COMMON PERIOPERATIVE PROBLEMS AND THE ANAESTHETIST

DEVELOPMENTS IN CRITICAL CARE MEDICINE AND ANESTHESIOLOGY

Prakash, O. (ed.): Applied Physiology in Clinical Respiratory Care. 1982. ISBN 90-247-2662-X.

McGeown, Mary G.: Clinical Management of Electrolyte Disorders. 1983. ISBN 0-89838-559-8.

Scheck, P.A., Sjöstrand, U.H., and Smith, R.B. (eds.): Perspectives in High Frequency Ventilation. 1983. ISBN 0-89838-571-7.

Stanley, T.H., and Petty, W.C. (eds.): New Anesthetic Agents, Devices and Monitoring Techniques. 1983. ISBN 0-89838-566-0.

Prakash, O. (ed.): Computing in Anesthesia and Intensive Care. 1983. ISBN 0-89838-602-0.

Stanley, T.H., and Petty, W.C. (eds.): Anesthesia and the Cardiovascular System. 1984. ISBN 0-89838-626-8.

Van Kleef, J.W., Burm, A.G.L., and Spierdijk, J. (eds.): Current Concepts in Regional Anaesthesia. 1984. ISBN 0-89838-644-6.

Prakash, O. (ed.): Critical Care of the Child. 1984. ISBN 0-89838-661-6.

Stanley, T.H., and Petty, W.C. (eds.): Anesthesiology: Today and Tomorrow. 1985. ISBN 0-89838-705-1.

Rahn, H., and Prakash, O. (eds.): Acid-base Regulation and Body Temperature. 1985. ISBN 0-89838-708-6.

Stanley, T.H., and Petty, W.C. (eds.): Anesthesiology 1986. 1986. ISBN 0-89838-779-5.

de Lange, S., Hennis, P.J., and Kettler, D. (eds.): Cardiac Anaesthesia: Problems and Innovations. 1986. ISBN 0-89838-794-9.

Stanley, T.H., and Petty, W.C. (eds.): Anesthesia, the Heart and the Vascular System. 1987. ISBN 0-89838-851-1.

Stanley, T.H. (ed.): What's New in Anesthesiology. 1988. ISBN 0-89838-367-6.

Woerlee, G.M.: Common Perioperative Problems and the Anaesthetist. 1988. ISBN 0-89838-402-8.

COMMON PERIOPERATIVE PROBLEMS AND THE ANAESTHETIST

by

G.M. WOERLEE M.B., B.S. (W. Aust.), F.F.A.R.C.S. (Eng.)

Consultant Anaesthetist, Department of Anaesthesia,
University Hospital of Leiden,
The Netherlands

KLUWER ACADEMIC PUBLISHERS
DORDRECHT / BOSTON / LONDON

Library of Congress Cataloging in Publication Data

Woerlee, G. M.
Common perioperative problems & the anaesthetist / G.M. Woerlee.
p. cm. -- (Developments in critical care medicine and anaesthesiology)
Includes index.
1. Anesthesia--Complications and sequelae. 2. Surgery--Complications and sequelae. I. Title. II. Title: Common perioperative problems and the anaesthetist. III. Series.
RD82.5.W64 1988
617'.96--dc19 88-13336
CIP

ISBN-13: 978-94-010-7089-8 e-ISBN-13: 978-94-009-1323-3
DOI: 10.1007/978-94-009-1323-3

Published by Kluwer Academic Publishers,
P.O. Box 17, 3300 AA Dordrecht, The Netherlands.

Kluwer Academic Publishers incorporates
the publishing programmes of
D. Reidel, Martinus Nijhoff, Dr W. Junk and MTP Press.

Sold and distributed in the U.S.A. and Canada
by Kluwer Academic Publishers,
101 Philip Drive, Norwell, MA 02061, U.S.A.

In all other countries, sold and distributed
by Kluwer Academic Publishers Group,
P.O. Box 322, 3300 AH Dordrecht, The Netherlands.

FOREWORD

Dr. G. M. Woerlee is well known in my department both as a clinician and teacher. Years of experience have taught him that the problems discussed here have as yet not been treated in this way in any single work.

In my opinion there is a real need for such a book, not only for resident and specialist anaesthetists, but also among surgeons and internists, specialist and trainee. Management of a patient in the operating room is a matter of teamwork, and knowledge of the problems encountered is the basis of any mutual understanding!

The information which has been assembled and clearly presented in this book should prove to be of great assistance in guiding our patients though an important phase of their lives.

Professor Dr. Joh. Spierdijk,
Department of Anaesthesia,
University Hospital of Leyden,
The Netherlands.

PREFACE

Much of the literature being published in the field of anesthesiology today concerns a narrow, in-depth scrutiny of a specific area or anesthetic technique that does not provide the novice with an overview of the perioperative period and the common everyday problems faced by the anesthetist. Dr G.M. Woerlee of the University of Leiden with his book, "Common Perioperative Problems and the Anaesthetist", has filled a void in the current anesthetic literature. Dr Woerlee reviews in a straightforward, no-frills manner problems routinely encountered during the perioperative period. Other anesthesia textbooks do not cover the material in quite the same logical, step-by-step fashion. This book contains an enormous amount of information. It is a very practical guide for residents in anesthesiology, surgery, critical care, and internal medicine.

Theodore H. Stanley M.D.,
Professor of Anesthesiology,
The University of Utah,
Salt Lake City, Utah,
U.S.A.

ACKNOWLEDGEMENTS

While this is a book written by one author, some cooperation from others was also essential, in particular from Madhuri, my wife, to whom I wish to express my gratitude for her uncomplaining acceptance of the many hours during which I was engaged in writing.

I also wish to express my thanks to Dr. S. de Lange, Professor of Anaesthesia in Maastricht for his initial kind comments and enthusiasm for this book. Professor J. Bovill, Dr J.R. de Jong, Dr P.J.Hennis, Dr. E. Briet, and Dr J.D.M. Feuth, all of the University Hospital of Leyden, provided valuable constructive criticism of the initial versions of the first few chapters that were written. Dr B. Cohn a fellow staffmember of the Department of Anaesthesia of the University Hospital of Leyden provided thoughtful comment on the initial version of the completed book. The anaesthetic residents, and my fellow staffmembers of the Department of Anaesthesia of the University Hospital of Leyden in the Netherlands, (Head of Department, Professor Dr. Joh. Spierdijk), were a continual source of encouragement and provided invaluable insights into the problems faced by the busy clinical anaesthesiologist, both trainee and specialist. I also wish to express my thanks to surgical colleagues of all departments whose views of these same problems provided further insights into what was practical in a clinical setting, and what was not. Last but not least, I wish to thank Mr B. van der Lans for his rapid photographic reproduction of the many drawings which he was presented and re-presented.

G.M. Woerlee,
Oegstgeest,
The Netherlands,
May 1988.

CONTENTS

INTRODUCTION

It is well worth stating in the beginning of this book those subjects which this work does not cover. While this is a book oriented towards anaesthetists, it is not intended to be a text on how to administer anaesthesia. It also does not deal with paediatric or cardiothoracic anaesthetic problems, nor does it contain any discussion of intensive care problems as such. All these subjects are more than adequately covered by the many excellent texts devoted specifically to these topics.

What this book does set out to do is present my own view of a practical, problem oriented approach to assessment and management of clinical problems commonly encountered in adult surgical patients in the perioperative period. Why only common problems? Very simply because these are the problems which the anaesthetist comes into contact with nearly every day, and which if well and efficiently managed result in greatly reduced perioperative morbidity and mortality.

Very little mention is made of specific diseases, except where the disease is anaesthesiologically significant in its own right. This is because the perioperative anaesthetic management of a surgical patient is of such short duration that usually no cure of any disorder can be made in this period. Healing and specific therapy of the vast majority of diseases are processes that occur over a period of days to weeks. The anaesthetist as well as intensive care physician have as a main priority the preservation of function until a cure can be effected, or healing has occurred. For this reason the functional consequences of organ dysfunction are emphasized rather than any specific disorders.

Most physicians engaged in the perioperative management of surgical patients have a rather pragmatic approach to the problems they encounter. This may be summed up as below.

- What is the problem?
- Why is it a problem?
- Is it significant in terms of morbidity or mortality?
- What is the physiological basis of the problem?
- How may the severity of the disorder be accurately assessed?
- At what level of severity does the problem become so significant that a change of management, or a specific therapy is required?
- What are the physiological effects of various anaesthetic techniques, and how do they relate to these problems. That is, at what level of severity of these problems

does the disorder become so significant that a modification of the anaesthetic technique is required, and what is the anaesthetic management.

Each chapter uses this approach to the problem discussed. Understanding of the physiological basis of each problem is emphasized, as a solution or a methodological approach to one problem may be used to solve or understand other less common problems.

Accurate assessment of the severity of all problems is stressed, as this is essential for purposeful and effective management. The requirement for unnecessary, possibly risky, as well as expensive treatment is also minimized by using such an approach. Much use is made for this purpose of simple clinical scoring systems, or parameters readily measured in most modern hospitals. Such an approach leads to the concept of "treatment or management thresholds", below or above which the level of dysfunction becomes so unacceptable that a specific form of monitoring, therapy, or anaesthesia is required. This approach may be criticized as being too rigid, and such criticism is true to some degree. However such an approach should be viewed in the same way as a recommended drug dosage, a "normal arterial blood pressure" or a "normal cardiac output". For example, a recommended drug dosage provides a guide as to the magnitude of the dosage required, and even if rigidly applied does not cause many problems, being non-lethal and effective in most cases. The experienced physician uses a recommended drug dosage as a guide, and adjusts the dosage according to the physiological condition of the patient. Management or treatment thresholds should be viewed in precisely the same way. Another advantage of these "thresholds" is that they provide some degree of decision support for the junior physician who has yet to acquire clinical experience.

The chapters on electrolyte disorders, acid-base disorders, and intravenous fluid therapy are somewhat extensive. But these three subjects are the source of much confusion and difficulty to junior physicians, and so much space has been devoted to explaining the clinical aspects of these problems and their practical management.

Another facet which is emphasized is the appropriate selection of drugs. The proper basis of effective drug administration is founded on a sound knowledge of the properties of the various drugs used. Pharmacokinetic concepts are extensively used to explain drug effects and the principles of drug administration. Part 15 provides a clinically oriented discussion of basic pharmacokinetic and pharmacodynamic principles and their application. Pharmacokinetic and pharmacodynamic properties of most commonly used anaesthetic drugs are listed in appendix-A. Selection of the appropriate drugs to use for any given patient is discussed in each chapter dealing with a particular problem. These discussions lean heavily on pharmacokinetic and pharmacodynamic concepts, and the implications of the elimination pathways of the drugs used. All this is further supplemented by tables listing systemic haemodynamic effects of the most commonly used anaesthetic drugs in chapter 2.1.

Many basic topics are extensively referenced. This is done so that the more critical reader can look these up for himself, and see on what evidence many so-called medical "truths" are based. Hopefully, this will encourage further investigation into some as yet poorly investigated areas, as well as encouraging a more critical approach to many subjects.

Part 1

PREOPERATIVE ASSESSMENT

Surgery always causes pain and often causes loss of blood, plasma or both. Both surgery and anaesthesia may profoundly alter perioperative cardiovascular, pulmonary, metabolic, neurological, and immune function. If the patient is unable to compensate for these changes, or in cases where the physicians are unaware of the changes that may occur, they may actually be life threatening in some situations.

The purpose of the preoperative visit is to assess the physiological functional reserve of the patient. That is, to find out if the level of physiological functioning is such that the patient can adapt to the changes that both anaesthesia and surgery certainly will induce. Such an assessment is made by asking the clinical history, by physical examination, and by use of parameters readily measured in most modern hospitals, as well as use of functional classification systems. The latter provide a rough semi-quantifiable measure of physiological function to which a specific form of management or an outcome may be coupled.

The anaesthetist, surgeon, and internist should consult with one another regarding the optimal management of any given patient in the perioperative period. While this is not necessary for most simple elective operations, it is certainly necessary for patients who are to undergo extensive surgery, or those who are very ill. If there is a query regarding the fitness of a patient for anaesthesia, it is the task of the anaesthetist to formulate an adequate opinion. No other specialist is aware of the full range of anaesthetic modalities able to be used to enable the patient to survive surgery and anaesthesia.

Chapter 1.1

CLINICAL PREOPERATIVE ASSESSMENT

Clinical investigation of the patient coming for operation is the most important part of preoperative assessment. It is what provides the most actual information as to the likely level of physiological stress that is able to be endured, and the likely physiological reserves possessed by the patient. The function of laboratory, roentgenological, haematological, biochemical, electrocardiographic, etc, investigations is to provide valuable supplementary information, in addition to a quantitative measure of any abnormality.

Of all the skills that a clinician may acquire, those of keen observation, and the ability to integrate the information acquired so as to draw the correct conclusions are the most important. ALL senses must be employed when assessing a patient preoperatively. The anaesthetist must not only see, but actually OBSERVE and CORRECTLY INTERPRET all relevant information.

HEARING

1. Moans of pain or distress.

2. Respiratory sounds.
a. The sound of respiration. If the respiration of a person at rest can be heard, then respiratory function is abnormal.
b. Respiratory stridor. This indicates severe airway obstruction if present at rest.
c. Listen for tachypnea.
d. Listen for abnormal respiratory sounds, wheezing, rattling.
e. Listen for coughing, and whether it is dry or productive.

SIGHT

1. Look at the general condition of the patient, sick or well, clean or filthy, well groomed or not. A very sick person is unable to undertake his normal personal care.

2. Look for medicines by the bedside.

3. Look for cigarettes, or other tobacco products, and for nicotine staining of the fingers.

4. Look into the sputum mug and assess the contents.

5. Look for signs of dehydration.

6. Look for cyanosis, jaundice, anaemia.

7. The behavior of the person being assessed, and how it is affected by disease.

SMELL

1. Smell for pus, urine, faeces, foetor hepaticum, uraemic breath.

2. The smell of ketones emanating from the patient may indicate dehydration or diabetic ketoacidosis.

HISTORY

1. Dental status. Loose teeth, jackets, bridges, dentures etc.

2. Lung disease, with specific enquiry as to the presence of bronchitis, emphysema, asthma, or the presence of an upper or lower respiratory tract infection.

3. Heart disease, with specific enquiry of history of myocardial infarction, angina pectoris, peripheral vascular disease, orthopnea and related nocturnal awakening, rheumatic fever in childhood etc.

4. Specific enquiry should be made as to the exercise tolerance in order to assess the cardiopulmonary reserve.Orthopnea indicates the presence of reasonably severe heart failure. Can the patient walk up steps? Quantify this in terms of the number of stories able to be climbed before a pause is needed. Does the patient play a sport, and if so, how vigorous a sport? Can he walk on level ground with or without a shopping bag etc. If the patient is able to sustain a moderate level of physical activity, then cardiopulmonary reserve is more than sufficient for most forms of surgery and anaesthesia.

5. Gastrointestinal function, mainly related to the presence of hiatus hernia, (patient may regurgitate gastric contents easily), peptic ulceration (surgery may exacerbate, or precipitate acute ulceration). When was the last time that the patient ingested solid food or liquids?

6. History of diseases transmissible to anaesthetists and other patients, especially jaundice, hepatitis-B, AIDS, etc.

7. Other major diseases.

8. What drugs does the patient take, and how often. These may be stopped or continued as indicated by the nature of the drug(s), and the disease for which they are given. Has the patient any drug allergies, or is he extraordinarily sensitive to any group of drugs?

9. History of previous anaesthesia, and of any anaesthesia related problems in blood relatives, and the patient himself.

PHYSICAL EXAMINATION

This is required to clarify points raised by the history, to provide more information as to the condition of the patient in conditions that are not symptomatic, or if the patient is unduly reticent about his physical condition.

LABORATORY INVESTIGATIONS

These provide valuable supplementary information, sometimes may detect disorders that cannot be detected clinically, in addition to providing a quantitative measure of the degree of any abnormality.

Chapter 1.2

ASA - PHYSICAL STATUS CLASSIFICATION

The most useful clinical information the anaesthetist can gather about a patient preoperatively is the preoperative physical functional level. That is, how much the diseases that the patient may have affect the level of physical functioning. This whole idea is based upon the simple premise that perioperative morbidity and mortality are increased in sick patients.

The American Society of Anesthetists (ASA), classification of physical status is a simple, albeit a rather subjective system of classification of patients according to their degree of physical disability. Because of the subjective element, different anaesthetists may score a patient differently. But even so, perioperative morbidity and mortality are related to the ASA class.

The condition for which the patient is to be operated must also taken into account in cases where this has a general systemic effect. Otherwise if the patient is quite healthy apart from the condition to be operated, e.g. a healthy man with an inguinal hernia, the surgical condition has no bearing on the ASA classification.

ASA-Class

1. A normally healthy person.

2. A person with mild systemic disease that does not limit normal physical activity,e.g. smoking, mild asthma.

3. A person with severe systemic disease that is not incapacitating, e.g. hypertension, diabetes mellitus.

4. A person with incapacitating systemic disease that is a constant threat to life,e.g. severe heart failure.

5. A moribund person not expected to survive longer than 24 hours, with or without an operation being performed.

E. The addition of the suffix "E" to the ASA-class indicates only that the operation is an emergency one, and hence is associated with a higher morbidity and mortality than the same operation would have if performed electively.

It should be noted that a high ASA-class is no reason to refuse to administer anaesthesia where a genuine surgical indication for operation is present, even if the ASA-class is 5E. If any given patient with a physical status of ASA class 5E severity has a better chance of surviving after having undergone an operation, this is justification enough for performing that operation, provided that patient, surgeon and anaesthetist are all aware of the somber prognosis, and have mutually agreed that this is the best course of action.

REFERENCES

1. Keats,A.S.(1978). The ASA Classification of Physical Status - A recapitulation. ANESTHESIOLOGY, 49, 233-236
2. Owens,W.D., et al.(1978). ASA Physical Status Classifications: A Study of Consistency Ratings. ANESTHESIOLOGY, 49, 239-243.

Chapter 1.3

INDICATIONS FOR IMMEDIATE OPERATION

All patients should be in the best possible physical condition prior to surgery and anaesthesia. Administration of anaesthesia to patients who are hypoxaemic, hypovolaemic, or have abnormal cardiovascular function only exacerbates these conditions or their effects. Preoperative restoration of normovolaemia, improvement of respiratory function, or treatment of abnormal cardiovascular function results in reduced perioperative morbidity and mortality. Accordingly, there are actually very few occasions where it is absolutely necessary that surgery be performed without delay.

The indication for immediate operation may be stated simply as being an operation required to save the life or physical function of a patient from the effects of a disorder or disease process which may very rapidly have a deleterious effect on either or both. Some of the most common indications for immediate operation are listed below.

1. Severe uncontrollable haemorrhage.

Patients with severe haemorrhage, the cause of which is surgically correctable, will require operation to treat the cause of the bleeding. However administration of general anaesthesia, or epidural and spinal anaesthesia is not without risk in hypovolaemic patients [see chapter 14.4]. For this reason it is desirable, if possible, to restore normovolaemia prior to induction of anaesthesia. Regrettably this is not always feasible, and so a careful differentiation should be made between the various types of haemorrhage, so that the feasibility of preoperative restoration of normovolaemia may be assessed.

a. If the bleeding is slow, or if it can be controlled by either pressure or use of a tourniquet, then the circulating blood volume can, and should be restored prior to administration of anaesthesia. Subsequently any type of anaesthesia may be administered without incurring any major problems due to administration of anaesthesia to a hypovolaemic patient.

b. Rapid bleeding from a ruptured liver, spleen, aorta or ectopic pregnancy obviously cannot be controlled by external pressure or a tourniquet, and immediate operation is required to stop any further haemorrhage. Under these circumstances both anaesthetist and surgeon must accept the less than ideal situation and treat the patient as efficiently as possible, as the only way to save the patient is to operate.

2. Surgically correctable respiratory failure.

Surgically correctable respiratory failure is respiratory failure due to conditions such as severe laryngeal trauma, laryngeal and epiglottic swelling or tumors, thoracic trauma with

ruptured bronchi or trachea. Such conditions may require rapid treatment if death is to be prevented.

3. Surgically correctable heart failure.

Speedy surgical correction of heart failure may be required for conditions such as rapid progression of existing valvular disease, valve prolapse subsequent to a myocardial infarction, sudden artificial valve malfunction, acute coronary vessel damage such as due to ruptured coronary vessels as a result of percutaneous coronary angioplasty, etc.

4. Foetal distress.

Rapid caesarean section may be required to save the life of a foetus, and to prevent or minimize foetal brain damage, when manifestations of foetal hypoxia are detected.

5. Surgically correctable increased intracranial pressure.

Urgent cranial decompression may be required for conditions causing surrgically correctable extreme elevation of the intracranial pressure, e.g. subdural haematoma, epidural haematoma, haemorrhage into an intracerebral tumor, or acute hydrocephalus.

6. Threatened organ or limb function.

There is also a requirement for urgent surgery if there are limbs or organs whose function will be unacceptably impaired if surgery is not rapidly performed.

This list of indications for immediate operation is at best only provisional. Common sense must also be used in determining the rapidity with which any operation should be performed. A practical, albeit a rather blunt and simple guide, are the simple questions; "Will the patient die, or suffer permanent and unacceptable functional damage if not operated upon immediately? What consequences will a delay in order to first resuscitate the patient have?" The answers to these simple questions determines the urgency of any operation.

Part 2

CARDIOVASCULAR DISEASE AND ANAESTHESIA

The blood transports oxygen, the lungs oxygenate the blood, the heart pumps the blood, and the blood vessels transport the blood to the tissues. These are the four vital links in the supply of oxygen to the tissues of the body. Blood also transports other metabolic substrates, and removes metabolic products. Should the cardiovascular system fail to supply the tissues of the body with sufficient volumes of oxygen and blood per unit time, tissue dysfunction will occur in the affected organs or the whole body. Proper functioning of the cardiovascular system is therefore vital to normal physiological function. The supply of adequate amounts of oxygenated blood may be threatened by one or more factors.

1. A reduction of cardiac output reduces flow to some or all organs of the body [see chapter 2.8 on heart failure].

2. Blood pressure may be reduced to such a degree that the resistance to blood flow presented by the vascular beds of some organs reduces the flow through those organs to below that required to maintain normal tissue function [see chapter 2.7 on hypotension].

3. Both factors may occur simultaneously.

Aside from his primary task of providing anaesthesia so as to make surgery possible, the other main tasks of the modern anaesthetist are to maintain adequate cardiovascular function and oxygenation in the patients he manages. This section discusses the effects of surgery and anaesthesia on cardiovascular function, and vice versa for a variety of common cardiovascular disorders, along with the practical management of these disorders.

Normal values for clinically relevant haemodynamic parameters are listed in table 2.0.1.

Table 2.0.1.
NORMAL VALUES AND DERIVATION OF HAEMODYNAMIC PARAMETERS

PARAMETER	ABBREVIATION	UNITS	FORMULA	NORMAL RANGE
ARTERIAL				
Heart rate	HR	beats/minute		60-90
Systolic Arterial Blood Pressure	SABP	mmHg		100-140
Diastolic Arterial Blood Pressure	DABP	mmHg		60-90
Mean Arterial Blood Pressure	MABP	mmHg	$\frac{SABP + 2 \times DABP}{3}$	70-105
Rate Pressure Product	RPP		HR x SABP	3600-13000
Systemic vascular resistance	SVR	dynes.sec /cm^{-5}	$\frac{80 \times (MABP - CVP)}{CO}$	800-1500
PULMONARY CIRCULATION				
Pulmonary artery systolic pressure	PASP	mmHg		15-30
Pulmonary artery diastolic pressure	PADP	mmHg		4-12
Mean pulmonary artery pressure	MPAP	mmHg		9-19
Pulmonary capillary wedge pressure	PCWP	mmHg		5-13
RIGHT HEART				
Mean right atrial pressure	MRAP	mmHg		2-10
Central venous pressure	CVP	mmHg		2-10
Right ventricular systolic pressure	RVSP	mmHg		15-30
Right ventricular end diastolic pressure	RVEDP	mmHg		2-10
LEFT HEART				
Mean left atrial pressure	MLAP	mmHg		5-15
Left ventricular systolic pressure	LVSP	mmHg		100-140
Left ventricular end diastolic pessure	LVEDP	mmHg		4-12
CARDIAC OUTPUT	CO	l/min		3-8
CARDIAC INDEX	CI	l/min/m^2		2.5-4.2
EJECTION FRACTION	EF		$\frac{\text{Stroke Volume}}{\text{End Diastolic Volume}}$	0.55-0.78

Chapter 2.1

CARDIOVASCULAR EFFECTS OF ANAESTHESIA & SURGERY

Surgery, trauma and anaesthesia may have a profound effect on systemic haemodynamics. The selection of any anaesthetic technique and drugs should always be based on a sound knowledge of the effects of these on cardiovascular function. This chapter contains a number of tables listing the systemic haemodynamic effects of many of the anaesthetic drugs and techniques in current use, as well as a short discussion on the cardiovascular effects of trauma and surgery. The purpose of this chapter is to provide a guide with which the relative advantages and disadvantages of various alternative drugs and techniques may be weighed against each other for the problems presented by administration of anaesthesia for a surgical procedure performed on any given patient.

EFFECTS OF SURGERY AND TRAUMA

The effects of surgery and trauma are essentially caused by the problems listed below.

1. Increased sympathetic nervous activity.

Pain due to surgery and trauma increases sympathetic nervous activity as well as increasing the plasma concentrations of adrenaline and noradrenaline. The effect of all this is to increase the blood pressure, heart rate and cardiac work, with all the possible effects of this, [see hypertension, and angina pectoris etc].

2. Hypovolaemia.

Bleeding and sequestration of plasma into traumatic oedema can be so extreme that hypovolaemia with all its consequences may occur, [see hypotension, hypovolaemia and other relevant chapters].

EFFECTS OF ANAESTHESIA

The effects of anaesthesia on cardiovascular function are due to a combination of three factors.

1. The anaesthetic technique used.
2. The anaesthetic drugs.
3. The effects of any intravenous fluids administered.

Only factors 1 and 2 will be discussed in this chapter, as the effects of intravenous fluids are discussed in part 14 on fluid balance and therapy.

Table 2.1.1.
Effects of various anaesthetic techniques on systemic haemodynamics in normovolaemic patients.

ANAESTHETIC TECHNIQUE	Cardiac output	Systemic vascular resistance	Mean arterial blood pressure
Local infiltration and hemispinal anaesthesia	0	0	0
Low spinal and epidural anaesthesia: (lower than T4) [2]	0/↑	0/↓	0/↓
High spinal anaesthesia: (higher than T4) [1]	↓	↓	↓
High epidural anaesthesia: (higher than T4) [2]	↑/↓	↓	↓
General anaesthesia: spontaneous respiration	0/↓	↑/↓	0/↓
General anaesthesia: IPPV with zero end expiratory pressure	0/↓	0	0/↓
General anaesthesia: IPPV with positive end expiratory pressure	↓	0	0/↓
General anaesthesia: IPPV with negative end expiratory pressure	0/↑	0	0

"↑" = increased above preanaesthetic value.
"↓" = decreased below preanaesthetic value.
"0" = no change from preanaesthetic value

1. EFFECTS OF THE ANAESTHETIC TECHNIQUE.

Anaesthesia may be loco-regional, general, or a combination of both. Table 2.1.1 shows the relative effects of various loco-regional and general anaesthetic techniques on systemic haemodynamics. It should be noted that this table is for normovolaemic healthy patients.

2. EFFECTS OF ANAESTHETIC DRUGS.

The haemodynamic effects of drugs commonly used for anaesthesia are listed in tables below for human investigations using bolus intravenous injections. Changes of the various haemodynamic parameters are given as a percentage change from control measurements in normovolaemic healthy patients who were not undergoing surgery at the time of the investigation. No levels of significance are given as these tables are intended to be used purely for the purpose of showing the comparative effects of the drugs listed.

The cardiovascular effects of the drugs used in anaesthesia determine the ultimate effects on systemic haemodynamics of any general anaesthetic technique. Anaesthetic drugs exert an effect by any one or more of the effects listed below.

- Central nervous system depression.
- Ganglionic blockade.
- Depression of the baroreflexes [see chapter 8.6].
- Depression of myocardial contractility.
- Depression of vascular smooth muscle contractility.
- Stimulation or depression of sympathetic nervous activity.
- The effect of any one drug may be potentiated by another drug or drugs.

a. Induction agents.

The haemodynamic effects of the intravenous anaesthetic induction agents are listed in table 2.1.2. As can be seen, many of these drugs, even ketamine, are direct myocardial and vascular smooth muscle depressants. The vasodilation and myocardial depression caused by these drugs activates the baroreflexes, which in turn increases sympathetic nervous system activity to such a degree that cardiac output, SVR and blood pressure are reasonably maintained, as occurs with etomidate and midazolam, or are actually increased as with ketamine. Some of these drugs such as the barbiturates, and benzodiazepines depress the baroreflexes to such a degree that they no longer function effectively. As a consequence the use of drugs such as the barbiturates, and profolol is associated with significant depression of cardiovascular function. Baroreflexes are discussed more extensively in chapter 8.6.

Ketamine is a special case. The direct effect of ketamine on the myocardium and vascular smooth muscle is depression. But it causes such a degree of central nervous system mediated sympathetic nervous activation that cardiac output, blood pressure, and heart rate are increased above normal.

These drugs all have a much more pronounced effect upon systemic haemodynamics in the elderly, who by virtue of the aging process have deficient baroreflex function [see chapter 8.6], and altered drug kinetics [see chapter 15.2]. In addition to this, all these drugs, even ketamine, can cause cardiovascular collapse in patients whose sympathetic nervous activity is already maximal due to their disease process [15,16]. In the latter situation the

sympathetic nervous system activity cannot be further increased, and as a consequence the direct myocardial and vascular smooth muscle depressant effects of these drugs manifests. The same is also true for these drugs when used in any patient whose autonomic nervous system activity is blocked or inhibited by either drugs or disease [see chapter 8.6].

Treatment of hypotension due to induction of anaesthesia may occasionally be required when the level of hypotension is such that myocardial or cerebral ischaemia are likely [see chapter 2.7 for threshold levels]. In situations where the patient is normovolaemic, it is illogical to treat this transient drug induced cardiovascular depression with intravenous fluids to increase cardiac output and blood pressure by increasing the blood volume. This may exacerbate heart failure in those with existing heart failure. A more logical form of therapy is to administer a drug which temporarily increases myocardial contractility and systemic vascular resistance, e.g. ephedrine administered at a dose of 5-10 mg to an adult [see chapter 2.2]. Hypovolaemic patients who become hypotensive as a result of induction of anaesthesia should of course be treated for hypovolaemia as well as hypotension.

Table 2.1.2.

Systemic haemodynamic effects of anaesthetic induction agents.The table gives the percentage change from control parameters measured in the same patients prior to intravenous injection of these agents in patients with normal preoperative systemic haemodynamics. Drugs are listed in order of the magnitude of their effect on arterial blood pressure.

DRUG	Dose	HR	CO	SVR	MABP	MC	VSMC
KETAMINE [4,5,6,7]	2	↑33	↑29	0	↑28	↓	↓
ALFENTANIL [3]	0.125	0	0	0	0		
MIDAZOLAM [8,9]	0.25	0	↓9	↓13	↓		
ETOMIDATE [10,13]	0.45	↑10	↓6	↓9	↓10	↓	
METHOHEXITONE [12]	1-2	↑30	↑15	↓28	↓14		
THIOPENTONE [8,10,11]	4	0	↓13	↓13	↓18	↓	↓
PROFOLOL [14]	1.6	↓9	↓22	↓17	↓28		

See appendix-C for abbreviations.
Dose = dose used in investigation in mg/kg.
MC = myocardial contractility.
VSMC = vascular smooth muscle contractility.
"↑" = increase; "↓" = decrease; "0" = no change.

b. Anaesthetic gases.

In addition to inducing sleep, the anaesthetic gases also cause a degree of skeletal muscle relaxation. They directly depress myocardial and vascular smooth muscle contractility, and also have an analgesic action. Some of these drugs, e.g. cyclopropane and diethyl ether, also stimulate the sympathetic nervous system, an action which accounts for the fact that the blood pressure and cardiac output are so well maintained with these two drugs. In the case of diethyl ether, the plasma noradrenaline concentration increases in direct proportion to the concentration of diethyl ether administered [34]. The anaesthetic gases also depress the efficacy of the baroreflex control of blood pressure. This latter effect is discussed more fully in chapter 8.6.

The haemodynamic effects of some gases commonly used in anaesthetic practice are listed in table 2.1.3. Hypotension due to the anaesthetic gases may be treated by discontinuing administration of the gas, or reducing the concentration administered.

Table 2.1.3.

Percentage changes of haemodynamic parameters relative to control values caused by administration of anaesthetic gases under conditions of near constant P_aCO_2. The gases are listed in order of the magnitude of their effect on arterial blood pressure.

GAS	%	MAC	HR	CO	SVR	MABP	MC	VSMC
CYCLOPROPANE [21,22]	17.3	1.7	↓1	↓1	↑32	↑31	↓30	
CO_2 [17,18]	6.3	?	↑26	↑32	↓14	↑10	↓	↓
NITROUS OXIDE [19,20]	40	0.36	↓12	↓19	↑25	↓5	0/↓	
DIETHYL ETHER [21,22]	3	1.4	↑24	↓2	↑1	↓2	↓20	
HALOTHANE [21.22]	1	1.2	↑2	↓22	↓8	↓24	↓39	
ISOFLURANE [24,25]	1.2	1	↑20	↑1	↓24	↓27	↓40	
ENFLURANE [22,23]	1.86	1	↑20	↓20	↓18	↓35	↓50	

See appendix-C for abbreviations.
% = gas concentration administered in %.
MAC = concentration relative to minimum alveolar concentration
MC = myocardial contractility.
VSMC = vascular smooth muscle contractility.
"↑" = increase; "↓" = decrease; "0" = no change

c. Neuromuscular blocking agents.

The neuromuscular junction blocking drugs also have an effect on the cardiovascular system. The magnitude of the systemic haemodynamic effects of these drugs varies, and may be caused by any one or more of the mechanisms listed below [26,33].

- Histamine release, e.g. d-tubocurarine.
- A degree of autonomic ganglion blockade, e.g. d-tubocurarine, fazadinium.
- Some stimulation of autonomic ganglia, e.g. suxamethonium.
- Stimulation of muscarinic receptors, e.g. suxamethonium.
- A vagolytic effect, e.g. gallamine, pancuronium.
- Sympathetic nervous system stimulation, e.g. gallamine, pancuronium.
- Cardiac preload and afterload reduction by virtue of reducing skeletal muscle tone, especially in patients with muscle spasm, those who are shivering, or those patients who are moving uncontrollably.

Table 2.1.4.

Haemodynamic effects of administration of neuromuscular junction blocking drugs during anaesthesia. The changes are given as percentage change from control values measured prior to administration of the drug in the same investigation. Drugs are listed in order of magnitude of effect on arterial blood pressure.

DRUG	Dose	HR	CO	SVR	MABP	HIST	GANG
SUXAMETHONIUM [26,33,46]	1	↑5	?	?	↑16	↑	*
PANCURONIUM [26,28]	0.074	↑12	↑15	↓7	↑12	0	0
GALLAMINE [26,27]	1	↑44	↑26	↓13	↑7	↑	↑
VECURONIUM [26,31]	0.28	0	↑9	↓12	↓3	0	0
ATRACURIUM [26,32]	0.4	↑3	↑5	0	↓5	↑↑	0
ALCURONIUM [26,30]	0.15	↑9	↑3	↓4	↓1	↑	↑
METOCURINE [29,33]	0.2	↑6	0	↓11	↓11	?	↑
d-TUBOCURARINE [26,28]	0.4	↑6	↓5	↓29	↓26	↑↑↑	↑↑

See appendix-C for abbreviations.
Dose = dose used in the investigation cited in mg/kg.
HIST = histamine release.
GANG = autonomic ganglion blockade.
* = suxamethonium stimulates autonomic ganglia [33].
"↑" = increase; "↓" = decrease; "0" = no change.

The final result of any one or more of the effects listed above is an alteration of systemic haemodynamics in patients to whom these drugs are administered [see table 2.1.4]. Extreme hypotension due to the administration of these drugs should be treated in the same way as hypotension due to the anaesthetic induction agents [see above]. Drugs with a significant ganglion blocking effect such as tubocurarine are in fact frequently used to aid in reduction of the arterial blood pressure during controlled hypotension.

Table 2.1.5.

Haemodynamic effects of opioid drugs are expressed as a percentage change from control values prior to administration of the opiate under investigation. The haemodynamic changes listed below are for situations where the opiates were administered with 100 % oxygen, or with oxygen enriched air, and no other drugs unless otherwise indicated.

DRUG	Dose	HR	CO	SVR	MABP	HIST	MC
PENTAZOCINE [37]	0.7	↑12	↑9	↑11	↑13	?	?
[43]	0.6	↑15	?	?	↑10	?	?
** [43]	0.6	↓20	?	?	↓20	?	?
PETHIDINE [44]	1	↑13	↑11	↓8	↑1	↑↑	↓
** [45]	1	↓8	↓8	0	↓2	↑↑	↓
MORPHINE [36]	10	↓6	↑3	↓4	↓6	↑↑	0
[42]	1	↓9	0	0	↓8	↑↑	↓
** [42]	1	↓18	↓34	↑22	↓13	↑↑	↓
ALFENTANIL [38]	0.125	0	↓10	↓5	↓8	0	?
* [39]	0.12	↓14	↓25	↓4	↓27	0	?
FENTANYL [38]	0.075	↓2	↓16	↓5	↓10	0	↓
* [39]	0.03	↓23	↓26	↓7	↓31	0	↓
SUFENTANIL [35,38]	0.015	0	↓15	↓8	↓11	0	?

See appendix-C for abbreviations.
Dose = dose of drug used in investigation cited in mg/kg.
HIST = histamine release.
MC = myocardial contractility.
* = drug administered simultaneously with an etomidate infusion at a rate of 8-30 μg/kg/min.
** = drug administered i.v. simultaneously with ventilation with 60-75% N_2O + 25-40% O_2.
"↑" = increase; "↓" = decrease; "0" = no change.

d. Opioid analgesic drugs.

Opioid analgesic drugs are seldom given alone during the perioperative period, usually being employed either as part of a premedication, for intraoperative analgesia in combination with other drugs, for postoperative analgesia, or all of these purposes.

As with all the drugs already mentioned above, these drugs also do not have any one single action. Drugs such as morphine and pethidine induce histamine release, causing vasodilation. Alfentanil and fentanyl have a pronounced muscarinic receptor stimulating action which may cause either bradycardia, bronchospasm, or both in some patients.

Most opiates when administered to patients who receive no other sedative or anaesthetic drugs, are relatively devoid of significant systemic haemodynamic effects [see table 2.1.5]. This is exploited by cardiothoracic anaesthetists who administer large doses of these drugs together with 100% oxygen to provide anaesthesia for cardiac operations. However some opiates are known to exert a direct myocardial depressant effect on myocardium in-vitro at plasma concentrations commonly achieved when these drugs are used clinically [47]. This partly explains the pronounced cardiovascular depression observed when opiates are administered simultaneously with other drugs also known to have myocardial depressant effects [see table 2.1.5]. That is, the cardiovascular depression due to opiates is additive to, or potentiates, cardiovascular depression due to other drugs which also have a cardiovascular depressant effect. The magnitude of the final effect on systemic haemodynamics is greater for such drug combinations than for each drug individually. In fact the degree of

Table 2.1.6.

Systemic haemodynamic effects of the muscarinic cholinergic receptor blocking drugs. Changes are expressed as a percentage change from control measurements in the same patients.

DRUG	Dose	HR	CO	SVR	MABP
ATROPINE [40]	0.1	↓8	↓9	↑10	0
	0.6	↑21	↑20	↓17	↑3
SCOPOLAMINE [40]	0.09	↓12	↓23	↑23	0
	0.55	↑30	↑16	↓14	↑3
GLYCOPYRROLATE [41]	0.35	↑7	?	?	?
	1.05	↑28	?	?	?

See appendix-C for abbreviations.
Dose = dose used in investigation cited, mg/70 kg.
"↑" = increase; "↓" = decrease; "0" = no change.

depression may be so great in some patients that severe hypotension occurs. This should be managed in the same way as hypotension due to the anaesthetic induction agents.

e. Anticholinergic drugs.

The systemic haemodynamic effects of the muscarinic cholinergic receptor blocking agents are shown in table 2.1.6 and in chapter 2.2. It is noteworthy that very low dosages of atropine and scopolamine cause a bradycardia and a reduction of the cardiac output, while in higher dosages they have the reverse effects.

FACTORS MODIFYING DRUG EFFECTS

It must be emphasized that the above tables only contain data from studies performed on healthy normovolaemic patients who were not undergoing surgery at the time of the investigation. Their purpose is to give an idea of the magnitude and nature of the cardiovascular effects of each of each drug relative to other drugs used for the same purpose.

In normal clinical practice the cardiovascular effects of these drugs are modified by various factors.

1. Surgery causes increased sympathetic nervous activity which tends to reverse the cardiovascular depression due to many drugs.

2. Hypovolaemia exacerbates the cardiovascular depression caused by many of these drugs [see chapters 14.4 and 15.2].

3. Baroreflex deficiency also exacerbates the cardiovascular depressant effects of many of these drugs [see chapter 8.6].

4. Cardiovascular diseases which limit any elevation of cardiac output, or actually reduce the cardiac output, are exacerbated by drug induced cardiovascular depression.

5. Simultaneous administration of two or more drugs, each of which possesses myocardial depressant activity, causes more profound cardiovascular depression than administration of one drug alone. This is due to addition or potentiation of the cardiovascular depressant effect of each drug, e.g. etomidate or nitrous oxide together with an opiate.

6. Cardiovascular depression is more likely after rapid intravenous injection than after slow intravenous injection [see chapter 15.2].

SELECTION OF ANAESTHETIC DRUGS & TECHNIQUES

It is quite obvious that a patient with severe systemic disease should not be subjected to anaesthetic techniques, or drugs which will exacerbate any existing cardiovascular dysfunction. In most cases the logical choice is to select the technique and drugs which have the least effect on the cardiovascular system. If this is done, the haemodynamic changes induced by anaesthesia are not usually too extreme. However, while this is generally true and applicable, factors such as drug availability and the experience of the anaesthetist are also important. Some drugs may simply not be available, and so recourse must be had to other drugs which may not be ideal. In this latter situation the experience of the anaesthetist is

important. An experienced anaesthetist who is fully aware of the properties of the drugs he uses, is able to administer drugs which have myocardial depressant properties to patients with minimal cardiovascular reserve without significantly exacerbating the existing haemodynamic disorder.

REFERENCES

1. Li,T.H., et al.,(1965), Methoxamine and cardiac output in non-anesthetized man and during spinal anesthesia. ANESTHESIOLOGY, 26, 21.
2. Bonica,J.J., et al.,(1970), Circulatory effects of peridural block: I. Effects of level of analgesia and dose of lidocaine. ANESTHESIOLOGY, 33, 619-626.
3. Sebel,P.S., et al.,(1982), Cardiovascular effects of alfentanil anaesthesia. BRITISH JOURNAL OF ANAESTHESIA, 54, 1129.
4. Tweed,W.A., et al.,(1972), Circulatory responses to ketamine anesthesia. ANESTHESIOLOGY, 37, 613-619.
5. Kaukinen,S.,(1978), The combined effects of antihypertensive drugs and anaesthetics (halothane and ketamine) on the isolated heart. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 22, 649-657.
6. Liao,J.C., et al.,(1979), Dual effect of ketamine on the peripheral vasculature. ANESTHESIOLOGY, 51, s116.
7. Fukuda,S., et al.,(1983), Direct effects of ketamine on isolated canine cerebral and mesenteric arteries. ANESTHESIA AND ANALGESIA, 62, 553-558.
8. Lebowitz,P.W., et al.,(1982), Comparative cardiovascular effects of midazolam and thiopental in healthy patients. ANESTHESIA AND ANALGESIA, 61, 771-775.
9. Reves,J.G., et al.,(1984), Negative inotropic effects of midazolam. ANESTHESIOLOGY, 60, 517.
10. Kissin,I., et al.,(1983), Inotropic and anesthetic potencies of etomidate and thiopental in dogs. ANESTHESIA AND ANALGESIA, 62, 961-965.
11. Altura,B.T., Altura,B.M.,(1975), Barbiturates and aortic and venous smooth muscle function. ANESTHESIOLOGY, 43, 432-444.
12. Todd,M.M., et al.,(1984), The hemodynamic consequences of high dose methohexital anesthesia in humans. ANESTHESIOLOGY, 61, 495-501.
13. Criado,A., et al.,(1980), Induction of anaesthesia with etomidate. Haemodynamic study of 36 patients. BRITISH JOURNAL OF ANAESTHESIA, 52, 803-805.
14. Prys-Roberts,C., et al.,(1983), Haemodynamic effects of infusions of diisopropylphenol (ICI 35 868) during nitrous oxide anaesthesia in man. BRITISH JOURNAL OF ANAESTHESIA, 55, 105-111.
15. Waxman,K., et al.,(1980), Cardiovascular effects of anesthetic induction with ketamine. ANESTHESIA AND ANALGESIA, 58, 355-358.
16. Halford,F.J.,(1943), A critique of intravenous anesthesia in war surgery. ANESTHESIOLOGY, 4, 67.
17. Cullen,D.J., Eger,E.I.,(1974), Cardiovascular effects of carbon dioxide in man. ANESTHESIOLOGY, 41, 345-349.
18. Bos,G.C. van den, et al.,(1979), The effect of carbon dioxide upon myocardial contractile performance, blood flow and oxygen consumption. JOURNAL OF PHYSIOLOGY (London), 287, 149-161.
19. Eisele,H.H., Smith,N.T.,(1972), Cardiovascular effects of 40 percent nitrous oxide in man. ANESTHESIA AND ANALGESIA, 51, 956-963.
20. Goldberg,A.H., et al.,(1972), Direct myocardial effects of nitrous oxide. ANESTHESIOLOGY, 37, 373-380.
21. Eger,E.I., et al.,(1971), A comparison of the cardiovascular effects of halothane, fluroxene, ether and cyclopropane in man: A resume. ANESTHESIOLOGY, 34, 25-41.
22. Brown,B.R., et al.,(1971), A comparative study of the effects of five general anesthetics on myocardial contractility: I. Isometric conditions. ANESTHESIOLOGY, 34, 236-245.
23. Calverley,R.K., et al.,(1978), Cardiovascular effects of enflurane anesthesia during controlled ventilation in man. ANESTHESIOLOGY, 57, 619-628.
24. Stevens,W.C., et al.,(1971), The cardiovascular effects of a new inhalation anesthetic,Forane, in human volunteers at constant arterial carbon dioxide tension. ANESTHESIOLOGY, 35, 8-16.
25. Kemmotsu,O., et al.,(1973), Inotropic effects of isoflurane on mechanics of contraction in isolated cat papillary muscles from normal and failing hearts. ANESTHESIOLOGY, 39, 470-477.

26. Hunter,J.M.,(1987), Adverse effects of neuromuscular blocking drugs. BRITISH JOURNAL OF ANAESTHESIA, 59, 46-60.
27. Stoelting,R.K.,(1973), Hemodynamic effects of gallamine during halothane - nitrous oxide anesthesia. ANESTHESIOLOGY, 39, 645-647.
28. Stoelting,R.K.,(1972), The hemodynamic effects of pancuronium and d-tubocurarine in anesthetized patients. ANESTHESIOLOGY, 36, 612-615.
29. Stoelting,R.K.,(1974), Hemodynamic effects of dimethyl-tubocurarine during nitrous oxide-halothane anesthesia. ANESTHESIA AND ANALGESIA, 53, 513-515.
30. Kennedy,,B.R., Kelman,G.R.,(1970), Cardiovascular effects of alcuronium in man. BRITISH JOURNAL OF ANAESTHESIA, 42, 625-629.
31. Morris,R.B., et al.,(1981), Cardiovascular effects of ORG NC45 (Norcuron) in patients undergoing coronary artery bypass grafting. ANESTHESIOLOGY, 55, A205.
32. Hilgenberg,J.C., et al.,(1983), Systemic vascular responses to atracurium during enflurane-nitrous oxide anesthesia in humans. ANESTHESIOLOGY, 58, 242-244.
33. Bowman,W.C.,(1982), Non-relaxant properties of neuromuscular blocking drugs. BRITISH JOURNAL OF ANAESTHESIA, 54, 147-160.
34. Black,G.W., et al.,(1969), Circulatory catecholamines and some cardiovascular, respiratory, metabolic and pupillary responses during diethyl ether anaesthesia. ANAESTHESIA, 24, 168.
35. Duthie,D.J.R., Nimmo,W.S.,(1987), Adverse effects of opioid analgesic drugs. BRITISH JOURNAL OF ANAESTHESIA, 59, 61-77.
36. Samuel,I.O., et al.,(1977), Some circulatory and respiratory effects of morphine without pre-existing cardiac disease. BRITISH JOURNAL OF ANAESTHESIA, 49, 927-933.
37. Alderman,E.L., et al.,(1972), Hemodynamic effects of morphine and pentazocine differ in cardiac patients. NEW ENGLAND JOURNAL OF MEDICINE, 287, 623-627.
38. Bovill,J.G., et al.,(1984), Comparison of fentanyl, sufentanil and alfentanil anesthesia in patients undergoing valvular heart surgery. ANESTHESIA AND ANALGESIA, 63, 1076-1080.
39. Ruquoi,M., Camu,F.,(1983), Cardiovascular responses to large doses of alfentanil and fentanyl. BRITISH JOURNAL OF ANAESTHESIA, 55, 223s-230s.
40. Gravenstein,J.S., et al.,(1964), Effects of atropine and scopolamine on the cardiovascular system in man. ANESTHESIOLOGY, 25, 123-130.
41. Mirkhur,R.K., et al.,(1980), Effects of intravenous administration of glycopyrrolate and atropine in anaesthetised patients. ANAESTHESIA, 35, 277-281.
42. Stoelting,R.K., Gibbs,P.S.,(1973), Hemodynamic effects of morphine and morphine-nitrous oxide in valvular heart disease and coronary-artery disease. ANESTHESIOLOGY, 38, 45-52.
43. Tammisto,T., et al.,(1970), A comparison of the circulatory effects in man of the analgesics fentanyl, pentazocine and pethidine. BRITISH JOURNAL OF ANAESTHESIA, 42, 317-324.
44. Tuominen,M., et al.,(1976), Comparison of the haemodynamic effects of pethidine and anileridine in patients with coronary artery disease. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 20, 169 -176.
45. Yrjola,H., et al.,(1981), Comparison of haemodynamic effects of pethidine and anileridine in anaesthetised patients. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 25, 412-415.
46. Harrison,G.A.,(1972), The cardiovascular effects and some relaxant properties of four relaxants in patients about to undergo cardiac surgery. BRITISH JOURNAL OF ANAESTHESIA, 44,485-494.
47. Strauer,B.E.,(1972), Contractile responses to morphine, piritramide, meperidine and fentanyl. A comparative study of effects on the isolated ventricular myocardium. ANESTHESIOLOGY, 37, 304-310.

Chapter 2.2

VASOACTIVE AND CARDIOACTIVE DRUGS

The cardiovascular function of a patient during the perioperative period is sometimes so compromised that either vasoactive or cardioactive drugs are required to restore or maintain acceptable haemodynamics. A large number of these drugs are available. Knowledge of the effects of these drugs on the cardiovascular system is an absolute requirement for the selection of the most appropriate drug, or drug combination.

An understanding of the effects of these drugs on cardiovascular function is facilitated by considering the equations below.

$$\textbf{MABP} = \textbf{CO} \times \textbf{SVR} \quad \text{.....(1)}$$

$$\textbf{MABP} = \textbf{HR} \times \textbf{SV} \times \textbf{SVR} \quad \text{.....(2)}$$

[See appendix-C for abbreviations].

These equations clearly show the differing mechanisms by which the vasoactive drugs listed in table 2.2.1 exert the effects on systemic haemodynamics observed.

Example 1.

Sodium nitroprusside causes the blood pressure to fall, despite the fact that the cardiac output is increased, because the reduction of SVR that it causes is usually proportionally greater than the elevation of cardiac output.

Example 2.

Phenylephrine is a potent α-adrenoreceptor agonist, and elevates the arterial blood pressure by causing arterial vasoconstriction. The elevation of the SVR and arterial blood pressure that it induces, causes a baroreflex mediated reduction of the heart rate, which reduces the cardiac output.

Such reasoning may be extended to the effects of all vasoactive drugs on the cardiovascular system.

Table 2.2.1.
Haemodynamic effects and dosage ranges of commonly available vasoactive and cardioactive drugs. [see appendix-B for kinetic parameters].

DRUG	HR	SVR	CO	MABP	Bolus dose (per 70kg)	Infusion (μg/kg/min)	References
Atropine	↑↑	↓	↑	0/↑	0.25-0.5 mg	-	27
Calcium	0/↓	0/↑	0/↑	0/↑	0.5-1.0 gm	-	1,2
Noradrenaline	↑	↑	↓/↑	↑	1-8 μg	0.02-0.12	3,4,5,10
Adrenaline	↑↑	↓	↑	↓/↑	2-16 μg	0.03-0.5	6,7,10
Ephedrine	↑	↓/↑	↑	↑	5-25 mg	14-140	8,9,10
Phenylephrine	↓	↑↑	↓	↑↑	0.05-0.75 mg	-	10
Methoxamine	↓	↑↑	↓	↑↑	2-10 mg	-	10,11
Metaraminol	↓/↑	↑↑	0/↓	↑↑	0.65 mg	-	10,11
Isoprenaline	↑↑	↓	↑	↓/↑	1-4 μg	0.014-0.07	4,12
Dopamine	↑	0/↑	↑	↑	0.4 mg	2-20	13,14,15
Dobutamine	0/↑	↑/↓	↑	↑	1-2 mg	2-10	12,13
Glucagon	↑	↓	↑	↑	2-5 mg	-	11
Digoxin	0/↓	0	0/↑	0	1-1.5 mg	-	16
Trimetaphan	↓	0/↓	↓	↓	2.5-5 mg	40-50	17
Hydralazine	↑	↓	↑	0/↓	10-40 mg	-	18,19
Phenoxybenzamine	↑	↓	↑	↓	50-100 mg	-	20
Phentolamine	↑	↓	↑	↓	5-15 mg	10-40	21,22
Labetalol	↓	↓	?	↓	25-100 mg	3-16	23,24
Nitroglycerin	↑	↓	↑	↓	50 μg	0.5-10	25,26
Sodium-nitroprusside	↑	↓	↑	↓	50 μg	0.5-8*	17

See appendix-C for abbreviations.
"↑" = increase. "↓" = decrease. "0" = no change.
* = maximum dosage permissable because of toxicity.

INDICATIONS FOR ADMINISTRATION OF VASOACTIVE DRUGS

1. Vasodilator drugs.

a. Controlled hypotension.

Vasodilator drugs such as sodium nitroprusside and nitroglycerin etc, may be used to reduce the arterial blood pressure for any operation during which hypotension is required for reduction of intraoperative bleeding.

The usual technique is to first administer a vasodilator drug alone. However many patients develop a tachycardia due to activation of baroreflexes, and this may increase the

cardiac output to such a degree that no hypotension occurs. In this latter situation, simultaneous administration of a ß-adrenergic blocking drug will prevent any elevation of heart rate, and the desired level of hypotension can be induced with a lower dose of the vasodilator drug.

b. Treatment of hypertension.

Extreme hypertension may cause significant morbidity, [see chapter 2.6 on hypertension]. If the level of hypertension, whether acute or chronic, is at a dangerous level, rapid therapy with a vasodilator drug is required. The efficacy of the vasodilator may be enhanced by simultaneous administration of a ß-adrenergic blocking drug. Likewise, the dose of any vasodilator drug should be reduced when administered to persons concurrently receiving ß-adrenergic blocking drugs, [see chapter 2.7 on hypotension].

c. Treatment of angina pectoris.

Elevation of blood pressure, or of the SVR may induce angina pectoris in patients with coronary vascular disease. Angina pectoris may be both relieved, or prevented by an intravenous nitroglycerin bolus of 50 μg/70 kg, or an intravenous infusion of nitroglycerin at a rate of more than 0.5 μg/kg/min, [see chapter 2.9 on myocardial ischaemia].

d. Treatment of heart failure.

Vasodilator drugs may be used to reduce heart work, and increase cardiac output in patients with cardiac failure. However, arterial blood pressure will be reduced in those patients with severe heart failure, as cardiac output is unable to increase [see chapter 2.8 on heart failure].

2. Vasoconstrictor drugs.

a. Shock and hypotension.

The most common use of vasoconstrictor drugs in the past was for treatment of hypotension of all sorts, regardless of etiology. But further elevation of the SVR in the presence of an already increased SVR and reduced cardiac output, reduces the cardiac output even more, although the blood pressure is increased. The result of such "therapy" is that blood flow to nearly all organs of the body is reduced [29], with all the associated consequences of this. Accordingly the use of vasoconstrictor drugs as a definitive therapy of shock or hypotension is not advisable in all situations.

However vasoconstrictor drugs do elevate myocardial [29] and cerebral [28,29] blood flows during hypotension, regardless of whether hypotension is due to sepsis, drugs, hypovolaemia, neurogenic, or cardiogenic causes. Hypotension may cause myocardial or cerebral ischaemia, and ischaemic damage in these organs can occur within three minutes, while a definitive form of therapy for the particular cause of a given hypotensive episode may take longer than three minutes to start having any significant effect. This may be too slow in some situations where cerebral or myocardial ischaemia are present, and so a vasoconstrictor drug should be administered to elevate the blood pressure. Vasoconstrictor drugs act within less than a minute to increase blood flow in heart and brain in this situation. It is true that administration of a vasoconstrictor drug does reduce blood flow to most other organs of the body, but it should be remembered that these organs can stand much longer periods of hypoxia than can the heart or brain [see chapter 2.7]. Subsequent specific therapy of the hypotensive episode will restore normal flow to these organs.

In short, the conclusion of the above is that circulatory shock or hypotension severe enough to cause manifestations of myocardial or cerebral ischaemia may initially be treated with a vasoconstrictor drug to increase myocardial and cerebral perfusion, and subsequently the cause of the shock specifically treated. The situations in which it is advisable to administer vasoconstrictor drugs to shocked patients are listed below.

- Shock due to any cause in which the level of hypotension is such that cerebral or myocardial perfusion is threatened [see chapter 2.7 on hypotension, and ref. 28].
- Hypotension in patients with elevated intracranial pressure, [see chapters 8.3 and 8.4].
- Myocardial ischaemia due to hypotension [see chapter 2.9].
- Vasoconstrictor drugs are not required for any patient in circulatory shock whose cerebral, myocardial perfusion is not immediately threatened. The cause of the episode of hypotension should be treated. Excessive use of vasoconstrictor drugs in these patients may actually exacerbate shock induced renal dysfunction.

b. Hypotension due to anaesthesia in normovolaemic patients.

Hypotension is frequently caused by general, epidural and spinal anaesthesia. The patients in these situations are often normovolaemic. Most anaesthetic drugs and anaesthetic techniques cause hypotension by reduction of the heart rate, cardiac output, SVR, or a combination of one or more of these factors, [see chapter 2.1]. Because of this, plus the fact that the effects of these techniques and drugs are only temporary, it is advisable to manage hypotension with drugs, and not by increasing the blood volume. The reason for the preference for drug therapy in normovolaemic patients is threefold. One, a vasoconstrictor/inotropic drug has as transient an effect as the cause of the systemic haemodynamic disorder due to anaesthesia. Two, drug therapy specifically increases the cardiac contractility, output and SVR, whereas increasing the blood volume only increases cardiac output without affecting myocardial contractility or the SVR. Thirdly, once the temporary anaesthesia caused systemic vasodilation has spontaneously returned to normal, the increased blood volume due to plasma volume expansion can precipitate heart failure in those with existing heart failure, or a tendency to heart failure.

Some examples of the use of such drug therapy are listed below.

- Hypotension due to bradycardia (heart rate < 50 beats/min). Administer atropine.
- Hypotension due to regional or general anaesthesia should be treated with a drug that is a combined vasoconstrictor and inotropic agent. Ephedrine is ideal for this purpose. If elevation of the heart rate due to any such drug is thought to be deleterious, e.g. patient has NYHA class-IV angina pectoris, a drug such as methoxamine, or phenylephrine is better. They do not increase the heart rate significantly.
- Hypotension occurring during epidural or general anaesthesia in obstetric practice should be treated with ephedrine, until the cause has been treated. Hypotension increases the chances of foetal hypoxia, while ephedrine itself has no deleterious effects on the foetus.

3. Inotropic drugs.

The use of inotropic drugs is indicated in patients with a low cardiac output, or those in whom a reduction of cardiac output is thought to be the cause of any hypotension. The choice of inotropic drug depends on the SVR and the cause of the cardiac output reduction.

