pericardial tamponade and is treated by emergency pericardiocentesis. The other complications of interventional coronary angiography are coronary artery dissection, coronary artery vascular spasm due to dysfunctional coronary artery endothelium and intraarterial thrombus formation. Once thrombus is formed, then intracoronary injection of urokinase or streptokinase may dissolve the thrombus. Sometimes, accute coronary artery occlusion does not respond to transluminal treatment in cardiac catheterization laboratory. Then it may require emergency CABG. The spectrum of treatment provided in the cardiac catheterisation laboratory is now constantly changing. Various combination of the above described procedures and some new procedures may be performed on individual patient. But it depends on the severity and location of the lesions and the frequency of practice, performed at each individual institution.

Cardiac catheterisation

Cardiac catheterisation is nothing but the placement of catheters in the great vessels or the chambers of heart through transvenous or transarterial route. It helps in determination of cardiac anatomy, valvular anatomy, pulmonary vascular anatomy, pressure measurement in different cardiac chambers and major blood vessels, injection of contrast media for radiological visualisation of various vascular structures, injection of indicator with distal sampling for flow determination (using Fick principle), blood sampling for measurement of O_2 and CO_2 tension to detect the presence and location of shunts, etc. Right side of the heart is accessed via the femoral, brachial, cephalic or internal jugular vein and the left side of the heart is accessed via the femoral or brachial artery. Although, all the above mentioned parameters can be meausred by echo and Doppler cardiography, still cardiac catheterisation is the 'gold standard' technique. For measurement of flow and pressure from different cardiac chambers and subsequently to measure shunt (by O_2 tension), a steady state preanaesthetic cardiovascular and respiratory function is necessary. Any change in flow and pressure in any chamber due to anaesthetic procedure may result in incorrect result for the measurement of shunt. So the arterial O_2 and CO_2 tension should be strictly maintained at the preanaesthetic levels or should not change (if abnormal for that patient) by any anaesthetic technique or by giving O_2. These constraints make anaesthetic management extremely difficult for cardiac catheterisation.

The cardiac catheterisation in adults is done under local anaesthesia and/or sedation produced by midazolam and/or fentanyl and if necessary with propofol. It is frequently performed in conjunction with coronary angiography. O_2 is administered only when O_2 saturation falls below the level of baseline and care must be taken to maintain the present arterial blood gas level if shunts or pulmonary haemodynamics are to be measured. Complications of cardiac catheterisation are similar to that of coronary angiography, because catheter is placed within the cardiac chambers. So, supraventricular and ventricular arrhythmias are very common during this procedure. Hence, anaesthetist must be ready to deal with these acute haemodynamic and/or respiratory instability in patients who may have severe valvular and myocardial dysfunction. Fortunately, however, these cardiac arrhythmias are usually resolved with immediate withdrawal of catheter. Sometimes IV medication, vagal maneuvers or cardioversion may be necessary to terminate these arrhythmias. Other than arrhythmias complications of cardiac catheterisation are: perforation of cardiac chambers, perforation of great vessels, bleeding, haematoma, aortic dissection, embolic phenomenon, etc.

Only children require GA for cardiac catheterisation. Children requiring cardiac catheterisation usually suffer from congenital heart disease and often present with cyanosis, dyspnoea, heart failure, etc. Congenital cardiac anomalies may vary from simple atrial septal defect to complex cardiac defects with shunts at various levels, as for example hypoplastic left heart syndrome with severe ventricular dysfunction etc. Paediatric patients may also have coexisting noncardiac congenital anomalies. So, only when an experienced cardiac anaesthetist is readily available, then it has now become the custom in many institutions to employ GA on children for cardiac catheterisation. During the procedure of cardiac catheterisation the aim of an anaesthetist is to maintain a steady circulatory state. This may require considerable preoperative preparation of patient in close conjunction with the cardiac physicians, surgeons and radiologists. Oxygen, digitalis and diuretic therapy together with the correction of electrolyte imbalance and acidosis should be carried out before cardiac catheterisation when possible. Some infants may be seriously ill and may present with cardiac failure as potential surgical emergencies.

During cardiac catheterisation an ideal anaesthetic technique (i) should not produce any myocardial depression, (ii) should avoid any hypertension / hypotension and tachycardia, (iii) must preserve

normal O_2 tension and maintain normocapnia (to avoid alterations in PVR) while maintaining respiration on air. Even in cyanotic patients, supplemental O_2 is not administered unless O_2 saturation falls below the baseline level. Spontaneous respiration with volatile anaesthetic agents may not be suitable for patients with significant myocardial disease. Controlled ventilation is essential using room air, as long as O_2 saturation does not fall below critical level. Controlled ventilation avoids the increase in P_aCO_2 which is frequently found in spontaneous respiration. As an alternative to volatile anaesthetic agents, patients can be managed with TIVA using various combination of opioids, midazolam, propofol and ketamine. During the procedure of cardiac catheterisation repeated blood gas analysis is essential, because the metabolic acidosis may be the initial sign of low cardiac output state due to myocardial depression. Even mild degrees of metabolic acidosis should be treated in critically ill patients by inotropic therapy. Initially, there was some reluctance in many centres for administering GA and this is because of the disturbances of the normal cardiopulmonary physiology during GA. Sudden cardiorespiratory failure may occur during cardiac catheterisation. Contrast medium in the coronary circulation may cause profound transient changes in the ECG. Therefore, continuous ECG and invasive arterial pressure monitoring should be used to allow rapid assessment of arrhythmias and hypotension for critically ill patients.

ANAESTHESIA FOR RADIOTHERAPY

The indications and the process of management of monitored anaesthetic care (MAC) or conscious sedation or GA for paediatric or adult group of patients for radiotherapy is same as CT and MRI. Radiotherapy in children is usually performed under GA. As the patient had received anaesthesia recently for a diagnostic procedure and then will require anaesthesia more than once for radiotherapy, so, halothane should be avoided. It is also, therefore, desirable to avoid repeated invasive procedures as far as possible and to keep the anaesthetic technique as simple as possible. During anaesthesia in radiotherapy, anaesthetist may be exposed to radiation repeatedly. So, proper precautions should be taken by anaesthetist.

The children usually undergo radiotherapy for variety of reasons, as for example Wilm's tumour, retinoblastoma, acute leukaemia, etc. The implications of radiotherapy on anaesthesia are: (i) as during radiotherapy high doses radiation (X-ray or any other) is administered by linear accelerator, so all staffs should remain outside the room leaving the anaesthetized patient alone. (ii) as radiotherapy needs repeated doses for several weeks, anaesthesia is also given repeatedly. (iii) the anaesthetised child must remain alone and motionless for a short period of time in the radiotherapy room. For that period clinical monitoring should continue and is observed by a close circuit television from the control room. (iv) as radiotherapy is arranged on an outpatient basis, recovery should be fast. (v) Patient's physical status may remain compromised before and it is due to malignant disease which has immense impact on general anaesthesia. (vi) Within the therapeutic radiology department there should have facilities and monitors that must satisfy or exceed the current standards promulgated by the ASA.

The actual process of radiotherapy is of very short duration, i.e. for only 30 to 60 sec. But considerable longer period of anaesthesia is required, i.e. for 20 to 30 minutes, because before treatment begins, the field which is to be irradiated is plotted and marked so that the X-ray can be accurately focussed on the marked radiation side without damaging the surrounding structures. During that period the child has to be remained motionless.

There is no pain in radiotherapy. So, the aim of anaesthesia for radiotherapy is only to keep the patient motionless for a few minutes. This can be achieved by oral sedation. But heavy oral sedation delays recovery time. Injection of ketamine, through IV or IM route is also helpful to keep the baby motionless, provided the patient does not have intracranial lesion. A need to increase the dose of ketamine gradually with successive radiation treatment (tachyphylaxis) may be observed. Intravenous propofol infusion can also be used satisfactorily for the children. Similarly, the increasing dose requirements have also been noted with propofol (tachyphylaxis).

If airway control is difficult during anaesthesia, then LMA can be instituted and anaesthesia can be given by a combination of N_2O, O_2 and volatile anaesthetic agents. In most of the cases LMA is sufficient and endotracheal intubation is rarely necessay. No analgesia is required and relatively light plane of anaesthesia is maintained which allows rapid emergence and recovery. Monitoring of the patient under GA during radiotherapy is only done by seeing the bag movement and by seeing the screens of different monitor through the close circuit camera from control room. A microphone can help to hear the sound of different monitors and also the saturation dictated by the pitch of pulse oximeter.

47 Neuromuscular and Muscular Diseases and Anaesthesia

INTRODUCTION

All the neuromuscular and muscular diseases usually manifest with some obvious clinical symptoms and signs which are mainly related to skeletal muscles. But many patients with some occult state of many of these disorders without any symptoms and signs may also be presented for anaesthesia and is very important to an anaesthetist because they may cause many complications during perioperative period. The most common neuromuscular diseases which an anaesthetist usually encounters during perioperative period are myasthemia gravis and Lambert-Eaton myasthenic syndrome (LEMS). They are presented in OT for treatment of these diseases or for surgical management of other disorders associated with these diseases. Other than neuromuscular diseases, the muscular diseases which are commonly encountered by an anaesthetist during perioperative period are initially divided under three broad headings such as: muscular dystrophies, myotonia and dyskalamic familial periodic paralysis, the subclassification of which will be discussed later.

All these neuromuscular and muscular diseases cause diminished muscle strength and increased sensitivity to neuromuscular blocking agent which predispose the patients to respiratory failure postoperatively. So, thorough understanding of all these neuromuscular and muscular disorders and their potential interactions with various anaesthetic agents is very crucial for an anaesthetist to avoid any morbidity and mortality of patients.

NEUROMUSCULAR DISEASES

Myasthenia Gravis

It is an acquired chronic autoimmune neuromuscular disorder and is characterised by weakness of different skeletal muscles due to the decrease in functioning of nicotinic ACh receptors at their motor end-plate caused by complement mediated destruction or inactivation of it by circulating antibodies which are formed against these receptors. However, the origin of these ACh receptor antibody is still unknown, but the thymus gland is suspected. This is due to the close association of the presence of thymus gland abnormalities with the disease of myasthenia gravis. This is because the muscle like cells (myoid cells) which also bear ACh receptors on their surface are present within the thymus gland and may serve as a source of autoantigen and trigger the autoimmune reaction within the thymus gland producing ACh receptor antibody. The antibody against the ACh receptors is not present in all the cases but found in 80 to 90% of patients with myasthenia gravis (Fig. 47.1).

Myasthenia gravis is not a rare disease, having a prevalance of atleast 1 out of 7500 general population. It affects individuals of all the age groups. But the women are affected more frequently and at early ages than men (3:2). So, the females are affected mainly in the second and third decades and males are affected mainly in fifth and sixth decades of life. Women with myasthenia gravis also experience increased muscular weakness in the last trimester of pregnancy and in the early postpartum period. The babies of myasthenic mothers may also show transient myasthenia for at least 1 to 3 weeks after delivery. This is due to the transplacental transfer of ACh receptors antibody, necessitating sometimes control ventilation in neonate. The disease myasthenia gravis usually runs in relapsing and remitting courses, especially during the early years of the onset of this disease. The Myasthenic patients also have an increased incidence of association with several other medical disorders. For example 10 to 20% of patients who are suffering from myasthenia gravis is associated with the presence of thymoma. Whereas 60 to 70% of patients with myasthenia develop thymic hyperplasia. The other autoimmune disorders which are also present in association with the myasthenia gravis in remaining 10% of patients are

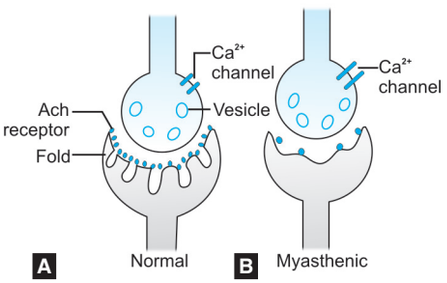


Fig. 47.1: Figure shows the normal A. and myasthenia gravis affected B. neuromuscular junction. In comparison to normal the myasthenic neuromuscular junction has shallow synaptic fold, few acetylcholine receptors and widened synaptic gap

rheumatoid arthritis, hypothyroidism, thyroiditis, Grave's disease, systemic lupus erythematosus, skin diseases, family history of autoimmune disorder, etc. Pernicious anaemia occurs more commonly in patients with myasthenia gravis than in those without that. The myasthenia gravis may also be more commonly associated with myocardiopathy and myocarditis which may result in atrial fibrillation and heart block (Table 47.1).

The cardinal features of myasthenia gravis are increased weakness and easy fatigability of skeletal muscles, but without any loss of tendon reflexes or any impairment of sensation or deficit of other neurological functions. The skeletal muscle strength is maintained at normal level in well rested patients and their atrophy is unlikely. These weakness and fatigability of skeletal muscles is characterised by its increaseness during repeated use and may improve following rest and sleep. The exacerbations and remissions of this muscular weakness usually occur particularly during the first few years after the onset of this disease. Then these remissions and exacerbations rarely occur and muscular weakness become a permanent.

The distribution of skeletal muscular weakness in myasthenia gravis has a characteristic pattern. The cranial muscles such as the muscles of lids and extraocular muscles are often involved most early. So, the ptosis and diplopia are the common initial manifestation of myasthenia gravis. Then difficulty in swallowing may occur and it is due to the result of weakness of the muscles of tongue, palate, pharynx larynx etc, giving rise to nasal regurgitation or aspiration of food, if the cough is ineffectual. This also causes dysarthria (difficulty in speak) and difficulty in clearing secretion from mouth, pharynx and larynx. Any limb muscle may be affected in this disease but it is often the proximal part of the upper limb such as shoulder girdle which is affected most commonly and may be asymetrical on both side. So, the patient is unable to work above the shoulder level such as combing of hair without taking frequent rest. Weakness of pharyngeal and laryngeal muscles during chewing and speaking is most noticeable after prolonged use as in chewing meat or delivery of continuous speech during teaching. If the respiratory muscles become very weak and requires respiratory assistance then the patient is said to be in myasthenic crisis. Infection, stress, electrolyte imbalance, pregnancy, surgery, etc, often cause exacerbation of this disease and may lead to myasthenic crisis. Some drugs such as aminoglycosides, penicillamine and ciprofloxacin usually exacerbate the neuromuscular blockade and should be avoided in patients with myasthenia gravis.

Table 47.1: Classification of myasthenia gravis

Class I	Weakness limited only to extraocular muscles.
Class IIA	Mild weakness to skeletal muscles other than extraocular muscles - mainly bulbar muscles. Respiratory muscles are spared.
Class IIB	Respiratory muscles are involved.
Class III	Moderate weakness of skeletal muscles with rapid deterioration.
Class IV	Acute onset or severe weakness of skeletal muscles. Tracheal intubation and ventilation may be needed.

The diagnosis of myasthenia gravis is suspected on the basis of the history of weakness and easy fatigability of the skeletal muscles in the typical distribution pattern described above. This suspician about diagnosis should always definitely be confirmed before the treatment of myasthenia gravis is undertaken. This is essential because: (i) other treatable conditions such as drugs, hyperthyroidism, Graves' disease, botulism, intracranial mass compressing cranial nerves, etc. may cause muscular weakness and closely resemble myasthenia gravis, (ii) the definite treatment of myasthenia gravis may involve surgery, and (iii) erroneously the prolonged use of drugs for the treatment myasthenia gravis has adverse side effects.

For clinical diagnosis of myasthenia gravis the IV injection of edrophonium (a short acting anticholinesterase whose onset of action is only 30 sec and duration of action is only 5 minutes) is taken as a very valuable diagnostic aid which is known as the Tensilon test. The whole procedure of this test is divided into two parts. In the first part 2 mg of edrophonium is given initially through IV route. Then if definite improvement (examinar should focus on one or more group of weak muscles and evaluate their strength objectively) of any muscle strength is occured, then the test is considered as positive and terminated. If there is no change, then the patient is again given additional 8 mg of edrophonium through IV route. This Tensilon test is divided in two parts, because maximum tests become positive by the initial small dose of edrophonium and does not need the 2nd large dose. Some patients react to this anticholinesterase by subsequent large doses with many adverse effects such as increased salivation, nausea, vomitting, diarrhoea, muscular fasciculation throughout the whole body and rarely syncope. So, the 2nd large dose is omitted if not needed and atropine (0.6 mg) should be given with edrophonium or be kept at hand for IV administration if these symptoms become troublesome.

Instead of edrophonium another long acting anticholinesterase agent such as neostigmine (1 mg) can also be used. However, the advantage of this long acting anticholinesterase is that it better permits more time for detailed evaluation of muscle power. Sometimes, false +ve test occurs with other neurological disorders such as amyotropic lateral sclerosis. Sometimes false-negative or equivocal result may also occur. In such circumstances neostigmine is more helpful than edrophonium by giving more time for evaluation of muscle power. However, virtually in all instances it is desirable to carryout further testing to establish the diagnosis of myasthenia gravis definitively by other investigations

such as EMG, estimation of ACh receptor antibody etc. Positive antiskeletal muscle antibodies suggest the presence of thymoma, but all patients should have a thoracic CT to exclude this condition which may not be visible on plain radiographic examination. Screening for other autoimmune disorders, particularly thyroid disease, is also important.

The principles of treatment of myasthenia gravis are: (i) to maximise the activity of ACh which acts as neurotransmitter on the remaining functional nicotinic ACh receptor at the motor end plate by reducing the activity of cholinesterase which destroys ACH by giving anticholinesterase, and (ii) to abolish or limit the immunological attack on ACh receptor at the motor end plate by surgical thymectomy, immunosuppression (corticosteroids, azathioprine, cyclosporine), and short term immunotherapy (plasma exchange, administration of immunoglobin). Among all these methods anticholinesterase is the first line of treatment for the mild to moderate cases of myasthenia gravis and for this pyridostigmine is the most widely used agent in the dose of 30 to 120 mg 6 hourly, producing an effect in 30 minute and peak effect in 120 minute. During the clinical use of anticholinesterase the muscarinic effect of pyridostigmine (or any anticholinesterase) such as excessive salivation, diarrhoeas, intestinal colic etc, is controlled by the subsequent use of propanthelin with pyridostigmine in the dose of 15 mg or as required. However, the dose and schedule of pyridostigmine should be tailored according to the patient's response, but the maximum dose rarely exceed 120 mg at the interval of every 3 hours. It produces fewer side effects than other anticholinesterase such as neostigmine and 60 mg oral pyridostigmine is equivalent to 2 mg of it through IM or IV route. Higher doses may precipitate cholinergic crisis by producing excessive muscarinic effect and muscular paralysis by blocking motor end plate. This cholinergic crisis is characterised by fasciculation, accentuation of skeletal muscular weakness or muscular paralysis, bradycardia, pallor, sweating, salivation, bronchospasm, miosis, etc. This should be distinguished from severe muscular weakness due to exaccerbation of myasthenia gravis (myasthenic crisis) by the clinical features and if necessary by the injection of a small dose of edrophonium (Table 47.2).

Although anticholinesterase make benefit most of the myasthenic patient, but their effects gradually wane after prolonged treatment and improvements become incomplete. So, thymectomy is the next alternative of the management of myasthenia gravis. But the actual mechanism of action of thymectomy (surgical removal of thymus) in the treatment of myasthenia gravis is still unknown. However there is definite improvement in clinical symptoms and there is decrease in the level of ACh receptor antibody, reducing the dose of immunosuppressive agents or completely eliminating the need for continuing medical treatment. It should be performed in the early stages of this disease leading to a better overall prognosis whether a thymoma is present or not. It should also be performed as soon as possible in any antibody positive patient with symptoms not only confined to the extra ocular muscles and unless the disease has been established for more than 7 years. Generally the myasthenic patients between the ages of puberty and about 50 years are the best candidates for the surgical removal of thymus.

Table 47.2: Diagnosis of myasthenia gravis

History
Weakness of muscle with characteristic distribution .
Ptosis and diplopia.
Fatigue of muscle due to repeated activity.
Muscle weakness improves by rest.
Effects of treatment.
Physical examination
Absence of other neurological defects.
Ptosis, diplopia.
Quantitative testing of muscle strength.
Forward arm abduction time (< 5 minuters)
Laboratory tests
1. *ACh receptor antibody*
If positive then diagnosis is confirmed,
80% positive in generalised myasthenia,
50% positive in ocular myasthenia,
Negative result does not exclude myasthenia.
2. *Tensilon test*
Highly probable of myasthenia if test is unequivocally positive.
3. *Repetitive nerve stimulation*
Decrement of 20% at 3 Hz highly probable of diagnosis.
4. *CT and MRI*
To exclude intracranial lesion.

Before thymectomy for the treatment of myasthenia gravis all the patients should always be prepared preoperatively to optimize the muscular strength, especially of the respiratory muscles. For example, if the patient's vital capacity is less than 2 litres, then plasmapheresis must be performed before surgery to improve the strength of the respiratory muscles. But the immunosuppressive drugs should not be continued (if started) before operation for the possible increased risk of postoperative infection. Endoscopic thymectomy through a small cervical incision is preferred than median strenotomy, because it is associated with smaller incision, less chance of infection and less postoperative pain. The benefit of thymectomy on the myasthenia gravis is not immediate and is typically delayed for months to years.

Immunosuppression by using glucocorticoids, azathioprine, cyclosporine and other immunosuppressive drugs are effective in nearly all patients with myasthenia gravis where the weakness of skeletal muscle is not adequately controlled by anticholinesterase. The choice of these drugs should be guided by their relative risks and benefits in individual patient. But corticosteroids are the most commonly used immunosuppressive agents for the treatment of myasthenia gravis. The improvement of muscle power by corticosteroid is commonly preceeded by marked exacerbations of myasthenic symptoms. So, the treatment should be initiated in hospital

and then is continued at home for months or years. They are also associated with the greatest likelihood of adverse side effects.

The indication for the use of immunoglobulins and plasmapheresis is more or less same, i.e. to produce rapid improvement for brief period during myasthenic crisis and to quickly prepare the patient before any surgery. But their mechanism of action is diferent. In plasmapheresis the antibodies are removed from the patient's circulation. Whereas the mechanism of action of immunoglobulins are not known, because it has no consistant effect on the measurable amount of circulating ACh receptor activity.

Anaesthetic Management

The patients with myasthenia gravis may present for thymectomy which is related to the treatment of this disease or other surgical procedures which are not related to the treatment of myasthenia gravis such as obstetric surgery, general surgery, urological surgery, etc. In all these cases the patient's medical condition mainly the muscular strength should be optimized prior to surgery. So, the myasthenic patients should carefully be evaluated preoperatively giving focus on the affected muscle groups, recent course of the disease, present history of drug therapy and other consisting illness. Patients with bulbar (pharynx, larynx, face, tongue, etc.) muscular and respiratory muscular involvement are at increased risk for postoperative respiratory complications and pulmonary aspiration. So, the proper preoperative preparation of myasthenic patients with immunoglobulins, plasmapheresis, metoclopramide and H_2 blocker may decrease these risks. During the preoperative preparation of myasthenic patients the continuation of anticholinesterase agents which was started before is controversial and should be individualized. The potential problems regarding the preoperative treatment of myasthenic patients by anticholinesterase include the possible drug interaction between it and the other anaesthetic agents mainly muscle relaxants (described later), increased vagal reflexes by anticholinesterase, and the possibility of disruption of bowel anastomosis due to hypersistalsis caused by anticholinesterase during bowel surgery. On the otherhand, patient's muscle power may deteriorate rapidly if the anticholinesterase agents are withheld preoperatively.

Patients with myasthenia gravis are very sensitive to the impairment of respiratory function during perioperative period and it is due to the respiratory muscular weakness or paralysis. So, drugs such as opioids, benzodiazepines, and other similar sedative agents should be used with caution as preoperative medication or is completely omitted if circumstances permits. It is already said that myasthenic patients are at increased risk for postoperative respiratory failure due to the muscular weakness or paralysis. So, the preoperative criteria that are predictive of the need for postoperative ventilatory support following transsternal thymectomy or any major surgery in myasthenic patients are: duration of disease for more than 6 years, the presence of some concomitant lung diseases, the dose of preoperative pyridostigmine is >750 mg/day, peak inspiratory pressure is >20 cm of H_2O, the preoperative vital capacity is < 4 ml/Kg. However, these criterias are less relevant to the endoscopic transcervical thymectomy, because these less invasive surgical procedures have a respiratory sparing effect.

Except thymectomy, in other surgical procedures where myasthenia gravis is present as coexistent disease epidural or spinal anaesthesia is preferred than GA because it avoids the potential problems of increased neuromuscular blocking effect with respiratory depression of muscle relaxant during postoperative period in GA. However, excessive high spinal level of motor blockade can also result in hypoventilation in RA and also should be avoided. During GA the induction in myasthenic patients is usually accomplished by all standard short acting IV anaesthetic agents but in small doses, keeping in mind that the relaxation effect of these inducing drugs on weak respiratory, laryngeal and pharyngeal muscles may be accentuated in such group of patients. Sometimes, tracheal intubation can also be performed without further addition of neuromuscular blocking agent in such patients by taking the advantage of muscular weakness of such disease, and the muscular relaxing effect of intravenous and volatile anaesthetic agents, used during induction. The only volatile anaesthetic agent based anaesthesia is usually sometimes satisfactory for intubation in some myasthenic patients. Because in myasthenic patients the deep anaesthesia produced by volatile anaesthetic agents provide sufficient muscle relaxation for tracheal intubation and intraoperative procedures. So, many anaesthetists try to avoid muscle relaxants and use only volatile anaesthetic agents in patients suffering from myasthenia gravis (Table 47.3).