ADMINISTRATION OF CARDIOACTIVE & VASOACTIVE DRUGS

When administering any of these drugs intravenously a few common sense principles must always be applied.

1. Monitoring.

Regularly and frequently monitor pulse rate, blood pressure and ECG whenever these drugs are administered, until haemodynamic stability has returned. There are various reasons for this.

a. Some drugs may cause cardiac arrhythmias.

b. The dose of the drug may not be sufficient for the effect desired, and an incremental dosage may be required.

c. Too high a dose of the drug(s) may have been administered and corrective measures may be required.

2. Initial dosage.

Once a drug has been administered, it cannot be removed from the body if the wrong drug, or too high a dosage was given. In addition, some patients may be very sensitive to the cardiovascular effects of these drugs. For these reasons it is always advisable that the initial bolus or infusion dosage of any of these drugs be at the lower end of the suggested dosage range. More drug can always be administered if the initial dose proves insufficient for the purpose for which it was required.

REFERENCES

1. Denlinger,J.K., et al.,(1975), Cardiovascular responses to calcium administered intravenously to man during halothane anesthesia. ANESTHESIOLOGY, 42, 390-397.
2. Scheidegger,D., et al.,(1980), Role of the systemic vasculature in the hemodynamic response to changes in plasma ionized calcium. ARCHIVES OF SURGERY, 115, 206-211.
3. Moss,A.J., et al.,(1966), Cardiovascular effects of sustained norepinephrine infusion: I. Hemodynamics. CIRCULATION RESEARCH, 18, 596-604.
4. Richards,D.A., richard,B.N.C.,(1978), Concurrent antagonism of isoproteranol and norepinephrine after labetalol. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 23, 253-258.
5. Silverberg,A.B., et al.,(1978), Norepinephrine: Hormone and neurotransmitter in man. AMERICAN JOURNAL OF PHYSIOLOGY, 234, E252-E256.
6. Barnes,G.A., et al.,(1980), Circulating adrenaline and blood pressure:the metabolic effects and kinetics of infused adrenaline in man. EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, 10, 401-406.
7. Clutter,W.E., et al.,(1980), Epinephrine plasma clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. JOURNAL OF CLINICAL INVESTIGATION, 66, 94-101.
8. Cohn,J.N.,(1965), Comparative cardiovascular effects of tyramine, ephedrine and norepinephrine in man. CIRCULATION RESEARCH, 16, 174-182.

9. Engberg,G., Wicklund,L.,(1978), The circulatory effects of intravenously administered ephedrine during epidural anaesthesia. ACTA ANAESTHESIOLOGICA SCANDINAVICA, suppl. 66, 27-36.
10. Aviado,D.M.,(1959), Cardiovascular effects of some commonly used pressor amines. ANESTHESIOLOGY, 20, 71-97.
11. Smith,N.T., Corbascio,A.N.,(1970), The use and misuse of pressor agents. ANESTHESIOLOGY, 33, 58-101.
12. Kersting,F., et al,(1976), A comparison of the cardiovascular effects of dobutamine and isoprenaline after open heart surgery. BRITISH HEART JOURNAL, 38, 622-626.
13. Leier,C.V., et al.,(1978), Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. CIRCULATION, 58, 466-475.
14. Wilson,R.F., et al.,(1976), Hemodynamic effects of dopamine in critically ill septic patients. JOURNAL OF SURGICAL RESEARCH, 20, 163-172.
15. Jarnberg,P.O., et al.,(1981), Dopamine infusion in man. Plasma catecholamine levels and pharmacokinetics. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 25, 328-331.
16. Goldstein,R.A., et al.,(1980), A comparison of digoxin and dobutamine in patients with acute infarction and cardiac failure. NEW ENGLAND JOURNAL OF MEDICINE, 303, 846-850.
17. Sivarajan,M., et al.,(1980), Blood pressure, not cardiac output, determines blood loss during induced hypotension. ANESTHESIA AND ANALGESIA, 59, 203-206.
18. Ludden,T.M., et al.,(1982), Clinical pharmacokinetics of hydralazine. CLINICAL PHARMACOKINETICS, 7, 185-205.
19. Greenberg,B.H., et al.,(1978), Beneficial effects of hydralazine in severe mitral regurgitation. CIRCULATION, 58, 273-279.
20. Misra,K.N., Kezdi,P.,(1973), Hemodynamic effects of adrenergic stimulating and blocking agents in cardiogenic shock and low output state after myocardial infarction. AMERICAN JOURNAL OF CARDIOLOGY, 31, 724-735.
21. Stern,M.A., et al.,(1978), Hemodynamic effects of intravenous phentolamine in low output cardiac failure. CIRCULATION, 58, 157-163.
22. Kelly,D.T., et al.,(1973), Use of phentolamine in acute myocardial infarction associated with hypertension and left ventricular failure. CIRCULATION, 47, 729-735.
23. Cope,D.H.P., Crawford,M.C.,(1979), Labetalol in controlled hypotension. Administration of labetalol when adequate hypotension is difficult to achieve. BRITISH JOURNAL OF ANAESTHESIA, 51, 359-365.
24. McNiel,J.J., Louis,W.J.,(1984), Clinical pharmacokinetics of labetalol. CLINICAL PHARMACOKINETICS, 9, 157-167.
25. Mutch,W.A.C., et al.,(1982), Hemodynamic effects of intravenous nitroglycerin: Importance of the delivery system. ANESTHESIA AND ANALGESIA, 61, 927-932.
26. Armstrong,P.W., et al.,(1980), Pharmacokinetic-hemodynamic studies of intravenous nitroglycerin in congestive cardiac failure. CIRCULATION, 62, 160-166.
27. Gravenstein,J.S., et al.,(1964), Effects of atropine and scopolamine on the cardiovascualr system in man. ANESTHESIOLOGY, 25, 123-130.
28. Mutch,W.A.C., Ringaert,K.R.A.,(1987), Effects of haemorrhage and phenylephrine on cerebral blood flow in rat during isoflurane anaesthesia. CANADIAN JOURNAL OF ANAESTHESIA, 34, s106-s107.
29. Bryan-Brown,C.W.,(1988), Blood flow to organs: Parameters for function and survival in critical illness. CRITICAL CARE MEDICINE, 16, 170-178.

Chapter 2.3

CLINICAL ASSESSMENT OF CARDIOVASCULAR DISEASE

Preoperative clinical investigation is of primary importance in assessing the fitness for anaesthesia of any patient with cardiovascular disease. It provides an idea of the maximum degree of physiological stress able to be endured, and as such provides information as to whether any patient is likely to be able to endure anaesthesia and surgery without developing unacceptable complications. Laboratory investigations provide confirmation of any dysfunction, diagnosis of asymptomatic disorders, diagnosis of disorders incapable of clinical diagnosis, in addition to providing a quantitative measure of any disorder.

The specific problems associated with various cardiovascular diseases are discussed in the relevant chapters. Basic principles of cardiovascular assessment are set out below.

HISTORY

1.History of specific diseases.

a. Hypertension.
b. Myocardial infarction.
c. Angina pectoris.
d. Rheumatic fever as a child.
e. Arrhythmias, and their type.
f. Valvular disease.

2. Symptoms experienced by the patient.

a. Palpitations.

These may be a manifestation of an arrhythmia.

b. Shortness of breath.

This may be due to primary lung disease, pulmonary oedema, or low cardiac output.

c. Orthopnea.

This is shortness of breath occurring in the supine position. It is due to pulmonary congestion occurring as a result of redistribution of blood from the peripheral vessels to the pulmonary vessels. This exacerbates the elevation of pulmonary closing capacity normally caused by the supine p sition. An elevation of closing capacity may cause significant hypoxaemia with shortness of breath. It is a manifestation of pulmonary congestion, and does not occur if the left ventricle functions normally. A person who cannot lie flat because of orthopnea is unlikely to tolerate any surgical procedure in the supine position under regional anaesthesia.

d. Sleep disturbance due to shortness of breath.

Pulmonary congestion can cause orthopnea and may progress to frank pulmonary oedema with bronchoconstriction, i.e. cardiac asthma. This causes the patient to awaken. It is a manifestation of left ventricular failure.

e. Swelling of ankles.

When does it occur? Ankle swelling occurring at the end of the day after the person has stood most of the day is more typical of gravitational venous congestion. Patients with right heart failure may also develop ankle oedema. This ankle oedema is also more pronounced towards the end of the day, but typically ankle oedema due to right heart failure never disappears overnight, which is not the case were it exclusively due to gravitational venous congestion.

f. Pain in the chest - Angina pectoris.

When is this experienced by the patient? How frequently? What are the manifestations? What relieves it? What precipitates it?

Inquiries should be made about other forms of chest pain too. What are their manifestations?

3. Functional history.

The most important part of the history is the functional level of the patient. It has direct bearing on the forms of anaesthesia possible. In general it may be stated that a person whose heart disease permits him to have a reasonable exercise tolerance has a good chance of surviving anaesthesia and surgery.

a. What is the exercise tolerance of the patient? Is the condition of the patient such that he can play a sport,and if so what sport? Can he ride a bicycle? Can he climb steps? If so, how many levels can he climb before his disease forces him to stop? If the person cannot climb steps, can he walk upon level ground, and how far? Can he go shopping for food, and in general care for himself? Or is the person so incapacitated by his disease that he is house or chair bound? Of primary importance is to ask what the symptom is that causes the limitation of exercise tolerance, angina pectoris, shortness of breath, etc.

b. What body positions are tolerated? Can the person lie flat? If not, why not? Does the patient have orthopnea, paroxysmal nocturnal dyspnea, etc? If a person cannot lie flat, or has any of the other conditions, they are unlikely to tolerate the supine or prone positions if the planned operation is to be performed under regional anaesthesia. Such persons should receive general anaesthesia for the procedure planned.

4. Medication.

What medication does the patient take? If necessary these drugs should be continued in the perioperative period.

5. Other concurrent diseases.

Specific enquiry should be made as to the existence of other concurrent diseases such as diabetes mellitus, hypertension, autoimmune diseases etc. These may also influence the anaesthetic management.

PHYSICAL EXAMINATION

This is the normal clinical examination of the patient. Valvular and hypertensive cardiovascular diseases do not usually become symptomatic until late in their course. Clinical physical examination reveals these disorders, in addition to providing additional information about the clinical condition of the patient.

LABORATORY TESTS AND INVESTIGATIONS

Electrocardiogram, chest X-Ray, electrolyte, haematological investigations are all required to clarify aspects of the clinical picture, confirm a diagnosis, or detect as yet undetected cardiovascular disorders. These investigations may be supplemented with more extensive cardiac physiological tests, e.g. ejection fraction, angiography, echocardiography, etc.

NOTE:

The results of clinical and laboratory investigations must be interpreted with a good measure of common sense. In general it may be stated that a person with cardiovascular disease who has a "reasonable" exercise tolerance, i.e., is able to climb steps, cycle etc, is usually able to undergo anaesthesia for most surgical procedures without developing life threatening complications.

Chapter 2.4

NYHA CLASSIFICATION OF CARDIAC FUNCTIONAL DISABILITY

This is a classification system based upon functional disability due to heart disease devised by the New York Heart Association (NYHA). It does not specify what type of heart disease the patient has, and accordingly can be used to grade the severity of all forms of heart disease.

NYHA-CLASS

I. A patient with asymptomatic heart disease.

The patient is free of any cardiac symptoms during normal activity, but may experience symptoms during sport, or protracted heavy work.

II. The patient is symptom free at rest, but has symptoms while carrying out moderate physical exertion.

The patient develops cardiac symptoms after climbing steps for more than three stories, cycling against the wind, or mowing the lawn with a hand mower.

III. The patient is symptom free at rest, but has symptoms during even minor physical exertion.

The patient develops symptoms after climbing steps for only one story, while shopping, or even walking along level ground for more than a given distance.

IV. The patient has cardiac symptoms at rest.

This functional classification, simple as it is, does have prognostic significance, and correlates reasonably well with perioperative morbidity and mortality for patients with heart disease [1].

REFERENCES

1. Goldman,L., et al.(1978). Cardiac risk factors and complications in non-cardiac surgery. MEDICINE, 57, 357-370.

Chapter 2.5

CARDIAC OPERATIVE RISK INDEX SCORE

This is a risk scoring system devised by L.S.Goldman et al [1,2] for patients with cardiac disease who are to undergo surgery.

Table 2.5.1.
CARDIAC OPERATIVE RISK SCORE (CRIS - SCORE)

CRITERIA	POINTS
HISTORY	
- Age > 70 years	5
- Myocardial infarction 6 months	10
PHYSICAL EXAMINATION	
- Aortic stenosis	3
- S3 gallop, heart failure, raised JVP	11
ELECTROCARDIOGRAM	
- Rhythm other than sinus rhythm	7
- > 5 premature ventricular contractions (PVC's) per minute	7
GENERAL STATUS	
- P_aO_2 < 60 mmHg (8 kPa)	3
- P_aCO_2 > 50 mmHg (6.7 kPa)	3
- Serum $[K^+]$ < 3 mmol/l	3
- Serum Urea > 8.4 mmol/l	3
- Serum creatinine > 265 μmol/l	3
- Bedridden	3
TYPE OF OPERATION	
- Emergency	4
- Intrathoracic	3
- Intraperitoneal	3
- Aortic surgery	3

The score for a patient is derived by adding the score for each factor present to arrive at a total score. This total score is related to the chance of developing perioperative cardiovascular complications [see table 2.5.2].

Table 2.5.2.
Frequency of severe perioperative cardiac complications related to the preoperative CRIS score in one series [1].

CRIS SCORE	LIFE THREATENING COMPLICATIONS	CARDIAC DEATH
0-5	0.7%	0.2%
6-12	5%	2%
13-25	11%	2%
26+	22%	56%

It is obvious that those patients with a CRIS score greater than or equal to 26 should never be considered for elective surgery.

This scoring system is somewhat more detailed than the NYHA functional classification [see chapter 2.4], but whether it has any more prognostic value is debatable. Survival and morbidity due to surgery and anaesthesia are also dependent on variables which are not scored, such as the skill of the anaesthetist, and surgeon, as well as the quality of postoperative therapy. However it does provide a more accurate insight into what constitutes a high risk patient than does the NYHA classification system.

REFERENCES

1. Goldman,L., et al.(1977). Multifactorial index of cardiac risk in non-cardiac surgical procedures. NEW ENGLAND JOURNAL OF MEDICINE, 297, 845-850
2. Goldman,L., et al.(1978). Cardiac risk factors and complications in non-cardiac surgery. MEDICINE, 57, 3-57-370.

Chapter 2.6

HYPERTENSION

Arterial hypertension is defined as a systolic arterial blood pressure (SABP) > = 160 mmHg and/or a diastolic arterial blood pressure (DABP) > = 95 mmHg measured repeatedly at rest [1]. The presence of hypertension in the perioperative period is associated with a variety of problems which can cause considerable perioperative morbidity if not recognized and prepared for.

PROBLEMS DUE TO PERIOPERATIVE HYPERTENSION

1. Hypertensive reactions.

a. Haemorrhagic complications.

Spontaneous haemorrhages may occur as a result of rupture of weakened or aneurysmatic blood vessels during any sudden increase of blood pressure, e.g. rupturing of existing aortic or intracerebral aneurysms, cerebral haemorrhage etc [8, 5 - page 1932].

b. Myocardial ischaemia/infarction.

Myocardial ischaemia or infarction may occur if the arterial blood pressure increases excessively. Elevation of the blood pressure increases myocardial oxygen consumption because of the increased heart work it causes [see chapter 2.9 on myocardial ischaemia]. Patients with a prior history of myocardial infarction have twice the chance of having a perioperative myocardial infarction if they have preoperative hypertension [7]. Those patients with both preoperative hypertension and angina pectoris, as well as a history of previous myocardial infarction, have a chance of perioperative myocardial infarction which approaches 23% [2, and see table 2.9.1].

c. Exaggerated responses to vasoconstrictor drugs.

The arterial blood pressure of chronically hypertensive patients increases to a greater degree than in non-hypertensive persons when they are administered a given dose of a vasoconstrictor drug such as phenylephrine etc [18].

2. Hypotensive reactions.

a. Deficient baroreflexes.

Hypertensive patients commonly have deficient baroreflex responses, and so may develop profound hypotension as a result of anaesthesia induced vasodilation and myocardial depression [18, chapter 8.6]. This effect is even more pronounced in patients who also ingest antihypertensive, and in particular, sympathetic nervous system blocking drugs

[1]. All drugs blocking the action of the sympathetic nervous system reduce the baroreceptor reflex response to vasodilation, hypotension, etc [see chapter 8.6].

b. Deficient organ blood flow autoregulation.

Atherosclerosis and arteriolosclerosis due to chronic hypertension reduces the efficiency of blood flow autoregulation in organs such as the brain, kidneys, and heart. Blood flow becomes more pressure dependent, being more directly related to the mean arterial blood pressure (MABP). Hypotension readily causes tissue ischaemia in organs where such changes have occurred [see chapter 2.7]. An example of this is observed in patients with NYHA classes III-IV coronary vascular disease. Hypotension due to induction of anaesthesia may produce ECG evidence of myocardial ischaemia in these patients, even when the MABP has fallen only as little as 6% of the pre-anaesthetic level [13].

3. Effects of antihypertensive medication [3].

a. Sudden withdrawal of antihypertensive medication.

The arterial blood pressure may rise to extreme levels after sudden discontinuation of some antihypertensive drugs. This is called "rebound hypertension". Clonidine is the best known example of an antihypertensive drug exhibiting this phenomenon, "rebound hypertension" sometimes occurring only 6-8 hours after sudden discontinuation of regular clonidine ingestion [4].

Regular administration of ß-adrenergic blocking drugs elevates the number of ß-adrenergic receptors present on the affected end organs [15]. The increased numbers of ß-adrenoreceptors remain present for a number of days after sudden ß-blocker drug withdrawal, increasing the sensitivity of these end organs to sympathetic nervous stimulation, and exogenously administered catecholamines. This causes manifestations of exaggerated sympathetic tone and reactivity, an effect which is maximum between 2 to 10 days after sudden ß-blocker drug withdrawal [14,16,17]. Sudden withdrawal of ß-blocker drugs may exacerbate myocardial ischaemia in patients with severe coronary vascular disease who regularly ingest these drugs, and can even precipitate lethal myocardial infarction in a significant number of such patients [14]. If ß-blocking drugs are abruptly discontinued longer than 10-48 hours preoperatively, exaggerated sympathetic cardiovascular responses such as tachycardia and hypertension may occur, as well as an increased frequency of ventricular arrhythmias in response to endotracheal intubation, surgery, postoperative and physiological stress in general [16,17].

b. Sympathetic blockade.

Many of the drugs used for the treatment of hypertension have α-and ß-adrenoreceptor blocking activity. Bradycardia, and other signs of parasympathetic over-activity are not uncommon in patients using drugs blocking sympathetic nervous system function [1,3].

c. Antihypertensive-anaesthetic drug interactions.

Interactions between antihypertensive medication and anaesthetic drugs may occur [3]. Some of the dugs used for treatment of hypertension are sedative, e.g. clonidine, and may potentiate any hypnotic or sedative drugs. Antihypertensive drugs also affect baroreflexes, an effect already discussed [see also chapter 8.6].

d. Hypokalaemia.

Patients receiving antihypertensive drug therapy may also be receiving a diuretic drug, usually a thiazide. Chronic ingestion of thiazide diuretic drugs without potassium supplements almost invariably causes hypokalaemia, with all the consequences of this [see chapter 12.3].

4. Neurological problems.

Hypertensive cerebral haemorrhages occur with increasing frequency when the arterial blood pressure rises above 170/90 mmHg [5-page 1932]. This is not the only problem. Blood-brain barrier integrity is impaired when the MABP rises above the upper limit of cerebral circulatory autoregulation because of loss of the arteriolar constrictor response [10,11,12]. Arteriolar constriction in response to increased arterial blood pressure limits the pressure in the cerebral capillaries. Elevation of cerebral capillary pressures above normal increases the amount of water diffusing out of the capillaries into the interstitium of the brain, and so increases the cerebral interstitial volume [see chapter 14.1 on transcapillary fluid exchange]. If the cerebral capillary blood pressure rises too high, actual damage to the capillary endothelium occurs, and so plasma then flows unhindered into the interstitium to cause interstitial oedema, or to exacerbate exisiting oedema [10,11]. These two effects are likely to be the cause of hypertensive encephalopathy.

The cerebral blood flow is autoregulated in normal persons, and in normotensive treated hypertensive persons up to an MABP of 130-150 mmHg. Chronic untreated hypertension causes the autoregulation range to be shifted upwards, and in this group of persons cerebral blood flow may be autoregulated up to an MABP of 145-175 mmHg [6,9,10].

MANAGEMENT OF HYPERTENSION

1. Chronic hypertension.

This has been the subject of many reviews, and is well covered in the standard medical texts.

2. Perioperative hypertension.

Perioperative hypertension should be treated when;

- the blood pressure exceeds one or more of the following, systolic > = 200 mmHg, mean > = 150 mmHg, and diastolic > = 120 mmHg,
- the patient has evidence of myocardial ischaemia,
- the patient has evidence of disturbed neurological function caused by hypertension.

a. Preoperative and intraoperative hypertension.

During operation the patient may become hypovolaemic, or his cardiovascular system may be depressed by anaesthetic drugs. Because of the rapidity with which systemic haemodynamic function may change in the perioperative period, hypertension occurring preoperatively or intraoperatively should ideally be controlled with short acting drugs. There are various methods of doing this.

- If the patient is under anaesthesia, deepen the level of anaesthesia. This is usually more than adequate.

- Administer a vasodilator drug by intravenous infusion. Table 2.2.1 lists a number of vasodilator drugs and their dosages.
- Sometimes administration of a vasodilator drug by itself has little effect because of baroreflexes. These may elevate the cardiac output to such a degree that the vasodilator drug does not decrease the blood pressure at all. In such cases administer a ß-adrenoreceptor blocking drug if it is obvious that the vasodilator has minimal effect. The dosages of a number of these are listed in table 3.2.1.

b. Postoperative hypertension.

Arterial blood pressure may be very labile postoperatively. This is due to a combination of one or more factors.

- Residual preoperative sedation.
- Residual effects of anaesthetic drugs or techniques.
- Postoperative analgesic drugs.
- Perioperative fluid and blood loss.
- Postoperative pain.
- Postoperative hypercarbia due to opiates, or restriction of respiration by pain.

If postoperative hypertension is not due to pain or respiratory depression, then antihypertensive therapy should be commenced. Patients receiving antihypertensive drugs preoperatively should receive these drugs postoperatively too. However these drugs should only be administered if the patient is in a stable haemodynamic situation, i.e. is not bleeding significantly or is losing large quantities of extracellular fluid. If the patient is unable to ingest drugs orally, the drugs should be administered parenterally. Administer the same antihypertensive drug as is used normally by the patient, only give it intramuscularly. Because the degree of initial hepatic extraction is less after intramuscular or intravenous administration, the initial dose should only be half that normally administered orally. Increase the dose as indicated by the response to therapy.

If the patient does not normally take any antihypertensive therapy, and the cause of the hypertension is neither pain nor hypercapnia, manage as for preoperative and intraoperative hypertension.

Table 2.6.1.
Maximum permissable preoperative arterial blood pressure

SYSTOLIC ARTERIAL BLOOD PRESSURE	**= 200 mmHg**
+/-	
MEAN ARTERIAL BLOOD PRESSURE	**= 150 mmHg**
+/-	
DIASTOLIC ARTERIAL BLOOD PRESSURE	**= 120 mmHg**

MAXIMUM PERMISSABLE PREOPERATIVE BLOOD PRESSURE

Measure the arterial blood pressure repeatedly with the patient at rest. This will provide a more accurate idea of its true value, as most persons are initially anxious in hospital. The level of hypertension at which elective surgical procedures should be delayed until hypertension has been properly treated has always been subject to wide, and sometimes rather arbitrary decision making.

The opinion of the author is that the maximum acceptable preoperative arterial blood pressure limits prior to elective surgery should be set at the levels given in table 2.6.1. The reasoning behind the choice of these levels is simple. If the DABP is > = 120 mmHg, exaggerated responses to anaesthetic and surgical manipulations occur, e.g. large increases of blood pressure, myocardial ischaemia etc [1]. If the MABP is greater than 150 mmHg, or the SABP is > = 200 mmHg, the chance of hypertensive encephalopathy and of cerebral haemorrhage are increased.

But while the above are useful thresholds for persons with no cardiac or cerebrovascular disease, they are not acceptable for persons with such disorders. Persons who have had a myocardial infarction less than one year prior to the date of planned elective surgery, have a left ventricular strain pattern on the ECG, have heart failure, angina pectoris, a history of transient cerebral ischaemic attacks (TIA's), or cerebrovascular accidents, should not be permitted to undergo elective surgery until their hypertension has been treated, even if it satisfies the criteria in table 2.6.1. This is because a hypertensive episode occurring in the perioperative period may exacerbate these problems, e.g. causing acute heart failure, myocardial ischaemia, rupture of cerbral aneurysms etc [8]. Such persons should have their hypertension treated for a period of of at least two weeks preoperatively, and not be treated on the day before operation. The effects of blood pressure reduction may then be observed without any of the alterations of physiology due to surgery and anaesthesia being present.

NOTE: Preoperative hypertension in persons with known carotid artery stenosis should not be treated, as hypertension may be necessary to force enough blood through the stenotic carotid vessels to maintain cerebral blood flow at an acceptable level.

ANAESTHETIC MANAGEMENT

Preoperative.

1. Cancel any elective operation if the blood pressure exceeds the limits given above.

2. If a person is discovered to have uncontrolled hypertension prior to emergency surgery, then this should be managed as is any other form of perioperative hypertension.

3. Hypokalaemia may be present due to therapy with diuretic drugs. This should be corrected prior to any elective operation [see chapter 12.3 for therapy of hypokalaemia].

4. Never stop any antihypertensive therapy suddenly before operation. "Rebound hypertension" together with acute cardiovascular problems may occur. Administer the normal morning dosages of the antihypertensive drugs on the morning of operation, with the exception of diuretic drugs. Acute bladder distension is an undesirable complication of the use of diuretic drugs in situations where the patient is unable to urinate easily.

5. Adequate preoperative sedation is required to pevent exacerbation of hypertension.

Anaesthesia.

1. Adequate analgesia is required with all anaesthetic techniques so as to prevent hypertension due to pain. Otherwise no recommendations can be made as to a preferred anaesthetic technique [1,3]. Extremes of hypotension and hypertension should be avoided.

2. Laryngoscopy is a stimulus that can cause large increases of arterial blood pressure. Elevation of the blood pressure in response to laryngoscopy has been reported to cause myocardial ischaemia, acute heart failure, and even rupture of intracerebral aneurysms [8]. The pressor response to laryngoscopy may be blunted or reduced by deep anaesthesia during laryngoscopy, topical anaesthesia of the larynx and trachea, intravenous fentanyl 5-10 μg/kg five minutes prior to laryngoscopy, or intravenous administration of a ß-blocker [1].

Postoperative.

Postoperative management of hypertension has already been discussed.

REFERENCES

1. Prys-Roberts,C.(1984). Anaesthesia and hypertension. BRITISH JOURNAL OF ANAESTHESIA, 56, 711-723.
2. Rao,T.L.K., et al.(1983). Reinfarction Following Anaesthesia in Patients with Myocardial Infarction. ANESTHESIOLOGY, 59, 499-505.
3. Foex,P., Prys-Roberts,C.(1974). Anaesthesia and the hypertensive patient.. BRITISH JOURNAL OF ANAESTHESIA, 46, 575-588.
4. Stevens,J.E.(1980). Rebound hypertension during anaesthesia. ANAESTHESIA, 35, 490-491.
5. Isselbacher,K.J., et al.(1981)." Harrison's Principles of Internal Medicine", 9th edn., pub. McGraw-Hill.
6. Langfitt,T.W.(1974). Cerebral circulation and metabolism. JOURNAL OF NEUROSURGERY, 40, 561-576.
7. Steen,P.A., et al.(1978). Myocardial Reinfarction After Anaesthesia and Surgery. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 239, 2566-2570.
8. Fox,E.J., et al.(1977). Complications Related to the Pressor Response to Endotracheal intubation. ANESTHESIOLOGY, 47, 524-525.
9. Smith,A.L., Wollman,H.(1972). Cerebral Blood Flow and Metabolism. ANESTHESIOLOGY, 36, 378-400.
10. Johansson,B., et al.(1974). On the Pathogenesis of Hypertensive Encephalopathy. CIRCULATION RESEARCH, 34, suppl.I, I-167-171.
11. Johansson,B.(1974). Blood-brain barrier dysfunction in acute arterial hypertension after papaverine-induced vasodilation. ACTA NEUROLOGICA SCANDINAVICA, 50, 573-580.
12. Ekstrom-Jodal,B., et al.(1977). The Pressure-Flow Relations of the Canine Brain in Acute Mechanically Induced Arterial Hypertension at Different Levels of Cerebral Blood Flow. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 21, 232-239.
13. Lieberman,W.W., et al.(1983). Hemodynamic Predictors of Myocardial Ischemia during Halothane Anesthesia for Coronary Artery Revascularization. ANESTHESIOLOGY, 59, 36-41.
14. Miller,R.R., et al.(1975). Propranolol-withdrawal rebound phenomenon: Exacerbation of coronary events after abrupt cessation of antianginal therapy. NEW ENGLAND JOURNAL OF MEDICINE, 293, 416-418.
15. Maze,M.,(1981), Clinical implications of membrane receptor function in anaesthesia. ANESTHESIOLOGY, 55, 160-171.
16. Rangno,R.E., et al.,(1982), Cardiac hyper- and hyporesponsiveness after pindolol withdrawal. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 31, 564-571.
17. Oka,Y., et al.,(1980), Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 10. Beta-adrenoreceptor blockade and coronary artery surgery. AMERICAN HEART JOURNAL, 99, 255-269.
18. Goldstein,D.S.,(1983), Arterial baroreflex sensitivity, plasma catecholamines, and pressor responsiveness in essential hypertension. CIRCULATION, 68, 234-241.

Chapter 2.7

HYPOTENSION

Hypotension in the perioperative period may be either accidental or induced. Excessively low levels of hypotension can reduce organ perfusion to such a degree that organ function or viability are reduced or threatened. The purpose of this chapter is to examine the effects of hypotension on a number of vital organ systems, and the practical consequences for the anaesthetist.

CAUSES

Hypotension may be the result of any one or more of a number of causes. Usually the causes of hypotension are listed according to aetiology as below.

1. Neurogenic

- spinal cord transection.
- spinal or epidural anaesthesia.
- administration of large doses of ganglion, or a- as well as ß-adrenergic receptor blocking drugs.
- extremely deep anaesthesia, or overdosages of central nervous system depressant drugs.

2. Cardiogenic

- heart failure.
- deep anaesthesia, e.g. halothane and most other anaesthetic gases directly depress cardiac output.
- abnormal rhythm, e.g. extreme tachycardias, rapid atrial fibrillation etc.

3. Hypovolaemic

- dehydration.
- plasma loss from burns, or during operation.
- haemorrhage.
- administration of drugs causing direct vascular smooth muscle relaxation and vasodilation, e.g. sodium nitroprusside, nitroglycerin, hydralazine etc.

PHYSIOLOGY

The function of blood is to supply metabolic substrates and to remove metabolic wastes as well as products of metabolism required elsewhere in the body. Tissue blood flow is

determined by a number of factors, such as the vascular resistance of any specific tissue and its relationship to the SVR, as well as the cardiac output and the mean arterial blood pressure. The relationships between these factors may be derived as below.

Blood flow through an organ is determined by the vascular resistance (R_O) of the organ under consideration, and the difference between the mean arterial blood pressure (MABP) and the mean venous blood pressure (MVBP).

$$\text{Organ blood flow} = \frac{\text{MABP - MVBP}}{R_O} \quad \text{.....(1)}$$

The above relationship may be expressed in terms of the cardiac output (CO). Consider the systemic vascular resistance (SVR) as being composed of two resistances in parallel. These are the resistance of the organ under consideration (R_O) and the vascular resistance of the rest of the body (R_X). In that case,

$$\frac{1}{R_O} = \frac{R_X - SVR}{R_X \times SVR} \quad \text{.....(2)}$$

The relationships below follow from substitution of equation 2 into equation 1.

$$\text{Organ blood flow} = (\text{MABP - MVBP}) \times \frac{R_X - SVR}{SVR \times R_X} = CO \times \frac{R_X - SVR}{R_X}$$

After rearrangement of (2) and substitution into the equation above this simplifies to;

$$\text{Organ blood flow} = \frac{\text{MABP - MVBP}}{R_O} = CO \times \frac{SVR}{R_O} \quad \text{.....(3)}$$

These equations do provide a useful conceptual framework with which to approach the subject of hypotension, but regrettably do not tell the whole story. It is necessary to expand on this by discussing the factors that determine tissue blood flow in greater detail below.

1. Autoregulation.

The blood flow through many organs is autoregulated within a given perfusion pressure, or MABP range. That is, the blood flow through such an organ is constant regardless of blood pressure, provided that the perfusion pressure or MABP is within the autoregulation range. Organ perfusion is directly proportional to the blood pressure if this is above or

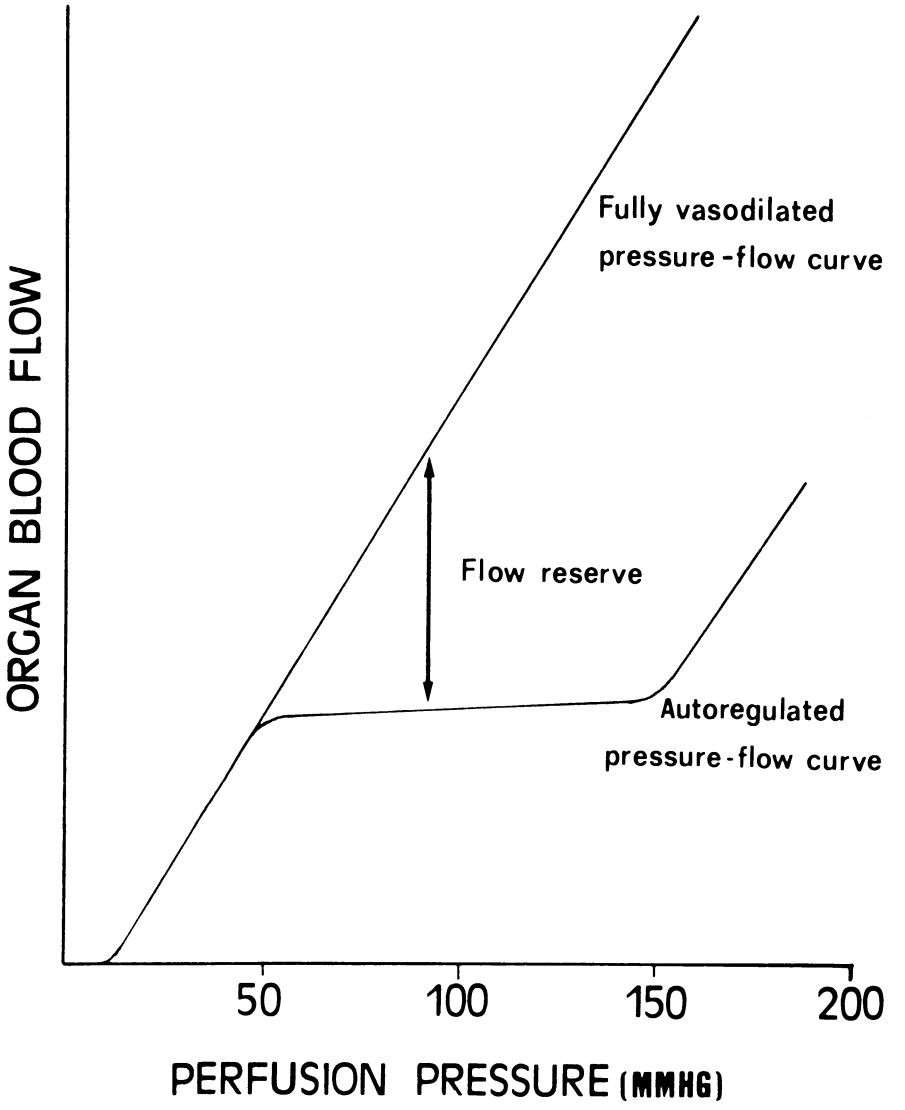

FIGURE 2.7.1. - The autoregulation curves of brain, heart and kidneys are shown. All these three organs have a blood flow which is relatively independent of the perfusion pressure in the pressure range 50-150 mmHg. PERFUSION PRESSURE = MEAN ARTERIAL BLOOD PRESSURE - MEAN VENOUS BLOOD PRESSURE. If the venous pressure is low or normal, perfusion pressure is approximately equal to the mean arterial blood pressure. Above or below the autoregulation pressure range the blood flow is pressure dependent. Under circumstances of maximal vasodilation, autoregulation no longer occurs, and blood flow is pressure dependent. At a given pressure, the difference between the flow possible for that pressure under circumstances of maximal vasodilation, and that occurring during normal autoregulation is called the flow reserve.

below the autoregulation range. Autoregulation of blood flow occurs in the brain, kidneys, and heart, the autoregulation range of these organs being an MABP range of 50-150 mmHg.

Autoregulation does not occur under conditions of maximum organ vasodilation, or when the arteries of that organ are so sclerotic that vasoconstriction or dilation cannot occur. Under these circumstances organ blood flow is directly related to the MABP or perfusion pressure. The relationship is then as shown in equation 1.

Figure 2.7.1 shows the pressure flow curves for autoregulation and vasodilation for the kidney, brain and heart.

2. Effect of tissue pressure.

Capillaries, and all other blood vessels too for that matter, act as "Starling" resistors. That is, they are collapsible tubes held open because the pressure within them is greater than the pressure exerted on them by the tissues in which they are situated. If the blood pressure within the vessels of an organ is less than the tissue pressure, the vessels collapse, and blood flow through that organ ceases. The resistance to blood flow is inversely proportional to the intravascular pressures, as blood vessel lumen diameter is directly proportional to the capillary pressure. It is obvious that for intravascular pressures marginally above the tissue pressure of a given organ, that the resistance to blood flow will be high, and blood flow will be minimal. A consequence of this is that tissue hypoxia begins to occur at a venous blood pressure somewhat greater than the tissue pressure of that organ. The tissue and capillary closing pressures of various organs are listed in table 2.7.1.

Table 2.7.1.
Tissue pressures and capillary closing pressures of various organs.

Cerebrospinal fluid or intracranial pressure = 5-13 mmHg
Renal intracapsular pressure = 10-18 mmHg
Coronary blood flow stops at MABP = 7-12 mmHg

The relationship between organ blood flow, the venous blood pressure (P_v), tissue pressure (P_t), and the arteriovenous pressure difference is shown in equation 4. (N.B. Venous pressure is used as it is always lower than arterial or capillary pressures, and so veins are the first vessels to be closed by tissue pressure during extreme hypotension.)

$$\text{Organ blood flow} = \frac{\text{MABP - MVBP}}{K} \times (P_v - P_t) \quad .....(4)$$

K = a complex vascular resistance related constant which for didactic purposes may be considered to be unvarying.

3. Cardiac output.

If the relative magnitudes of the vascular resistances of the various organs and tissues of the body remains constant, blood flow through any organ is directly proportional to the cardiac output, as long as the MABP is greater than the tissue pressure [see equation 3]. Indeed organ blood flow under such circumstances may be adequate despite profound hypotension. This is well demonstrated in humans by the fact that sodium nitroprusside induced hypotension down to blood pressures of 40/20 mmHg for periods of to 70 minutes or more does not cause organ damage in young healthy humans [8]. A feature of sodium nitroprusside induced hypotension is that the cardiac output is maintained or actually increased by baroreflexes as the SVR is decreased.

The situation is different for hypotension due to factors which reduce the cardiac output, e.g. hypovolaemia, myocardial depressant drugs, etc. As the cardiac output decreases, selective vasoconstriction increases the proportion of the cardiac output going to the brain and coronary circulation, and reduces perfusion of all other organs [see table 2.8.1]. If the cardiac output declines still further, coronary and cerebral perfusion are reduced too.

4. Arterial blood pressure.

Regrettably, cardiac output is not always able to be measured, and so the only measure of the adequacy of the perfusion of any organ is the arterial blood pressure, in addition to any clinical manifestations of organ ischaemia such as urine production, myocardial ischaemia, level of consciousness etc. All that is certain is that the blood flow through any particular organ is directly related to the MABP and inversely related to the vascular resistance of that organ. And this is where the problem lies, as the vascular resistance of any particular organ during a hypotensive episode depends on the cause of the hypotension. This means that when the blood pressure is the only parameter of the adequacy of tissue perfusion, that management is also dictated by the cause of the hypotensive episode. This is well demonstrated by animal experimental work on the cerebral effects of induced hypotension. Hypotension induced by haemorrhage is associated with a lower cardiac output than hypotension induced by drugs such as trimetaphan or sodium nitroprusside, and because of this cerebral ischaemia occurs at a higher MABP during haemorrhagic, than drug induced hypotension [9,10,11].

The conclusions from the above are obvious. Hypotension due to factors which reduce cardiac output is more likely to cause organ ischaemia at any given level of blood pressure, and as such should be more aggressively treated, and treated at a higher blood pressure, than hypotension due to factors which do not reduce cardiac output.

EFFECTS OF HYPOTENSION ON VARIOUS ORGANS

Organ dysfunction occurs once perfusion of any given organ is reduced below a minimum required for normal function. If the blood pressure is reduced still further, a point is reached at which organ perfusion is so low that hypoxic damage occurs, and in extreme cases, organ death. Different organs vary in their tolerance of hypotension, and this is discussed below. Further discussion of the pathophysiology of shock states is beyond the scope of this book.

1. Brain.

The brain is an organ whose function is critically dependent on an adequate supply of oxygen. Human investigation of cerebral circulatory arrest produced with a pneumatic neck

tourniquet have shown that the average person becomes unconscious by 6-7 seconds after sudden cessation of cerebral blood flow [1]. Clinical experience with patients experiencing circulatory arrest due to ventricular asystole or fibrillation have confirmed this experimental finding, and has further shown that more than three minutes of circulatory arrest results in permanent brain damage.

Much investigation has been performed on the effects of differing cerebral blood flows on brain function. The normal cerebral blood flow is about 45-55 mls/100 gm brain tissue/min. Investigations using conscious persons aged between 30-93 years, with and without resting arterial hypertension, subjected to induced hypotension with a hexamethonium infusion have shown that clinical manifestations of cerebral hypoxia, such as sighing, yawning, staring, confusion and inability to carry out simple commands, began to manifest when the cerebral blood flow (CBF) falls below 31.5 ml/100 gm/min [5]. Measurement of cerebral blood flows in patients undergoing carotid artery surgery have shown that the electroencephalogram (EEG) remains normal until the CBF drops below 18-22 mls/100 gm/min. Slowing of the EEG occurs at a CBF of 16-20 mls/100 gm/min, while flattening of the EEG signal, indicative of severe cerebral ischaemia occurs at a CBF between 11-19 mls/100 gms/min [6]. Regrettably, CBF measurement is not easily performed in most clinical settings, and the only indications that most clinicians have of the adequacy of the CBF are the level of consciousness and arterial blood pressure. Arterial blood pressure measurement is easily performed in all clinical circumstances and does have some relationship to the CBF.

The CBF is autoregulated, being constant in the MABP range of 50-130 mmHg in patients with normal cardiovascular function [2,3]. Above and below these autoregulation limits the cerebral blood flow is directly proportional to the MABP. These autoregulation limits are changed by disease, the upper limit of the autoregulation range being increased by chronic hypertension up to 145-175 mmHg [4]. Anaesthesia with anaesthetic gases, e.g halothane etc, decreases the degree of autoregulation by causing cerebral vascular dilation, so making cerebral blood flow more pressure dependent [3].

Because of individual variation of cerebrovascular autoregulation limits, the blood pressure at which cerebral hypoxia occurs varies from one person to another. From the data of Finnerty et al [5], it is possible to relate the MABP at which symptoms of cerebral ischaemia occurred, to the resting MABP measured prior to an episode of acute induced hypotension in conscious volunteers. The subjects used by Finnerty et al [5], had mean arterial blood pressures at rest which varied from 55-203 mmHg, and ages ranging from 30-93 years. Because subjects with hypertension had a greater cerebrovascular resistance than those who were normotensive, it is not surprising that they developed cerebral ischaemic symptoms at a higher blood pressure than normotensive subjects [see equation 1]. No person in this investigation [5], developed cerebral ischaemia when their blood pressure during induced hypotension was greater than that given by equation 5 [see also figure 2.7.2].

$$\textbf{MABP(no cerebral ischaemia)} > 20 + \frac{\textbf{MABP(resting)}}{2} \quad .....(5)$$

MABP(no cerebral ischaemia) = MABP above which no person developed cerebral ischaemia in the investigation of Finnerty et al [5].
MABP(resting) = MABP at rest prior to induced hypotension.

Clinical investigation has confirmed this to some degree, in that the chance of brain damage as a result of induced hypotension during anaesthesia is increased when the systolic blood pressure is less than 80 mmHg [7]. Hypotension in man appears to be better tolerated during general anaesthesia [8], as anaesthesia depresses cerebral oxygen requirements [3]. Investigations performed on a group of patients undergoing carotid artery surgery under halothane-nitrous oxide-opiate anaesthesia, showed that the EEG was normal when the internal carotid artery stump pressure was above 36-55 mmHg [6]. When the internal carotid artery stump pressure was in the range 29-46 mmHg, slowing of the EEG was observed, and when it was in the range 15-36 mmHg, flattening of the EEG, indicative of cerebral ischaemia was observed [6, table 2.7.2]. It may be concluded from these investigations that the cerebral blood flow in normovolaemic humans is so reduced at a MABP of 15-36 mmHg that actual cerebral ischaemia will occur. This agrees well with what is predicted by equation 4, that is that if the mean arterial blood pressure is less than 13 mmHg, cerebral blood flow can be expected to cease, as the intracranial pressure is then certainly equal to, or greater than cerebral venous pressure.

The effect of hypotension on the brain varies according to the etiology of the hypotension too. Animal experiments have shown that a given level of hypotension induced by

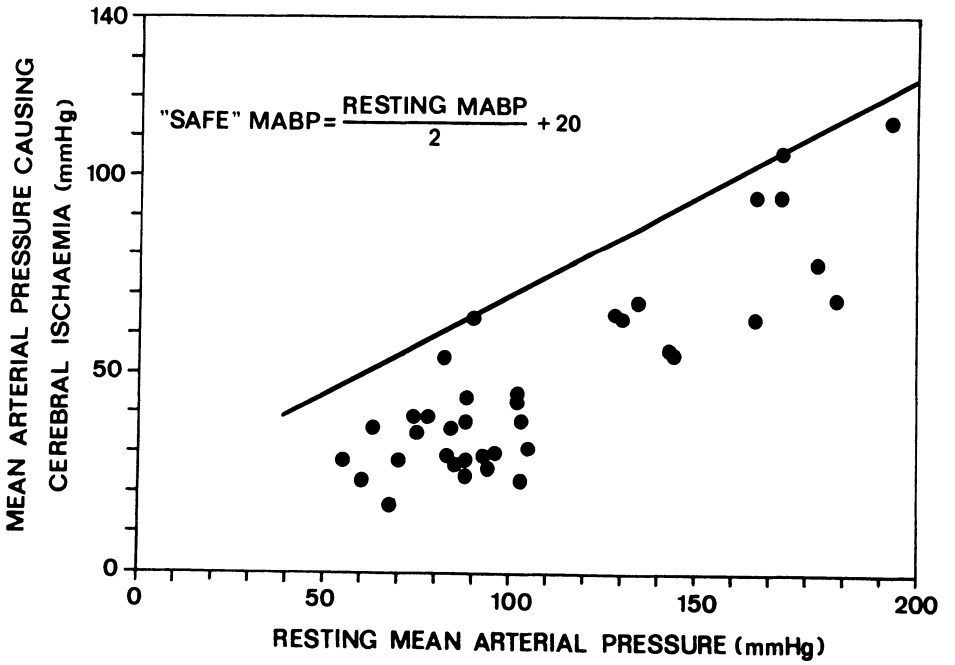

FIGURE 2.7.2. - The mean arterial blood pressure (MABP) at which signs of cerebral ischaemia occurred during induced hypotension in 37 awake subjects, (whose ages varied between 30-93 years), is related to their normal resting MABP [5]. The line shows the MABP above which none of the subjects developed signs of cerebral ischaemia. The equation of the line giving the "safe MABP" is also shown.

Table 2.7.2.
Relation of the CBF and cerebral function to the MABP during hypotension in man [5,6].

Mean arterial blood pressure (mmHg)	Cerebral blood flow (mls/100 gm/min)	Clinical manifestations
Normal	45-55	Normal CBF and oxygenation
20 + ((Resting MABP)/2)	31	Threshold of clinical cerebral ischaemia. Sighing, yawning, staring, confusion, and inability to carry out simple commands.
36-55	18-22	Reduced level of consciousness. Normal EEG.
< 29-46	< 16-20	Slowing of EEG frequencies due to cerebral ischaemia.
< 15-36	< 11-19	Flat EEG, i.e. no cerebral electrical activity. Irreversible cerebral hypoxic damage occurs if blood flow remains at this level.

haemorrhage results in cerebral oxygenation being reduced to a greater degree than an equivalent level of hypotension induced either by ganglion blockade or sodium nitroprusside [9,10,11]. This is presumably due to the reduction of cardiac output caused by haemorrhage, while pharmacologically induced hypotension usually elevates the cardiac output [9,10,11]. The chance that a given degree of hypotension will cause cerebral ischaemia is therefore increased by low cardiac output and hypovolaemia.

2. Heart.

Blood flow through the coronary arteries is also subject to autoregulation. The MABP range in which autoregulation occurs in dogs is 70-130 mmHg [12]. Coronary blood flow is pressure dependent below an MABP of 70 mmHg, and coronary blood flow ceases in dogs when the MABP falls below 23 mmHg [12]. However, the canine coronary circulation differs from the human, and it is thought that the zero flow pressure in humans is nearer 7-12

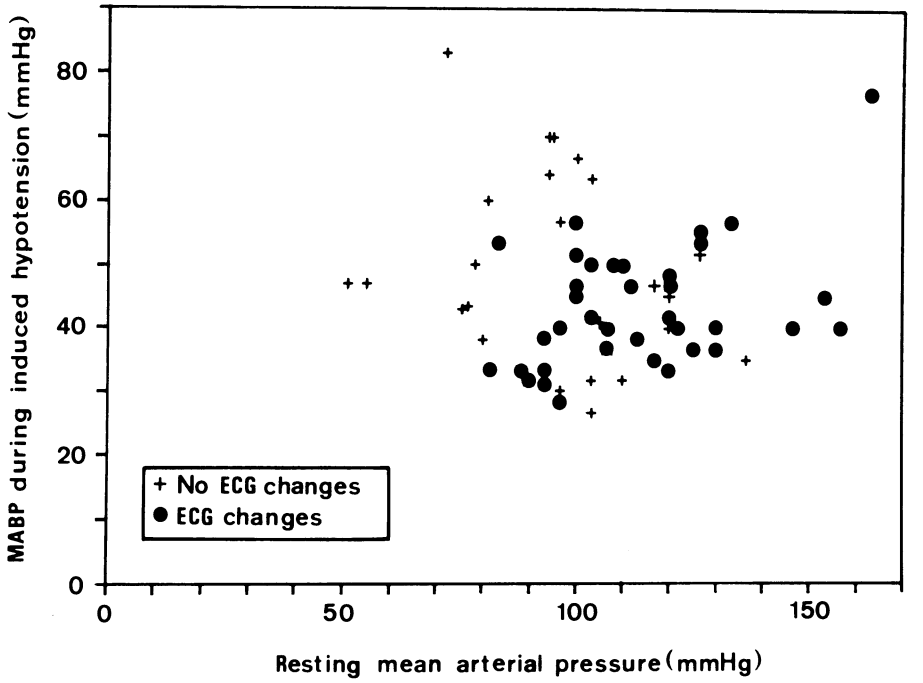

FIGURE 2.7.3. - The MABP during induced hypotension is related to the normal resting MABP in the same patient, and to the occurrence or non-occurrence of ECG changes during hypotension. There is no relationship evident, except that an extremely low MABP may cause ECG changes. The data are derived from Simpson,P., et al., (1976), Anaesthesia, 31, 1172- 1178 : Rollason,W.N. & Hough,J.M., (1960), Brit.J.Anaesth., 32, 276-285 : Eckenhoff,J.E., et al., (1963), J.Appl. Physiol., 18, 1130-1138.

mmHg [26]. During conditions of maximum vasodilation, e.g. due to drugs or hypoxia, autoregulation no longer occurs and coronary flow is dependent purely on the coronary perfusion pressure [12,13].

Hypotension may induce electrocardiographic (ECG) changes. Studies of patients with no known preoperative heart disease in whom deep hypotension was induced with a variety of techniques, have shown that 64% develop an increased or decreased T-wave height, while 13% develop ST-segment depression or elevation in lead V5 of the ECG [8,14]. In one series the authors found that ECG changes were more common when the systolic blood pressure had fallen below 60 mmHg [14]. There is no evident relationship between the preoperative resting MABP and the occurrence of ECG changes during intraoperative hypotension [see figure 2.7.3]. The significance of these ECG changes in patients with normal hearts is uncertain, as none of the ECG changes observed in the series reported above were permanent [13,14]. ECG changes observed may have been induced by a variety of mechanisms, actual myocardial ischaemia, or changes in intramyocardial electrical conduction due to emptying of heart chambers secondary to hypotension.

Patients with coronary vascular disease are not so tolerant of hypotension. Because of the varying degrees of coronary artery stenosis that they have, the reduction of blood pressure necessary to induce myocardial ischaemia is highly variable. Studies on patients with angina pectoris of NHYA functional classes I-III have shown that myocardial ischaemia may occur with a blood pressure reduction of as small as 6% [16], or as large as 56% [15] of the normal preoperative resting blood pressure. The development of myocardial ischaemia due to hypotension has not been found to correlate with the rate pressure product, but does correlate well with the systolic arterial blood pressure, the MABP, central venous pressure, and the pulmonary capillary wedge pressure [16].

3. Kidney.

Renal blood flow is autoregulated in the MABP range 60-150 mmHg. Hypotension whether induced, or due to haemorrhage reduces the renal blood flow [17,18], the urine output [18,19], and the creatinine clearance [20,21].

The minimum MABP able to be endured by human kidneys without permanent renal dysfunction occurring is not precisely known. It may be assumed that renal capillary blood flow ceases when the mean arterial pressure falls below the renal intracapsular pressure, i.e. below 18 mmHg. Urine production should theoretically cease when the mean arterial blood pressure falls below 40-50 mmHg, as glomerular filtration only occurs when the glomerular capillary pressure exceeds the renal intracapsular pressure plus the plasma colloid osmotic pressure. Indeed clinical experience with humans has shown that urine production ceases when the MABP falls below 40-50 mmHg [see chapter 9.2]. Transplanted kidneys from dogs subjected to haemorrhagic hypotension at a level of 50 mmHg for one hour prior to nephrectomy, do not function in the recipient dogs [22]. This is a finding which accords with human clinical experience in which prolonged severe hypovolaemic hypotension has been found to cause renal insufficiency.

Urine production in humans usually ceases when the cardiac index drops below 1.8 $l/min/m^2$ [see chapter 9.2]. Human kidneys beigin to develop cellular changes due to hypoxic damage after 30-45 minutes of warm circulatory arrest, and these changes are irreversible if circulatory arrest is prolonged beyond this time [27]. Indeed it has been found that human kidneys can rapidly recover normal function after transplantation even if they have undergone a period of 30 minutes warm circulatory arrest [23].

Cardiac output is one of the main determinants of renal viability during hypotension. Prolonged haemorrhagic or hypovolaemic hypotension in humans and animals often causes acute renal failure [22]. But human investigation has shown that profound sodium nitroprusside induced hypotension down to an arterial blood pressure of 40/20 mmHg for periods of up to 70 minutes, does not cause renal failure or cerebral damage. Again the difference here is that cardiac output is increased or maintained at normal levels by sodium nitroprusside infusion, while the cardiac output always is reduced by hypovolaemia or haemorrhage.

From the above it may be concluded that renal insufficiency is likely when a period of hypovolaemic hypotension with a mean arterial blood pressure lower than 50 mmHg lasts for longer than one hour, or a period of warm circulatory arrest lasts longer than 30 minutes.

4. Liver.

Liver blood flow is not autoregulated and is directly proportional to the arterial blood pressure. Hepatic damage, specifically due to hypotension has never been reported [24].

Table 2.7.3.
Effects of varying levels of hypotension on cerebral, renal and myocardial function. [Data derived from this chapter].

BRAIN	- Increased chance of cerebral ischaemia. when the MABP is < 20 + ((resting MABP)/2). - Cerebral ischaemia/damage as manifested by absent EEG activity when the MABP < 15-36 mmHg. - Cerebral blood flow ceases when MABP < 13 mmHg.
HEART	- Increased chance of ECG changes when the SABP < 60 mmHg. - Myocardial ischaemia occurs when the MABP drops 6-65% below resting values in patients with coronary vascular disease. - Coronary blood flow ceases when the MABP <7-12 mmHg.
KIDNEYS	- Urine output ceases when MABP < 40-50 mmHg, or when cardiac index is < 1.8 l/m^2/min. - Renal blood flow ceases when MABP < 18 mmHg. - Renal failure after MABP < 50 mmHg for 1 hour. - Warm ischaemia > 30 minutes causes renal damage in direct proportion to duration of the ischaemic period.

5. Decubitous ulceration/necrosis.

A reduction of the MABP reduces capillary pressure. Less externally applied pressure is then required to reduce the tissue blood flow at any pressure point to such a degree that ischaemic necrosis occurs. This manifests as decubitous ulceration of the skin and subcutaneous tissues at pressure points. Necrosis of other tissues may also occur, especially of tissues subjected to retraction during operations performed under hypotension. This is particularly relevant to cerebral tissue when the brain is retracted during intracranial operations performed under induced hypotension.

CONTROLLED HYPOTENSION DURING ANAESTHESIA

Indications for controlled hypotension.

The indication for induction of hypotension during anaesthesia is to reduce operative blood loss. Blood loss during operation is dependent to some degree on blood flow to a region, but appears to be principally dependent on the arterial blood pressure [25]. Operations for which controlled hypotension is usually necessary are;

1. In the past, hypotension was used to facilitate dissection and clipping of cerebral aneurysms. But a major problem with prolonged intracranial surgery under hypotension is that necrosis may occur in those regions of brain on which pressure is exerted by the retractors used to facilitate access to the brain. In present day neurosurgical practice, hypotension is really usually only required if the aneurysm is bleeding during the operation.

2. Middle ear microsurgical procedures.

3. Operations on vascular tumors, e.g. haemangiomas.

Minimum level of controlled hypotension.

The brain is the organ most sensitive to the effects of hypotension. Arterial blood pressure should never be permitted to drop below the level given by the equation derived from the work of Finnerty et al [5, and see discussion above].

$$\text{Minimum permissable MABP} = 20 + \frac{\text{Resting MABP}}{2} \quad ...(6)$$

If the blood pressure is lower than these minimal levels, then reversal of hypotension is essential to prevent possible brain damage.

It is true that the criterion above is for conscious persons, but no difference should be made between awake and anaesthetized patients. This is because the degree of metabolic depression due to general, or any form of anaesthesia is very variable, differing considerably from one form of anaesthesia to another, and one patient to another. For this reason it is always better to be cautious and manage all hypotensive patients using blood pressure and flow criteria for conscious persons.

Techniques for induction of hypotension.

1. Haemorrhage.

An old technique is to remove a significant proportion of the blood volume, so inducing what is actually haemorrhagic shock. This is obviously quite undesirable.

2. Spinal or epidural anaesthesia.

Both spinal and epidural anaesthesia reduce the arterial blood pressure. The degree of hypotension is directly related to the height of the analgesia. Regrettably the effects of both forms of anaesthesia are long lasting, i.e. one or more hours. In addition to this, the level of hypotension is not readily controlled.

3. Deep general anaesthesia.

Deep general anaesthesia also induces hypotension. A combination of anaesthetic drugs that is particularly effective for both maintenance of anaesthesia and induction of hypotension is halothane and d-tubocurarine [see chapter 2.1]. One disadvantage of induction of hypotension using such a drug combination is that the cardiac output is reduced as well as the blood pressure.

4. Vasodilator drugs.

Intermittent intravenous injection or infusion of short acting vasodilator drugs are very effective methods of induction of hypotension. The advantages of such drugs are their short duration of action. If the level of hypotension is excessive, discontinuation of the drug causes the blood pressure to return to safe levels very rapidly. In addition the level of hypotension that may be induced is able to be reasonably precisely controlled. Another advantage of these drugs is that they usually increase the cardiac output. Dosages and infusion rates for a variety of vasodilator drugs are listed in table 2.2.1.

Sometimes administration of a vasodilator drug alone does not reduce the arterial blood pressure. This usually occurs in younger patients, and is due to a baroreflex mediated elevation of heart rate and cardiac output, which eliminates the effect that reduction of the SVR has on the arterial blood pressure. Concurrent administration of a ß-adrenoreceptor blocking drug blocks the baroreflex mediated increase of heart rate, potentiating the hypotensive effects of the vasodilator drugs. Dosages of a variety of ß-adrenoreceptor blocking drugs are listed in table 3.2.1.

MANAGEMENT OF UNDESIRED HYPOTENSION

1. Indications for treatment.

The principal indications for treatment of hypotension are listed below [see "vasoconstrictor drugs" in chapter 2.2 for further discussion].

- hypotension due to disease,
- excessively low levels of controlled hypotension,
- unintentional hypotension,
- any of the above combined with manifestations of myocardial or cerebral ischaemia.

Excessive hypotension should always be aggressively treated, especially when the degree of hypotension is below any of the critical levels given in table 2.7.3.

2. Treatment.

An acceptable arterial blood pressure must be restored as rapidly as possible so as to minimize the chance of organ damage. Therapy is based upon the cause of hypotension, although in situations where the level of hypotension is life threatening, the most rapid form of therapy should be administered regardless of etiology, [see chapter 2.2 and also below].

a. Drug and anaesthesia induced hypotension.

Discontinuation of drug administration and waiting are all that are required for hypotension due to short acting drugs, e.g. nitroglycerin, sodium nitroprusside. If the drug causing hypotension has a somewhat longer duration of action, and the level of hypotension is such that therapy is required, then therapy should be instituted immediately.

- Drugs whose main action is vasodilation should have their effect reversed with a vasoconstrictor drug, e.g. ephedrine, methoxamine, phenylephrine, etc [see table 2.2.1].

- Drugs causing myocardial depression as well as vasodilation, should be antagonized with a drug, or drug combination which elevates the cardiac output as well as elevating the SVR, e.g. dopamine, ephedrine, etc [see chapter 2.2].
- Some drugs causing hypotension block α- or ß-adrenoreceptors, or both. The effects of many inotropic and vasoconstrictor drugs is then reduced, or even nonexistent. In such a situation, the plasma volume should be increased with fluids such as plasma, albumin, dextran, or gelatine solutions. These cause the greatest elevation of plasma volume for the least volume of fluid infused. The effect of this is to increase the filling pressures of the heart, and the cardiac output increases along with the blood pressure. One disadvantage of using intravenous fluids to increase the blood volume, is that once the effects of the hypotensive drug are gone, the degree of hypervolaemia may be such that pulmonary oedema or heart failure occurs [also see chapter 2.2].

b. Neurogenic hypotension.

This is usually due to vasodilation, sometimes paired with a reduction of cardiac output.

- If the cause of hypotension is of short duration, e.g. spinal or epidural anaesthesia, or drug overdosage, a vasoconstrictor drug is all that is required.
- Hypotension due to neurological damage lasts longer. Therapy consists of plasma volume expansion, and as required, a inotropic/vasoconstrictor drug, e.g. dopamine.

c. Cardiogenic hypotension.

The cause of hypotension is a reduction of cardiac output. Management consists of elevation of the cardiac output with an inotropic drug.

d. Hypovolaemic hypotension.

The cause is a blood volume which is too low for baroreceptor mediated vasoconstriction and tachycardia to maintain cardiac output and blood pressure. Infusion of either plasma volume expanding fluids or blood corrects this situation.

Rapidity of effect of therapy for hypotension.

A further consideration when considering therapy, is the rapidity with which the various therapeutic modalities exert their effect. If the level of hypotension is life threatening, therapy that acts within seconds is required, regardless of the etiology of the hypotension. Any therapy that acts within minutes may be too slow to prevent brain damage or death. In situations where the level of hypotension is not so potentially damaging, more time may be taken to correct hypotension.

Vasoconstrictor and inotropic drugs act in less than one minute.

Intravenous infusion of fluids takes minutes to act.

ANAESTHETIC MANAGEMENT OF HYPOTENSIVE PATIENTS

Preoperative.

1. No hypotensive patient should be allowed to undergo elective surgery and anaesthesia. Hypotension should always be corrected prior to induction of anaesthesia.

2. No sedative, hypnotic or opiate premedication should be given. These may exacerbate the existing haemodynamic abnormality. The same also applies to the anticholinergic drugs. Tachycardia and reduction of the SVR may have a deleterious effect on systemic haemodynamics.

Anaesthesia.

1. Local infiltration or hemispinal anaesthesia are the best choices of anaesthesia. Systemic haemodynamic alterations are minimal with these techniques [see chapter 2.1].
2. Epidural and spinal anaesthesia are contraindicated in all hypotensive patients because they will profoundly exacerbate existing hypotension.

3. Should general anaesthesia be required, care must be taken to select drugs and techniques which minimally affect systemic haemodynamics. This is may be done using the tables in chapter 2.1. Ventilation should be controlled so that the already increased alveolar-arterial PO_2 difference is not exacerbated by alveolar hypoventilation due to general anaesthesia.

4. Monitoring should at least consist of regular measurement of arterial blood pressure and pulse rate. Urine output should be measured as this is a reasonable, if somewhat gross guide to the degree of vascular filling and the cardiac output. ECG monitoring is required to detect both cardiac arrhythmias as well as myocardial ischaemia. The ideal ECG lead configuration is the CB5 configuration. Severely ill patients require more invasive forms of monitoring to accurately guide any therapy, e.g. central venous pressure, or pulmonary artery pressure monitoring, with or without cardiac output measurement.

Postoperative.

All hypotensive patients should be aggressively monitored and treated in an intensive care unit until haemodynamic stability has returned, and the requirement for any haemodynamic support therapy is no longer present.

REFERENCES

1. Rossen,R., et al.,(1943), Acute arrest of cerebral circulation in man. ARCHIVES OF NEUROLOGY & PSYCHIATRY, 50, 510-528.
2. Lassen,N.A.,(1959), Cerebral blood flow and oxygen consumption in man. PHYSIOLOGICAL REVIEWS, 39, 183-238.
3. Lassen,N.A., Christensen,M.S.,(1976), Physiology of the cerebral blood flow. BRITISH JOURNAL OF ANAESTHESIA, 48, 719-734.
4. Langfitt,T.W.,(1974), Cerebral circulation and metabolism. Summary of international symposium, June 6-10 1973. JOURNAL OF NEUROSURGERY, 40, 561-576.
5. Finnerty,F.A., et al.,(1954), Cerebral hemodynamics during cerebral ischemia induced by acute hypotension. JOURNAL OF CLINICAL INVESTIGATION, 33, 1227-1232.
6. Trojaborg,W., Boysen,G.,(1973), Relation between EEG, cerebral blood flow and internal carotid artery pressure during carotid endarterectomy. ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY, 34, 61-69.

7. Nilsson,O.B., Vinnars,E.,(1957). Investigation of cerebral damage following induced hypotension. BRITISH JOURNAL OF ANAESTHESIA, 29, 146-150.
8. Simpson,P., et al.,(1976), Electrocardiographic studies during hypotensive anaesthesia using sodium nitroprusside. ANAESTHESIA, 31, 1172-1178.
9. Maekawa,T., et al.,(1979), Brain-surface oxygen tension and cerebral cortical blood flow during haemorrhagic and drug-induced hypotension in the cat. ANESTHESIOLOGY, 51, 313-320.
10. Michenfelder,J.D., Theye,R.A.,(1977), Canine systemic and cerebral effects of hypotension induced by hemorrhage, trimetaphan, halothane, or nitroprusside. ANESTHESIOLOGY, 46, 188-195.
11. Grubb,R.L., Raichle,M.E.,(1982), Effects of haemorrhagic and pharmacologic hypotension on cerebral oxygen utilization and blood flow. ANESTHESIOLOGY, 56, 3-8.
12. Mosher,P., et al.,(1964), Control of coronary blood flow by an autoregulatory mechanism. CIRCULATION RESEARCH, 14, 250-259.
13. Hoffman,J.I.E.,(1984), Maximal coronary flow and the concept of coronary vascular reserve. CIRCULATION, 70, 153-159.
14. Rollason,W.N., Hough,J.M.,(1960), A study of hypotensive anaesthesia in the elderly. BRITISH JOURNAL OF ANAESTHESIA,32, 276-285.
15. Reiz,S., et al.,(1985), Coronary haemodynamic effects of surgery during enflurane-nitrous oxide anaesthesia in patients with ischaemic heart disease. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 29, 106-112.
16. Lieberman,R.W., et al.,(1983), hemodynamic predictors of myocardial ischaemia during halorthane anesthesia for coronary artery revascularization. ANESTHESIOLOGY, 59, 36-41.
17. Birch,A.A., Boyce,W.H.,(1977), Changing renal blood flow following sodium nitroprusside in patients undergoing nephrolithotomy. ANESTHESIA AND ANALGESIA, 56, 102-109.
18. Lauson,H.D., et al.,(1944), The renal circulation in shock. JOURNAL OF CLINICAL INVESTIGATION, 23, 381-402.
19. Behnia,R., et al.,(1979), Renal function and hemodynamics during induced hypotension in dogs. ANESTHESIOLOGY, 51, s81.
20. Behnia,R, et al.,(1978), Sodium nitroprusside-induced hypotension: Effect on renal function. ANESTHESIA AND ANALGESIA, 57, 521-526.
21. Behnia,R., et al.,(1982), Trimetaphan-induced hypotension: Effect on renal function. CANADIAN ANAESTHETISTS' SOCIETY JOURNAL, 29, 581-586.
22. Grundmann,R., et al.,(1981), Effect of hypotension on the results of kidney storage and the use of dopamine under these conditions. TRANSPLANTATION, 32, 184-187.
23. Hartley,L.C.J., et al.,(1971), Kidney preservation for transportation. Function of 29 human-cadaver kidneys preserved with an intracellular perfusate. NEW ENGLAND JOURNAL OF MEDICINE, 285, 1049-1052.
24. Lindop,M.J.,(1975), Complications and morbidity of controlled hypotension. BRITISH JOURNAL OF ANAESTHESIA, 47, 799-803.
25. Sivarajan,M., et al.,(1980), Blood pressure, not cardiac output, determines blood loss during induced hypotension. ANESTHESIOLOGY, 59, 203-206.
26. Sethna,D.H., Moffitt,E.A.,(1986), An appreciation of the coronary circulation. ANESTHESIA AND ANALGESIA, 65, 294-305.
27. Rosetti,S.R.,(1983), Impact of acute ischemia on human kidney. In "International Perspectives in Urology", volume 8, Marberger,M., Dreikorn,K. editors, published Williams & Wilkins, Baltimore/London, pages 21-35.

Chapter 2.8

HEART FAILURE

Heart failure, just as its name implies, is failure of the heart to perform its normal function. The output of either the left, right, or both sides of the heart is reduced below normal. This has major consequences for systemic cardiovascular function in the perioperative period.

PHYSIOLOGY AND MANIFESTATIONS OF HEART FAILURE

The basic problem with all forms of heart failure is a reduced cardiac output because of inability to pump all the blood returned to the heart. An important change induced by a lowered cardiac output is a change in the distribution of the cardiac output [see table 2.8.1], and this has significant consequences for electrolyte and fluid exchange as well as drug effects and elimination.

Table 2.8.1.
Change in the percentage regional distribution of the cardiac output in heart failure [15].

ORGAN	Normal cardiac output (% of cardiac output)	Heart failure (% of cardiac output)
Splanchnic region	24	27
Skeletal muscle	21	27
Kidneys	19	12
Brain	13	17
Skin	9	1.7
Heart	4	10
Other	10	6.3

The left, right, or both sides of the heart may fail. The manifestations of both forms of failure on the systemic circulation are similar, [see chapter 3.1 for a more detailed description of the clinical manifestations of a reduced cardiac output].

1. Left ventricular failure

a. Reduced cardiac output.
b. Increased sympathetic nervous system activity due to activation of baroreflexes. This elevates the systemic vascular resistance and the heart rate.
c. Increased pulmonary vascular pressures causing pulmonary congestion or oedema.
d. Reduced renal and hepatic blood flows, in addition to reduced blood flow to other organs.

2. Right ventricular failure

a. Reduced systemic cardiac output due to reduced right heart output. The consequences of this are the same as for left heart failure. However if only pure right ventricular failure exists, pulmonary congestion and oedema do not occur.
b. Increased venous pressure as a result of inability to pump all venous blood returned to the heart.
c. Peripheral oedema, e.g. ankle and sacral oedema, secondary to chronic elevation of systemic venous pressure.
d. Engorgement of the liver with clinical hepatomegally due to elevation of venous pressure.

PROBLEMS IN THE PERIOPERATIVE PERIOD

1. Abnormal baroreflex responses.

The sympathetic nervous system activity of patients with chronic heart failure is chronically elevated, with as a result the SVR is greatly increased [18,19]. Elevated sympathetic nervous system activity causes the 24 hour urinary excretion of noradrenaline to be increased in direct proportion to the severity of the heart failure, and is in fact directly related to the NYHA class [18]. Further elevation of sympathetic nervous system activity by surgery or trauma increases the SVR even more, and may exacerbate existing heart failure if the failing heart is unable to maintain output in the face of an even higher SVR.

Myocardial noradrenaline concentration is much decreased in patients with chronic heart failure, and so sympathetic stimulation has a minimal effect on heart rate because of reduced sympathetic nerve terminal catecholamine content. The end result of reduced myocardial responsiveness to sympathetic stimulation is that baroreflex function in patients with heart failure is deficient [18]. This manifests as a more profound degree of hypotension as a result of most anaesthetic procedures [see also chapter 8.6]. Another consequence of reduced myocardial noradrenaline concentration is that myocardial responsiveness to exogenously administered catecholamines is enhanced because of increased numbers of postsynaptic adrenergic receptors [18].

2. Reduced tolerance to fluid loads.

The output of the failing heart is does not increase to the same degree as that of a normal heart in response to a given fluid load, i.e. in response to a given elevation of right and left end-diastolic pressures [15]. Because of this even minor degrees of circulatory overfilling may precipitate or exacerbate heart failure in patients with poor myocardial function.

3. Anaesthetic drug exacerbation of heart failure.

Many drugs used for anaesthesia have a negative inotropic effect [see chapter 2.1]. Normal or excessive dosages of these drugs may exacerbate heart failure by further decreasing the cardiac output. This is especially likely if they are administered under circumstances where the SVR is increased by pain, or if the patient is hypervolaemic.

4. Altered drug kinetics.

The primary problem in cardiac failure is a reduction of the cardiac output. This results in lower hepatic and renal blood flows [15, and table 2.8.1]. A reduction of hepatic and renal blood flows decreases the clearance of those drugs eliminated by these two organs, and prolongs their elimination half lives [14].

Another problem is caused by the interstitial oedema occurring in inadequately treated patients. This increases the distribution volume of highly water soluble drugs, e.g. dobutamine [12].

Table 2.8.2.
Percentage frequency of perioperative exacerbation of heart failure related to the preoperative presence of heart failure, its type and severity [1].

Severity or type of failure	% with postoperative worsening of failure
NYHA - I	5
NYHA - II	7
NYHA - III	18
NYHA - IV	31
Jugular venous distension	35
S3 gallop	47
History of pulmonary oedema	32
Left heart failure	26

5. Altered anaesthetic drug effects.

The dosage of thiopentone required for induction of sleep is directly proportional to the cardiac output [16]. Patients with cardiac failure may be expected to require a lower dosage than patients with a normal cardiac output, and indeed this is observed clinically [17]. The same may be expected for any other intravenously injected hypnotic drugs, and indeed this is also observed by most anaesthetists.

These effects may also be readily predicted from the altered distribution of blood flow occurring in patients with heart failure. The increased proportion of the cardiac output flowing into the coronary and cerebral circulations means that more drug is delivered per unit time to these two organs, and because the cardiac output is reduced, they are also redistributed more slowly away from these organs too. This means that central nervous system effects and myocardial depression occur at a lower dosage of any given drug in patients with cardiac failure, and that the duration of these effects is prolonged.

6. Increased perioperative morbidity.

Because of the above factors, patients with heart failure, especially the more severe degrees of failure, are at considerable risk of developing perioperative cardiogenic pulmonary oedema, and other manifestations of worsening of failure [1, see table 2.8.2]

Ischaemic heart disease is a common cause of heart failure, and some patients have a history of previous myocardial infarction. Such patients have an increased risk of developing a perioperative myocardial infarction [see table 2.8.3].

Table 2.8.3.

Percentage frequency of perioperative myocardial reinfarction in the presence of coexisting heart disease [2].

Prior myocardial infarction + heart failure	11.1-18
Prior myocardial infarction + heart failure + angina pectoris	8.2-67

MANAGEMENT OF HEART FAILURE

The principles of management of heart failure are the same, regardless of whether failure is chronic or acute, and consists of three basic maneuvers.

a. Inotropic drugs.

Inotropic drugs increase the cardiac output, reducing venous, pulmonary vascular, and cardiac filling pressures. Inotropic drugs increase myocardial oxygen consumption in persons with normal hearts, but usually decease myocardial oxygen consumption in patients with heart failure, as contractile efficiency is improved in the latter group of persons.

Selection of an appropriate inotropic drug is determined to some degree by the cause of the heart failure. A common cause of heart failure is ischaemic heart disease. In such patients, an inotropic drug should be chosen that does not increase the heart rate excessively, as this may induce myocardial ischaemia.

b. Diuretic drugs.

Should manifestations of heart failure not be resolved by use of an inotropic drug alone, a diuretic drug should be administered to decrease both the interstitial oedema and reduce the central venous pressure, i.e. the preload. Hypokalaemia is one of the disadvantages of diuretic therapy, and may cause myocardial arrhythmias in patients being administered digoxin or other inotropic drugs. Another problem due to enthusiastic diuretic therapy is hypovolaemia.

c. Reduction of systemic vascular resistance (SVR).

Reduction of the SVR and pulmonary vascular resistance, reduces the resistance to flow of blood out of the ventricles during systole. The result of this is increased stroke volume and cardiac output [3].

1. Chronic management of heart failure.

The chronic management of heart failure is colored by the fact that at present there is no really effective and safe inotropic dug that is able to be orally ingested, and which maintains its activity after chronic long term administration. For this reason, chronic therapy of heart failure is at present oriented towards use of diuretic and vasodilator drugs.

a. Diuretic drugs.

The initial treatment for all patients with chronic heart failure, without atrial fibrillation, is a diuretic. Usually a thiazide is the type of diuretic initially used. This reduces any hypertension and reduces symptoms due to interstitial oedema. Care must be taken that neither hypokalaemia nor hypovolaemia are induced.

b. Inotropic drugs.

The only orally ingestible inotropic drugs available for long term therapy are the digitalis glycosides. Digitalis glycosides elevate the cardiac output, albeit to no great degree, even after long-term therapy in patients with a sinus rhythm [4]. However this group of drugs is of most benefit in patients with rapid atrial fibrillation or flutter, in whom they significantly elevate the cardiac output by reducing the ventricular rate below 100 beats/minute [see chapter 3.1].

At present the use of digitalis glycosides is considered somewhat controversial for the chronic management of heart failure in patients without atrial fibrillation. However despite this they are still frequently employed for this purpose.

c. Vasodilator drugs.

The effect of the digitalis glycosides and diuretics may be supplemented by administration of a peripheral vasodilator drug, so as to reduce the SVR. One drug used for this purpose is prazosin, an α-adrenoreceptor blocking drug which is effective after oral administration [5]. A more recent development, is the use of angiotensin converting enzyme (ACE) blocking drugs to chronically reduce the systemic vascular resistance. This latter group of drugs have the added advantage that they have no negative inotropic effect, and do not block catecholamine receptors.

2. Management of acute heart failure.

Management of acute heart failure in the perioperative period uses the same principles, but requires the use of different drugs. The emphasis is on increasing the cardiac output with short acting inotropic drugs, rather than the use of diuretics.

a. Inotropic drugs.

The digitalis glycosides have a number of disadvantages in the management of patients with acute heart failure. For example, digoxin at a dose of 0.75-1.25 mg administered i.v. elevates the cardiac output by only 25% of the increase able to be induced by an i.v. infusion of dobutamine at a rate of 8.5 μg/kg/min [6]. In addition to this, digoxin reduces cardiac filling pressures and the SVR to a lesser degree than does dobutamine [6]. A further disadvantage of digoxin in the perioperative period is the sometimes rapidly changing electrolyte status of the patient, especially potassium. Patients given digoxin while hypokalaemic may develop malignant, or at best, troublesome arrhythmias. As if this were not enough, digoxin has a long elimination half life, and should toxicity or arrhythmias be induced by this drug, it takes a long time for the drug to be eliminated from the body.

The drugs dopamine and dobutamine are the drugs of choice for use in the management of acute heart failure, as their use is not associated with the above problems. Both of these drugs have short elimination half lives, dopamine having a plasma elimination half life of 9 minutes [11], while dobutamine has a plasma elimination half life of only 2.4 minutes [12]. This accounts for the very rapid spontaneous termination of their effects once administration is discontinued. In addition to this, the effects of both of these drugs is apparent within seconds after administration, and they do not cause arrhythmias in hypokalaemic patients. Because of their very short elimination half lives, they are ideal drugs to administer by continuous intravenous infusion. A new steady state plasma concentration after beginning an intravenous infusion, or changing its rate is achieved after about 30 minutes with dopamine, and after only 7-8 minutes with dobutamine [i.e. 3 times the elimination half life, see chapter 15.1 for explanation of intravenous infusion principles]. Administration of a bolus dose speeds this up. Should they cause deleterious haemodynamic effects, or the drug is no longer required, administration may be discontinued, and the effect of either drug is gone after a maximum of 30 minutes (three elimination half lives).

Dobutamine is a better inotropic drug to use for patients with heart failure than dopamine. It increases the heart rate less than equivalent doses of dopamine, and reduces the SVR slightly, unlike dopamine which increases the SVR and cardiac filling pressures. Both drugs elevate the cardiac output significantly when infused intravenously in the dosage range 2-10 μg/kg/min [7,8]. However dopamine elevates SVR and cardiac filling pressures at higher inotropic dosages, (>10 μg/kg/min), and so it should be administered simultaneously with an intravenous infusion of nitroglycerin at a rate of 0.5-3 μg/kg/min to minimize or to eliminate these effects at these doses [9].

b. Vasodilator drugs.

Vasodilator drugs such as sodium nitroprusside, nitroglycerin etc, may be used alone to increase the cardiac output by means of afterload reduction, (i.e. reducing the SVR) [3,10]. The main disadvantage of vasodilator therapy, especially in persons with ischaemic heart disease, is that the arterial blood pressure may be reduced. However this effect may be minimized by concurrent administration of an inotropic drug such as dopamine [9].

c. Diuretic drugs.

A diuretic drug may be indicated to relieve hypervolaemia, pulmonary and peripheral oedema. Frusemide is the best drug to use for this purpose. Administered in the usual therapeutic dosage of 20-40 mg/70 kg, it rapidly relieves pulmonary congestion and oedema, an effect that precedes any significant diuresis. The effect of frusemide is twofold. It has an immediate direct venodilating effect which rapidly lowers left ventricular filling pressures, so relieving pulmonary congestion and oedema, and a more well known potent diuretic effect [13].

PREOPERATIVE ASSESSMENT

1. Use the NYHA cardiac functional disability scale to grade the severity of the heart failure. The NYHA score may be used to determine the level of monitoring required during anaesthesia.

2. The existence of orthopnea indicates the presence of significant heart failure. Patients with orthopnea will usually require general anaesthesia as they cannot lie flat.

3. As can be seen from tables 2.8.2 and 2.8.3, preoperative heart failure is associated with a considerable risk of potentially severe complications. Elective operations should be postponed for any patient whose condition is such that he fits into the higher risk categories.

ANAESTHETIC MANAGEMENT

Preoperative.

1. Elective operations of patients with untreated heart failure should be postponed until the heart failure is adequately treated, as the potential perioperative morbidity and mortality are considerable.

2. Atropine may be administered preoperatively unless the patient has atrial fibrillation, or coronary vascular disease.

3. A sedative drug may be administered preoperatively, unless this is contraindicated by the presence of hypoxaemia.

Anaesthesia.

1. Monitoring.

Patients with heart failure of NYHA classes III-IV, or who have jugular venous distension, an S3 gallop, a history of pulmonary oedema, florid left heart failure, or heart failure plus angina pectoris and hypertension, are patients with a high risk of developing perioperative cardiac complications. After having been brought into the best possible condition preoperatively, they should be maximally monitored in the perioperative period.

NYHA classes III-IV patients should optimally be monitored with direct intra-arterial blood pressure measurement, and a pulmonary artery catheter. Serial measurements of cardiac output, SVR, and pulmonary vascular pressures, provide actual measurements of the parameters being treated. The result is more effective therapy with vasodilator and inotropic drugs. Measurement of urinary output is required. ECG monitoring using the CB5 configuration to detect myocardial ischaemia is advisable.

At the very least, a central venous catheter to measure right atrial pressure, in addition to the normal measures of blood pressure, pulse rate and ECG, is required.

2. Loco-regional anaesthesia.

Loco-regional anaesthetic techniques are to be preferred where possible. But persons with orthopnea are unable to lie in a recumbent position for any length of time, and so regional anaesthesia is sometimes not possible for such patients.

While techniques such as spinal and epidural anaesthesia reduce the SVR, the magnitude of the SVR reduction is unpredictable and profound hypotension may occur due to inability to elevate the cardiac output sufficiently to compensate for the reduction of SVR. Because of this general anaesthesia is to be recommended for patients with heart failure of NYHA classes III-IV severity who otherwise would be suitable candidates for these techniques.

3. General anaesthesia.

The selection of drugs and techniques to use for administration of general anaesthesia in a person with heart failure is quite understandably aimed at maintaining or increasing the cardiac output. Various factors should be considered.

a. Controlled ventilation is required as part of any general anaesthetic technique so as to guarantee oxygenation in the face of pulmonary congestion and oedema.
b. Minimal use should be made of drugs, or combinations of drugs which depress myocardial contractility. Myocardial depressant drugs may exacerbate existing heart failure, or even precipitate it in patients with marginal ventricular function.
c. Prevent excessive elevation of the heart rate. This will increase myocardial oxygen consumption. The most common cause of heart failure is coronary vascular disease, and excessive tachycardia may induce myocardial ischaemia.
d. Some slight reduction of the SVR is beneficial as it increases the cardiac output. But excessive reduction of the SVR may cause hypotension as the capacity of the cardiac output to increase may be exceeded.
e. Excessive elevation of the SVR further reduces cardiac output in patients with heart failure. For this reason adequate analgesia is required to prevent pain induced elevation of the SVR, and any possible exacerbation of heart failure. Selection of an analgesic drug should be made with the aim of selecting the least cardiodepressive of these drugs.

A selection of the most appropriate anaesthetic drugs to be used may be made using the tables in chapter 2.1. All drugs should only be administered according to clinical requirements because of prolongation of the elimination of many drugs, and in some case the reduction of their effective dosage by the low cardiac output.

Postoperative.

Patients with NYHA classes III-IV cardiac failure should be admitted to an intensive care unit postoperatively until haemodynamic stability has returned.

REFERENCES

1. Goldman,L., et al.(1978). Cardiac risk factors and complications in non-cardiac surgery. MEDICINE, 57, 357-370.

2. Rao,T.L.K.(1983). Reinfarction Following Anaesthesia with Myocardial Infarction. ANESTHESIOLOGY, 59, 499-505.
3. Cohn,J.N., Franciosa,J.A.(1977). Vasodilator therapy of cardiac failure. Parts 1 and 2. NEW ENGLAND JOURNAL OF MEDICINE, 297, 27-31, 254-258.
4. Arnold,S.B., et al.,(1980), Long-term digitalis therapy improves left ventricular function in heart failure. NEW ENGLAND JOURNAL OF MEDICINE, 303, 1443-1448.
5. Miller,R.R., et al.,(1977), Sustained reduction of cardiac impedance and preload in congestive heart failure with the antihypertensive vasodilator prazosin. NEW ENGLAND JOURNAL OF MEDICINE, 297, 303-307.
6. Goldstein,R.A., et al.,(1980), A comparison of digoxin and dobutamine in patients with acute infarction and heart failure. NEW ENGLAND JOURNAL OF MEDICINE, 303, 846-850.
7. Loeb,H.S., et al.,(1977), Superiority of dobutamine over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure. CIRCULATION, 55, 375-381.
8. Leier,C.V., et al.,(1978), Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. CIRCULATION, 58, 466-475.
9. Loeb,H.S., et al.,(1983), Beneficial effects of dopamine combined with intravenous nitroglycerin on hemodynamics in patients with severe left ventricular failure. CIRCULATION, 68, 813-820.
10. Armstrong,P.W., et al.,(1980), Pharmacokinetic-hemodynamic studies of intravenous nitroglycerin in congestive cardiac failure. CIRCULATION, 62, 160-166.
11. Jarnberg,P.O., et al.,(1981), Dopamine infusion in man. Plasma catecholamine levels and pharmacokinetics. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 25, 328-331.
12. Kates,R.E., Leier,C.V.,(1978), Dobutamine pharmacokinetics in severe heart failure. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 24, 537-541.
13. Dikshit,K., et al.,(1973), Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. NEW ENGLAND JOURNAL OF MEDICINE, 288, 1087-1090.
14. Benowitz,N.L., Meister,W.,(1976), Pharmacokinetics in patients with cardiac failure. CLINICAL PHARMACOKINETICS, 1, 389-405.
15. Zelis,R., et al.,(1975), Abnormalities in the regional circulations accompanying congestive cardiac failure. PROGRESS IN CARDIOVASCULAR DISEASE, 18, 181-199.
16. Christensen,J.H., et al.,(1982), Pharmacokinetics and pharmacodynamics of thiopentone. A comparison between young and elderly patients. ANAESTHESIA, 37, 398-404.
17. Christensen,J.H., et al.,(1985), Increased thiopental sensitivity in cardiac patients. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 29, 702-705.
18. Rutenberg,H.L., Spann,J.F.,(1973), Alterations of cardiac sympathetic neurotransmitter activity in congestive heart failure. AMERICAN JOURNAL OF CARDIOLOGY, 32, 472-480.
19. Zelis,R., et al.,(1973), Peripheral circulatory control mechanisms in congestive heart failure. AMERICAN JOURNAL OF CARDIOLOGY, 32, 481-490.

Chapter 2.9

MYOCARDIAL ISCHAEMIA

Ischaemia is defined as a condition of tissue oxygen deprivation secondary to reduced tissue blood flow. Any situation in which the coronary blood flow is inadequate to supply the contracting myocardium with sufficient oxygen will cause myocardial ischaemia. If myocardial ischaemia is prolonged, myocardial infarction with all its consequences will occur. Angina pectoris, ST-segment, T-wave changes and ventricular arrhythmias are all evidence of myocardial ischaemia.

Prior to any discussion of myocardial ischaemia, it is of value to briefly review current ideas about the coronary circulation.

PHYSIOLOGY OF THE CORONARY CIRCULATION

When considering the coronary circulation, a careful differentiation must be made between the coronary circulation as a whole, the circulation of the myocardium of the left ventricle, and the myocardium of the rest of the heart.

1. Whole heart.

The coronary circulation may be considered in its entirety. Coronary blood flow is regulated in the coronary perfusion pressure (CPP) range of 50-140 mmHg. CPP is the difference between the mean arterial blood pressure (MABP) and the coronary sinus pressure (CSP).

$$CPP = MABP - CSP \quad .....(1)$$

If coronary venous pressure is relatively low, then perfusion pressure is approximately equal to the mean arterial pressure.

2. Left ventricle.

The physiology of the circulation of the myocardium of the left ventricle is somewhat different to that in the rest of the heart, and so will be considered separately in some detail as it has consequences for the practical management of patients with coronary vascular disease.

The main difference between the left ventricle and the rest of the heart is that the pressures developed in the subendocardium of the left ventricle during systole exceed the pressures in the arteries perfusing the subendocardium. The reason for this is simple. Con-

sider the subepicardial myocardium. During systole, the pericardium does not contract as it is only a membrane, and so the pressure compressing the vessels in the uppermost layer of subepicardial muscle is about equal to that within the pericardial cavity, i.e. near atmospheric, to lower than atmospheric. Contracting subepicardial muscle compresses the underlying layers of muscle, compressing the blood vessels within these layers of muscle too. Each deeper layer of muscle is compressed in its turn by the immediately surrounding layer, and the layers above, as well as contracting itself. This means that the deeper the muscle layer, the greater the pressures compressing the blood vessels within it, until at the innermost layer of myocardial muscle, the subendocardium, the pressures within the muscle due to compression from surrounding muscle layers, and subendocardial contraction are about equal to, or greater than the pressures developed within the cavity of the left ventricle during that contraction. As a result of this, subendocardial blood vessels are compressed shut during systole. This may be expressed in a simplified form by equations 2 and 3.

$$\textbf{SYSTOLIC PERFUSION PRESSURE}_{(\text{subendocardium})} = \textbf{SABP - LVSP} \quad .....(2)$$

$$\textbf{SYSTOLIC PERFUSION PRESSURE}_{(\text{subepicardium})} = \textbf{SABP - CSP} \quad .....(3)$$

LVSP = left ventricular systolic pressures.
[see appendix-C and above for other symbols].

From the discussion above, and equations 2 and 3, it is apparent that a transmural gradient of intramyocardial blood flow exists during systole. Flow is greatest in the subepicardial regions and continues throughout systole, while no blood flow occurs in the subendocardial myocardium during systole.

The myocardium relaxes during diastole, and the intramyocardial pressures within the subendocardium and subepicardium tend to equalize. However, the pressure within the subendocardium is somewhat higher than that in the subepicardium because of the pressure of blood within the cavity of the left ventricle which compresses the subendocardium. This means that even during diastole, a slight transmural blood flow gradient exists. The perfusion pressures of the subendocardial and subepicardial myocardium during diastole may be expressed by equations 4 and 5.

$$\textbf{DIASTOLIC PERFUSION PRESSURE}_{(\text{subendocardium})} = \textbf{DABP - LVDP} \quad ....(4)$$

$$\textbf{DIASTOLIC PERFUSION PRESSURE}_{(\text{subepicardium})} = \textbf{DABP - CSP} \quad .....(5)$$

LVDP = left ventricular diastolic pressures.

It is obvious from the above discussion that blood flow in the subendocardial myocardium of the left ventricle only occurs during diastole, and is directly proportional to the difference between DABP and LVDP.

A detailed review of the physiology of transmural blood flow distribution in the myocardium is to be found in a paper by Hoffman,J.I.E. [21].

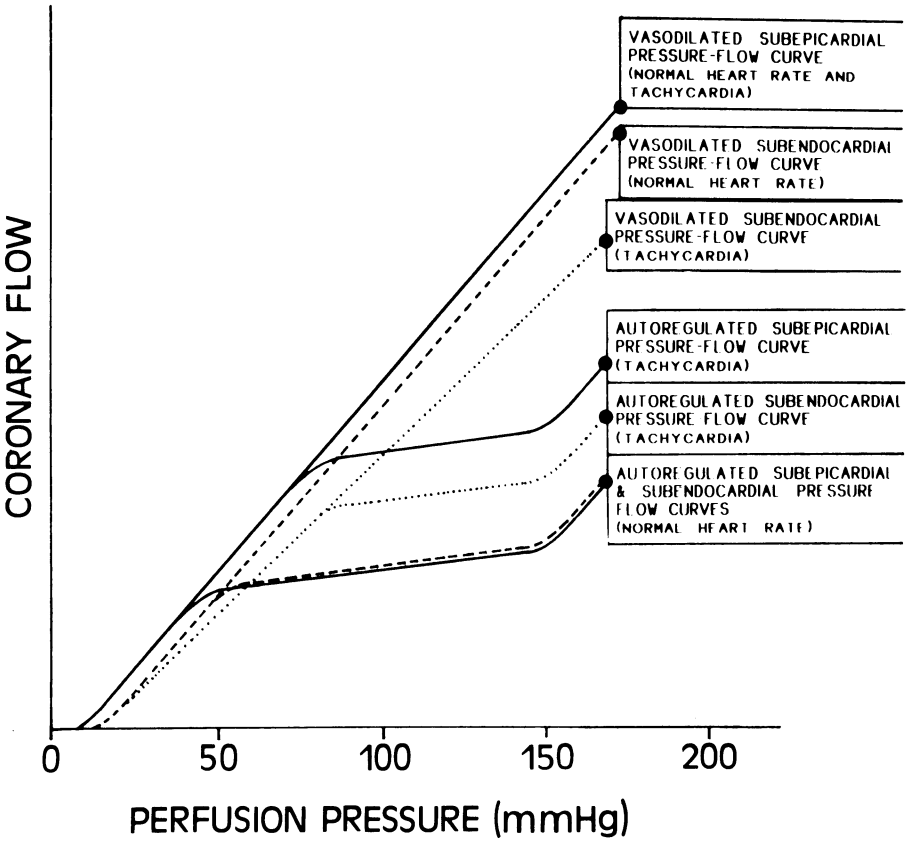

FIGURE 2.9.1. - This is an idealized diagram of the coronary circulation under conditions of normal autoregulation and of maximal vasodilation, at both normal heart rates and during tachycardia. Zero flow pressure is higher for subendocardial than for subepicardial regions of myocardium. Myocardial flow is directly proportional to mean arterial, or coronary perfusion pressure at nearly all pressures, except in the autoregulation pressure ranges. Flow is also usually less in the subendocardial regions than in the subepicardial myocardium. Tachycardia decreases the coronary flow reserves at all blood pressures, in particular reducing the subendocardial flow relative to the subepicardial flow at all coronary perfusion pressures. [See figure 2.7.1 for definitions of terms].

Various other factors also influence the blood flow of the myocardium of the left ventricle.

a. Blood pressure.

In general, elevation of the arterial blood pressure increases blood flow in all regions of the myocardium, while decreasing the arterial blood pressure has the reverse effect. But this simplistic view is modified by the fact that there is a transmural blood flow gradient, and the coronary circulation is also autoregulated.

During hypotension the subendocardium has a lower blood flow per unit weight of muscle than the subepicardium [20]. This is a consequence of the left ventricular diastolic pressure becoming a significant fraction of the diastolic blood pressure, and so the perfusion pressure of this region is proportionally lower. In the normal autoregulatory pressure range, blood flow per unit weight of subendocardial and subepicardial muscle is approximately equal [16,20], because flow is regulated to each muscle layer according to metabolic requirements. Elevation of the arterial pressure above the autoregulatory range increases coronary blood flow equally in both the subendocardial and subepicardial regions [16, see fig. 2.9.1], although subendocardial flow is always lower than subepicardial flow.

In the maximally dilated coronary circulation, blood flow to all regions of the myocardium is directly proportional to the coronary perfusion pressure or MABP. However the subendocardial blood flow is lower than the subepicardial flow at all arterial pressures [19,21, and see fig.2.9.1].

b. Heart rate.

Blood flow in the left ventricular subendocardium only occurs during diastole. The proportion of time spent in diastole in relation to systole decreases with increasing heart rate. This means that left ventricular subendocardial perfusion is inversely proportional to the heart rate. The result of all this is that tachycardia causes an absolute reduction of left ventricular subendocardial flow, and so also increases the transmural flow gradient [16,21]. The reverse effects occur with bradycardia.

3. Right ventricle and atria.

The physiological principles of blood flow regulation through the myocardium of the right ventricle and the atria are the same as for the left ventricular myocardium. However the pressures developed within the cavities of these chambers during myocardial contraction never exceed the SABP, and so perfusion occurs in all levels of the myocardium throughout systole and diastole. There is also a transmural flow gradient as in the left ventricle, as the pressures within these heart chambers are higher than the pressure within the pericardial cavity.

FACTORS AFFECTING DEVELOPMENT OF MYOCARDIAL ISCHAEMIA

The conclusion to be drawn from the above brief review of the coronary circulation is that it is the subendocardium of the left ventricle which is most likely to become ischaemic as a result of any change of cardiovascular function. In itself this is a clinically useful fact, but the busy practical clinician often has too little time in which to derive the clinical consequences from this, and so the discussion that follows describes the problems caused by common haemodynamic disorders in patients with coronary vascular disease.

1. Hypertension.

Myocardial contraction is a process which requires oxygen to generate energy, and the cardiac oxygen consumption is directly proportional to the work performed by the heart pumping blood against the flow resistance presented by the vascular system. Hypertension is common during the perioperative period, being due to anaesthetic procedures such as endotracheal intubation [6,7], surgical stimulation, or administration of vasoconstrictor drugs etc, and any of these may induce myocardial ischaemia.

But despite the fact that myocardial oxygen consumption is directly related to systolic arterial blood pressure, intraoperative hypertension alone has not been found to correlate well with the occurrence of myocardial ischaemia [9]. This is a finding which corresponds well with what has been shown experimentally. In one study it was found that myocardial ischaemia is infrequent after induction of hypertension, even in persons with 70% or more stenosis of one or more coronary vessels, despite the fact that such induction of hypertension does markedly increase myocardial oxygen consumption [15].

Hypertension may in fact be necessary for maintenance of coronary blood flow in some patients with severe coronary vessel stenosis, as a higher than normal pressure is required to generate an adequate flow through a stenotic vessel [15].

2. Hypotension.

The effects of hypotension on the normal heart have been dealt with in some depth in chapter 2.7. Clinical investigation has revealed that the occurrence of myocardial ischaemia during intraoperative hypotension is unrelated to the level of diastolic hypotension, but is related to the MABP and the systolic arterial blood pressure [9].

The heart with coronary vascular disease is less tolerant of hypotension, and myocardial ischaemia develops at a lower percentage reduction of blood pressure than in normal persons. However the percentage reduction of blood pressure required to induce myocardial ischaemia is highly variable, depending the severity of coronary vessel stenosis. In one series a reduction of MABP as little as 6% below the normal resting MABP was sufficient to induce myocardial ischaemia during anaesthesia [9], while in another series, the MABP reduction required before ECG signs of myocardial ischaemia occurred was 56% [8].

3. Tachycardia.

Each contraction of the heart is an energy requiring process, the more rapidly the heart contracts, the more energy it requires per unit time. In addition to this, the subendocardial blood flow is reduced by tachycardia. As the metabolic substrates which provide energy for myocardial contraction must flow through the coronary blood vessels in order to reach the muscle cells, it is not surprising that the occurrence of intraoperative myocardial ischaemia in patients with coronary vascular disease is directly related to the occurrence of tachycardia [6,9].

4. Tachycardia and hypotension.

Hypotension reduces the coronary perfusion pressure, so reducing the coronary blood flow, especially in the subendocardium, and this is even more pronounced in persons with coronary vascular disease. Tachycardia increases the myocardial oxygen consumption, in addition to reducing subendocardial blood flow. Because of this, the combination of tachycardia and hypotension is particularly likely to cause myocardial ischaemia in patients with coronary vascular disease [9].

5. Tachycardia and hypertension.

Both tachycardia and hypertension can induce myocardial ischaemia, especially in those persons with coronary vascular disease. But a given degree of elevation of myocardial oxygen consumption due to tachycardia is more likely to induce myocardial ischaemia than the same elevation of myocardial oxygen consumption due to hypertension [15].

The most likely explanation for this effect of tachycardia is that the percentage of the cardiac cycle during which diastole occurs decreases with increasing heart rate. Left ventricular subendocardial perfusion only occurs during diastole, and so a percentage shortening of this time significantly reduces left ventricular subendocardial blood flow. In fact the blood flow and oxygen delivery in this region may decrease, or remain unchanged, and in any case certainly does not increase in proportion to the elevation of myocardial oxygen consumption that occurs with increasing heart rate [21].

The situation is different for hypertension. If the arterial blood pressure increases without any increase in heart rate, the percentage time spent in diastole remains unchanged. Coronary blood flow increases in all levels of the myocardium with increasing blood pressure, so despite the fact that the myocardial oxygen consumption increases with increasing arterial blood pressure, oxygen delivery to all levels of the myocardium also increases with increasing blood pressure.

6. Rate pressure product (RPP).

Myocardial oxygen consumption increases in direct proportion to the arterial blood pressure and the heart rate, and not surprisingly the product of the heart rate (HR) and the systolic arterial blood pressure (SABP), the RPP has been found to directly correlate with myocardial oxygen consumption [21].

$$\mathbf{RPP = SABP \times HR} \quad \text{.....(6)}$$

Patients with coronary vascular disease develop myocardial ischaemia at a lower RPP than patients with no coronary vascular disease. The RPP at which patients with coronary vascular disease develop angina pectoris varies from patient to patient. It has been found that conscious, non-anaesthetized patients with NYHA classes III-IV coronary vascular disease may develop angina pectoris when the RPP is as low as 12,000 [5]. But despite being directly related to the onset of myocardial ischaemia in conscious persons, the RPP has not been found to correlate well with the occurrence of myocardial ischaemia of persons under anaesthesia [9,17,18].

This apparent contradiction is able to be explained by the fact that the RPP is used as an index of heart work even during hypotensive episodes, and hypotension is common during anaesthesia. For example, consider a person with an SABP = 120 mmHg and HR = 60 beats/min who becomes hypotensive after induction of anaesthesia with an SABP = 60 mmHg and an HR = 120 beats/min. In both situations the RPP = 7200, but everyone would agree that the two haemodynamic situations are quite different, and that myocardial ischaemia was more likely in the latter situation. Obviously the application of the RPP as a measure of the risk of developing myocardial ischaemia in such a situation is meaningless. For this reason the RPP should only be applied in situations where the SABP of a patient is equal to, or greater than the control SABP. In this way the effect of hypotension is eliminated and the RPP retains its value as a useful index of heart work.

7. Central venous and pulmonary arterial pressures.

Elevation of the central venous pressure, the pulmonary capillary wedge pressure, or both are directly related to the occurrence of intraoperative myocardial ischaemia [9]. This is not surprising as both are measures of cardiac preload, and as such are a measure of the heart work. In addition to this, they significantly reduce coronary perfusion pressure at low arterial blood pressure levels.

8. Anaemia.

Anaemia reduces the maximum amount of oxygen that can be carried by a given volume of blood. Because of this, a larger blood flow is required to deliver a given volume of oxygen per unit time to any tissue, including the myocardium. The reduction of myocardial oxygen transport due to coronary vascular disease is therefore exacerbated by anaemia [21].

PERIOPERATIVE MORBIDITY & PROBLEMS

1. Decreased cardiac output.

Ischaemic myocardium does not contract effectively, and if the ischaemia is severe enough, it does not contract at all [26,30]. This increases the work of the remaining non-ischaemic myocardium, which has been shown to eventually develop a "compensatory" increase in contractility. Contractile failure of ischaemic myocardium develops very rapidly, being able to be demonstrated within one minute of onset of ischaemia. The likely causes are thought to be depletion of myocardial intracellular adenosine triphosphate (ATP) stores [27,28], and intracellular acidosis induced depression of muscle contractility due to reduced calcium ion binding to troponin [29].

The haemodynamic effect of myocardial ischaemia depends upon the size of the ischaemic region of myocardium. Clinical evidence of heart failure occurs after >20-25% of the myocardium becomes ischaemic and non-contractile. "Pump failure", or cardiogenic shock develops when >40% of the myocardium no longer contracts [26].

2. Ventricular arrhythmias.

Electrophysiological function of the myocardial cells in an acutely ischaemic region changes within minutes. Initially the cells depolarize to some degree, and the refractory periods of the affected myocardial cells decrease. The effects of ischaemia are not uniform for all affected cells, some cells being affected less than others [23,24].

Ventricular arrhythmias such a premature beats, tachycardia, flutter and fibrillation may occur within minutes of onset of experimental acute myocardial ischaemia [23]. The ventricular fibrillation threshold is decreased within 10 minutes after onset of ischaemia, an effect which is further exacerbated by catecholamines [25].

The cause of ventricular arrhythmias arising during myocardial ischaemia/infarction is thought to be due in part to local injury currents stimulating the myocardium. A local injury current occurs because an electrical current flows between a partly depolarized ischaemic region of myocardium and an adjacent normally polarized area of myocardium. This current, called an "injury current", stimulates excitable regions of myocardium so inducing local abnormal myocardial activity, which if it propagates affects the activity of the whole heart [23]. In addition to local injury currents, the pattern of depolarized refractory regions, and regions of normal excitability provides an ideal electrophysiological substrate

Table 2.9.1.
Perioperative myocardial reinfarction incidence related to the presence of preoperative angina pectoris and other cardiovascular disease [4].

	% perioperative myocardial reinfarction
Prior myocardial infarction alone	0.06-0.1%
Prior myocardial infarction + angina pectoris	1.0-2.8%
Prior myocardial infarction + angina pectoris + hypertension	2.1-23.0%
Prior myocardial infarction + angina pectoris + heart failure	8.2-67.0%

for circulatory excitatory phenomena, (i.e. re-entrant arrhythmias), which have been shown to be a major cause of arrhythmias in ischaemic myocardium [23].

3. Increased chance of myocardial infarction.

Angina pectoris significantly increases the chance of developing a myocardial infarction. Perioperative angina pectoris [1], and perioperative myocardial ischaemic episodes [2,3], triple the chances of a perioperative myocardial infarction [3], and cardiac death [2].

The chances of perioperative myocardial infarction are considerably increased in those who have had a prior myocardial infarction as well as having preoperative angina pectoris [4, see table 2.9.1].

ECG MONITORING FOR MYOCARDIAL ISCHAEMIA

The occurrence of ST segment depression where there was none before, is a manifestation of myocardial ischaemia [11], and occurs in about 38% of patients with coronary artery disease who undergo noncardiac surgery [12]. It is essential to be able to detect and treat any episode of myocardial ischaemia, as perioperative myocardial ischaemia predisposes to myocardial infarction [3]. Various ECG lead systems are in common use.

Standard lead II.

The lead most commonly used for ECG monitoring on most operating room ECG monitors is standard lead II. Its electrical axis is parallel with the electrical axis of the atria, making P-waves easily visible, which is useful for arrhythmia monitoring. ST segment depression which is observed in lead II is specific for ischaemia occurring in the area supplied by the right coronary artery [13]. Because of this last limitation, only 18% of all episodes of myocardial ischaemia are observed when only lead II is used [12].

Lead V5.

Lead V5 is more efficient at detecting perioperative myocardial ischaemia than is lead II. All episodes of myocardial ischaemia are able to be detected with this lead [13,12]. ST segment depression observed in this lead reflects ischaemia occurring in the regions supplied by the circumflex coronary artery and the left anterior descending artery [13].

Lead CB5.

It is impractical to attach all 12 standard ECG leads to all patients undergoing noncardiac surgery, in addition to which it is not required for most patients. The CB5 lead system is a simple 2 lead system which provides a lead configuration equivalent to that of V5. As with the V5 configuration, all episodes of intraoperative myocardial ischaemia are able to be detected with this lead configuration, instead of the meager 18% detection rate of myocardial ischaemic events with lead II [12,13].

The CB5 lead system uses two leads only. The negative electrode is placed on the back over the middle of the right scapula, and the positive electrode is placed above the 5th interspace over the left anterior axillary line [14]. The advantage of this lead configuration is that the electrical axes of the V5 and CB5 leads are nearly identical, with the further advantage that due to the slight difference in electrical axes, both P-waves and T-waves are greater in magnitude than in V5.

The CB5 system may be used with most presently available three lead operating room ECG monitors by just changing the position of the negative electrode.

PERIOPERATIVE MANAGEMENT OF MYOCARDIAL ISCHAEMIA

Should myocardial ischaemia occur in the perioperative period, the cause should be rapidly determined, and treatment rapidly administered. Myocardial infarction may occur if myocardial ischaemia is prolonged.

1. Ischaemia due to arterial hypertension.

Hypertension may cause myocardial ischaemia by elevating myocardial work. Treatment is directed at reducing heart work by any means possible. A variety of techniques are available.

a. Deepen anaesthesia, although this may take minutes.
b. Administer an intravenous bolus of a vasodilator drug, e.g. nitroglycerin 50-100 μg/70 kg, phentolamine 5-10 mg/70 kg etc. This should be followed up with a nitroglycerin infusion at a rate of 0.5 + μg/kg/min.
c. If a tachycardia is also present, a ß-adrenoreceptor blocking drug may also be administered, e.g. pindolol 0.1-0.4 mg/70 kg, propranolol 1-10 mg/70 kg, etc.

2. Ischaemia due to arterial hypotension.

Hypotension may be due to hypovolaemia, myocardial depression, or excessive vasodilation, and the effects of anaesthetic drugs. In all cases the coronary perfusion pressure should be restored as rapidly and effectively as possible to minimize the harmful effects of myocardial ischaemia. Treatment should be directed at the cause.

a. Hypovolaemia should be corrected as rapidly as possible. If it is expected that elevation of the blood pressure by an intravenous infusion will take several minutes, then an intravenous injection of a vasoconstrictor/inotropic drug should be administered simultaneously with administration of intravenous fluids. This will elevate the blood pressure, so restoring coronary perfusion pressure, and relieving myocardial ischaemia until normovolaemia has been restored. Prolonged myocardial ischaemia in persons with severe coronary vascular disease may cause a myocardial infarction. Suitable drugs are any drugs that are immediately available. But the preferred drugs and doses are; ephedrine 5-10 mg/70 kg, phenylephrine 0.1-0.2 mg/70 kg, methoxamine 2-5 mg/70 kg, metaraminol 0.5-1 mg/70 kg, or noradrenaline 0.025-0.05 mg/70 kg.
b. Myocardial depression or vasodilation should be treated with a drug which possesses inotropic as well as vasoconstrictor properties. Suitable drugs are ephedrine and noradrenaline. However these may cause a slight tachycardia at the recommended doses, and so are drugs of second choice in patients with NYHA classes III-IV coronary vascular disease. Preferred drugs are phenylephrine, methoxamine and metaraminol, as they cause minimal elevation of the heart rate. The doses are listed in the paragraph above and in table 2.1.1. However common sense should be used with the selection of drugs. Prolonged ischaemia while waiting for any of the preferred drugs to be fetched may have a more damaging effect on the myocardium than the minimal tachycardia due to administration of either ephedrine or noradrenaline, if either of these two drugs is more rapidly available than one of the drugs of choice.

3. Ischaemia due to tachycardia.

Provided that the tachycardia is not associated with hypotension or hypovolaemia, then myocardial ischaemia should be treated with a ß-adrenoreceptor blocking drug. If the patient is also hypovolaemic or hypotensive, these conditions should be treated first, prior to any reduction of the heart rate because tachycardia may be secondary to either condition.

4. Ischaemia in the presence of normal haemodynamics.

Myocardial ischaemia may occur in the presence of normovolaemia, a normal heart rate and blood pressure. The cause is either coronary artery thrombosis, or constriction of one or more coronary arteries. Coronary vasoconstriction can, and should be treated rapidly, initially with a bolus of 50-100 μg/70 kg of nitroglycerin. This should be followed by an infusion of nitroglycerin at a rate of 0.5 + μg/kg/min. Should this be ineffective, coronary thrombosis is likely to have occurred, and anticoagulant or streptokinase therapy are possibly required.

ANAESTHETIC MANAGEMENT

Myocardial ischaemia in the perioperative period should be prevented, or rapidly treated, as it triples the chances of postoperative myocardial infarction [3]. This is the guiding principle for any form of anaesthesia in patients with coronary vascular disease.

Preoperative.

1. Patients with NYHA class IV disease should never be considered for any elective surgery, except coronary artery bypass grafting.
2. Do not use atropine in the premedication of patients with a high NYHA score. Tachycardia may induce angina pectoris.

3. Adequate preoperative sedation is required to prevent anxiety induced angina pectoris.

Anaesthesia.

1. ECG monitoring is mandatory for all patients with coronary vascular disease so that episodes of ischaemia may be treated as rapidly as possible. The best ECG lead configurations for detection of ischaemia are V5 or CB5.

2. All patients with classes III-IV angina pectoris should receive an infusion of nitroglycerin perioperatively at a rate of 0.5 μg/kg/minute which should be continued for 24 hours postoperatively. This decreases heart work by decreasing cardiac preload. The efficacy of such a regime may be disputed by some [6], but subsequent investigation has found that the use of a nitroglycerin infusion definitely does reduce the frequency of perioperative myocardial ischaemia in patients with coronary vascular disease [7].

In situations where no nitroglycerin infusion is possible, placement of 1/4-1/2 tablet of nitroglycerine (1 mg tablets), under the tongue will have the same, although a less predictable haemodynamic effect.

3. The combination of tachycardia and hypotension should be prevented as this is the combination of events most likely to induce myocardial ischaemia.

ß-blocking drugs, with or without vasodilators, may be used to prevent tachycardia and excessive elevation of blood pressure during the perioperative period.

Episodes of myocardial ischaemia should be treated as outlined above.

4. Loco-regional anaesthetic techniques provide the best analgesia. But anxious patients should be well sedated. Loco-regional techniques may be combined with general anaesthesia.

5. The choice of a general anaesthetic technique and drugs to use for general anaesthesia in patients with coronary vascular disease is aimed at minimizing any haemodynamic changes that may induce myocardial ischaemia.

a. The patients should receive adequate analgesia to prevent pain induced elevation of the SVR [7]. Periods where more analgesia are required are endotracheal intubation [7,10], and periods of intense surgical stimulation such as sternotomy, peritoneal traction etc.
b. The anaesthetic technique used should not induce hypotension. Patients with severe symptomatic coronary vascular disease may develop myocardial ischaemia if the MABP drops as little as 6% [9], or as much as 56% [8] below the normal resting level.

The tables in chapter 2.1 may be used to select the most suitable drugs.

6. Hypothermia, even mild hypothermia down to 34-35°C, may have haemodynamically undesirable effects in patients with compromised cardiac function. The main problems occur postoperatively, especially when shivering occurs. Human studies have shown that postoperative shivering may elevate the oxygen consumption of the body by as much as 500%, causing the cardiac output to double, increasing the SVR, and embarrassing spontaneous respiration [31]. Such an increase of the cardiac output may not be possible in those with coronary vascular disease, or poor myocardial function. Heart failure, myocardial ischaemia, or both can occur in such patients.

Postoperative.

1. Patients with myocardial ischaemia of NYHA classes III-IV should be admitted into an intensive care unit postoperatively until haemodynamic stability has been restored.

2. Mechanical ventilation, together with sedation and use of muscle relaxants should be considered for patients with NYHA classes III-IV disease whose postoperative body temperature is less than 35°C. Muscle relaxation will prevent shivering while rewarming occurs, and so prevents shivering induced disorders of cardiovascular function [see above]. Mechanical vetilation may be discontinued once the body temperature is normal.

REFERENCES

1. Kennedy,J.W., et al.(1980). Multivariate discriminant analysis of the clinical and angiographic predictors of operative mortality from the Collaborative Study in Coronary Artery Surgery. JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, 80, 876-887.
2. Goldman,L., et al.(1978). Cardiac risk factors and complications in non-cardiac surgery. MEDICINE, 57, 357-370.
3. Slogoff,S., Keats,A.S.(1985) Does Perioperative Ischaemia Lead to Postoperative Myocardial Infarction? ANESTHESIOLOGY, 62, 107-114.
4. Rao.T.L.K., et al.(1983) Reinfarction Following Anaesthesia in Patients with Myocardial Infarction. ANESTHESIOLOGY, 59, 499-505.
5. Wynands,J.E.(1982) Anaesthesia for cardiac patients having non-cardiac operations. CANADIAN ANAESTHETISTS' SOCIETY JOURNAL, 29, 341-348.
6. Thomson,I.R., et al.(1984). Failure of Intravenous Nitroglycerin to Prevent Intraoperative Myocardial Ischaemia during Fentanyl-Pancuronium Anaesthesia. ANESTHESIOLOGY, 61, 385-393.
7. Fusciardi,J., et al.(1986). Roles of Fentanyl and Nitroglycerin in Prevention of Myocardial Ischaemia Associated with Laryngoscopy and Tracheal Intubation in Patients Undergoing Operations of Short Duration. ANESTHESIOLOGY, 65, 617-624.
8. Reiz,S., et al.(1985). Coronary Haemodynamic Effects of Surgery during Enflurane - Nitrous Oxide Anaesthesia in Patients with Ischaemic Heart Disease. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 29, 106-112.
9. Lieberman,R.W., et al.(1983). Hemodynamic Predictors of Myocardial Ischaemia during Halothane Anesthesia for Coronary Artery Revascularization. ANESTHESIOLOGY, 59, 36-41.
10. Prys-Roberts,C.(1984). Anaesthesia and Hypertension. BRITISH JOURNAL OF ANAESTHESIA, 56, 711-723.
11. Rifkin,R.D., Hood,W.B.(1977). Bayesian analysis of electrocardiographic exercise stress testing. NEW ENGLAND JOURNAL OF MEDICINE, 297, 681-686.
12. Roy,W.L., et al.(1979). Myocardial ischaemia during non-cardiac surgical procedures in patients with coronary-artery disease. ANESTHESIOLOGY, 51, 393-397.
13. Kaplan,J.A., King,S.B.(1976). The precordial electrocardiographic lead (V5) in patients who have coronary artery disease. ANESTHESIOLOGY, 45, 570-574.