The response of succinylcholine in myasthenic patients is unpredictable. The patients may show a relative resistance or higher sensitivity and a prolonged effect or an unusual phase II block in response to succinylcholine. The mechanism by which the myasthenic patients are resistant to succinylcholine are not known, but the reduced number of ACh receptor at the motor end plate may be the possible explanation of it. On the otherhand, the anticholinesterase agents such as pyridostigmine not only inhibits the true cholinesterase at the motor end plate, but also inhibits the plasma cholinesterase causing the possibility of higher sensitivity and prolonged effects of succinylcholine. In contrast to succinylcholine, the myasthenic patients always show the high sensitivity to nondepolarizing muscle relaxant and it is due to the decrease in total number of the functional ACh receptors. The balance between the number of functional and nonfunctional ACh receptors determine

Table 47.3: Comparison between myasthenia gravis and myasthenic syndrome

	Myasthenia gravis	*Myasthenic syndrome*
Gender	Myasthenia gravis Females > Males	Myasthenic syndrome Males > Females
Associated pathology	Thymoma, thymus hyperplasia	Small cell carcinoma of lungs
Manifestation	Ocular, bulbar, facial muscles are more commonly affected Arms > Legs Exercise worsens strength No muscle pain Tendon reflex normal	Not common Legs > Arms Exercise improves power Muscle pain Tendon reflex absent
Response to muscle relaxant	Resistant to succinylcholine Sensitive to nondepolarizing agent Good repsonse to anticholinesterase	Sensitive to succinylcholine Sensitive to nondepolarizing agent Poor response to anticholinesterase

the degree of sensitivity of myasthenic patients to the nondepolarizing muscle relaxing agnets. Sometimes the small dose of nondepolarizing agent desired to attenuate the succinylcholine induced fasciculations may produce adequate muscle relaxation for intubation. So, if nondepolarizing agents are required, then small doses of a relatively short acting agent such as cisatracurium and mivacurium are preferred. The potency of atracurium is increased two times in mild to moderate myasthenic patients compared to normal individual. As mivacurium is eliminated rapidly, so it can be titrated easily to achieve the desired level of muscular paralysis with confidence that this can be reversed predictably at the end of surgery. During the whole intraoperative period the neuromuscular blockade should be closely monitored by peripheral nerve stimulator and at the end of surgery the ventilatory function should carefully be evaluated prior to extubation and this is to avoid any postoperative pulmonary complications. Theoretically, the anticholinesterase drugs which are usually taken by the patients during preoperative period may antagonize and decrease the sensitivity of nondepolarizing agents. But practically this does not happen. Conversely, the preoperative corticosteroid therapy may produce resistance to neuromuscular blocking effect of nondepolarizing agents.

Monitoring of the neuromuscular blockade at the wrist or elbow by a peripheral nerve stimulator may over or underestimate the degree of neuromuscular blockade caused by muscle relaxant in patients with myasthenia gravis. So, it is better to monitor the neuromuscular blocking effect of a muscle relaxant at the orbicularis oculi muscle which is most commonly affected in myasthenic patient to avoid any complication. Intraoperative anaesthesia is usually maintained by N_2O and volatile anaesthetic agents which decrease the dose of muscle relaxants or completely eliminate the need for their use. However, if it is absolutely necessary to use the non depolarizing agents, then their initial dose should be reduced to atleast half or two third of the usual dose and the response is observed by nerve stimulator. At the end of surgery it is wise not to extubate, until the patient shows an adequate functional ability for ventilation. It is very interesting in myasthenic patients that the strength of the skeletal muscles often seem adequate during the early postoperative period, but only deteriorate a few hours later.

Lambert-Eaton Myasthenic Syndrome (LEMS)

There are other many conditions like myasthenia gravis which also present with muscle weakness due to transmission defect at the motor end plate. The most common of these is the LEMS which is also a autoimmune disease producing antibodies against the presynaptic voltage gated Ca^{2+} channels and reducing the quantal release of ACh at the motor end plate. This is in contrast to myasthenia gravis which is not due to the defect in quantitative release of ACh, but is due the defect in ACh receptor where the released ACh acts. In a high percentage of cases this condition is usually associated with an underlying malignancy, mainly the small cell carcinoma of lungs where these small carcinoma cells express the identical voltage gated Ca^{2+} channels, serving as a trigger antigen for the autoimmune response. Otherwise, LEMS is also seen with other occult cases of malignancy or as an idiopathic autoimmune disease. As it is an autoimmune disease, so LEMS is also associated with dry mouth, male impotence and other manifestations of autoimmune dysfunction. The cardinal differences (the other differences are tabled) between LEMS and myasthenia gravis are that in the former there is absence of tendon reflexes and the muscle weakness improves with repeated contraction. So, this condition is diagnosed electrophysiologically by the presence of post tetanic potentiation of motor response after stimulation of nerve fibre at the rate of 20 to 30 per second and the investigations are directed towards the detecton of underlying malignancy.

The 3,4, diaminopyridine (DAP) and guanidine hydrochloride are two drugs which increase the release of ACh. So, they can be used in LEMS to improve the muscle power. But the use of guanidine for the treatment of LEMS is limited due

to its hepatotoxic effect. So, the DAP is only used for the treatment of LEMS in most of the countries. Like myasthenia gravis the most patients with LEMS also improve with immunosuppression and/or plasmapheresis by decreasing the level of antibodies against the Ca^{2+} channel. The anticholinesterase agents which are effective in the management of myasthenia gravis do not produce any improvement of muscle strength in myasthenic syndrome. Unlike myasthenia gravis the patients with myasthenic syndrome are sensitive to both the succinylcholine and nondepolarizing neuromuscular blocking agents. So, the potential presence of undiagnosed myasthenic syndrome and the subsequent reduction of the dose of muscle relaxant always should be kept in mind during anaesthetic management of patients with known malignancies or during anaesthetic management of patients for diagnosis of malignancy by bronchoscopy, mediastinoscopy, exploratory thoracotomy for suspected lung cancer. The response of other anaesthetic drugs such as opioids, benzodiazepines, IV inducing agents and volatile anaesthetic agents etc., and intraoperative monitoring in myasthenic syndrome during anaesthetic management of it is similar to that of myasthenia gravis. The postoperative management of myasthenic syndrome is also similar to that of myasthenia gravis.

MUSCULAR DISEASES

Other than the disorders at neuromuscular junction, the skeletal muscles itself is also subjected to a range of disorders with limited spectrum of symptoms and signs. These are initally classified as muscular dystrophies, myotonias, and dyskalemic familial periodic paralysis. Muscular dystrophies are a heterogenous group of hereditary diseases of skeletal muscles. It is characterised by painless degeneration and atrophy of voluntary muscles. So, there is symmetrical progressive weakness and wasting of skeletal muscles but with intact sensation and reflexes, indicating normal skeletal muscle innervation. The main pathology of muscular dystrophy is increased permeability of muscle cell fibres, leading to necrosis, degeneration and fibrosis. The muscular dystrophy is again of different types and according to decreased frequency these are: Duchenne's muscular dystrophy, Becker's muscular dystrophy, myotonic dystrophy, Limb-Girdle dystrophy, fascioscapulohumeral dystrophy, etc.

Muscular Dystrophy

Duchenne's muscular dystrophy

It is also known as the pseudohypertrophic muscular dystrophy and is the most common form among others. It is caused by the mutation of gene which is responsible for producing normal dystrophin. Actually, dystrophin is a protein in nature and is localised to the inner surface of the sarcolemma of muscle fibre. With a glycoprotein molecule it forms a dystrophin glycoprotein complex which confers stability to the sarcolemma. In the absence of this dystrophin protein the sarcolemma of muscle cells or fibres becomes weak and more permeable, leading to tear and a cascade of events causing the death of muscle fibres and necrosis. This chain of events occur repeatedly during the whole life of a patient suffering from Duchenne muscular dystrophy.

The incidence of this type of muscular dystrophy varies between 2 and 3 per 10,000 life births. It is an X-linked recessive disorder. So, the males are affected almost exclusively and the females are usually become carrier. It is present from birth, but becomes apparent between 3 and 6 years of life when they fall frequently on the ground due to muscle weakness while playing with their friends. Running, jumping, hopping, and climbing up the stair are invaribly abnormal. By the age of 6 years this muscle weakness in the patients will become obvious and is characterised by using hands to climb up himself when a child tries to get up from floor (Gower's maneuver) after fall. In younger children the muscles, particularly of the calves are usually enlarged and it is due to true compensatory mascular hypertrophy due to over use. But later the affected muscles become apparently larger as a result of fatty infiltration and this accounts for the designation of this disorder as pseudohypertrophic. The involvement of legs in this disease is more frequent and severe than the arm. After that there is a steady deterioration of the strength of many other skeletal muscles and fixed contractures of joints are developed. By the age of 12 years, most of the patients are confined to a wheel chair and it is due to weakness of large group of muscles and contracture of many joints. Progressively, scoliosis and kyphoscoliosis are also often developed which may be associated with pain. This is due to the unopposed action of antagonistic group of muscles against the affected weak dystrophic groups of muscles in body. Thus, gradually the severe chest deformity associated with scoliosis is developed which impair the pulmonary function that is already previously diminished by muscle weakness. The skeletal muscle atrophy can also predispose to long bone fractures. In this disorder the intellectual impairment is also common, but generally nonprogressive. In patients with muscular dystrophy the degeneration of respiratory muscles also interfers the mechanism of effective coughing and thus causes retention of secretion and frequent pulmonary infection.

Then gradually by the age of years 20, patients are predisposed to serious and sometimes fatal pulmonary infection leading to death. Other causes of death in this muscular disorder include aspiration of food and acute gastric dilatation. The degenerative changes of cardiac muscles is also common in patients with muscular dystrophy. This results in dilated or hypertrophic cardiomyopathy. Mitral

regurgitation may also accompany with muscular dystrophy in 25% cases and this is due to the dysfunction of papillary muscles in ventricle. The characteristic ECG changes associated with muscular dystrophy are : short PR interval, tall R wave in V_1 and deep Q wave in periodical leads. Cardiac failure is also an important cause of death in patients suffering from this type of muscular dystrophy which usually occurs between 15 to 25 years of age.

The level of serum creatine phosphokinase (CK) are invariably elevated and reach between 10 and 100 times of the normal value. This reflects the increased permeability and necrosis of muscle fibres. The female carriers often also have high plasma CK levels though there is no manifestation of this disease. In affected male child the increased level of CK is found at birth. But it declines later with the progress of disease and it is due to the loss of muscle mass. EMG of patients suffering from this type of muscular dystropy demonstrates the features of typical myopathy. The diagnosis of Duchenne's muscular dystrophy is only confirmed by muscle biopsy showing necrosis, degeneration fibrosis and subsequently some regeneration of muscle fibres. The connective tissues replace the lost muscle fibres. The definite diagnosis of Duchenne muscular dystrophy can only be established on the basis of determination of the amount and alteration in the size of dystrophin molecule (present on the sarcolemma of muscle cell) by western blot analysis of muscle specimen taken for biopsy, or analysis of DNA on peripheral blood leucocytes showing deletion and duplication of dystrophin gene. Actually there is no treatment in this disease, but prednisolone in the dose of 0.5 to 1 mg/kg/day has been shown to delay significantly the progress of this disease. However, this is only for 2 to 3 years.

Becker's muscular dystrophy

Like Duchenne's muscular dystrophy, Beoker's muscular dystrophy is also a X-linked recessive disorder with almost same manifestations, but in less severe and delayed form. So, it is often also called as the benign form of the pseudohypertrophic muscular dystrophy. It is less frequent than Duchenne's and the incidence rate is about 3 per 1,00,000 male life births. Till recently it is not known whether these two diseases such as Duchenne's and Becker's muscular dystrophy are the genetically two distinct disorders or not. Like Duchenne's it is also thought to be due to point mutation or deletion of dystrophin gene which is located on the X-chromosome leading to defect in the production of dystrophin protein of sarcolemma of muscle fibre. But the amount of mutation and deletion varies.

The onset of symptoms in Becker's dystrophy occurs usually around 10 years of age, although it may delay to 3rd or 4th decade of life and progress very slowly. The proximal muscles, especially of the lower limbs are first involved and as the disease progresses the weakness spreads to other muscles and becomes more generalized. By definition the patient suffering from Becker muscular dystrophy can ambulate beyond the age of 15 which is not possible in Duchenne's and this is the clinical distinction between the Duchenne's and Becker's muscular dystrophy. Mental retardation may be seen in Becker's dystrophy, but is not as common and severe as in Duchenne's. Cardiac involvement may also occur in this type of dystrophy, leading to heart failure. Though the life expectancy in Becker's muscular dystrophy is reduced than normal, still the most patients reach the 4th or 5th decade of life and some may survive up to their 70s. During diagnosis of Becker's dystrophy the findings from the serum CK measurement, EMG, and muscle biopsy closely resemble with those of Duchenne's dystrophy. But the definite disgnosis of Becker's dystrophy requires western blot analysis of muscle tissue taken by biopsy demostrating dystrophin gene of reduced amount and abnormal size.

Limb-girdle muscular dystrophy

It represents a heterogenous group of more than one muscular disorders which are further classified by the analysis of the molecular genetics. In this type of group of dystrophy each disorder is slowly progressive and benign. The muscular weakness in this type of dystrophy affects both the male and female group of patients with onset varying from 2nd to 5th decades of life. Mainly the muscles of shoulder girdle or hip girdle or both are involved in this disease. So, it is named like that. The distribution of weakness of muscles and the rate of progress of this disease vary from family to family. The respiratory insufficiency from the weakness of diaphragm may occur. In some patients the involvement of cardiac muscle may also result in congestive heart failure or arrhythmia. Intellectual function remains usually normal in this type of muscular disorder. The plasma CK levels are usually elevated. The EMG findings and muscle biopsy represent the characteristic changes in limb girdle dystrophy.

Myotonic dystrophy (or Dystrophia myotonica)

It is the most common form of adult (not childhood) muscular dystrophy and is a multisystem disorder involving many organs other than muscles. The incidence of this disorder varies between 10 and 15 per 1,00,000 live births and both the males and females are affected. It is an autosomal transmitted disease and caused by the expansion of a trinucleotide repeat on chromosome 19. The diagnosis of this myotonic dystrophy is now possible by measuring this repeat.

The myotonic dystrophy usually manifests between the 2nd and 3rd decades of life. During the early stage of this disease process myotonia (slowing of relaxation after contraction of muscle, for example slow relaxation of hand grip following forced voluntary closure) but not weakness is the main manifestation. But as the disease progress the weakness and atrophy

of the muscles become more evident. This weakness and atrophy of the muscles usually affect the cranial group of muscle such as fascial, temporalis, masseter, etc, and result in the typical appearance of face which is known as the 'hatched face'. As opposed to the other muscular dystrophies the distal muscles are more involved than proximal muscles in myotonic dystrophy. So, the weakness of wrist extensors, finger extensors and intrinsic hand muscle impair the function of hand. The weakness of ankle dorsiflexor may cause foot drop. The involvement of the muscles of tongue, palate and pharynx produce dysarrthria of speech, nasal voice and swallowing problems. Some patients have weakness of diaphragm and intercostal muscles, resulting in respiratory in sufficiency. Congenital myotonic dystrophy is rare, and represents a more severe form of this disease and occurs approximately in 25% of infants of affected mothers. It is characterisd by severe fascial and bulbar weakness and neonatal respiratory insufficiency.

Cardiac disturbances occur in most of the patients with myotonic dystrophy. The ECG abnormalities include different types of conduction defects or heart block. Mitral valve prolapse occurs commonly in myotonic dystrophy patients. As in myotonic dystrophy the multiple organ or systems are affected, so it is associated with premature frontal baldness, presenile cataract, multiple endocrine dysfunction (such as thyroid, adrenal, pancreatic and gonadal insufficiency) decreased oesophageal and colonic motility, etc. Uterine atony can prolong labour and will increase the chance of retained placenta.

The diagnosis of myotonic dystrophy can usually be made on the basis of clinical findings. The serum CK level may be normal or mildly elevated. The evidence of myotonia in this type of muscular dystrophy by EMG will readily be found in most cases. Usually the severity of myotonia in patients suffering from myotonic dystrophy is mild and rarely warrant any treatment. But if the treatment is required then it is undertaken by membrane stabilizing agents such as phenytoin, quinidine or procainamide. Among these the phenytoin is the preferred agent, whereas the quinidine and procainamide has the cardiac adverse effects precipitating or worsening conduction defect. The insertion of cardiac pacemaker may be considered in some patients suffering from myotonic dystrophy with unexplained syncope or major conduction abnormalities with evidence of second degree heart block or trifascicular block with marked prolongation of PR interval.

Facioscapulohumeral dystrophy

It is an autosomal dominant disorder due to deletion of DNA in chromosome 4 at locus q35. It affects both the males and females and the incidence varies between 1 and 3 per 1,00,000 live births. The patients usually present with muscular weakness in the 2nd and 3rd decade of life and as the name signifies the weakness is confined primarily to the muscles of face and shoulder girdle. So, there is inability to smile, whistle, fully close the eyes or elevate the arms. The scapular winging becomes apparent with attempts to abduction or forward movement of arm. The muscles of lower limbs are rarely affected and the respiratory muscles are usually spared. Cardiac involvement is also rare in this disease. The serum CK level may be normal or mildly elevated. The EMG usually indicates myopathic pattern. The muscle biopsy also shows the features of myopathy.

Anaesthetic Management

Duchenne's and Becker's muscular dystrophy

The patients with these two diseases of muscular dystrophy usually come for anaesthesia to do muscle biopsy for diagnosis or for correction of progressive orthopaedic deformities caused by these two diseases or for other surgical causes unrelated to these muscular dystrophies. Unlike myasthenia gravis the anaesthetic management of patient associated with these two types of muscular dystrophies is complicated not only for the presence of muscle weakness and paralysis, but also for the presence of associated cardiopulmonary complications due to the presence of these diseases. In these group of patients the hypomotility of GI tract may delay gastric emptying. So, this GI hypomotility further in the presence of weak laryngeal reflexes and respiratory muscular weakness increases the risk of pulmonary aspiration. So, some definite preoperative and intraoperative measures should be taken to avoid this complications. Any sedative or opioid as preoperative medication should also be avoided due to the same reasons.

Succinylcholine should also be avoided in these group of patients and this is because of the fear of rhabdomyolysis, hyperkalaemia, malignant hyperthermia and subsequent cardiac arrest. In some patients sudden ventricular fibrillation leading to cardiac arrest during induction of anaesthesia and intubation using succinylcholine has been proved later to have these type of muscular dystrophies. Patients with these two types of muscular dystrophies also usually exibit higher sensitivity to the nondepolarising muscle relaxant. Malignant hyperthermia has also been observed in these group of patients when succinylcholine and volatile anaesthetic agents are administered. So, RA is always preferred for these group of patients to avoid these unique risks of GA related to these muscular dystrophies. The intraoperative monitoring during anaesthesia of these patients is directed to the early detection of malignant hyperthermia, hyperkalaemia, and cardiac arrhythmia. In the postoperative periods the need for temporary mechanical ventilation for these patients due to the weakness of respiratory muscles should always be kept in mind.

Myotonic dystrophy

The anaesthetic management of patients suffering from myotonic dystrophy

becomes frequently complicated and it is due to the commonly presence of patient's pulmonary and cardiac abnormalities and altered response of these patients to a number of anaesthetic medicines. It is presumed that the asymptomatic patients with myotonic dystrophy also have some degree of cardiomyopathy which may alter the course of anaesthesia. The patients of myotonic dystrophy become very sensitive to sedatives and opioids. So, any small doses of it can cause sudden and prolonged apnoea. Hence, these should be avoided (if possible) as premedicant and should be used in small doses during induction of anaesthesia. Succinylcholine is not used in these patients, because prolonged skeletal muscle contraction, triggered by it, may occur. So, the trismus and contraction of laryngeal muscles can prevent the opening of mouth and may make the intubation difficult. The rigidity of chestwall also may make the ventilation difficult or impossible. Conversely, the response of these myotonic dystrophic patients to nondepolarizing agents is normal. But reversal of neuromuscular blockade by neostigmine can aggravate the myotonia. This is due to the falicitation of depolarization at neuromuscular junction by anticholinesterase. Hence, short acting nondepolarizing agent not requiring reversal such as cisatracurium, mivacurium, etc. are preferred.

There is also a theoretical concern that these patients are susceptible to malignant hyperthermia. Intraoperative maintenance of body temperature and postoperative avoidence of shivering is important for these group of patient, because cold may induce myotonia. Although intraoperative high concentration of volatile anaesthetic agents may abolish myotonic contraction, but it is associated with postoperative shivering and myotonic contraction in postoperative room. In such situations small dose of meperidin can often prevent such shivering and perhaps the myotonic contraction. So, due to these above mentioned complications GA should be avoided in known myotonic dystrophic patients, if not absolutely indicated. Therefore, preoperative diagnosis of myotonic dystrophy is very vital to an anaesthetist. But patients with this disease may be undiagnosed before or he may not divulge intentionally the information preoperatively. Sometimes the diagnosis of myotonic dystrophy comes to light when the patient suffers from prolonged apnoea or myotonia after GA.

Myotonia

It is defined as a type of muscular disorder where tonic spasm of a single muscle or a group of muscles occur and it is probably due to the repeated depolarization of muscle cells or fibres causing contraction, stiffness and impaired relaxation of it. In this disease the skeletal muscles are only involved, but the other organ or systems are not affected like myotonic dystrophy. There is no cardiac involvement in this disease like muscular dystrophy. This disease of myotonia does not progress. So, it does not result in decreased life expectancy. However, in contrary the myotonic dystrophy (described before) is associated with myotonia and other systemic manifestations and muscle weakness. In myotonia there is usually no weakness of muscle, rather the muscles are very well developed due to constant muscular contraction.

In myotonia the contraction of muscles is painless. But still it disables the patients by interferring the movement of extremities and ambulation. In myotonia the stiffness of muscle is often exaggerated by cold, but is characteristically reduced by repeated muscular exercise. The flaccid muscular paralysis in myotonia may be produced by warming the muscles. The EMG is normal at room temperature, but typical myotonic discharges start when the muscles are cooled.

Principally, there are two types of myotonia such as myotonia congenita and paramyotonia congenita. The myotonia congenita is caused by mutation of gene on chromosome 7 at locus q35, resulting defects in function of chloride channel. It has both autosomal dominant and recessive variant. On the otherhand, the paramyotonia congenita is due to the defect of gene on chromosome 17 and is very rare autosomal dominant disorder. The defect of Na^+ channel is associated with this disease and is characterised by paradoxical myotonia, i.e. the myotonia which worsens with repeated muscular activity. So, it is named as paramyotonia congenita. In myotonia the stiffness or contraction of muscles are alleviated by quinine, phenytoin, or mexiletine. Other medications that have been used in the treatment of myotonia include prednisolone, dantrolene, tocainide, etc.

The anaesthetic management of myotonia is complicated by the abnormal responses of patients to the muscle relaxants. The nondepolarizing muscle relaxant paradoxically causes the generalised contraction of muscles such as trismus, contraction of vocal cord, etc, leading to difficult intubation and ventilation. Intraoperative hypothermia may also lead to muscular contraction in myotonia patients. This disease does not cause malignant hyperthermia. Infiltration of muscles with local anaesthetic solutions (diluted) at operative field reduces the myotonic contraction.

Dyskalaemic Familial Periodic Paralysis

It is a spectrum of muscular disorders characterised by the intermittent acute attack of weakness or paralysis of skeletal muscles of limbs. Pecuiliarly it does not affect the respiratory muscles including the cranial and thoracic musculature like muscular dystrophy. The attack usually lasts for few hours and frequent attacks may lead to progressive long-term muscular weakness in some patients. This weakness or paralysis of muscles are due to the loss of excitability of muscle fibres. This is again due to the incomplete depolarization of the resting muscle potential because of either

decrease in K^+ conductance or increase in Na^+ conductance due to the defect in channels of some ions such as Ca^{2+}, Na^+ or K^+ etc. However, both are associated with, fluid and electrolyte disturbances.

This whole spectrum of diseases is classified into primary genetic or congenital and secondary or acquired form. The primary genetic form of this dyskalaemic familial periodic paralysis is inherited as an autosomal dominant traits, but have a number of mozaic variants, resulting indifferent manifestations in different families. The genetic or inherited form is due to the mutation of gene responsible for the voltage gated Ca^{2+}, Na^+ or K^+ ion channels. The inherited defect in voltage gated Ca^{2+} channels is typically associated with low serum K^+ level during periodic attack of weakness or paralysis. On the otherhand the inherited defect in Na^+ channels is typically associated with increased serum K^+ level during the attack of periodic weakness or paralysis. So, both these defects result in hypokalaemia, hyperkalaemia or normokalaemia associated with non excitable muscle membrane causing weakness or paralysis of muscle. This spectrum of diseases is classified according to the clinical manifestations, but not according to the defect of ion channels. This is because it is useful as a guide to the prognosis and therapy, and defect in same channel can cause different clinical pictures and defect in different channels has same clinical picture.

Hypokalaemic form of familial periodic paralysis (Ca^{2+} channelopathy)

This disease is due to the defect of voltage gated Ca^{2+} ion channel and the mechanism of this disease is unrelated to the defect of ion channel at the neuromuscular junction. It is the most common form of familial periodic paralysis and is sometimes associated with hyperthyroidism. It may present at any decade of life between the childhood to adulthood and as the time progresses the frequency of attack increases, although it may subside at later life. The episodes of attack of weakness or paralysis of muscle are most common in the morning, lasting for 3 to 4 hours, but it may last for whole day. This episode of muscular weakness or paralysis is precipitated by heavy exercise or high carbohydrate diet and is characterised by low serum K^+ level. On the contrary the mild exercise actually prevents it. There may be ECG changes consistent with low serum K^+ level. The onset of unexpected skeletal muscular weakness at the postoperative period may suspect familial periodic hypokalaemic paralysis which is with or without additive action from the trailing effects of nondepolarising muscle relaxants used during anaesthesia and surgery. The diagnosis of this disease is usually made from patient's history, family history, EMG and ECG changes, etc. The weakness of skeletal muscle provoked by the infusion of glucose and insulin confirms the diagnosis of this type of familial hypokalaemic periodic paralysis. Barium blocks the K^+ channel. So, consumption of large amount of barium for any diagnostic purposes may precipitate this hypokalaemic familial periodic paralysis. The secondary acquired form of hypokalaemic paralysis caused by the loss of K^+ through kidney and GI tract may also develop and should not be confused with primary genetic cause. An acute attack of this disease is treated with 5 to 10 gm of potassium through oral route, but without glucose. This is because uptake of glucose by cells may increase hypokalaemia and weakness. During the treatment of this familial paralysis of periodic hypokalaemic form, the administration of K^+ through IV route is not recommended, because it may lead to sudden unwanted hyperkalaemia.

Anaesthetic considerations of this hypokalaemic periodic paralysis include the avoidence of factors which trigger the hypokalaemic attacks. These are heavy excercise, cold, heavy carbohydrate diet, etc. So, carbohydrate diet should be avoided 24 hours before surgery in the patients suffering from this disease. The drugs known to cause hypokalaemia by shifting K^+ into the cell such as β-blocker, insulin, etc. should also be avoided. The IV glucose infusion should also be avoided. As succinylcholine increases the serum K^+ level, so it is suitable for this group of patients. In patients with periodic weakness or paralysis, the response of nondepolarizing muscle relaxant is unpredictable. Therefore, the short acting nondepolarizing agents are preferred and the neuromuscular function should be carefully monitored by nerve stimulator. In the intraoperative period if diuresis is needed due to any cause, then K^+ losing diuresis should be avoided for the fear of hypokalaemia. Hence, infusion of mannitol is a better alternative. The RA can safely be applied on these patients.