14. Bazaral,M.G., Norfleet,E.A.(1981). Comparison of CB5 and V5 leads for intraoperative electrocardiographic monitoring. ANESTHESIA AND ANALGESIA, 60, 849-853.
15. Loeb,H.S., et al.,(1978), Effects of pharmacologically induced hypertension on myocardial ischaemia and coronary haemodynamics in patients with fixed coronary obstruction. CIRCULATION, 57, 41-46.
16. Hoffman,J.I.E.,(1987), A critical view of coronary reserve. CIRCULATION, 75, supp. I., 6-11.
17. Kissin,I., et al,(1980), Is the rate pressure product a misleading guide? ANESTHESIOLOGY, 52, 373-374.
18. Reves,J.G., et al.,(1979), Violation of RPP exercise threshold in coronary patients. ANESTHESIOLOGY, 51, s64.
19. Mosher,P., et al.,(1964), Control of coronary blood flow by an autoregulatory mechanism. CIRCULATION RESEARCH, 14, 250-259.
20. Bache,R.J., Schwarz,J,S.,(1982), Effect of perfusion pressure distal to a coronary stenosis on transmural myocardial blood flow. CIRCULATION, 65, 928-935.
21. Hoffman,J.I.E.,(1978), Determinants and prediction of transmural myocardial perfusion. CIRCULATION, 58, 381-391.
22. Hillis,L.D., Braunwald,E.,(1977), Myocardial ischaemia. (First of three parts). NEW ENGLAND JOURNAL OF MEDICINE, 296, 971-978.
23. Janse,M.J., Kleber,A.G.,(1981), Electrophysiological changes and ventricular arrhythmias in the early phase of regional myocardial ischaemia. CIRCULATION, 49, 1069-1081.
24. Downar,E., et al.,(1977), The effect of acute coronary artery occlusion on subendocardial transmembrane potentials in the intact porcine heart. CIRCULATION, 56, 217-224.
25. Noakes,T.D., et al.,(1983), Physical training increases ventricular fibrillation thresholds of isolated rat hearts during normoxia, hypoxia and regional ischaemia. CIRCULATION, 67, 24-30.
26. Amsterdam,E.,(1973), Function of the hypoxic myocardium. Experimental and clinical aspects. AMERICAN JOURNAL OF CARDIOLOGY, 32, 461-471.
27. Hearse,D.J.,(1979), Oxygen depivation and early myocardial contracile failure: A reassessment of the possible role of adenosine triphosphate. AMERICAN JOURNAL OF CARDIOLOGY, 44, 1115-1121.
28. Kubler,W., Katz,A.M.,(1977), Mechanism of early "pump" failure of the ischaemic heart: Possible role of adenosine triphosphate depletion and inorganic phosphate accumulation. AMERICAN JOURNAL OF CARDIOLOGY, 40, 467-471.
29. Katz,A.M.,(1973), Effects of ischaemia on the contractile processes of heart muscle. AMERICAN JOURNAL OF CARDIOLOGY, 32, 456-460.
30. Parker,J.O., et al.,(1969), Reversible cardiac failure during angina pectoris. Hemodynamic effects of atrial pacing in coronary artery disease. CIRCULATION, 39, 745-757.
31. Bay,J., et al.,(1968), Factors influencing arterial PO_2 recovery from anaesthesia. BRITISH JOURNAL OF ANAESTHESIA, 40, 398-407.

Chapter 2.10

MYOCARDIAL INFARCTION

Myocardial infarction is a consequence of myocardial ischaemia which has been prolonged beyond the point at which myocardial tissue recovery is possible. The causes, and factors predisposing to it are the same as for myocardial ischaemia [see chapter 2.9].

FREQUENCY OF PERIOPERATIVE MYOCARDIAL INFARCTION

The chances of a myocardial infarction occurring in the perioperative period are very low for a person without preoperative myocardial problems. But this is not the case for patients with a prior history of myocardial infarction, [see table 2.10.1].

Table 2.10.1.
Percentage frequency of perioperative myocardial infarction related to history of prior myocardial infarction [1]. [Perioperative = 0 to 7 days postoperative]

	% Myocardial infarction
No prior myocardial infarction	0.13
Prior myocardial infarction	6.6

The percentage reinfarction rates for patients with a previous history of myocardial infarction in the perioperative period is given for a number of series in table 2.10.2. This table also clearly shows that there is a large difference in mortality between a myocardial infarction that occurs in the perioperative period, and one which occurs at random in any person who has not undergone any surgery at the time the infarct occurred. This is able to be explained by the effects of surgery. Surgery always causes pain. The people undergoing

Table 2.10.2.
Percentage perioperative myocardial reinfarction rates related to interval between previous myocardial infarction and subsequent surgery as reported in three different series. [Perioperative = day of operation plus 6 to 7 days]

INTERVAL BETWEEN MYOCARDIAL INFARCTION AND ANAESTHESIA	Tarhan et al [1]. (Study period from 1967-1968)	Rao et al [2]. (Study period from 1973-1976)	Rao et al [2]. (Study period from 1977-1982)
0-3 months	37%	36%	5.8%
3-6 months	16%	26%	2.3%
6-12 months	4%	5%	1.0%
12+ months	5%	5%	1.56%

NON-PERIOPERATIVE MYOCARDIAL INFARCTION MORTALITY = 12-20% [5]

PERIOPERATIVE MYOCARDIAL INFARCTION MORTALITY = 64% [1,3]

N.B. A non-perioperative myocardial infarction is a myocardial infarction that occurs in a patient who has not undergone any surgical procedure.

surgery are often anxious. Hypokalaemia or hyperkalaemia may develop in the perioperative period. Hypovolaemia or hypervolaemia may occur. Anaemia due to blood loss is possible. Hypercarbia may be present due to respiratory depression caused by opiates administered for pain, or restriction of respiration due to pain itself. Many patients are hypoxaemic postoperatively. Sympathetic nervous system activity is increased by most of these effects, as are plasma catecholamine concentrations. The effect of all these changes is to increase the likelihood of a myocardial infarction occurring in a predisposed person. In addition to this, these changes make it more likely that possibly malignant arrhythmias will occur after infarction, and that the infarction will be more extensive than otherwise.

Table 2.10.2 shows that Rao et al [2] obstained a startling reduction in perioperative reinfartion rates for their 1977-1982 patient group. These results were ascribed to a policy of aggressive and invasive monitoring, with rapid reaction to, and treatment of, any abnormal haemodynamic parameter in any of their high risk patients. This is not possible in some hospitals, and so the more pessimistic statistics are likely to be applicable in those hospitals where monitoring facilities such as pulmonary artery catheterization with regular cardiac output and SVR measurement etc, together with therapeutic modalities such as intravenous

infusions of dopamine, dobutamine, nitroglycerine etc, are not available, or are used ineffectively.

PREDISPOSING FACTORS

There are a variety of factors predisposing to perioperative myocardial reinfarction. These are listed below.

1. Recent myocardial infarction [1,2].

2. Duration of operation. The frequency of reinfarction is directly proportional to the duration of the operation [3].

3. Site of operation. Intrathoracic surgery, upper abdominal operations, and great vessel surgery are associated with a significantly higher reinfarction rate [3].

4. Preoperative angina pectoris [2], angina pectoris + hypertension [2], angina pectoris with heart failure [2], see table 2.9.1.

5. Preoperative heart failure [2].

6. Preoperative hypertension [3].

7. Intraoperative hypotension [3].

8. Perioperative myocardial ischaemia [4].

ANAESTHETIC MANAGEMENT

Preoperative.

1. If possible postpone any elective operation until at least 6 months after a myocardial infarction.

2. Any emergency operation performed before this 6 month period has elapsed, should only be performed by the most experienced, gentle, and rapid surgeon available, so as to minimize trauma and operation time.

3. Prevent possible preoperative myocardial ischaemia due to anxiety with adequate preoperative sedation.

4. Anticholinergic drugs should not be administered preoperatively unless they are indicated. Tachycardia may induce myocardial ischaemia.

Anaesthesia.

1. Any patient who has had a myocardial infarction less than 3 months prior to a moderately large, or major surgical procedure should be maximally monitored. A pulmonary artery catheter enables haemodynamic support therapy to be more effectively directed. If this is not available, a central venous catheter should be used to monitor right heart filling pressures, and administer drugs. Any haemodynamic abnormality that is detected must be rapid-

ly and efficiently corrected, so as to minimize the chance of perioperative ischaemia or infarction.

Such a level of monitoring is not required for minor procedures. However as most such minor procedures are elective, these should be postponed until at least 6 months have elapsed since the myocardial infarction.

2. Anaesthetic management is the same as for patients with myocardial ischaemia [chapter 2.9]. The aim of the anaesthetist is the same as for patients with coronary vascular disease. That is, to prevent any elevation of heart work load, or hypotension, both of which may cause myocardial ischaemia and infarction.

Postoperative.

Any patient who has had a recent (< 6 months), myocardial infarction should be admitted into an intensive care unit postoperatively for aggressive monitoring and treatment for at least 48 hours. Management is otherwise the same as for patients with myocardial ischaemia.

REFERENCES

1. Tarhan,S., et al.(1972). Myocardial Infarction After General Anesthesia. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 220, 1451-1454.
2. Rao,T.L.K., et al.(1983). Reinfarction Following Anesthesia in Patients with Myocardial Infarction. ANESTHESIOLOGY, 59, 499-505.
3. Steen,P.A., et al.(1978). Myocardial Reinfarction After Anesthesia and Surgery. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 239, 2566-2570.
4. Slogoff,S., Keats,A.S.(1985). Does Perioperative Ischaemia Lead to Postoperative Myocardial Infarction. ANESTHESIOLOGY, 62, 107-114.
5. Amsterdam,E.A.,(1973), Function of the hypoxic myocardium. Experimental and clinical aspects. AMERICAN JOURNAL OF CARDIOLOGY, 32, 461-471.

Chapter 2.11

ANTICOAGULANT THERAPY IN CARDIAC PATIENTS

There are various categories of patients with cardiac disease who are on long term anticoagulant therapy.

- Those who have had a myocardial infarction, especially those with a ventricular aneurysm.
- Those with cardiac valvular disease,e.g. mitral stenosis.
- Those with prosthetic cardiac valves.

The purpose of anticoagulant therapy is to prevent reinfarction in those with a history of myocardial infarction, thromboembolism from ventricular aneurysms, to prevent thrombus formation and thromboembolism in those with prosthetic cardiac valves, or those with diseases of cardiac valves associated with thromboembolism, e.g. mitral stenosis.

It is desirable to reverse the anticoagulant activity prior to surgery so as to minimize haemorrhagic complications. This raises the question of whether it is safe to do so. Does an unacceptable increase in the risk of thromboembolic disease occur?

Regrettably this is not a well researched topic. The most well known study investigating this problem is that of Tinker and Tarhan (1978) [1]. They studied 159 patients who underwent a total of 180 non-cardiac operations subsequent to prosthetic cardiac valve implantation. The anticoagulant therapy of these patients was stopped preoperatively, and on the morning of the day of operation, the prothrombin time was normal in 37% (67/180) of the patients, and only elevated to less than 20% above normal in 32% (57/180) of the preoperative patients. This state of affairs was continued for an average of 2.7 days postoperatively, and and no patient developed embolic compilcations in the perioperative period. Six patients did develop embolic complications later, but as the shortest period between surgery and occurrence of an embolic episode was 14 months, it is debatable whether these embolic episodes were due to perioperative discontinuation of anticoagulant therapy.

It is not unreasonable to assume that these results would also apply to other forms of valvular disease, and possibly even to those with other cardiac diseases for which chronic anticoagulant drug therapy is indicated.

MANAGEMENT

A reasonable guideline is to stop the anticoagulant therapy for the required number of days so that the activity of the drug will decrease spontaneously [see table 6.6.1]. Never fully reverse the effect of any anticoagulant drug therapy. Most operations can be carried

out provided that the haemostatic parameters of the patient satisfy the criteria set out in chapter 6.3. That is;

Prothrombin time < 1.5 times normal

Partial thromboplastin time < 1.5 times normal

If the planned operation is urgent, antagonize the anticoagulant drug with vitamin-K. It takes about 6 hours for vitamin-K to be effective, as it takes this period of time for hepatic synthesis to sufficiently elevate the plasma concentration of the deficient factors. Fresh frozen plasma may be used if there is no time to wait for the effects of vitamin-K to occur. Four factor concentrates should only be used as a last resort because of the thrombogenic effect some batches of this preparation have [2]. Most patients presenting for emergency surgery have lost blood or plasma, and fresh frozen plasma is definitely to be preferred above four factor concentrate in these cases, as it replaces both the blood volume deficiency as well as the deficient coagulation factors. Further discussion on the correction of the effects of oral anticoagulant drugs is to be found in chapter 6.6.

REFERENCES

1. Tinker,J.H., Tarhan,S.(1978). Discontinuing Anticoagulant Therapy in Surgical Patients With Cardiac Valve Prostheses. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 239, 738-739.
2. Urbaniak,S.J., Cash,J.D.(1977). Blood Replacement Therapy. BRITISH MEDICAL BULLETIN, 33, 273-282.

Chapter 2.12

SUBACUTE BACTERIAL ENDOCARDITIS PROPHYLAXIS

Subacute bacterial endocarditis (SBE) prophylaxis is sometimes required to prevent infection of cardiac valves or intracardiac structures by bacteria entering the circulation as a result of surgery or instrumentation. The usual conditions for which SBE prophylaxis is indicated are listed below.

- Congenital and acquired intracardiac abnormalities.
- Congenital and acquired valvular lesions.
- Prosthetic cardiac valves.
- Patients with intracardiac pacemakers.

CLASSIFICATION OF PATIENTS

Patients are divided into high and low risk categories. A high risk patient is defined as one possessing any of the attributes below.

- A patient who has previously had one or more episodes of SBE.
- A patient who has a prosthetic cardiac valve(s).
- A patient for whom SBE prophylaxis is indicated and who has an infection.

All other patients are classified as low risk.

REGIMES PROPOSED FOR SBE PROPHYLAXIS

There is general agreement as to the indications for SBE prophylaxis, and the classification of what constitutes a high risk patient. But there is no general consensus about the SBE prophylaxis regimens used. SBE prophylaxis regimens vary widely from place to place, depending upon the personal preferences of physicians, local policy with regard to SBE prophylaxis, available antibiotics, and antibiotic sensitivities of the local bacteria.

The regimens presented below are a collection of those suggested by various societies [1,2], and employed in the Netherlands [3,4].

1. Infections, or operations in infected regions.

This requires aggressive i.v./i.m. antibiotic therapy with an antibiotic to which the infecting organism is sensitive.

2. Prophylaxis for outpatient procedures.

Prophylaxis for outpatient procedures in regions of the body ABOVE the level of the diaphragm. Includes dental, otorhinolaryngological, outpatient surgical and investigative procedures in these regions. Dental and upper airway procedures are mostly associated with Streptococcus viridans bacteraemia.

A. No allergy or recent (< 1 month) penicillin treatment.

Oral amoxycillin 3 G (children 60 mg/kg), 45-60 minutes before the procedure. Repeat the dose once 6-8 hours later.

OR

Oral penicillin-V 2 G given 30-60 minutes before the procedure. Then give penicillin-V 500 mg every 6 hours for 48 hours.

OR

I.M. procaine penicillin + penicillin-G mixture (e.g. Bicillin), 2 megaunits 30-60 minutes before the procedure. Subsequently give penicillin-V 500 mg every 6 hours for 48 hours.

B. Penicillin allergy or penicillin therapy < 1 month previously.

Give oral erythromycin 1 G (children 20 mg/kg), 1.5-2 hours preoperatively. Subsequently repeat this dose 6 and 12 hours later.

3. Prophylaxis for high risk patients.

Prophylaxis for high risk patients and for procedures in regions BELOW the diaphragm. High risk patients should receive an SBE antibiotic prophylaxis regime that has a broader antibacterial spectrum than lower risk patients. Operations in this region are usually associated with enterococcal bacteraemia.

A. No allergy or recent (< 1 month) penicillin therapy.

Ampicillin/amoxycillin 1 G (children 20 mg/kg) + gentamycin 1.5 mg/kg (maximum 80 mg) i.v./i.m. 30-60 minutes before the procedure. Repeat the ampicillin/amoxycillin every 6 hours for 24 hours, and the gentamycin every 8 hours for 24 hours.

B. Penicillin allergy or penicillin therapy < 1 month previously.

Give vancomycin 1 G (children 20 mg/kg) + gentamycin 1.5 mg/kg (maximum 80 mg) i.v. 30-60 minutes before the procedure. The vancomycin may be repeated once after 12 hours, and the gentamycin 8 and 16 hours after the procedure.

4. Obstetrical practice.

Patients undergoing delivery, or caesarean section either as day care patients or inpatients should all receive amoxycillin 1G i.v./i.m. every 6 hours for 24 hours + metronidazole 500 mg orally/i.v. every 8 hours for 24 hours.

REFERENCES

1. Simmons,N.A., et al.(1982). The antibiotic prophylaxis of infective endocarditis - Report of a Working Party of the British Society for Antimicrobial Chemotherapy. LANCET, 2, 1323-1326.
2. Committee of Prevention of Rheumatic Fever and Bacterial Endocarditis of the American Heart Association. (1977). Prevention of Bacterial Endocarditis. CIRCULATION, 56, 139A-143A.
3. Schelling,A., et al.(1985). Kliniekboek in gebruik op de afdeling Cardiologie van het Sint-Fransiscus Gasthuis Rotterdam. pub. Squibb.
4. "Richtlijnen inzake antibiotica prophylaxe', from the Report of the Committee for Clinical Pharmacotherapy of the University Hospital of Leyden, the Netherlands, 1983.

Chapter 2.13

DISORDERS OF THE CARDIAC VALVES AND SHUNTING

The anaesthetist should be aware of the presence of any form of cardiac valvular or congenital heart disease. Induction and maintenance of anaesthesia in such patients can be fraught with hazards, which if not anticipated and prepared for, may result in serious complications.

Mortality associated with valvular disease.

The mortality associated with valvular heart disease is quite considerable, and gives a very good idea of the magnitude of the haemodynamic upset caused by these disorders. Mitral and aortic disease are the most common types of valvular heart disease, and the mortality associated with them is shown in table 2.13.1.

Table 2.13.1.
Time related mortality after diagnosis of mitral and aortic valvular disease [1]. (Medical treatment only)

VALVULAR DISEASE	% SURVIVING AFTER DIAGNOSIS	
	5 years	10 years
Mitral regurgitation	80%	60%
Mitral stenosis		
- All cases	80%	60%
- NYHA class III	62%	38%
- NYHA class IV	15%	0%
Combined mitral stenosis and regurgitation	66%	33%
Aortic regurgitation	75%	50%
Aortic stenosis	38%	20%

Special considerations in valvular disease and shunting.

1. Always enquire about a history of congenital and acquired heart disease, e.g. rheumatic fever.

2. These patients may have disorders of cardiac rhythm and/or heart failure. These should be treated preoperatively so that the patient comes for surgery in optimal condition.

3. All patients with intracardiac abnormalities, diseased or prosthetic valves are at risk of acquiring SBE as a result of surgery. SBE prophylaxis is required for most forms of surgery.

4. Some patients may ingest anticoagulant drugs to prevent the possible thromboembolic consequences of their disease. Any such therapy will need to be reduced preoperatively,

5. In all cases where the patient has severe cardiac disease, some myocardial function and physiological performance test data should be available preoperatively. This facilitates decisions as to the perioperative management required.

6. The basic requirement for any anaesthetic in these patients is to at least maintain the preoperative haemodynamic situation, and if possible, to even improve it. The blood pressure should also be maintained at near normal levels so as to facilitate normal tissue perfusion, especially in those organs whose perfusion is pressure dependent. The type of anaesthetic depends greatly upon the skill of the anaesthetist and the available resources. Selection of appropriate drugs for anaesthesia is aided by use of the tables listing the systemic haemodynamic effects of anaesthetic drugs in chapter 2.1.

7. The degree of monitoring depends upon the severity of the heart disease, the nature of the operation, and the anaesthetic technique. Patients whose disease severity is NYHA class III-IV, may be haemodynamically very unstable during general anaesthesia as well as during major surgery. These categories of patients should be monitored with a pulmonary artery catheter, direct arterial blood pressure monitoring, as well as serial arterial blood gas tension measurements. They should also be admitted to an intensive care unit postoperatively until haemodynamic stability has returned.

8. ECG monitoring should always be used. The electrodes should be placed in such a configuration that any myocardial ischaemia and cardiac arrhythmia is optimally displayed, e.g. the CB5 configuration as described in chapter 2.9.

REFERENCES

1. Rapaport,E.,(1975). Natural history of aortic and mitral valve disease. AMERICAN JOURNAL OF CARDIOLOGY, 35, 221-227.

Chapter 2.14

MITRAL STENOSIS

Mitral stenosis is a condition restricting the flow of blood into the left ventricle during diastole. This restricts any elevation of cardiac output during physical exertion, or due to any other cause. Restriction of left ventricular filling during diastole may be so severe that a reduction of cardiac output also occurs during rest. However it is not the reduction of systemic cardiac output that causes most problems, but pulmonary congestion and oedema. This is because left heart output does not increase to the same degree in response to a given stimulus as does the right heart output, as right heart function is well maintained in patients with mitral stenosis [7].

PROBLEMS

1. Mortality.

The mortality associated with mitral stenosis is quite considerable, and gives a very good idea of how serious the haemodynamic disorder may be [see table 2.14.1].

Table 2.14.1.
10 year survival after diagnosis of mitral stenosis. (Medical treatment only)

All cases of mitral stenosis - 61-80% [1,2]
Symptomatic mitral stenosis - 30% [2]
NYHA class III mitral stenosis - 38% [1]
NYHA class IV mitral stenosis - 0% [1]

2. Atrial fibrillation and embolization.

Atrial fibrillation occurs in 40% of patients with mitral stenosis, and is always associated with a reduction of cardiac output [2, see also chapter 3.1]. The reduction of cardiac output due to onset of atrial fibrillation may be sufficient to render a previously asymptomatic patient symptomatic.

In one postmortem study of a random sample of patients with known premortem atrial fibrillation as well as mitral valvular disease, 41% were found to have pathological evidence of one or more arterial emboli [3]. In another study of a random series of patients with premortem mitral stenosis, with or without atrial fibrillation, 9-14% had evidence of an arterial embolism [2]. The conclusions to be drawn from these studies is that patients with mitral stenosis alone have an increased risk of developing arterial embolic disease, and this risk is approximately tripled by the advent of atrial fibrillation.

For these reasons atrial fibrillation in patients with mitral stenosis should be treated aggressively, so that the degree of stasis in the left atrium is reduced, so lessening the chances of thrombus formation within the fibrillating atria, as well as minimizing the effects of atrial fibrillation on systemic haemodynamics. Long term anticoagulant drug therapy should also be instituted so as to further reduce the chance of left atrial thrombus formation.

Table 2.14.2.

Relationship of clinical severity of mitral stenosis caused disease to haemodynamic disorder. (Data are derived from references 4,5,6.)

NYHA CLASS	VALVE AREA	C.I.	PCWP	PVR	SVR
Normal	3	2.5-3.6	5-13	20-120	770-1500
I(n=32)	1.6	3.2	16	226	629
II(n=48)	1.2	2.7	18	395	914
III(n=30)	0.97	2.3	20	412	1263
IV(n=7)	0.7	2.0	24	1861	2881

VALVE AREA is in cm^2
C.I. = cardiac index as $l/min/m^2$.
PCWP = pulmonary capillary wedge pressure in mmHg.
PVR = pulmonary vascular resistance in $dyne.sec.cm^{-5}$.
SVR = systemic vascular resistance in $dyne.sec.cm^{-5}$.

3. Relation of symptoms to haemodynamic disorder.

The clinical severity of mitral stenosis correlates with the valve area and the degree of haemodynamic disorder as is shown in table 2.14.2. The normal area of the mitral valve

is about 3 cm^2. It is not until the valve area is reduced below 1.5 cm^2 that clinical symptoms become significant. Symptoms may occur at rest when the valve orifice area is below 1 cm^2.

4. Effects of physical exertion, stress.

The cardiac output of persons with mitral stenosis of NYHA classes I-II functional severity increases in proportion to the severity of any physical exertion [6]. But the cardiac output of patients with mitral stenosis of NYHA classes III-IV does not increase significantly in response to exercise [6], and the patients become symptomatic. The same applies to haemodynamic changes due to other forms of stress such as pain, trauma, cold etc.

Pulmonary vascular pressures are often elevated in patients with mitral stenosis of NYHA classes II-IV severity. While physical exertion can increase the cardiac output in some patients with lesser degrees of mitral stenosis, symptoms can occur due to the disproportionately large increase of existing elevated pulmonary artery pressures induced by exertion, which may rise so high that frank pulmonary congestion or oedema may occur [6].

5. Tachycardia.

The cardiac output of patients with mitral stenosis of NYHA classes I-III functional severity does increase when the heart rate rises. But this is not so in patients with mitral stenosis of NYHA class IV severity in whom the cardiac output either does not change, or actually decreases with inreasing heart rate, or physical exertion [6]. Patients with mitral stenosis of NYHA functional class IV may be said to have a fixed cardiac output.

Sudden elevation of heart rate due to physiological stress such as surgery, pain, or cold, are likely to be associated with a reduction of cardiac output, as these stimuli also increase the SVR.

Atrial contraction plays an important role in left ventricular filling in patients with mitral stenosis. Diastolic filling of the left ventricle is aided by atrial contraction, and so is not solely dependent on passive flow of blood through the narrowed amitral valve. So it is not surprising that the onset of atrial fibrillation may convert a previously asymptomatic patient to a symptomatic one, due to a reduction of the cardiac output [4, and chapter 3.1].

6. Change of systemic vascular resistance (SVR).

a. Increased SVR.

Increased SVR in a person with mitral stenosis causes the cardiac output to decrease in proportion to the elevation of the SVR [5]. In addition to the decreased cardiac output, the pulmonary vascular pressures also increase, which can precipitate pulmonary congestion/oedema. SVR may be increased by a variety of stimuli.

- Vasoconstrictor drugs.
- Hypothermia.
- Pain, or surgical stress.
- Anxiety.

b. Deceased SVR.

Drugs that reduce the SVR induce no significant change, or at most a slight increase of cardiac output, in patients with NYHA classes III-IV mitral stenosis [5,8]. This demonstrates the "fixed" nature of the cardiac output in persons with such severe mitral stenosis. Mitral stenosis limits ventricular filling rate such that once maximum mitral valvular flow is attained for a given left atrial pressure, the ventricular filling rate and hence

cardiac output, can increase no further. Further reduction of the SVR causes the blood pressure to fall. A good example of this is hypotension due to an infusion of sodium nitroprusside in mitral stenosis patients with NYHA classes III-IV disease at a dose which has little effect on the MABP in normal persons [5,8]. This effect is also well described by the equation below.

$$\mathbf{MABP = CO \times SVR}$$

(N.B. See Appendix-C for abbreviations)

7. Effects on drug kinetics.

The reduced cardiac output of severe mitral stenosis means that drug elimination will be retarded [see chapter 15.2], with all the consequences of this.

ASSESSMENT

The important factors to keep in mind are listed below.

1. The functional severity of the mitral stenosis, and the type of surgery planned, determine the level of monitoring

2. Patients with atrial fibrillation have a lower cardiac output than those with sinus rhythm [4].

3. Patients with congestive cardiac failure are at high risk because of the presence of pulmonary vascular congestion or oedema, both of which may be exacerbated in the perioperative period.

ANAESTHETIC MANAGEMENT

Preoperative.

1. Elective operation of any patient with atrial fibrillation, whose ventricular rate is greater than 100 beats/min, should be delayed until the ventricular rate has been reduced below 100 beats/min [see chapter 3.1].

2. Anticoagulant therapy should be discontinued or reversed preoperatively so as to minimize the risk of haemorrhagic complications. Acceptable levels for haemostatic function are given in chapter 6.3.

3. Anticholinergic drugs such as atropine should not be administered to patients with atrial fibrillation as they may significantly increase the heart rate.

4. Preoperative sedation is not contraindicated. In fact some sedation is even desirable, as it reduces any elevation of the SVR due to anxiety.

5. SBE prophylaxis is required for most operations.

Anaesthesia.

1. The reduced cardiac output associated with the more severe grades of mitral stenosis means that the elimination of most drugs is retarded. This should be taken into account when considering repeat dosages of any drug.

2. Maintain the body temperature above 35°C, as hypothermia elevates the SVR. Postoperative shivering may elevate the oxygen consumption by as much as 500%, and increases the cardiac output as well as the SVR [9]. However the cardiac output cannot increase in patients with mitral stenosis of NYHA classes III-IV severity, and an elevation of the SVR actually reduces it. As a consequence, peripheral oxygen transport is reduced in a time when tissue oxygen consumption is increased by rewarming. The end result of this physiologically disadvantageous combination is that tissue hypoxia is likely due to an inadequate cardiac output.

3. Strict attention must be paid to perioperative fluid balance Flow through a narrowed mitral valve is dependent on the maintenance of a left atrial pressure that is higher than normal. If the left atrial pressure is reduced due to hypovolaemia, cardiac output will fall. Such a fall will be more pronounced in patients whose cardiac output is maintained only by means of elevation of the left atrial pressure, i.e. NYHA classes III-IV mitral stenosis [see table 2.11.2].

4. Low dosage infusions of vasodilator drugs such as sodium nitroprusside or nitroglycerine reduce the pulmonary vascular resistance and pressures. This reduces the likelihood of pulmonary oedema, as well as allieviating existing congestion/oedema. The dosage used must be adjusted according to the haemodynamic effects observed.

5. General anaesthesia and surgery in patients with NYHA classes III-IV mitral stenosis elevates the left atrial pressure, PVR, and SVR, as well as simultaneously reducing the cardiac output [8]. For this reason maximal monitoring is required for patients with NYHA classes III-IV mitral stenosis who are operated upon under general anaesthesia, and some forms of loco-regional anaesthesia. Such monitoring should include a pulmonary artery catheter so that central venous and pulmonary artery pressures, as well as the cardiac output and the SVR can be measured. The effects of any therapy to improve systemic haemodynamics may then be more effectively monitored and adjusted.

The use of only central venous pressure monitoring to assess the pulmonary vascular pressures is inadequate. Right heart function and pressures are normal even in severe mitral stenosis, unless right heart failure is present [7].

6. Regional anaesthesia using techniques causing a significant reduction of SVR, such as spinal and epidural anaesthesia, should be used with caution. Hypotension will occur if the SVR decreases to a greater degree than can be compensated for by an elevation of the cardiac output. This is especially likely in persons with NYHA classes III-IV disease, in whom these techniques are contraindicated. Persons with mitral stenosis of NYHA classes I-II functional severity may undergo these forms of anaesthesia as their cardiac output does increase when the SVR is reduced. Other regional anaesthetic techniques are not contraindicated in persons with mitral stenosis.

7. There are several factors of importance to be considered when considering general anaesthesia in patients with mitral stenosis.

a. General anaesthesia should ideally only minimally affect myocardial contractility, while causing only a slight to no reduction of the SVR.
b. A technique using controlled ventilation should be used to minimize the possibility of hypoxaemia due to a reduced cardiac output and pulmonary congestion/oedema.
c. Induction and maintenance of anaesthesia should be done with drugs causing minimal cardiovascular depression and alterations of systemic haemodynamics.

The selection of appropriate drugs and anaesthetic techniques may be done using the above guidelines and the tables in chapter 2.1.

Postoperative.

1. Patients with mitral stenosis of NYHA classes III-IV severity who have undergone moderate to major surgery, should be admitted to an intensive care unit postoperatively for monitoring and therapy until their haemodynamic status has stabilized.

2. Postoperative mechanical ventilation with sedation and muscle relaxation should be considered for patients with mitral stenosis of NYHA classes III-IV who have a postoperative temperature of 35°C or less. This will prevent elevation of the SVR and a reduction of the cardiac output due to shivering. Mechanical ventilation may be discontinued once normothermia has returned.

REFERENCES

1. Rapaport,E.(1975). Natural history of aortic and mitral valve disease. AMERICAN JOURNAL OF CARDIOLOGY, 35, 221-227.
2. Selzer,A., Cohn,K.E.(1972). Natural history of mitral stenosis : A review. CIRCULATION, 45, 878-890.
3. Hinton,R.C., et al.(1977). Influence of etiology of atrial fibrillation on incidence of systemic embolism. AMERICAN JOURNAL OF CARDIOLOGY, 40, 509-513.
4. Dubin,A.A., et al.(1971). Longitudional hemodynamic and clinical study of mitral stenosis. CIRCULATION, 44, 381-389.
5. Bolen,J.L., et al.(1975). Analysis of left ventricular function in response to afterload changes in patients with mitral stenosis. CIRCULATION, 52, 894-900.
6. Giuffrida,G., et al.(1979). Hemodynamic response to exercise after propranolol in patients with mitral stenosis. AMERICAN JOURNAL OF CARDIOLOGY, 44, 1076-1082.
7. Wroblewski,E., et al.(1981). Right ventricular performance in mitral stenosis. AMERICAN JOURNAL OF CARDIOLOGY, 47, 51-55.
8. Stone,J.G., et al.(1980). Nitroprusside and mitral stenosis. ANESTHESIA AND ANALGESIA, 59, 662-665.
5. Bay,J., et al.,(1968), Factors influencing arterial PO_2 recovery from anaesthesia. BRITISH JOURNAL OF ANAESTHESIA, 40, 398-407.

Chapter 2.15

MITRAL REGURGITATION

Mitral regurgitation is a valvular disease characterized by a heart where the systemic cardiac output is determined by the relative resistances presented by pulmonary and systemic circulations during ventricular systole. Because of regurgitation through the mitral valve, the left atrial and pulmonary vascular pressures are increased above normal. This causes pulmonary congestion or oedema in more severe degrees of mitral regurgitation.

PROBLEMS

1. Mortality.

The mortality statistics shown in table 2.15.1 give a reasonably good idea of the magnitude of the haemodynamic disorder caused by mitral regurgitation.

Table 2.15.1.
Mortality after diagnosis of mitral insufficiency [1]. (Medical treatment only)

Acute mitral insufficiency may progress to death within days.	
Chronic mitral insufficiency	- 5 year survival = 80% - 10 year survival = 60%

2. Pulmonary congestion/oedema.

Acute and chronic mitral regurgitation elevate the left ventricular end diastolic pressure, pulmonary artery wedge pressure, and left atrial A-wave, V-wave, and mean pressures [3,4]. As a result of these haemodynamic changes pulmonary congestion or oedema frequently occur in patients with mitral regurgitation.

The principal consequence of these changes for the anaesthetist is that the supine or prone positions will exacerbate any pulmonary congestion or oedema, thus making surgery in these positions difficult or impossible for awake patients.

3. Effects of changes of left ventricular volume.

A reduction of both left ventricular and left atrial volumes decreases the functional valve area, and hence the regurgitant fraction [3,4]. This in turn decreases the amplitude of the left atrial V-wave, and allieviates any pulmonary vascular congestion [4].

Left ventricular and atrial volumes are reduced by a variety of factors.

- Tachycardia.
- Positive end expiratory pressure ventilation.
- Hypovolaemia.
- Drugs inducing tachycardia.
- Vasodilator drugs.

The reverse haemodynamic changes occur when the left ventricular and atrial volumes increase.

4. Heart rate.

Tachycardia reduces both atrial and ventricular pressures throughout the cardiac cycle, reducing the volumes of both the left atrium and ventricle, which decreases the functional mitral valve area, and so reduces the regurgitant fraction [3]. At ventricular rates > 150 beats/min induced by atrial pacing, the amplitude of the left atrial V-wave increases due to early atrial contraction, and this may exacerbate any pulmonary congestion [2]. These results correspond with those where tachycardia is induced with isoprenaline. But isoprenaline, as opposed to atrial pacing, causes the left atrial V-wave amplitude to decrease [3], a finding which corresponds to what is clinically observed during tachycardia in patients with mitral regurgitation [4].

In conclusion, tachycardia alone cannot be regarded as causing deleterious haemodynamic effects in patients whose mitral insufficiency is not accompanied by coronary vascular disease.

5. Systemic vascular resistance.

a. Increased SVR.

Increasing the SVR has haemodynamically disadvantageous effects. The left atrial and ventricular pressures are increased, with as a result, the volumes of these two chambers increases, as well as the area of the regurgitant mitral valve. The increased functional valve area elevates the regurgitant fraction, and the cardiac output decreases [2,5]. Increased left heart pressures may exacerbate any pulmonary congestion or oedema.

b. Decreased SVR.

Reduction of the SVR causes an improvement of the haemodynamic situation [3,6,7,-8]. The left atrial and ventricular pressures are decreased, reducing the the left atrial and ventricular volumes as well as the functional mitral valve area. This decreases the regurgitant fraction, and the cardiac output increases. Because the pulmonary vascular pressures are also decreased by the reduced left heart pressures, any pulmonary vascular congestion/oedema present is also relieved.

6. Effects of volume loading.

Augmentation of the blood volume with an infusion of a blood volume expanding fluid raises the left ventricular and atrial pressures, stroke volume, and cardiac output [2]. While the increased cardiac output is advantageous, the elevation of the left heart pressures may exacerbate or precipitate pulmonary congestion or oedema in those patients who are unable to increase their cardiac output, i.e. NYHA classes III-IV patients.

7. Myocardial contractility.

Increasing the contractility of the myocardium with calcium or sympathomimetics improves the haemodynamic situation of persons with mitral regurgitation [2,5]. Left atrial and ventricular pressures and volumes are decreased, which reduces the functional valve area and regurgitant fraction, and so the cardiac output increases.

ASSESSMENT

Besides assessing the level of functional disability of the patient, special attention should be paid to the presence of left ventricular failure. In particular, whether the patient has orthopnea, pulmonary congestion or oedema. Patients with these problems are unable to lie flat while awake because of the positional exacerbation of their condition. They are usually unsuitable candidates for any regional anaesthetic techniques where the sitting position cannot be maintained.

A further practical point is that the medical treatment to which these patients are subjected for heart failure, may result in the patient coming to surgery both hypokalaemic and hypovolaemic due to diuretic drugs.

ANAESTHETIC MANAGEMENT

Preoperative.

1. Heart failure should be adequately treated prior to elective surgery [see chapter 2.8].

2. Preoperative sedation is not contraindicated except in patients who are hypoxaemic due to pulmonary oedema. Most sedative drugs decrease the hypoxic and hypercarbic respiratory drives and will exacerbate any existing hypoxaemia [see table 4.5.1].

3. Anticholinergic drugs may be administered, except to patients with an existing tachycardia, atrial fibrillation, or coronary vascular disease.

4. SBE prophylaxis is required for most forms of surgery.

Anaesthesia.

1. Patients with mitral insufficiency of functional severity grade NYHA classes III-IV should be maximally monitored. A pulmonary artery catheter should be used so that cardiac output, SVR, and pulmonary vascular pressures may be measured. Therapy is then more effectively directed to correct haemodynamic abnormalities.

As with mitral stenosis, measurement of the central venous pressure is of limited use. Right ventricular function and pressures are normal unless right ventricular failure has occurred.

2. The haemodynamic situation of the person with mitral regurgitation, with or without heart failure, is improved by any drug regime which enhances myocardial contractility while reducing the SVR and the pulmonary vascular resistance (PVR). There are a large variety of vasodilator and inotropic drugs available which are suitable, some of which are listed below [see table 2.2.1].

a. Dobutamine alone. Dobutamine increases the cardiac output in addition to reducing the SVR.
b. Dopamine + nitroglycerin or sodium nitroprusside. Dopamine has a positive inotropic and chronotropic action, increasing the cardiac output, and elevating the SVR. The latter effect may be reversed by a vasodilator.
c. Nitroglycerin or sodium nitroprusside alone. This reduces the SVR and PVR as well as increasing the cardiac output.

The problem with using a vasodilator drug alone is that the arterial blood pressure may be significantly reduced. This problem may be reduced by combining administration of the vasodilator with an inotropic drug. Or by administration of a vasodilator together with increasing the blood volume with an appropriate fluid, so that despite the vasodilation the central venous and pulmonary capillary wedge pressure remain in the high normal range [6].

3. Hypovolaemia should be prevented so that normal cardiac filling pressures and cardiac output can be maintained.

4. Peroperative reduction of the body temperature below 35°C should be prevented. Hypothermia itself increases the SVR, and postoperative shivering further elevates the SVR and can increase the oxygen consumption by as much as 500% above normal [9].

But in patients with mitral regurgitation, the regurgitant fraction is increased by elevation of the SVR. This limits any increase of cardiac output required by the increased oxygen consumption, making any elevation of peripheral oxygen deliver impossible, and tissue hypoxia likely.

5. Regional anaesthetic techniques may be employed where appropriate. Persons with orthopnea may be unable to lie flat and so are unsuitable candidates for regional anaesthetic techniques where a recumbent position is required for the performance of any surgical procedure.

Techniques which reduce the SVR, such as epidural or spinal anaesthesia have haemodynamically advantageous effects. However as the magnitude of the SVR reduction is unpredictable, these techniques are unsuitable for patients with mitral regurgitation of NYHA functional severity classes III-IV.

Unilateral spinal anaesthesia and all other forms of regional anaesthesia may be used in all patients with mitral regurgitation as they normally exert no profound systemic haemodynamic effects.

6. Any selection of techniques and drugs for administration of general anaesthesia in patients with mitral regurgitation must take a number of factors into account.

a. A technique causing some slight reduction of SVR is ideal, as the cardiac output is increased together with a reduction in the regurgitant fraction. Provided that the reduction of SVR is not excessive, the arterial blood pressure will not be greatly reduced.
b. A technique using controlled ventilation is best for most patients with severe mitral insufficiency. Controlled ventilation ensures adequate oxygenation despite the presence of pulmonary congestion/oedema.
c. Induction of anaesthesia may be complicated by the fact that some patients will come for surgery in a hypovolaemic condition due to preoperative diuretic therapy. Hypovolaemia exacerbates the cardiovascular depression due to anaesthetic drugs.
d. Drugs which have a powerful myocardial depressant effect, such as the halogenated volatile anaesthetics, increase the ventricular volume and hence the regurgitant fraction too. By increasing regurgitant fraction they also decrease cardiac output, and may exacerbate any pulmonary congestion or oedema. For this reason volatile anaesthetic drugs should be used with some caution in patients with severe grades of mitral regurgitation.

The selection of suitable anaesthetic drugs and techniques should be made using the above guidelines, and the tables listing the systemic haemodynamic effects of anaesthetic drugs in chapter 2.1.

Postoperative.

Patients with NYHA classes III-IV disease should be admitted into an intensive care unit postoperatively so that haemodynamic monitoring and therapy can be continued until any haemodynamic disorder has resolved, and normal body temperature is restored.

REFERENCES

1. Rapaport,E.(1975). Natural history of aortic and mitral valve disease. AMERICAN JOURNAL OF CARDIOLOGY, 35, 221-227.
2. Yoran,C., et al.(1983). Effects of heart rate on experimentally produced mitral regurgitation in dogs. AMERICAN JOURNAL OF CARDIOLOGY, 52, 1345-1349.
3. Sasayama,S., et al.(1979). Dynamic geometry of the left atrium and left ventricle in acute mitral regurgitation. CIRCULATION, 60, 177-186.
4. Bolen,J.L., Alderman,E.L.(1977). Ventriculographic and hemodynamic features of mitral regurgitation of cardiomyopathic, rheumatic and nonrheumatic etiology. AMERICAN JOURNAL OF CARDIOLOGY, 39, 177-183.
5. Borgenhagen,D.M., et al.(1977). The effects of left ventricular load and contractility on mitral regurgitant orifice size and flow in the dog. CIRCULATION, 56, 106-113.
6. Stone,J.G., et al.(1980). Afterload reduction and preload augmentation improve the anaesthetic management of patients with cardiac failure and valvular regurgitation. ANESTHESIA AND ANALGESIA, 59, 737-742.
7. Goodman,D.J., et al.(1974). Effect of nitroprusside on left ventricular dynamics in mitral regurgitation. CIRCULATION, 50, 1025-1032.
8. Lappas,D.G., et al.(1978). Systemic and pulmonary effects of nitroprusside during mitral valve replacement in patients with mitral regurgitation. CIRCULATION, 58, Supp. I, 18-22.
9. Bay,J., et al.,(1968), Factors influencing arterial PO_2 recovery from anaesthesia. BRITISH JOURNAL OF ANAESTHESIA, 40, 398-407.

Chapter 2.16

MITRAL VALVE PROLAPSE

Mitral valve prolapse is a syndrome characterized by a systolic "click" and/or late systolic murmur. These are caused by the mitral valve leaflets prolapsing into the left atrium during systole. It is one of the most common valvular disorders, occurring in all age groups and sexes in 1.4-6% of the population [1].

About 50-70% of patients complain of palpitations [1], and chest pain unrelated to myocardial ischaemia occurs in about 33-50% [1]. 55% complain of dyspnea, and 60% experience easy fatigability [4]. Noradrenaline and adrenaline production and plasma concentrations in patients with mitral prolapse are twice as high as those in patients with normal hearts [4].

PROBLEMS

1. Abnormal electrocardiogram (ECG).

a. Significant arrhythmias are observed in 66-75% of mitral prolapse patients when 24 hour Holter monitoring is used [1,4].

b. The frequency with which cardiac arrhythmias occur, varies during the day, being directly related to the plasma adrenaline and noradrenaline concentrations [4]. Arrhythmias are more frequent in patients that are awake than those that are sleeping, and also occur more frequently after physical exertion.

c. Tachyarrhythmias and premature ventricular contractions are the most frequently occurring types of arrhythmia. Premature ventricular contractions are observed in 33-70% of patients [1,4].

d. 33% of patients have flattened or inverted T-waves in leads II, III, AVF and V4-6.

e. Atrial fibrillation may occur in association with mitral prolapse, but usually only occurs when there is also a degree of mitral regurgitation too. Atrial fibrillation in association with mitral valvular disease is associated with a much increased chance of developing systemic arterial embolism [3]. Prevention of embolism secondary to intra-atrial thrombus formation requires that these patients be chronically anticoagulated.

f. Physical exertion induces arrhythmias in 50-75% of patients with mitral prolapse [1,4]. These arrhythmias vary from unifocal or multifocal premature ventricular premature beats to ventricular tachycardia. The arrhythmias typically occur during isometric physical

exertion, and after stopping isotonic physical exertion [4]. The frequency of occurrence of exertion related arrhythmias is directly related to the exertion induced increase of plasma adrenaline and noradrenaline concentrations [4].

Because the frequency of arrhythmias is related to the plasma catecholamine concentrations, it may be expected that trauma, anxiety and surgery will also induce arrhythmias. All these events also elevate plasma catecholamine concentrations.

2. Change of left ventricular volume [1].

a. Decreased left ventricular volume.

A reduction of left ventricular volume increases not only the degree of mitral prolapse, but the valve begins to prolapse at an earlier phase of systole too. Manifestations of mitral prolapse such as arrhythmias etc, are exacerbated or even precipitated by any factor reducing left ventricular volume. There are various causes of reduced left ventricular volume.

- Sitting and standing.
- Hypovolaemia.
- Reduced SVR.
- Vasodilator drugs.
- Valsalva maneuver.
- Positive end expiratory pressure.
- Tachycardia.
- Drugs inducing tachycardia, such as atropine.

b. Increased left ventricular volume.

Factors increasing left ventricular volume decrease the degree of mitral valve prolapse. Because of this the frequency of arrhythmias is reduced. Various factors cause the left ventricular volume to increase.

- Lying flat, either prone or supine.
- Hypervolaemia.
- Increased SVR.
- Vasoconstrictor drugs.
- Bradycardia.
- Drugs inducing bradycardia, e.g. ß-adrenergic blocking drugs.

ANAESTHETIC MANAGEMENT [1,2]

The aim of the anaesthetist is to minimize the frequency of any prolapse manifestations by maintaining a normal left ventricular volume and preventing further prolapse of the mitral valve.

Preoperative.

1. Discontinue any anticoagulant drug preoperatively.

2. SBE prophylaxis is required for most patients.

3. Patients with frequent arrhythmias should be considered for preoperative therapy with ß-blocking drugs. Propranolol administered at a dosage of 10 mg four times a day is usually effective in controlling mitral prolapse induced arrhythmias [1]. This is probably related to both the bradycardia inducing effects of this drug, and also to the catecholamine blocking effect.

4. Sedative or opiate drugs may be administered preoperatively so as to diminish tachycardia secondary to anxiety.

5. Administer no atropine preoperatively, as this increases the heart rate, which may cause arrhythmias.

Anaesthesia [1,2].

1. Position is important. Operations in the sitting, or antitrendelenburg position are not advisable because of the arrhythmias that may be induced by these positions secondary to a reduction of left ventricular volume.

2. Tachycardia and most arrhythmias may be treated with ß-blocking drugs. Arrhythmias should be treated specifically if therapy with ß-blocking drugs is ineffective.

3. Regional anaesthetic techniques such as spinal or epidural anaesthesia should be used with caution, because of the reduction of SVR with secondary reduction of left ventricular volume that they may cause. If regional anaesthetic techniques are used, the patient should be adequately sedated to prevent any tachycardia due to anxiety.

4. There are some factors to be considered when administering general anaesthesia to patients with mitral prolapse.

a. A technique should be used where the patient is mechanically ventilated. This minimizes the chance that arrhythmias occur due to elevation of plasma catecholamine concentrations secondary to hypercapnia induced by hypoventilation.
b. Anaesthetic vapors cause a reduction of the SVR, and by causing myocardial depression they also induce a degree of left ventricular dilation. The latter is beneficial as it reduces the degree of mitral prolapse. However when they are used at still higher concentrations they may reduce the SVR by such an amount that mitral prolapse may be exacerbated.
c. Induction of sleep is perhaps best done using a drug such as etomidate. This latter drug causes minimal myocardial depression and vasodilation in comparison with the other drugs available for anaesthetic induction [see chapter 2.1]. Ketamine is an unsuitable drug because of the tachycardia it induces.
d. A ß-blocking drug such as pindolol or propranolol may be administered during anaesthesia to prevent or minimize tachycardia and arrhythmias due to stress.

Selection of the most appropriate anaesthetic techniques and drugs may be done taking the considerations listed in this chapter into account, and the systemic haemodynamic effects of anaesthetic drugs listed in chapter 2.1.

5. Carefully replace any fluid and blood losses so as to minimize the chance of hypovolaemia occurring. Hypovolaemia reduces the cardiac volume and exacerbates mitral prolapse.

Postoperative.

Postoperative therapy is dependent on the clinical condition of the patient and the nature of the operation.

REFERENCES

1. Devereux,R.B., et al.(1976). Mitral valve prolapse. CIRCULATION, 54, 3-14.
2. Krantz,E.M., et al.(1980). Mitral valve prolapse. ANESTHESIA AND ANALGESIA, 59, 379-383.
3. Hinton,R.C., et al.(1977). Influence of etiology of atrial fibrillation on incidence of systemic embolism. AMERICAN JOURNAL OF CARDIOLOGY, 40, 509-513.
4. Boudoulas,H., et al.(1980). Metabolic studies in mitral valve prolapse syndrome. A neuroendocrine - cardiovascular process. CIRCULATION, 61, 1200-1205.

Chapter 2.17

AORTIC STENOSIS

Aortic stenosis represents a condition in which flow of blood out of the left ventricle into the aorta is limited by the flow resistance presented by a narrowed aortic valve. This limits any increase of cardiac output in patients with more severe degrees of aortic stenosis, and so the cardiac output is said to be "fixed" in these patients. In more severe degrees of stenosis the cardiac output is reduced below normal levels even at rest [see chapter 3.1 for clinical manifestations of reduced cardiac output].

Angina pectoris occurs in 35-50% of patients [1], and congestive cardiac failure in 33% [2]. Syncopal attacks may occur in about 30% of NYHA classes II-IV patients with aortic stenosis [1,2].

PROBLEMS

1. Mortality.

The mortality of aortic stenosis is higher than for the other valvular disorders, except for combined valvular disorders. As has already been mentioned, the mortality statistics also give a very good idea of the degree of haemodynamic disorder caused by the disease [see table 2.17.1].

Table 2.17.1.
Mortality after diagnosis of aortic stenosis [3]. (Medical treatment only)

All patients	- 5 year survival = 38% - 10 year survival = 20%
Symptomatic patients - average survival = 5 years	
With Angina pectoris, Dyspnea, Congestive cardiac failure, or Syncope. Average survival = 1.5-3 years	

2. Relation of clinical status to haemodynamic disorder.

The normal aortic valve area in an adult is about 2-4 cm^2. If the valve area is reduced below 1 cm^2, left ventricular systolic pressure begins to increase, as does the peak systolic ventriculo-aortic pressure gradient (normal gradient = 0 mmHg) [3]. Patients with systolic ventriculo-aortic pressure gradients greater than 40-50 mmHg are more likely to have significant symptoms and haemodynamic disorder, and often have a functional disorder graded in the range NYHA functional classes III-IV [see below in this chapter for discussion].

3. Angina pectoris.

Angina pectoris occurs in 35-50% of patients with aortic stenosis, because the myocardium of persons with aortic stenosis has a lower blood flow per unit mass of muscle than is the case in persons with normal hearts [1]. This predisposes to the development of myocardial ischaemia.

Myocardial ischaemia may be treated as usual by infusion of vasodilator drugs. But these drugs may also markedly reduce the arterial blood pressure in persons with severe aortic stenosis, because the cardiac output does not increase significantly in patients with aortic stenosis of NYHA classes III-IV severity who are administered vasodilator drugs [4,5,6]. Unfortunately, hypotension may also induce myocardial ischaemia.

In general, administration of vasodilator drugs for treatment of myocardial ischaemia in patients with aortic stenosis should be done cautiously regardless of the clinical severity of the disease. Only short acting vasodilators such as nitroglycerine or sodium nitroprusside administered by intravenous infusion should be used as their effect is rapidly terminated after stopping the infusion. The infusion rate should be cautiously increased until myocardial ischaemia is allieviated.

4. Congestive cardiac failure.

Chronic excessive overloading of the left ventricle by severe aortic stenosis causes left ventricular failure in 33% of patients [2]. Left ventricular failure is exacerbated by increased SVR, such as may occur during anaesthesia and surgery.

5. Syncope.

Syncopal episodes occur in about 33% of patients with aortic stenosis of NYHA classes II-IV functional severity [1,2]. The cause is either an abnormal nonfunctional cardiac rhythm, or a period of inadequate cardiac output.

The cardiac output of patients with severe, (NYHA III-IV), aortic stenosis does not increase with an increased heart rate [7], or in response to vasodilation [5,6], and decreases as a result of vasoconstriction [8]. Patients may experience tissue hypoxia in situations where oxygen requirement exceeds the ability of the cardiac output to supply oxygen saturated blood, e.g. physical exertion, shivering due to hypothermia. If tissue hypoxia is severe enough, unconsciousness, cardiac arrhythmias, or both occur.

6. Tachycardia.

Tachycardia up to a rate of 135 beats/min in patients with aortic stenosis with a mean aortic valvular gradient of 40 mmHg or more causes no change in cardiac output or arterial blood pressure, but the left ventricular end-diastolic pressure and stroke volume do decrease [7]. Accordingly, tachycardia as such does not exacerbate the haemodynamic disorder due to aortic stenosis, and in fact betters it by reducing chamber pressures in the heart.

But patients with significant coronary vessel disease may develop myocardial ischaemia as a result of increased oxygen consumption due to tachycardia. Myocardial ischaemia of sufficient severity also reduces the cardiac output.

7. Systemic vascular resistance.

a. Increased SVR.

Increasing the SVR elevates the systemic blood pressure, cardiac stroke work, left ventricular pressures, and decreases cardiac output [8]. This can exacerbate or precipitate angina pectoris and cardiac failure.

b. Decreased SVR.

A ventriculo-aortic systolic pressure gradient of more than 40-50 mmHg is an indicator of a "fixed" cardiac output. This has been well demonstrated by the observation that administration of vasodilator drugs to persons with a ventriculo-aortic gradient of less than 40 mmHg does cause the cardiac output to increase [4], but does not elevate the cardiac output in persons with a gradient of more than 50 mmHg [5,6]. Reduction of the SVR in persons with a cardiac output that cannot increase, decreases the arterial blood pressure. This is also able to be inferred from the formula below.

$$\mathbf{MABP = CO \times SVR}$$

[See Appendix-B for abbreviations].

ASSESSMENT

During the normal clinical assessment, special attention must be paid to the occurrence of heart failure, angina pectoris, and syncopal attacks. These latter indicate that there is minimal ability for baroreflex compensation for anaesthesia and surgery induced haemodynamic changes, which may induce myocardial ischaemia, exacerbate heart failure, or further reduce the cardiac output. This is especially likely in those patients with aortic valvular pressure gradients in excess of 40-50 mmHg, or those with NYHA functional classes III-IV disease.

ANAESTHETIC MANAGEMENT

Preoperative.

1. SBE prophylaxis is required for most forms of surgery.

2. Administer sedative drugs preoperatively to prevent elevation of the SVR due to anxiety. This may induce or exacerbate angina pectoris or heart failure.

3. There is no contraindication to the use of any anticholinergic drug, even atropine. However it is advisable not to administer atropine to those patients with known myocardial ischaemia, as a tachycardia may induce angina pectoris.

Anaesthesia.

1. Maintain normovolaemia. Hypovolaemia elevates the SVR, reduces left atrial and ventricular pressures as well as filling, which decreases the cardiac output.

2. Body temperature should be maintained above 35°C. Hypothermia elevates the SVR, reducing the cardiac output, while postoperative shivering further increases the SVR and may increase oxygen consumption by up to 500% [9]. In the latter situation, actual tissue hypoxia may occur due to inability to increase the cardiac output.

3. Should an inotropic drug be required, dobutamine is the drug of choice. This drug increases the cardiac output without greatly increasing the heart rate or elevating the SVR. In fact it even slightly reduces the SVR. This is unlike dopamine, which may actually reduce the cardiac output due to elevation of the SVR, in addition to which dopamine also causes a tachycardia [see chapter 2.2].

4. Any anaesthetic procedure may cause acute hypotension. This is due to depression of cardiac output, reduction of the SVR, or both. Hypotension may induce myocardial ischaemia in those with significant coronary vascular disease. For this reason it is recommended that a vasoconstrictor drug be rapidly available to restore normotension should significant hypotension occur. The drug usually recommended for this purpose is phenylephrine, (0.1-0.2 mg/70 kg administered as an i.v. bolus). This drug is a pure α-adrenoreceptor agonist, and increases the SVR and arterial blood pressure, but simultaneously causes a baroreflex mediated reduction of cardiac output. The physiological advantage gained by administration of phenylephrine or other α-adrenoreceptor agonists is simply that the cerebral and myocardial perfusion increase as a result of the elevation of arterial blood pressure.

5. Patients with NYHA functional classes III-IV aortic stenosis, those with myocardial ischaemia, heart failure, and a history of syncopal attacks, should be optimally monitored in the perioperative period. A pulmonary artery catheter should be used so that administration of any vasoactive drug therapy may be more effectively guided.

As with mitral valvular disease, central venous pressure does not correlate with the left atrial pressure, as right heart function is normal until late in the course of aortic stenosis.

6. Regional anaesthetic techniques causing a reduction of the SVR, e.g. epidural and spinal anaesthesia, should be used with caution, if at all, in patients with NYHA functional classes III-IV disease. The magnitude of reduction of the SVR is unpredictable. Severe, difficult to manage hypotension may occur as the cardiac output is unable to increase in response to any reduction of SVR.

Other regional anaesthetic techniques are not contraindicated, and in fact are to be preferred where possible, as they cause minimal changes of systemic haemodynamics.

7. Several factors are important to consider when deciding on a suitable anaesthetic technique and drugs to use when administering general anaesthesia to patients with aortic stenosis.

a. The ideal systemic haemodynamic situation during anaesthesia is one where there is minimal use of myocardial depressant drugs, minimal to no reduction of the SVR, but at the

same time no elevation of the SVR. All these factors combine to maintain cardiac output and blood pressure in patients with NYHA functional classes III-IV disease. Patients with NYHA classes I-II disease may be administered anaesthesia much as any patient with a normal heart.

b. A technique using controlled ventilation should be used so as to guarantee adequate oxygenation in the face of possible heart failure or pulmonary congestion. These may be exacerbated by the prone or supine positions.

Selection of the most appropriate drugs and techniques to use for general anaesthesia may be done using the tables listing the systemic haemodynamic effects of anaesthetic drugs and techniques in chapter 2.1.

Postoperative.

1. All patients with severe aortic stenosis of NYHA functional classes III-IV should be admitted to an intensive care unit postoperatively for monitoring and therapy of any haemodynamic disorder until cardiovascular stability has been restored.

2. Postoperative mechanical ventilation using adequate analgesia, sedation and muscle relaxation should be considered for those patients with NYHA classes III-IV disease who have a postoperative temperature of less than 35°C. This will prevent further elevation of the SVR due to shivering. Once normal body temperature has returned, mechanical ventilation may be discontinued.

REFERENCES

1. Johnson,L.L., et al.(1978). Reduced left ventricular myocardial blood flow per unit mass in aortic stenosis. CIRCULATION, 57, 582-590.
2. Carabello,B.A., et al.(1980). Hemodynamic determinants of prognosis of aortic valve replacement in critical aortic stenosis and advanced congestive heart failure. CIRCULATION, 62, 42-48.
3. Rapaport,E.(1975). Natural history of aortic and mitral valve disease. AMERICAN JOURNAL OF CARDIOLOGY, 35, 221-227.
4. Greenberg,B.H., Massie,B.M.(1980). Beneficial effects of afterload reduction therapy in patients with congestive heart failure and moderate aortic stenosis. CIRCULATION, 61, 1212-1216.
5. Awan,N.A., et al.(1977). Vasodilator therapy in valvular aortic stenosis: Improved cardiac performance, reduced left ventricular pressure overload and preservation of coronary blood flow. CIRCULATION, 56, Supp. III, 38.
6. Grose,R., et al.(1979). Mechanism of nitroglycerin effect in valvular aortic stenosis. AMERICAN JOURNAL OF CARDIOLOGY, 44, 1371-1377.
7. Linhart,J.W.(1972). Hemodynamic consequences of pacing induced changes in heart rate in aortic stenosis. CIRCULATION, 45, 300-309.
8. Perloff,J.K., et al.(1967). The use of angiotensin in the assessment of left ventricular function in fixed orifice aortic stenosis. CIRCULATION, 35, 347-357.
9. Bay,J., et al.,(1968), Factors influencing arterial PO_2 recovery from anaesthesia. BRITISH JOURNAL OF ANAESTHESIA, 40, 398-407.

Chapter 2.18

AORTIC REGURGITATION

Aortic regurgitation is a relatively "benign" valvular disease in comparison with some of the other valvular disorders. It is characterized by a large pulse pressure, (Corrigan's pulse, or Water hammer pulse), due to regurgitation of blood through the insufficient aortic valve. The disorder causes left ventricular dilation, and hypertrophy, and is associated with elevated left ventricular and atrial pressures which cause pulmonary vascular congestion. Eventually congestive cardiac failure and death may occur.

PROBLEMS

1. Mortality.

As with the other forms of valvular heart disease, the mortality statistics shown in table 2.18.1 for the various grades of severity of aortic regurgitation provide some insight into the severity of the haemodynamic disturbance.

Table 2.18.1.

Mortality after diagnosis of aortic regurgitation [1]. (Medical treatment only).

Acute aortic regurgitation.
Death usually occurs within a period of hours to days
Chronic aortic regurgitation.
All cases - 75% survive 5 years.
- 50% survive 10 years.
Aortic regurgitation + congestive cardiac failure.
- most patients are dead after 2 years.
Aortic regurgitation + angina pectoris.
- average survival is about 5 years.

2. Congestive cardiac failure.

The onset of congestive cardiac failure has a profound effect on the prognosis of aortic regurgitation, causing death in most patients with aortic regurgitation within 2 years after its onset [see table 2.18.1]. The factors predisposing to developing congestive cardiac failure in patients with aortic regurgitation are listed in table 2.18.2.

Table 2.18.2.
Factors predisposing to patients with aortic regurgitation developing congestive cardiac failure within 10 years [2].

Parameter	% Developing failure
Left ventricular enlargement	20-35%
2 or more ECG abnormalities	35%
Left ventricular enlargement + 2 or more ECG abnormalities + DABP < = 40 mmHg +/- SABP > = 140 mmHg	60%

3. Angina pectoris.

The development of myocardial ischaemia also has a deleterious effect upon the prognosis of aortic regurgitant disease [see table 2.18.1].

4. Heart rate.

Elevation of heart rate and tachycardia reduce left ventricular pressures and volume, decreasing the functional valve area, which reduces the percentage regurgitation and so increases the cardiac output [3]. Pulmonary congestion and oedema are allieviated by these changes. Bradycardia has the reverse effects.

5. Systemic vascular resistance.

a. Increased SVR.

Increasing the SVR of patients with aortic regurgitation of functional severity NYHA classes I-III elevates left ventricular pressures, so increasing left ventricular volume, and with it the functional aortic valve area, which in turn increases the regurgitant fraction and

so decreases the cardiac output [4]. All these changes exacerbate the existing haemodynamic disorder.

b. Decreased SVR.

Reduction of the SVR in patients with aortic regurgitation of functional severity NYHA classes II-IV decreases pulmonary vascular pressures and left ventricular pressures and volumes, so reducing the functional aortic valve area, decreasing the regurgitant fraction and so increasing the cardiac output [5,6]. While the cardiac output does increase, arterial blood pressure may not be maintained if the SVR is excessively reduced [5]. The overall effect of SVR reduction is an improvement of systemic haemodynamics.

6. Physical exertion.

In general, physical exertion is well tolerated by persons with aortic regurgitation, and the level of exertion able to be tolerated correlates with the ability to tolerate general anaesthesia and surgery. The cardiac output and pulmonary artery pressures increase, while the SVR decreases slightly in patients with aortic stenosis of functional severity of NYHA classes I-III who engage in any physical exertion [6]. However, exacerbation of pulmonary vascular congestion is a problem during physical exertion, and is the main factor limiting exercise tolerance.

ASSESSMENT

Special attention should be paid to the presence of congestive cardiac failure, angina pectoris and multiple ECG abnormalities. Diuretics used to treat congestive cardiac failure may cause hypovolaemia [see chapter 14.4].

ANAESTHETIC MANAGEMENT

Preoperative.

1. Preoperative congestive cardiac failure should be optimally treated prior to any elective surgery.

2. Preoperative sedation is desirable so as to avoid the haemodynamically disadvantageous consequences of anxiety, i.e. arrhythmias and elevation of SVR. Patients who are hypoxaemic due to heart failure etc, should not receive any sedative drugs preoperatively.

3. Anticholinergic drugs may be administered preoperatively, unless the patient has atrial fibrillation or flutter, or coronary vascular disease.

4. SBE prophylaxis is required for most operations.

Anaesthesia & postoperative.

Same as for mitral regurgitation.

REFERENCES

1. Rapaport,E.(1975). Natural history of aortic and mitral valve disease. AMERICAN JOURNAL OF CARDIOLOGY, 35, 221-227.

2. Spagnuolo,M., et al.(1971). Natural history of rheumatic aortic regurgitation. Criteria predictive of death, congestive heart failure, and angina in young patients. CIRCULATION, 44, 368-380.
3. Judge,T.P., et al.(1971). Quantitative hemodynamic effects of heart rate in aortic regurgitation. CIRCULATION, 44, 355-367.
4. Bolen,J.L., et al.(1976). Evaluation of left ventricular function in patients with aortic regurgitation using afterload stress. CIRCULATION, 53, 132-138.
5. Bolen,J.L., Alderman,E.L.(1976). Hemodynamic consequences of afterload reduction in patients with chronic aortic regurgitation. CIRCULATION, 53, 879-883.
6. Grennberg,B.H., et al.(1980). Beneficial effects of hydralazine on rest and exercise hemodynamics in patients with chronic severe aortic insufficiency. CIRCULATION, 62, 49-55.

Chapter 2.19

INTRACARDIAC SHUNTING

Shunting may occur at atrial, ventricular, and arterial levels, or wherever there is a communication between the left and right hearts. The direction of the principal volume of blood flow through the shunt determines whether it is from left-to-right (LTR) or from right-to-left (RTL).

In LTR shunting blood flows from the left heart into the right, causing the pulmonary blood flow to be greater per unit time than that in the systemic circulation, which is usually normal or near normal.

In RTL shunting blood flows from the right heart into the left, causing the systemic blood flow to be greater per unit time than that through the pulmonary circulation, which is lower than normal, or near normal.

CAUSES

Intracardiac shunting is usually congenital in origin. The most common disorders and their relative frequencies are shown in table 2.19.1.

Table 2.19.1.
Relative frequencies of the most common congenital disorders causing intracardiac shunting.

Disorders causing shunting [1].	
Ventricular septal defect (VSD)	17%
Patent ductus arteriosus	14.5%
Atrial septal defect (ASD)	17.5%
Tetralogy of Fallot	14.5%
Pulmonary stenosis	13%
Potential cause of shunting [2].	
Patent foramen ovale	20%

LEFT-TO-RIGHT SHUNTING

Clinical features.

The major causes of this are atrial septal defect (ASD), ventricular defect (VSD), and patent ductus arteriosus.

Usually pressures in the left atrium and ventricle are higher throughout the cardiac cycle than in the right heart. This causes blood to flow through any atrial or ventricular defect present into the right atrium or ventricle, as a result of which the pulmonary blood flow is greater than the systemic blood flow. Ratios of pulmonary to systemic blood flow of two and more, are associated with clinically significant disease [3,4]. Similarly, the pulmonary artery pressures are also directly related to the severity of the disease, mean pulmonary artery pressures above 20 mmHg being associated with clinically significant disease in patients with ASD [3] and VSD [4].

Problems.

1. Pulmonary congestion/congestive heart failure.

Patients with high pulmonary/systemic flow ratios, and high pulmonary arterial pressures often have pulmonary congestion or oedema. Heart failure may occur, and in fact about 22% of adult patients with ASD have congestive heart failure, and 74% are dyspneic due to pulmonary congestion [3].

2. Systemic vascular resistance.

Increasing the SVR causes the magnitude of the shunt to increase, due to the resulting elevation of left atrial and ventricular pressures. This exacerbates any pulmonary congestion or oedema present. Reducing the SVR has the reverse effect.

Both ASD and VSD are diseases that frequently progress to more severe forms where the pulmonary vascular resistance (PVR) increases until the direction of the shunt reverses, causing RTL shunting with all the consequences of this. Extreme reduction of the SVR may in theory cause shunt direction reversal in patients with clinically more severe forms of ASD or VSD.

3. Pulmonary vascular resistance (PVR).

Elevation of the PVR, e.g. with positive pressure ventilation or PEEP, reduces the degree of LTR shunting. The reverse occurs with reduction of the PVR.

Anaesthetic management.

1. The principles of anaesthetic management are similar to those for mitral regurgitation. The possibility of shunt reversal, and the effects of SVR as well as PVR changes should be taken into account.

2. SBE prophylaxis is required for most operations.

RIGHT-TO-LEFT SHUNTING

Clinical features.

RTL shunting may be caused by reversal of the LTR shunting of ASD, VSD and patent ductus arteriosus as a result of progressive elevation of the PVR, i.e. Eisenmenger's syndrome [5]. Other major causes are the other major congenital heart diseases as listed in table 2.19.1.

The foramen ovale is not sealed shut in 20% of adults (i.e. it is "probe patent"), and functions as a valve kept shut by the left atrial pressure which is normally higher than that in the right atrium. Elevation of right atrial pressures, by pulmonary embolus, PEEP, hypoxia, volume overloading, and right heart failure, in persons with a patent foramen ovale may also cause RTL shunting. This may be the cause of sudden unexplained hypoxaemia in some patients, especially hypoxaemia which is unresponsive to oxygen [2].

Typically, the pulmonary arterial blood flow is equal to, or less than the systemic blood flow. The degree of physical disability is inversely related to the relative resistances of the pulmonary and systemic circulations, a PVR/SVR ratio of 0.5 and more being associated with clinically significant heart disease in patients with VSD [4]. Patients with Eisenmenger's syndrome due to all causes have clinically significant heart disease when the pulmonary artery pressure approaches the arterial blood pressure [5].

Problems.

1. Hypoxaemia.

Hypoxaemia is common, being present in 50% and more of patients with Eisenmenger's syndrome [5], and 64-100% of patients with tetralogy of Fallot [1]. It is a manifestation of low pulmonary blood flow relative to systemic blood flow, and as such is directly related to the magnitude of the shunting.

2. Embolic disease.

Cerebral abscesses, due to passage of bacteria from the venous into the arterial circulation.

Embolism, usually cerebral, may occur due to passage of emboli from the venous into the arterial circulation.

3. Systemic vascular resistance.

Decreasing the SVR increases the degree of RTL shunting, and consequently any hypoxia. The hypoxia in these cases is resistant to oxygen therapy.

Increasing the SVR decreases the degree of RTL shunting, improving pulmonary blood flow relative to systemic blood flow. This has the effect of improving peripheral oxygenation.

Anaesthetic management.

1. Preoperative sedation is not advisable in patients who may already be hypoxaemic.

2. General anaesthesia should be administered with the object of maintaining the SVR at the preoperative level, if not higher, so as not to exacerbate the degree of RTL shunting and hypoxia. The tables in chapter 2.1 may be used to guide the choice of anaesthetic drugs and techniques.

3. Always have a vasoconstrictor drug immediately available during any anaesthetic or surgical procedure in case hypoxia suddenly occurs, or is exacerbated by the procedure. If hypoxia occurs during the perioperative period that is resistant to oxygen therapy, then its most likely cause is worsening, or precipitation of RTL shunting. Administration of the vasoconstrictor drug will elevate the SVR, and reduces the severity of the RTL shunt present, e.g. methoxamine 2 mg/70 kg.

4. Hypovolaemia should be prevented, as it results in reduced left ventricular and atrial pressures, which will exacerbate any RTL shunt.

5. When injecting any drugs, ensure that no air bubbles are injected. Arterial embolization with possible disastrous neurological damage may occur. The same applies to particulate emboli too. Clearing a blocked infusion cannula by flushing the thrombus into the venous circulation may also have disastrous consequences. In the latter situation it is better to insert a new intravenous cannula.

REFERENCES

1. Bonchek,L.I., et al.(1973). Natural history of tetralogy of Fallot in infancy. Clinical classification and therapeutic implications. CIRCULATION, 48, 392-397.
2. Moorthy,S.S., Losasso,A.M.(1974). Patency of the foramen ovale in the critically ill patient. ANESTHESIOLOGY, 41, 405-407.
3. Dave,K.S., et al.(1973). Atrial septal defect in adults.Clinical and hemodynamic results of surgery. AMERICAN JOURNAL OF CARDIOLOGY, 31, 7-13.
4. Weidman,W.H., et al.(1977). Clincal course in ventricular septal defect. CIRCULATION, 56, Supp. I, 56-69.
5. Brammell,H.L., et al.(1971). The Eisenmenger syndrome. A clinical and physiological reappraisal. AMERICAN JOURNAL OF CARDIOLOGY, 28, 679-692.
6. Lumley,J., et al.(1977). General anesthesia in the presence of Eisenmenger's syndrome. ANESTHESIA AND ANALGESIA, 56, 543-547.

Part 3

CARDIAC ARRHYTHMIAS & ANAESTHESIA

Disorders of cardiac rhythm occur frequently during anaesthesia as a result of existing cardiac diseases, electrolyte disorders, hypoxaemia, anaesthetic drugs, increased sympathetic activity etc. The anaesthetist should be familiar with the diagnosis and treatment of all but the most complicated arrhythmias.

This section contains a practically oriented discussion of common arrhythmias together with indications and guidelines for their treatment. The reader is assumed to already have some knowledge of ECG diagnosis of the more common arrhythmias, as this is beyond the scope of this work, in addition to which there are many excellent books on this subject which can be referred to.

The various aspects of the management of cardiac arrhythmias covered are listed below.

- Why is it necessary to treat cardiac arrhythmias?
- When is it necessary to treat a given cardiac arrhythmia?
- What is the treatment, and why?
- Does a given arrhythmia affect the perioperative management of the patient?

Chapter 3.1

CARDIAC ARRHYTHMIAS - GENERAL

Except for arrhythmias such as sinus arrhythmia, sinus tachy- or bradycardia, a cardiac arrhythmia is the product of abnormal electrical activation and/or intracardiac conduction. The latter group of arrhythmias causes the heart to contract in an abnormal manner. While it is true that all arrhythmias do cause abnormal myocardial function, not all arrhythmias require treatment, as the effects of many arrhythmias are such that they exert a minimal effect on systemic haemodynamics. Treatment of cardiac arrhythmias is really only indicated for three main reasons.

- The arrhythmia significantly reduces the cardiac output, so reducing peripheral oxygen and metabolic substrate transport, e.g. rapid atrial fibrillation.
- The arrhythmia causes myocardial ischaemia, e.g. a tachycardia.
- The arrhythmia is associated with a poor prognosis, e.g. ventricular tachycardia.

HAEMODYNAMIC EFFECTS OF ARRHYTHMIAS

The haemodynamic effects of arrhythmias are due to a low cardiac output, and the physiological consequences of this. A low cardiac output causes symptoms and signs related directly to the low output, and baroreflex mediated increased sympathetic nervous activity. The clinical manifestations in conscious persons are listed below.

a. Minimal or normal levels of physical exertion cause rapid exhaustion. The patient may feel chronically tired.
b. Pale or "ashen-grey" hands, face and skin, due to increased sympathetic nervous activity causing peripheral vasoconstriction.
c. Sweating, due to increased sympathetic nervous activity.
d. The patient may feel anxious or nauseated, as a result of increased sympathetic nervous activity and increased plasma catecholamine concentrations.
e. Subjective feelings such as weakness, or a feeling of faintness may be experienced. Consciousness may be reduced in very low output states.
f. The patient may hyperventilate as a response to hypoxaemia and tissue hypoxia.
g. Blood pressure may be normal, or, if peripheral vasoconstriction is inadequate, hypotension may occur.
h. Heart rate depends on the specific arrhythmia.

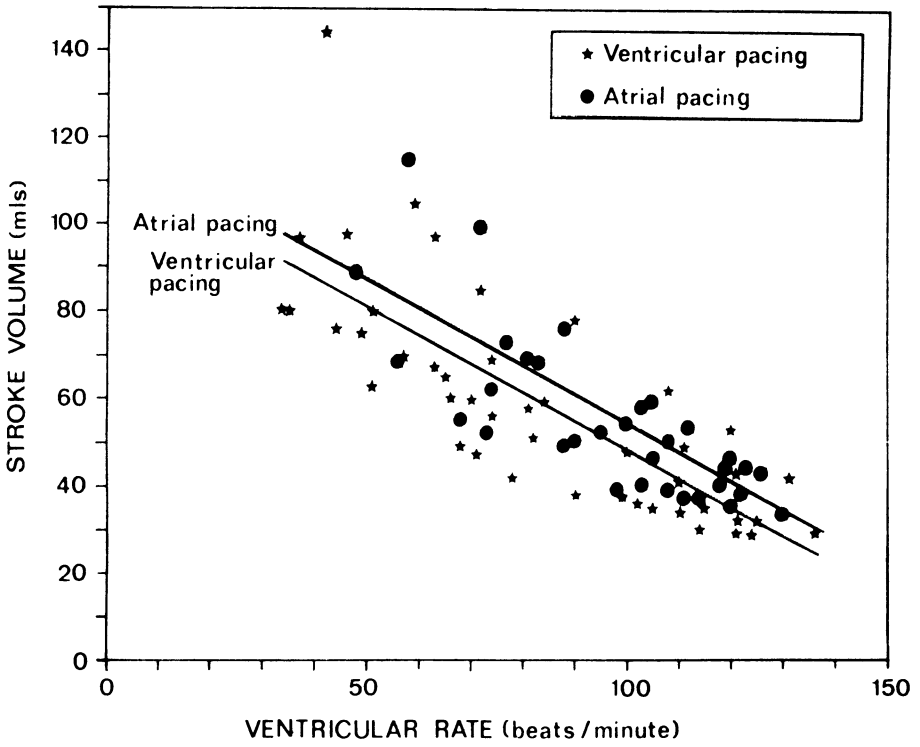

FIGURE 3.1.1. - Stroke volume is related to ventricular rate in healthy patients subjected to both sequential atrioventricular pacing and ventricular pacing. The upper line is the regression line for sequential atrioventricular pacing, Y = 120 - 0.66 x X, (r = 0.79). The lower line is the regression line for stroke volume due to ventricular pacing, Y = 114 - 0.66 x X, (r = 0.79). The data used are from P.Samet et al.[2].

1. Loss of the "atrial kick".

Diastolic filling of the ventricles is mostly passive. Blood flows from the atria down a pressure gradient into the ventricles. Atrial contraction in the last third of diastole increases ventricular end diastolic volume, and contributes about 6-40% of the cardiac output at heart rates between 40-150 beats/minute [1,2]. Atrial facilitation of cardiac output is called the "atrial kick", "atrial assist", "atrial conduction", or "atrial transport". The percentage increment of the cardiac output caused by atrial contraction during diastole increases in direct proportion to the heart rate, and is lower in people with normal hearts than in patients with heart disease [1]. Human studies of persons subjected to ventricular as well as sequential atrioventricular pacing in the same experimental session [1,2], have shown that the increment of the stroke volume due to atrial facilitation of ventricular filling was found to vary with the ventricular rate in the manner shown in figures 3.1.1 and 3.1.2 [2].

An "atrial kick" is absent in rhythms where the atria do not contract, or contract in the wrong part of the cardiac cycle, e.g. atrial flutter or fibrillation, nodal rhythms, etc. Figure

3.1.2 shows that at heart rates below 100-110 beats/minute the difference in stroke volume between patients with, and without an "atrial kick" is minimal, being less than 10%. At ventricular rates greater than 100-110 beats/minute the difference becomes significant, becoming even more pronounced at higher heart rates. Cardiac output in patients with no "atrial kick" falls when the ventricular rate rises above 100-120 beats/minute [see fig. 3.1.3], and in some cases hypotension occurs. Induction of anaesthesia, or reduction of the systemic vascular resistance under these circumstances exacerbates the situation further.

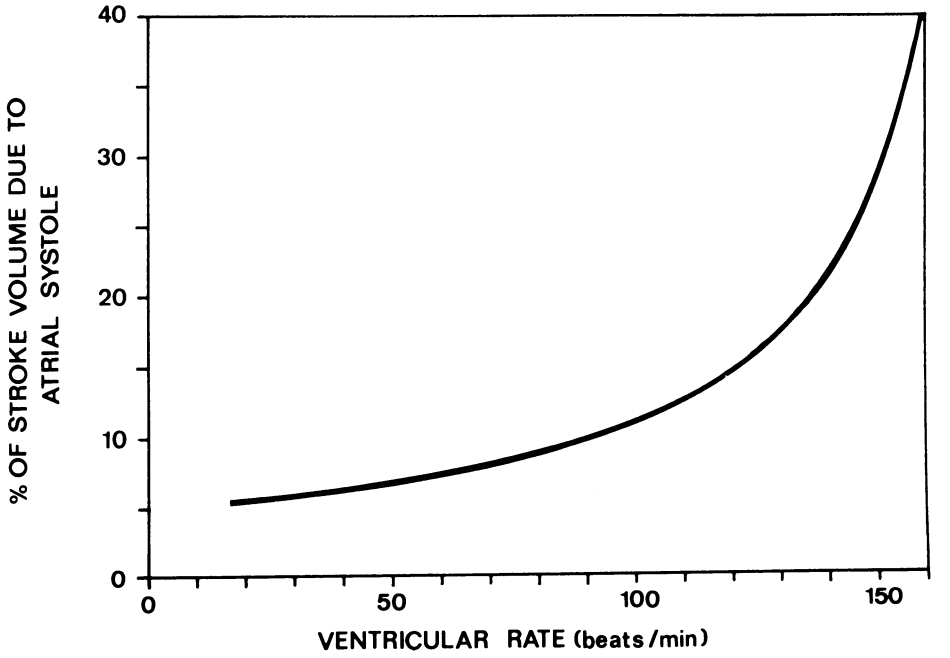

FIGURE 3.1.2. - This figure shows the relationship between the percentage of the stroke volume due to atrial contraction during sinus rhythm, and the heart rate. The curve is described by the equation $Y = 600/(120 - 0.66 \times X)$. The equation is derived from the regression lines of figure 3.1.1.

2. Altered heart rate.

In the normal awake active person, cardiac output is directly proportional to the whole body oxygen consumption, which in its turn is directly proportional to the activity level and metabolic rate [6]. But a person at rest in bed, or under anaesthesia, is in quite a different situation. The oxygen consumption under these circumstances is relatively constant, and so is the cardiac output. Any alteration of cardiac output under these circumstances is due to changing blood volume, systemic vascular resistance, myocardial contractility and heart rate. In the situation where the oxygen consumption, myocardial contractility, blood

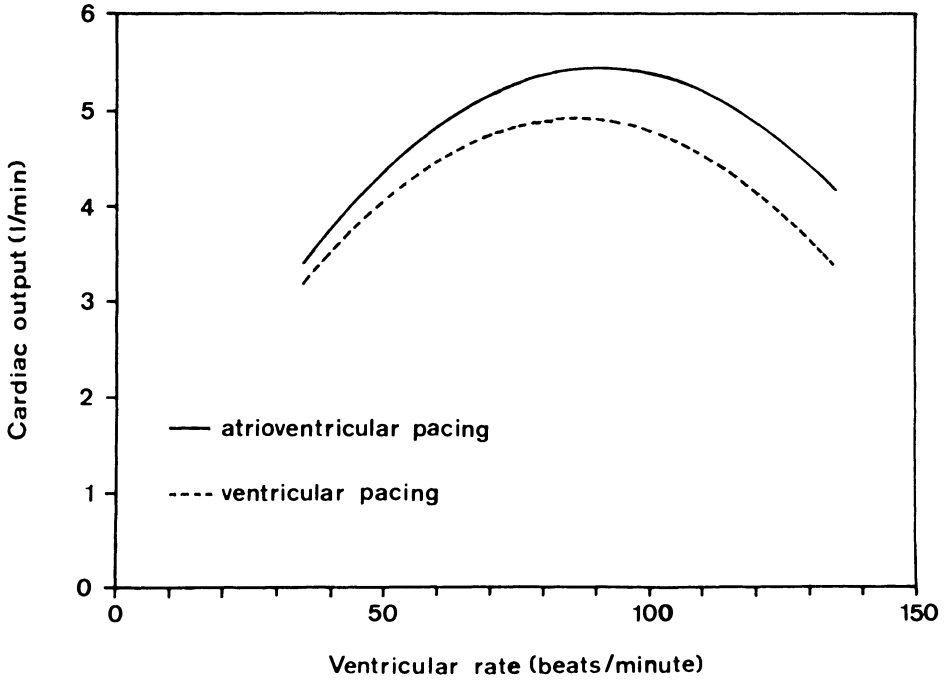

FIGURE 3.1.3. - Cardiac output is shown related to the ventricular rate for normovolaemic patients at rest with a relatively constant systemic vascular resistance and whole body oxygen consumption. The curves were constructed using equations 2 and 3. The cardiac output of persons without atrial augmentation of the stroke volume is significantly less than that of persons with an atrial "kick", except at lower ventricular rates. This relationship between heart rate and cardiac output is generally applicable to all persons at rest with a constant whole body oxygen consumption and systemic vascular resistance, although the actual position of the curves and the magnitudes of the outputs do vary from one person to another.

volume, and systemic vascular resistance are relatively constant, the cardiac output is a function of the heart rate and rhythm.

This relationship has been investigated in normal persons [1], patients with heart disease [1], and patients with total heart block [2], who were subjected to both sequential atrioventricular pacing, or ventricular pacing at various rates while at rest. Cardiac output and stroke volume was always higher during sequential atrioventricular pacing, than during ventricular pacing alone, and cardiac output was directly proportional to the ventricular rate, until the ventricular rate exceeded 80-100 beats/ minute [1,2, fig. 3.1.3].

The relationship between heart rate, stroke volume and cardiac output is in part expressed by equation 1.

$$CO = SV \times HR \quad .....(1)$$

(See Appendix-A for abbreviations).

The regression equations for the relationship of the stroke volume to heart rate in figure 3.1.1 may be used to express the relationship of the cardiac output to ventricular rate (**VR**) [see graphs in fig. 3.1.3, and data from reference 2].

$$\text{Atrioventricular pacing : } CO = VR \times (120 - 0.66 \times VR) \quad .....(2)$$

$$\text{Ventricular pacing alone : } CO = VR \times (114 - 0.66 \times VR) \quad .....(3)$$

It should be stressed that these are regression equations derived for patients with total heart block undergoing atrioventricular or ventricular pacing at different rates while at rest in bed [2]. Because of this these equations are **NOT APPLICABLE TO PERSONS WHO ARE NOT AT REST IN BED OR UNDER ANAESTHESIA.**

However within these limitations, figure 3.1.3 and equations 2 and 3 do show the relationship between heart rate and cardiac output for normovolaemic patients at bed rest, or under anaesthesia, with a relatively constant systemic vascular resistance and whole body oxygen consumption. The exact cardiac output associated with a given heart rate will of course vary from one patient to another. But some conclusions may be drawn which are applicable to adults who are at rest in bed, or under anaesthesia.

- Cardiac output is always greater at any heart rate if there is augmentation of the stroke volume by atrial contraction. This difference is more pronounced at ventricular rates greater than 80-100 beats/minute.
- Cardiac output increases with increasing ventricular rates until a peak cardiac output is achieved at a ventricular rate of about 80-100 beats/minute.
- At ventricular rates of about 120-140 beats/minute, the cardiac output is about the same as that at a ventricular rate of 50 beats/minute, and at rates greater than this the cardiac output is lower than at 50 beats/minute, decreasing with increasing ventricular rate [see fig. 3.1.3, and below for haemodynamic significance of tachycardia].

a. Bradycardia.

Cardiac output decreases with decreasing heart rate at all rates below 100 beats/minute [see fig. 3.1.3]. Clinical manifestations of low cardiac output occur in conscious persons when the ventricular rate falls below 40-50 beats/minute for both sinus bradycardia [4,7], as well as in patients with third degree heart block [3 page 735]. The symptoms of reduced cardiac output usually experienced are weakness, dizziness, vertigo, faintness and syncope. Athletes and healthy young persons may normally have a sinus bradycardia with a rate less than 50 beats/minutes. In these persons such a bradycardia is not pathological and is associated with a normal cardiac output.

The situation during the perioperative period is different. Cardiac output may be reduced by myocardial depression due to anaesthetic drugs [see chapter 2.1], by some

anaesthetic techniques [see chapter 2.1], by hypovolaemia [see chapter 14.4], and by pain and hypothermia induced elevation of the SVR. Under such circumstances cardiac output is significantly lower at any given ventricular rate than it is in conscious normovolaemic persons not undergoing surgery and anaesthesia. In addition to reducing the cardiac output, bradycardia also predisposes to the development of ectopic atrial and ventricular activity [5]. Ectopic activity is even more likely during surgery as a result of increased sympathetic nervous activity, elevated plasma catecholamine concentrations, the effects of drugs used for anaesthesia, and electrolyte disturbances. Elevation of the heart rate inhibits the occurrence of such ectopic activity [5].

A consequence of all the above is that no patient should be accepted for elective operation under general anaesthesia if their ventricular rate is below 40-50 beats/minute. Bradycardia occurring in the perioperative period should be treated if the rate is less than 50 beats/minute.

b. Tachycardia.

Tachycardias of all types reduce the cardiac output if the rate is high enough. Cardiac output is reduced by only one mechanism, the rate of ventricular contraction is so high that the time available for ventricular filling during diastole at normal ventricular filling pressures is inadequate to maintain the cardiac output at that heart rate [see equation 1. in this chapter]. The main difference between the tachycardias as regards the reduction of cardiac output is the rate at which they cause a significant reduction of cardiac output, and this depends on the type of tachycardia.

Tachycardias may be conveniently divided into two basic types on the basis of the presence or absence of an "atrial kick".

i. Tachycardia with "atrial assist".

These are those tachycardias of supraventricular origin in which the atria actively contribute to the filling of the ventricles during diastole. Because an atrial assist is present, the heart rate that may be achieved without a significant fall of cardiac output occurring is much higher than in those tachycardias in which no atrial kick is present [see fig 3.1.3]. Examples of these tachycardias are rapid sinus rhythm, and paroxysmal atrial tachycardia.

In patients at rest in bed, or under anaesthesia, who have a tachycardia with a functional atrial "kick", the cardiac output is maintained at a level greater than the output at a heart rate of 50 beats/minute until the heart rate exceeds 130-140 beats/minute. Therapy should be considered at rates above 130-140 beats/minute.

ii. Tachycardia with no "atrial assist".

This group of tachycardias comprises by far the greater number of different diagnostic types of tachycardias, e.g. fast atrial fibrillation, Wolff-Parkinson-White, ventricular tachycardia, A-V junctional tachycardias etc. All these different types of tachycardias have one thing in common, there is no atrial augmentation of stroke volume. In such a situation the heart rate at which cardiac output begins to fall significantly is lower than that for a tachycardia where atrial contraction augments the stroke volume [see fig. 3.1.3].

The cardiac output of patients with a tachycardia due to a cardiac rhythm without any atrial "kick" who are at bed rest, or under anaesthesia, falls below the level it would be at a rate of 50 beats/minute, when the ventricular rate increases above 110-120 beats/minute. A rate of 100 beats/minute may be considered a threshold ventricular rate at which treatment of rhythms where no "atrial kick" is present should be considered.

iii. General therapeutic considerations for tachycardias.

During tachycardia, the heart rate at which the cardiac output begins to be lower than that existing at a rate of 50 beats/minute is also dependent on the physical condition of the patient, the myocardial contractility, baroreflex function, blood volume, systemic vascular resistance, activity level, whether the person is under general anaesthesia, and the oxygen consumption of the body. Hypotension occurs when the systemic vascular resistance no longer increases to compensate for a decreasing cardiac output.

Ventricular rates at which therapy of a tachycardia should be considered have been mentioned, but these rates should always be regarded as a recommendation which must be applied after taking the clinical condition of the patient into account too. Therapy of a tachycardia should really only be commenced if there is evidence of a clinically significant reduction of cardiac output, hypotension, myocardial ischaemia, or patient discomfort.

RHYTHMS INDUCING MYOCARDIAL ISCHAEMIA

Any rhythm which induces myocardial ischaemia should be rapidly treated. The rhythms most often associated with myocardial ischaemia are the tachycardias [see chapter 2.9].

RHYTHMS ASSOCIATED WITH POOR PROGNOSIS

1. Premature ventricular contractions.

Premature ventricular contractions (PVC's), are thought to predispose to ventricular tachycardias and/or fibrillation in patients with myocardial ischaemia, and shortly after a myocardial infarction. The frequency of the PVC's, and their relation to QRST complexes is of importance, as some types of PVC are more likely to be associated with ventricular tachyarrhythmias. These are listed below.

- When the R-wave of the PVC occurs during the T-wave of the previous QRST complex, the "R on T" phenomenon.
- Multifocal PVC's.
- More than 5-6 PVC's per minute.

2. Mobitz-II rhythm.

Mobitz-II second degree heart block frequently progresses to complete heart block.

3. Ventricular tachyarrhythmias.

Rapid idioventricular rhythms, such as ventricular tachycardia, with a rate of more than 100 beats/minute are also associated with a significant reduction of cardiac output, due to the shortened diastolic time available for passive ventricular filling, in addition to loss of atrial augmentation of ventricular filling [see fig. 3.1.3].

Ventricular tachycardia also predisposes to the development of more malignant arrhythmias.

REFERENCES

1. Benchmol,A., et al.(1965). Hemodynamic Consequences of Atrial and Ventricular Pacing in Patients with Normal and Abnormal Hearts - Effect of Exercise at Fixed Atrial and Ventricular Rate. AMERICAN JOURNAL OF MEDICINE, 39, 911-922.
2. Samet,P., et al.(1965). Atrial Contribution to Cardiac Output in Complete Heart Block. AMERICAN JOURNAL OF CARDIOLOGY, 16, 1-10.
3. Braunwald,E., et al, (1984),"Heart Disease - A Textbook of Cardiovascular Medicine", pub. Saunders.
4. Reiffel,J.A., et al.(1977), Ability of holter electrocardiographic recording and atrial stimulation to detect sinus nodal dysfunction in symptomatic and asymptomatic patients with sinus bradycardia. AMERICAN JOURNAL OF CARDIOLOGY, 40, 189-194.
5. Han,J.,(1971), The concepts of reentrant activity responsible for ectopic rhythms. AMERICAN JOURNAL OF CARDIOLOGY, 28, 253-262.
6. Denison,D., et al.,(1971), Estimates of the CO_2 pressures in systemic arterial blood during rebreathing on exercise. RESPIRATION PHYSIOLOGY, 11, 186-196.
7. Dighton,D.H.,(1974), Sinus bradycardia. Autonomic influences and clinical assessment. BRITISH HEART JOURNAL, 36, 791-797.

Chapter 3.2

ANTIARRHYTHMIC DRUGS

Table 3.2.1.
KINETICS & DOSAGES OF ANTIARRHYTHMIC DRUGS IN ADULTS

DRUG	$T_{1/2e}$ (hrs)	V_d (l/kg)	Cl (l/kg /hr)	MEC (mg/l)	Toxic conc. (mg/l)	Intravenous bolus dose (mg/kg*mg/min)	Infusion rate (mg/hour)
Verapamil	4.8	4	0.71	0.1		0.15*1	5
Amiodarone	25 days	66	0.114	0.5	>2.5	5*20	4
Quinidine	6.2	2.7	0.28	2	>6	6*20	40
Disopyramide	6	0.6	0.072	3		1-2*50	15
Lignocaine	1.8	1.1	0.55	1.5	>9	1-2*50	60
Tocainide	13.5	3	0.156	6		10*25	65
Procainamide	3	1.9	0.71	3	>14	6*20	150
Phenytoin	15	0.64	0.02	10	>20	7*20	13
Aprindine	21.5	3.7	0.156	1		4*10	11
Mexiletine	10.4	9.5	0.62	0.7	>2	7*10	30
Bretylium	8.9	5.9	0.6	0.5	>3	5*20	60
BETA-ADRENERGIC BLOCKING DRUGS							
Propranolol	3.9	3.9	0.72	0.02		0.1*1	1
Pindolol	3.6	2.3	0.5	0.06		0.01*0.1	2
Acebutalol	2.7	1.2	0.41	0.2		0.25*3	1-4
DIGITALIS GLYCOSIDES							
				MEC (µg/l)	Loading dose (mg)	Maintenance (mg/day)	Onset (mins)
Digoxin	39	0.41	0.007	0.8-2.4	0.5-1.5	0.125-0.5	15-60
Digitoxin	6.7 days	0.54	0.003	10-30	0.2-0.3	0.05-0.3	25-120
Oubain	21				0.25-0.5	15-120	

Cl = total body clearance (l/hr/kg). $T_{1/2e}$ = Elimination half life of drug in hours.
V_d = Distribution volume of drug (liters/kg). **MEC** = Minimum effective concentration in mg/l.
Intravenous bolus dose = maximum intravenous bolus dose required for acute treatment, and as a loading dose for an intravenous infusion (mg/kg) * maximum rate of administration (mg/70 kg/min). Only administer one half of this dose initially.
Infusion rate = intravenous infusion rate (mg/70 kg/hour).

KINETIC PARAMETERS AND DOSES OF ANTIARRHYTHMIC DRUGS

Table 3.2.1 gives a view of the clinically most relevant kinetic and dynamic parameters of drugs used for treatment of cardiac arrhythmias. The dosages used are those commonly cited in the literature. They may also be calculated using the pharmacokinetic principles and formulae in chapter 15.1.

EFFECTS AND USES OF ANTI-ARRHYTHMIC DRUGS

Table 3.2.2 gives a simplified view of the effects of the various drugs used in the management of cardiac arrhythmias, and the principal type of arrhythmia for which they are used.

Table 3.2.2.
EFFECTS AND USES OF ANTIARRHYTHMIC DRUGS

DRUG	Type of arrhythmia treated	S-A cycle length	ERP atrium	ERP AV-Node	ERP AVBT	ERP HPS
Atropine	S	↓	↓	↓	?	0
Isoprenaline	S,V	↓	↓	↓	?	0
Digitalis	S	0/↑	↑	↑	↓	0
Propranolol	S	↑	0	↑	0	0
Lignocaine	V	0	0	0	↑	0/↓
Tocainide	V	0	0	0/↓	?	0/↓
Verapamil	S	0/↑	0	↑	↑/↓	0
Disopyramide	S,V	0/↓	↑	↑/↓	↑	0/↑
Procainamide	V	0/↓	↑	0	↑	↑
Quinidine	S,V	0/↓	↑	↓	↑	↑
Ajmaline	V	?	↑	0/↑	↑	↑
Amiodarone	S,V	↑	↑	↑	↑	↑
Aprindine	V	↑	↑	↑	↑	↑

('?' = unknown :'↑' = increase :'↓' = decrease : '0' = no effect)
S = supraventricular.
V = ventricular.
S-A cycle length = sinoatrial node cycle length.
ERP = effective refractory period.
AV-Node = atrioventricular node.
AVBT = atrioventricular bypass tract.
HPS = His-Purkinje system.
Vent = Ventricle.

While such a table appears rather forbidding at first sight, careful study reveals the reasons why the various anti-arrhythmic drugs are used as they are.

Example 1.

Quinidine is sometimes administered to patients with atrial fibrillation prior to electrical cardioversion, but it should never be given to patients with atrial fibrillation unless that patient has been first digitalized. This is because the ventricular frequency in atrial fibrillation is dependent on the rate at which the atrial impulses are transmitted through the AV-Node, and the reduction of the ERP of the AV-Node by quinidine can cause a tachycardia, or increase the rate of an existing tachycardia. Pre-treatment with digitalis glycosides prevents this by increasing the ERP of the AV-node.

Example 2.

Drugs such as amiodarone, aprindine or ajmaline, are not available in some countries, or their cost is prohibitive, or they cause unacceptable side effects in some persons. Combination drug therapy may then be used to treat patients with the Wolff-Parkinson-White syndrome. For example, propranolol may be used to retard AV-Node transmission together with procainamide, quinidine, or disopyramide to retard AVBT conduction.

USE OF ANTIARRHYTHMIC DRUGS

1. Many of the antiarrhythmic drugs can cause myocardial depression. Accordingly they should never be injected rapidly, or the intracardiac concentrations may be so high that significant myocardial depression occurs.

2. Another reason for not injecting antiarrhythmic drugs rapidly, is that rapid injection of a drug that can depress atrioventricular conduction may cause total heart block if the intracardiac concentrations of the drug are very high.

3. Because of the above problems these drugs should never be administered as intravenous boluses without continuous ECG , and regular blood pressure monitoring.

4. The doses recommended in table 3.2.1 are maximum doses. Always administer only half this dose initially, and subsequently administer more as required. The rates of injection are also listed in table 3.2.1.

REFERENCES

1. Braunwald,E., et al, (1984),"Heart Disease - A Textbook of Cardiovascular Medicine", pub. Saunders.
2. Opie,L.H.(1980). Drugs and the heart. LANCET, 1, 693-698.
3. Opie,L.H.(1980). Drugs and the heart - III. Calcium antagonists. LANCET, 1, 806-809.
4. Opie,L.H.(1980). Drugs and the heart - IV. Antiarrhythmic agents. LANCET, 1, 861-867.
5. Opie,L.H.(1980). Drugs and the heart - V. Digitalis and sympathomimetic stimulants. LANCET, 1, 912-918.
6. Gilman,L.S., et al.(1985)."Goodman and Gilman's Pharmacological Basis of Therapeutics", 7th edn., pub. MacMillan.

Chapter 3.3

SPECIFIC CARDIAC ARRHYTHMIAS

This chapter deals with the practical perioperative management of specific common cardiac arrhythmias. It is not intended to be a complete discussion of cardiac arrhythmias, but instead is a discussion of the way that these disorders are viewed and managed by the clinical anaesthetist. Indications for treatment of arrhythmias have been discussed in chapter 3.1. Antiarrhythmic drugs and their dosages have been listed and very briefly discussed in chapter 3.2. If reference is made to a drug without any mention of the dosage, the reader should consult table 3.2.1. It is assumed that the reader is able to diagnose these arrhythmias from a rhythm electrocardiogram (ECG), and it is for this reason that neither example ECG's, nor diagnostic criteria are presented unless it is necessary to illustrate a therapeutic concept.

3.3.1 - SINUS TACHYCARDIA

This is defined as a sinus rhythm with a heart rate > 100 beats/minute. It may caused by physical exertion, pain, anxiety, hypovolaemia, hyperthyroidism, drugs and elevated body temperature.

Sinus tachycardia is nearly always a manifestation of an underlying disorder, or of pain or anxiety. As such, therapy is not required for the tachycardia itself, but the condition causing the tachycardia may require treatment.

Chronic management

Treat the cause if it is pathological, otherwise no treatment is required.

Acute management

As for chronic management.

Anaesthetic management

If the patient has an existing tachycardia, avoid the use of tachycardia inducing drugs, e.g. atropine or pancuronium. Otherwise no other specific anaesthetic technique, drugs or management can be recommended.

3.3.2 - SINUS BRADYCARDIA

Sinus bradycardia is defined as a sinus rhythm with a heart rate < 60 beats/minute. It may be seen in athletes, after myocardial infarction, sick sinus syndrome, or drugs, e.g. ß-blockers.

Bradycardia has been discussed in chapter 3.1. No patient should be permitted to undergo general anaesthesia if the heart rate is less than 40-50 beats/minute. During the perioperative period, bradycardia with a rate less than 50 beats/minute should be treated.

Chronic management

If sinus bradycardia is associated with a symptomatic low cardiac output, as evidenced by syncopal attacks, weakness, fatigability, low exercise tolerance etc, then pacemaker insertion is required. Otherwise chronic management is not necessary.

Acute management

Administer 0.25 mg atropine intravenously. Repeat this dose if it has minimal to no effect. If 1.5-2 mg of atropine has been administered with little to no effect over a period of 15 minutes, then administer an intravenous isoprenaline infusion. The starting dose of the isoprenaline infusion should be 1 µg/min in an adult [see also table 2.2.1]. Pacemaker insertion may be required if the bradycardia is resistant to isoprenaline, or not temporary in nature.

Anaesthetic management

1. If the patient has symptomatic bradycardia of < 40-50 beats/minute preoperatively, then cancel any elective operation and treat the cause.

2. If the heart rate of a patient about to undergo urgent surgery is < 40 beats/minute, consider temporary pacemaker insertion for use in the perioperative period until the cause of the bradycardia has passed, e.g. effects of ß-blocking drugs. A permanent pacemaker can be inserted postoperatively if necessary.

3. If the heart rate falls below 50 beats/minute intraoperatively then the bradycardia should be treated, unless the patient is an athlete and normally has a heart rate below this frequency. Management is the same as for acute management.

4. No special anaesthetic techniques or drugs can be recommended.

3.3.3 - SICK SINUS SYNDROME

This comprises a variety of manifestations of a diseased sinoatrial node.

- sinus bradycardia without a cause.
- sinoatrial arrest.
- tachy-bradycardia syndrome.
- a combination of sinoatrial and atrioventricular conduction disorders.

Chronic management

Pacemaker insertion is required for those with symptomatic bradycardia, syncopal attacks, or other symptoms of a low cardiac output. This may be combined with drug therapy to prevent tachycardia.

Acute management

Treat the arrhythmias as they occur.

Anaesthetic management

1. If the patient is symptomatic, cancel any elective operation, until the arrhythmia has been effectively treated.

2. Avoid the use of atropine so as to minimize the chance of a tachycardia occurring.

3. Otherwise no other specific drugs or anaesthetic techniques can be recommended.

3.3.4 - PREMATURE ATRIAL CONTRACTIONS

These may occur during anaesthesia, as a result of infectious diseases, inflammatory disorders, after myocardial infarction, and due to the effects of drugs.

Occasionally they may cause haemodynamic problems. Frequent premature atrial contractions reduce the efficiency of ventricular filling. Very rarely they may precede or cause ventricular or supraventricular tachycardias.

Chronic management

Treat the cause if known, otherwise treatment is only indicated if they adversely affect systemic haemodynamics.

Acute management

If haemodynamic problems due to a reduced cardiac output occur, then treatment is required. The drug of first choice is verapamil, and of second choice, disopyramide.

Anaesthetic management

1. If the patient has haemodynamically significant premature atrial contractions, delay any elective operation until the arrhythmia has been treated.

2. Symptomatic patients coming for emergency operation should be treated prior to induction of general anaesthesia, as general anaesthesia will reduce the cardiac output even further.

3. No specific drugs or anaesthetic techniques can be recommended.

3.3.5 - ATRIAL FIBRILLATION

Atrial fibrillation may be chronic or intermittent. Chronic atrial fibrillation is usually due to heart disease, but may also occur as a result of thyrotoxicosis, thoracotomy etc.

During atrial fibrillation atrial muscle fibers contract randomly. This generates a barrage of electrical impulses some of which are transmitted to the AV-node. The ventricles are activated by atrial impulses which are transmitted through the AV-node, and the more rapidly such impulses pass through the AV-node, the more rapid the ventricular rate. For this reason, pharmacological therapy of patients with atrial fibrillation is usually directed at increasing the effective refractory period (ERP) of the AV-node. This decreases the rate at which atrial impulses can be transmitted through the AV-node, and reduces the ventricular rate.

During atrial fibrillation the atria contract in an uncoordinated manner, and so there is no atrial contribution to the stroke volume, i.e. there is loss of the "atrial kick" or atrial conduction [see chapter 3.1]. Because of this atrial fibrillation is associated with a significantly reduced cardiac output in comparison with the same heart rate during sinus rhythm, especially when the ventricular rate is more than 100 beats/minute [see figs 3.1.2, and 3.1.3]. Accordingly, therapy of patients with atrial fibrillation is aimed at maintaining a ventricular rate of less than 100 beats/minute.

Chronic management

1. Treat the cause if able to be found, e.g. thyrotoxicosis.

2. Chronic atrial fibrillation is resistant to conversion to sinus rhythm by means of electrical cardioversion or drugs. Because of this therapy is only directed at reducing the ventricular rate by means of drugs.

3. The drugs of choice for chronic management of atrial fibrillation are the digitalis glycosides. Because of their long elimination half lives, they are able to be administered once daily, which makes them eminently suitable for chronic therapy. Digitalis glycosides act by increasing the ERP of the AV-node. If therapeutic plasma concentrations of these drugs are insufficient to lower the ventricular rate below 100 beats/minute, then administer verapamil or a ß-blocker, e.g. propranolol. Both verapamil and the ß-blockers also increase the ERP of the AV-node [see chapter 3.2].

Acute management

1. Acute atrial fibrillation may be successfully converted to sinus rhythm by means of electrical cardioversion. In fact, if an episode of acute atrial fibrillation acutely precipitates or exacerbates heart failure, electrical cardioversion is the treatment of choice. An energy of about 50 Joules is usually recommended for conversion of atrial fibrillation.

If acute atrial fibrillation causes no significant haemodynamic disorder,drug therapy may be employed.

2. If the ventricular rate is > 100 beats/minute, slow intravenous administration of digitalis glycosides is indicated, e.g. intravenous digoxin 0.5 mg injected over 10 minutes. Before administering digitalis glycosides intravenously, the plasma potassium concentration must be > =4 mmol/l, otherwise there is an increased chance of digitalis induced arrhythmias [see chapter 12.3 on hypokalaemia].

3. If the patient has a ventricular rate > 100 beats/minute and is already digitalized with a plasma digoxin concentration which is within the therapeutic range, administration of an AV-node blocking drug such as verapamil, or a ß-adrenergic blocker is required to further reduce the ventricular response rate.

Caution is required when initiating intravenous administration of verapamil or a ß-blocking drug to an already digitalized patient. Hypotension is likely if they are administered too rapidly, as these patients often have poor myocardial function and so are very sensitive to the negative inotropic effects of these drugs. In addition to this they are sensitive to the AV-node blocking effects of these drugs, as their effect is additive to that of the digitalis glycoside. Extreme bradycardia or asystole may occur as a result of incautious rapid administration of these drugs. For these reasons administer these drugs to these patients in small increments until the desired effect is achieved. Table 3.2.1 gives recommended rates of administration, and these should not be exceeded in this situation.

Anaesthetic management

1. Delay any elective operation until the ventricular rate is < 100 beats/minute. This is because the cardiac output in atrial fibrillation at this heart rate is already reduced at this ventricular rate [see figs. 3.1.2, 3.1.3], and induction of anaesthesia will further reduce the cardiac output. Hypotension is likely in this situation as anaesthesia not only further reduces the cardiac output but also reduces the systemic vascular resistance [see chapter 2.1].

2. If the patient is to undergo an emergency operation, treat as in acute management.

3. Do not administer atropine in the premedication, nor any other drug that can cause a tachycardia.

4. Otherwise no specific anaesthetic drugs or techniques can be recommended.

3.3.6 - ATRIAL FLUTTER

This may also be chronic or intermittent, and as with chronic atrial fibrillation, chronic atrial flutter is also usually associated with heart disease.

The problems due to atrial flutter are the same as for atrial fibrillation. Chronic, acute, chronic, and anaesthetic management are also the same as for atrial fibrillation.

N.B. Quinidine is used prior to electrical cardioversion after digitalis pretreatment in both atrial fibrillation and flutter. Quinidine should never be used alone, without pretreatment with digitalis glycosides as it decreases the ERP of the AV-node, and so doing increases the ventricular response rate [see table 3.2.2].

3.3.7 - ATRIOVENTRICULAR (A-V) JUNCTIONAL DISORDERS

A-V junctional arrhythmias have only a minimal effect on systemic haemodynamics, unless the ventricular rate is less than 50 beats/minute. No atrial "kick" is present, and so these arrhythmias also cause a significant reduction of cardiac output if the ventricular rate

is greater than 100-110 beats/minute [see chapter 3.1]. Occasionally other ventricular arrhythmias may be initiated.

A-V junctional arrhythmias commonly occur as a result of digitalis glycoside use, in association with halothane anaesthesia, myocardial ischaemia and infarction, and excessive vagal stimulation.

Chronic management

No treatment is necessary unless the patient is symptomatic.

Acute management

No treatment is necessary unless the arrhythmia has adverse haemodynamic effects. Treatment varies according to whether the problem is a bradycardia or a tachycardia.

Bradycardia is treated the same as sinus bradycardia, while tachycardia is managed in the same way as the paroxysmal supraventricular tachycardias.

Anaesthetic management

1. Elective surgery should be delayed until any symptomatic A-V junctional arrhythmias have been effectively treated.

2. Management of A-V junctional arrhythmias in patients requiring emergency surgery is the same as for acute management.

3. No specific anaesthetic technique or drugs can be recommended.

3.3.8 - PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIAS (PSVT's)

This term describes a range of supraventricular tachycardias. For example paroxysmal atrial tachycardia (PAT), where the P-wave occurs before the QRS complex, and paroxysmal junctional tachycardia where the P-wave occurs during or just after the QRS complex.

Extreme tachycardia is associated with a reduction of the cardiac output due to insufficient time being available during diastole for effective ventricular filling. This manifests clinically as hypotension, or any other manifestation of a reduced cardiac output.

Patients with recurrent PSVT's commonly have no detectable organic heart disease, except for the problem of recurring tachycardia. The cause of tachycardia is re-entrant conduction in all cases. Most of the patients have normal atrioventricular conduction pathways terminating at the AV-node. However one of these pathways is capable of fast retrograde conduction. This is activated by atrial impulses arriving at the AV-node, and conducts impulses retrogradely back to the atria, which upon being activated again transmits impulses anterogradely to the AV-node again. About 15-30% of patients with PSVT's have an abnormal accessory pathway capable of fast retrograde conduction, and which functions in the same way as a retrogradely conducting normal pathway.

The fact that the ventricles are activated by the normal His-Purkinje system, which arises from the AV-node, has a number of significant diagnostic and therapeutic consequences.

- The QRST complexes are normal is shape and duration.

- Ventricular rate is never greater than 200 beats/minute, as the functional refractory period of the AV-node is normally 330-525 milliseconds.
- Because impulses activating the ventricles arise in the atria, and are always transmitted through the AV-node, maneuvers that increase the AV-node refractory period are effective in slowing tachycardia due to a PSVT.

Chronic management

If the episodes of tachycardia are frequent, symptomatic or both, they require treatment. Digitalis glycosides are the drugs of first choice as they only require to be administered once daily. If digitalis glycosides alone are not effective, administer verapamil as well, or a ß-adrenergic blocking drug, or any other drug which also increases the refractory period of the AV-node.

Acute management

1. Carotid sinus massage is the treatment of first choice, and subsequently any other maneuvers to increase vagal tone, e.g. Valsalva maneuver, drinking a glass of water rapidly etc.

2. Should this fail, drug treatment is required. Verapamil or diltiazem are the drugs of first choice. Should one of these fail, or be unavailable, a ß-adrenergic blocking drug may be used, or slow intravenous injection of a digitalis glycoside. If none of these drugs are effective, administer disopyramide, procainamide, or quinidine. These last three drugs all block conduction in the fast retrogradely conducting pathway.

3. If tachycardia induces acute heart failure, or exacerbates existing heart failure, electrical cardioversion with an energy of 50 Joules is indicated.

4. In some cases, an episode of PSVT is triggered by baroreceptor reflexes activated by hypotension in the perioperative period. If the cause of the hypotension is vasodilation, then administration of an α-adrenergic stimulating drug such as methoxamine, phenylephrine, or noradrenaline may be tried. This raises the blood pressure by vasoconstriction, and a subsequent baroreceptor mediated relative decrease in sympathetic tone may terminate the tachycardia in some cases. If hypotension is due to hypovolaemia, then the volume deficit should be corrected prior to attempting any other therapy.

5. Atrial overpacing may also be used to terminate a severe attack.

Anaesthetic management

1. Administer no anaesthesia during an acute attack of PSVT. Cardiovascular depression due to anaesthesia reduces the cardiac output even further. If an episode of PSVT occurs perioperatively, management is the same as for acute management.

2. Avoid the use of atropine or any other tachycardia inducing drugs in the hope that no episode of PSVT will be triggered.

3. No other special anaesthetic drugs or techniques can be recommended.

3.3.9 - WOLFF-PARKINSON-WHITE (WPW) SYNDROME

The Wolff-Parkinson-White (WPW) syndrome is one of a group of arrhythmias called the "pre-excitation arrhythmias". Regardless of the precise aetiology, the clinical manifestations are due to a reduction of the cardiac output due to extremely rapid tachycardia.

In all these syndromes there is an accessory atrioventricular pathway present which does not terminate at the AV-node, but at some other site within the ventricle. The atrial impulses activating the ventricle are not delayed by passage through the AV-node, but activate the ventricle directly by anterograde conduction along the atrioventricular bypass tract (AVBT). Because of this they excite the ventricle before impulses which are conducted through the AV-node do, a phenomenon which is called pre-excitation. The shorter delay between atrial and ventricular activation is seen on the ECG as a shortened P-Q time. As the pre-excitation induced ventricular depolarization does not occur via the His-Purkinje system, the initial rate of ventricular depolarization is slower than normal as ventricular depolarization is "piecemeal". That is, a depolarized section of myocardium depolarizes adjacent sections of myocardium. This process continues until the ventricles are eventually depolarized, or until the atrial impulses conducted through the AV-node and His-Purkinje system rapidly depolarizes the remaining regions of non-depolarized ventricles. This explains the delta-wave typically seen in the ECG of patients with a WPW syndrome.

Tachycardia in patients with a WPW syndrome may be caused by one of two mechanisms.

1. "Re-entrant" tachycardia due to retrograde AVBT conduction.

The cause of tachycardia in many patients with the WPW syndrome is the same as for PSVT, i.e., re-entry. The ventricles are activated via the AV-node. Ventricular activation subsequently activates the AVBT which conducts the signal retrogradely to the atria, reactivating the atria, which initiates the process again. This is called a "re-entrant" tachycardia. Typically the frequency of the tachycardia due to this mechanism is <200 beats/minute because the AV-node refractory period is such that it does not permit transmission of impulses at frequencies much higher than this. The QRS complexes during a tachycardia of this type are normal in duration and form as activation of the ventricles occurs only through the rapidly conducting His-Purkinje system.

2. Tachycardia due to anterograde AVBT conduction.

In some cases tachycardia is due to anterograde conduction of atrial impulses along the AVBT. If the AVBT refractory period is <220 milliseconds, the rate of impulse transmission can be very rapid, permitting very rapid ventricular activation and tachycardia with a rate which may be >200 beats/minute. The ventricular rate may be so fast that ventricular fibrillation may occur. In cases where the rate of the tachycardia is >200 beats/minute, the origin of such rapid atrial impulses is usually atrial fibrillation or flutter. As ventricular activation is via the AVBT, and not the rapid His-Purkinje system, the duration of the QRS complexes is longer than normal due to "piecemeal" ventricular activation.