Hyperkalaemic form of familial periodic paralysis (Na^+ channelopathy)

It is due to the defect of voltage gated Na^+ ion channel and the muscular weakness or paralysis is triggered by the abnormal activation of Na^+ channel with prolonged depolarisation like depolarising muscle relaxant (succinylcholine) which causes prolonged depolarisation at the motor end plate. So, Na^+ with water flow into the cells and K^+ comes out causing hyponatraemia, hyperkalaemia and haemoconcentration. It is manifested during the early childhood of life usually at the morning and these attacks are shorter and more frequent than the hypokalaemic one. The muscular weakness and paralysis is worse during rest after heavy exercise, but mild exercise prevents it. During periodic attacks the serum K^+ level rises above 5 to 6 mEq/L. But remains normal inbetween the attacks. Hypothermia, hypoglycaemia, glucocorticoids, pregnancy, etc, aggravates this condition. The diagnosis of this disease is usually made from patient's history, family history, serum K^+ level during attack, EMG, etc. The skeletal muscle weakness in response to oral administration of K^+

confirms the presence of hyperkalaemic form of periodic paralysis.

The anaesthetic management of hyperkalaemic periodic paralysis includes the avoidance of factors which increase the hyperkalaemic attacks or to take the measures which will decrease the serum K^+ level. So, perioperative voluntary K^+ depletion by frusemide induced diuresis is very important and succinylcholine is contraindicated as it is associated with hyperkalaemia. The potassium containing solutions or the potassium releasing drugs should always be avoided in the perioperative period during anaesthetic management of such patients. Carbohydrate depletion during fasting should be managed by glucose containing IVsolutions. Frequent monitoring of serum concentration of K^+ is indicated during perioperative course of anaesthesia. Careful ECG monitoring is indicated to detect cardiac arrhythmias associated with hyperkalaemia. Hypothermia and shivering trigger the hyperkalaemia. So, the maintenance of body temperature during perioperative period is very important.

48 Malignant Hyperthermia

INTRODUCTION

The term malignant hyperthermia (MH) refers to a clinical syndrome which is characterised by rapidly increasing temperature (as great as 1°C/ 5min), ↑cellular metabolism, ↑O_2 consumption, ↑CO_2 production, metabolic and respiratory acidosis, ↑lactate production, muscular rigidity, ↑sympathetic activity and high mortality. This results from the acute uncontrolled increase in skeletal muscle metabolism that may proceed to severe rhabdomyolysis. It is also defined as a pharmacogenetic disease because the susceptile patients have a genetic predisposition for the development of this syndrome and is not manifested until they are exposed to some triggering pharmacological agents such as mainly the volatile anaesthetic agents and succinylcholine (SCh). There are also many other pharmacological agents which trigger this syndrome.It is also an example of subclinical myopathy that becomes unmasked after exposure to the triggering factors.

There is no doubt that this syndrome had been responsible for many anaesthetic deaths from the middle of the 19th century to the middle of the 20th century since the introduction of ether, chloroform and succinylcholine. But during that period nobody knew about this syndrome. Among these incidences the few remarkable examples are: between 1915 and 1925 one family experienced three anaesthetic deaths from MH featuring muscular rigidity and hyperpyrexia. In 1960 Denborough and Lovell described a 21-year-old Australian who was suffering from an open leg fracture and was more anxious about anaesthesia than surgery, because 10 of his relatives had died due to anaesthesia before. This had given a very good description of anaesthetic reaction leading to death and its inheritance as an autosomal dominant character. Later, this anaesthetic reaction was described as malignant hyperthermia (MH). However, actually the genetic inheritance of MH which has been confirmed recently is more complex than this simple straight forward autosomal dominant veriety. It may be autosomal recessive, multifactorial or unclassified.

In 1966, Wilson first used the term malignant hyperthermia in his book. In the past death related to anaesthesia was not uncommon and the causes of these deaths were multiple including MH. So, this relatively rare cause of death only due to MH during anaesthesia was not given any importance and was not recognised. But, after that as the anaesthesia has become progressively safer, so the high mortality due to MH have become more and more significant. During earlier period the mortality rate due to MH was 70 to 80%. But with earlier diagnosis, increased awareness among anaesthetist, and improvement in monitoring this mortality rate due to MH had dropped significantly to 25%. Then in 1979 with the advent of dandrolene this mortality rate due to MH has further dropped to 5%. When the volatile agents and SCh are considered as the principal cause, then the overall estimated incidence of MH in UK population is approximateley 1 in 8000.

Aetiology

Normally, during muscular contraction the wave of depolarisation moves from the end plate of muscle fibre to the sarcoplasmic reticulum (SR) within the cell through the T-tubules of sarcolemma. At the end of these T-tubules which come in contact with the SR possesses voltage gated Ca^{2+} channel of type I. These are labelled as dihydropyridine receptors (DHPR). Through these Ca^{2+} channels or DHPR small amount of Ca^{2+} ions first enter into the muscle cell from ECF in response to the T-tubular depolarisation. The end of the SR which come in contact with T-tubules also contain ryanodine receptors (RYR). These are also known as the Ca^{2+} efflux channel or foot plate protein and connect between the DHPR of T tubules and SR. With the wave of depolarisation and intracellular entry of small amount of Ca^{2+} from ECF through DHPR, these receptors of T-tubules (i.e. DHPR) make coupling with the RYR of SR and transfers the wave of depolarisation from T-tubules to SR, resulting in the release of huge amount of Ca^{2+} from SR. Thus, the free ionised intracellular Ca^{2+} level within the muscle cell fibre rises from 10^{-7} M to about $10^{-5} \times 5$ M due to depolarisation of SR. Then this increase in intracellular Ca^{2+} removes the inhibition of troponin from the contractile elements of muscle cell causing muscular contraction. After that when contraction of muscle is over then the multiple intracellular Ca^{2+} pumps situated on SR and mitochondria rapidly transfers the free intracellular Ca^{2+} back into the SR causing relaxation. This increased intracellular concentration

of Ca^{2+} also stimulates multiple intracellular function such as ↑ metabolism, ↑ heat production, ↑ enzyme secretion, ↑ hormone secretion, etc.

Now, there is general agreement that the MH is due to the defect or abnormal properties of these RYR (Ryanodine receptor) causing increased release of intracellular Ca^{2+} from SR leading to intense contracture of muscles and marked increase in intracellular metabolism. It is very well known that Ca^{2+} is an important ion controlling different functions of cell. So the loss of this haemostasis of Ca^{2+} causes many abnormal metabolism with in the cells which depend not only on the RYR but on the other organelle of cells such as T-tubules, DHPR, inositol phosphate, oxidation – reduction activity, etc. So, this explains why different chemical agents such as SCh, halothane, etc, trigger the same MH and there is strong evidence of heterogeneity of this syndrome (Fact file-I).

Genetics

Ryanodine receptor (RYR) is the largest known receptor in our body and is four to five times larger than the ACh receptor. In MH the properties of these RYR is altered due to the genetic mutation and these alterations include: increased rate of Ca^{2+} release from SR, changes in the patterns of binding of RYR with DHPR and the effects of Ca^{2+} on this binding and the increased sensitivity of RYR to caffiene which is also known to cause the increased release of Ca^{2+} from SR. It proves that the muscles of an individual susceptible to MH are more sensitive to caffiene.

Ryanodine is a toxic plant alkaloid. It was first extracted by Rogers and his co-workers from a plant named Ryania Speciosa Vahl. It acts on these RYR (from where these receptors get this name) and has profound poisonous effect producing rigidity of skeletal muscle. Later, it was purified and radiolabelled and extensively used in the research of MH. The research to establish the relationship between the RYR gene and MH gets its fuel with the subsequent identification of link between the mutation of RYR gene and MH. There are three forms of RYR (such as RYR_1, RYR_2, RYR_3) and for these three forms of RYR there are three types of genes. But among these only the mutation of RYR_1 gene have been linked to the MH. The gene of RYR responsible for MH is located on human chromosome 19, which is also the genetic coding site of the Ca^{2+} release channel of SR.

At the beginning of research on MH the identification of Hal genes in pig which is responsible for the similar MH syndrome in pig (but not identical and is known as the porcine stress syndrome) is the first step. Then subsequently the identification and localisation of RYR_1 genes on human chromosome 19 at q13-13·2 position and transportation of Hal gene at that place had stimulated intense research of this subject. Gradually, it was found that the gene responsible for MH is not only situated on chromosome 19, but is also situated on the chromosome 1 and 7 and also possibly 3, 5, 17. These many genes are also responsible for the various subunits of DHPR which forms the triadic junction complex with the RYR at the SR. Over the next past 20 years with the revolution in the technique of molecular biology, it has also been possible to study the susceptibility of a family to MH using DNA markers of known chromosomal location.

In swine a single genetic mutation of RYR gene is responsible for all the cases of MH. But in human a series of different mutations or even a lack of any mutation of this RYR gene indicates the heterogenous character of genetic basis of human MH.

Clinical Features

The onset of clinical features of this MH syndrome may be acute and rapid when volatile anaesthetic agents and / or SCh are used in full doses or may be delayed and show for several hours when the inhalational agents have been used in low concentration to prevent the only patients's awareness during anaesthesia and not become evident until the patient enters the recovery room. But once the reaction or pathology of MH is initiated, then the next course of it cannot be stopped by the discontinuation of triggering factors and will must progress to a full blown picture. However, the reaction of MH does never start after the discontinuation of triggering factors.

The affected person had undergone tremendous increase in muscle rigidity and cellular metabolism after the onset of MH due to exposure to volatile anaesthetic agents and/or SCh. This leads to intense production of heat (body temperature may exceed 108°F), increased production of CO_2 (P_aCO_2 may exceed 100 mm Hg) and increased plasma lactate level. This causes metabolic and respiratory acidosis and altered acid base balance. So, the plasma pH may be less than 7. The increase in temperature is the cardinal feature of MH, because muscle is the pathological site of this disease which constitute 40 to 45% of total body weight. Another important feature of MH is MMS (masseter muscle spasm) or whole body muscle rigidity. Associated with this muscular rigidity there is also increased permeability of muscle cell membrane causing increased level of serum K^+, CK and serum myoglobin, leading to hyperkalaemia and myoglobinuria.

FACT FILE - I

MH susceptible skeletal muscle differs from normal muscle in that it is always closer to the loss of control of Ca^{2+} concentration within the muscle fibre. It also involves a generalised alteration in cellular or subcellular membrane permeability. This is an excitation contraction (EC) coupling defect resulting from alteration in the ryanodine receptor (RYR) encoded by gene. It is a heterogenous disorder having 30 mutations in RYR-1 gene. Evaluation of affected families is guided by the measurements of circulating CK, *in vitro* drug induced contracture test and genetic testing of DNA samples.

Sometimes moderate to severe form of rhabdomyolysis may also occur during an acute episode of MH. But milder form of it occurs more often than realised and it would have to kept in an anaesthetist's mind. Due to the false indentification of myoglobin for haemoglobin, the myoglobinuria can be misdiagnosed as haemolysis when a massive shift of fluid occur during an episode of MH.

In exception to other muscles of body, the only masseter and lateral pterygoid muscles contain the slow tonic fibres. So, they sometimes response abnormally to SCh with contracture or spasm when other muscles become flaccid. This abnormal response of masseter muscle may or may not be a part of the MH syndrome. It may occur isolatedly. This spasm of jaw muscles cannot be altered by pretreatment with defasciculating dose of non-depolarising muscle relaxant. It can be graded as tight jaw, rigid jaw and very rigid jaw. When spasm of these jaw muscles is very severe which is designated as 'very rigid jaw' (impossible to open mouth) and especially prolonged then this condition is designated as a separate syndrome named masseter muscle spasm (MMS), and greatly increases the risk of MH (Fact file- II).

This MMS or severe form of masseter spasm caused by SCh is entirely considered as pathological and its causes may include MH, myotonia, or other pathological situations. In the absense of family history the first indication of susceptibility of an individual to MH is this exaggerated response of masseter muscle to a depolarising muscle relaxing agent. When this MMS is associated with rigidity of other body muscles, then the chance of MH is absolute. In such circumstances anaesthesia should be stopped immediately and the treatment for MH should be started.

When the MMS is appeared alone without other manifestations, then the chance of MH is 30%. But when it is associated with the rigidity and damage of other muscles which is evidenced by increased plasma level of CK and myoglobinuria, then this chance of MH associated with MMS is increased to 70 to 80%. The true response of jaw muscles to SCh in MH as opposed to the only exaggerated response of rigidity of jaw muscles to SCh is that the former is associated with metabolic stimulation and the consequences of the loss of sarcolemmal integrity leading to hyperkalaemia and myoglobinaemia. When the clinical signs of MH such as ↑ $ETCO_2$, tachycardia, ↑muscle rigidity, ↑ temperature suggest this syndrome, then the diagnosis of MH is not strong unless more than one abnormal sign is noted. When there is a single suggestive adverse sign, then the diagnosis is usually not MH. If the patient suffering from MH is carefully monitored during the perioperative petriod, then one or more abnormalities will always be detected. A postoperative pyrexia occurring after a normal intraoperative and immediate postoperative period is not always an indication of MH.

Other than MMS increased sympathetic activity due to increased cellular metabolism may frequently be the first sign of MH. This increased sympathetic activity causes tachycardia, sweating, hypertension, tachypnoea, hypoxia, etc. With metabolic exhaustion the cellular permeability may also increase in MH. It may cause generalized oedema including cerebral oedema. As MH progresses to DIC (due to cellular destruction), so cardiac failure and renal failure may also develop. Hyperkalaemia due to increased cellular permeability and acidosis may also cause cardiac arrhythmia, even asystole.

FACT FILE - II

Evaluation of affected families is guided by the measurement of circulating creatine phosphokinase and subsequently by the analysis of drug induced (caffeine, halothane) contracture in muscle biopsy specimen in laboratory. The measurement of plasma creatine phosphokinase (CK) also provides a basic screening test for MH, because it reflects the stability of muscle cell membrane which is distributed in MH. It is elevated to 70 to 80% in affected people. When the plasma CK value is elevated in a close relative of a susceptible person, then this relative is also considered as susceptible to MH, and requiring contracture testing. On the otherhand, the CK value remains normal in the susceptible patients on several occasions. In the same way isolated CK elevations in normal asymptomatic individual are seldom associated with positive contracture test. So, in such circumstances it has no predictable value and muscle biopsy is necessary for contracture study. The contracture study also becomes positive in patients who are suffering from myopathies and not related to MH in any way. Dantrolene should not be given to patient before muscle biopsy, because it may mask the contracture test.

Diagnosis

In the absence of specific drug such as dandrolene the treatment of MH is difficult. But the diagnosis of it during intraoperative period (however not in postoperative period) is more difficult than its treatment. This is becasue the MH is a disorder of cellular metabolism and so the early signs and symptoms of it are masked or subtle during the course of anaesthesia. The diagnosis of MH is also difficult, because the onset of it may sometimes be delayed until the patient is recovered from anaesthesia. During the course of anaesthesia the effects of different anaesthetic drugs on different systems of body may also complicate and confuse the signs of MH and make the diagnosis of it difficult. When the hyperthermia is taken as the important diagnostic point, then this syndrome of MH should also be differentiated from other disorders which have same manifestations such as hyperthermia and increased muscular nigidity and confuse the diagnosis of MH. These include: heat stroke, preoperative atropine, septicaemia, hyperthyroidism, pheochromocytoma, neuroleptic malignant syndrome, pontine haemorrhage, etc. However, the differentiating point is that these above mentioned disorders confusing the diagnosis of MH are not associated with the other clinical and laboratory evidence of MH.

The most important point for the intraoperative diagnosis of MH is the measurement of $ETCO_2$ tension at the constant rate of ventilation. This is because if

ventilation is increased with the increase of $ETCO_2$ tension, then the $ETCO_2$ tension will remain same and the diagnosis of MH will be masked and delayed. However, the other causes increasing the tension of $ETCO_2$ should also be ruled out such as stuck valve, exhausted soda lime, inadequate fresh gas flow, inappropriate breathing circuit, etc. In general MH is not expected in any patient when GA is administered with the help of barbiturates, propofol, N_2O, opiates, benzodiazepines and non-depolarising muscle relaxants. On the other hand, when GA is administered with the help of volatile anaesthetic agents and depolarising agent such as SCh, then the chance of occurrence of MH should always be kept in mind of an anaesthetist and will start to suspect it when the patient will develop undue tachycardia, tachypnoea, increased body temperature, cyanosis, arrhythmia, rigidity of muscle, sweating, molting of skin, etc. Then the diagnosis of MH should be confirmed by the subsequent evaluation of serum pH, hyperkalaemia, arterial blood gases, myoglobinuria, etc.

For the diagnosis of MH, the level of O_2 and CO_2 tension in arterial blood is less important than that of the central venous blood as it is the disease of increased cellular metabolism, and the $ETCO_2$ and central venous CO_2 level are the more accurate reflection of whole body CO_2 stores. In normal condition the level of CO_2 in venous blood is only 5 mm Hg higher than the arterial blood. But in MH this difference will exceed this normal value. The upper limit of the venous PCO_2 and PO_2 is suggested as 55 mm Hg and 35 mm of Hg respectively, provided the arterial PO_2 is higher than 100 mm Hg. If venous PCO_2 is > 60 mm Hg and base deficit is > −5 to −7 mEq/L, then the diagnosis of MH is confirmed. So, from this above discussion it is found that the most important monitoring devices for the early detection of MH are capnography, pulse oximeter, blood gas analysis and ECG. But the most appropriate prerequisite for early diagnosis of MH is an appropriate suspecious mind of an anaesthetist.

Triggering Factors and Diagnosis of Susceptibility

There are many factors which trigger the onset of MH in human being. But, among these the volatile anaesthetic agents and depolarising agent such as SCh are the prime triggering agents. Again, among the volatile anaesthetic agents the halothane is the most potent, while the desflurane and sevoflurane are the less potent triggering agent, causing gradual onset of MH. The onset of MH may be explosive, if SCh is concomitantly used with volatile anaesthetic agents and muscular rigidity is developed within 5 minutes. The response of susceptible patients to the triggering agents such as SCh may be different. It may be only muscular contracture or only increased permeability of muscle cells causing hyperkalaemia and myoglobinuria or increased cellular metabolism in association with the muscular contracture and increased permeability. It is most unlikely that N_2O acts as a triggering factor, because previously it has been used safely and repeatedly in a susceptible individual patient without any evidence of MH. The non-depolarising muscle relaxant is not a triggering agent for MH. Rather they block or at least attentuate the effects of SCh and volatile anaesthetic agents cause MH. Propofol is not a triggering factor for MH. On the other hand, it stabilises the cell membrane of MH affected muscle cells and has opposite effects to those of volatile anaesthetic agents. Like propofol, the other intravenous anaesthetic agents such as thiopentone, benzodiazepines, opioids, ketamine also have no triggering effect causing MH. Previously, it was believed that the amide group of local anaesthetic agents such as lignocaine and others also may trigger MH. But later it was proved that they are safe for patients who are susceptible to MH (Table 48.1).

The predictability of the onset of MH in susceptible persons are not always correct. Because many affected persons have previously experienced the exposure to the triggering factors without the onset of MH. So, from this history, we can not say that this patient is not susceptible to MH during the present course of anaesthesia. On the other hand, many patients suffer from MH during anaesthesia without any exposure to known triggeirng factors. So, from this history, we also always cannot product which patient will develop MH even if triggering agents are not used. All these events dictate that the exact mechanism of triggering of MH by factors during anaesthesia is still unresolved. Recently, two *in vitro* tests were described to diagnose the preanaesthetic susceptibility of an individual to MH. These are the open muscle biopsy and the exposure of some strips of living muscles to halothane and caffeine, producing abnormal contracture response to these two agents. This later test is also known as the *in vitro*

Table 48.1: Classification of drugs according to their potentiality for triggering MH

Unsafe	*Safe*	*Probably safe*
All volatile anaesthetic agents	Benzodiazepines	Tricyclic antidepressants
Succinylcholine	Propofol	Monoamine oxidase inhibitors
Decamethonium	Ketamine, opiates	Phenothiazines
	Barbiturates	Haloperidol
	Metoclopramide	
	Atrope, glycopyrrolate	
	Non-depolarising muscle relaxants	
	All local anaesthetics	
	Epinephrine, norepinephrine	
	Nitrous oxide	
	Neostigmine	

contracture test (IVCT) and offers 93% specificity and 99% sensitivity. This IVCT test is not offered to children who are below 10 years of age as screening for susceptibility to MH. Because in children this test may yield more false negative result. After a patient is diagnosed as susceptible to MH syndrome by IVCT, then a DNA testing for mutations from muscle biopsy should follow. If one is detected as positive, then the other relatives of this person with that mutation are considered to have susceptibility to MH syndrome and do not need IVCT. The result of the use of DNA screening test from biopsied muscle for the diagnosis of susceptibility to MH is not always straight forward. This is due to the marked heterogeneity and the lack of orderly mutations in many families. However, all these tests to diagnose the susceptibility to MH is invasive and destructive. So, recently the noninvasive nuclear magnetic resonance test probably has the greatest promise to diagnose the susceptibility. There are also many diseases which make the individual more susceptible to MH. Among these the myopathies are most important. For example, Duchenne muscular dystrophy may result in an episode of MH after exposure to any triggering factors despite normal contracture testing. Patients with occult myopathies of any type may also have the potentiality to develop rapidly this disastrous anaesthetic event. Other muscular disorders that have inconsistent association with MH include myotonia, neuroleptic malignant syndrome (NMS), sudden infant death syndrome (SIDS), etc (Fact file- III).

All the patients who are suspected to develop MH are referred to higher medical centres which are recognized to tackle this type of patients for anaesthesia and surgery. Because due to any reason the surgery should not be denied to these group of patients only for the fear of uncapability to manage a case of MH if it develops. The key to safe anaesthesia for this type of patient is to avoid the use of triggering factors, mainly SCh and volatile anaesthetic agents. So, the regional anaesthesia is the best option to these individuals who are susceptible to MH as local anaesthetic agents do not trigger it. If GA is required, then it is best provided by barbiturates, propofol, benzodiasepine, N_2O, opiates and non-depolarising muscle relaxant only. Hence, the routine use of TIVA to deliver GA in these patients who are susceptible to MH is more straight forward. However, when a patient who is susceptible to MH is presented with difficult airway, then they are truly exposed to greater risk. This is because in such circumstances either an rapid sequence intubation by SCh or inhalation technique for tubation by volatile anaesthetic agents (due to the fear of failed intubation and failed ventilation if mondepolarizing muscle relaxants is used) cannot be used.

FACT FILE - III

The muscular rigidity which occurs during the onset of MH and is known as contracture is not the normal contraction of it which is the usual form of muscle movement. The process of muscular contraction is reversible, brief and is due to a propagated wave of depolarisation. On the otherhand, the process of contracture is irreversible, nonpropagated and prolonged. In laboratory the degree of contracture of cut muscle fibres in tissue both are used to study the various aspects of MH under the strict guidance of European or North American protocol with different concentration of caffeine and halothane which vary between this protocol.

Theoretically to deliver general anaesthesia on a MH susceptible patient, a dedicated vapour free anaesthetic machine is ideal. But if this is not available, then both the machine and the ventilator is made ready to use for these susceptible patients by removing all the vapourisers from machine and flusing the ventilator with maximum flow of O_2 for at least 30 minutes. As volatile anaesthetic agents are absorbed by the rubber or plastic, so new breathing circuit and face mask should be used mandetarily. If all these preventive measures are taken meticulously and all the well known triggering factors are avoided, then the prophylactic use of dandrolene to avoid the onset of MH is not recommended or required.

Treatment

The keypoint of the treatment of MH after its development is the immediate discontinuation of all the triggering factors as soon as it is diagnosed or suspected. This can be accomplished by quick turning off the vaporiser, and by quick and total eliminating of all volatile anaesthetic agents from the body of patient by hyperventilation and by changing the anaesthetic circuit. If the episode of MH is diagnosed as a fulminate one (venous PCO_2 above 90 mm Hg, base defect less than 5 mEq/L and the rate of increase of temperature 1°C/15 min) then an aggressive therapy should be started immediately to save the life of patient.

Dantrolene is the specific drug for the treatment of MH. It rapidly halts the increase in cellular metabolism and return back the level of catecholamine and K^+ to normal. The dantrolene acts by inhibiting the release of Ca^{2+} from SR, but does not affect the uptake of it by SR and mitochondria. The site of action of dantrolene is at the level of DHPR and interrupt the transmission of impulses from DHPR to RYR. Thus, it decreases the resting level of intracellular Ca^{2+}. In the past it was used in neuromuscular disorders with better results which are due to the increased intracellular Ca^{2+} level from any cause. Then this gives the idea of using dantrolene in MH. It is used in the dose of 2 mg/kg through intravenous route and in fulminate case this dose may be repeated after every 5 minutes up to the maximum dose of 10 mg/kg.

Dantrolene is available now as orange coloured powder in vial. Each vial of it contains 20 mg dantrolene sodium, 3 gm mannitol and NaOH. It is reconstituted prior to the use by mixing it with 60 ml of water. The pH of this preparation is 9 to 10 and this is due to the presence of NaOH.

The high pH of this reconstituted solution (or high alkalinity) helps the dantrolene to dissolve in water. The mannitol is added in this preparation to make the solution isotonic. It is not dissolved by 5% Dextrose solution, because it may lead to salting out effect with greater difficulty in dissolving. If it does not dissolve immediately into water producing a clear yellow to yellow orange colour solution, then it should be heated under tap water or autoclaved for few minutes. During extreme emergency it can be administered through the filter of blood transfusion set without worrying about the crystals of dantrolene. In some fulminant cases of MH the cardiac output falls rapidly. So, it should be given while adequate cardiac output and muscle perfusion is still present. The half-life of dantrolene is 10 to 15 hours. So, it can be repeated after every 10 to 15 hours for several doses. If there is no recurrence of MH, it can be then discontinued.

Though the administration of dantrolene is the key to therapy of MH, but, still the use of other symptomatic therapy to control the body temperature, acid-base balance and renal perfusion etc. which are developed with the onset of MH is also very important. But during this symptomatic therapy of MH an anaesthetist should always keep a notion in his mind that this supportive therapy will not be able to stop the uncontrolled increased metabolism mayhem within the muscle cells or the actual pathology of MH. So, he or she will not be much preoccupied or busy with such supporting symptomatic works neglecting the prime factor in therapy. Hence, active cooling is not a prominant feature. Usually, hyperthermia is tried to control by applying ice sponging all over the whole body and putting ice pack over the axilla and groin, IV infusion of refrigerated crystalloid solution, peritoneal lavage with sterile iced fluids and in extreme cases blood heat exchanger with pump oxygenerator, where this facility is available. The cooling of body only prevents the potentially harmful effect of hyperthermia on other cellular function but it does not stop the pathology of hyperthermia. During cooling it will also have to keep in mind that cooling causes peripheral vasoconstriction which prevents further heat loss and may produce sudden inadvertent hypothermia. So, the cooling should be halted when the body temperature comes down to 38° to 39°C. In such circumstances adequate intravascular fluid load is only the answer. IV methylprednisolone in the dose of 10 mg/kg is also effective vasodilator and has been shown to reduce the muscular contracture (Fact file- IV).