Chronic management

1. Frequent, haemodynamically significant, or life threatening tachycardias require chronic treatment to prevent their occurrence. The drug of choice is amiodarone, but aprindine may also be used. If these are not available, or cannot be used for various reasons, combination drug therapy to block both limbs of the re-entry loop may be used, e.g. propranolol to

retard conduction through the AV-node, and procainamide to retard conduction in the AVBT. Table 3.3.1 lists a variety of drugs and their actions on the AV-node and the AVBT.

2. Drug resistant recurrent life-threatening tachycardias may be managed with atrial overpacing.

3. Surgical interruption of the AVBT may be performed in persons with frequent life threatening, drug therapy resistant tachycardias.

Table 3.3.1.
Effects of drugs used in treatment of the WPW syndrome on conduction pathways.

DRUG	Refractory period AV-node	Refractory period AVBT
Digitalis	↑	↓
Propranolol	↑	0
Verapamil	↑	↑/0
Lignocaine	0	↑
Disopyramide	0	↑
Procainamide	0	↑
Quinidine	↓	↑
Ajmaline	0/↑	↑
Amiodarone	↑	↑
Aprindine	↑	↑

↑ = increase; ↓ = decrease; 0 = no effect.
AV-node = Atrioventricular node.
AVBT = Atrioventricular bypass tract.

Acute management

1. If tachycardia occurs at a rate <200/minute, and the form and duration of the QRS complex are normal, all indicative of a re-entrant tachycardia, then therapy is the same as for a PSVT.

2. If the ventricular frequency is >200/minute, and the duration of the QRS complex longer than normal, then it is likely that the tachycardia is due to anterograde conduction of atrial fibrillation/flutter impulses along the AVBT to the ventricles. Drug therapy in this situation consists of use of drugs retarding transmission along the AVBT by increasing the AVBT

refractory period. The drug of first choice is amiodarone. If intravenous amiodarone is not available, administer lignocaine, disopyramide, quinidine or procainamide, as these all increase the refractory period of the AVBT [see table 3.3.1]. No digitalis glycosides should be used as these decrease the refractory period of the AVBT and will increase the rate of the tachycardia.

3. If tachycardia is so rapid that cardiac failure or shock occur, consider electrical cardioversion with an energy of 50 Joules. This condition is sometimes difficult to distinguish from ventricular tachycardia. But even if the differentiation is difficult or impossible, the matter is relatively academic as the drug therapy and cardioversion are the same in both situations.

4. Tachycardia due to either of the above mechanisms may be treated with intravenous amiodarone. This is effective treatment for both types of tachycardia [see table 3.3.1].

Anaesthetic management

1. Avoid the use of atropine or other tachycardia inducing drugs. Prevent pain and anxiety by use of adequate analgesia and anxiolytic therapy. Hypovolaemia should be prevented by use of adequate fluid therapy. In other words, manage the anaesthetic so as to minimize the chances of tachycardia in the perioperative period. Otherwise there are no specific anaesthetic guidelines.

2. Treat tachycardia occurring during the perioperative period as in acute management.

3.3.10 - ATRIOVENTRICULAR (A-V) BLOCK

1. First degree block

This is prolongation of the P-Q interval to longer than 0.2 seconds. This may occur in patients with a normal heart, but classically occurs during rheumatic fever, and as a result of digitalis toxicity.

The most significant problem due to first degree heart block is bradycardia. This can reduce the cardiac output to such a degree that clinically significant manifestations of a low cardiac output occur.

Chronic management

Pacemaker implantation is the only treatment available for chronic symptomatic bradycardia.

Acute management

1. No treatment is required unless severe symptomatic bradycardia occurs, in which case 0.25 mg atropine should be administered intravenously. If repeated doses of atropine up to a total dose of 2 mg are administered within 15 minutes are unsuccessful, then an isoprenaline infusion is required, initially at a rate of 1 μg/minute.

2. If the cause of the bradycardia is not transient, consider temporary or permanent pacemaker implantation.

Anaesthetic management

1. Delay any elective operation if a bradycardia with a rate of <40-50 beats/minute is present. If the operation cannot be delayed, consider temporary pacemaker insertion.

2. No particular anaesthetic drugs or techniques can be recommended.

2. Second degree block

a. Mobitz - I.

This is the Wenkebach rhythm. The P-Q interval increases in successive beats until a P-wave is no longer followed by a QRS complex. The whole process then repeats itself. It may be a manifestation of atrioventricular nodal disease, and may occur after myocardial infarction. Drugs such as the digitalis glycosides, ß-blockers, and neostigmine also may induce a Mobitz-rhythm. Sometimes a Wenkebach rhythm occurs in an otherwise perfectly healthy person, and also may occur in athletes. It seldom progresses to a more malignant type of arrhythmia.

No chronic, acute, or special anaesthetic management required, unless it is also associated with a significant bradycardia.

b. Mobitz - II.

Here there are regularly occurring P-waves relating to QRS complexes with a fixed time interval. But at irregular intervals there are periods when the P-wave is generated, but is not followed by a QRS complex for one or more beats. This is called atrioventricular (A-V) block, and represents failure of conduction of the sinoatrial impulse to the ventricle. If the duration of A-V block is longer than one beat, syncopal attacks (Adams-Stokes attacks) may occur as a result of absence of cardiac output in these periods. Mobitz type II block frequently progresses to complete heart block, and so is a rhythm with a poor prognosis.

Chronic management

Permanent pacemaker implantation is required if the patient has syncopal attacks, or haemodynamic disturbances of any sort due to bradyarrhythmias.

Acute management

No treatment is required unless there are episodes of symptomatic bradyarrhythmia as above. If therapy is required, administer intravenous atropine to increase the heart rate. The initial dose is 0.25 mg/70 kg, with repeat doses to a maximum of 2 mg within 15 minutes. If this is not successful, commence an intravenous isoprenaline infusion at an initial rate of 1 µg/70 kg/minute. Subsequent pacemaker implantation is required if episodes of A-V block recur.

Anaesthetic management

1. Delay any elective operation until the arrhythmia has been treated. In the case of emergencies, temporary pacemaker implantation should be considered, or at least an isoprenaline infusion.

2. No specific anaesthetic techniques or drugs can be recommended.

3. Third degree heart block, complete A-V dissociation

Absolutely no atrial impulses are transmitted to the ventricles, which contract at the idio-ventricular rate of about 40-50 beats/minute. Congenital heart block does occur but is rare, and so third degree heart block is usually a manifestation of heart disease. A heart rate of < 50 beats/minute correlates with the occurrence of Adams-Stokes syncopal attacks, and low cardiac output. The cardiac output may be so low as to threaten life or organ function.

Chronic management

Pacemaker insertion is required in symptomatic patients.

Acute management

If the patient is symptomatic, or has a ventricular rate <40-50 beats/ minute, then start an intravenous infusion of isoprenaline, initially at a dose of 1 μg/70 kg/minute to increase the heart rate until a pacemaker can be inserted. Simultaneous cardiopulmonary resuscitation may be required if the cardiac output is low enough to cause circulatory failure.

Anaesthetic management

1. Delay any elective operation. Otherwise management is as in acute management.

2. Techniques causing a reduction of the SVR should not be used. The cardiac output cannot increase in response to baroreflex influences, and so techniques such as spinal and epidural anaesthesia may cause profound hypotension. Otherwise no special anaesthetic drugs or techniques can be recommended.

3.3.11 - BUNDLE BRANCH BLOCK AND BIFASCICULAR BLOCK

1. Left bundle branch block.

This is usually a manifestation of heart disease. No special anaesthetic management is required, except for any disease that may have caused it.

2. Right bundle branch block

No special management is required, except for any disease which may have caused it.

3. Bifascicular block [7,8,9]

This is a condition where there is a right bundle branch block combined with a left anterior hemiblock, or a left posterior hemiblock. Patients with this condition all have cardiac disease, usually ischaemic.

Only one additional hemiblock is required to convert bifascicular block into total heart block. This may occur as a result of a perioperative myocardial ischaemic episode. It was once thought advisable to insert a pacemaker in all patients with bifascicular block prior to any operation. More recent studies have shown that patients with bifascicular block can be divided into three groups.

a. Patients without symptomatic heart disease, but with a bifascicular heart block. These patients do not have an increased risk of developing total heart block, and the perioperative management can be the same as for any other patient coming for that operation.
b. Patients with bifascicular block and symptomatic cardiac disease. For example those with syncopal attacks, heart failure, angina pectoris, Mobitz II block, etc. This group of

patients should be considered for prophylactic preoperative pacemaker insertion, as they have an increased chance of developing perioperative total heart block.

c. Recently it has been found that patients with the combination of right bundle branch block plus left posterior hemiblock, are at a higher risk than normal of developing total heart block. These patients should also be considered for pacemaker insertion prior to any operation.

3.3.12 - PREMATURE VENTRICULAR CONTRACTIONS

Premature ventricular contractions (PVC's) may be caused by myocardial ischaemia, anxiety, or be due to drug or electrolyte effects, and also occur commonly in the aged.

Prognostic significance

1. They have little to no significance in patients with an otherwise normal heart and normal biochemical and physiological condition.

2. Bigeminy, trigeminy, etc are of no significance unless they are associated with haemodynamic dysfunction.

3. Ventricular tachycardia or fibrillation after a recent myocardial infarction, or in patients with cardiac disease may be preceded by;

- more than 5-6 PVC's per minute,
- multifocal PVC's,
- PVC's beginning during the T-wave of a previous QRST complex. This is the "R-on-T" phenomenon.

Chronic management

Chronic therapy is required for patients in category '3' above, especially after a myocardial infarction. In order of preference the drugs used for chronic therapy are; disopyramide, procainamide, quinidine or amiodarone.

Acute management

Therapy is not required for patients in categories 1 and 2, unless there is significant haemodynamic dysfunction. Patients in category 3 should be treated. Before any treatment is commenced, check to see if a treatable cause for the PVC's can be found, e.g. excessive sympathetic nervous stimulation, hypoxaemia, hypercarbia, hypokalaemia, digitalis intoxication, other drugs etc.

In order of preference, the drugs required for acute therapy are lignocaine, disopyramide, procainamide, and amiodarone.

Anaesthetic management

Delay any elective operation in category 3 patients until the patient has been investigated and treated. Otherwise there are no anaesthetic guidelines, except that adequate analgesia is necessary to lessen the chances of myocardial ischaemia or pain, both of which may increase the frequency of PVC's.

3.3.13 - VENTRICULAR TACHYCARDIA

This is an idioventricular rhythm with a ventricular rate > 60 beats/ minute. If the rate is very rapid this may be difficult to distinguish from tachycardia due to PSVT or the WPW syndrome. However the broadened QRS complex is diagnostic in most cases. The main problem is a reduction of cardiac output if the ventricular rate is less than 50 beats/minute, or more than 100-110 beats/minute [see chapter 3.1].

Chronic management

This is required in patients with recurrent tachycardia. The drugs most commonly used are procainamide, quinidine, and tocainide.

Acute management

1. No cardiovascular collapse.

The drug of first choice is lignocaine administered as an intravenous bolus, followed by an intravenous lignocaine infusion. Drugs of second choice are disopyramide, procainamide, etc.

2. With associated cardiovascular collapse.

a. The initial treatment of choice is electrical cardioversion using an energy of 50 Joules. An intravenous bolus of lignocaine should be administered immediately prior to cardioversion and followed by a lignocaine infusion. Drugs of second choice are as above.

b. If ventricular tachycardia is due to drugs such as sympathomimetics, or digitalis glycosides, drug therapy but not electrical cardioversion is indicated. Otherwise the management is the same outlined in acute management.

Anaesthetic management

1. Delay induction of any form of anaesthesia until the episode of ventricular tachycardia has been treated, or spontaneously resolved. General anaesthesia will exacerbate any reduction of cardiac output, and the stress of surgery plus the effects of anaesthetic drugs may increase the frequency of the tachycardia, or precipitate a more malignant arrhythmia.

2. Otherwise no specific recommendations can be made as to anaesthetic management.

3.3.14 - VENTRICULAR FLUTTER/FIBRILLATION

No effective ventricular systole occurs during either ventricular fibrillation or flutter. The absence of cardiac output means that these arrhythmias are a disaster which will rapidly cause the death of the patient if no rapid corrective or resuscitative measures are undertaken.

Management

1. Restore cardiac output with external cardiac massage, and commence artificial respiration to oxygenate the patient. These measures should be continued until the arrhythmia has been treated.

2. Insert an intravenous line, preferably in a central vein.

3. Give calcium chloride/gluconate 1 G to an adult to antagonize the effects of any possible hypoxaemia induced elevation of plasma potassium concentration.

4. Administer sodium bicarbonate 8.4%. The initial dose is usually 1 ml/kg. This reduces any acidosis that may be present [see chapters 13.2 and 13.3 for a discussion on the indication for bicarbonate solutions]. Subsequent doses may be administered according to the acid-base status.

5. Administer an intravenous bolus of 1 mg/kg of lignocaine, both to treat and prevent the occurrence of further ventricular arrhythmias.

6. Subsequently the treatment of choice is electrical cardioversion with an energy of 200-400 Joules.

7. If no measurable cardiac output is able to be achieved with closed chest cardiac massage, either before or after restoration of a functional cardiac rhythm, then administer a bolus of adrenaline of 1 mg to adult patients. This has a vasoconstrictor effect, and results in a higher blood pressure being able to be generated by cardiac massage. At the same time it also has a positive inotropic effect which is useful when a functional heart rhythm is present.

8. Treat any arrhythmia resulting from this therapy.

9. After restoration of a functional cardiac rhythm, the patient should be placed in an intensive care unit for further treatment, and until neurological and cardiac recovery have occurred.

3.3.15 - VENTRICULAR ASYSTOLE

The heart pumps no blood during ventricular asystole, and death will rapidly occur as if no corrective and resuscitative measures are undertaken to restore cardiac output.

Management

1. Begin at once with controlled respiration and cardiac massage to both restore cardiac output.

2. Insert an intravenous line, preferably in a central vein.

3. Administer the following drugs.

a. Administer adrenaline 1 mg/70 kg. The route used may be either intracardiac or intravenous. This elevates the SVR, and so makes heart massage more effective in raising the arterial blood pressure.
b. Administer calcium gluconate/chloride 1 G intravenously to reverse the effects of any hyperkalaemia due to hypoxia [see chapter 12.3].
c. Acidosis should always be corrected in patients with ventricular asystole or ventricular fibrillation. In both cases the patients frequently have a diseased heart, or take drugs which depress myocardial function. Either of these two factors makes the myocardium more susceptible to the effects of acidosis [see chapter 13.2]. Administer sodium bicar-

bonate 8.4% intravenously at a dose of 1 ml/kg to partially reverse the acidaemia that is present. This also increases the efficacy of adrenaline and other inotropic drugs. Further doses of bicarbonate solutions should be administered according to the acid-base status as induction of alkalosis can also have dire consequences [see chapters 13.2 and 13.3].

4. The main principle in the treatment of asystole, apart from the initial resuscitative measures, is to elicit a heart rhythm by any means possible. After a rhythm of some sort has been established, it can then be treated appropriately. Asystole itself is always fatal. A heart rhythm may be initiated by chemical, mechanical or electrical stimuli.

a. Before beginning any cardiopulmonary resuscitative measures administer a "precordial thump". This is a sharp forceful blow to the mid-sternum. In some cases this will stimulate the heart into activity. This is mechanical stimulation of rhythm.
b. Intracardiac or intravenous adrenaline at a dose of 1 mg in an adult may stimulate the heart into some sort of activity. This is chemical stimulation of rhythm.
c. Electrical cardioversion may also elicit a cardiac rhythm which can subsequently be treated. This is electrical stimulation of rhythm.

5. After successful restitution of a functional cardiac rhythm, the patient should be admitted into an intensive care or coronary care unit for further therapy of arrhythmias, acid-base and electrolyte disorders, and until neurological and cardiac recovery has occurred.

REFERENCES

1. Braunwald,E., et al, (1984),"Heart Disease - A Textbook of Cardiovascular Medicine", pub. Saunders.
2. Opie,L.H.(1980). Drugs and the heart. LANCET, 1, 693-698.
3. Opie,L.H.(1980). Drugs and the heart - III. Calcium antagonists. LANCET, 1, 806-809.
4. Opie,L.H.(1980). Drugs and the heart - IV. Antiarrhythmic agents. LANCET, 1, 861-867.
5. Opie,L.H.(1980). Drugs and the heart - V. Digitalis and sympathomimetic stimulants. LANCET, 1, 912-918.
6.Gilman,L.S., et al.(1985)."Goodman and Gilman's Pharmacological Basis of Therapeutics", 7th edn., pub. MacMillan.
7. Pastore,J.O., et al.(1978). Risk of Advanced Heart Block in Surgical Patients with Right Bundle-Branch Block and Left Axis Deviation. CIRCULATION, 57, 677-680.
8. Bellocci,F., et al.(1980). The risk of cardiac complications in surgical patients with bifascicular block: a clinical and electrophysiologic study in 98 patients. CHEST, 77, 343-348.
9. Coriat,P., et al.(1981). Risk of advanced heart block during extradural anaesthesia in patients with right bundle branch block and left anterior hemiblock. BRITISH JOURNAL OF ANAESTHESIA, 53, 545-547.

Chapter 3.4

PACEMAKERS

The function of a pacemaker is to provide a cardiac rhythm that maintains a cardiac output adequate for normal activity, and in extreme situations, an output compatible with life. As such, a pacemaker may be required for maintenance of a normal cardiac output in patients with chronic or repetitive disorders of cardiac rhythm that cause a lethally low cardiac output. These disorders may be either temporary or permanent.

INDICATIONS FOR PACEMAKER IMPLANTATION

1. Permanent pacemaker implantation.

a. Symptomatic sick sinus syndrome, (bradycardia, sinus arrest).
b. Symptomatic extreme bradycardia (< 40 beats/minute).
c. Mobitz II heart block.
d. Total heart block.
e. Demand atrial pacing for recurring atrial tachyarrhythmias.
f. Pacing of patients with bifascicular block.

2. Temporary pacemaker insertion.

a. Inadequate drug therapy of supraventricular tachyarrhythmias prior to anaesthesia and surgery.
b. Drug induced bradycardia where the ventricular rate is < 40 beats/ minute, e.g. due to ß-blocker drugs.
c. Bifascicular block in patients with cardiac symptoms.
d. Any of the indications for permanent pacemaker insertion, until a permanent pacemaker can be inserted.

TYPES OF PACEMAKER [2]

There are many types of pacemaker on the available. The range of functions they offer, and their control methods vary widely. The anaesthetist should inform himself beforehand of the properties of the type of pacemaker possessed by the patient who is to be operated.

PROBLEMS WITH PACEMAKERS [1,2]

1. Changes of plasma potassium concentration.

Normokalaemia is essential for safe and efficient pacemaker function. Plasma potassium should be monitored carefully in patients with pacemakers during surgery. The pain

and stress of surgery can cause hypokalaemia [see chapter 12.3], perioperative fluid shifts, and intravenous infusion fluids also may cause rapidly changing potassium concentrations.

a. Acute hypokalaemia.

Acute hypokalaemia causes a more negative cell membrane potential, i.e. hyperpolarization. This raises the stimulus intensity required to initiate membrane depolarization. The consequence of this can be loss of pacing if the pacemaker stimulus is below the new stimulation threshold.

b. Acute hyperkalaemia.

Acute hyperkalaemia causes a more positive cell membrane potential, i.e. hypopolarization. The result is a lowered stimulus intensity required to initiate cell membrane depolarization. The stimulus intensity of the pacemaker under such circumstances may be well above threshold for the myocardial cell membrane. The possibility even arises that the pacing stimulus may initiate a ventricular arrhythmia.

2. Electrosurgical apparatus.

Electrical apparatus used during surgery, e.g. diathermy, may induce currents within the pacemaker. Such induced currents may seriously interfere with pacemaker function, or even damage it. This is however a problem more likely to occur with older models of pacemaker. New pacemakers are usually protected against current surges. There are a number of solutions to this problem if it occurs.

a. Do not permit the use of electrosurgical apparatus.
b. Ensure that the current flow path of any electrosurgical apparatus used never flows through the regions of the body where the pacemaker and its leads are situated. Bipolar diathermy is to be recommended as the current flow is only through the two tips of the diathermy forceps.
c. Place a strong magnet directly above the pacemaker. Many pacemakers are so programmed that the presence of a strong magnetic field converts the pacemaker into a fixed rate pacemaker, minimizing the effects of other external electromagnetic interference.

3. Cardioversion.

Current flow through a pacemaker as a result of electrical cardioversion may damage the electronic components. Pacemaker function should always be checked subsequent to any cardioversion. Again, this is a problem more likely to affect older models of pacemaker. Newer models usually have protective circuitry which prevents damage due to this cause.

4. Fixed cardiac output.

Most pacemakers provide a maximum pacing rate, or pace at a fixed rate. In either situation the heart has a fixed maximum rate, and any variation of the cardiac output is only provided by variations in the degree of ventricular filling. Because of this the paced heart acts in the same way as a heart with deficient baroreflexes [see chapter 8.6].

ANAESTHETIC MANAGEMENT

1. Most patients carry a card with a description of the type of pacemaker that they have, or alternatively they have the telephone number of their cardiologist who may be contacted for details. Such knowledge is useful for planning the most appropriate form of anaesthesia, and for management of any problems due to interference with pacemaker function.

2. Epidural or spinal anaesthesia cause a significant reduction of the SVR. Patients with a fixed rate pacemaker effectively have a fixed cardiac output, and so may become more hypotensive during this type of anaesthesia than a normal patient, (remember that MABP = CO x SVR). Treatment with a vasoconstrictor drug is required to elevate the SVR and blood pressure in such patients, e.g. phenylephrine, ephedrine.

3. A person with a pacemaker has cardiac disease, otherwise they would not require such a device. In general, any general anaesthetic drugs and techniques may be used that are appropriate for patients with depressed baroreflexes, and a limited ability to increase their cardiac output [see chapter 8.6].

4. ECG monitoring should always be used during any anaesthetic or surgical procedure, so that pacing failure, or arrhythmias can be rapidly detected and treated.

REFERENCES

1. Chung,D.C.,(1983). Anaesthetic problems associated with the treatment of cardiovascular disease: III. Artificial pacemakers. CANADIAN ANAESTHETISTS' SOCIETY JOURNAL, 30, suppl. 3, s1-s4.
2. Zaidan,J.R.,(1984). Pacemakers. ANESTHESIOLOGY, 60, 319-334.

Part 4

RESPIRATORY DISEASE AND ANAESTHESIA

The function of the respiratory system is to oxygenate the blood so that oxygen is available for tissue metabolism. Severe respiratory disease may impair blood oxygenation to such a degree that blood oxygen content is no longer sufficient to sustain life.

Anaesthesia and surgery nearly always exacerbate pulmonary dysfunction, and acute respiratory failure may occur postoperatively in some patients who have preoperative severe pulmonary disease. The anaesthetist must always be aware of this potential problem, and must have a system of preoperative respiratory function assessment which will detect those patients at risk of developing significant exacerbation of existing pulmonary problems as a result of anaesthesia and surgery. With knowledge of the possible consequences, a plan of management may be made for such patients which will minimize the consequences of any possible perioperative exacerbation of existing pulmonary dysfunction.

This section emphasizes these aspects of respiratory disorders, and also discusses the practical management of some of the more common disorders.

Chapter 4.1

BLOOD GASES - ARTERIAL AND VENOUS

Prior to commencing any discussion of the way in which anaesthesia and surgery can affect pulmonary function it is of value to first discuss the physicochemical basis of oxygen transport. The transport and exchange of oxygen and carbon dioxide causes changes in blood, and acid-base status and blood gas values are a reflection of these changes. Normal values of these parameters for arterial and venous blood are shown in table 4.1.1.

Table 4.1.1.
Normal arterial and venous blood gas values for adults.

PARAMETER	ARTERIAL	VENOUS
pH	7.36-7.44	7.34-7.42
PO_2	11.3-13.3kPa(80-100mmHg)	5.5-6kPa(37-42mmHg)
PCO_2	4.8-5.9kPa(36-44mmHg)	5.6-6.7kPa(42-50mmHg)
$[HCO_3^-]$	21-25 mmol/l	21-25 mmol/l
Base excess	+/- 2 mmol/l	+/- 2 mmol/l
O_2 saturation	98%	75%

pH.

This is the negative logarithm to the base 10 of the hydrogen ion concentration.

$$pH = -\log[H^+] \quad .....(1)$$

P_aO_2

The partial pressure of oxygen in arterial blood.

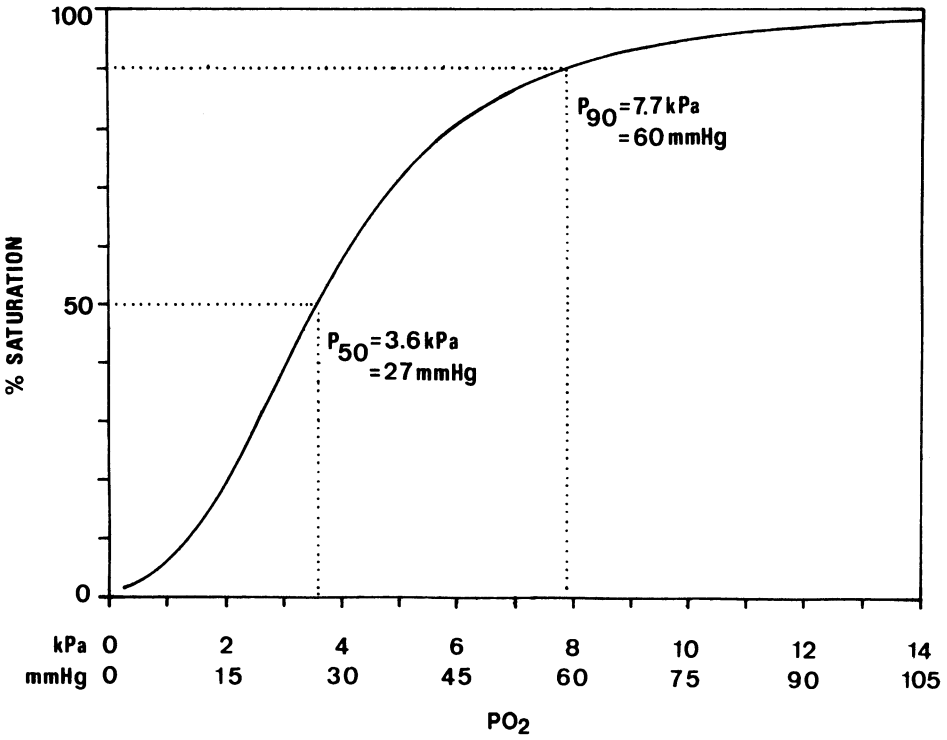

FIGURE 4.1.1. - The normal oxygen-haemoglobin dissociation curve, showing the P_{50} and P_{90} for blood at pH = 7.4, PCO_2 = 5.33 kPa = 40 mmHg, and temperature = 37°C.

Bicarbonate ion concentration [HCO_3^-].

The concentration of bicarbonate ion in the plasma, expressed in millimoles per liter, or milliequivalents per liter.

Base excess.

This is a measure of the acidity or alkalinity of the blood. It is defined as the number of millimoles of an acid or base required to bring the pH of one liter of the blood sample under investigation to a pH of 7.40, if that blood sample is kept at a temperature of 38°C, and at a PCO_2 of 5.33 kPa (40 mmHg).

Oxygen saturation.

This is the percentage saturation of haemoglobin with oxygen. The binding of oxygen to haemoglobin is not linearly related to the partial pressure of oxygen, as is shown by the well known oxygen-haemoglobin saturation curve, [see fig 4.1.1]. The equations describing the oxygen-haemoglobin curve, equations 2,3,4 [1] are set out below, as they are used in other chapters.

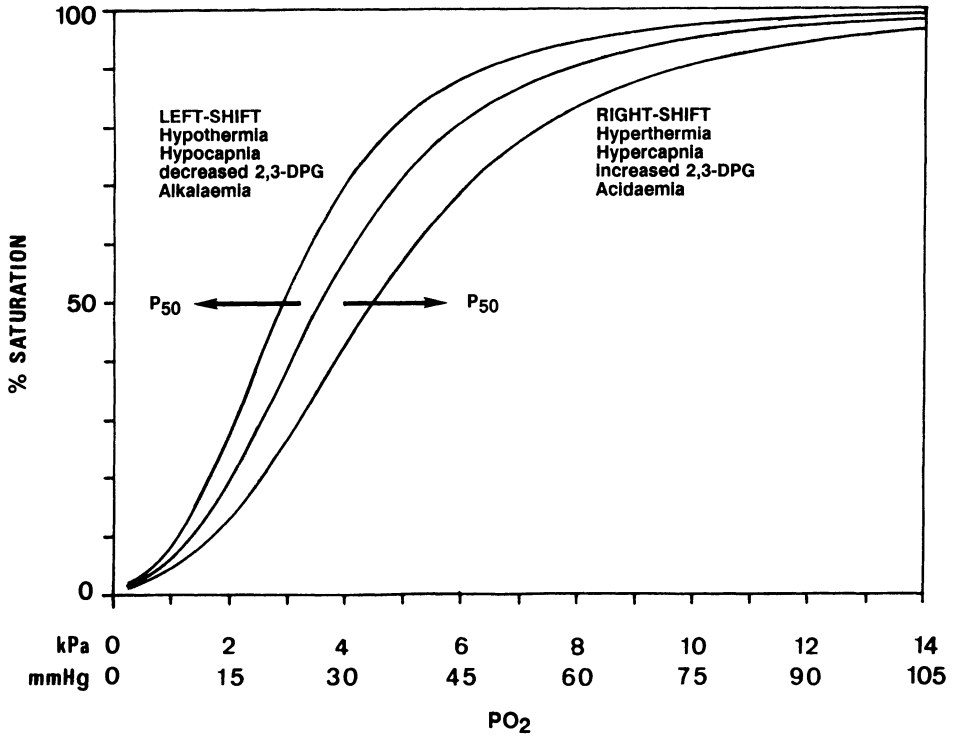

FIGURE 4.1.2. - The normal oxygen-haemoglobin dissociation curve, together with a right- and a left-shifted curve. The principal causes of both right- and left- shifting of the dissociation curve are shown.

$$Z = 0.024(37-T) + 0.4(pH-7.4) + 0.06(1.602-\log_{10}(PCO_2 \times 7.5)) \quad ..(2)$$

and

$$P_V = 7.5 \times PO_2 \times 10^Z \quad .....(3)$$

and

$$SO_2 = 100/(1 + 23400/(P_V(P_V^2 + 150))) \quad .....(4)$$

In some situations it is useful to be able to calculate the PO_2 from the known saturation, pH, PCO_2, and temperature. Equation 5 may then be used.

$$P_V = \exp[0.38 \times \log_e(S/(100-S)) + 3.32 - (S \times 0.72)^{-1} - (S^6/6 \times 10^{12})] \quad .....(5)$$

T = temperature of blood in degrees Celsius.
PCO_2 = measured partial pressure of carbon dioxide in kPa.
PO_2 = the measured partial pressure of oxygen in kPa.
P_V = the calculated virtual partial pressure of oxygen in mmHg.
S, SO_2 = percentage saturation of haemoglobin with oxygen.
(N.B. those wishing to express all gas partial pressures in mmHg should remove the conversion factor "7.5" from equations 2 and 3).

Because of the size and complexity of equations 2,3, 4 and 5 they are not easily used in daily clinical practice, except by those possessing a pocket computer. However some aspects of these equations are useful, and the practical anaesthetist should remember the important points of the curve. These are the P_{50} and the P_{90} for a pH = 7.4 and under conditions of normocarbia and normothermia. These are the partial pressures of oxygen at which haemoglobin is 50% saturated with oxygen (P_{50} = 3.6 kPa = 27 mmHg), and at which haemoglobin is 90% saturated with oxygen (P_{90} = 7.7 kPa = 60 mmHg) [see fig. 4.1.1].

REFERENCES

1. Gabel,R.A.,(1980), Algorithms for calculating and correcting blood-gas and acid-base variables. RESPIRATION PHYSIOLOGY, 42, 211-232.

Chapter 4.2

CALCULATION OF EXPECTED P_aO_2

Chapter 4.1 shows the normal P_aO_2 and P_vO_2 to be expected in healthy young persons with normal respiratory function who are breathing air. But some persons may be breathing oxygen enriched air at the time that arterial blood gases are sampled. The aging process reduces the P_aO_2. Some persons may have abnormal respiratory function. In such situations, simple reference to the normal P_aO_2 of healthy young persons breathing air is inadequate as a means of determining if a P_aO_2 measured in any person is what would be expected for that person, under the clinical circumstances existing at the time of sampling. For this reason a method of calculation of the expected P_aO_2 is developed below which enables the P_aO_2 to be calculated for all values of inspired oxygen concentration. Two obvious examples of the clinical uses to which such an equation may be put are given below.

Example 1.

A patient is brought into a emergency department after an accident. Arterial blood gases measured at the time of admission while the patient is still breathing air reveals that the P_aO_2 is lower than would be expected. That patient has respiratory dysfunction.

Example 2.

During mechanical ventilation in an intensive care unit, or during general anaesthesia, a patient receives a known inspiratory oxygen concentration. If the measured P_aO_2 is significantly less than what could be reasonably expected from the calculated P_aO_2, then that patient has respiratory dysfunction.

VARIATION OF P_aO_2 WITH AGE, BREATHING AIR

P_aO_2 declines with age due to the multiple changes in cardiopulmonary function caused by the aging process. For the normal person breathing air the P_aO_2 declines with age in a manner given by the formulae below [2].

$$P_aO_2(mmHg) = 106 - Age/2 \quad .....(1)$$

OR

$$P_aO_2(kPa) = 14.5 - Age/14.5 \quad .....(2)$$

CALCULATION OF P_aO_2 FOR ANY INSPIRED OXYGEN CONCENTRATION

Many patients with abnormal lung function are administered oxygen. The difference between expected and measured P_aO_2 under such circumstances is a measure of the severity of pulmonary disease. A simple equation to calculate the expected P_aO_2 may be derived using a simplified version of the alveolar air equation [1, pages 384-386].

$$P_AO_2 = (P_{atm} - P_{H2O}) \times F_iO_2 - P_ACO_2/RQ \quad .....(3)$$

F_iO_2 = fractional inspired oxygen concentration.
P_{atm} = atmospheric pressure = 101.33 kPa (760 mmHg).
P_{H2O} = saturated water vapor pressure at BTP = 6.27 kPa (47 mmHg).
RQ = respiratory quotient = CO_2 production/O_2 consumption = 0.8 in normal adults.

Equation 3 above may be simplified assuming that RQ = 0.8, and P_{H2O} = 6.27 kPa;

$$P_AO_2 = 0.94 \times P_iO_2 - 1.25 \times P_aCO_2 \quad .....(4)$$

P_iO_2 = inspired oxygen partial pressure.

The alveolar arterial oxygen partial pressure difference, the $(A\text{-}a)D_{O2}$, varies with age according to equation 5.

$$(A\text{-}a)D_{O2}(kPa) = -0.57 + AGE/17.5 \quad .....(5)$$

Subtracting the $(A\text{-}a)D_{O2}$ in equation 5 from the P_AO_2 in equation 4 yields the P_aO_2. If the assumption is made that the P_aCO_2 is relatively unchanging and constant at 5.33 kPa (40 mmHg), and ignoring the negligible contribution of the correction for saturated water vapor pressure in the lungs, the simple clinically useful equation below, equation 6 may be derived.

$$P_aO_2(kPa) = P_iO_2(kPa \text{ or } \%) - 6 - \frac{Age}{17.5} \quad .....(6)$$

This equation may be used to calculate a rough estimate of the expected P_aO_2 for any given P_iO_2 in adults.

N.B.(1) - As the PO_2 in kPa at standard atmospheric pressure is about equal to the concentration in percent (1 Atm = 101.33 kPa), the P_iO_2 may be given as percentage oxygen concentration or in kPa.

N.B.(2) - This calculated P_aO_2 may be converted to mmHg by multiplying the result by 7.5.

REFERENCES

1. Nunn,J.F.,(1977)."Applied Respiratory Physiology", 2nd edn., pub. Butterworths.
2. Gillies,I.D.S., et al.(1977). Analysis of possible factors influencing P_aO_2 and (P_AO_2 - P_aO_2) in patients awaiting operation. BRITISH JOURNAL OF ANAESTHESIA, 49, 427-437.

Chapter 4.3

OXYGEN CONTENT AND OXYGEN FLUX

Oxygen content and oxygen flux are two important concepts in understanding the meaning of any arterial P_aO_2.

The body requires a minimum amount of oxygen per unit time in order to function properly. In order that this requirement be met, at least that amount of oxygen must be pumped out of the heart into the body per unit time. A given volume of blood contains an amount of oxygen that is dependent upon the P_aO_2 and haemoglobin concentration. This is the oxygen content. Flow of oxygen into the body is dependent on the cardiac output, and the oxygen content of the blood. This is the oxygen flux. The same principles may be applied to the blood flow to a given organ and the oxygen requirement of that organ. Here one speaks of oxygen flux to an organ.

The meaning of these concepts is well demonstrated by the cerebral circulation. Brain tissue requires a relatively large amount of oxygen per unit time. But the volume of blood in the human brain is very small, and the oxygen contained in it is therefore rapidly exhausted. Because of this humans lose consciousness in 6-7 seconds after bilateral occlusion of the carotid arteries [1], or after circulatory arrest. The minimal flow of fully oxygen saturated blood through the brain that is necessary to maintain cerebral function is about 16-17 mls/100 gms brain tissue/minute, [see chapter 2.7]. Assuming a normal haemoglobin concentration, and full saturation of the haemoglobin with oxygen, this means an oxygen flux of about 3.4 mls oxygen/100 gm brain tissue/minute.

BLOOD OXYGEN CONTENT

1 gram of haemoglobin can bind with a maximum of 1.34 mls of oxygen at Body Temperature and Pressure (Saturated) (BTPS). The amount of oxygen dissolved in blood in physical solution is 0.225 ml O_2/l/kPa PO_2, (0.003 ml O_2/100 mls/mmHg PO_2). The oxygen content of blood may thus be calculated.

$$\mathbf{O_2\ CONTENT = SO_2 \times [Hb] \times 0.134 + PO_2 \times 0.03} \quad \text{.....(1)}$$

OR

$$\mathbf{O_2\ CONTENT = SO_2 \times [Hb] \times 0.216 + PO_2 \times 0.225} \quad \text{....(2)}$$

O_2 CONTENT - mls oxygen per liter blood.
SO_2 - percentage oxygen saturation.
[Hb] - haemoglobin concentration, gm/100 mls in 1; mmol/l in 2.
PO_2 - PO_2 as mmHg in 1; and kPa in 2.

N.B. A haemoglobin concentration of 1 mmol/l = 1.612 gm/100 mls.

OXYGEN FLUX

This is the volume of oxygen pumped into the body per minute. It is calculated using equation 3 below.

$$\mathbf{O_2\ FLUX = Cardiac\ Output \times O_2\ CONTENT} \quad .....(3)$$

O_2 FLUX = oxygen flux in mls O_2 pumped out of the heart per minute.
Cardiac Output = cardiac output in l/min.
O_2 CONTENT = oxygen content in mls O_2/l blood.

This formula gives the total amount of oxygen pumped out of the left ventricle per unit time.

EFFECT OF P_{50}

The P_{50}, or degree of right- and left-shifting of the haemoglobin dissociation curve has considerable clinical importance [see chapter 13.2]. Adequate oxygen transport to tissues is not only dependent on the cardiac output and percentage saturation of the haemoglobin, but is also dependent on the partial pressure of oxygen in the capillary blood. It is the difference between the capillary PO_2 and the intracellular PO_2 which is the force driving the diffusion of oxygen from the capillaries into the surrounding cells. Tissue, especially brain hypoxia, begins to occur when the venous PO_2 is less than 2.67 kPa (20 mmHg) [2,3]. Below this PO_2, the capillary oxygen partial pressure is insufficient for enough oxygen to diffuse into cells lying around capillaries rapidly enough to enable normal cellular aerobic metabolism to occur. This PO_2 may be taken as the lowest capillary PO_2 compatible with normal organ function.

In order for oxygen to diffuse into the cells, it must first be released from its bond with haemoglobin. If no oxygen is released from its bond with capillary blood haemoglobin, no oxygen will diffuse out of the capillaries into the cells, even if the capillary PO_2 is much greater than 2.67 kPa (20 mmHg). The P_{50} is an index of the affinity, or strength of the bonding of oxygen with haemoglobin.

Oxygen diffuses out of the blood during its transit through the capillaries, and as a result of this the capillary PO_2 is lower at the venous end of the capillary than at the arterial end. If capillary blood PO_2 drops below 2.67 kPa (20 mmHg) before it reaches the venules, tissue hypoxia is likely. This is because the capillary PO_2 in the region of capillary downstream from the point at which the PO_2 dropped to 2.67 kPa is lower than this level, and is insufficient to drive the diffusion of oxygen into the surrounding tissues at a rate fast enough for normal aerobic metabolism. Such a situation is likely if the P_{50} is low as the oxyhaemoglobin curve is left-shifted, and the affinity of haemoglobin for oxygen is high. This means that little oxygen is released from haemoglobin until the capillary PO_2 is quite low, and this PO_2 may be lower than 2.67 kPa (20 mmHg). A reduction of the P_{50} makes tissue hypoxia likely under conditions of anaemia or increased oxygen consumption, even at quite high levels of arterial saturation and P_aO_2. Some of the more common causes of left-shifting of the oxyhaemoglobin curve are alkalosis, hypothermia, hypocarbia, and reduced 2,3-DPG concentration [see figure 4.1.2]. Chapter 13.2 contains a discussion of the

effects of extreme alkalosis on oxygen delivery, a typical example of the effects of a reduced P_{50}. Another example is given below.

Example showing effect of changing the P_{50}.

Alkalaemia reduces the P_{50}. Consider a theoretical patient with a cardiac output = 6 l/min, arterial SO_2 = 98%, [Hb] = 8 mmol/l = 12.8 gm/100 mls, and blood pH = 7.38. Let the P_vO_2 = 2.67 kPa = 20 mmHg, which means that the mixed venous SO_2 = 31%. These parameters mean that the total body oxygen consumption is 695 mls/minute [use equations 2 and 4 in this chapter to calculate this]. Suddenly, because he has been administered sodium bicarbonate, his blood pH increases to 7.6, while cardiac output, oxygen consumption, and [Hb] remain the same. But at pH = 7.6 the mixed venous SO_2 = 42.8% at a P_vO_2 = 2.67 kPa = 20 mmHg [see table 13.2.2]. Let us calculate the oxygen delivery possible at this new pH before tissue hypoxia becomes likely. This is also able to be calculated using equations 2 and 4 in this chapter. The result is that an oxygen delivery of only 572 mls/minute is possible before the P_vO_2 drops below 2.67 kPa = 20 mmHg. But as the oxygen consumption of this hypothetical patient has stayed unchanged at 695 mls/minute, this patient requires more oxygen per minute than is delivered, and so tissue hypoxia will occur.

The effects of increased P_{50}, or right shifting of the oxyhaemoglobin curve, are the reverse of those of those of left shifting. Release of oxygen is greater than normal, and tissue oxygenation is enhanced at all levels of PO_2.

MINIMUM PERMISSABLE ARTERIAL OXYGEN SATURATION

The brain is the organ most sensitive to the effects of hypoxaemia. Electroencephalographic evidence of cerebral hypoxia occurs at a jugular venous PO_2 of 2.67 kPa = 20 mmHg [2,3]. Using this as a minimum acceptable venous PO_2, and rearranging the Fick equation, an equation giving the minimum arterial SO_2 compatible with normal cerebral function can be derived. The amount of oxygen dissolved in physical solution may be ignored at lower levels of P_aO_2 without any loss of accuracy.
The Fick equation is;

$$\mathbf{V_{O2} = CO \times (C_aO_2 - C_vO_2)} \quad \text{.....(4)}$$

$\mathbf{V_{O2}}$ = body oxygen consumption in mls/minute.
$\mathbf{CO}$ = cardiac output in l/min.
$\mathbf{C_aO_2}$ = concentration of oxygen in arterial blood in ml/l.
$\mathbf{C_vO_2}$ = concentration of oxygen in venous blood in ml/l.

Substitution of equation 2 into 4 after removing the term for dissolved oxygen, and rearranging leaves equation 5 below.

$$\mathbf{S_aO_2} = \frac{\mathbf{V_{O2}}}{\mathbf{0.216 \times [Hb] \times CO}} + \mathbf{S_vO_2} \quad \text{....(5)}$$

[Hb] = haemoglobin concentration in mmol/l.
$\mathbf{S_aO_2}$, $\mathbf{S_vO_2}$ = arterial and venous percentage oxygen saturation.

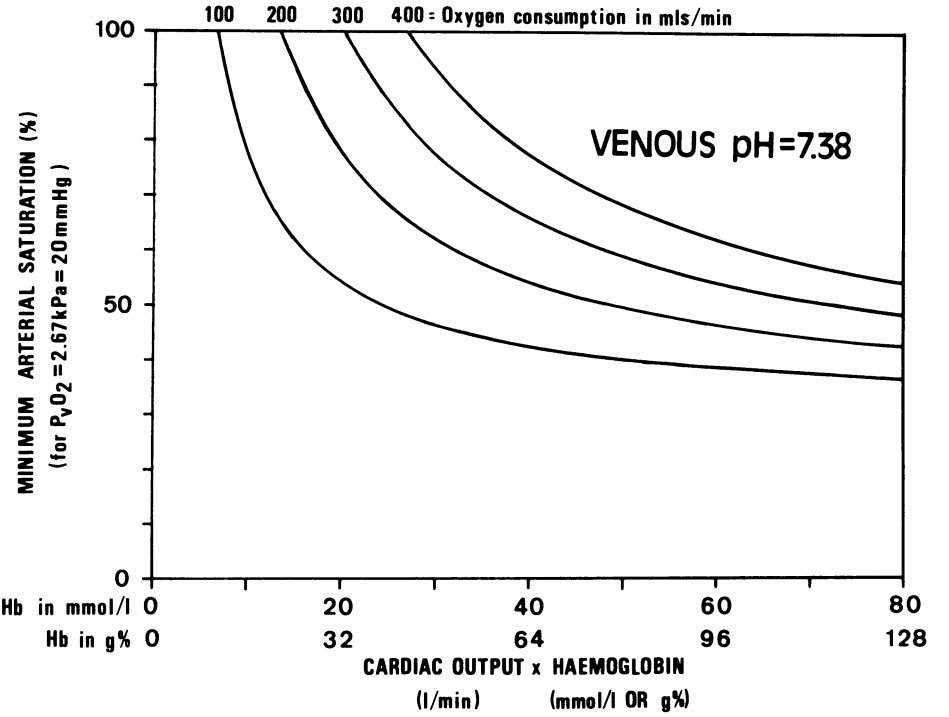

FIGURE 4.3.1. - The minimum percentage arterial oxygen saturation of haemoglobin that is required to prevent cerebral hypoxia occurring is related to the **CARDIAC OUTPUT x HAEMOGLOBIN CONCENTRATION PRODUCT** for various levels of oxygen consumption. This series of curves assumes normal plasma pH, and that cerebral hypoxia occurs when the jugular venous PO_2 is lower than 2.67 kPa (20 mmHg). If the measured arterial oxygen saturation is less than that indicated by the graph for a given oxygen consumption and CO x [Hb] product, then tissue and cerebral hypoxia are likely.

Equation 5 may be used to calculate the minimum S_aO_2 above which tissue hypoxia, especially brain hypoxia, will not occur. The jugular venous PO_2 below which cerebral hypoxia becomes likely is 2.67 kPa, which means a S_vO_2 = 31% at a venous pH = 7.38. The assumption may be made that venous pH is nearly equal to arterial pH. Equation 5 may then be rewritten for the situation of normocarbia using the S_vO_2 = 31%. This equation allows the minimum S_aO_2 for any given level of oxygen consumption, cardiac output and haemoglobin concentration to be calculated. Tissue hypoxia, especially brain hypoxia, is likely to occur if the measured S_aO_2 is lower than that calculated by equation 6, or given by figure 4.3.1.

$$S_aO_2(\text{minimum}) = \frac{V_{O2}}{0.216 \times [Hb] \times CO} + 31 \quad \text{.....(6)}$$

Example 1.

An example of the use of equation 6 and figure 4.3.1 is the threshold of unconsciousness due to acute hypoxia. Unconsciousness due to hypoxaemia occurs at a P_aO_2 of 3.3-4 kPa (25-30 mmHg) in healthy humans made acutely hypoxic [4]. Assuming maximal ability to increase the cardiac output, and a normal haemoglobin concentration, a [Hb] x CO product of 80 may be assumed if the [Hb] = 8 mmol/l = 13 gm/100 mls and the CO rises acutely to 10 l/min. An awake, but totally inactive young adult consumes oxygen at a basal rate of about 300 mls/minute. From these data, and using figure 4.3.1, the threshold of unconsciousness due to cerebral hypoxia may be expected to occur at an S_aO_2 of about 50%. Such a saturation corresponds with a PO_2 of 3.6 kPa (27 mmHg), corresponding quite well with the experimentally measured value. Increasing the cardiac output to levels such as 20 l/min reduces the minimum S_aO_2 compatible with consciousness to about 40%.

Example 2.

A patient who is elderly, ß-blocked, has a fixed rate pacemaker, or has heart disease, often simply cannot increase his cardiac output to even 10 l/min. Unconsciousness and general tissue hypoxia, due to acute hypoxia will occur at a much higher S_aO_2 in such a person. For example consider such a sick, septic, ß-blocked elderly patient who has lost blood during surgery, and who can only increase his cardiac output to a maximum of 6 l/min, has a [Hb] = 5 mmol/l = 8 gm/100 ml, and a basal oxygen consumption increased by surgery and sepsis to 400 mls per minute. Such a patient is likely to develop tissue hypoxia and become unconscious at an S_aO_2 = 93%, which as is seen from the oxyhaemoglobin dissociation curve is about equal to a P_aO_2 of 8 kPa (about 60 mmHg). Such a P_aO_2 is not uncommon in such sick patients. A blood transfusion to increase the haemoglobin concentration will lessen the risk of tissue hypoxia, as will administration of an inotropic drug to increase the cardiac output.

Example 3.

Let us consider the effects of a blood transfusion or inotropic therapy on the patient of example 2.

a. A blood transfusion to elevate the [Hb] to 6.7mmol/l = 10.7 gm/100 mls while the cardiac output remained at 6 l/min would alter the situation such that tissue hypoxia would only occur once the S_aO_2 dropped below 77.3%. This is a large improvement, and well demonstrates the value of a blood transfusion in such patients.
b. The same effect can be achieved by increasing the cardiac output to 8 l/min by an inotropic drug, or an inotropic/vasodilator drug combination. Here the CO x [Hb] product would also be equal to 40. This is a solution which obviously has application as a temporary measure until blood can be fetched. Because the cardiac output must be elevated this solution is not recommeded for patients with severe ischaemic heart disease.

IMPLICATIONS OF THE CONCEPT OF OXYGEN FLUX

1. If the haemoglobin concentration falls, the cardiac output must increase, or the S_vO_2 decrease, to maintain the same oxygen delivery.

2. If the P_aO_2 falls the cardiac output must increase, or the S_vO_2 decrease, to maintain the same oxygen delivery.

3. A person with a low cardiac output is more likely to develop tissue hypoxia at any given haemoglobin concentration and P_aO_2 than a person with a higher cardiac output. If the patient has cardiovascular disease, or is hypovolaemic, the cardiac output cannot increase, and tissue hypoxia will occur at a higher haemoglobin concentration and P_aO_2 than in a person with the same haemoglobin concentration, but whose cardiac output can increase.

N.B. The clinical consequences of the concept of oxygen flux and P_{50} are discussed further in chapters 5.1, 13.2 and 13.3.

REFERENCES

1. Rossen,R., et al.,(1943). Acute arrest of cerebral circulation in man. ARCHIVES OF NEUROLOGY AND PSYCHIATRY, 50, 510-528.
2. Gotoh,F., et al.,(1965), Cerebral effects of hyperventilation in man. ARCHIVES OF NEUROLOGY, 12, 410-423.
3. Meyer,J.S., et al.,(1965), Effects of anoxia on cerebral metabolism and electrolytes in man. NEUROLOGY, 15, 892-901.
4. Refsum,H.E.,(1963), Relationship between state of consciousness and arterial hypoxemia in patients with pulmonary insufficiency breathing air. CLINICAL SCIENCE, 25, 361-367.

Chapter 4.4

RESPIRATORY FUNCTION TESTS

At the present time it is possible to have a large number of pulmonary function tests performed in the lung physiology laboratory attatched to many large hospitals. In fact the clinician is sometimes overwhelmed by the amount of information presented. But what the physician wishes to know from these test results is simply what the clinical implications of any abnormal test results are. The purpose of this chapter is to provide a simple explanation of the clinical implications of the most commonly measured respiratory function tests.

Table 4.4.1.
NORMAL VALUES FOR RESPIRATORY PARAMETERS IN ADULTS [1,2,3,4]

Oxygen consumption (V_{O2})		4 mls/kg/min
Carbon dioxide production (V_{CO2})		3 mls/kg/min
Respiratory rate (**RR**)		12-16 breaths/minute
Tidal volume (V_T)		7-10 mls/kg
Minute volume (**MV**)		100 mls/kg/min
Anatomical dead space (V_{da})		2.2 mls/kg
Total lung capacity (**TLC**)	Male =	94 x HEIGHT(cms) - 9800 (mls)
	Female =	79 x HEIGHT(cms) - 7800 (mls)
Vital Capacity (**VC**)	Male =	51 x HEIGHT(cms) - 4300 (mls)
	Female =	33 x HEIGHT(cms) - 2300 (mls)
	OR =	52 mls/kg for males and females
Functional Residual Capacity (**FRC**)		46.4 x HEIGHT(cms) - 6040 mls
Closing Capacity(**CC**)/**FRC** (supine)		0.64 + 0.01 x AGE
Forced Expiratory Volume in one second (FEV_1)		0.75 x VC mls
FEV_1/VC		> 0.75
Maximum Breathing Capacity (**MBC**)		35 x FEV_1 liters/min
Peak Expiratory Flow Rate (**PEFR**)		710 - 4.5 x AGE(yrs) l/min
Resting P_aO_2 (air)		109 - AGE/2 mmHg 14.5 - AGE/14.5 kPa
(**A-a**)D_{O2} (supine)		- 0.57 + AGE/17.5 kPa

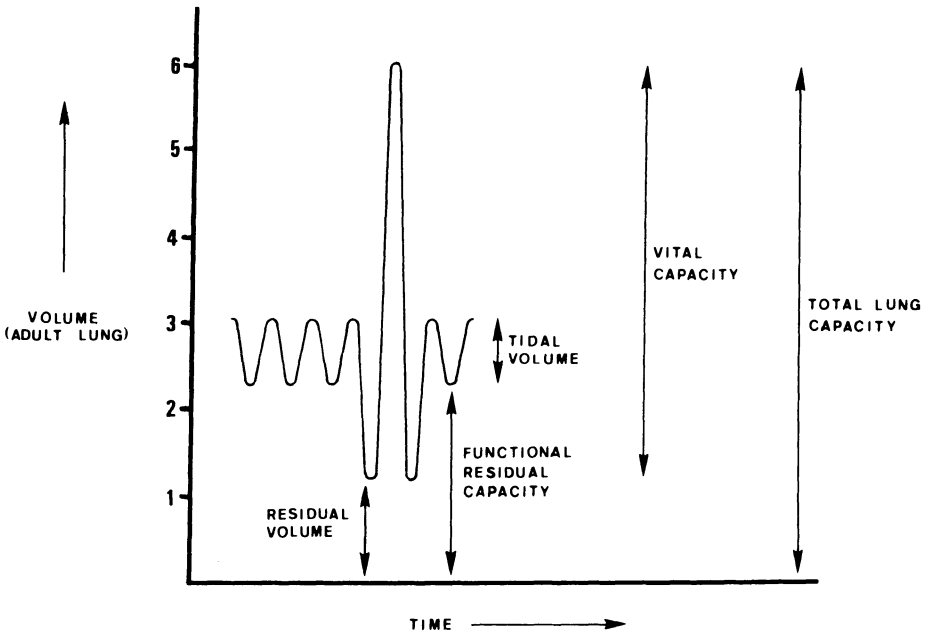

FIGURE 4.4.1. - Drawing of a spirometer tracing showing the various lung volumes in liters for adult lungs.

LUNG VOLUMES

The time available for gas exchange during a respiratory cycle is limited. Within that time CO_2 must be eliminated, and enough oxygen must diffuse from the alveoli into the blood for metabolic requirements.

In order that enough oxygen can diffuse into the blood, and CO_2 out of the blood, within the time available, gas exchange must take place across a minimum given area of alveolar membrane, that is within a minimum lung volume. If the static and dynamic lung volumes that are measured for any particular person are less, or more than is normal for that person's age, body weight, and sex, the existence of abnormal pulmonary function is likely.

The usual lung volumes measured are Vital Capacity (VC), Functional Residual Capacity (FRC), Closing Capacity (CC), Residual Volume (RV), Dead Space, and Total Lung Capacity (TLC). These are commonly measured with a spirometer, and/or body box technique in a pulmonary physiology laboratory, although devices for bedside measurement of these parameters are becoming increasingly available. These volumes are defined below, and shown in figure 4.4.1.

1. Total Lung Capacity (TLC).

The total volume of gas in the lungs after a maximal inspiration.

2. Expiratory Vital Capacity (VC).

This is the volume of gas measured during a maximal forceful exhalation, which has been preceded by a maximal inhalation.

3. Residual Volume (RV).

The volume of gas left in the lungs after a maximal expiration.

4. Tidal Volume (TV).

This is the volume of gas inhaled or expired during a normal respiratory cycle.

5. Functional Residual Capacity (FRC).

The volume of gas left in the lungs at the end of tidal expiration.

6. Dead Space.

This may be anatomical or physiological. In either case it may be defined as the volume within the respiratory system in which gas exchange does not occur.

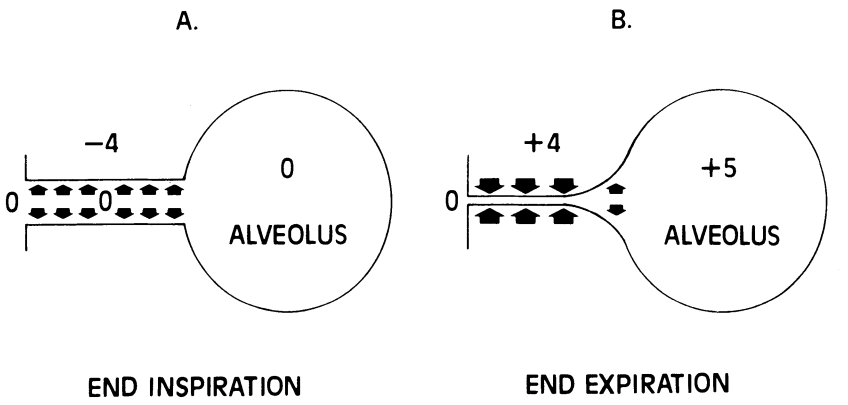

FIGURE 4.4.2. - Closing capacity. At the end of inspiration the pressures inside the alveoli and small airways are greater than the intrapleural pressure, as is depicted in A. During expiration to residual volume, a lung volume occurs at which intrapleural pressure exceeds that inside the small airways, as is depicted in B. The small non-cartilagenous airways then close, trapping the remaining gas in the alveoli. This lung volume is the closing capacity.

7. Closing Capacity (CC), or Closing Volume (CV).

This is that lung volume during expiration at which closure of small airways occurs, trapping gas in the alveoli distal to the closed airway.

During expiration the intrathoracic pressure increases, and eventually the intrathoracic pressure is so increased that small airways closure occurs. The airways affected are the small non-cartilagenous airways, which close because the pressure outside those airways is greater than that within the airways. This is shown diagrammatically in figure

4.4.2. As the gas in the regions of lung where this occurs is not as completely refreshed with each new breath, as it is in lung regions where airway closure does not occur, the PO_2 in those regions decreases, and the PCO_2 increases. That is, there is hypoventilation of those regions of lung where such air-trapping occurs. This occurs mainly in dependent regions of the lungs, as the intrapulmonary and intrapleural pressures are highest here due to the effects of gravity on the lungs.

The practical anaesthetist should remember that the CC increases with age, and that in the healthy adult;

- at 20 years of age CC < FRC in the supine awake person.
- at 40 years of age CC = FRC in the supine awake person.
- at 60 years of age CC = FRC in the standing awake person.

INDICES OF HYPOVENTILATION

An example of a hypoventilated lung volume is the functional residual capacity (FRC). This is the gas volume remaining in the lungs at the end of a tidal expiration. At the end of expiration this gas remains in the lungs, and because gas exchange still continues across the alveoli during expiration, the PCO_2 in this gas volume continues to increase, and the PO_2 to decrease. This gas then mixes with the fresh inspired gas, reducing the PO_2 and increasing the PCO_2 of the gas mixture in the alveoli so that the end-inspiratory alveolar gas composition is never the same as the inspired gas composition. The volume of lung which makes up the FRC is therefore hypoventilated, as the gas in this volume is never completely refreshed with each respiratory cycle.

If the FRC/TLC ratio is larger than normal, as occurs in patients with chronic obstructive airways diseases, the volume of CO_2 rich, and O_2 poor gas which then mixes with the fresh inspiratory gas is also greater than normal, and as a result the end-inspiratory alveolar PO_2 is lower, and the end-inspiratory PCO_2 is higher than normal. This is pathologically increased hypoventilation, and if extreme enough actually causes hypoxaemia and hypercarbia. Hypoventilation not only predisposes to hypoxaemia and hypercarbia, but also predisposes to absorbtion atalectasis.

It is apparent from the above discussion that indices of hypoventilation are therefore measures of how much gas remains in the lungs at the end of an expiration relative to the VC, TLC or FRC. Such indices are therefore all ratios using one of these three parameters as a denominator. Indices of hypoventilation are: FEV_1/VC, CC/FRC, RV/TLC, VC/TLC, RV/TLC etc.

General anaesthesia and surgery both increase all measures of hypoventilation, and should a patient have a greater than normal hypoventilated lung volume, this will certainly be greater postoperatively, with as a result the patient will develop a greater than normal degree of postoperative hypoxaemia and hypercarbia.

INDICES OF OBSTRUCTION TO GAS FLOW

Obstruction to respiratory flow has a number of deleterious effects.

a. Obstruction to expiratory gas flow causes hypoventilation.

If there is obstruction to expiratory gas flow so that a given level of respiratory minute ventilation cannot be maintained, the increasingly larger volumes of gas remaining in the

lung at the end of inspiration increases the intrapulmonary gas pressures, increasing the pressure driving gas out of the lungs, so that eventually the required expiratory volume can be exhaled within the time available for this. This manifests as an increased FRC/TLC ratio, the effect of which is to cause pathologically increased hypoventilation, e.g. as is present in patients with chronic obstructive airways disease.

b. Obstruction to inspiratory flow also causes hypoventilation.

Obstruction of inspiratory gas flow limits the volume of gas entering the lung, and so limits gas flow out of the lungs too. The effect of this is that hypoventilation occurs if respiratory muscle activity is unable to maintain normal gas exchange.

c. Obstruction to expiratory gas flow impairs clearance of bronchial secretions.

A patient with severely impaired ability to generate a sufficiently high expiratory flow rate, e.g. during coughing, is unable to cough bronchial secretions out of the lungs, and so has an increased chance of developing pulmonary atelectasis and infection [see chap. 4.6].

The importance of being able to efficiently cough bronchial secretions out of the lungs cannot be stressed enough. It is one the main causes of postoperative respiratory infection. A patient who cannot do this effectively has a very high risk of developing postoperative respiratory complications related to infection and hypoventilation.

Indices of obstruction

The usual tests of obstruction used are indices of expiratory flow restriction as this is by far the most common type of respiratory obstruction. Tests such as Forced Expiratory Volume in one second (FEV_1), FEV_1/VC, Peak Expiratory Flow Rate (PEFR), Maximum Breathing Capacity (MBC), and Mean Mid-Expiratory Flow Rate (MMEFR), are all indices of how rapidly gas may be moved out of the lungs. They give a measure of the resistance of the airways to flow of respiratory gases, These parameters are defined below.

a. Forced Expiratory Volume in one second (FEV_1).

This is the volume of gas that is able to be forcefully exhaled from the lungs through an open mouth during a time period of one second, after a preceding maximal inspiration.

b. Peak Expiratory Flow Rate (PEFR).

The is the maximum flow rate able to be developed during a forceful maximal expiration through an open mouth after a preceding maximal inspiration.

c. Mean Mid-Expiratory Flow Rate (MMEFR).

This is the gas flow rate measured at the point during a maximal forceful expiration, when one half of the vital capacity has been exhaled. This measure is said to be less dependent upon the degree of respiratory effort than the MBC, PEFR, or FEV_1.

d. Maximum Breathing Capacity (MBC).

This is the maximum volume of air that can be breathed per minute, usually the maximum expired minute volume that is possible. This is measured over a period of 15 seconds and the volume measured multiplied by four. It is a measure of both inspiratory as well as expiratory obstruction in persons with normal neuromuscular function, simply because the less air that can be displaced per unit time, the greater the degree of respiratory obstruction present

EFFICIENCY OF GAS DIFFUSION ACROSS ALVEOLAR MEMBRANES

Gas diffusion tests, such as the carbon monoxide diffusing capacity, give an idea of the efficiency of gas diffusion across the alveolar membranes.

REFERENCES

1. Wahba,W.M.(1983). Influence of Aging on Lung Function - Clinical Significance of Changes from Age Twenty. ANESTHESIA AND ANALGESIA, 62, 764-776.
2. Marshall,B.E., Wyche,M.Q.(1972). Hypoxemia during and after Anesthesia. ANESTHESIOLOGY, 37, 178-210.
3. Gillies,I.D.S., et al.(1977). Analysis of possible factors influencing P_aO_2 and (P_AO_2 - P_aO_2) in patients awaiting operation. BRITISH JOURNAL OF ANAESTHESIA, 49, 427-437.
4. Hirdes,J.J., van Veen,G.,(1952), Spirometric lung function investigations. II.. The form of the expiration curve under normal and pathological conditions. ACTA TUBERCULOSA SCANDINAVICA, 26, 264-279.

Chapter 4.5

PULMONARY EFFECTS OF ANAESTHESIA AND SURGERY

It has been appreciated for many years that anaesthesia and surgery exert a deleterious effect on pulmonary function, both during and after surgery. The alveolar-arterial oxygen gradient ((A-a)D_{O2}), is increased during anaesthesia, and may remain elevated for some days postoperatively. Such an elevation of the (A-a)D_{O2} may be the cause of significant hypoxaemia, especially in the elderly, or those with disordered pulmonary function.

One of the tasks of the anaesthetist is to detect patients at risk of perioperative exacerbation of existing respiratory problems, or of developing serious perioperative respiratory insufficiency. This requires a basic knowledge of the effects of anaesthesia and surgery on respiratory function.

CAUSES OF PERIOPERATIVE HYPOXAEMIA

1. Position of the patient.

In the normal adult, the supine position causes the diaphragm to rise 4 cm higher in the chest than its level in an erect position [12]. This causes an elevation of the mean intrathoracic pressure, as a result of which the closing capacity increases, and the FRC decreases. Both of these factors cause the physiological dead space to increase [13]. The end result of all these changes is hypoventilation of a larger volume of lung tissue than normal, and a decrease of alveolar ventilation.

These changes are exacerbated even further by the Trendelenberg, side, prone, etc positions.

2. Operative technique.

The operative technique may also adversely affect intraoperative oxygenation. Operative sites and operations that spring to mind are;

- thoracotomy where one lung is collapsed,
- upper abdominal surgery with retraction of intra-abdominal viscera against the diaphragm,
- laparoscopy where large amounts of intra-peritoneal gas restrict diaphragmatic movement,
- and surgery in the Trendelenberg position, where the weight of intra-abdominal viscera pressing against the diaphragm restrict respiratory movements.

3. Hypovolaemia.

Hypovolaemia causes the (A-a)D_{O2} to increase and the P_aO_2 to decrease [14]. This is due to a combination of increased oxygen consumption, and a reduction of cardiac output due to hypovolaemia which reduces both peripheral oxygen transport and availability [14, 15].

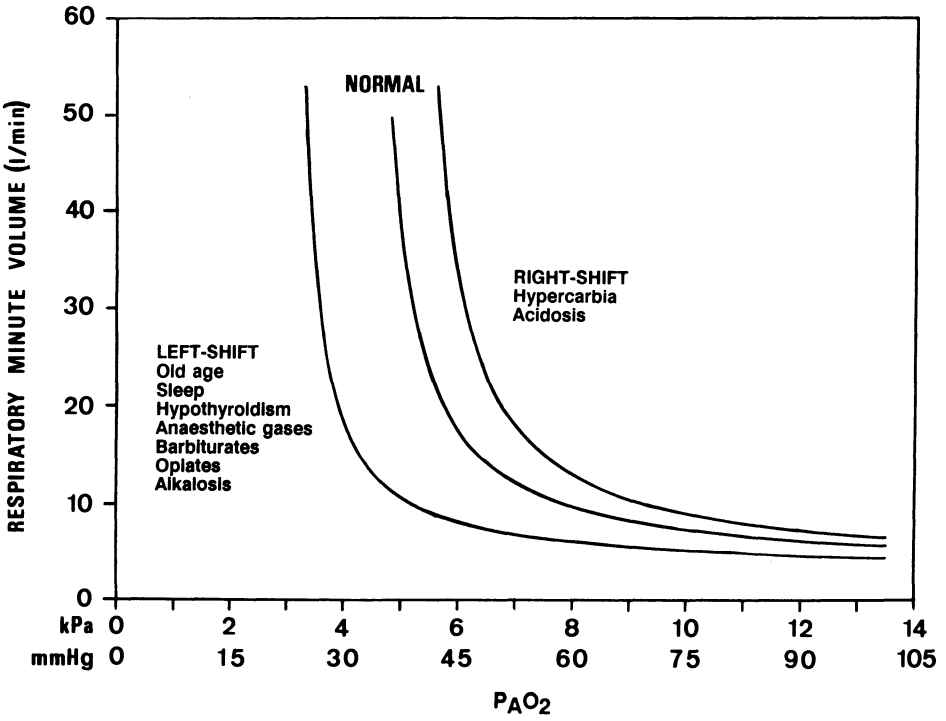

FIGURE 4.5.1. - The normal and abnormal response of the respiratory minute volume to changes of P_AO_2 are shown for various conditions. The respiratory minute volume does not normally begin to increase significantly until the P_AO_2 has fallen below 8 kPa (60 mmHg).

4. Reduced respiratory drive.

a. Hypoxic respiratory drive.

The normal respiratory response to changes of P_AO_2 in humans whose pH and P_ACO_2 are kept constant is described by equation 1 below [1], and shown in figure 4.5.1.

$$V_m = V_o + A/(P_AO_2 \times 7.5 - 32) \quad \text{.....(1)}$$

P_AO_2 = alveolar PO_2 in kPa (N.B. remove the factor 7.5 for P_AO_2 in mmHg).
V_o = normal resting, or initial minute volume in l/min.
V_m = respiratory minute volume in l/min.
A = a constant for normal adults = 186 if the P_aCO_2 is kept constant at 4.8 kPa (35.9 mmHg) [1].

As can be readily appreciated from figure 4.5.1 and equation 1, the respiratory minute volume only increases significantly if the P_AO_2 falls below 8 kPa (60 mmHg). The change of respiratory minute volume in response sudden to changes of P_AO_2 is rapid, being essentially complete in 18-23 seconds [2]. The response to changes of P_AO_2 is influenced by a number of factors some of which are listed in table 4.5.1 and in fig. 4.5.1.

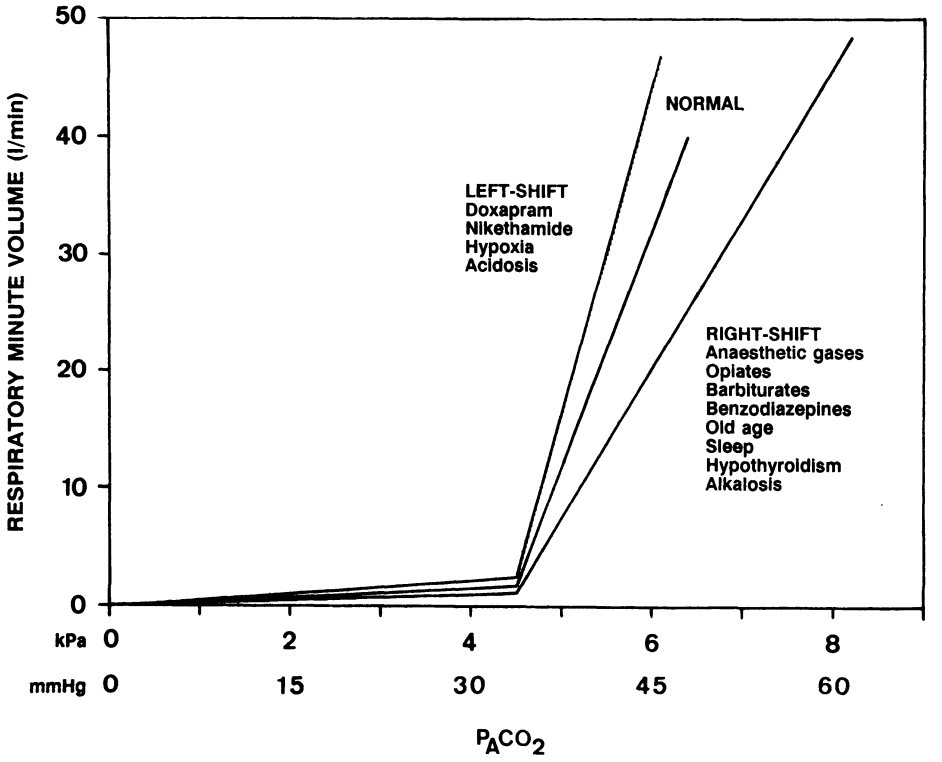

FIGURE 4.5.2. - The normal and abnormal responses of the respiratory minute volume to increasing P_ACO_2 are shown for various conditions. If the P_ACO_2 is acutely reduced below 4 kPa (30 mmHg) in this example, spontaneous respiration ceases.

b. Hypercarbic respiratory drive.

The normal respiratory response to changes of P_ACO_2 is an increase of the respiratory minute volume in direct proportion to any increase of P_ACO_2 and vice versa. This response may be described in normal adults by equation 2 [1], and which is plotted in figure 4.5.2.

$$V_m = S \times (P_ACO_2 \times 7.5 - B) \quad \text{.....(2)}$$

P_ACO_2 = alveolar PCO_2 in kPa (remove the factor 7.5 for P_ACO_2 in mmHg).
S = a constant for normal adults = 2.69 [1].
B = a constant for normal adults = 33.1 [1].
V_m = respiratory minute volume in l/min.

Respiratory response to changes of PCO_2 is affected by many factors that are present in the perioperative period. Some of these are listed in figure 4.5.2 and in table 4.5.1.

Table 4.5.1.
Factors affecting respiratory response to hypoxaemia and hypercapnia.

FACTOR AFFECTING RESPONSE	Response to HYPOXAEMIA	Response to HYPERCAPNIA
P_aCO_2		
Hypercapnia [2]	↑	
Hypocapnia [2]	↓	
P_aO_2		
Hypoxia [3,5]		↑
pH		
Acidaemia [3,10]	↑	↑
Alkalaemia [5,10]	↓	↓
Disease & Physiology		
Hypothyroidism [4]	↓	↓
Fever [5]	?	↑
Old age [8]	↓	↓
Drugs		
Opiates [5,6]	↓	↓
Barbiturates [11]	↓	↓
Benzodiazepines [9]	?	↓
Anaesthetic gases, including N_2O [7,11]	↓	↓

"↓" = depressed; "↑" = enhanced.

c. Factors affecting hypoxic and hypercarbic respiratory drives.

Both the hypoxic or the hypercarbic respiratory drives may be affected by disease or drugs in patients coming for operation. Some of the most common factors affecting respiratory response to alterations of P_aCO_2 and P_aO_2 are shown in figures 4.5.1 and 4.5.2, and also listed in table 4.5.1. As may be expected from table 4.5.1 patients who have undergone general anaesthesia have postoperative depression of both the hypoxic and hypercar-

bic respiratory drives. In some patients with marginal preoperative respiratory function this may be sufficient to exacerbate any tendency to respiratory failure.

5. Acid-base disorders.

Acidaemia and alkalaemia both affect respiratory control. Induction of acidaemia while maintaining a constant P_aO_2 and P_aCO_2, causes the respiratory minute volume to increase, and alkalosis has the reverse effect [10]. The degree to which the respiratory minute volume changes per unit change of pH is highly variable from person to person [10].

In addition to its effect on minute ventilation, change of blood pH has a profound effect upon the ventilatory responsiveness to changes of P_aCO_2 as well as P_aO_2. Alkalaemia decreases the magnitude of the normal response to increasing P_aCO_2 or decreasing P_aO_2. Acidaemia has the reverse effect [see table 4.5.1, and figure 4.5.2].

6. General anaesthesia.

General anaesthesia, regardless of whether anaesthetic gases alone, or neuromuscular blocking agents are used always causes some degree of muscle relaxation. This has a profound effect on respiratory physiology, especially when combined with the effects of the position of the patient, e.g. supine, trendelenberg, prone etc.

a. In the supine position, pressure exerted by the intra-abdominal contents tends to push the diaphragm up into the thorax. General anaesthesia exacerbates this by causing relaxation of the diaphragmatic muscle fibers. The diaphragm rises higher into the chest in supine patients during all phases of the respiratory cycle during anaesthesia than it does in consciousness [16].
b. In the case of patients spontaneously breathing a gaseous anaesthetic, the depth of anaesthesia required for surgery to be possible causes significant skeletal and diaphragmatic muscle relaxation. Techniques of anaesthesia using controlled ventilation and muscle relaxant drugs cause a similar degree of muscle relaxation. It is for this reason that no significant difference in the degree of diaphragmatic relaxation is observed when the two anaesthetic techniques are compared [16].
c. In addition to a reduction of the diaphragmatic component of respiratory movement, movement of the chest wall is also reduced during general anaesthesia as a result of relaxation of the intercostal and other accessory respiratory muscles. Chest wall contribution to tidal respiration is accordingly reduced [17].

The effect of diaphragmatic and intercostal relaxation is to reduce the intrathoracic volume during all phases of the respiratory cycle during anaesthesia. This reduces the FRC below the volume existing prior to general anaesthesia. The reduction of the FRC is maximal within 13 minutes after induction of general anaesthesia, and is reduced to 90-75% of the value in consciousness, regardless of whether the patient receives a muscle relaxant drug and is mechanically ventilated, or whether he spontaneously breathes an anaesthetic gas [18,19,21]. As the mean intrathoracic pressure is increased by the reduction of thoracic volume, the closing capacity of the lungs also increases during anaesthesia [20,21].

If the FRC is less than the closing capacity (CC), air trapping with hypoventilation occurs. A measure of this effect is the CC/FRC ratio. The CC/FRC ratio always increases during general anaesthesia. Equation 3 below shows the change of the CC/FRC ratio with age for supine awake adults [13].

$$CC/FRC = 0.64 + 0.01 \times AGE(yrs) \quad .....(3)$$

The greater the CC is in relation to the FRC, the greater the (A-a)D_{O2} [20]. As is to be expected, the (A-a)D_{O2} in supine awake adults also increases in direct proportion to the age of the patient [24].

$$(A\text{-}a)D_{O2}(kPa) = -0.57 + AGE/17.5 \quad .....(4)$$

These changes are magnified by the changes of pulmonary physiology induced by general anaesthesia. The ultimate effect of all these changes is to increase pulmonary hypoventilation. This accounts for the measured increase of venous admixture that occurs during general anaesthesia, regardless of whether ventilation is controlled or spontaneous [21].

It is obvious from the above that it is not only those with disordered pulmonary function that are at risk from possible hypoxaemia during anaesthesia, but that the aged are also especially likely to develop intraoperative hypoxaemia.

7. Regional anaesthesia.

Pulmonary function is unaffected by most loco-regional anaesthetic techniques. However both spinal and epidural anaesthesia do cause the physiological dead space to increase, although without otherwise affecting pulmonary function [21]. Hypotension during any regional anaesthetic technique does cause the (A-a)D_{O2} to increase, as would be expected from the altered pulmonary ventilation-perfusion relationship that this induces.

POSTOPERATIVE RESPIRATORY EFFECTS OF REGIONAL ANAESTHESIA

Regional anaesthesia itself has a minimal effect on respiratory function. When used alone, in combination with sedation, or together with general anaesthesia, regional anaesthesia eliminates wound pain, and by reducing the total intraoperative as well as postoperative opiate requirements, results in patients having a much more rapid recovery of normal respiratory function [21].

POSTOPERATIVE HYPOXAEMIA AFTER GENERAL ANAESTHESIA

1. Magnitude of postoperative hypoxaemia.

It has been appreciated for many years that most patients develop a degree of postoperative hypoxaemia after undergoing operations performed under general anaesthesia. The magnitude of the postoperative reduction of P_aO_2 is dependent both on the age of the patient and the operative site [see fig. 4.5.3]. The regression equations shown in fig 4.5.3 show what has been known for many years. That is, that the elderly are more hypoxaemic postoperatively than younger patients, and that operations in the upper abdomen and thorax cause significant postoperative hypoxaemia [21,22,23].

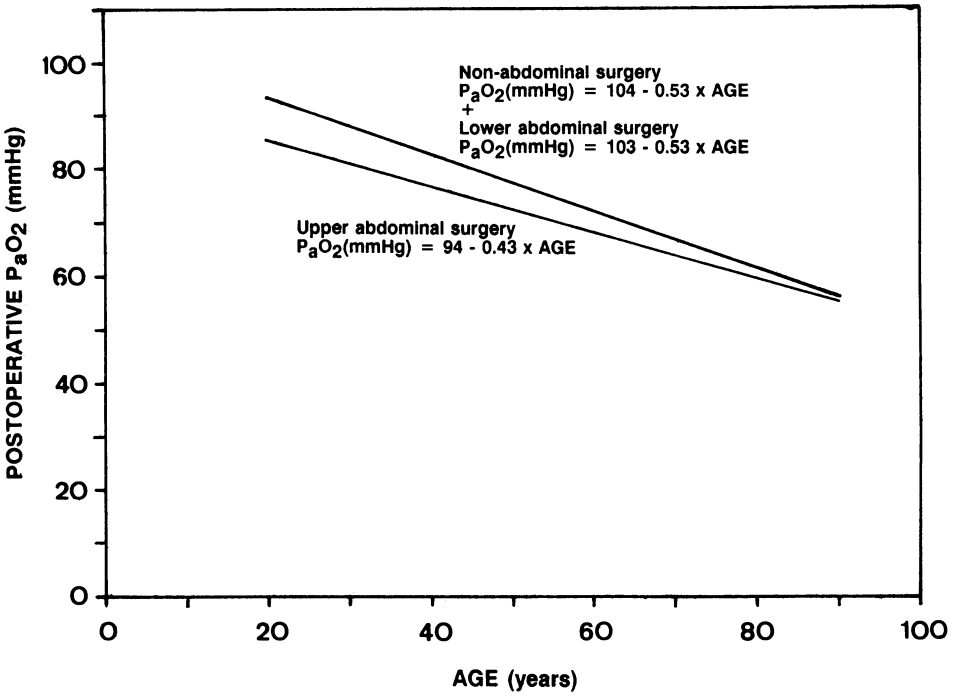

FIGURE 4.5.3. - Various regression equations along with their curves are shown relating P_aO_2 in the immediate postoperative period to age and the region of the body operated [23].

2. Duration of postoperative hypoxaemia.

The duration of postoperative hypoxia is dependent upon the nature of the operation and the type and duration of general anaesthesia.

a. Non-abdominal operations of <30 minutes duration.

General anaesthesia lasting less than 30 minutes for non-abdominal operations causes hypoxaemia that is maximal upon discontinuation of anaesthesia, after which the P_aO_2 returns to preoperative values by about 3 hours postoperatively [21].

b. Lower abdominal surgery of >30 minutes duration.

General anaesthesia administered longer than 30 minutes for lower abdominal surgery causes a period of postoperative reduction of P_aO_2, and vital capacity which may last for up to 3 days [22].

c. Upper abdominal surgery of >30 minutes duration.

General anaesthesia administered longer than 30 minutes for upper abdominal surgery causes a reduction of the vital capacity, FRC, and P_aO_2 for a period of about 7-10 days [22].

3. Causes of postoperative hypoxaemia.

a. Residual effects of anaesthesia.

Diffusion hypoxia occurs if oxygen is not administered for at least 3 minutes after discontinuation of nitrous oxide. Such hypoxia only lasts a few minutes.

Respiration may be depressed by reduction of hypoxic and hypercarbic drives due to the remaining effects of barbiturates, benzodiazepines, opiates and anaesthetic vapors. Respiratory muscle strength may be reduced if the effects of any non-depolarizing neuromuscular junction blocking drug have not been adequately reversed.

b. Hypovolaemia.

Hypovolaemia reduces cardiac output if severe enough. This in turn reduces blood flow to all tissues, as well as altering the distribution of pulmonary blood flow. An elevation of the $(A\text{-}a)D_{O2}$ is the result of these changes.

c. Effects of surgery.

Wound pain inhibits respiratory movement in patients who have been operated in the upper abdomen and thorax. Pain also suppresses coughing, reducing the clearance of pulmonary secretions.

d. Effects of postoperative analgesia.

All opiates depress respiration by depressing the hypoxic and hypercapnic respiratory drives. In addition to these effects, opiates depress coughing, and so the clearance of pulmonary secretions. Postoperative administration of opiates can therefore exacerbate any tendency to hypoxaemia.

e. Postoperative pulmonary complications.

It has been appreciated form the beginning of this century that patients may develop postoperative pulmonary complications. These are particularly likely to occur after thoracic and upper abdominal surgical procedures, are less likely after lower abdominal surgery, and are least likely to occur after minor limb surgery [25].

Postoperative pathological changes are either due to a variety of mechanisms [see 25 for review].

i. Retention of bronchial secretions.

This is the result of depressed mucociliary clearance due to inhibition of cough by wound pain, suppression of coughing by drugs, or weakened respiratory muscles causing ineffective cough. Retention of secretions may either cause obstruction of airways and atelectasis, and the secretions themselves are a fertile breeding ground for bacteria.

ii. Atelectasis.

Atelectasis may be due to diffuse microatelectases which are not visible on a chest X-ray. Or atelectasis may be more gross causing collapse of one or more lung lobes. The latter is visible on a chest X-ray.

Postoperative atelectasis may be produced by a variety of causes, decreased postoperative lung volumes, lung volumes that are decreased below closing capacity, retention of bronchial secretions, and loss of the normal physiological sigh.

iii. Pulmonary infection.

Infection may occur in a region of atelectasis or in retained pulmonary secretions. The result varies in severity from mild bronchitis to severe life-threatening pneumonia.

iv. Hypoxaemia.

Atelectasis, and severe pulmonary infections may cause hypoxaemia if they are severe enough. This will further exacerbate postoperative hypoxaemia due to any of the other causes discussed earlier in this chapter.

REFERENCES

1. Hirshman,C.A., et al.(1975). Normal values for hypoxic and hypercapnic ventilatory drives in man. JOURNAL OF APPLIED PHYSIOLOGY, 38, 1095-1098.
2. Weil,J.V., et al.(1970). Hypoxic ventilatory drive in normal man. JOURNAL OF CLINICAL INVESTIGATION, 49, 1061-1072.
3. Cunningham,D.J.C., et al.(1961). The effect of maintained ammonium chloride acidosis on the relation between pulmonary ventilation and alveolar oxygen and carbon dioxide in man. QUARTERLY JOURNAL OF EXPERIMENTAL PHYSIOLOGY, 46, 323-334.
4. Zwillich,C.W., et al.(1975). Ventilatory control in myxedema and hypothyroidism. NEW ENGLAND JOURNAL OF MEDICINE, 292, 662-665.
5. McClain,D.A., Hug,C.C.(1984). Pharmacodynamics of opiates. INTERNATIONAL ANESTHESIOLOGY CLINICS, 22, 75-84.
6. Weil,J.V., et al.(1975). Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. NEW ENGLAND JOURNAL OF MEDICINE, 292, 1103-1106.
7. Eger,E.I.(1981). Isoflurane: A review. ANESTHESIOLOGY, 55, 559 -576.
8. Kronenberg,R.S., Drage,G.W.(1973). Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal man. JOURNAL OF CLINICAL INVESTIGATION, 52, 1812-1819.
9. Forster,A., et al.(1980). Respiratory depression by midazolam and diazepam. ANESTHESIOLOGY, 53, 494-497.
10. Gabel,R.A., Weiskopf,R.B.(1975). Ventilatory interaction between hypoxia and $[H^+]$ at chemoreceptors in man. JOURNAL OF APPLIED PHYSIOLOGY, 39, 292-296.
11. Knill,R.L., Clement,J,L.(1982), Variable effects of anaesthetics on the ventilatory response to hypoxaemia in man. CANADIAN ANAESTHETISTS' SOCIETY JOURNAL, 29, 93-99.
12. Wade,O.L., Gibson,J.C.(1951), The effect of posture on diaphragmatic movement and vital capacity in normal subjects. THORAX, 6, 103.
13. Wahba,W.M.,(1983), Influence of aging on lung function - clinical significance of changes from age twenty. ANESTHESIA AND ANALGESIA, 62, 764-776.
14. Vladeck,B.C., et al.(1971), Rapid and slow hemorrhage in man: II. Sequential acid-base and oxygen transport responses. ANNALS OF SURGERY, 173, 331-336.
15. Bassin,R., et al.(1971), Rapid and slow hemorrhage in man: I. Sequential hemodynamic responses. ANNALS OF SURGERY, 173, 325-330.
16. Froese,A.B., Bryan,A.C.,(1974). Effects of anesthesia and paralysis on diaphragmatic mechanics in man. ANESTHESIOLOGY, 41, 242-255.
17. Jones,J.G., et al.(1976), The relative contribution to tidal volume of the chest wall and the abdomen in awake and anaesthetised patients. BRITISH JOURNAL OF ANAESTHESIA, 48, 812.
18. Hewlett,A.M., et al.(1974), Functional residual capacity during anaesthesia. II: Spontaneous respiration. BRITISH JOURNAL OF ANAESTHESIA, 46, 486-494.
19. Hewlett,A.M., et al.(1974), Functional residual capacity during anaesthesia. III: Artificial ventilation. BRITISH JOURNAL OF ANAESTHESIA, 46, 495-503.
20. Bergman,N.A., Tien,Y.K.,(1983), Contribution of the closure of pulmonary units to impaired oxygenation during anesthesia. ANESTHESIOLOGY, 59, 395-401.
21. Marshall,B.E., Wyche,M.Q.,(1972), Hypoxemia during and after anesthesia. ANESTHESIOLOGY, 37, 178-209.
22. Craig,D.B.,(1981), Postoperative recovery of pulmonary function. ANESTHESIA AND ANALGESIA, 60, 46-52.

23. Kitamura,H., et al.(1972), Postoperative hypoxaemia: The contribution of age to the maldistribution of ventilation. ANESTHESIOLOGY, 36, 244-252.
24. Gillies,I.D.S., et al.,(1977), Analysis of possible factors influencing P_aO_2 and (P_AO_2 - P_aO_2) in patients awaiting operation. BRITISH JOURNAL OF ANAESTHESIA, 49, 427-437.
25. Tisi,G.M.,(1979), Preoperative evaluation of pulmonary function. AMERICAN REVIEW OF RESPIRATORY DISEASE, 119, 293-310.

Chapter 4.6

PREOPERATIVE ASSESSMENT OF RESPIRATORY FUNCTION & ITS CONSEQUENCES

The purpose of preoperative respiratory function assessment is to detect those patients whose respiratory function is likely to be seriously adversely affected by anaesthesia and surgery. In general it may be stated that the worse the preoperative lung function, the more likely it is that the patient will suffer significant postoperative exacerbation of existing pulmonary dysfunction [15,16,19]. Actual respiratory failure may occur postoperatively in patients with severe preoperative pulmonary disease.

Armed with knowledge of the severity of any pulmonary disease, a plan of management for the type of anaesthesia, and postoperative respiratory therapy may be made so as to limit any exacerbation of respiratory dysfunction in the perioperative period. If such therapy is aggressive and effective, most patients with severely disordered lung function will survive anaesthesia and surgery, even those whose lung function test parameters are in a so called "lethal" region [4]. Anaesthesia and surgery need never be refused a patient purely on the basis of severely disordered lung function.

Both clinical and laboratory investigations may be used to assess respiratory function. Clinical assessment of respiratory function gives a reasonably accurate idea of the degree of respiratory function impairment. But this is not quantifiable data, and so tests which yield a quantifiable value should also be used where indicated to more accurately diagnose the nature of the disease, to provide a quantifiable measure of its severity, and to measure the effects of any therapy.

CLINICAL ASSESSMENT

Clinical assessment includes history taking, careful observation of both the behavior and mental status of the patient, and physical examination.

History.

A detailed history of the level of physical activity of the patient should be made. Factors such as ability to work, carry out normal household activities, shopping, walking, stair climbing, sport, and cycling are all important. A simple physical functional classification may be made based on this information [3].

Functional Classification

Class 1. Patients with lung disease, but no limitation of activity except with heavy or protracted physical exertion.

Class 2. Patients with lung disease. They are able to work, to some extent. Dyspnea occurs after climbing steps for more than one story.

Class 3. The person is unable to work due to lung disease, but is able to manage personal requirements, and to leave home to go shopping. Dyspnea occurs after climbing steps for less than one story.

Class 4. Severe lung disease. Causes such severe disability that the person is bedridden, or unable to leave his room or house. Unable to manage personal requirements without help.

Table 4.6.1.
Mortality after admission to intensive therapy unit (ITU) for acute respiratory failure, related to lung disease severity prior to acute failure [3].

Functional class	% mortality after admission to respiratory ITU.
2	12%
3	30%
4	50%

The mortality due to an acute exacerbation of existing lung disease in patients admitted to a respiratory intensive care unit, is directly related to the functional class of the person prior to the acute worsening of respiratory dysfunction [3, and see table 4.6.1].

This simple clinical classification has relevance to anaesthetic practice as it gives a very clear idea of functional lung disease severity. Patients in functional classes 3 and 4 should be considered as having a high risk of developing postoperative pulmonary complications, and be managed accordingly in the perioperative period.

While assessing the functional level of the patient, the anaesthetist can also gain further information as to the degree of pulmonary dysfunction by observation of the patient.

Simple observation.

1. Smell for pus, and look at the contents of the sputum mug.

2. Look for tachypnea, whether accessory respiratory muscles are being used, for cyanosis, clubbing and nicotine staining of the fingers, and at the activity level of the patient.

3. Listen for respiratory sounds, wheezing, bubbling, coughing, stridor etc. If the breathing of a person at rest can easily be heard, then the respiratory function of that person is abnormal.

4. Carefully assess the story of the patient to see if it is consistent. Some patients may be somewhat reticent about their true level of dysfunction. For example, a person sitting upright in bed gasping and wheezing, with bright yellow nicotine staining of the fingers, is very unlikely to have no limitation of physical activity, much less be able to walk up steps easily, to be able to run a marathon, and to smoke only two cigarettes per day.

Physical examination.

Physical examination of the patient aids in providing a pathological diagnosis of any respiratory disorder. This is of use when planning anaesthesia and perioperative respiratory management.

Simple clinical bedside respiratory function tests.

In addition to the above clinical examination, some rudimentary respiratory function tests which provide a more quantitative idea of the magnitude of the respiratory disorder may be performed. Such tests, in addition to the history and physical examination, provide a more reasonable basis as an indication for the requirement of more extensive laboratory respiratory function testing.

1. Snider match test.

Here a maximal expiration is succeeded by a maximal inspiration, and the patient then exhales with maximum force through his widely opened mouth, and tries to extinguish a steadily burning **PAPER** match held at a distance of 7.5 or 15 cms (3 or 6 inches) from the mouth. This is repeated 3-6 times until a consistent result is obtained. Inability to extinguish a match held at a distance of 7.5 cm (3 inches) from the mouth indicates that there is a 90% chance that the maximum breathing capacity (MBC) is less than 40 l/min, and the maximum mid-expiratory flow is less than 6 l/sec [12]. Failure to extinguish a match held at 15 cms (6 inches) from the mouth indicates that there is an 85% chance that the FEV_1 is less than 1.6 l/min, and the MBC is less than 60 l/min [13].

A maximum breathing capacity of less than 40 l/min is an important critical value. If the maximum breathing capacity is less than 40 l/min, the person is likely to have a lower P_aO_2, and a higher P_aCO_2 than normal. In addition to this, such persons are unable to sustain minute ventilation above resting levels for any length of time, and are more likely to have a reduced hypercapnic respiratory drive. In short, this test may be used to define the surgical patient with a higher than normal risk of developing postoperative respiratory complications [1].

2. Duration of expiration.

For this test, the physician places his stethoscope in the sternal notch, requests the patient to exhale maximally, subsequently to inhale maximally, and then to exhale as rapidly as possible through his widely opened mouth. The duration of audible expiration is timed.

This maneuver is repeated three or more times, until variation in the duration of the expiratory maneuver so performed is minimal.

The duration of audible expiration is directly proportional to the ratio of the FEV_1/VC, and is also related to the peak expiratory flow rate (PEFR). If the duration of audible expiration measured in the manner described above is longer than 5 seconds, then there is a more than 90% chance that the FEV_1/VC ratio is less than 60%, and that the PEFR is less than 250 l/min [2].

Table 4.6.2.
Relationship of bedside clinical respiratory function tests to laboratory respiratory function tests [see text for description and references].

Bedside test result	Corresponding laboratory test results in >85% of patients
MATCH TEST - unable to extinguish match held at;	
- 7.5 cms (3 inches) from mouth	MBC < 40 l/min
- 15 cms (6 inches) from mouth	MBC < 60 l/min FEV_1 < 1.6 l/min
DURATION OF EXPIRATION > 5 sec	FEV_1/VC < 60% PEFR < 250 l/min FEV_1 < 1.7 l
BREATH HOLDING DURATION < 20 sec	Significantly abnormal pulmonary function

3. Breath-holding test.

The maximum length of time a person can hold their breath is also a simple guide to global cardiopulmonary function. Breath holding time is determined by the volume of oxygen in the lungs and blood at the start of breath holding, the rate at which oxygen is transferred from the alveoli to the blood, the rate of oxygen consumption and carbon dioxide production, in addition to the haemoglobin concentration, and the cardiac output.

If a cooperative healthy adult sitting at rest and breathing air is asked to exhale to residual volume, and to subsequently inhale to total lung capacity and hold their breath as

long as possible, the maximum breath holding time is about 76-87 seconds [7,8,11]. As breath holding time is determined principally by the size of pulmonary oxygen stores, it is not surprising that when a cooperative healthy adult breathing air is asked to hold their breath at residual volume, the maximum breath holding time is only 20 seconds, about a quarter of that possible at total lung capacity [11]. Indeed it has been found experimentally that breath holding time is directly proportional to the lung volume at the start of breath holding [11]. Breath holding time is also directly proportional to the initial P_AO_2 at the start of breath holding if the P_AO_2 is less than 8 kPa (60 mmHg), and is unrelated to the initial P_AO_2 if it is above this level [9,10]. Hypercapnic respiratory drive also has a major influence on the maximum breath holding time, and maximum breath holding time is inversely proportional to the P_ACO_2 at the start of breath holding [9].

The practical clinician need only remember two figures for the average healthy adult breathing air. Breath holding time is about 80 seconds if breath holding was started at total lung capacity, and about 20 seconds if started at residual volume. This forms the basis for the simple breath holding test below.

A cooperative adult sitting at rest and breathing air is asked to exhale maximally, subsequently to inhale maximally, and then to hold their breath as long as possible. If the maximum breath holding time is less than 20 seconds, respiratory or cardiac function is very likely to be abnormal, as that person can only hold his breath for a time corresponding with breath holding starting at residual lung volume, while they actually started breath holding at total lung capacity.

LABORATORY RESPIRATORY FUNCTION TESTING

Clinical history alone is not always effective in the detection of patients with significant respiratory disease, as some patients never admit to even severe functional impairment or any respiratory problems [20]. The bedside tests of respiratory function discussed above will detect many of these patients. However laboratory pulmonary function tests will detect milder degrees of respiratory function impairment, in addition to providing a quantitative measure of their severity. These provide quantitative information as to thresholds at which the anaesthetist must consider more than usually careful and aggressive perioperative respiratory therapy. In other words they permit a more quantitative definition of what constitutes a patient with a high risk of developing postoperative pulmonary complications.

Some criteria as to minimum acceptable lung function for elective surgery are set out below.

1. Single test criteria for all surgical patients.

a. Peak Expiratory Flow Rate (PEFR).

The peak expiratory flow rate (PEFR) may be used. This gives a measure of the maximum rate at which air can be exhaled out of the lungs, and as such is a measure of the degree of airway obstruction present. A low PEFR means that the ability of the patient to generate a bronchial airflow during coughing, which is sufficient to clear secretions, is reduced. Such patients are at high risk of developing postoperative retention of pulmonary secretions with all the consequences of this, i.e. atelectasis, infection etc.

The PEFR in an adult at which this problem becomes significant is one which is less than tracheal flow generated by a cough. In an adult the tracheal flow generated during a cough is about 4-6 l/sec, i.e. about 240-360 l/min [14]. PEFR in adults is normally greater than this [see table 4.4.1]. Investigations performed on surgical patients have shown that

postoperative pulmonary morbidity is increased in patients whose preoperative PEFR is less than 200 l/min [15,16], while patients whose preoperative PEFR is less than 100 l/min have a very high risk of developing pulmonary complications [4,5].

b. Forced Expiratory Volume in one second (FEV_1).

The FEV_1 is also a measure of the rate at which air can be expired out of the lungs, as well as being a measure of the volume of air present, especially when measured in conjunction with the vital capacity. The FEV_1 is therefore a complementary test to the PEFR, and the both tests are linearly related. One study has provided regression equations relating the two parameters ($r = 0.94$) [2].

$$\mathbf{FEV_1(liters) = 0.00567 \times PEFR(l/min) + 0.29}$$

OR

$$\mathbf{PEFR(l/min) = [FEV_1(liters) - 0.29]/0.00567}$$

A PEFR of 250 l/min is equivalent to a FEV_1 of 1.71 liters, while a PEFR of 200 l/min corresponds with an FEV_1 of 1.36 liters, and a PEFR of 100 l/min corresponds with an FEV_1 of 0.79 liters. These levels of FEV_1 also correspond with what is generally considered to be associated with an increased risk of developing postoperative pulmonary complications [18].

c. Maximum breathing capacity (MBC).

Most patients are in pain after an operation, some are anxious, they may be hypoxaemic, hypercarbic, or even be febrile. The normal respiratory response to these stimuli is an increase of respiratory minute volume. But patients with severe obstructive airways disease are unable to maintain a significant elevation of their respiratory minute volume for any length of time, becoming rapidly exhausted as a result of the increased respiratory work. This exacerbates any existing hypoxaemia and hypercapnia, and may actually be severe enough to precipitate actual respiratory failure and cause death. It is obviously of great clinical utility for planning postoperative management to have an idea which patients are likely to be easily exhausted by increased respiratory work. Such patients may require postoperative respiratory support after major operations.

The above group of patients is defined by a MBC of less than 40 l/min, as patients with this degree of respiratory obstruction are unable to sustain involuntary hyperventilation in response to hypercapnia for longer than 6 minutes without developing respiratory discomfort [17].

d. Vital capacity.

The vital capacity is a measure of the maximum volume of gas able to be exchanged per breath from which oxygen can be extracted and carbon dioxide excreted. In addition to this it is also a useful, albeit crude, measure of respiratory muscle strength. Because of this the vital capacity is able to be used as a parameter to determine the requirement for assisted ventilation, it being recommended that assisted ventilation is required for persons whose vital capacity is less than 10-15 mls/kg body weight [22]. Various authors state that such a vital capacity is associated with a high risk of postoperative pulmonary complications [4, 19, 23], although this is not so for lesser degrees of vital capacity reduction [15,16]. A vital capacity of less than 15 mls/kg body weight in an adult also indicates that the PEFR and FEV_1 are in the "high risk" range, and so also defines a "high risk" patient.

2. A multiple test criterion for upper abdominal, and thoracic surgery.

A preoperative multiple parameter definition of an adult patient who has a high risk of developing pulmonary complications after upper abdominal and thoracic surgery is one with VC < 1.85 liters, FEV_1 < 1.2 liters, and an MBC < 28 l/min [18].

4. Arterial blood gases.

Arterial blood gases usually remain normal until quite severe pulmonary dysfunction is present. Measurement of arterial blood gases alone is therefore a totally inadequate way of assessing respiratory function. They should only be considered in conjunction with other respiratory function tests, as well as the clinical condition of the patient. However despite these limitations, preoperative hypoxia and hypercarbia are both factors indicating that patient has a higher than normal risk of developing postoperative pulmonary complications [16]. Equation 6 in chapter 4.2 may be used as a guide to the expected P_aO_2.

5. Chest X-ray.

This provides further data as to the pathology of any respiratory disorder.

DEFINITION OF THE "AT RISK" PATIENT

The preceding paragraphs have described a plethora of respiratory function tests along with their clinical significance in some cases. However it presents a lot of information, and bears some recapitulation in a form which enables practical clinical consequences to be drawn. A surgical patient "at risk" of developing postoperative pulmonary complications is a person with pulmonary dysfunction existing in the preoperative period, and has one or more of the following characteristics.

1. Pulmonary function test parameters.

The pulmonary function test parameters which define a patient with an increased risk of postoperative pulmonary complications are listed below.

- Preoperative hypoxaemia with a P_aO_2 < 9 kPa (>65-70 mmHg). Such a person will be even more hypoxaemic in the perioperative period.
- A preoperative P_aCO_2 > 6 kPa (>45 mmHg), is also an indicator of abnormal gas exchange, and certainly that a degree of pulmonary hypoventilation is present. This is only exacerbated by anaesthesia and surgery.
- The respiratory minute volume may increase as a result of pain, hypoxaemia, hypercarbia, and fever, all of which are likely after surgery and anaesthesia, and certainly after major surgery. If a patient becomes rapidly exhausted by sustained tachypnea in response to these physiological stimuli, then he is at risk of developing even worse hypoxaemia and hypercarbia due to hypoventilation. Such a person may require postoperative mechanical ventilation. This group of patients is defined by a MBC < = 40 l/min [see above].
- A person who is unable to cough effectively is unable to clear bronchial secretions efficiently. Such persons are at risk of developing atelectasis, pulmonary infections etc. This group is defined by inability to generate a tracheal air flow equal to, or greater than, the airflow generated by coughing. This group of patients has a PEFR < 200-250 l/min, or a FEV_1 < 1.36-1.71 liters [see above].

- A vital capacity of less than 15 mls/kg body weight is an indicator of severe muscle weakness, or respiratory disease, and a PEFR as well as FEV_1 in the high risk range in adult patients.

While the presence of any one of these factors alone indicates an increased risk of developing postoperative pulmonary dysfunction, the presence of more than one factor obviously increases the likelihood.

2. Other factors of importance.

While the respiratory function parameters are of importance, other factors also have an important influence in determining whether any given patient will develop postoperative respiratory complications.

a. Age.

The aged have a greater chance of developing postoperative respiratory disorders [19, and see chapter 4.5].

b. Obesity.

The obese patient has an increased chance of developing postoperative respiratory complications [19].

c. Smoking.

A person who smokes more than 10 cigarettes per day is more likely to develop postoperative respiratory complications [see chapter 4.12].

d. Site of operation.

Surgery in some regions of the body is associated with a lower risk of developing postoperative respiratory complications. In order of frequency of complications, going from the operative regions associated with the least postoperative respiratory complications to the highest [19];

fewest complications	- peripheral non-abdominal, non-thoracic surgery
	- lower abdominal surgery
	- upper abdominal surgery
	- thoracic surgery without resection of functional lung tissue
most complications	- thoracic surgery with resection of functional lung tissue.

ANAESTHETIC PLANNING FOR THOSE WITH IMPAIRED RESPIRATORY FUNCTION

Nearly all patients with severe preoperative pulmonary disease can undergo anaesthesia and surgery and survive the operation. Major problems, such as respiratory failure, usually occur in the postoperative period, seldom during the operation. Indeed, this is only to be expected when one considers that the oxygenation of such patients can nearly always be improved, or at least maintained intraoperatively with modern intraoperative anaesthetic management. But in the postoperative period, the patient is exposed to both the deleterious effects of surgery, and the residual effects of anaesthesia on already disordered respiratory function [see chapter 4.5]. Because of this, the anaesthetist, surgeon and inter-

nist should plan the perioperative management of such patients in consultation with eachother. In this way, with optimum use of modern methods of anaesthesia and respiratory therapy in the perioperative period, even patients with crippling pulmonary disease may be operated upon and have a good chance of surviving surgery [4].

The steps to be followed with such "at risk" patients are detailed below and in table 4.6.3.

1. Recognition of the "at risk" patient.

The most important aspect of the management of the "at risk patient" is to recognize that the patient is "at risk". Perioperative managment of the patient has a number of aspects.

2. Management of the "at risk" patient.

The fact that a patient has an increased risk of developing postoperative pulmonary complications does not automatically mean that he will develop them, and that all such patients should be admitted to an intensive care postoperatively for mechanical ventilation regardless of the type of operation. This is unnecessary, as well as being very expensive medicine, in addition to which intensive care units are invariably experienced by most patients as unspeakably horrible places in which to be admitted.

There are several steps which should be followed, and which when carefully followed, do reduce the pulmonary consequences of surgery and anaesthesia in this unfortunate group of patients.

a. Preoperative therapy.

Preoperative physiotherapy, bronchodilator therapy, and antibiotic therapy should be administered preoperatively as indicated. In this way the patient may be brought into the best possible condition prior to operation. This therapy should be continued postoperatively, and has been shown to significantly reduce postoperative respiratory complication rates in "at risk" patients [15,19].

b. Anaesthetic management.

The type of anaesthesia that is most appropriate depends on the nature of the planned operation, the availability of respiratory care facilities, the skill and experience of both surgeon and anaesthetist. The exact type of anaesthesia may be of secondary importance [19], however at the present time, regional anaesthetic techniques with or without combination with light general anaesthesia are considered preferable because there is evidence that their use is associated with fewer postoperative respiratory complications [24]. This is quite probable as regional anaesthetic techniques cause only minimal respiratory depression.

c. Postoperative management.

The anaesthetist, internist and surgeon should all consult with one another regarding the postoperative management of high risk patients who undergo major upper intra-abdominal and thoracic procedures. Such patients usually should be admitted to an intensive care preoperatively, and planning should be made for postoperative controlled ventilation as indicated by the operation, postoperative temperature, haemodynamic status, and (A-a)D_{O2} as indicated by the P_aO_2 [see chapter 4.2].

Intensive physiotherapy, with or without antibiotic or bronchodilator therapy, is absolutely essential for reduction of the postoperative pulmonary complication rate [15,19,21].

Table 4.6.3.
Classification and management of patients with reduced pulmonary function [modified from 6].

1. NORMAL CARDIOPULMONARY RESERVE

Respiratory function tests	Anaesthetic management.
Normal	- Any form of anaesthesia may be used. - Administer oxygen postoperatively.

2. REDUCED CARDIOPULMONARY RESERVE

Respiratory function tests	Anaesthetic management
VC and/or FEV_1 < 50% normal P_aCO_2 normal P_aO_2 > 9.3 kPa (70 mmHg)	- Loco-regional anaesthesia is best. - Controlled ventilation is necessary to ensure adequate oxygenation during all forms of general anaesthesia. - Administer oxygen postoperatively. - Postoperative physiotherapy.

3. SEVERE REDUCTION OF CARDIOPULMONARY RESERVE

Respiratory function tests	Anaesthetic management
VC and or FEV_1 20-50% normal P_aCO_2 normal P_aO_2 < 9.3 kPa (70 mmHg)	- Use loco-regional anaesthesia wherever possible. - Controlled ventilation is necessary to ensure adequate oxygenation during all forms of general anaesthesia. - Administer oxygen postoperatively. - Postoperative physiotherapy.

4. NO CARDIOPULMONARY RESERVE

Respiratory function tests	Anaesthetic management
Cardiac and/or respiratory failure. VC and/or FEV_1 < 25% normal P_aCO_2 > 6.5 kPa (50 mmHg) P_aO_2 < 6.5 kPa (50 mmHg)	- Anaesthesia as in 3 above. - An arterial catheter is useful for regular blood gas measurement. - Make arrangements for postoperative admission to an intensive care unit for possible ventilatory support. - Caution with administration of oxygen postoperatively because of possible absence of a hypercarbic respiratory drive.

REFERENCES

1. Ravin,M.B.(1964). The Match Test as an Aid to Preoperative Pulmonary Evaluation. ANESTHESIOLOGY, 25, 391-392
2. Lal,S., et al.(1964). Forced expired time: a simple test for airways obstruction. BRITISH MEDICAL JOURNAL, 1, 814-817.
3. Kristensen,H.S., Rasmussen,K.(1967). Tracheostomy and artificial ventilation in chronic lung disease. LANCET, 2, 9-12.
4. Williams,C.D., Brenowitz,J.B.(1976). "Prohibitive" Lung Function and Major Surgical Procedures. AMERICAN JOURNAL OF SURGERY, 132, 763-766.
5. Schwaber,J.R.,(1970), Evaluation of respiratory status in surgical patients. SURGICAL CLINICS OF NORTH AMERICA, 50, 637.
6. Rigg,J.R.A., Jones,N.L.(1978). Clinical Assessment of respiratory function. BRITISH JOURNAL OF ANAESTHESIA, 50, 3-13.
7. Hill,P.M.,(1973), Hyperventilation, breath holding and alveolar oxygen tensions at the breaking point. RESPIRATION PHYSIOLOGY, 19, 201-209.
8. Gross,P.M., et al.,(1976), Role of the carotid bodies in the heart rate response to breath holding in man. JOURNAL OF APPLIED PHYSIOLOGY, 41, 336-340.
9. Godfrey,S., Campbell,E.J.M.,(1968), The control of breath holding. RESPIRATION PHYSIOLOGY, 5, 385-400.
10. Kelson,S.G., et al.,(1976), Effect of hypoxia on the pressure developed by inspiratory muscles during airway obstruction. JOURNAL OF APPLIED PHYSIOLOGY, 40, 372-378.
11. Mithoefer,J.C., in Chapter 38, "Handbook of Physiology", section 3: Respiration, volume 2, edited Fenn,W.O. & Rahn,H., pub American Physiological Society, Washington D.C., 1965.
12. Olsen,C.R.,(1962), The match test: A measure of ventilatory function. AMERICAN REVIEW OF RESPIRATORY DISEASES, 86, 37-40.
13. Snider,T.H., et al.,(1959), Simple bedside test of respiratory function. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 170, 1631-1632.
14. Ross,B.B., et al.,(1955), Physical dynamics of cough mechanism. JOURNAL OF APPLIED PHYSIOLOGY, 8, 264-268.
15. Stein,M., Cassara,E.,(1970), Preoperative pulmonary evaluation and therapy for surgical patients. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 211, 787-790.
16. Stein,M., et al.,(1962), Pulmonary evaluation of surgical patients, JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 181, 765-770.
17. Zocche,G.P., et al.,(1960), Fraction of maximum breathing capacity available for prolonged hyperventilation. JOURNAL OF APPLIED PHYSIOLOGY, 15, 1073-1074.
18. Lockwood,P.,(1973), The principles of predicting risk of post-thoracotomy function related complications in bronchogenic carcinoma. RESPIRATION, 30, 329-344
19. Tisi,G.M.,(1979), Preoperative evaluation of pulmonary function. AMERICAN REVIEW OF RESPIRATORY DISEASE, 119, 293-310.
20. Diament,M.L., Palmer,K.N.V.,(1967), Spirometry for preoperative assessment of airways resistance. LANCET, 1, 1251-1253.
21. Alexander,G.D., et al.,(1981), Maximal inspiratory volume and postoperative pulmonary complications. SURGERY, GYNECOLOGY & OBSTETRICS, 152, 601-603.
22. Feeley,T.W., Hedley-Whyte,J.,(1975), Weaning from controlled ventilation and supplemental oxygen. NEW ENGLAND JOURNAL OF MEDICINE, 292, 903-906.
23. Hodgkin,J.E., et al.,(1973), Preoperative evaluation of the patient with pulmonary disease. MAYO CLINIC PROCEEDINGS, 48, 114-118.
24. Yeager,M.P., et al.,(1987), Epidural anesthesia and analgesia in high risk surgical patients. ANESTHESIOLOGY, 66, 729-736.

Chapter 4.7

UPPER RESPIRATORY TRACT INFECTIONS AND ANAESTHESIA

Upper respiratory tract infections (URTI's) are common disorders, and it is not uncommon for patients to present for surgery with an active URTI. The anaesthetist and surgeon must then decide whether the presence of the URTI introduces an unacceptable increase in operative risk. Usually a safe and conservative course is chosen, and elective surgery is postponed until the URTI has resolved. But this is not always necessary for elective surgery, and is certainly not possible for emergency surgery. It is therefore well worth examining the effects of these common infections on perioperative morbidity.

COMPLICATIONS IN THE OPERATION FIELD

1. Many viral URTI's are characterized in their later phases by secondary bacterial infection, and those with bacterially caused URTI's are already infected with bacteria. Any operation in the head and neck region may be complicated postoperatively by wound infection due to the proximity of the wound to a source of bacterial contamination, e.g. facial, nasal, periorbital and intraocular operations.

2. The severity of any pulmonary infection that occurs secondary to an URTI is likely to be exacerbated by anaesthesia and surgery. Instrumentation of the airway during anaesthesia may introduce pathogens into the lungs. In addition to this, anaesthesia and surgery both suppress specific and non-specific immune function [4].

3. Repeated frequent coughing due to an URTI or respiratory infection secondary to an URTI is not without complications in the operation field. Abdominal stitches may break loose after an intra-abdominal operation, causing a wound hernia or burst abdomen. Bursting of subcutaneous and fascial sutures due to coughing may render hernia repairs ineffective. Repeated coughing may cause vitreous bleeding or retinal detachment after intraocular operations such as lens extraction.

MIDDLE EAR AND PARANASAL SINUS PROBLEMS

A chronic or acute URTI may block drainage from the paranasal sinuses or block the eustachian tubes. This may not be a problem while the patient is breathing room air, but administration of nitrous oxide may cause acute problems, because nitrous oxide diffuses rapidly into gas containing spaces where it is not present until blood and gas compartment nitrous oxide partial pressures equalize. Nitrous oxide diffuses 34 times faster across biological membranes than does nitrogen [6]. The result of this is that nitrous oxide enters

at a faster rate than nitrogen leaves. A sudden influx of gas into an undrained gas containing space elevates the gas pressure inside that space.

1. Patients with obstruction of sinus drainage will develop raised gas pressure inside any blocked sinus. This may cause severe postoperative headache.

2. Patients with obstructed eustachian tubes develop raised middle ear pressure. The maximum pressure increase occurs by 5-10 minutes after starting nitrous oxide administration [1,2]. The raised middle ear pressure may cause tympanic membrane rupture [2,3], or even dislocation of the ossicles [2].

SURGERY AND ANAESTHESIA CAUSED IMMUNE SUPPRESSION

Surgery and anaesthesia are known to depress both specific and non-specific immunity [4]. The greater the stress response of the patient to anaesthesia and surgery, the greater the degree of immune suppression. This depression involves not only cellular and humoral immunity, but also phagocytosis, and such other non-specific factors such as mucociliary clearance too [4]. There is evidence that anaesthesia and surgery may also exacerbate any existing infections [4].

ANAESTHETIC MANAGEMENT

1. While many minor operations can undoubtedly be carried out safely and with no increased incidence of postoperative complications in many cases [5], it is still a good principle to cancel any elective operation while an URTI is present, unless one or a number of conditions are satisfied.

a. The operation is to treat the URTI ,e.g. tonsillectomy for tonsillar abscess, paracentecis of a pus containing middle ear etc.
b. The operation is to treat the consequences of URTI, e.g. grommet insertion in patients with "glue ear", paranasal sinus drainage operations such as the Caldwell-Luc operation. This also simultaneously relieves any increase of gas pressure in the sinuses or middle ear due to nitrous oxide use.
c. The operation is to treat the predisposing cause of repeated URTI, e.g. adenotonsillectomy.

2. If the operation is necessary despite the presence of an URTI, then loco-regional anaesthesia is to be preferred. If general anaesthesia is required, then a few common sense precautions should be taken.

a. The patients should receive anaesthetic drugs, and a technique of anaesthesia that causes minimal postoperative respiratory depression. This reduces the chance of postoperative pulmonary infection secondary to depression of cough, lack of movement, and depression of deep inspiration.
b. Chest physiotherapy is also indicated for those with URTI caused pulmonary infection.
c. The anaesthetist should take precautions not to be infected himself, and also take precautions so as not to transmit the infection to other patients, e.g. wear gloves, and wash his hands before touching another patient.