After the discontinuation of volatile anaesthetic agent (if only it is used and the patient develops MH) the patient should be hyperventilated with 100% O_2. This will help to increase the elimination of volatile anaesthetic agents from the patient's body, and compensate the metabolic acidosis. With increased aerobic metabolism within the cell during episode of MH, the CO_2 production will also be increased. This is because of the neutralisation of fixed or noncarbonic acid produced during intracellular metabolism by plasma bicarbonate. Thus, hyperventilation is needed to remove this additional CO_2. Due to hypermetabolism excessive lactate is also formed by skeletal muscle which may result in recurrent metabolic acidosis. This is further corrected by titrating with sodium bicarbonate at the dose of 2 to 4 mEq/kg.

The serum K^+ level should be measured frequently since the onset of MH. If there is alarming hyperkalaemia, then it should be treated immediately but slowly. The best way of treating mild to moderate hyperkalaemia is reversal of MH by proper doses of dantrolene. Otherwise, it is corrected by infusion of dextrose with insulin or ion exchange or haemodialysis (only in refractory case). To correct hyperkalaemia IV calcium can be used, but only when there is impending life threatening arrhythmia. This is because the influx of extracellular Ca^{2+} may further trigger MH response.

MH is associated with myoglobinaemia. This may block the renal tubules leading to renal failure. So, it is essential to maintain the normal urine output at any cost. Hence, all the patients suffering from MH should be catheterised and diuresis is ensured by mannitol or furosemide. Dopamine is also used to increase the renal blood flow which subsequently will increase the urine output in acute phase of illness to prevent renal failure. Myoglobinuria can usually be detected by coca colour urine in first voided specimen. But the increased level of CK due to muscle damage which is diagnostic of myoglobinaemia and subsequently MH takes 24 hours to develop. However, it is obvious that significant amount of myoglobinaemia should have to develop before myoglobinuria has to be detected.

Ultimately DIC develops in a severe fulminating case of MH. It is due to the

FACT FILE- IV

The anaesthetist will response according to the degree of tightness of jaw due to masseter spasm and its duration during induction and intubation after administration of SCh and / or volatile anaesthetic agents. If the mouth is impossible to open and the jaw is very tight, then the anaesthetic procedure should be halted immediately and the patient should be monitored closely for impending MH. The therapy including the use of dantrolene should be started immediately if there is any suggestion of the onset of MH. On the otherhand, if the jaw is moderately tight and the anaesthetist has any suspician of the onset of MH in his mind, then there is two options. First, if the facilities for subsequent monitoring and management of MH (if it occurs) are available, then the anaesthetist can procede the anaesthetic procedure slowly and cautiously with nontriggering agents still the onset of MH is confirmed. Second, the anaesthetist can halt the procedure if he thinks that this medical centre is not well equipped to tackle such cases. Patients who are suffering from fever may have exaggerated reaction to SCh and increased tightness of jaw. So, the patients who develop trismus under the influence of SCh and volatile anaesthetic agents should be screened for susceptibility to MH.

tissue damage, release of thrombopalastin and haemolysis. It is treated according to the standard lines of treatment.

Management of Susceptible Patients

Before anaesthesia and surgery an anaesthetist will must discuss the special anaesthetic problems with the patient who is susceptible to and to his or her relatives. This will make the patient very anxious. So, with this discussion of problems an anaesthetist will also assure the patient and his or her party with the confidence that maximum care will be taken to avoid these problems and if problems occur then the appropriate management of international standard with best drugs, knowledge and skill will also be taken. Hence, the patient will enter the OT in relaxed mind with full confidence that he or she will not die.

If a particular surgery can be performed under RA, then it should be performed under this technique as RA is very safe for the MH susceptible patients. However, if GA is required, then it should be delivered by benzodiazepines, propofol, barbiturates, ketamine, N_2O, opioids, non depolarising muscle relaxant, neostigmine, atropine and glucopyrrolate. However, by any cost volatile anaesthetic agents and depolarising muscle relaxant should be avoided in any concentration, even in the presence of dantrolene. Some susceptible patients develop hypermetabolic state despite all these precautions. Then these patients should be treated by dantrolene and usually they respond. So, the present consensus is that the preoperative use of dantrolene as a prophylactic measure to MH is superfluous in susceptible patients and the avoidance of triggering factors and the only use of non triggering agents are sufficient for the anaesthetic management of MH susceptible patients. But if any anaesthetist wants to use preoperative dantrolene, then it should be given in the dose of 2 mg/kg IV just before induction of anaesthesia. In obstetric susceptible patients this prophylactic dose of dantrolene is given after the cord is clamped. This is becasue if dantrolene is administered before the cord is clamped then the cord blood level of dantrolene may approach to 60 to 70% of the patient's plasma level which may result in floppy child.

49 Neurosurgery and Anaesthesia

INTRODUCTION

Usually the neurosurgical operations are relatively high-risk procedures. The patients who are undergone neurosurgical procedures present many problems to an anaesthesiologist. This is because the soft brain tissue is positioned in a bony skull which acts as a rigid closed box and its functions depend mainly on the ICP which subsequently depends on the cerebral circulation and dynamics of CSF within this closed bony cavity. The diseases for which the patients are presented for neurosurgeries itself interfere this cerebral circulation and dynamics of CSF with flactuation of ICP that predisposes to cerebral ischaemia and, therefore, cerebral damage. For example, an intracranial space occupying lesion causes increased ICP and as the lesion grows the danger increases. The other examples are the patients who are presented for neurosurgeries for subarachnoid haemorrhage may suffer from cerebral vascular spasm and subsequently cerebral ischaemia and infarction. The patients with pituitary diseases who are presented for neurosugery usually suffer from endocrine disorders that increases the risk of anaesthesia during surgery. Anaesthetic drugs also have powerful effects on ICP as they also have immense effects on cerebral circulation and dynamics of CSF.

So, during anaesthesia of neurosurgical procedures an anaesthesiologist needs profound knowledge regarding the physiology of CNS including the cerebral metabolism, cerebral blood flow, dynamics of CSF, intracranial volume, intracranial pressure and the effects of anaesthetic agents on this physiology of CNS, etc. Hence, the goal of this chapter is to provide adequate information to an anaesthesiologist for rational approach during anaesthetic management of intracranial, spinal or any other neurosurgical procedures.

CEREBRAL PHYSIOLOGY

Cerebral Metabolism

The brain has tremendously high rate of energy utilisation, reflecting the high metabolic rate. But, it has very limited energy storage capacity. It is found that 60% of the total cerebral energy utilisation is needed to maintain the electrophysiological function of brain such as depolarisation – repolarisation activity of neuronal cells which is shown in EEG and synthesis, transport and reuptake of neurotransmitter. Another 40% of total cerebral energy utilisation is used to maintain the cellular homeostatic activities of brain tissues including the integrity of cell membrane (i.e. basic functions of cell). The adult human brain weighs about 1350 gm which represents approximately 2% of total body weight. At rest for production of energy the human brain consumes O_2 at an average rate of 3.5 ml/100 gm of brain tissue/min. Therefore, the whole human brain consumes O_2 at the rate of 47 ml/min ($13.5 \times 3.5 = 47$). This represents 20% of the total body O_2 consumption in a minute. The cerebral metabolic O_2 consumption rate ($CMRO_2$) is maximum at the gray matter of cerebral cortex and is parallel with the electrical activity of it.

The neuronal brain cells mainly utilise glucose aerobically as their substrate to produce energy in the form of ATP. Normally, the rate of utilisation of glucose by brain is 5/100 mg of tissue/min. But, during starvation ketone bodies such as β-hydroxybutyric acetate and acetoacetate and acetone also become the substrate for energy production. In the absence of supply of O_2 lactic acid is formed as a result of anaerobic glycolysis with the little production of energy. Therefore, for proper function of brain and for this the continuous supply of huge amount of energy in the form of adequate ATP, two things are needed – glucose and O_2 through circulation of blood. Hence, the failure of adequate supply of any one, i.e. glucose (hypoglycaemia) and O_2 (hypoxia) cause devastating damage to the brain. The interruption of supply of O_2 through circulation for 10 sec in brain tissues results in unconsciousness. If this supply of O_2 cannot be reestablished within 3 to 5 minutes, then irreversible brain damage occurs, as the energy store in neuronal tissue in the form of ATP is very limited. On the contrary, hyperglycaemia (explained later) and hyperboric O_2 (by vasoconstriction) cause global or focal hypoxic brain injury by producing cerebral acidosis and cellular injury.

Cerebral Blood Flow (CBF)

Previously, it is described that energy expenditure by brain tissue is parallel to the cerebral metabolic rate (CMR).

This CMR is also parallel (or directly proportional) to CBF. The normal approximate value of CBF in an healthy adult human is 50 ml/100 gm of tissue/min. Among these as the gray matter is metabolically more active, so here the CBF is estimated to about 30 ml/100 gm of tissue/min. But as the white matter of brain is metabolically less active, so the CBF in this region is estimated to only 20 ml/100 gm of tissue/min. This total CBF including gray matter and white matter is estimated to about 675 ml/min (13.5 × 50 = 675) which is 12 to 15% of total cardiac output. The CBF has a critical value below which level the function of brain deteriates. For example, when the CBF has fallen to approximately 20 ml/100 gm of tissue/min then the evidence of ischaemia of brain in EEG begins to appear. At CBF level of approximately 15 ml/100 gm of tissue/min the cortical EEG becomes isoelectric. However, when the CBF is reduced below 10 ml/100 gm of tissue/min then the irreversible damage of brain occurs.

Regulation of CBF

There are elaborate mechanisms for the regulation of CBF. These include chemical, myogenic (auto), neurogenic and some other extrinsic mechanisms.

Chemical mechanism

The chemical mechanism for the regulation of CBF include the changes in CMR, P_aCO_2, and P_aO_2. It is already stated that increased neuronal activity results in increased cerebral metabolism and this increase in CMR is associated with well matched proportional increase in CBF. For this a variety of metabolic byproducts have been considered to act as intermediaries to increase the cerebral blood flow. These include: H^+ conc, extracellular K^+ and/or Ca^{2+} conc, thromboxane, certain prostaglandins, adenosine, etc. (Fig. 49.1)

CBF also varies directly with the changes in P_aCO_2. But this effect is greatest within the normal range of physiological

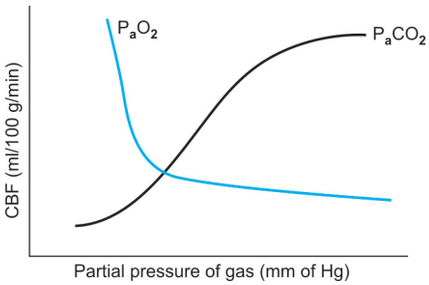


Fig. 49.1: Relationship of CBF with arterial O_2 tension (green line) and arterial CO_2 tension (red line)

changes in P_aCO_2, i.e. between 30 to 70 mm of Hg. Within this range of change in P_aCO_2 the CBF changes by 1 to 2 ml/100 gm of tissue/min for each 1 mm of Hg change in P_aCO_2. This response is attenuated when the P_aCO_2 falls below 25 mm of Hg. This change in CBF caused by P_aCO_2 is due to the changes in pH of ECF (or CSF) of brain, but not due to the changes in H^+ conc which increases in metabolic acidosis. This is because H^+ can not readily cross the blood brain bariers. So this change in P_aCO_2 cause the free CO_2 to diffuse freely across the cerebrovascular endothelium. Thus, acute metabolic acidosis which has where is mainly concerned with the increase in H^+ conc little effect than respiratory acidosis (where CO_2 level mainly increases) on CBF. After 6 to 8 hours the CBF returns to normal in spite of the elevation of P_aCO_2. This is because the pH of ECF of brain gradually normalises due to the adjustment of HCO_3^-. Similarly the reduction in P_aCO_2 reduces the CBF. But several investigations indicate that in normal subjects ischaemia will not occur at P_aCO_2 above 20 mm of Hg. However, physiological alterations of brain function as evidenced by EEG and metabolic abnormalities is observed when P_aCO_2 is reduced below 15 mm of Hg by hyperventilation. So there is little benefit in terms of improvement of ICP, rather it causes harm if P_aCO_2 is reduced lesser than 20 to 25 mm of Hg.

Like P_aCO_2, the P_aO_2 has not much effect on CBF. The changes in P_aO_2 between 60 to 300 mm of Hg have little influence on it. But when P_aO_2 falls below 60 mm of Hg, then CBF increases rapidly. However, this mechanism of vasodilatation caused by hypoxia is not exactly known. But the probable mechanism of this vasodilatation is neurogenic influence which is initiated by peripheral chemoreceptor and direct hypoxic effects on vascular smooth muscles, mediated by lactic acidosis.

Myogenic (auto) regulation or mechanism

Over a wide range of change in mean arterial pressure (MAP) the CBF is maintained automatically by changing the resistance of cerebral vessels (constriction or dilatation) intrinsically. This is called as the myogenic regulation or autoregulation of CBF. In normal human beings the range of MAP through which the CBF is maintained by autoregulation at constant level is 60 to 160 mm of Hg. Above and below this level of MAP the CBF is not autoregulated and becomes pressure dependent and changes (reduce or increase) accordingly in linear fashion. The difference between the MAP and ICP is known as the cerebral perfusion pressure (CPP), which determines the rate of diffusion of substrates into the brain tissue from vessels. When the MAP goes above 160 mm of Hg and autoregulation fails, then ICP rises and CPP falls. The increased MAP beyond autoregulation can disrupt the blood brain barrier. This may result in intracranial haemorrhage and cerebral oedema. The exact mechanism of this autoregulation of CBF is not known. But still it is postulated that the intrinsic characteristic of the smooth muscle of cerebral blood vessles is responsible for this auto regulation of CBF. Another theory is also put forward for this autoregulation of CBF. This is known as the metabolic mechanism. This theory explains that cerebral metabolic demand determines the cerebral arteriolar tone and CBF. Thus, when the brain tissue demands more metabolic

need, then the cerebral vessels dilate and CBF increases and *vice versa*. So, it is also known as the myogenic regulation. This autoregulation or myogenic reflex of CBF is influenced by various pathological processes such as: Intracranial tumours, head injury, many disease processes of cerebral vessels, subarachnoid haemorrhage, volatile anaesthetic agents, vasodilators, etc. This myogenic or autoregulation of CBF is not a fixed one. If a person suffers from chronic essential hypertension for long time, then this autoregulation curve with its upper and lower end shifts to the right. It means the CBF is maintained at higher level of upper and lower range of MAP (Fig. 49.2).

Neurogenic mechanism or regulation

There is strong evidence for extensive innervation of cerebral vessels. These are sympathetic (vasoconstrictive), parasympathetic (vasodilatory), serotonergic, vasoactive intestinal peptidergic (VIP), etc. But the density of innervation decreases with the decrease of vessel's size. So, the neurogenic regulation exists only on the large cerebral vessels. The exact functional significance of this neurogenic regulation of CBF is not known. But, still it may play an important role in some pathological states. For example, in haemorrhagic shock increased sympathetic activity causes lowering of CBF by vasoconstriction at a given MAP than which is found when hypotension is produced by sympatholytic agents. This is probably because during shock the vasoconstrictive effect caused by sympathetic over activity shifts the lower end of autoregulation curve of CBF to the right. The sympathetic and parasympathetic innervation may also play an vital role in regulating CBF during stroke and brain injury.

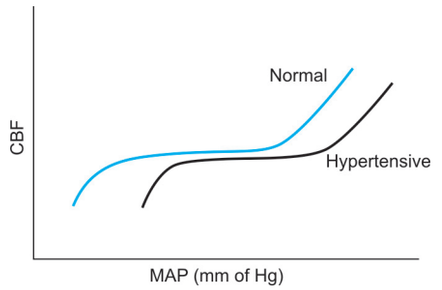


Fig. 49.2: Autoregulation curve of CBF in normal (green) and hypertensive (red) subject. In hypertension, it is shifted to the right

Some extrinsic mechanisms or factors

Temperature

The CMR and subsequently the CBF immensely depend on the temperature of brain tissue. It is found that the CMR and CBF decreases by 5 to 6% for every 1°C reduction of temperature (hypothermia) of brain. So, the CMR and CBF falls to 50% of its original value for reduction of temperature of brain from normal 37°C to 27°C. Then, with further reduction of temperature of brain to 20°C, the EEG which signifies the electrophysiological activity of brain becomes isoelectric with further reduction of CMR and CBF. With further reduction of temperature of brain from 20°C to downwards the CMR will also further decrease with CBF. This is because hypothermia causes decrease in CMR which is associated with both the electrophysiological function and maintenance of basic cellular integrity. The reduction of temperature upto 20°C is responsible for reduction of CMR which is associated with cerebral electrical activity and reduction of temperature below 20°C is responsible for reduction of CMR which is associated with basic cellular activities. In contrast, the anaesthetic agents with deepening of anaesthesia by increasing the dose of it reduce the CMR which is only associated with the electrophysiological function of brain and is evidenced by only EEG. So after the EEG becomes isoelectric with further increase of the dose of anaesthetic agents the CMR and subsequently the CBF will not reduce further. With the reduction of temperature from 27°C to 17°C there is further 50% reduction in CMR and CBF. Therefore, it probably accounts for the brain's tolerance to total circulatory arrest for moderate periods at this level of hypothermia. Hyperthermia has opposite effect to hypothermia or cerebral physiology. Between 37°C to 42°C both the CMR and CBF increase. But above 42°C the CMR again begins to fall. This indicates that 42°C is the threshold level for the toxic effect of hyperthermia and this is due to the neuronal cell damage, resulting from protein (enzymes of cell) degradation due to heat.

Viscosity

One of the single most important determining factor for viscosity of blood is the haematocrit value of it. So, the effect of viscosity of blood on CBF is estimated from the angle of haematocrit level. The viscosity of blood or haematocrit level of it has some influence on CBF. But this is not found within the normal range of haematocrit value (33 to 45%) in a healthy adult individual. But beyond this range the changes in CBF dur to changes in haematocrit value are more substantial. A decrease in haematocrit value (anaemia) improves the CBF. This is due to the decrease in viscosity of blood. On the otherhand, simultaneously it reduces the O_2 carrying capacity of blood to brain. But, practically this occurs after getting the maximum benefit from increased blood flow to brain due to decreased level of haematocrit and viscosity. Thus, anaemia can potentially impair O_2 delivery in brain, but below a certain level of haematocrit value where maximum beneficial effect of increase in CBF has already taken.

The reduction of haematocrit (anaemia) or viscosity increases the CBF by reducing the vascular resistance (i.e. by vasodilatation) in response to low O_2 carrying capacity in blood. This effect of reduction of viscosity on CBF is more important in the case of focal cerebral ischaemia, where local vasodilatation in response to low O_2 delivery is maximum. In this setting reduction of viscosity produced by haemodilution

results in increased CBF in the ischaemic territory. It is also evidenced from different studies that the optimum delivery of P_2 to brain in anaemia can occur at haematocrit value of 30%. Increased haematocrit and viscosity in polycythaemia has opposite effect and reduce CBF.

Vasoactive drug

Many vasoactive drugs such as systemic vasodilators, sympathetic agonists and antagonist, etc; which are used rampantly in anaesthetic practice have some definite effects on CBF. The systemic vasodilators which are used for induced hypotension during anaesthesia practice such as Na-nitroprusside, nitroglycerine, calcium channel blockers, etc, cause cerebral vasodilatation and increase CBF or maintain it at prehypotensive level up to a certain level of MAP which is lower than when it is caused by haemorrhagic shock or any other shock. If hypotension is induced slowly by these agents, then ICP does not rise due to increased CBF. This is probably explained by the shifting of CSF and venous blood (as compensatory mechanism) when changes in increase of CBF occur very slowly. Otherwise, vasodilator drugs will cause increased CBF and increased ICP.

The sympathetic α_1 agonists do not increase CBF, though cause acute increase in MAP. This is probably due to the presence of autoregulation and intact blood brain barrier (BBB). In defective BBB or in the absence of autoregulation these α_1 agonists may increase CBF and ICP tremendously. In case of β agonists it is found that in low doses they have little direct effect on CBF. But in higher doses they definitely increase CMR, coupling with increased CBF. The β blockers probably have no effect on CBF or reduce it with the reduction of CMR. However, the level of circulating plasma catecholamines at the time of administration of β blockers and the status of BBB may influence the effects of these agents on CBF. There is unlikely to have side effects of these agents on patients with intracranial pathology, other than the secondary changes due to reduction in CPP caused by decrease in CBF.

The effect of dopamine on CBF is very interesting. In low doses (2 to 6 µg/Kg/min) it probably causes the dilatation of cerebral vessels and increase in CBF. But there is possibility of vasoconstriction and reduction of CBF in higher doses (6 to 20 µg/Kg/min). In doses lesser than 2 µg/Kg/min dopamine also causes cerebral vasoconstriction.

EFFECTS OF ANAESTHETIC AGENTS ON CEREBRAL PHYSIOLOGY

Except ketamine all the anaesthetic agents reduce the electrical activity of CNS. Therefore, they increase the amount of energy stored in the form of ATP, ADP and phosphocreatine. However, this study of effects of anaesthetic agents on cerebral physiology is difficult. This is because it is often complicated by some other factors during surgery and anaesthesia such as continuous change in MAP due to sympathetic over activity during surgery due to stimuli, concomitant use of many drugs during anaesthesia, continuous change in P_aCO_2 which affect the CBF and subsequently the cerebral blood volume (CBV) during that period, etc. For example, over a wide range with the change in P_aCO_2 (20 to 80 mm of Hg) the CBF also changes by about 0.04 ml/100 gm of brain tissue/min/mm of Hg change in P_aCO_2 provided the MAP remains constant. Thus, in an adult brain weighing about 1.4 Kg this can be an amount to ($14 \times 30 \times 0.04 = 16.8$) 16.8 ml (approximately 17 ml) for every 1 mm of Hg change in P_aCO_2 from 25 to 55 mm of Hg. On the otherhand, this change in CBF is different when the MAP is variable and P_aCO_2 remains a constant factor. It is already stated that autoregulation serves to prevent the MAP related change in CBF and CBV. In the face of rising MAP the cerebral blood vessels constrict to maintain a constant CBF and thus CBV decreases to normal and *vice versa*. But when this autoregulation is impaired by anaesthetic agents or its upper and lower limit (150 mm of Hg and 50 mm of Hg) is exceeded, then the CBF and CBV increase or decrease as arterial pressure increase or decrease.

Intravenous Agents

Barbiturates

They produce dose dependent reduction in CMR and CBF. With the onset of anaesthesia this reduction of CMR and CBF is 30%. But with the deepening of anaesthesia by gradually increasing the doses of barbiturates when the EEG becomes isoelectric, then this reduction of CMR and CBF touches to 50%. However, further increase in dose of barbiturates beyond this point had no effect on CMR, CBF and CBV. This is because barbiturates only cause the reduction in the component of cerebral metabolism which is related only to the neurophysiological activity of brain, but not the component of cerebral metabolism which is related to the basic cellular activity such as ion transport etc. which is responsible for the maintenance of integrity of cell membrane. This is in contrast to hypothermia where both the CMR and CBF is reduced still beyond the point of isoelectric EEG (described before) (Fig. 49.3).

The reduction of CMR by barbiturates is greater than that of CBF. So, there is always some store of metabolic energy during barbiturate anaesthesia as supply (CBF) exceeds the demand (CMR). Barbiturates also cause the constriction of smooth muscles of cerebral blood vessels and is the cause of reduction of CBF along with the reduction of CMR (this mechanism is separate from the reduction of CBF when CMR is reduced due to hypothermia or other causes). But this is found in normal brain tissue. In ischaemic brain tissue barbiturate causes dilatation of vascular

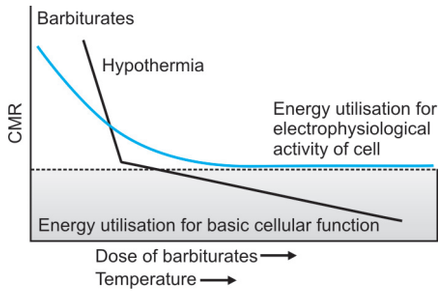


Fig. 49.3: Effects of barbiturates (green line) with increasing dose and gradual lowering of temperature or hypothermia (red line) on CMR. The maximum reduction of CMR that occurs with the increased dose of barbiturate, result in silent EEG. At this point the energy utilisation by cell for electrophysiological activity comes to zero. But the energy utilisation for basic cellular activity remains unchanged which is only reduced by hypothermia

smooth muscle and divert the blood flow from the normal to the ischaemic area of brain which is helpful. It is known as the reverse steal or Robin Hood phenomenon. So, the ischaemic areas of brain get maximum amount of blood supply during barbiturate anaesthesia.

Other than reduction of ICP by reducing CBF in neurosurgeries, the barbiturates also help by facilitating the dynamics of CSF. It helps in absorption of CSF. So the ICP is further reduced and protects the brain from damage by increased ICP and reduction of CPP. Barbiturates have also anticonvulsant property. Thus it prevents convulsion and reduces the CMR along with the reduction of CBF and ICP (convulsion is associated with increased CMR, CBF and ICP), causing decrease in the chance of ischaemia of brain.

Propofol

Like babiturates propofol also reduces the CMR and CBF. These reduction of CMR and CBF caused by propofol are approximately 30% and 50% respectively. Hence, it shows that there is more reduction of CBF than CMR in propofol anaesthesia which is unlike to barbiturates. Thus, it is also helpful in neurosurgery by reducing ICP and protecting brain from ischaemia. Though, propofol causes choreiform and dystonic movements, but it has anticonvulsant property like barbiturates. So, it also protects the brain from ischaemic injury during convulsion. Both autoregulation and CO_2 responsiveness of CBF appear to be preserved during administration of propofol.

Benzodiazepines

Like propofol and barbiturates the benzodiazepines also cause the reduction of CBF and CMR. But the extent of this reduction of CMR and CBF is probably intermediate in position lying between the narcotics (minimal) and barbiturates (maximum). For example, 15 mg diazepam reduces CMR and CBF to 25% provided respiratory depression and increase in P_aCO_2 do not occur.

Narcotics

They have minimal reduction effect on CMR and CBF in the normal unstimulated patients. So, they cannot decrease CMR and CBF especially if there is any factor which increases the $\uparrow P_aCO_2$, $\uparrow$MAP, etc. The CO_2 responsiveness and autoregulation to CBF remain unaffected by narcotics. Regarding the effect of narcotics on ICP it is found that morphine and fentanyl reduce ICP by reducing the CMR, CBF, CBV and CSF pressure. But it is found that sufentanil and alfentanil sometimes increase ICP.

Ketamine

Among all the intravenous anaesthetic agents ketamine is the only one which increases the CMR and subsequently the CBF by dilating the cerebral vessels. Thus it increases the ICP also. It selectively activates the limbic structure and the area of reticular formation, while it selectively depresses the cortical area of brain. Seizure caused by ketamine further increases ICP by increasing CMR and CBF. So it is not beneficial for neurosurgery. Hyperventilation can reduce the elevation of ICP caused ketamine, because CO_2 responsiveness to CBF remains intact by it.

Inhalational Anaesthetic Agents

Volatile agents

The pattern of influence of volatile anaesthetic agents on cerebral physiology is strikingly different from that of the intravenous anaesthetic agents. Here the reduction of CBF does not follow the foot print of the reduction of CMR caused by the volatile anaesthetic agents. All the volatile anaesthetic drugs dilate the cerebral vessels (in contrast to barbiturates and propofol which constrict these vessels). Thus they all increase the CBF and CBV while simultaneously produce dose related reduction in CMR. Hence all the volatile anaesthetic agents increase ICP, especially in patients with reduced intracranial compliance. Regarding the effects of volatile agents on CMR, CBF, CBV and ICP halothane is the most potent and isoflurane is least potent agent. The influence of the newer volatile anaesthetic drugs such as sevoflurane and desflurane on cerebral physiology is more or less similar to that of isoflurane. For example, halothane increases CBF up to 200% compared to 20% produced by isoflurane at the equivalent dose of MAC and similar reduction of BP.

On the otherhand, halothane produces relatively homogenous changes in CBF in brain. Therefore, the CBF is globally increased and CMR is globally decreased by halothane. In contrary, these changes (reduction of CMR and increase in CBF) caused by isoflurane are more heterogenous resulting on increase in CBF in subcortical and hind brain structures than the structures of neocortex. However, for the CMR the reverse is true for isoflurane causing greater reduction in neocortex than that in subcortex and hind brain. All these datas dictate that isoflurane is preferred in neurosurgery, if volatile anaesthetic agents are at all used in the setting of impaired (decrease) intracranial compliance. But that does not indicate that halothane is completely contraindicated

in these circumstances. It is clearly demonstrated that halothane can safely be used in such circumstances if only P_aCO_2 is maintained at normal level by hypo or hyperventilation, the explanation of which is described as follows (Table 49.1).

All these volatile anaesthetic agents abolish the autoregulation of CBF in response to increase or decrease in MAP. So, the CBF changes not in parallel to the changes in MAP. But, after few hours the increased CBV due to increased CBF returns to normal due to compensatory mechanism. However, this time course needed for compensation is dependent on the magnitude of the initial elevation of CBF. It is already previously stated that the reduction of CMR caused by volatile anaesthetic agents is not similar to that of hypothermia. In hypothermia the CMR is further reduced after the EEG becomes isoelectric which is not found in volatile agents and intravenous anaesthetic agents. CO_2 responsiveness to the changes in CBF is well preserved during anaesthesia by all the volatile anaesthetic agents. Therefore, hyper or hypoventilation can control the CBF, CBV and ICP when anaesthesia is provided by volatile anaesthetic agents.

From the above discussion it is learnt that the volatile anaesthetic agents cause uncoupling of the normal relationship between the CBF and CMR, i.e. reduce CMR but increase CBF. So, this aspect of influence of volatile anaesthetics on cerebral physiology is beneficial by preventing ischaemia, especially during the use of isoflurane in neurosurgery. But this beneficial effect is off set by the steal phenomenon, caused by these volatile anaesthetic agents. This steal phenomenon explains that the volatile anaesthetic agents though dilates the vessels of normal brain tissue, but do not dilate the vessels of ischaemic area which are already maximally dilated due to ischaemia. So, the ultimate result is the starved ischaemic area due to the stealing of the supply of blood to normal healthy area of brain. Further, they increase ICP especially in patients with decreaed intracranial compliance, causing further damage to brain.

Table 49.1: Effects of anaesthetic agents on cerebral physiology

Agents	*CMR*	*CBF*	*CBV*	*ICP*
Barbiturates	↓↓↓↓	↓↓↓	↓↓↓↓	↓↓↓
Propofol	↓↓↓	↓↓↓	↓↓	↓↓
Benzodiazepines	↓↓	↓↓	↓	↓
Opioids	↓	↓	↓	↓
N_2O	↓	↓	↓	↓
Halothane	↓↓	↑↑↑↑	↑↑↑	↑↑↑
Isoflurane	↓↓↓	↑	↑	↑
Sevoflurane	↓↓↓	↑	↑	↑↑
Desflurane	↓↓↓	↑	↑	↑↑
Ketamine	↑	↑↑↑	↑↑	↑↑↑

Nitrous oxide

Nitrous oxide causes vasodilatation of cerebral vessels. This vasodilating effect of N_2O is clinically more significance during neurosurgery in patients who have reduced intracranial compliance. Hence, the available datas till now unequivocally suggest that N_2O produces substantial increase in CBF, CBV and ICP when used alone in neurosurgeries. For example, when N_2O is used alone during removal of intracranial tumours then ICP may rise from the mean value of 10 to 13 mm of Hg to 30 to 40 mm of Hg. But the magnitude of this effect varies considerably according to the presence or absence of other anaesthetic agents such as intravenous or volatile. When N_2O is used in combination with IV anaesthetic agents such as thiopentone, propofol, benzodiazepines, etc. then the vasodilating property of N_2O is completely inhibited or attentuated. So, there is no increase in CBF and ICP. Again during neurosurgery the combination of N_2O and narcotics also have the similar effects. On the contrary, when N_2O is used in combination with volatile anaesthetic agents, then substantial increase in CBF, CBV and ICP is occurred. So, the present status regarding the use of N_2O in neurosurgery is that till now there is no strong adequate evidences to prohibit its use. Hence, N_2O is now widely used in neurosurgery, but in circumstances where ICP is persistently elevated causing tight surgical field, then N_2O should be taken as the responsible factor for this and avoided.

Muscle Relaxants

Depolarising agents

In a lightly anaesthetized patient succinylcholine is found to produce elevation of ICP. This is possibly due to the result of cerebral activation caused by affarent impulses to the brain from muscle spindle during fasciculation. So, this elevation of ICP is found to be maximum after 1 to 3 minutes of administration of succinylcholine and return to base line after 8 to 10 minutes. Thus, the succinylcholine induced elevation of ICP can be attenuated by deepening induction of anaesthesia and preventing fasciculation by using a small defasciculating dose of nondepolarising agent. Hence, its use need not be viewed as contraindication in neurosurgery with elevated ICP, where rapid achievement of skeletal muscle paralysis and intubation by succinylcholine is justified due to any cause such as difficult airway. Little hazard should follow its use if it is administered with proper control of MAP, P_aCO_2, depth of anaesthesia and using the method of defasciculation.

Nondepolarising agents

These agents cannot penetrate the blood brain barrier (BBB). So, they have no direct effect on cerebral vasculatures and the only indirect effect of it on CBF is via the release of histamine by these agents. Histamine decreases MAP by systemic vasodilatation and increases ICP by cerebral vasodilatation. Thus, it can result in reduction of cerebral perfusion pressure (CPP). Among the nondepolarising agents tubucuraine is the most notorious for the release of maximum amount of histamine. But the commonly used nondepolarising agents in clinical anaesthesia such as atracurium,

mivacurium, rocurium, vecuronium, etc. release histamine in lesser quantities. So, their use in neurosurgeries with elevated ICP is clinically inconsequent unless they are administered in large doses which are necessary to achieve rapid intubating condition. The nondepolarising agents which increase MAP such as pancuronium may elevate the ICP. But this is only possible when the rise of this MAP is abrupt and autoregulation is disrupted by the disease processes of CNS for which the surgeries are shouted. On the otherhand, the nondepolarising agents can reduce ICP by decreasing the impedence of cerebral venous outflow by preventing the coughing and straining. In most of the cases during neurosurgery the increase in ICP following the administration of muscle relaxants, laryngoscopy and intubation is due to the hypertensive response for light plain of anaesthesia.

CEREBROSPINAL FLUID (CSF)

A clear, colourless, transparent, modified tissue fluid fills all the ventricles, the whole spinal canal and the total subarachnoid space bathing the whole CNS. This is called the CSF. Its major function is to protect the CNS from trauma and maintain its physiology. The CNS is devoid of lymphatic supply. So, in CNS the CSF replaces the lymph. In a healthy adult human the volume of CSF is about 150 ml. It is continuously formed and absorbed. The normal rate of production of CSF in an healthy adult is about 500 ml/day or 20 ml/hour or 0.3 ml/minute. About 59 to 70% of CSF is produced by the choroid plexus of ventricles, mainly the lateral. The remaining 30% is secreted directly from the ependymal cells lining the ventricles. Yet the smaller quantities is formed by fluid leaking into the surrounding of perivascular space from cerebral vessels. The production of CSF is independent of ICP and everyday it is totally exchanged three times (Fact file I).

After formation from the two lateral ventricles (right and left) the CSF first passes through the foramina of Monro (right and left intraventricular foramina) to the third ventricle which is situated in the midline. Then, it flows through the aqueduct of Sylvius which is a channel in the midbrain to enter the fourth ventricle of medulla. After that from the fourth ventricle the CSF passes through three foraminas to the subarachnoid space. These three foramina are: central one named foramen of Magendie which ends directly into the *cisterna magna* and two lateral ones named the foramen of Luschka which end into the *cisterna pontis* which is situated at the basal aspect of brainstem. From the fourth ventricle the CSF also passes into the central canal of spinal cord. The ciliary movement of the ependymal cells which lines the of ventricles and spinal canal help in the circulation of CSF (Fig. 49.4).

From the subarachnoid space the CSF is absorbed through the arachnoid villi into the veins of cranial cavity, primarily the cerebral venous sinuses. These villi consist of some projections formed by the fused arachnoid membrane and endothelium of venous sinuses. The projections act as valves that permit the bulk direct flow

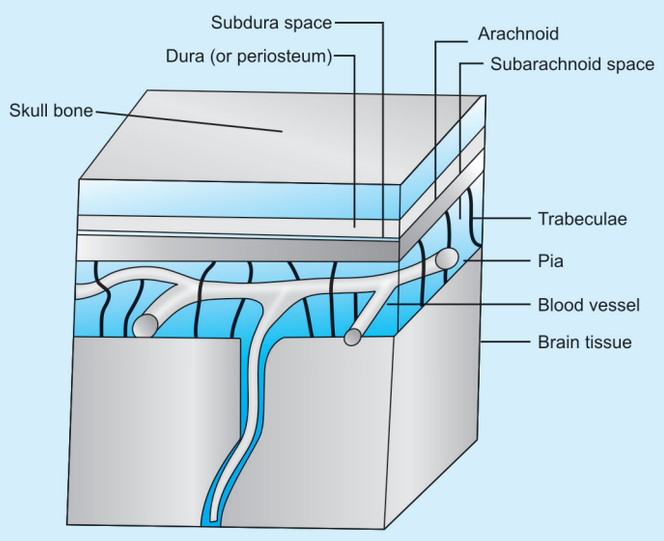
FACT FILE- I

Protective function of CSF

The meninges and CSF protect the brain. In cranial cavity the dura is firmly attached to the bone and acts as a priosteum. But in spinal canal the periosteum and dura is separated by epidural space and this two layers unite at the margin of the foramen magnum. So, epidural space does not extend into the cranial cavity. There is a thin potential space between dura and arachnoid which is known as the subdural space. It contains thin film of fluid. Thus arachnoid is held with dura by surface tension of this thin layer of fluid. The brain with its pia mater covering hangs or floats within the CSF filled subarachnoid space supported by blood vessels, nerve roots and multiple fine fibrous arachnoid trabeculae which pass from arachnoid mater to pia mater through subarachnoid space.

The brain weighs about 1400 gm in air. But in its CSF bath it has net weight of only 50 gm. So, the buoyancy of this organ (brain) in CSF permits these relatively flimsy attachment such as blood vessels, nerve roots and arachnoid trabeculae to suspend it very effectively. When the head receives a blow, the arachnoid mater slides on the dura mater and the brain moves. But this motion is gently checked by the CSF cushion and the arachnoid trabeculae.

Leaking of CSF after lumbar puncture causes severe headache. This is because after removal of more CSF the floating effect of brain in CSF lost. So, it hangs more by the vessels and nerve roots and traction on them stimulates pain fibres.



Different layer from skull bone to brain

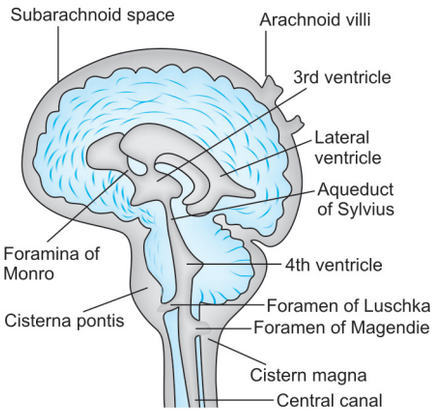


Fig. 49.4: The passage of flow of CSF

of CSF into the venous blood of sinuses. This bulk flow of CSF through these villi accounts for about 500 ml/day. The additional small amount of CSF is also being absorbed by direct diffusion into the cerebral blood vessels and at the nerve root sleeves and by meningeal lymphatics. The large amount of CSF accumulates when the reabsorption capacity of these arachnoid villi is impaired. Then this is called the external or communicating hydrocephalus. On the other hand, when there is obstruction at foramina of Luschlka and Magendie or within the ventricular system, then there is also accumulation of CSF proximal to the block and ventricles are distended. Then this is called the internal or noncommunicating hydrocephalus.

The components of CSF is essentially same as that of ECF of brain. Its formation involves active secretion of Na^+ from choroid plexuses along with water and is isotonic with plasma, though the concentration of K^+, bicarbonate and glucose is low. In comparison to plasma the protein content of CSF is very low and is only due to the small leak of it in perivascular fluid, other than some pathological conditions. The normal CSF pressure which normally reflect the ICP varies between 110 to 130 mm of H_2O. The absorption of CSF which takes place largely in the cranial venous sinuses is proportional to this pressure and inversely proportional to the cerebral venous pressure which is again proportional to the CVP. At a pressure (ICP) of 110 mm of H_2O secretion and absorption of CSF is equal. But below a pressure of approximately 65 mm of H_2O the absorption of CSF stops. The CSF pressure rises on standing, coughing, sneezing, crying, etc. Compressing of internal jugular vein also increases the CSF pressure by inhibiting its flow in the intracranial venous sinuses. It is known as the Queckenstedt's sign. Acetazolamide (carboxy anhydrase inhibitor), diuretics, corticosteroids, vasoconstrictor, etc, decrease the pressure of CSF by attenuating its secretion (Fact file II).

INTRACRANIAL PRESSURE (ICP)

The brain tissue, the blood vessels supplying it and the intracranial part of CSF are all situated in the cranial cavity which is encased by a rigid bony enclosure named the skull. In an adult cranial cavity the brain usually weighs about 1400 gm, the volume of blood is 75 ml and the volume of CSF is 75 ml. They constitute about 80%, 12% and 8% of the total volume of cranial cavity, respectively. Among these the brain tissue and the CSF component is incompressible one and the blood component is compressible one. It is postulated that at any time the total volume of brain tissue, blood and CSF in cranial cavity will remain constant at a certain ICP which is known as the Monro Kellie doctrine. Therefore, any increase in the volume of any one component must be offset by an equivalent decrease in volume of another component of cranial cavity to keep the ICP constant or to prevent the rise of it. As blood is the only compressible component of cranial cavity (CSF is partially compressible), so any increase or decrease of ICP the main burden will come on CBV and *vice versa,* i.e. any change in CVP promptly causes a similar change in ICP (Fig. 49.5).

In the closed cranial cavity the ICP, MAP and CVP interplay within themselves

FACT FILE- II

Blood brain barrier

The cerebral vessels have a number of unique anatomical features. In the capillary wall of choroid plexus there are gaps (65°A) between the endothelial cells which is like the capillaries of other tissues in the body. But the chroid epithelial cells that separate them from CSF are connected to one another by tight junctions. However, in the capillaries of other portion of brain there are tight junction between the endothelial cells (the gap is only 8°A) and limit the passages of substances through this endothelial junction. As a result large molecules such as protein and most ions are prevented from entering the brain's interstitial space. This unique limited exchange of substances into the brain tissue itself is referred to as the blood brain barrier. But some physiologist use this term only to refer to the barrier in the capillary wall of brain tissue and use the term blood CSF barrier to refer to the barrier in the choroid epithelium. However, the barrier are similar and it seems more appropriate to use the term blood brain barrier to refer to both the barriers. There is little evidence that anaesthetic agents alter the function of this blood brain barrier in most of the circumstances. But it has been repeatedly demonstrated that the acute hypertension can breach this barrier.

Multiple transport system (active and carrier mediated) are present in the capillary endothelial cells. Water, CO_2 and O_2 can penetrate the brain easily. So, do the lipid soluble free forms of many substances including anaesthetic drugs. Whereas their protein bound form and all proteins do not. The easy penetration of CO_2 in contrast to slow penetration of H^+ and HCO_3^- has definite physiologic significance in the regulation of respiration. Glucose is the major source of energy for nerve cells. Its passive transport through blood brain barrier is slow. But its transport through the walls of brain capillaries by the glucose transporter GLUT-1 is rapid. The brain contains two forms of GLUT-1 such as GLUT-1, 55K and GLUT-1,45K. Both are encoded by the same gene. Infants with congenital deficiency of GLUT-1 develop low CSF glucose concentration in the presence of normal plasma glucose. So they have seizures and delayed development.

Another important transporter in the cerebral capillaries is Na^+-K^+-$2Cl^-$ transporter. It helps to keep the brain K^+ concentration low. In addition there are specific transporter system for each several organic acids, thyroid hormone, choline, nucleic acids, etc.

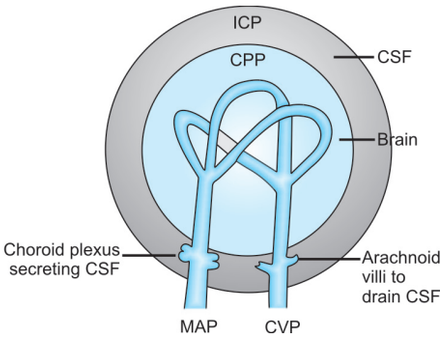


Fig. 49.5: The relationship between the MAP, CVP and ICP. The normal value of ICP is 10 mm of Hg. Elevation of ICP above 30 to 40 mm of Hg significantly compromise the CPP even in the presence of normal MAP. The CPP below 50 mm of Hg shows the EEG. When it is between 20 to 40 mm of Hg, EEG becomes flat. CPP below 20 mm of Hg cause irreversible brain damage

to determine the pressure which help to diffuse the different nutrient substrates and gases from blood to the cerebral tissue. This diffusion pressure in the tissue of brain is known as the cerebral perfusion pressure (CPP). Normally this CPP varies between 80 to 100 mm of Hg. This CPP is the difference between the MAP and ICP or CVP which will be the greater. Due to any condition when CVP exceeds ICP, then CPP will be the difference between MAP and CVP. Thus the CPP = MAP − ICP or MAP − CVP. So any elevation of ICP tremendously reduces the CPP and will impair the cerebral function. Increase in CVP also will decrease CPP by increasing ICP.

Conventionally, the pressure measured in CSF at the supratentorial level from lateral ventricle or over the cortex is considered as ICP. This was first introduced by Lundberg in 1960 and still remains the gold standard technique for the measurement of ICP with which other techniques are compared. In this technique a small catheter or a needle is introduced into the CSF of lateral ventricles and connected to an external standard pressure transducer. This always should be zeroed and calibrated and monitored with currently available electronic display system. During the measurement of ICP the zero reference point of the transducer is important, because CSF pressure is very position dependent. So a standard practice is to calibrate the pressure transducer at the level of the external auditory meatus and to correct the difference in height between the level of heart and head when calculating CPP.

This method of measuring ICP is an invasive one and the complications of this technique are: Infection, haematoma, injury of nerve tissue during passage of catheter through brain, etc. Sometimes a large mass, haematoma, severe brain swelling, etc. may distort the cavity of ventricle and make the introduction of catheter into it very difficult. Other less invasive techniques for measurement of ICP was thought and these include: Threading of a hollow bolt into the skull above a small supracortical dural opening, placement of a subdural catheter, intracranially implanted transducer, etc. (Fig. 49.6).

In lateral recumbent position the CSF pressure measured at the lumbar spinal level very closely approximates with the value supratentorial ICP. The intracranial compliance is measured by determining

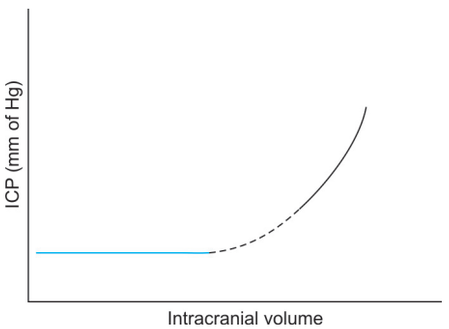


Fig. 49.6: Cerebral compliance curve. Dotted red part of the curve signifies the onset of cerebral ischaemia (focal ischaemia). Then the continuous red part of the curve signifies global ischaemia. In the initial part of the curve (blue line) ICP increases slightly though bulk of brain tissue expands. This buffering is due to the reduction of other intracranial volumes, usually CSF. The rate of increase of ICP is determined by the rate of expansion of intracranial mass, the compliance of CSF space and resistance to CSF absorption

the changes in ICP in response to changes in every unit of intracranial volume. Normally the brain tissue outside the cranial cavity is very much compliant, but this complacency is lost when it is put in a rigid box like skull for protection. So, the initial increase in volume of brain is well compensated without increasing ICP. But when this compensatory mechsnism is lost or exhausted quickly (as there is no scope for much expansion of brain due to rigid bony skull) then further slight increase in the volume of brain tissue will cause precipitous increase in ICP.

There are four compensatory or buffering mechanism which prevent the increase in ICP during increase in intracranial volume. These are: Decrease in CSF production, increase in CSF absorption, displacement of CSF from cranial cavity to spinal compartment, decrease in CBF and CBV. The major causes of increase in intracranial volume and increase in ICP are cerebral oedema due to any trauma, intracranial haemorrhage (extradural, subdural, subarachnoid, within the brain tissue) expansion of CSF or CBV, and growing intracranial mass. The location and the expansion rate of these lesions are the determining factors of the rate of rise of ICP and the rate and the degree of above mentioned compensatory buffering mechanism. So, a lesion situated on the pathways of CSF flow causes a rise in ICP proximal to the block at an accelerated rate by blocking the flow of CSF. Obliteration of CSF pathway can also block the transmission of pressure along the craniospinal axis. So, in this situation the measurement of CSF pressure at the lumbar spinal level does not reflect the actual change in ICP.

Increased ICP causing ischaemia and damage of nervous tissue is the end result of a number of different cerebral pathology. The normal value of ICP at supine position is 10 to 15 mm of Hg. If there is sustained elevation of ICP over 20 mm of Hg, then it is called intracranial hypertension. Although according to definition the elevation of ICP > 20 mm of Hg indicates

a pathological states, but it does not always indicate that this high ICP impair the function and viability of CNS. Becasue the impairment of function and viability of CNS depend directly on the type of pathological process, but not on the intensity of the rise of ICP. The increased ICP impair the function and viability of nerve tissue indirectly by jeopardizing the CBF to nerve tissue. It is also often found that during normal coughing, vomiting, straining, etc. the ICP goes well above 30 mm of Hg without any cerebral dysfunction. With high sustained elevation of ICP there is vascular compression, regional ischaemia and/or intracranial tissue shift which is called herniation of brain. This herniation of brain occurs through one of these four sites such as: Through any defect in the bony skull, under the falx cerebri, through foramen magnum, through tentorium cerebelli (Fig. 49.7).

METHODS OF REDUCTION OF ICP OR STRATEGIES FOR PROTECTION OF BRAIN

The strategies for protection of brain is theoretically most effective if it is started before the onset of ischaemia. But practically this is always not possible due to many socioeconomic reasons. There are different types of injury to brain such as trauma, haemorrhage, thrombosis, infarction, vascular spasm, intracranial mass, etc. But the ultimate insult of all these injuries is the reduction of CBF and ischaemia of brain tissue which stops the function of it. The ischaemia involves a process when the supply of energy falls short below the need of it. In the presence of ischaemia the intracellular enviornment deteriorates (by increase in Ca^{2+} and decrease in pH), cell membrane damages and accumulation of free radicals occur that aggravate the insult of ischaemia. The ischaemic brain injury is usually classified as the complete or gobal and the incomplete or focal one. The best example of complete or global ischaemia is cardiac arrest and the best examples of incomplete or focal ischaemia are thromboembolism, rupture of arteriovenous malformation, subdural haematoma, etc. But whatever (focal or global) may be the cause, the importance lies on the rapidity of development of ischaemic insult. Where the occlution of supply of O_2 and subsequently the supply of energy is not acute, then there is a potential period for manipulation of collateral cerebral blood to attenuate the ischaemic insult.

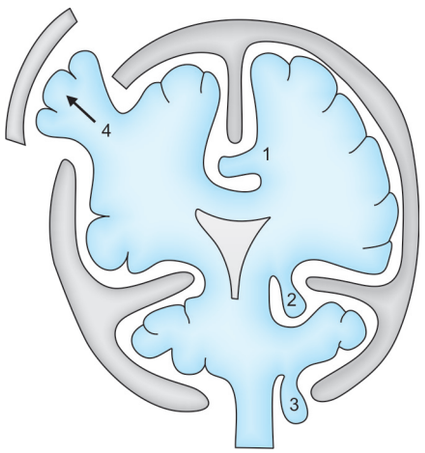


Fig. 49.7: Different herniation site of brain. 1. Under the falx cerebri, 2. Through the tentorium cerebelli, 3. Through the foramen magnum, 4. Through defect in skull.

Whether the insult is focal or global, the goal for the protection of brain from ischaemia are: (i) optimisation of CPP by reducing ICP, by (ii) decreasing in cellular metabolic rate of brain tissue by different methods and (iii) by blocking the action of mediators which cause further cellular injury. There are different methods which helps to reduce the ICP. These are: Cerebral dehydration by using osmotic and loop diuretics, use of corticosteroids, hyperventilation, reduction of cerebral venous pressure, drainage of CSF, surgical decompression, and the use of drugs which increase the cerebral vascular resistance and reduction of CBF. For protection of brain the CMR can be reduced by hypothermia, by anaesthetic agents and by some other specific adjustments. To block the action of different mediators which may cause further cellular injury the corticosteroid is the main stay of treatment.

Reduction of ICP

ICP is reduced by different agents or methods. These are:

Osmotic diuretics

Among the osmotic diuretics the most commonly used drug is 20% mannitol and is used in the dose of 0.25 to 1 gm/Kg average 0.5 gm/Kg) of body weight. It is an inert osmotic agent and preferentially remove more water from brain than other tissues. This is because intact BBB impedes the diffusion of mannitol into the nerve tissue of brain maintaining a strong osmotic diffusion gradient between the nerve tissue and the blood in vessel and withdrawing more water. The decompression action of mannitol on ICP occurs within 10 to 15 minutes after its administration and is independent of its diuretic action. The renal excretion of mannitol and subsequently the osmotic diuresis produced by it occurs within 20 minutes after its administration. This also causes systemic dehydration which also helps to keep the ICP low. Mannitol also reduces ICP by decreasing the formation of CSF. However, with larger doses and repeated administration of mannitol great abnormality in plasma osmolality and electrolyte balance and excessive intravascular volume depletion may occur. Other complications caused by mannitol are congestive heart faliure and rebound increase in ICP. The congestive heart failure is due to the transient initial intravascular hypervolaemia (before onset of diuresis) produced by mannitol as it draws fluid from the extracellular compartment to the intravascular compartment. In pathological conditions when BBB is disrupted, then mannitol itself enters the nerve tissues of brain rapidly (mannitol penetrates the BBB very slowly under normal circumstances)

and potentially can draw water back from circulation into the brain tissue, causing rebound increase in ICP when the plasma concentration of mannitol declines. This rebound increase in ICP can be prevented by restricting the replacement of intravascular volume to about 2/3rd 0.5 gm/Kg of that lost during osmotic diuresis caused by mannitol. Mannitol sometimes also causes transient increase in ICP. This is due to the hyperosmolarity induced dilatation of cerebral and extracerebral vascular smooth muscles (Fact file III).

Mannitol is contraindicated prior to surgical opening of cranium in patients suffering from ruptured cerebral aneurysm, rupture arteriovenous malformation, and sub or extradural haematoma. In such circumstances the osmotic agents (such as the mannitol which is in the collected blood) encourage the further expansion of haematoma (intra or extracerebral) and shrinkage of the healthy brain tissue. In aged patients this sudden shrinkage of brain may rupture the fragile veins entering the sagittal sinus from dura causing further subdural haematoma. Prolonged use of mannitol combined with loop diuretics and fluid restriction may also cause the state of systemic hyperosmolality and electrolyte depletion. The upper limit of hyperosmolality of plasma is 320 mOsm, where beyond this level renal and neurological dysfunction may occur.

FACT FILE - III

Cerebral Oedema

It is defined as the increase in water content of brain and is due to the loss of function of blood brain barrier (BBB). It occurs in three forms — vasogenic, nonvasogenic and interstitial. The vasogenic cerebral oedema is most common and is due to the vascular defect (breakdown of tight junctions between the endothelial cells of cerebral capillaries constituting BBB) allowing the intravascular protein and fluid to escape in the extracellular space of brain parenchyma. The causes of this vascular defect in BBB are trauma, acute hypertension inflammation and endothelial destructive (or vasoactive) substances such as histamine, bradykinin, free readicals, excitating, neurotransmitters, arachidonic acids, etc, releasing from tumour cells. In the pathogenesis of cerebral oedema once the plasma constituents cross the BBB, it draws more water from capillaries and produce swelling. Corticosteroids and Ca^{2+} channel blocker are helpful to reduce this cerebral oedema. Steroids act directly on the capillary endothelial cells by inhibiting the activity of phospholipase A_2 which results in decrease in concentration of lipoxygenase. Ca^{2+} channel blockers act by inhibiting the effect of Ca^{2+} which increase the permiability of capillary endothelium in hypertension.

In nonvasogenic cerebral oedema the integrity of BBB remains intact. The probable explanation of this type of nonvasogenic cerebral oedema are increase in osmolality of brain than that of plasma and toxin. The most common representations of cerebral oedema where brain osmolality increases than plasma osmolality and water is drawn within the brain parenchyma are water intoxication and rapid reduction of blood glucose level during treatment of nonketotic hyperglycaemic coma. The examples of nonvasogenic cerebral oedema where toxin is cause are hepatic encephalopathy, hypoxia, cardiac arrest, different drugs and poisons, etc. The example of interstitial cerebral oedema is obstructive hydrocephalons where over distended ventricles rupture and allow the CSF to enter into the parenchyma of brain.

The clinical manifestation of cerebral oedema is due to the increased ICP. There are no pathognomonic signs and symptoms of increased ICP. The common signs and symptoms are: nausea, vomiting, headache, papilloedema, unilateral dilatation of pupil, paralysis of abducent and occulomotor nerve, etc. In extreme cases there is abnormal ventilatory pattern and loss of consciousness. In such situation clinical examination does not determine the severity of cerebral oedema. So, it is assessed by measuring the ICP directly by measuring the CSF pressure.

The severity and location of cerebral oedema is also assessed by CT scan or MRI. The management of cerebral oedema depends on the pathophysiology of it and several approaches are taken simultaneously. This is because different antioedema measures act synergistically due to different mechanism of action. For example, to reduce the formation of vasogenic cerebral oedema steroid is used to decrease the permiability of BBB and BP is controlled to reduce the hydrostatic pressure which drives the fluid across the capillary wall into the tissue interstitial space. Another example is to increase the reabsorption of oedema fluid in the capillary the osmotic pressure of blood is increased by mannitol.

Loop diuretics

Among the loop diuretics the commonly used agent to reduce ICP is furosemide. It reduces the ICP by three mechanisms: diuresis mediated dehydration of brain like all other tissues reduction of formation of CSF and improved cellular water transport. Its action on brain tissue starts 30 to 45 minutes after intravenous administration. It does not have the problems on CVS such as congestive failure which are inherent to osmotic diuretics. Hence, it is the agent of choice to reduce the ICP in patient suffering from congestive heart failure. In extreme cases the combination of osmotic and loop diuretics is indicated, but it is at the cost of severe intravascular volume and electrolyte depletion. So, the use of these combination is only restricted to patients where there is no pre-existing renal diseases and electrolyte disturbances.

Corticosteroids

These agents are more frequently used to reduce the ICP, which are mainly related to cerebral ischaemia and cerebral oedema. The probable mechanism of action of steroids to reduce ICP are: brain dehydration, inhibition of lysosomal and phospholipase A_2 activity, improvement of the action of BBB, etc. Some thought that the role of corticosteroids to improve the cerebral compliance is still not definitely established. But the general dictum is that the steroids should be used, because if it does not do any good, it does not do any harm. The main drawback of steroids is that it takes hours to be effective in lowering ICP. The side effects during the use of steroids in neurosurgeries are: hyperglycaemia, glycosuria, increased chance of infection, GI bleeding, electrolyte imbalance, etc.

Hyperventilation

In previous discussion it is already stated that lowering of P_aCO_2 has beneficial effect on cerebral insult. It provides this beneficial effect by increasing the cerebral vascular resistance by vasoconstriction

and thus reducing CBF, CBV and ICP. Reduction of P_aCO_2 up to 25 to 30 mmHg by hyperventilation has maximum beneficial effect on ICP with minimum risk of cerebral ischaemia. However, this positive effect of hyperventilation acts till the responsiveness of CO_2 to vascular smooth muscle remains intact. When this reactivity is impaired, (such as during anaesthesia) then hypocapnia may be ineffective in reducing elevated ICP. To control increased ICP the hyperventilation should be initiated as early as possible. Hence, in conscious and cooperative patients with increased ICP hyperventilation is instituted by asking him to take deep and quick repeated breath before induction of anaesthesia during preoxygenation. But if this is not possible, then hyperventilation is immediately started after induction and intubation. So, intubation and hyperventilation is mandatory to reduce ICP in patients with score 7 or less in Glassgow Coma Scale.

Reduction of cerebral venous pressure

When there is impairment of cerebral venous drainage, then the cerebral venous pressure is increased. This increased cerebral venous pressure is associated with increased CBV and increased ICP. So, during neurosurgeries always attempts are made to reduce ICP by removing the factors which impede the venous drainage from brain. Hence, most neurosurgeons prefer to raise the postition of head above the level of chest and avoid any flexion or rotation of neck that impede cerebral venous outflow and cause increased ICP and increased tissue bulk of brain. It is obvious that osmotic diuretics, loop diuretics, hyperventilation, etc. are ineffective in reducing ICP if the cerebral venous drainage is not properly maintained. So, a simple change in head position which impedes the cerebral venous drainage can immediately achieve the desired goal.

Increase in central venous pressure also increases ICP by obstructing the cerebral venous drainage. This is observed in PEEP or any other mode of ventilation where there is potential to increase the intrathoracic pressure causing increased central venous pressure. So, if PEEP is required to improve arterial oxygenation then the rise in P_aO_2 is against the proper cerebral venous drainage and its sequelae. Hence, these two opposite factors have to be balanced. Muscle relaxants can reduce this elevated ICP by decreasing resistance to mechanical ventilation and intrathoracic pressure which impedes the cerebral venous outflow.

Drugs increasing cerebral vascular resistance

Increase in cerebral vascular resistance by vasoconstriction acutely reduces ICP by reducing CBF and CBV. The pharmacological agents causing this effect are propofol, thiopentone, etomidate, lignocaine, etc. However, these drugs receive their best application during induction and maintenance of anaesthesia but not in nonanaesthetised patient. Hyperventilation also reduce ICP by constricting the vessels. But the difference is that these pharmacological agents require coupling between the decrease in CMR caused by these agents and subsequent reduction of CBF, CBV and ICP, which is not seen during the reduction of ICP by hyperventilation. Reduction of ICP by hyperventilation does not decrease CMR, but only constrict the blood vessel and reduce CBF.

Drainage of CSF

Drainage of CSF is a definite method which instantly controls the raised ICP by creating sufficient operative space. This is performed by transdural ventricular CSF tap, prior to dural opening especially when the brain is tight. This is applicable for large supratentorial masses and for decompressing hydrocephalus secondary to posterior fossa tumours. Excessive drainage of CSF through spinal route is also useful for surgery of pituitary lesion, aneurysms, arteriovenous malformation, repair of skull defects, etc. This is performed by introduction of a malleable needle connected with catheter into the lumbar subarachnoid space following induction of anaesthesia. Successful chronic control of high ICP due to hydrocephalus can also be obtained by implanting CSF shunts.

Reduction of secretion of CSF

The reduction of secretion of CSF is an another method of reducing ICP. Approximately 50% of CSF production can be inhibited by acetazolamide. But this effect is transient and has only been used clinically during acute elevation of ICP in chronic hydrocephalus.

Surgical decompression

There are two types of surgical decompression – internal and external. The internal surgical decompression includes complete or partial removal of intracranial tissues or masses. Besides reducing ICP, the internal Surgical decompression can also stop the shifting of brain tissue that are associated with herniation. External surgical decompression includes removal of a portion of skull. But in contrast to internal decompression this external decompression may exaggerate the shifting of brain tissue, while still reduce the ICP. For this reason the external surgical decompression is usually performed only as a last step in the sequence of treating persistent intracranial hypertension.

Protection of Brain

Hypothermia

Hypothermia is justifiably and firmly established as the principal cerebral protective measure in the face of circulatory arrest. This effect is largely due to the reduction of CMR which enhances the cerebral tolerance to the episode of both focal and global ischaemia. Indeed severe hypothermia is often applied for up to 1 to 1½ hours of total circulatory arrest with

little evidence of impairment of neurological function. Hypothermia not only reduce CMR, but also subsequently reduce CBF, CBV, and CSF secretion rate along with ICP. However, this reduction of ICP is more expeditiously accomplished by pharmacological agents and the use of hypothermia to reduce ICP is practised rarely. Pharmacological agents reduce (60%) only that component of CMR which is only associated with the electrical activity of neural cells measured by EEG. Whereas hypothermia causes the reduction of CMR which is responsible for both the electrical (60%) and basal cellular activity (40%). Therefore, hypothermia causes continued decrease in metabolic requirement of nerve cell even after the complete electrical silence of it. A large number of studies have demonstrated that even a mild degree of hypothermia (33° to 35°C) can also offer substantial protection of brain as evidenced by histologically. But Cardiac arrhythmias and a number of other complications related to hypothermia may occur if temperature goes below 28°C. Whenever hypothermia technique is employed to protect the brain, then the use of muscle relaxant and other drugs that centrally suppress shivering may need mechanical ventilation (Fact file IV).

Anaesthetic agents

Previously it is already stated that some anaesthetic agents have protective effect on brain. Among these barbiturates, propofol, etomidate and isoflurane are the most remarkable. With gradual increasing doses they reduce CMR and produce electrical silence. Thus, they eliminate metabolic cost for electrical activity of brain cells. But, like hypothermia they cannot eliminate the metabolic cost for basal cellular activity of neuronal cells of brain. It is also true that like hypothermia these anaesthetic agents are not protective against global ischaemia. Furthermore, their protective effct on brain is not uniform. They are helpful only for focal ischaemia. Other than reduction of CMR, the other mechanisms of protection of brain caused by these anaesthetic agents are: blockade of Na^+ channel, inhibition of free radical formation and inhibition of Ca^{2+} influx. They also protect the brain by reducing ICP by constricting the cerebral vessels and decreasing the CBF and CBV.

Specific adjustments

Among the specific adjustments which have protective value of brain from ischaemia, the Ca^{2+} channel blockers are very important. Further, among the Ca^{2+} channel blockers the nimodipine and nicardipine have been shown to have better neurological outcome if administered following stroke or subarachnoid haemorrhage. But, unfortunately it is not used throughout the whole world uniformly, because still there is some controversy about its positive outcome and nonavailability of parenteral form of these agents. Other agents that have protective effect for brain from ischaemic insult are: dextromethorphan, magnesium, dexmedetomine, etc. Methylprednisolone also has been shown to reduce neurological deficit following spinal cord injury.

Other measures

All the measures which are taken to reduce ICP protect the brain from ischaemic injury. There are also many other measures which protect the brain and reduce the neurological deficit following injury of it. The haematocrit value should be maintained between 30 to 35% for optimum delivery of O_2 to brain tissue. An elevated haematocrit value will reduce CBF because of increased viscosity effect. Lowering of haematocrit value below this optimum level also does not prove effective. Arterial O_2 tension also should be maintained at normal level. The maintenance of high normal CPP is also very important. This is achieved by maintaining normal or slightly

FACT FILE- IV

Pathophysiology of cerebral ischaemia

The brain has very low energy storage capacity, but has very high rate of utilisation of it. So, it is very vulnerable to injury (or ischaemia) in the face of interruption of the supply of energy in the form of substrates such as glucose and O_2. In the pathology of the ischaemic injury of the brain calcium ion acts as a most vital role. All the cellular functions are controlled or mediated by the intracellular Ca^{2+} and its concentration is strictly maintained. Calcium enters the cell through the voltage gated and neurotransmitter gated calcium channel. It is also released from the intracellular storage site such as ER and mitochondria by the action of inositol triphosphate (IP) which is generated by the action of neurotransmitter and the receptor on the cell surface. This intracytoplasmic input of Ca^{2+} is balanced in a narrow range by the extrusion of it from the cytoplasm. This extrusion of Ca^{2+} from the cytoplasm is energy dependent and the processes are: resequestration in ER and mitochondria, extrusion from the cell and inhibition of process that helps to release it from the intracellular storage site.

In ischaemia there is failure of supply of energy (ATP). So, all the energy dependent extrusion processes which help to bring out the Ca^{2+} from cytoplasm are stopped in the absence of ATP. On the otherhand, cerebral ischaemia causes the excessive release of neurotransmitter in the synaptic cleft which activate the influx of Ca^{2+} into the cell through receptor. Thus, in cerebral ischaemia the concentration of intraneuronal Ca^{2+} increases tremendously and over activate the various intracellular enzymatic processes such as lipases, proteases, nucleases, etc. Thus, the over activation of this enzymatic processes cause the structural damage of cell and release of free fatty acid such as arachidonic acid from the cell membrane. Then, this arachidonic acid forms various prostaglandins and leukotrienes with the help of cyclo-oxygenase and lipo-oxygenase and these prostaglandins and leukotrienes bring out all the effects such as vasodilatation, vasoconstriction, change in membrane permeability, leukotaxis, etc., all of which contribute to the evolution of ischaemic insult of neuronal cell of brain tissue.

In the failure of supply of O_2 (ischaemia) lactic acid is formed by the process of anaerobic glycolysis and intracellular pH is decreased. This decrease in intracellular pH further deteriorates the intracellular enviornment and cause injury of neuronal cells. The excessive presence of glucose into the cell stimulate the anaerobic glycolysis and aggravate the lactic acidosis and increase the neuronal injury. So, infusion of glucose solution is not advised in neurosurgery. Thus, lactate formation is an additional element of pathophysiology of cerebral ischaemia.

elevated MAP and avoiding the increase in CVP and ICP. Measures designed to improve CBF is also very important. This is because small increase in CBF have the potential to prolong the survival time of nerve cells.

Hyperglycaemia aggravates the neurological injury following complete or incomplete ischaemia of brain. So, in the presence of cerebral ischaemia withholding of intravenous infusion of glucose containing solution is a standard practice. The plasma glucose level should be maintained below 150 to 180 mg/dl. Still it is in controversy that glucose elevation associated with brain injury may be the result of stress caused by cerebral insult (either traumatic or ischaemic) or hyperglycaemia itself. Hypercapnia and hypocapnia always should be avoided, because both has adverse effects on cerebral injury (ischaemia). Hypercapnia has the potential to worsen the intracellular pH and cause intracerebral steal. On the otherhand, hypocapnia has not generally been proved to be effective in laboratory and clinical setting, inspite of the favourable inverse steal (Robin Hood) effect.

ELECTIVE NON-NEUROSURGICAL PROCEDURES AFTER A STROKE

After a stroke the loss of normal vasomotor responses to P_aCO_2 and MAP (autoregulation) in the early post-insult period is very common. In case of a small infarct this usually persist for 2 weeks, though may last beyond that period depending on the location and the size of infarct. The CBF undergoes marked changes following stroke and the area of both high and low blood flow in brain occur. This is apparent for 2 to 4 weeks. Abnormality in the function of BBB is also found following stroke which is evidenced by accumulation of contrast agent in brain used for CT scan. This is also apparent for approximately 4 weeks in the post-insult period in case of small infarction. However, the histological resolution is not complete for several months and years following stroke which depend on the size and the location of the insult. So, there is no definite statement as to how long elective non-neurosurgical procedures should be deferred following a stroke. But a general agreement is that in case of a small infarct a 6 weeks interval can give some assurances of likely recovery of CO_2 responsiveness, autoregulation MAP and integrity of BBB, though in large infarction this interval may extend up to 6 months. So, at end the conclusion is that it seems reasonable to defer any elective surgery for atleast 6 weeks after small infarction or is performed after 6 weeks from the point at which stable neurosurgical state has been achieved in case of large infarct.

DIFFERENT POSITIONING OF PATIENT DURING NEUROSURGERY

Only for neurosurgeries different pequilar position of patient are required to facilitate the surgical procedures. Among these the supine, prone, lateral and sitting position with their many modifications to a specific procedure are commonly encountered. Certain neurosurgical procedures are long. Hence, some complications only due to these prolonged abnormal position of patient may occur which should be prevented by taking proper care, e.g. good padding of pressure point, avoiding hyperflexion or hyperextension of head, neck and extrimities, etc. During neurosurgical procedures due to prolonged immobilisation of patient in abnormal position the incidence of thromboembolism is also very high which can be lowered by the intraoperative use of pneumatic venous compressive devices on legs and taking other measures.

Supine Position

This position is indicated for frontal, parietal, temporal or sometimes occipital incision with head rotated to one or other side. This rotation of head can impair cerebral venous drainage by obstructing the jugular venous system due to twisting. So, slight reverse Tredelenburg position (10° to 20°) with modest shoulder lift promotes better cerebral venous drainage. In supine position the head is kept at midline without rotating to any side during trans-sphenoidal approach for pituitary and bifrontal craniotomy. For anterior approach to cervical spinal cord this supine position is also used with moderate head traction. In all neurosurgeries, especially for frontal incision, the eyes should be closed and covered properly with thick pad to prevent the antiseptic solution, used for preparation of skin, to come in contact with the eyes.

Lateral Position

This position is used for some special surgeries on spinal cord, and during some surgeries on lateral and posterior cranial fossa. It may be an alternative to supine or prone position and *vice versa*. The main disadvantage of this position is to maintain the stability of patient's trunk exactly in this position for prolonged period because the body is usually inclined automatically due to its weight towards front or backwards. So, sometimes vacuum mattress is used which greatly helps to maintain the patient's body in this position.

Prone Position

This position is used especially for surgery on posterior cranial fossa and for posterior approach of spinal cord. Before positioning to prone, induction of anaesthesia and intubation of patient is done in supine position. Then the patient is turned to prone position carefully with required additional personal. During this positioning from supine to prone the major problem is the maintenance of basic cardiovascular monitoring. Because all the monitoring systems require long cables from the patient's site of attachment to the display modulus which make complicate

this rotation of patient through 180° arc. Frequently they are detached from the patient end or be entangled with each other or give incorrect result due to the movement of patient with continuous buzzing of alarm which distract the attention of anaesthetist from patient in respect to tube position, ventilation, oxygenation, stability of CVS, etc. The Positioning of an anaesthetised patient also may cause circulatory instability. So the total blackout of monitoring during this positioning of patient is also not desirable. Hence, if it occurs then only palpation of peripheral pulses by an anaesthetist during turning of patient from supine to prone can provide a continuous qualitative assessment of cardiovascular status. The ECG contact pads are positioned on the patient's back or side so that patient will not lie on them after positioning.

In prone position if the ET tube comes out of trachea then it is very difficult to reintubate and sometimes it becomes impossible. So, hundred percent full proof fixation of ET tube after intubation is of paramount importance when neurosurgery is done on prone patient. This full proof fixation of tube is again complicated by the inability to use a circumferential tie around the neck which is the location of surgery. So, sometimes to avoid difficulties during turning of patient from supine to prone, awake tracheal intubation in prone position is tried under combination of good local anaesthesia of airway and judicious selection and titration of narcotics or sedatives. Currently this technique is kept reserved only for severely obese patients which cannot be turned from supine to prone after anaesthesia.

After turning the anaesthetised patient from supine to prone position, the head should be kept on a horseshoe shaped rest or on a depression at the head end of the operating table or on a customised disposable head holder. There are many options of supporting the trunk of patient in prone position according to the need of planned operation. First, firm supports are applied under the chest and pelvis, leaving the abdomen free. Second, for lumbar spine surgery the surgeon needs support and fixation of lumbar spine which can be offered by Wilson frame. But whatever may be the support, the compression on abdomen by faulty position should be avoided. Otherwise, the diaphragm will be pushed more towards the thoracic cavity and it will result in increased central venous pressure causing impairment of cerebral venous drainage and engorged epidural veins.

A dreaded complication of prone position during neurosurgery is blindness. This is due to the retinal ischaemia caused by prolonged compression on eyeball in prone position. This may be catalysed by low arterial BP and impaired cerebral venous drainage which will reduce the retinal blood flow and will encourage retinal venous thrombosis. Other pressure points that have to be cared in prone position like eyes are the breasts, genitalias, knees, iliac crest, etc.

Sitting Position

The indications for sitting position in neurosurgery include the lesions in posterior cranial fossa (infratentorial lesions) and posterial cervical spine. However, its use is now diminishing gradually due to the potential serious complications caused by this position, and the presence of alternative position permitting to perform the above mentioned neurosurgeries. The two major hazards which are confronted by patients in sitting position are: the first is due to the influence of gravity on the distribution of intravascular fluid volume, cardiac filling pressure and CPP, and the second is due to (also gravity related) the venous air entrainment resulting in pulmonary and/ or systemic air emboli. Thus, the potential complications caused by sitting position are the venous air embolism (VAE), pneumo-encephalus, circulatory instability, quadriplegia etc. But the sitting position has also many advantages which facilitate the neurosurgical procedures. These are: Better access to midline lesion, low ICP, better venous drainage, better drainage of blood from surgical field by gravity facilitating surgery rather than collecting at the operating site, better drainage of CSF by gravity, less blood loss requiring less blood transfusion, etc. Though its use is gradually diminishing, but it is still used in some centres and some recently developed new neurosurgical procedures find its usefulness (Fig. 49.8).

Actually, the term sitting position is a misnomer. Because the properly done position is nothing but a modified recumbent position where the legs are kept as high as possible which promote better systemic venous drainage (pre-load) and enhance circulatory stability. Recently many modifications are also done of sitting position which permit lowering of head when necessary without taking the patient out of the head holder and not disturbing the continuation of surgery. This is important because it is not always possible to alter the conventional sitting position in the middle of surgery without disturbing it, if VAE is suspected and this will allow precious moments to pass without appropriate treatment is instituted. In sitting position some degree of head flexion is mandatory for better visualisation of surgical site and easy access to the posterior

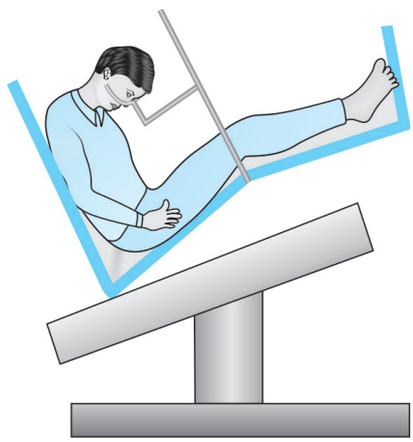


Fig. 49.8: Sitting position of a patient with the head rested on a holder

cranial and spinal structures. But excessive flexion of head has also many disadvantages and should be avoided, maintaining at least a finger breath's distance between the patient's sternum and chin.

Venous Air Embolism (VAE)

In sitting position as the head is positioned above the level of heart, so an open vein and negative intravenous pressure relative to atmospheric pressure during neurosurgery promotes the entry of air in the cerebral venous system causing VAE. The vertical distance between the head and heart varies between 20 to 60 cm in different position of patient during different neurosurgical procedures. So, the incidence of VAE varies as 25, 18, 15 and 10 percent in sitting, lateral, supine and prone position respectively. However, this incidence rate is calculated when the central venous catheter is used for air aspiration and to diagnose VAE. But when the Doppler and other more sensitive monitoring methods are used to diagnose VAE, then the incidence of VAE is increased enormously. For example, this incidence is increased to 50% when Doppler is used to diagnose VAE in suboccipital craniotomy. So, the use of more sensitive monitoring system like Doppler for early diagnosis of VAE also decreases the occurrence of clinically significant VAE (this is because diagnosis at subclinical level make the anaesthetist prompt to take the steps which will prevent the progress of subclinical stage to the clinically significant stage), but increases the reported rate of incidence. Poor surgical technique also increases the incidence of VAE. So, the incidence and the danger of VAE can be reduced only with good monitoring, better surgical and anaesthetic technique and early good communication between the surgeon and the anaesthetist.

Though VAE occurs at any time during craniotomy in any position, but the peak incidence and occurrence time of it is during the sitting position and exposure of bony venous sinusoids at the time of dissection of bone and skin muscles. The maximum incidence of VAE occurs when the major dural sinuses are opened in sitting position. Once air embolism has occurred, the factors which influence the severity are: The volume of air that enters the venous system, the rate of entry, the pressure of the right side of heart, the presence or absence of patent foramen ovale, or VSD, cardiac contractility and the presence or absence of N_2O. The entry of large amount of air within a short period in venous system causes foaming of blood within the heart. This leads to the mechanical obstruction to right ventricular outflow (obstruction to left ventricular outflow occurs if there is patent foramen ovale or VSD) and reflex pulmonary vasoconstriction which results in increased PAP and decrease in the venous return to the left side of heart. Thus, effective pumping action of the left side of the heart is interrupted (cardiac output falls) and cardiovascular collapse is resulted.

The entry of small amount of air in venous system has little clinical significant. It is absorbed at the pulmonary level with little increase of pulmonary arterial pressure (PAP) by reflex mechanism with the release of vasoactive substances which constrict the pulmonary arterial tone. But with the entry of more and more air in venous system and during absorption of it at pulmonary level, the PAP gradually rises coming to a plateau or equilibrium when the entry of air and its maximum absorption capacity by lungs become equal. Crossing this equilibrium causes further increase in PAP, increase in intrapulmonary shunt, decrease in left ventricular output and cardiovascular collapse. The increase in intrapulmonary shunt leads to decline in end tidal CO_2 excretion. Thus, the measurement of $ETPCO_2$ gives an opportunity to detect VAE. The diagnosis of VAE is confirmed by blood gas analysis which shows increased difference in tension between $ETCO_2$ and arterial CO_2, in the absence of recent change in controlled ventilation. Hypoxaemia is the late feaure of VAE and is mainly secondary to the great increase in intrapulmonary shunt.

The use of N_2O as an anaesthetic gas increases the size of intravenous air bubble, because it is 34 times more soluble in blood than N_2 and rapidly diffuses in the air bubbles. Hence, it is suggested that avoidance of N_2O during neurosurgery enhances the safety, especially in sitting position or N_2O should be used only when the sensitive monitor to detect VAE is used and in any suspicion of VAE ventilation with 100% O_2 is immediately instituted, stopping N_2O. With the confirmed diagnosis of VAE attempts are also made to aspirate air from the right side of the heart by central venous catheter which is already placed there for intraoperative monitoring of CVS. The cardiovascular drugs are administered as required to support the circulation. To prevent further entry of air in the venous system the elevation of central venous pressure by elevating airway pressure is not always suggested. This is because it may further reduce the venous return to the heart and may aggravate the cardiovascular instability. The rapid inflation of antigravity G-suit may provide transient cardiovascular support during this critical period by increasing the venous pressure and venous return. After that still if the stability of cardiovascular system is not attained quickly, then the patient is repositioned to supine and cardiopulmonary resuscitation is started as required. Further entry of air in venous system at the surgical site can also be prevented by lowering the head, increasing the cerebral venous pressure by applying compression on internal jugular vein (unilateral or bilateral), packing the wound and flushing the surgical site with sterile saline. So, as soon as the VAE is suspected or diagnosed, then surgeon will be quickly informed and he will immediately flood the operation site with saline. Neck compression is is also given to occlude the neck veins. This will prevent further air

embolism and will cause venous bleeding from the operative site which will allow the surgeon to detect and seal the point at which the air is entering. A central venous catheter should always be placed during neurosurgery in sitting position. Because it will help to aspirate air easily if the above mentioned simple methods fail to prevent large amount of air entering the venous system. It is found that catheter placed in superior vena cava is more helpful to aspirate air than it is placed in the right atrium. The most sensitive method in detecting VAE is the Doppler technique where probe is placed at the right sternal edge between the 3rd and 4th intercostal space. By Doppler method air bubbles as small as 0.5 ml can also be detected. However, the main disadvantages of Doppler in detecting VAE is that its signal is interrupted by the radiofrequency signal of diathermy. Hence, during the peak time of occurrence of VAE, i.e. during the muscle incision and bone work the diathermy is also in full use for this muscle incision and boen work so it will interfre the work of Doppler which is necessary to work at the same time to detect VAE. But the good news is that the newer model of Doppler are now provided with some special filters which are able to reject the diathermy signal and are capable to work without interference.

Pneumoencephalus

It is an another complication of neurosurgery when after dural closure air remains trapped inside the skull and acts as a intracranial mass lesion. Some degree of pneumoencephalus always occurs after neurosurgery in any position, but is found maximum in sitting position (3 to 4 times higher than prone and park bench position). During neurosurgery in sitting position after opening the dura, CSF drains away from the intracranial space and air enters in the cranial cavity like an inverted pop bottle. The air in pneumoencephalus which causes mass effect after the closer of craniotomy wound may be asymptomatic or symptomatic (depending on the amount of air) producing headache, lethargy, confusion, impaired memory, etc. The huge amount of air in pneumoencephalus may also cause shifting of brain tissue along the midline. In the absence of severe symptoms or extensive brain shifting the patient with pneumoencephalus is usually managed conservatively. Because symptoms are commonly non-progressive and resolve after few days in postoperative period. Breathing of 100% O_2 helps to absorb air and tries to resolve pneumoencephalus quickly. Postoperatively the air in pneumoencephalus can be detected both by CT scan and plain X-ray. In the postoperative period if there is expansion of brain due to cerebral oedema (caused by surgical trauma), then the air pocket will be pressurised and may exaggerate the mass effect. Sometimes due to development of tension pneumoencephalus like the tension pneumothorax high pressure may be built-up in the air cavity. The tension penumoencephalus is suspected in patients who shows progressive deterioration of cerebral function or do not awaken following surgery.

N_2O anaesthesia is not contraindicated and can safely be continued until neurosurgery is completed, provided there is no VAE. This is because during surgery with open dura equilibration of N_2O with intracranial air occurs and does not increase ICP. Rather, when the dura is closed at the end of surgery, then the faster reabsorption of N_2O than air reduce the ICP or counter the rise of ICP caused by brain expansion (cerebral oedema) postoperatively.

Cardiovascular instability

Cardiovascular instability evidenced by hypotension is an another complication of sitting position during neurosurgery. It may be mild (when reduction of BP varies between 20 and 30 mmHg) or moderate (when reduction of BP is greater than 50 mmHg) and their incidence is 30% and 5% respectively. So, the preoperative history indicating coronary artery disease, heart failure and cerebrovascular occlusive disease, etc. are contraindication for sitting position during neurosurgery. There are many measures which can prevent the incidence of this hypotension. These are: (i) Slow changes in position from supine to sitting, titrated with the changes in BP, (ii) Use of vasopressor, (iii) Optimum preoperative hydration, (iv) Wrapping of legs with elastic bandages to counteract the gravitational shifting of intravascular blood volume into the lower extramities, and (v) use of antigravity compression device (G-suit). When pins are applied from the head holder to make the head steady in sitting position, then the abrupt elevation of arterial blood pressure occurs and this is due to the stimulus arising from the application of pin on head. The infiltration of the site of pin prick by local anaesthetic agent or addition of bolous dose of IV anaesthetic agent just before application of pin blunt this response of hypertension. However, some anaesthetists apply the pins from headholder to keep the head steady just prior to arrange the patient in sitting position and tries to counteract the hypertension caused by pinprick by hypotension caused by immediate sitting posture.

MONITORING DURING NEURO-ANAESTHESIA

Extensive monitoring during neuroanaesthesia is very important for better outcome, because neurosurgery is frequently complicated by rapid and large amount of blood loss, different positions of patient required for surgery has different special complications, surgeries especially those in the posterior fossa may involve cardiovascular instability, hypotension, etc. So, all the patients undergoing neurosurgery need: (i) a large bore intravenous cannula for rapid transfusion of crystalloid, colloid or blood, (ii) arterial cannulation for beat to beat monitoring of arterial blood

pressure, (iii) central venous cannulation for measurement of central venous pressure and diagnosis of VAE, (iv) cannulation of cerebral ventricle (usually lateral) for measurement of ICP from where CPP can be derived, etc. For correct measurement of CPP the pressure transducer should be placed at the level of the base of the skull for referencing the zero adjustment. In sitting position the pressure transducer which measures the MAP should be placed at the level of the base of the skull to know accurately the pressure by which the blood is forced into the brain. The importance of acurate measurement of CPP is that as little as 5 to 10 mmHg difference in pressure below the critical ischaemic threshold value may cause the brain damage if maintained for prolonged period. The central venous catheter provides measurement of intravascular volume status, diagnose air embolism and evacuate intravascular gas.

In addition to the above mentioned monitorings the measurement of SPO_2, core temperature (preferably nasopharyngeal or oesophageal) and $P_{ET}CO_2$ are also mandatory during neurosurgery. The measurement of O_2 saturation is very important, because the patients undergoing neurosurgical procedures are more sensitive to arterial hypoxaemia and it causes brain swelling (oedema) from hypoxaemia induced hyperaemia. Moreover, many of the conditions for which neurosurgery is shouted is related to focal cerebral ischaemia to which the addition of slight degree of hypoxaemia causes more danger. As it is previously stated that the control of P_aCO_2 is one of the factor of improving the quality of neuroanaesthesia, so the measurement of $P_{ET}CO_2$ is immense importance. It helps to set accurately the levels of ventilation and to monitor the occurance of VAE. At the beginning of surgery the difference between $P_{ET}CO_2$ and P_aCO_2 is measured from capnography and blood gas analysis and then it is repeated throughout the whole intraoperative procedures intermitently. Normally, this difference varies between 2 to 5 mmHg.

The measurement of body core temperature is also important because most of the neurosurgical procedures are prolonged and these prolonged surgeries are associated with large fall in body temperature. This hypothermia causes postoperative shivering producing hypoxaemia, increased intrathoracic pressure, ventilatory impairment, etc. Measurement of oxygen saturation (SPO_2) from internal jugular vein also provides a useful guide to the occurrence of global cerebral ischaemia. The normal range of value SPO_2 in the blood of internal jugular vein is 55 to 85%. Values above this range indicate hyperaemia and values below this range indicate that demand of O_2 is greater than supply of it.

For monitoring of venous air embolism the Doppler technique has already been described. But the transesophageal echocardiography (TEE) is 10 times more sensitive than Doppler technique in detecting VAE. This is because it provides visual representation of air bubble in the right and left side of the heart. It also can detect patent foramen ovale and VSD by detecting air in the left side of the heart. But the disadvantage of TEE is lack of specificity. This is because it can detect fat and blood emboli and cannot differentiate them from air.

Attempts are also taken for the electrophysiological monitoring of brain by analysis of EEG and evoked potential to assess the functional integrity of CNS. But the proper application of these monitoring system depends on the specific area from where the signal is picked up or monitoring is done and recognition of anaesthesia induced changes of this area (depth and dose related changes and changes related to physiological variables such as blood pressure, body temperature and respiratory gas tension).

EEG is very helpful for assessing the adequacy of cerebral perfusion and the depth of anaesthesia, especially during controlled hypotension in neurosurgery and in carotid endarterectomy. The changes in EEG are described as either depression or activation. The EEG depression is manifested by high voltage and low frequency curve and found in deep anaesthesia or cerebral damage. Whereas the EEG activation is manifested by low voltage and high frequency curve, and in found in light anaesthesia or surgical stimulation. Most of the inhalational and intravenous anaesthetic agents cause initial cerebral activation, followed by dose dependent depression of EEG. This is called the biphasic pattern of change in EEG. With the further increase of dose all these anaesthetic agents produce burst suppression with or without changes of EEG to isoelectric level (Electrical silence). With the high dose the desflurane and sevoflurane produce burst suppression, but not the electrical silence. Whereas the isoflurane causes isoelectric EEG. The barbiturates and propofol produce both burst suppression and isoelectric EEG at high doses. Whereas, opioids cause only monophasic dose dependent EEG changes, i.e. depression. Ketamine only causes activation of EEG which is consist of rhythmic high amplitude theta activity. With the increase in dose of ketamine this theta waves are replaced by high amplitude gamma and low amplitude beta waves.

Evoking the response of a nerve, either motor or sensory, after giving a stimulus is called the evoked potential. Analysis of this evoked potential for monitoring of nervous system is more complicated than EEG which does not need any stimulus for its evoking (and recording) and is the difference between the two. All the evoked potential have the latency period which are classified as short, intermediate and long. The evoked potential of intermediate and long latency period arise from the cortex, whereas the evoked potential of short latency period arise from the brainstem, spinal cord and spinal nerves. These short latency evoked potentials are least affected by anaesthetic agents, while the intermediate and long latency evoked potentials are

affected even by the subanaesthetic doses of inhalational and intravenous anaesthetic agents. But evoked potential with long latency period cannot be measured during intraoperative period. So, the short and intermediate latency evoked potential are only used during the intraoperative monitoring of neuroanaesthesia.

There are two types of evoked potential sensory and motor. The sensory evoked potential is again of two types—somatosensory (general sensation) and special (auditory and visual). The motor evoked potential is best useful to assess the adequacy of function of spinal cord during aortic surgery. Whereas the somato-sensory evoked potential is best useful to assess the functional integrity of sensory cortex and dorsal spinal columns carrying the sensory nerve fibres during surgeries on spine and aorta. Among the visual and auditory, the visual evoked potential are easily affected by anaesthetic agents, whereas the auditory evoked potential are the least and last to be affected. The visual evoked potential is usually used to monitor the upper brainstem and optic nerve during surgery on large pituitary tumours. The auditory evoked potential is used to monitor the 8th cranial nerve during surgery in posterior fossa.

All the anaesthetic agents, intravenous and inhalational, depresses (decrease in amplitude and increase in latency) the both motor and sensory evoked potential. But the effect of volatile agents are greater than the intravenous agents. However, among the intravenous anaesthetic agents the barbiturates do not depress the evoked potential, even when the EEG becomes isoelectric. Opioids depress the evoked potential by increasing the period latency, but not decreasing the amplitude.

ANAESTHETIC MANAGEMENT

Anaesthesia for surgery or diagnosis of different neuropathological conditions may be required in OT or in the imaging room for CT scan, MRI, or X-ray. Usually, these patients are very sick. So, proper assessment of these patients for fitness of anaesthesia is very important. In addition many special risk factors arising from neuropathological diseases for which surgery or radiodiagnosis and anaesthesia is shouted must be evaluated as if appropriate anaesthetic procedure can be taken. The most common neuropathological condition for which neuroanaesthesia and neurosurgery is shouted is the intracranial mass. It may be congenital or acquired. The acquired variety again may be again noninfective or infective (cyst or abscess), neoplastic (benign or malignant and primary or secondary), vascular (aneurysm, haematoma, arterio-venous malformation). The primary neoplastic tumour may arise from supporting tissues (meningioma), ependymal cells (ependymoma), glial cells (astrocytoma, medulloblastoma, glioblastoma) or pituitary gland (pituitary adenoma). Astrocytoma and medulloblastoma are the most common primary brain tumour in children. Whereas the most common acquired primary brain tumour in adult are meningioma, glioblastoma, pituitary adenoma. The secondary metastatic brain tumour is also common in adult and the primary sites are lungs and colon. Astrocytoma is a typically benign slow growing tumour in any cerebral hemisphere and medulloblastoma most often arise from cerebellum.

The signs and symptoms of patients with intracranial mass or any space occupying lesion presenting for neuroanaesthesia and surgery depends on the location and the growth rate of this mass or this space occupying lesion and the rate of increase of ICP. A benign slow growing tumour may be asymptomatic for long periods. Whereas a rapidly growing tumour present with a lot of symptoms and signs within a short period before anaesthesia and surgery. Increased ICP is the most likely explanation for signs and symptoms caused by a brain tumour. So, the common symptoms of intracranial mass are headache, nausea and vomiting, convulsions, focal neurological deficit, mental changes, disturbances of consciousness, etc. The supratentorial lesions usually relate to the cerebral hemisphere dysfunction and present as hemiplegia, convulsions, spatial disorientation, dysphagia, etc. Whereas the infratentorial lesions rapidly cause obstructive hydrocephalus and intracranial hypertension. Ataxia, nystagmus, dysarthria and abnormalities in respiratory pattern localize the lesions at posterior fossa.

Preoperative Assessment and Premedication

The preoperative evaluation of a patient with intracranial mass presented for neurosurgery and anaesthesia and anaesthesia is primarily directed towards the establishment of presence or absence of increased ICP and the assessment of neurological status using general and neurological examinations which consist of documentation of the patient's present level of consciousness, any cranial nerve dysfunction, any other gross focal neurological deficit, presence or absence of vomiting, mydriasis, palpilloedema, bradycardia, breathing disturbances, etc. This examination of patient should also be repeated in the OT just prior to the induction of anaesthesia. This is because any changes in patient's neurological status can occur overnight and/or precipitated by premedication. When the spinal surgery is planned, then the preoperative neurological assessment should be focussed on the function of the structures which is controlled by the segment of spinal cord that is involved in the surgical procedure (Table 49.2).

The neurosurgical patients are often dehydrated, hyperglycaemic and have the history of convulsions. Among the factors which contribute to this dehydration include: Decreased fluid intake due to reduced level of consciousness, use of diuretics (osmotic and loop) to reduce ICP, iatrogenic restriction of water input

Table 49.2: Glasgow coma scale

Sign	*Evaluation*	*Score*
Eye opening	Spontaneous	4
	To speech	3
	To pain	2
	Nil	1
Verbal response	Oriented	5
	Confused conversion	4
	Only few inappropriate words	3
	Few sounds	2
	Nil	1
Motor response	Obey command	6
	Localises pain	5
	Withdrawl	4
	Flexion response	3
	Extension response	2
	Nil	1

to reduce cerebral oedema, neuroendocrine abnormalities, etc. Patients are often hyperglycaemic because steroids are used in high doses to reduce ICP by decreasing brain oedema. So, the history of preoperative medication should be focussed on the use of diuretics, corticosteroids and the anticonvulsant medications. Laboratory investigations are also should be directed to rule out any electrolyte disturbances caused by diuretics, or hyperglycaemia induced by corticosteroid. Radiological investigations such as CT scan, MRI, straight X-ray must be reviewed to find out any shifting of brain tissue along the midline, the size of the ventricle and the presence or absence of cerebral oedema. The supratentorial lesions are usually presented to an anaesthetist with problems related to increased ICP due to cerebral oedema. Whereas the infratentorial lesions are presents to an anaesthetist with problems related to different surgical position during surgery (prone or sitting), the proximity of surgical site to vital brainstem structures involved in circulatory and respiratory controls, and hydrocephalus.

Premedication before neurosurgery depends on the level of consciousness of the patient. Usually, heavy sedation with or without narcotics is not appropriate in this group of patients. This is because respiratory depression causes increase in P_aCO_2 which may produce cerebral vasodilatation and further increase in ICP. But many patients who have no impairment in the level of consciousness is very apprehensive at the thought of having a neurosurgery and is associated with the increased level of plasma catecholamines. This causes undue hypertension which is obviously dangerous in respect to rupture of an unclipped aneurysm. So, for these group of patients premedication with proper sedation is appropriate which is provided by oral benzodiazepines in titrating doses. Patients who are waiting for spinal surgery due to disk prolapse suffer from acute pain. In this group of patients the use of strong analgesic (narcotic or non narcotic) as premedicant is very valuable.

Induction and Intubation

Induction and intubation are an art in neuroanaesthesia for patients with elevated ICP and compromised cerebral compliance. The aim of an anaesthetist during induction and intubation in neuroanaesthesia is to prevent the elevation of ICP at any cost by maintaining the arterial blood pressure at normal level and controlling ventilation to maintain P_aCO_2 between 30 and 35 mmHg. Arterial hypertension during induction and intubation increases CBF, CBV and ICP. Thus, it decreases the CPP and promotes cerebral ischaemia and oedema. However, excessive reduction of MAP also decreases CPP and impair cerebral function. Some neurosurgical conditions for which anaesthesia and surgery is shouted such as subarachnoid haemorrhage from ruptured aneurysm and head injury, etc. produce local cerebral ischaemia by vasospasm. So, in such circumstances hypotension should be avoided to prevent further increase in ischaemia. During induction the position of patient should be such that the drainage of blood from cerebral veins should not be obstructed.

Before induction all the measures (described before) are taken to reduce ICP, if it is already elevated. At all the stages of induction and intubation procedure the hypoxia, hypercarbia and vasodilating agents should also be avoided at any cost. For induction in neuroanaesthesia the most commonly used agents are thiopentone, propofol and etomidate. Thiopentone and propofol are very useful for this purpose, because both these agents reduce CMR with resultant reduction in CBF and ICP, particularly when an SOL with increased ICP is present. Etomidate also reduces CMR like thiopentone and propofol, but give better cardiovascular stability and is associated with greater rise in MAP during laryngoscopy and intubation than the other two inducing agents. All the cooperative and conscious patients are asked to hyperventilate for hypocapnia during preoxygenation before induction of anaesthesia. After induction the patient is also hyperventilated manually by mask and bag and this can also easily be done with the help of neuromuscular blocking agent which will facilitate later in intubation and will prevent coughing, bucking and straining, all of which will abruptly increase ICP.

In neuroanaesthesia the intubation is usually performed by nondepolarising muscle relaxant. Among these vecuronium, cisatracuranium, rocuronium, etc. provide the greater haemodynamic stability. Preoperative neurological impairment frequently leads to muscle wasting. When this degenerative process of muscle is of recent onset or is chronically progressive, then the use of succinylcholine for intubation is contraindicated. In such circumstances the depolarising agent causes development of severe hyperkalaemia and related arrythmia. Succinylcholine may also increase ICP during fasciculation. So, it is not generally used in neuroanaesthesia. But, succinylcholine is the agent of choice in neuroanaesthesia when there is probability of difficult intubation or risk of aspiration. Intubation should always be attempted, when the peak effect of muscle relaxant is reached and the muscular

relaxation is complete and maximum. Otherwise coughing, bucking, straining, etc. resulting from premature attempts of intubation prior to the establishment of deep muscular relaxation will cause increased ICP due to marked pressure response and increased intrathoracic pressure which impedes the cerebral venous drainage. Laryngoscopy and intubation is associated with acute surge of sympathetic overactivity causing acute hypertension and increased ICP. This acute pressure response during laryngescopy and intubation presents an obvious extra risk to neurosurgical patients with an arterial weakness such as in aneurysm or arteriovenous malformation for haemorrhage. There is also a great danger for patients with vascular tumour. This is because with the acute rise of blood pressure during intubation, the bulk of the tumour also rises causing increase in ICP. Indeed, there is also likely to be an increase in ICP in patients in whom there is no vascular tumour. This is because the rapidity of the pressure response due to intubation exceed the ability of cerebral circulation to be autoregulated (Fact file V).

So, this pressure response related to laryngescopy and intubation should be attenuated at any cost and is usually achieved by the use of any short acting opioids such as fentanyl in the dose of 2 to 3 µg/Kg or any of its congener just prior to induction and intubation. Other measures which attenuate this pressure response are the use of β-blockers (esmolol 0.5 to 1 µg/Kg), or lignocaine (0.5 to 1 mg/Kg IV 90 sec before intubation) or deepening the anaesthesia with the additional dose of thiopentone or propofol. This intubation related pressure response can also be attenuated by hyperventilation with low dose (less than 1 MAC) of isoflurane and sevoflurane. Due to the potentially deleterious effect on cerebral blood flow and ICP the vasodilators such as nitroprusside, calcium channel blockers, nitroglycerine, etc. should generally be avoided, till the dura is opened. The transient hypotension due to any cause during induction and intubation or during the course of anaesthesia is generally treated by incremental doses of vasopressors (noradrenaline, phenylephrine or ephedrine) rather than intravenous fluids.

FACT FILE- V

There are many causes for the subarachnoid haemorrhage (SAH) and among these causes the subarachnoid rupture of intracranial aneurysm (75 to 80%), rupture of arteriovenous malformation (5%), idiopathic (15%) and the rupture of vascular tumours account for the majority. Following SAH the neurological status of a patient is classified by Hunt Hess gradation. This is a follows:

Grade I	Minimum headache, slight nuchal rigidity, or asymptomatic.
Grade II	Moderate to severe headache and nuchal rigidity, cranial nerve palsy (often occulomotor).
Grade III `	Drowsiness, confusion, focal neurological deficit.
Grade IV	Stupor, hemiparesis, early decrebrate rigidity.
Grade V	Deep coma.

The rebleeding (principal cause of death) after spontaneous stoppage of bleeding from ruptured aneurysm and cerebral vasospasm (principal cause of ischaemia) are the two devastating early comlications of SAH following rupture of an aneurysm. So, for grades I to IV the early clipping by surgical intervention within 72 hours of the initial rupture of aneurysm is the management of choice. But, unfortunately this early treatment is technically more difficult due to oedema of tissue and there is less time to stabilise the patient with concomitant medical conditions. If early intervention is not possible, then surgery is often delayed till the risk of maximum vasospasm has decreased. A number of aneurysms are currently treated by endovascular coiling and these patients are very sick with greater number of medical comorbidities.

Cerebral vasospasm following SAH due to ruptured aneurysm or other reasons is the cause of delayed cerebral ischaemia. It can present as neurological continuum form drowsiness to stroke. The aetiology of this cerebal vasospasm following SAH is believed to be due to the presence of blood in subarachnoid space around the circle of Willis in the basal cisterns. So, the blood clot should be removed at the time of clipping of a ruptured aneurysm to decrease the incidence of vasospasm. The signs and symptoms of vasospasm is usually seen is 40% of patients after 5 to 15 days following rupture of an aneurysm. Angiography most early demonstrates vasospasm and surgery is delayed if it is suspected.

The cerebral vasospasm following SAH is usually treated by hypertensive, hypervolaemic haemodilution. This hypervolaemia is achieved by intravenous infusion of crystalloid or colloid solution, maintaining CVP between 8 to 12 mm of Hg and PCWP between 18 to 20 mm of Hg. This hypervolaemia will result in haemodilution with ideal haematocrit value between 27 to 30%. This reduces the viscosity of blood and improves the microcirculation of brain. After the clipping of aneurysm vasopressor (dopamine) is used to induce hypertension maintaining MAP at 20 to 30 mm of Hg above the baseline systolic pressure. This will also counteract cerebral vasospasm and improve circulation. Calcium channel blockers (nimodipine, nicardipine) have also been found to decrease the vasospasm if started within 4 days of SAH. They are not affective if vasospasm is already established.

Maintenance of Anaesthesia

During maintenance of neuroanaesthesia an anaesthetist must concentrate his mind on some important factors which will help him to provide good quality of anaesthesia and avoid many complications. These are: Maintenance of stable arterial BP (no hypertension, no hypotension), avoidance of factors that lead to increased ICP (such as hypoxia, hypercarbia, vasodilating drugs, cerebral venous obstruction), maintenance of adequate CPP, reduction of brain bulk (cerebral swelling), avoidance of cerebral ischaemia, etc. Now, to provide neuroanaesthesia of good quality by maintaining the above mentioned factors a deep plane of anaesthesia is required, sometimes with induced hypotension and hypothermia. But, on the otherhand after surgery rapid recovery of consciousness is essential, so that the level of response can properly be assessed to know the functional integrity of central nervous system. So, the neuroanaesthesia is essential to balance between these two-deep anaesthesia but quick recovery.

After opening the skull and dura (the most painful part of neurosurgery) the part

of neurosurgery which is only confined within the brain matter itself is painless unless the dura is stretched during the handling of brain tissue which is most likely to occur near the points of dural attachment. During neurosurgery the only painful part is the initial craniotomy which includes cutting of the skin, reflecting of the galea, drilling of the bar holes and stripping of the dura or periosteum from the bones. The another painful part of neurosurgery is when the head is held by a head clamp in which pins (mounted in a frame) are fixed into the outer table of the skull. This pain can be ameliorated by giving appropriate analgesic just before the pins are applied or infiltrating the skin by local anaesthetic agent. Hence, in neurosurgery even through the period of pain stimulus is fairly limited, still the neuromuscular blocking agents are used judiciously to maintain the deep plain of anaesthesia. This is because: (i) It helps to prevent any slight intraoperative movements, coughing, bucking and straining, etc. which increases the ICP; (ii) it helps to reduce the dose of anaesthetic agents and quick recovery, (iii) it helps in proper ventilation and reduction of ICP, etc.

Neuroanaesthesia is usually prolonged and lasts for several hours. It is frequently maintained by N_2O, opioids (fentanyl or any of its congener) and nondepolarising muscle relaxant. During the maintenance of neuro anaesthesia the airways, venous access and monitoring lines etc, should be well secured in such a way that an anaesthetist can completely rely on it up to the end of surgery as the clinical monitoring is not possible intraoperatively due to inaccessibility of the upper portion of the patient. Normally, during neuroanaesthesia an armoured ET tube is used to avoid kinking due to the different position of patient. It is fixed in such a fashion that the fixation tape or rope does not produce any pressure on the vein of head and neck and will leave the cerebral venous drainage free. Many anaesthetists like to support the ET tube by orrpharyngeal pack, especially if prone or sitting position is chosen. The placement of tube is also very critical. Because if it is placed too close to the carina, then slight flexion of patient's head and neck to facilitate the surgery will cause the tube to be advanced into any of the main bronchous – right or left. On the otherhand, if it is placed too close to the vocal cord, then slight extension of patient's head and neck will cause the tube to come out of the trachea (Fact file VI).

The intraoperative part of neuroanaesthsia is maintained by hyperventilation, keeping the P_aCO_2 between 30 and 35 mmHg, the cause of which is discussed before. But lowering of P_aCO_2 below 25 mmHg by more and more hyperventilation provides a little additional benefit. Rather it causes some disadvantages by shifting the O_2-Hb dissociation curve to the left which offset the release of O_2 from Hb in tissues. Thus, it causes tissue hypoxia. Hypocapnoea also causes cerebral vasoconstriction and cerebral ischaemia. Wrong ventilating patterns such as PEEP or rapid and small tidal volume ventilation should be avoided. This is because they cause high mean airway pressure which has adverse effect on ICP by increasing CVP. But in severely hypoxic patients due to lung pathology PEEP is used to maintain arterial oxygen tension at normal level to save the life.

All the volatile anaesthetic agents cause the cerebral vasodilatation and increase the cerebral blood flow in different proportions. Thus, they increase the bulk of brain tissue and is not used in neuroanaesthetic. But isoflurane, sevoflurane and desflurane are used by some anaesthetist in low doses below the value of 1 MAC to control the intraoperative persistent hypertension. In such circumstances it is thought that the gradual increase in hypertension may cause more danger than this small dose of volatile agents. However, some anaesthetists have opinion that volatile anaesthetic agents can be used successfully if hyperventilation is maintained at the same time. This is because increase in CBF caused by volatile anaesthetic agents is counteracted by the reduction of CBF caused by hyperventilation. Volatile anaesthetic agents affect the reactivity of cerebral vessels to the changes in P_aCO_2. This affect is greater with isoflurane than sevoflurane. So the decrease in ICP by hyperventilation is more successful in isoflurane anaesthesia than in sevoflurane and desflurane anaesthesia.

Blood loss in neurosurgery is usually less than 500 ml. But sometimes during handling of some vascular tumours such as meningioma, aneurysm, arteriovenous malformation, etc. rapid extensive blood loss may occur. Therefore, the ability of an anaesthetist to replace the blood which is lost and to control the arterial pressure

FACT FILE - VI

With the opening of skull by craniotomy the ICP falls to atmospheric pressure. But, if the factors which was responsible for the increased brain bulk due to increased ICP are still remain active, then it will be difficult for a surgeon to retract the swelled up brain during surgery. Sometimes surgery becomes impossible or increased pressure on oedematous brain by retractor cause neuronal damage. Moreover, if the swelling of brain is marked, then part of it protrudes through the dural incision and tight edges of dura will impair the CBF causing cerebral infarction. It is also true that if there is moderate swelling of brain, then closure of dura at the end of surgery will be difficult causing pressure underneath the dura by swelled brain which also result in cerebral infarction or sometimes the closure of dura becomes impossible.

Therefore, it is important to prevent the increase in brain bulk. This is possible by avoiding the factors (faulty) which help to increase the brain bulk (swelling of brain) and by using drugs which will reduce swelling of brain after it occurs.

The faulty factors which causes swelling of brain are:

1. Poor cerebral venous drainage
   a. Head down position
   b. Jugular venous obstruction
      ↑Intrathoracic pressure
      Neck rotation and tapes around neck
      Bad ventilator setup
   c. PEEP
2. Hypercapnia and hypoxia
3. Inadequate muscle relaxation
4. Arterial hypertension

is important. In neurosurgical patients hyperglycaemia is a common occurrence and this is due to the stress and the use of high doses of corticosteroids to reduce ICP. Hyperglycaemia causes increase in ischaemic brain injury. So, the intraoperative intravenous fluid management should be restricted to only glucose free isotonic crystalloid (normal saline) or colloid solution. But the large amount of crystaloid solutions is avoided in nueurosurgical patients, because it may precipitate severe brain oedema. So, the amount of intraoperative fluid replacement by crystalloid solution should be below the calculated required value. Colloid solutions are generally used to restore the intravascular volume deficit, whereas the isotonic crystalloid solutions are used as a maintenance fluid. Urethral catheterisation is essential during neuroanaesthesia, because it helps to know that diuresis has developed after the use of osmotic diuresis and it also helps in the intravascular fluid management.

Extubation and Emergence from Anaesthesia

At the end of surgery after the dressing of head and bandages are applied, the decision should be taken if the patient remains intubated or is extubated, on the basis of the intactness of the neurological function. If the decision is taken that the patient remains intubated, then more sedation and / or muscle relaxant is added. But if the extubation is decision, then it is a hard task to an anaesthetist. Because it should be very smooth and at any cost coughing, bucking or any other type of straining which may precipitate the intracranial haemorrhage or worsen the cerebral oedema by increasing ICP should be avoided. When the surgical team is moved away from the side of the patient by completing everything, then the anaesthetic team takes this site and the patient with the table is turned back to their original position. Then all the monitoring and the IV lines are checked, and the oropharyngeal pack is removed if it is placed. After that anaesthetic gases are turned off and attempts are made to have the patient breathe spontaneously by reversing the neuromuscular block. When this reverse is judged as complete and the patient is able to take full breathe, then a gentle laryngoscopy should be carried out and the pharynx is cleared quickly from secretion. After that the patient is extubated smoothly.

Some anaesthetists use lignocaine (1 to 1.5 mg/Kg IV) or small dose of thiopentone (20 to 40 mg) or small dose of propofol (20 to 30 mg) 90 seconds before suctioning, in an attempt to suppress the coughing and bucking during extubation. Some anaesthetists use esmolol, verapamil (0.1 mg/Kg) and / or remifentanil (1 µg/Kg) to attenuate the cardiovascular responses during extubation. After extubation rapid awakening and rapid return of cerebral function is desirable, because it helps to assess the neurological function. However, delayed awakening may occur and is due to the overdose of opioid or prolonged use of volatile anaesthetic agents. Postoperative pain after neurosurgery is less severe than the other form of surgeries. So, analgesics should be given very carefully and the overdose of it may confuse the neurological assessment of patient. However, some patients experience severe postoperative pain, especially those who have undergone frontal craniotomy. In such patients adequate analgesia is needed to avoid over sympathetic activity. In the postoperative period after neurosurgery most patients are sent to ICU for close intensive monitoring of neurological, cardiovascular and respiratory function. When the surgery is finished and craniotomy is closed, then some air is frequently left in cranial cavity. This is seen in all the scans or X-ray which are taken on the first postoperative day. Among these 2/3 collections are judged as moderate or large. This incidence comes down to 70% at the end of the first week following surgery. At the end of the 2nd postoperative week 10% collection of air is judged to be moderate and large.

SOME SPECIAL NEUROSURGICAL PROCEDURES

Cerebral Aneurysm

The cerebral vascular aneurysms are usually located at the bifurcations of major cerebral vessels at the base of the brain (circle of Willis) and rupture of it is the most common cause of non-traumatic intracranial haemorrhage. The cerebral aneurysms are diagnosed both in ruptured or unruptured phases. In ruptured aneurysm the bleeding is manifested as subarachnoid, epidural or intracranial haemorrhage and among all the causes of subarachnoid haemorrhage (SAH) the rupture of cerebral aneurysm in subarachnoid space is the most common. The aneurysm is usually manifested as a single one and of different sizes. But only 10 to 20% of patients have more than one aneurysm and those which are larger than 5 to 7 mm in diameter are considered for elective surgical obliteration if it is diagnosed in unruptured state.

The acute mortality following rupture of an aneurysm is very high. Of those that survive from the initial acute insult of haemorrhage, about 10% subsequently die within one week and about next half of the survivors die within next 3 months after the onset of rupture. Further, among these survivors half of the patient have major neurological deficits. Despite successful surgical clipping of a ruptured aneurysm, 1/3 of the patients do not get back the preruptured quality of life. The major causes of this high rate of morbidity and mortality following subarachnoid haemorrhage from ruptured aneurysm are: rebleeding, ischaemic cerebral injury, infarction due to cerebral vasospasm which is the characteristic of SAH, development of hydrocephalus, etc. The cerebral vasospasm following rupture of an aneurysm in subarachnoid space is probably due to the breakdown products of oxyhaemoglobin which causes scavenging

of nitric oxide from the wall of blood vessels and thus block the vasodilating effect of it. The development of hydrocephalus due to the rupture of cerebral aneurysm in subarachnoid space is caused by the interference of absorption of CSF by RBC. The cerebral vasospasm occurs in 25 to 30% of patients and is the major cause of morbidity and mortality following rupture of an cerebral aneurysm in subarachnoid space. So, the Ca^{2+} channel antagonists (nimodipine) are used to prevent this cerebral vasospasm and reduce the morbidity and mortality of SAH following ruptured aneurysm (Fig. 49.9).

Usually most of the patients suffering from aneurysm of cerebral vessels present after rupture. But before rupture the prodromal signs and symptoms of an undiagnosed aneurysm are: Headache, third cranial nerve palsy (most common), visual field defect, convulsion, trigeminal neuralgia, hypothalamic pituitary dysfunction, etc. These are due to the local compression of nerve tissues by expanding aneurysm. The unruptured aneurysm are usually diagnosed incidentally by CT angiography, MRI angiography or simple angiography. The treatment of unruptured intracranial aneurysm are elective surgical clipping following craniotomy or obliteration of it by interventional radiology. These patients are usually of good health and aged between 40 to 50 years.

On the other hand, the ruptured aneurysm presents with acute signs and symptoms which depends on the amount of blood in subarachnoid space. Minor bleeding in the subarachnoid space presents only with slight nuchal rigidity, headache and other minor signs of meningeal irritation. The transient increase in ICP in this type of subarachnoid haemorrhage reduces the pressure gradient across the ruptured aneurysm and subarachnoid space and promotes the tamponade effect on bleeding. So, bleeding from aneurysm is stopped and partial to complete neurological functional recovery may occur spontaneously with this type of subarachnoid haemorrhage. However, more severe bleeding in subarachnoid space may lead to tremendous increase in ICP formation of clot, hrniation of brain, unconsciousness and rapid demise. All these are due to the rapid development of severe intracranial hypertension, precipitous fall in CPP and cerebral ischaemia. These acutely comatosed patients are managed in intensive care unit by proper maintenance of airway, ventilation, oxygenation, etc. In this life threatening condition medical intracranial decompression therapy is instituated immediately which is followed by craniotomy, evacuation of clot and then control of bleeding by clipping of the ruptured aneurysm. However, the lowering of ICP by medical decompression therapy may increase the chance of rebleeding from a ruptured anewrysm by withdrawing the tamponade effect. But it should be kept in mind that this chance of rebleeding should be balanced against the risk of death caused by the extremely high ICP and ischaemia of brain, if ICP is not reduced. So, the general opinion is that ICP should always be reduced by medical intracranial decompression thereby before craniotomy aimed for the clipping of aneurysm (Fact file VII).

The aim of neurosurgery on patients who survive the immediate insult resulting from the acute huge intracranial bleeding due to ruptured aneurysm is to exsanguinate the haemorrhage from the rupture site and prevention of cerebral vasospasm. It is evident that cerebral vasospasm occurs in about 70% of subarachnoid haemorrhage due to the rupture of aneurysm and cerebral ischaemia and/or infarction of brain tissue due to this cerebral vasospasm is

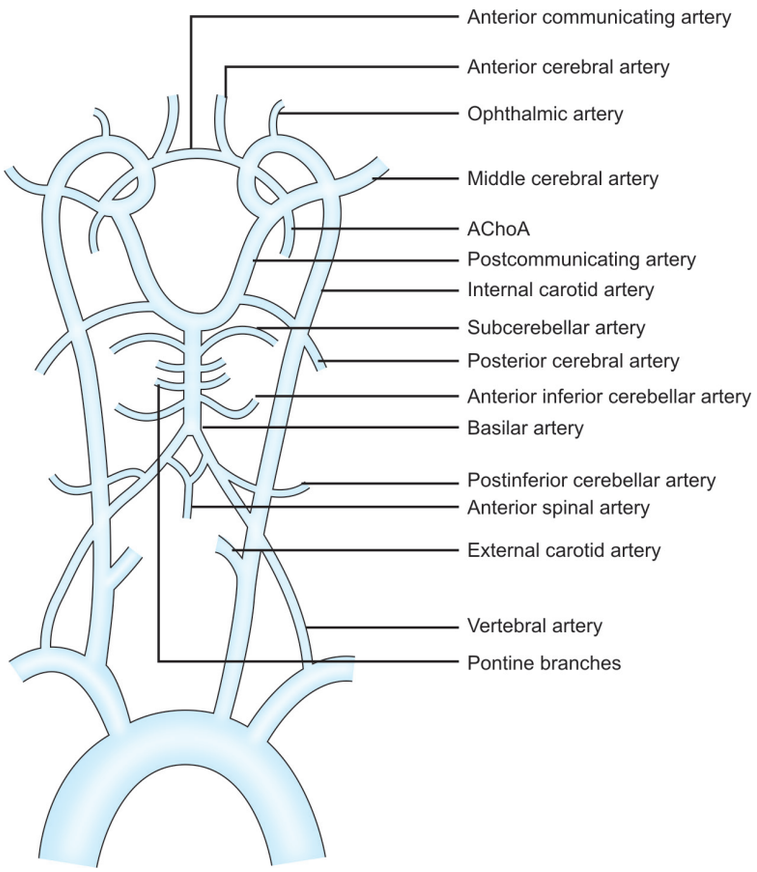


Fig. 49.9: Cerebral arteries

FACT FILE- VII

Arterial supply of brain

The prinicipal arterial flow to the brain in human is by four arteries: two internal carotid arteries and two vertebral arteries. The two vertebral arteries join together at the lower border of pons to form the basilar artery. At the base of the brain the branches of these four main arteries are interconnected forming an arterial circle named the circle of Willis. These interconnection between the branches of four main arteries helps to equalise the pressure in arteries of the two sides. The internal carotid artery, the basilar artery and the vertebral artery give the following branches at the base of the brain.

A. Internal carotid artery:
   Opthalmic a, anterior cerebral a, middle cerebral a, posterior communicating a, anterior choroidal a.
B. Basilar artery:
   Pontine a, labyrinthine a, anterior inferior cerebellar a, superior cerebellar a, posterior cerebral a.
C. Vertebral artery:
   Meningeal a, anterior spinal a, posterior spinal a, posterior inferior cerebellar a, medullary a.

Substances injected into one carotid artery are distributed almost exclusively to the cerebal hemisphere on the same side. This is due to the equal pressure on both sides. Even when it is present the anastomotic channels in the circuit do not permit a very large flow between the two sides. So, obstruction in one carotid artery often causes ischaemia on the same side. There are precapillary anastomoses between the cerebral arterioles. But flow through these colateral channels is generally insufficient to maintain the circulation and prevent the infarction when a cerebral artery is occluded.

responsible for the delayed neurological deficit. If the patient is conscious and ICP is normal, then he is sedated until the anaesthesia is induced. This sedation will help to prevent the rebleeding from ruptured aneurysm by lowering BP. But if the patient is not conscious, then obviously there is no question of sedation. During intraoperative management of aneurysm every attempts should be made to prevent the bleeding or rebleeding (if it is sealed) from the unruptured or ruptured aneurysm. So, arterial blood pressure should be controlled accurately. This is accomplished by avoiding the precipitous increase in arterial BP during laryngoscopy and intubation. Rebleeding from ruptured aneurysm may also be prevented by maintaining a low intra aneurysmal to intracranial transmural pressure gradient, but not much lowering the ICP which acts as a tamponade. The intraoperative severe hypotension (except when induced hypotension is decided) also should be avoided which will aggravate the cerebral ischaemia, already caused by cerebral vasospasm. The patients with subarachnoid haemorrhage from ruptured aneurysm and increased ICP are prone to hypovolaemia and hypotension. So, the liberalization of intake of IV fluid reduces the cerebral ischaemia and mortality due to vasospasm without altering the risk of rebleeding. Thus, restoration of adequate blood volume preoperatively is important, not only for the intraoperative cardiovascular stability, but also for the improvement of neurological function, prior to the neuroanaesthesia and surgery.

During preoperative assessment before neurosurgery and anaesthesia for control of bleeding from ruptured aneurysm by clipping, in addition to neurological finding evaluation of patient should also include the search for other coexisting diseases that may be contraindication for the institution of elective hypotension in the intraoperative period which will facilitate the surgery. The preoperative presence of severe hypertension, renal dysfunction, cardiac diseases, etc may be contraindication to the induced hypotension. The subarachnoid haemorrhage from ruptured aneurysm are also commonly associated with sympathetic overactivity with abnormalities in ECG and arrhythmia. So, these do not necessarily always reflect the underlying cardiac diseases and do not prevent the institution of induced hypotension.

Reduction of MAP in induced hypotension decreases the bleeding from ruptured aneurysm. Thus, it reduces the blood loss, improves the visualization of bleeding site from ruptured anewrysm and facilitates the surgical clipping. Hence, the elective induced hypotension but not up to that level which will cause cerebral ischaemia is useful for aneurysmal surgery. But, it is not without danger, because it may cause ischaemic damage to the brain and other organs. It has been suggested that the MAP should not be reduced more than 50 mm of Hg from the preexisting MAP level. This is because chronic arterial hypertension shifts the hypotensive threshold level for autoregulation of CBF to the right. So, the maximum lower limit of this reduction of BP to which a hypertensive patient can tolerate without producing any cerebral ischaemia is adjusted upward. In addition to recognizing the lower limit of autoregulation, it is also important to understand that this autoregulation takes times. Thus, the slow and controlled induced hypotension is safer than the rapid induction of hypotension.

Sometimes, more profound induced hypotension is required than it is recommended for facilitation of aneurysmal surgery. In such situation when more profound hypotension is used, then their duration should be restricted as less as possible to reduce the ischaemic damage of brain tissue. Recently, the induced hypotension has fallen into disuse. This is because patients with cerebral vasospasm due to subarachnoid haemorrhage have disorder in autoregulation to CBF, causing reduction of CPP and ischaemia of brain. So, induced hypotension in such patients aggravates this ischaemia. During surgery the pressure exerted by the retractors further decreases the local CPP and aggravates ischaemia. So, moderate hypotension combined with intermittent unilateral or bilateral manual carotid artery compression better facilitates the surgery by reducing the intracranial bleeding dramatically. Thus, it avoids the dangers of induced hypotension. Further, the combination of slightly head up position and use of isoflurane in low doses (<1 MAC) enhances the effects of any of the commonly used hypotensive agents and is better than induced hypotension. Recently,

due to some technical improvements and introduction of temporary vascular clips it has enabled the surgeons to cut down the blood flow to the surgical site temporarily during aneurysmal surgery with out applying induced hypotension. On the contrary, the arterial blood pressure of patient is kept at normal or slightly at higher level to protect cerebral perfusion during aneurysmal clipping. During prolonged vascular occlusion or induced excessive hypotension the administration of thiopentone and mild hypothermia may protect the brain from ischaemia. Rarely, for surgery on aneurysm arising from large basilar artery total hypothermic circulatory arrest is used

Carotid Endarterectomy (CEA)

Carotid artery stenosis may be symptomatic or asymptomatic. Asymptomatic carotid stenosis, diagnosed accidentaly by bruits during auscultation with stethoscope, are heard in 5 to 10% of general population. The complication of carotid artery stenosis are mainly TIA and stroke. The CEA is the surgical treatment of both sympmatic and asymptomatic carotid artery stenosis when its lumen's diameter is <70% (1.5 cm). Asymptomatic patients (diagnosed by bruits) are also treated, because they have also the high incidence rate of TIA and stroke than the patient who are without bruits.

Stenosis in carotid artery also induces autoregulation in CBF. So, in an effort to maintain CBF due to the drop of pressure beyond the obstruction the cerebral vasculatures dilate. As the degree of stenosis progresses the cerebral vasculature dilates maximally to a point beyond which they lose the ability of autoregualtion. Then with the further progress of stenosis the CBF will become passive and arterial pressure dependent. So, it is important to maintain intraoperative arterial BP in a patient during CEA operation, because they have no autoregulation to counter the anaesthesia induced hypotension. The normal CBF inhuman is 50 to 60 ml/100 gm/min of tissue (15% of cardicac output) and requirement of O_2 for cerebral metabolism is 3 to 4 ml/100gm/min (20% of whole body O_2 consumption). The reduction of CBF at which level the ischaemia occurs (that is evidenced by EEG) is termed as the critical regional cerebral blood flow (rCBF) and is 18 to 20 ml/min. The surgery of CEA does not cause much fluid shift. So, the introduction of pulmonary artery catheter is not necessary if not otherwise indicated for other causes such as pulmonary hypertension, low ventricular function etc. However, intraarterial pressure monitoring is mandatory during CEA to maintain autoregulation deprived pressure dependent CBF.

During CEA operation the stump pressure which is measured immediately cephalad to the carotid cross clamp does not always provide the reliable information regarding the status of cerebral perfusion. Because it is found that the brain in some patients with stump pressure less than 50 to 60 mm of Hg are adequately perfused, whereas the brain in some patients with adequate stump pressure have suffered cerebral ischaemia. So, in CEA the intraoperative monitoring by evoked potential to judge the integrity of cerebral function, jugular venous or transconjunctival O_2 saturation to know the hyporia at nerve tissue level, transdoppler, echocardiography etc provides better method of monitoring of cerebral perfusion. Although EEG is a highly selective and early indicator of global cortical ischaemia, but it is not applicable in CEA operation. So, no data shows that monitoring by EEG during CEA operation result in better outcome.

The CEA can be performed under both regional and general anaesthesia and these two procedures have both advantages and disadvantages. But the ultimate choice between the RA and GA depends on the patient's stability, surgeon and patient's preference, and surgeon and anaesthetist's experience. The main advantage of doing CEA under RA is the ability to evaluate the adequacy of cerebral perfusion by continuous neurological assessment in a awake cooperative patient. But the disadvantage of RA is that if the patient develops cerebral ischaemia then he or she may lead to disorientation, inadequate ventilation, hypoxia and disturbed surgical field. In such setting immediate rescue induction, followed by ET intubation and institution of GA which provide maximum cerebral protection may prove difficult. The advantages of GA are good control of airway, a quiet undisturbed operation field and ability to provide maximum cerebral protection if ischaemia develops. But the main disadvantages of GA is loss of continuous neurological evaluation like of an awake patient (Fact file VIII).

FACT FILE- VIII

A. Modulation of arginine-NO-GMP system is the central to the changes in cerebral vascular tone, caused by several processes. NO which is responsible for vasodilatation caused by Na-nitroprusside is the mediator of cerebral vasodilatation caused by hypercapnia, ↑CMR, volatile agents and neurogenic stimulation.

B. In normal subject the initial increase in CBV does not result in significant elevation of ICP. This is because there is general tendency for compensatory adjustment by other intracranial compartment such translocation of venous blood and CSF to extracranial vessels, shifting of CSF from cranium to spinal space.

C. Hyperventilation has circulatory side effects requiring consideration. Shallow rapid positive pressure ventilation actually increase mean airway pressure which impedes cerebral venous drainage and increase ICP. Similarly PEEP elevate ICP and reduce MAP. Whereas, ventilation with long expiratory periods result in low mean airway pressure and ↓ICP during hyperventilation. Hypocapnia has no effect on CSF secretion and absorption. Besides reducing ICP, extreme alkalosis caused by hyperventilation impair dissociation of O_2 from Hb at tissue by shifting the curve to left. Respiratory alkalosis also increase O_2 consumption and in the presnce of pulmonary shunting this can reduce arterial oxygenation. Hypocapnia also reduce coronary blood flow. Hypocapnia also lower inotropic sympathetic influence on heart and reduce arterial BP and CPP.

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