REFERENCES

1. Casey,W.F., Drake-Lee,A.B.(1982). Nitrous oxide and middle ear pressure. ANAESTHESIA, 37, 896-900
2. Man,A., et al.(1980). Ear Injury Caused by Elevated Intratympanic Pressure During General Anaesthesia. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 24, 224-226.
3. Perreault,L., et al.(1982). Tympanic Membrane Rupture after Anesthesia with Nitrous Oxide. ANESTHESIOLOGY, 57, 325-326.
4. Walton,B.(1978). Anaesthesia, surgery and immunology. ANAESTHESIA, 33, 322-348.
5. du Moulin,G.C., Hedley-Whyte,J.(1983). Hospital-associated Virus Infection and the Anesthesiologist. ANESTHESIOLOGY, 59, 51-65.
6. Munson,E.S.(1974). Transfer of nitrous oxide into body air cavities. BRITISH JOURNAL OF ANAESTHESIA, 46, 202-209.

Chapter 4.8

PULMONARY INFECTIONS AND ANAESTHESIA

No patient with an active pulmonary infection should be permitted to undergo elective surgery. Anaesthesia and surgery both may exacerbate any respiratory infection.

EFFECTS OF ANAESTHESIA AND SURGERY

1. Depression of mucociliary clearance by anaesthetic drugs.

2. Many drugs used for general anaesthesia depress both the hypoxic and hypercapnic respiratory drives [see table 4.5.1]. This reduces pulmonary ventilation, exacerbates postoperative hypoxaemia, and predisposes to the development of atalectasis. All of this is especially likely when respiratory movements are limited by pain, as occurs after thoracic or upper abdominal surgery.

3. Muscle weakness due to prolonged action, or inadequate reversal of non-depolarizing muscle relaxant drugs also depresses respiration.

4. Depression of either the cough reflex by drugs, (e.g. opiates, barbiturates), or cough strength, (e.g. non-depolarizing muscle relaxants, pain caused limitation of cough), also decreases clearance of bronchial secretions and predisposes to exacerbation of any respiratory infection.

5. Endobronchial or endotracheal instrumentation may introduce more pathogens into already infected lungs, or spread any infection further throughout the lungs.

6. General anaesthesia and surgery depress specific and nonspecific immunity to infection [see chapter 4.7].

ANAESTHETIC MANAGEMENT

Preoperative.

1. It is obvious that no patient with an active respiratory infection should be permitted to undergo elective surgery. The increased risk of postoperative respiratory complications is unacceptable. Patients undergoing emergency operations must be managed for both the condition which is being operated as well as their respiratory infection.

Categories of operation where the patient must be operated on despite an active respiratory infection are listed below.

a. Surgically correctable respiratory infections, e.g. lung abces, or lobectomy for bronchiectasis, etc.
b. If the condition for which the person is to be operated is a greater threat to life or function than any potential risk from the respiratory infection [see chapter 1.3].

2. Antibiotics are required in the perioperative period. The exact type of antibiotic depends upon the nature of the planned operation and the infecting organism.

3. No premedication is required, neither sedative nor anticholinergic. The former may depress respiration, while the latter may cause significant thickening of secretions, rendering them difficult to shift.

Anaesthesia.

The exact anaesthetic technique to be employed depends on the nature of the surgery to be carried out.

1. Loco-regional anaesthetic techniques are to be preferred where possible. They may either be used as the sole form of anaesthesia, or as part of a general anaesthetic technique so as to minimize the dosages of any analgesic or anaesthetic drugs which may cause postoperative respiratory depression. In addition, if the analgesia is extended into the postoperative period, postoperative wound pain is eliminated or reduced such that pain caused inhibition of cough, and hypoventilation are effectively reduced. The patient is then able to breath deeply and maintain normal alveolar ventilation, with as a consequence postoperative hypoxaemia is reduced. The ability to cough effectively means that bronchial secretions are more efficiently cleared.

2. Any general anaesthetic technique should be adjusted to the clinical and surgical circumstances. By preference, a technique should be used with endotracheal intubation and controlled ventilation. This ensures adequate intraoperative oxygenation, as well as enabling efficient removal of any endobronchial secretions.

Chapter 4.9

CHRONIC OBSTRUCTIVE AIRWAYS DISEASE

Chronic obstructive airways disease (COAD) comprises the syndromes of asthma, chronic bronchitis, and emphysema. All these disease are characterized by obstruction of the small airways which manifests predominantly during expiration. The degree of airway obstruction is not as great during inspiration, as the small airways are held open by lung parenchyma in this phase of respiration. The anaesthetic problems associated with COAD have been well reviewed recently [1,2], and the anaesthetically most significant points are discussed below.

PROBLEMS

1. Restriction of expiratory airflow.

Restriction of expiratory airflow limits the ease with which bronchial secretions and pus may be shifted by coughing or forceful expiration, and so patients with COAD have an increased risk of developing postoperative pulmonary infections.

Because of the restriction to expiratory gas flow, gas exchange is abnormal due to hypoventilation of a larger than normal lung volume, and so patients with COAD also have an increased risk of developing hypoxaemia, if they are not already hypoxaemic [see chapter 4.4].

2. Effects of drugs used for management of COAD.

Drugs that are used for management of COAD may affect the action of drugs used during anaesthesia.

a. Xanthine derivatives.

Xanthine derivatives such as theophylline or aminophylline are frequently used for chronic and acute therapy of patients with COAD. These drugs antagonize the enzyme phosphodiesterase which is present in many tissues, including the motor nerve terminals. The effect of phosphodiesterase inhibition in skeletal muscle motor nerve terminals is to enhance release of acetylcholine into the synapses. This is the most likely explanation for the observation that these drugs antagonize the action of non-depolarizing muscle relaxant drugs, e.g. pancuronium, tubocurarine, and prolong the action of depolarizing muscle relaxants such as suxamethonium [3].

b. Catecholamine agonists.

Many of the ß-adrenergic agonist drugs used for treatment of COAD also cause some degree of central nervous system arousal, an effect which increases the amounts of anaesthetic agents required to ensure sleep during general anaesthesia.

3. Increased risk of laryngospasm.

The frequency of laryngospasm during anaesthesia and surgery is increased in patients with COAD. This is most likely due to the known increased laryngeal reactivity to instrumentation of the upper airways, stimuli from oropharyngeal airways, blood, saliva etc.

4. Increased chance of bronchospasm.

a. Histamine.

Persons with COAD are very sensitive to the bronchoconstrictive effects of histamine. The use of drugs such as d-tubocurarine, alcuronium, atracurium which cause significant histamine release should be avoided so as to minimize the chances of intraoperative bronchospasm.

b. Acetylcholine.

Persons with COAD are also very sensitive to the bronchoconstrictive effects of acetylcholine. Drugs which of themselves have acetylcholinergic activity such as suxamethonium, and drugs which enhance acetylcholinergic activity such as neostigmine, edrophonium, pyridostigmine, physostigmine may cause bronchospasm.

c. Mechanical and surgical stimulation.

Airway reactivity is increased in patients with COAD. Both direct mechanical stimulation of the airways as during anaesthesia, or surgical stimulation elsewhere in the body can initiate bronchospasm, laryngospasm, or both.

ANAESTHETIC MANAGEMENT

Preoperative.

1. Preoperative pulmonary function should be optimal. If necessary delay operation until respiratory function has been improved by a period of intensive drug and physiotherapy. No COAD patient should undergo an elective operation with an active lung infection.

2. The purpose of any premedication in a patient with COAD is to minimize the chance that anaesthetic drugs or manipulations will provoke an acute episode of bronchospasm. A number of methods are available to reduce the likelihood of bronchospasm.

a. Reduce preoperative anxiety as this may induce bronchospasm. Administer a benzodiazepine or barbiturate sedative preoperatively.
b. Administer a bronchodilator drug, or a combination of drugs. Use the usual combination of a xanthine, such as theophylline administered by suppository or intravenous infusion, plus any ß-adrenergic stimulant normally used by the patient.
c. Administer an anticholinergic drug preoperatively. This has a number of desirable effects.
    - Bronchial gland secretion rate is increased in patients with COAD, and may be even more increased by some anaesthetic drugs and techniques as well as opera-

tion. Excessive quantities of bronchial secretions increase the chance of postoperative laryngospasm, and cause excessive coughing. Excessive coughing is certainly not desirable as suture lines may be ruptured by protracted forceful coughing. Intramuscular administration of 0.5 mg atropine significantly reduces the bronchial gland secretion rate within 30 minutes after administration, and the effect lasts 3-4 hours in an adult [4].

- Anticholinergic drugs also improve mucociliary clearance by increasing the viscosity of bronchial secretions [4].
- Anticholinergics such as atropine also cause a significant degree of bronchodilation as is indicated by the 30% increase of respiratory dead space that is measured after intramuscular administration of 0.5 mg atropine in adults, an effect that lasts for up to 3 hours after injection [4].

d. Corticosteroids are used in the management of acute episodes of bronchospasm. They act by increasing ß-adrenergic receptor sensitivity to ß-adrenoreceptor stimulating drugs. This effect is clinically significant by one hour after intravenous administration of 40 mg of prednisolone to adult patients [6]. For this reason it is often useful to administer a single dose of a corticosteroid as a part of the premedication of COAD patients.

Table 4.9.1.
Premedication scheme for adult COAD patients. Administer all the drugs simultaneously 2 hours preoperatively,

- Diazepam - 10 mg orally.
- Theophylline suppository 5 mg/kg

OR

Theophylline infusion [table 4.9.2]

- Atropine - 0.5 mg imi.
- Prednisone 25 mg imi.

3. A wholly empirical premedication based on the above, and used by the author is given in table 4.9.1. It should be noted that all the drugs are administered simultaneously. This is simply for the practical reason that it is simpler for the nursing staff to administer all drugs at once. The duration of the desired actions of all the drugs mentioned in table 4.9.1 is longer than two hours, and prednisone does not begin to exert a significant effect until about 1-2 hours after intramuscular administration in any case.

Intravenous theophylline infusions are commonly used for prevention and therapy of bronchospasm in COAD patients. The infusion rate is usually calculated as shown in table 4.9.2.

Table 4.9.2.
Theophylline infusion rates for adults.

Loading dose	= 5-6 mg/kg.
Maintenance dosage	= 20 mg/kg/day for young adults. = 16 mg/kg/day for patients above 50 years. = 10 mg/kg/day for those with heart failure or liver disease.

5. The normal medication that the patient ingests for management of COAD should be continued in the postoperative period. However the dosage and type of drugs used may require to be adjusted because of perioperative circumstances, e.g. the impossibility of oral ingestion necessitating intravenous infusion of the drugs.

Anaesthesia.

1. Loco-regional anaesthetic techniques should be employed where feasible, as they cause minimal disturbance of pulmonary function.

2. If general anaesthesia is required there are various considerations when selecting the most appropriate drugs and general anaesthetic techniques.

a. A technique should be used with endotracheal intubation and controlled ventilation [see chapter 4.6]. This will guarantee adequate ventilation and oxygenation in spite of poor lung function. Patients with lesser degrees of COAD may undergo any general anaesthetic technique provided that some caution is exercised with regard to choice of drugs as is discussed below.
b. Induction of anaesthesia in patients with severe bronchospasm is best done with ketamine, as this has a bronchodilator effect [5]. Otherwise it makes very little difference which intravenous hypnotic drug is used [1,2].
c. All opiates without exception, including pethidine, increase airway resistance, so it make very little difference which opiate is used intraoperatively. However morphine and alfentanil should perhaps be avoided as morphine causes some degree of histamine release, while alfentanil has a pronounced muscarinic effect in some patients.
d. Volatile anaesthetic agents all possess bronchodilator properties, the most potent bronchodilator vapor being diethyl-ether. General anaesthesia is less likely to be as-

sociated with bronchospasm when a volatile agent is used as primary anaesthetic agent or as a supplement.

e. The acetylcholinesterase blocking drugs such as neostigmine should be used with caution, as their use may be followed by bronchospasm. To minimize the chance of this, try to avoid the use of these drugs by allowing non-depolarizing muscle relaxant effects to disappear spontaneously. If their use cannot be avoided, administer atropine 3 minutes before the administration of neostigmine, in the hope that this will block the effects of the subsequently increased acetylcholine concentration.

f. Light general anaesthesia should be avoided. The presence of an endotracheal tube, or oropharyngeal airway, instrumentation of the pharynx or airways, blood, or secretions, as well as pain all may initiate cardiac arrhythmias, bronchospasm, or laryngospasm. The chances of such events are minimized by adequate general anaesthesia, regional anaesthesia combined with light general anaesthesia, and adequate local anaesthesia of the larynx and trachea.

Postoperative.

The degree of postoperative care required depends upon the severity of the COAD and the nature of the operation.

Table 4.9.3.

Criteria for adults defining the risk of developing respiratory depression due to oxygen administration, according to parameters measured during spontaneous air breathing while not under the influence of respiratory depressant drugs.

LOW RISK	- P_aO_2 > 8-9 kPa (60-70 mmHg) P_aCO_2 normal
INCREASED RISK	- P_aO_2 < = 8-9 kPa (60-70 mmHg) - P_aCO_2 = > normal - MBC < 40% of predicted value - VC < 50% of predicted value

ADMINISTRATION OF OXYGEN TO PATIENTS WITH COAD

Because of the possibility of the occurrence of respiratory depression when oxygen is administered to patients with COAD, many physicians are hesitant to administer oxygen, even to patients who would benefit from oxygen therapy and never develop respiratory depression. What then defines the group of patients who will develop, or are likely to develop respiratory depression as a result of oxygen administration?

Chronically hypercarbic persons with COAD have an elevated plasma, and whole body HCO_3^- concentration. Because of this, a given change of PCO_2 causes less change in the plasma pH than the same change of PCO_2 in a normal person. Regulation of respira-

tion by PCO_2 is purely by virtue of the pH change induced by acute alterations of PCO_2. This is effect is lost or minimal if the HCO_3^- concentration is elevated high enough [see Henderson-Hasselbach equation in chapter 13.1]. If carbon dioxide control of respiration is lost, all that remains to stimulate respiration is the hypoxic drive. This only begins to become active when the P_aO_2 is lower than 8 kPa (60 mmHg) [see chapter 4.5]. Therefore patients with a preoperative P_aO_2 greater than 8-9 kPa (60-67.5 mmHg) are unlikely to have a purely hypoxic respiratory drive. Those persons who normally have a $P_aO_2 <= 8$-9 kPa (60-67.5 mmHg), with or without hypercapnia are likely to have their respiration regulated principally by a hypoxic drive. Indeed this is confirmed by clinical investigation of persons with COAD, where it has been found that patients at risk of developing hypercapnia as a result of oxygen administration normally have a VC < 50% of the predicted value, a MBC of less than 40% of the predicted value, and a $P_aO_2 <= 8$ kPa (60 mmHg), with or without hypercapnia [7].

From the above it is apparent that patients with COAD may be divided into two categories for oxygen therapy according to the likelihood of developing respiratory depession due to oxygen administration. The criteria defining those persons with an increased risk of oxygen induced respiratory depression, and those with a low risk are shown in table 4.9.3. Persons who are not at risk of developing respiratory depression due to administration of oxygen may be administered any desired concentration of oxygen. But spontaneously breathing persons with an increased risk of developing respiratory depression due to oxygen administration should never be administered more than 30% oxygen [7]. This latter may be achieved by means of administration of oxygen through a calibrated oxygen mask, or administration of oxygen through a nasopharyngeal catheter at a rate of 2-3 l/min.

REFERENCES

1. Kingston,H.G.G., Hirshman,C.A.(1984). Perioperative Management of the Patient with Asthma. ANESTHESIA AND ANALGESIA, 63, 844-855.
2. Hirshman,C.A.(1983). Airway Reactivity in Humans. ANESTHESIOLOGY, 58, 170-177.
3. Standaert,F.G., Dretchen,K.L.(1981). Cyclic Neucleotides in Neuromuscular Transmission. ANESTHESIA AND ANALGESIA, 60, 91-99.
4. Shutt,L.E., Bowes,J.B.(1979). Atropine and hyoscine. ANAESTHESIA, 34, 476-490.
5. White,P.F., et al.(1982). Ketamine - Its Pharmacology and Therapeutic Uses. ANESTHESIOLOGY, 56, 119-136.
6. Ellul-Micallef,R., Fenech,F.F.,(1975), Effect of intravenous prednisolone in asthmatics with diminished adrenergic responsiveness. LANCET, 2, 1269-1271.
7. Froeb,H.F., et al.,(1958), The induction of respiratory acidosis by oxygen breathing. AMERICAN REVIEW OF TUBERCULOSIS, 77, 737-748.

Chapter 4.10

UPPER AIRWAY OBSTRUCTION

This chapter deals with the problems of airway obstruction occurring in the airways from the pharynx to the carina.

ASSESSMENT

Clinical history.

When taking the clinical history from a patient with upper airway obstruction, there are several points requiring specific questioning.

1. Exercise tolerance.

The smaller the exercise tolerance, the greater the degree of obstruction.

2. Can the patient lie flat?

a. This gives an idea of the degree of the respiratory "reserve". The FRC is normally lower in the supine position than when sitting or standing. Similarly the CC (closing capacity) is also increased by the supine or prone positions. These effects are exacerbated by respiratory obstruction. Hypoxia secondary to alveolar hypoventilation due to the relative changes of FRC and CC may make the supine position impossible in some patients with severe upper airway obstruction.

b. Mediastinal or peritracheal tumors situated between the sternum and trachea may be large enough to cause tracheal compression in the supine position, purely by the effect of their weight upon the trachea. This effect is further exacerbated by any tracheomalacia that may be present.

3. Can the patient sleep, and if so in what position?

a. Severe respiratory obstruction may cause such distress due to the struggle to breathe that sleep is impossible.

b. During sleep, and especially during Rapid Eye Movement (REM) sleep, muscle relaxation occurs. This muscle relaxation is particularly prominent in the neck muscles, but is also observed in other muscles too. Relaxation of tongue, palatal and pharyngeal muscles during sleep causes partial obstruction of the upper airway, and is one of the causes of snoring. Lying on the side, or in the prone position alleviates the problem, as the tongue when it relaxes can no longer sag into the pharynx. Upper respiratory obstruction, plus sleep induced muscle relaxation of tongue, pharyngeal, and palatal muscles, may cause such a de-

gree of airway obstruction that sleep in the supine position is impossible, or the person awakens repeatedly as a result of airway obstruction.

A person with upper respiratory tract obstruction who can sleep undisturbed in the supine position is able to breath adequately in the presence of a degree of muscle relaxation due to REM sleep. This has consequences for the type of anaesthetic induction that is able to be safely performed. Such a person is unlikely to develop complete respiratory obstruction while spontaneously breathing an anaesthetic gas, as this also does not cause complete relaxation of oropharyngeal muscles.

Physical examination.

Physical examination may be used to grade the patient according to a simple classification of severity of airway obstruction.

Class

1. Stridor is not present during rest. Only occurs during coughing, crying or physical exertion.

2. Stridor is present during rest, but there is no use of accessory respiratory muscles, nor indrawing of intercostal spaces. No cyanosis, nor raised pulsus paradoxus.

3. Stridor is present during rest, significant use of accessory respiratory muscles is present, as well as a pulsus paradoxus > 10 mmHg (normal is 0-5 mmHg), indrawing of intercostal spaces, but no cyanosis or exhaustion.

4. Stridor is present during rest, along with indrawing of intercostal spaces, use of accessory respiratory muscles, much increased pulsus paradoxus, plus cyanosis, and sometimes exhaustion as a result of the enormous respiratory effort required.

MANAGEMENT OF UPPER AIRWAY OBSTRUCTION

1. Most of the patients are more comfortable sitting upright. In addition less tracheal compression occurs in this position in patients whose obstruction is due to a mediastinal tumor.

2. Patients whose disease severity is in classes 1 and 2, require no immediate resuscitative measures. The cause of the stridor can, and should be thoroughly investigated prior to treatment.

3. Patients in class 3 require more urgent investigation, and moderately urgent therapy if they are not to progress to class 4. However unlike class 4 patients there is some time available for investigation of the cause of obstruction.

4. Class 4 patients constitute a medical emergency. They require immediate endotracheal intubation or tracheostomy to provide a clear airway, otherwise they will die. Treatment is especially urgent in those persons who are exhausted.

5. If the person is severely hypoxic as a result of respiratory obstruction, tracheostomy is best performed using local anaesthesia, while concurrently administering oxygen to the patient.

6. In situations where tracheostomy under local anaesthesia is not practicable, general anaesthesia must be administered to enable a tracheostomy or endotracheal intubation to be carried out. There are some factors which must be kept in mind when planning endotracheal intubation.

a. If endotracheal intubation is planned, the initial intubation should be performed by the easiest route possible, i.e. the oral route.
b. Subsequently, and only provided that the condition of the patient, or the clinical circumstances permit, naso-tracheal intubation should be performed, as this is more comfortable for the awake patient.
c. Endotracheal intubation should only be done after consultation with the surgeon treating the patient. It should always be done in the presence of a surgeon ready and capable of carrying out immediate and rapid tracheostomy in case the attempt(s) at endotracheal intubation fail.

ANAESTHETIC MANAGEMENT

Premedication.

1. NO hypnotic or sedative drugs should be administered. All these drugs depress the respiratory drive, and this may be sufficient to cause severe hypoxaemia is an already hypoxic patient.

2. Anticholinergic drugs may be administered as these reduce the amount of secretions in the upper airway.

Preparations for anaesthesia.

1. A large assortment of cuffed and uncuffed endotracheal tubes must be present and ready for immediate use.

2. An assortment of endotracheal tube introducers must be ready for immediate use.

3. Magill forceps for guiding tubes and introducers into position if necessary.

4. More than one functioning laryngoscope is required, in case one fails.

5. A small diameter rigid bronchoscope, and a person capable of using it. This can be used to dilate and bore through an obstructed region so creating an air passage should the situation become desperate.

6. Equipment and personnel ready to perform an immediate tracheostomy should attempt(s) at intubation fail.

7. The drugs that should be immediately available are thiopentone or etomidate for use as required, atropine for treatment of bradycardia, and suxamethonium to facilitate endotracheal intubation as required. Lignocaine spray for use upon the larynx or trachea should regional analgesia be required to facilitate investigation of upper airway pathology while the patient is breathing spontaneously.

8. Adequate monitoring, blood pressure, ECG, and if possible transcutaneous oxygen saturation measurement.

9. A well trained assistant is absolutely essential.

Induction of anaesthesia.

Gaseous induction of anaesthesia is the preferred technique. This type of induction is to be preferred as upper airway patency is maintained only by muscle tone in some patients [3]. Total loss of muscle tone as occurs after administration of neuromuscular blocking drugs may cause further, or total airway obstruction [3]. If the patient cannot be very rapidly intubated, or a rapid tracheotomy performed, death will occur. Anaesthetic vapors also cause muscle relaxation, but the degree of relaxation is not as extreme as with neuromuscular blocking drugs. Because of this airway patency is better maintained during a gaseous induction. An indication that the person is likely to tolerate a gaseous anaesthetic induction is provided by a history of being able to sleep without interruption in the supine position. If during a gaseous induction, it is found upon testing, that the airway is such that the patient may be manually ventilated without difficulty, then a muscle relaxant may be administered with safety, and the whole procedure of endotracheal intubation is very much simplified.

Gaseous induction of anaesthesia is slow because of the restricted gas flow due to airway obstruction. Patience is required to achieve a depth sufficient for laryngoscopy and endotracheal intubation.

The choice of carrier gas for the anaesthetic vapor makes a difference to both speed of induction and oxygenation of the patient. Gas flow through a stenosis is non-laminar gas flow, i.e. turbulent gas flow. As such the situation is physically equivalent to flow through an orifice [2]. Flow (**F**), of gases through a narrow orifice is determined by the area of the orifice (**A**), the gas pressure difference across the orifice (Δ**P**), and the density of the gas (**D**), but NOT the viscosity of the gas [1]. The relationship below is derived from Bernoulli's equation for fluid flow [1].

$$F = A \times ((2 \times \Delta P)/D)^{1/2}$$

Various carrier gases are available. Their densities relative to that of air are set out in table 4.10.1, together with the gas flows for these mixtures, relative to air, that are able to be developed for a given respiratory effort. In addition the amount of oxygen entering the lungs, relative to air, for a given respiratory effort is also shown.

From table 4.10.1 it is seen that the flow through any stenosis is greatest for the helium/oxygen mixtures, implying that gaseous anaesthetic induction time will be reduced when such mixtures are used. In addition the amount of oxygen entering the lungs for a given respiratory effort is greater, due to both greater gas flow, and higher inspired oxygen concentration. More oxygen entering the lungs per unit time means that any hypoxaemia will be alleviated. But despite all these advantages, there is no hard indication for using helium/oxygen mixtures for anaesthetic purposes, [see next paragraph]. The main indication for administering a helium/oxygen gas mixture is to reduce the work of breathing in patients whose respiratory obstruction cannot be immediately relieved. In this way any exhaustion due to increased respiratory effort is reduced [4].

The best and cheapest mixture for anaesthetic purposes is 100% oxygen. The total gas flow into the lungs for a given respiratory effort is only slightly less than that for

helium/oxygen mixtures. But it is not much less than for air, while the flow of oxygen into the lungs for a given gas flow into the lungs is much greater than for any other gas mixture. Should the airway suddenly become totally obstructed, there is a greater oxygen reserve in the body to maintain life while an emergency tracheostomy is performed. The slightly increased gaseous anaesthetic induction speed observed with the helium/oxygen mixtures is no great advantage in comparison with the improved oxygenation and oxygen reserve. For this reason, the value of helium/oxygen gas mixtures in anaesthesia is questionable.

Nitrous oxide/oxygen mixtures are the least desirable gas mixtures because the flow of gas into the lungs for a given respiratory effort is less than that for the other mixtures. This implies a very much slower anaesthetic induction speed than with the other mixtures. True, the oxygen transport into the lungs is increased, but as is obvious from table 4.10.1 the use of these mixtures has absolutely no advantage in comparison with 100% oxygen.

Table 4.10.1.
The density of various gas mixtures is shown, along with the total gas flow as, well as the oxygen flow through a stenosis relative to air, assuming a constant inspiratory effort and stenosis diameter.

GAS MIXTURE	DENSITY (relative to air)	FLOW THROUGH STENOSIS (relative to air)	FLOW OF OXYGEN INTO LUNGS (relative to air)
AIR	1	1	1
100% O_2	1.12	0.95	4.51
50% N_2/50% O_2	1.33	0.87	2.10
70% N_2/30% O_2	1.40	0.84	1.20
50% He_2/50% O_2	0.70	1.20	2.85
70% He_2/30% O_2	0.53	1.37	1.96

Maintenance of anaesthesia and endotracheal intubation.

1. When the patient is in a sufficiently deep plane of anaesthesia, careful and gentle laryngoscopy and endotracheal intubation may be performed. Laryngoscopy or bronchoscopy of a spontaneously breathing patient is facilitated by topical anaesthesia.

2. Maintenance of anaesthesia is carried out using drugs and techniques appropriate to the nature of the procedure to be undergone by the patient.

Postoperative management.

Extubation of the patient after the surgical, or other procedure has occurred should only be done if it is certain that the patient is able to breathe adequately through the obstructed airway. One test of this is to obstruct the endotracheal tube, after deflating any tracheal cuff, and testing to see if the airway diameter is such that the patient can breathe around the tube. If this is not so, then the patient should remain intubated until the cause of the obstruction has resolved, been treated, or tracheostomy performed.

REFERENCES

1. Sears,F.W., et al.(1978). "University Physics", 5th edn., pub. Addison Wesley, page 237, equation 13.11.
2. Friman,L., et al.(1976). Stenosis following tracheostomy - A quantitative study of long term results. ANAESTHESIA, 31, 479-493.
3. Mackie,A.M., Watson,C.B.(1984). Anaesthesia and mediastinal masses - A case report and review of the literature. ANAESTHESIA, 39, 899-903.
4. Mizrahi,S., et al.(1986). Major airway obstruction relieved by helium/oxygen breathing. CRITICAL CARE MEDICINE, 14, 986-987.

Chapter 4.11

PRIMARY LUNG TUMORS

Primary lung tumors may present the anaesthetist with a number of problems. The ones of most significance for anaesthetic practice are discussed below.

PROBLEMS

1. Airway obstruction.

A tumor may cause partial or complete obstruction of the airways anywhere from the level of the trachea to the smallest of the alveolar ducts. Hypoxaemia will occur if a sufficient volume of lung tissue can no longer take part in gas exchange because of occlusion of the airways. Infection may occur in the regions of lung distal to any obstruction.

2. Endocrine disorders [1].

Clinically manifest Cushing's syndrome occurs in 0.4-2% of all patients with primary lung tumors, and 25% of all those with small cell cancers. Clinically evident inappropriate ADH secretion occurs in 8-10% of patients with small cell tumors. Plasma and urinary calcitonin concentrations are elevated in 17-75% of all patients with primary lung tumors. Non-metastatic hypercalcaemia occurs in 1-7.5% of all patients with primary lung tumors, and in 15% of patients with squamous cell carcinoma. Gynecomastia is evident in 0.5-0.9% of all patients, and in 2% of patients with small cell tumors. Hyperthyroidism occurs in up to 1.4% of all patients with lung tumors.

The clinical anaesthetic consequences of these endocrinopathies and hypercalcaemia are dealt with in the relevant chapters of this book.

3. Myopathy, (Eaton-Lambert syndrome).

A myasthenic state occurs in 1% of all patients with lung tumors, and in 6% of those with small cell tumors [1]. The weakness is typically in the shoulder arm and thigh muscles, with sparing of ocular and bulbar muscles. It appears to be due to a defect in the calcium mediated release of acetylcholine from the nerve terminals [3]. These patients are very sensitive to the effects of both depolarizing and non-depolarizing muscle relaxants [2].

Neostigmine does not, but 4-aminopyridine does, reverse the muscle weakness due to the Eaton-Lambert syndrome [2]. As the action of 4-aminopyridine is thought to be due to phosphodiesterase inhibition in the nerve terminals, other phosphodiesterase blocking drugs such as physostigmine, theophylline, or azathioprine should also reverse the myopathy [4].

4. Coexisting disease.

Many patients presenting with a primary lung tumor also have coexisting cardiopulmonary disease. Certainly many have a history of smoking, in which case they also have an increased chance of having cardiovascular and chronic obstructive airways disease.

ANAESTHETIC MANAGEMENT

Preoperative.

1. Adequate preoperative investigation and treatment of any coexisting medical problems is required.

2. An anticholinergic premedication is useful, especially when instrumentation of the airway is contemplated. Reduction of bronchial secretion rate reduces the chance that there will be any significant volume of secretions accumulating distal to a bronchial obstruction, as well as making any procedure such as bronchoscopy or laryngoscopy easier.

3. A sedative premedication may be administered to those patients who are not hypoxaemic.

Anaesthesia.

1. If the operation permits, loco-regional anaesthesia is preferable. Instrumentation of the airway is avoided, as well as the use of significant quantities of respiratory depressant drugs. If general anaesthesia is required there is really no preferred technique or drugs.

2. If the patient has a myopathy, and is to receive general anaesthesia, use a nerve stimulator so as to be able to dose any neuromuscular blocking drugs according to requirements. Such patients should also be mechanically ventilated to prevent hypoventilation due to the muscle weakness.

Postoperative.

1. Postoperative management depends on the type of anaesthesia and surgery.

2. Patients with significant muscle weakness may require postoperative mechanical ventilation.

REFERENCES

1. de Vita et al.(1982). "Cancer - Principles of Practice of Oncology", pub. Lippincott.
2. Agoston,S., et al.(1978). Effects of 4-aminopyridine in Eaton Lambert syndrome. BRITISH JOURNAL OF ANAESTHESIA, 50, 383-385.
3. Isselbacher,K.J., et al.(1980)."Harrison's Principles of Internal Medicine", pub. 9graw-Hill.
4. Standaert,F.G., Dretchen,K.L.(1981). Cyclic Nucleotides in Neuromuscular Transmission. ANESTHESIA AND ANALGESIA, 60, 91-99.

Chapter 4.12

SMOKING

Tobacco smoking is a common habit which causes a vast range of pathophysiology. It is necessary that the anaesthetist have an idea of the problems caused by smoking as it significantly affects perioperative morbidity.

PROBLEMS [1,2]

Effects of smoking one cigarette.

Even smoking one cigarette can profoundly affect pulmonary function, albeit temporarily. Some of these effects are listed below.

- A 30% increase of pulmonary airway resistance.
- A 20% decrease of dynamic lung compliance.
- Tracheobronchial ciliary paralysis.
- Partial pressure of carbon monoxide in the blood rises.

Effects of chronic smoking.

1. The bronchial gland and goblet cell numbers are increased to 15 times their pre-smoking numbers.

2. There is loss of tracheobronchial ciliary cells. After 3 months of chronic smoking the ciliary cell density per unit area mucosal surface is reduced to only 10% of the pre-smoking density.

3. Alveolar macrophage activity is reduced.

4. The FEV_1/VC ratio is decreased.

5. The carbon monoxide partial pressure is increased so that 3-15% of the haemoglobin is in the form of carbomonoxyhaemoglobin in chronic heavy smokers, i.e. >20 cigarettes per day.

6. Chronic smokers have an increased chance of developing chronic obstructive airways disease as well as cardiovascular disease.

7. Tracheal, laryngeal, and bronchial reactivity is increased.

Anaesthetic problems.

1. Chronic smoking of 10 cigarettes and more per day increases the chance of experiencing postoperative respiratory complications. This is not surprising in view of the fact that the mucociliary transport system, as well as macrophage function, and the FEV_1/VC ratio are decreased. This is in addition to the increased volumes of bronchial gland secretions being produced.

2. Tracheal, bronchial, and laryngeal irritability are increased, and it is found that chronic smokers have an increased risk of perianaesthetic laryngospasm and bronchospasm due to the stimulation caused by anaesthetic apparatus, blood and secretions in the airways.

3. A carbomonoxyhaemoglobin concentration of as little as 4.5% can cause a significant reduction of the myocardial work level at which angina pectoris occurs in patients with severe coronary vascular disease. Carbomonoxyhaemoglobin has the same effects as anaemia, as carbomonoxyhaemoglobin does not transport oxygen and effectively reduces the amount of haemoglobin available to do so.

4. The cardiopulmonary diseases associated with smoking may also require special attention and management, e.g. coronary vascular disease, peripheral vascular disease, chronic obstructive airway disease etc.

REQUIRED DURATION OF PREOPERATIVE ABSTINENCE FROM SMOKING

Smoking should be stopped prior to any elective surgery so as to minimize the increased rate of postoperative pulmonary complications due to smoking, e.g. atelectasis, bronchopulmonary infection, pneumonia etc. The period of abstinence required depends on whether it is desired to only eliminate the carbomonoxyhaemoglobin, or to also reduce the increased postoperative respiratory complication rate.

1. Elimination of carbomonoxyhaemoglobin.

Carbomonoxyhaemoglobin has an elimination half life of between 4-11 hours. The greater the respiratory minute volume the shorter the elimination half life. For 90% elimination of the carbomonoxyhaemoglobin to have occurred, the smoker should cease smoking for 3-4 elimination half lives. This means that smoking should be stopped for at least 24 hours prior to any operation.

2. Reduction of postoperative respiratory complications.

The respiratory complication rate after major anaesthesia and surgery only starts to decline after a minimum of 8 weeks abstinence from smoking [2]. Abstinence of less than 8 weeks prior to elective surgery is useless if the intention is to reduce the pulmonary complication rate.

ANAESTHETIC MANAGEMENT

Preoperative.

Because of the increased bronchial secretion rate, an anticholinergic premedication is advisable. Preoperative sedation may be administered as thought necessary.

Anaesthesia.

1. Heavy smokers with significant respiratory disease should preferably undergo surgery under loco-regional anaesthesia, provided that the operation and mental state of the patient permit it. This minimizes the chance of postoperative respiratory depression due to effects of general anaesthetic drugs.

2. If general anaesthesia is required, no specific general anaesthetic technique can be recommended. Management of general anaesthesia in these patients depends on the severity of any coexisting disease, or disorders caused by smoking.

REFERENCES

1. Pearce,A.C., Jones.R.M.(1984). Smoking and Anesthesia: Preoperative Abstinence and Perioperative Morbidity. ANESTHESIOLOGY, 61, 576-584.
2. Warner,M.A., et al.(1984). Preoperative Cessation of Smoking and Pulmonary Complications in Coronary Artery Bypass Patients. ANESTHESIOLOGY, 60, 380-383.

Part 5

HAEMATOLOGICAL PROBLEMS AND ANAESTHESIA

Some patients coming for surgery have a haematological disorder. Most haematological disorders are not affected by anaesthesia and surgery. But the anaesthetist and surgeon should be conversant with the management of those disorders that are exacerbated or affected by anaesthetic or surgical procedures.

Haematological diseases may cause problems in the perioperative period by a number of mechanisms.

1. By causing anaemia, with all its associated problems [see chapter 5.1].

2. The disorder may be exacerbated by anaesthesia and surgery, e.g. sickle cell disease.

This section deals with the problems caused by those few haematological disorders which are affected by anaesthesia and surgery, and themselves have an effect on perioperative management. Other haematological disorders which do not affect perioperative management, nor are affected by surgery and anaesthesia are not discussed.

Chapter 5.1

ANAEMIA

Anaemia is a common manifestation of many disorders, both haematological and non-haematological. Any specific treatment of most forms of anaemia is impossible in the short perioperative period, unless anaemia is due to haemorrhage. For this reason, the anaesthetist usually looks at most types of anaemia from the viewpoint of the physiological consequences rather than at a specific diagnosis, unless the particular disorder causing the anaemia affects the type of anaesthesia that can be administered. The principal effect of anaemia is to reduce the oxygen transporting capacity of blood, and this is the cause of the majority of the clinical effects of anaemia.

OXYGEN TRANSPORT

The function of haemoglobin is to transport oxygen. A reduction of the haemoglobin concentration reduces the oxygen transporting capacity of the blood. The concept of oxygen transport has been discussed in chapter 4.3. Nearly all the problems caused by anaemia of any cause are due to reduced tissue oxygen availability, and the cardiopulmonary adaptations required to maintain adequate tissue oxygenation.

Equation 5 of chapter 4.3 may be rearranged to show the relationship of cardiac function to haemoglobin concentration very clearly. One then gets the relationship below.

$$S_vO_2 = S_aO_2 - \frac{V_{O2}}{0.216 \times CO \times [Hb]} \quad \text{.....(1)}$$

CO = cardiac output (l/min).
V_{O2} = oxygen consumption (ml/min).
[Hb] = haemoglobin concentration in mmol/l, (1 mmol/l = 1.612 g%).
S_aO_2 & S_vO_2 = percentage arterial and venous saturation of haemoglobin with oxygen (%).

The variation of S_vO_2 with the [Hb] and the cardiac output for various levels of oxygen consumption are shown in figure 5.1.1 [see also fig. 4.3.1, which is similar]. This figure assumes a normal blood pH, a constant S_aO_2 of 95%, and a threshold venous PO_2 of 2.67 kPa (20 mmHg) at which cerebral hypoxia begins to occur. These parameters have been substituted in equation 1 to produce equation 2 below.

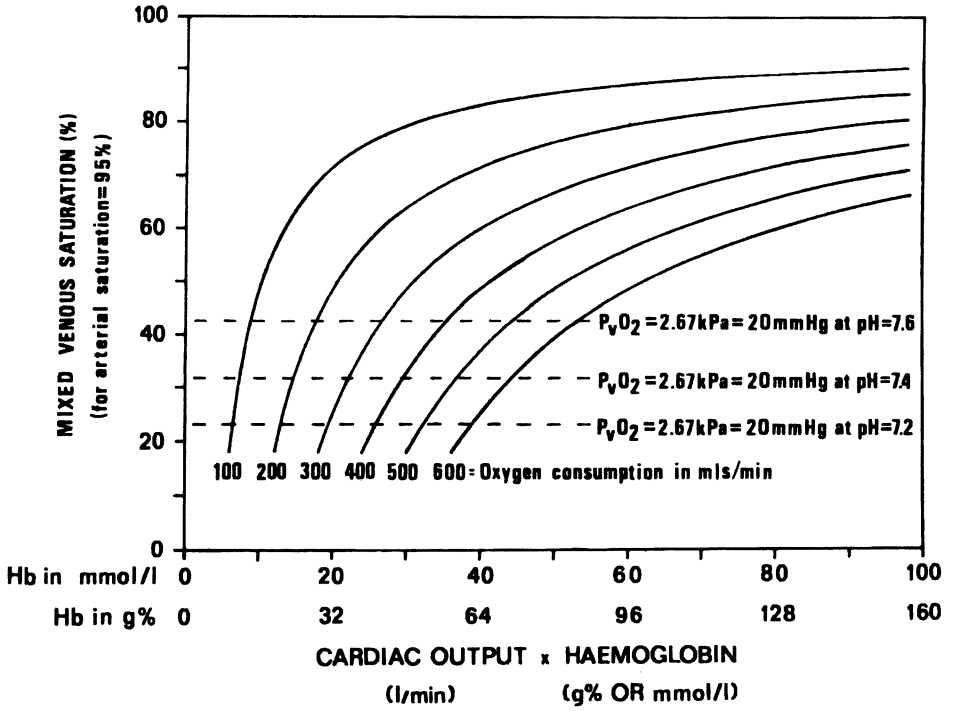

FIGURE 5.1.1. - The mixed venous oxygen saturation is related to the product of the cardiac output and haemoglobin concentration for various levels of oxygen consumption using equation 2, which assumes a constant S_aO_2 = 95%, pH = 7.4, and that the threshold for cerebral hypoxia is a P_vO_2 = 2.67 kPa = 20 mmHg. If the mixed venous oxygen saturation falls below one of the lines for a given pH, tissue hypoxia, especially cerebral hypoxia is likely. Acidosis and the elevation of erythrocyte 2,3-DPG concentration cause right-shifting of the oxyhaemoglobin dissociation curve. This figure shows that right-shifting of the oxyhaemoglobin dissociation curve lessens the likelihood of tissue hypoxia if either the haemoglobin concentration or cardiac output are low. It also shows that oxygen flux at any given degree of anaemia is maintained principally by elevation of the cardiac output, or a reduction of the mixed venous oxygen saturation.

$$S_vO_2 = 95 - \frac{V_{O2}}{0.216 \times CO \times [Hb]} \quad \text{.....(2)}$$

The use of equations 1 and 2, as well as figure 5.1.1 may be illustrated by the examples below.

Example 1.

Consider an adult patient with a resting cardiac output of 4.5 l/min, a [Hb] of 8 mmol/l (12.8 gm/100 mls), a blood pH of 7.4, and a basal oxygen consumption of 300 mls/min. From

fig 5.1.1 it is seen that the S_vO_2 would be about 56%, which is much greater than that at which cerebral hypoxia would occur. But if the [Hb] were to fall acutely to 4 mmol/l (6.4 gm/100 mls), and the blood pH as well as oxygen consumption remained the same, then a cardiac output of 4.5 l/min is no longer adequate, as the S_vO_2 is now about 18%, well below the S_vO_2 at which cerebral hypoxia is likely. The cardiac output in this example patient must increase to at least 5.42 liters/minute in order to make cerebral or tissue hypoxia less likely. Some patients, such as those with pacemakers, excessive ß-blockade or heart failure are unable to increase their cardiac output to any significant degree and are therefore likely to develop just such problems due to acute anaemia. A young healthy person can increase his cardiac output to well over 10 liters/minute, and will not develop any manifestations of cerebral or tissue hypoxia due to acute anaemia.

Example 2.

If a person engages in some very slight physical activity, such as very slow walking, then the oxygen consumption rises to 600 mls/min. Assume that the [Hb] = 8 mmol/l (12.8 gm/100 mls), the blood pH = 7.4, and the resting cardiac output = 4.5 l/min. If the cardiac output of this hypothetical person were unable to increase, even a [Hb] of 8 mmol/l is insufficient, as the S_vO_2 will fall to 17.8%, well below the level at which tissue or cerebral hypoxia is likely. The cardiac output must increase to at least 5.43 l/min to prevent such hypoxia. Acute anaemia exacerbates the problem even further. Activity of any sort obviously reduces the tolerance to anaemia, depending upon the degree of the anaemia and the level to which the cardiac output can increase.

Example 3.

Good examples of the value of blood transfusion in patients with compromized cardiovascular systems are given in example 3 of chapter 4.3 on oxygen content & oxygen flux, and for the situation of acid-base disorders in chapter 13.2 on factors modifying clinical manifestations of acid-base disorders.

The above correlates well with what is observed in the clinical situation during acute and chronic anaemia. However it should always be remembered that these changes do not manifest to the same degree during chronic, as during acute anaemia [see below for definitions of acute and chronic anaemia].

ACUTE AND CHRONIC ANAEMIA

Anaemia may be acute or chronic, and while the differentiation may at first seem pedantic, it does have clinical implications as implied above.

1. Acute anaemia.

Acute anaemia differs from chronic anaemia in that the erythrocyte 2,3-DPG concentration is lower than that in the erythrocytes of a chronically anaemic person [5]. On the basis of this, acute anaemia may be defined as anaemia of less than 24 hours duration, as it takes about 24 hours for the erythrocyte 2,3-DPG concentration [5] and P_{50} [6] to increase to a new steady state level after an acute reduction of the haemoglobin concentration.

The above has significance, in that the P_{50} of the blood of acutely anaemic persons is normal [see chapter 4.3 for a discussion of the meaning of the P_{50}]. This means that the situation is one where the oxygen content of the blood is reduced, while the rate of oxygen

Table 5.1.1.
Clinical manifestations of chronic anaemia related to the haemoglobin concentration [3,4].

Haemoglobin concentration	Symptoms
5.6-6.8 mmol/l (9-11 gm/100 mls)	- Slight pallor, and slight tachycardia.
4.3-5 mmol/l (7-8 gm/100 mls)	- More pronounced pallor, dyspnea on exertion.
3.7 mmol/l (6 gm/100 mls)	- All the above, plus many patients complain of weakness.
1.9 mmol/l (3 gm/100 mls)	- All the above, plus many patients complain of dyspnea at rest.
1.2-1.6 mmol/l (2-2.5 gm/100 mls)	- All the above, plus congestive heart failure may occur.

transfer from erythrocytes to oxygen requiring tissues is essentially unchanged. Either an elevation of cardiac output, or reduction of the S_vO_2 is then required to maintain oxygen flux.

The usual cause of acute anaemia is haemorrhage with subsequent partial, or full replacement of the lost blood volume by transcapillary refill [see chapter 14.1], or infusion of a colloid solution.

3. Chronic anaemia.

Chronic anaemia may be defined as anaemia which has lasted longer than 24 hours. Blood volume is usually normal, or near normal, and the 2,3-DPG concentration and P_{50} have increased to a new higher level [5].

As the oxygen-haemoglobin dissociation curve is right-shifted due to the elevation of the 2,3-DPG concentration, peripheral oxygen transfer rate for a given oxygen consumption can be maintained at the same level at a lower haemoglobin concentration. This means that the haemoglobin concentration at which the cardiac output must rise to maintain the same peripheral oxygen supply is lower during chronic, than acute anaemia. In fact, the cardiac output does not increase as a result of chronic anaemia until the haemoglobin concentration is less than 4.3 mmol/l (7 gm/100 mls). Below this haemoglobin concentration, the cardiac output is inversely proportional to the haemoglobin concentration [3].

Table 5.1.2.
Transfusion thresholds for anaemia.

ACUTE ANAEMIA	< = 5.5-6 mmol/l < = 9-10 gm/100 mls
CHRONIC ANAEMIA	< = 4.3 mmol/l < = 7 gms/100 mls

MANIFESTATIONS AND PROBLEMS DUE TO ANAEMIA

These are all due to the reduced oxygen transporting capacity of the blood, and are related to the haemoglobin concentration [see table 5.1.1].

1. Symptoms.

The severity of the cardiopulmonary manifestations of anaemia are inversely proportion to the haemoglobin concentration [see table 5.1.1].

2. Impairment of wound healing.

The rate and strength of wound healing may be diminished [1].

3. Myocardial ischaemia.

Patients with coronary vascular disease will develop myocardial ischaemia a lower level of heart work when anaemic because of the increased cardiac output, and hence heart work, required to maintain oxygen flux at all levels of physical exertion and metabolic rate [3].

4. Heart failure.

The increased cardiac output required to maintain an adequate oxygen flux in anaemia may precipitate or exacerbate heart failure.

THRESHOLDS FOR BLOOD TRANSFUSION

The indication for blood transfusion in anaemic patients depends on a number of factors, such as whether the anaemia is acute or chronic, the acid-base status, the cause of the anaemia, coexisting diseases, and in particular cardiovascular disease.

1. Transfusion threshold for acutely anaemia patients.

A not unreasonable threshold to initiate blood transfusion acutely anaemic patients is a haemoglobin concentration of < = 5.5-6 mmol/l (< = 9-10 gm/100 mls). This is a haemoglobin concentration which is at the threshold of being symptomatic in patients with chronic anaemia [see table 5.1.1], but above the minimum concentration required to adequately oxygenate the body during physical rest, with a total body oxygen consumption of less than 400 mls/min, even if the cardiac output is as low as 4 l/min, and the patient is slightly alkalaemic [see fig 5.1.1 and equation 2].

2. Transfusion threshold for chronically anaemic patients.

A haemoglobin concentration threshold for transfusion therapy of chronic anaemia may be set at < = 4.3 mmol/l (< = 7 gm/100 mls), as this is the threshold haemoglobin concentration during chronic anaemia above which resting cardiac output is normal. Below this haemoglobin concentration, the cardiac output is inversely proportional to the haemoglobin concentration [3].

3. Cardiovascular disease.

A patient who is unable to increase his cardiac output, has myocardial ischaemia, cardiac valvular disease, or heart failure, is less able to tolerate a given degree of anaemia than a person with a normal cardiovascular system. Such persons may not be able to maintain sufficient oxygen flux for a given level of metabolism due to myocardial ischaemia, valvular disease, heart failure, etc, and require blood transfusion at a higher haemoglobin concentration than a person with normal cardiovascular function.

4. Acid-base status

Tissue hypoxia is more likely at any level of anaemia in patients who are alkalaemic than in patients who are acidaemic [see chapter 13.2, and fig. 5.1.1]. Alkalaemia should be corrected, or blood transfusion will be required at a higher haemoglobin concentration than in a person who is acidaemic or has a normal plasma pH.

PREOPERATIVE BLOOD TRANSFUSION

The generally accepted threshold haemoglobin concentration below which preoperative blood transfusion is requested, or the operation is postponed, is a haemoglobin concentration of less than 5.5-6 mmol/l (9-10 gm/100 mls). There are exceptions to this rule, such as patients undergoing organ transplantation, as it is desirable to limit the number of blood transfusions in this group of patients.

There are a number of reasons for this threshold.

a. Surgery may cause significant blood loss. Acute blood loss such that the haemoglobin concentration falls below 6 mmol/l (10 gm/100 mls) may not be well tolerated in patients unable to elevate their cardiac output to any significant degree, or in whom such an elevation of cardiac output causes angina pectoris.
b. Hypovolaemia due to haemorrhage, or significant third space fluid loss, reduces the cardiac output, or at best does not allow it to increase. Such a situation may occur during surgery, in which case it is better that the patient have a haemoglobin that is above 6 mmol/l (10 gm/100 mls), so that oxygen flux is able to be maintained with a relatively low cardiac output.
c. General anaesthesia, high spinal, and high epidural anaesthesia reduce the cardiac output. Tissue hypoxia is possible if both the haemoglobin concentration as well as cardiac output are low.
d. General anaesthesia increases the alveolar-arterial oxygen partial pressure gradient. A reduced P_aO_2 makes it more likely that tissue hypoxia will occur during anaemia, especially if the cardiac output is also reduced.

In theory it is better to administer an elective preoperative blood transfusion at least 24 hours prior to operation. This is because transfused erythrocytes have a lower 2,3-DPG

content than normal erythrocytes, and it takes about 24 hours for the 2,3-DPG content [2], and the P_{50} [6] of transfused erythrocytes to increase to normal levels. After this time the oxygen-haemoglobin dissociation curve of the transfused erythrocytes is normal. However this is more of a theoretical than a practical consideration in patients with normal cardiovascular function, as erythrocytes with a low 2,3-DPG concentration still transport and release oxygen. This is well demonstrated by the survival of patients after massive blood transfusions of more than 5 liters during surgery in which an equally massive blood loss occurred.

ANAESTHETIC MANAGEMENT

Preoperative.

1. Patients coming for emergency operation should be treated according to their clinical circumstances. Anaemia is frequently a consequence of the operative indication, e.g. trauma, wounding etc. The cause of any other form of anaemia may be investigated postoperatively.

2. Cancel or delay any elective operation of patients with chronic anaemia whose haemoglobin concentration is less than 6 mmol/l (9.5-10 gm/100 mls). While surgery is usually not lethal is such patients, a delay is required to improve the clinical condition of the patient so that perioperative morbidity is minimized, e.g. patients with vitamin-B12, iron or folate deficiencies. This is however not possible in patients who are coming for surgery of disorders which themselves cause anaemia, e.g. patients coming for renal transplantation.

Anaesthesia and Postoperative management.

Except for patients with sickle cell disease, or porphyria, the choice of anaesthetic technique and postoperative management depends on the patient and the nature of the surgery.

REFERENCES

1. Gillies,I.D.S.,(1974). Anaemia and anaesthesia. BRITISH JOURNAL OF ANAESTHESIA, 46, 589-602.
2. Kopriva,C.J., et al.,(1972), Biochemical and hematological changes associated with massive transfusion of ACD-stored blood in severely injured combat casualties. ANNALS OF SURGERY, 176, 585-589.
3. Varat,M.A., et al.,(1972), Cardiovascular effects of anemia. AMERICAN HEART JOURNAL, 83, 415-426.
4. Linman,J.W.,(1968), Physiologic and pathophysiologic effects of anemia. NEW ENGLAND JOURNAL OF MEDICINE, 279, 812-818.
5. Torrance,J., et al.,(1970), Intraerythrocytic adaptation to anemia. NEW ENGLAND JOURNAL OF MEDICINE, 283, 165-169.
6. Weisel,R.D., et al.,(1978), Adverse effects of transfusion therapy during abdominal aortic aneurysmectomy. SURGERY, 83, 682-690.

Chapter 5.2

SICKLE CELL ANAEMIA

INCIDENCE

1. Sickle cell disease and trait mainly occurs in people of African negro origin. In Central Africa the incidence is about 20%, while in the West Indies the incidence in the population of negro origin is about 8% [1].

2. The disease is genetically transmitted, transmission being via an autosomal dominant, non-sex linked gene, according to the usual Mendelian principles. There are two forms of the disease. Sickle cell disease is the severe form of the disorder, and is due to inheritance of genes for sickle cell haemoglobin (HbS) from both parents (homozygous). Sickle cell trait is the milder form of the disease due to inheritance of the gene for HbS from only one parent (heterozygous). The characteristics of the two forms of sickle cell disease are listed in table 5.2.1.

PROBLEMS [1]

Sickle cell haemoglobin (HbS) containing erythrocytes undergo a change from the usual biconcave shape to a sickle or crescent shape when the HbS is deoxygenated. The erythrocyte conformational change occurs because deoxygenated HbS binds with other deoxygenated HbS molecules forming insoluble complexes, which come out of solution in the cytoplasm as filaments or tubules of varying size. These filaments aggregate to form fibers, and bundles of fibers, which can distort the erythrocyte shape. Upon oxygenation of the "sickled" erythrocytes, the oxygenated HbS goes back into solution, and the cells resume their normal biconcave shape. However not all cells resume their normal shape on oxygenation, as repeated conformational changes eventually causes membrane damage of such magnitude that potassium and water leak out of the damaged cells, which then remain in the "sickled" shape. About 2-30% of the erythrocytes of patients with sickle cell disease are irreversibly sickled and subsequently undergo haemolysis.

The changes described above have a number of important clinical consequences.

1. Anaemia and haemolysis.

Because patients with sickle cell disease always have a degree of sickling occurring somewhere in their bodies, haemolysis of damaged cells occurs at a rate increased above the normal rate of erythrocyte clearance. The increased rate of haemolysis necessitates an increased rate of haemopoiesis, which also occurs in these patients. However the rate of erythrocyte destruction is so great in patients with sickle disease that some degree of anaemia is always present.

Haemolysis may be so rapid in some persons with sickle cell disease that hyperbilirubinaemia occurs.

Table 5.2.1.
Characteristics of the two forms of Sickle Disease.

	SICKLE CELL TRAIT	SICKLE CELL DISEASE
Phenotype	Heterozygote	Homozygote
Usual haemoglobin concn.	Normal	Anaemic
% Haemoglobin as HbS	<50%	90-95%
% Foetal haemoglobin	-	5-10%
PO_2 at which sickling occurs	2.7-4 kPa (20-30 mmHg)	8-9.3 kPa (60-70 mmHg)

2. Embolic disease.

Blood which contains sickled cells is more viscous than blood which does not contain sickled cells. Sickled cells are more rigid than biconcave cells, do not pass easily through capillaries, and may even cause microvascular obstruction. Hypoxaemia occurs in the blood in vessels distal to any vascular obstruction, inducing sickling in the erythrocytes remaining in these vessels. This process may extend the area of circulatory obstruction to such a degree that a small infarction occurs. The end result of this is diffuse microinfarction of many organs, in particular organs with a low PO_2, e.g. renal medulla, spleen, bone. This also determines the clinical manifestations of the disorder.

a. During a "sickling crisis", when a major degree of sickling is occurring, multiple small micro-emboli or infarctions can cause pain in various areas of the body, e.g. abdomen.
b. Neurological lesions may occur as a result of embolization or infarction occurring in the central nervous system.
c. Sickling occurs frequently in the renal medulla and papillae because these regions have a low PO_2 as well as being hypertonic relative to blood. This causes renal medullary and papillary damage. It is not infrequent that patients with severe sickle cell disease are unable to concentrate their urine, and some even have renal failure.
d. Aseptic bone necrosis is also frequent, as a result of sickling within bones.

3. Effect of dehydration.

Factors such as dehydration which cause erythrocyte dehydration also promote sickling, e.g.;

- dehydration,
- hypernatraemia,

- or any hypertonic extracellular environment, e.g. the renal papillae.

ANAESTHETIC MANAGEMENT [1,2]

The main rule in the anaesthetic management of these patients is PREVENT HYPOXAEMIA, and ACIDAEMIA, as both of these cause desaturation of haemoglobin, which in its turn causes sickling of erythrocytes. See figure 4.1.2 for other factors predisposing to right-shifting, and hence desaturation of oxyhaemoglobin.

Preoperative.

1. Suspect all patients of negro origin of having sickle cell disease or trait, especially if they are anaemic. In many countries a quick screening test for sickle cell haemoglobin is routinely performed preoperatively on all patients of African origin.

2. Patients with sickle cell disease who are to undergo elective major surgery should undergo a preoperative series of exchange transfusions to raise the percentage of erythrocytes containing normal haemoglobin to above 50% [2]. This does not prevent the erythrocytes which contain HbS from sickling at 8-9.3 kPa (60-70 mmHg), but what it does do is reduce the percentage of cells that can sickle. This means that the chance of significant embolization from the cells that do sickle is reduced.

3. The use of preoperative anticholinergic and sedative drugs depends upon the requirement for these drugs and the personal preferences of the anaesthetist.

Anaesthesia.

1. Acidaemia causes a right shift of the oxygen-haemoglobin dissociation curve and a greater degree of desaturation of the haemoglobin at a given P_aO_2 [see chapter 4.1], with as result that sickle cell patients will commence sickling at a higher P_aO_2 [see table 5.2.1].

Prophylactic administration of sodium bicarbonate solutions is sometimes advocated to prevent acidaemia, and to induce left-shift of the oxygen-haemoglobin dissociation curve. But unless acidaemia is present, or is likely to occur, the use of sodium bicarbonate may cause more problems than are justified by the problem.

2. Maintain normovolaemia and an adequate cardiac output. Hypovolaemia and dehydration may both reduce the cardiac output, and a reduction of tissue blood flow causes acidaemia and desaturation of haemoglobin. In addition, regional hypoperfusion causes areas of local hypoxaemia where sickling may occur, e.g. in bone or fat.

3. Acidaemia causes right-shifting of the oxyhaemoglobin dissociation curve, encouraging desaturation of the haemoglobin, and so promoting sickling. Release of an arterial tourniquet from a limb which has been emptied of blood for more than an hour can cause significant generalized acidaemia, and certainly causes localized acidaemia. Accordingly never use an arterial tourniquet to provide a blood free surgical field in patients with sickle cell disease. The use of arterial tourniquets in patients with sickle cell trait is usually not associated with significant sickling.

4. Hypothermia below 35 °C should be prevented. Postoperative shivering can increase oxygen consumption by up to 500% above normal levels [3], and this may cause postoperative hypoxaemia severe enough to cause sickling in some patients.

5. If possible use loco-regional anaesthetic techniques so as to avoid the use of respiratory depressant drugs.

6. If general anaesthesia is required, a number of factors should be considered.

a. All patients should be preoxygenated for at least 2 minutes prior to induction of anaesthesia so as to minimize than chance of hypoxia in this period.
b. A general anaesthetic technique using controlled ventilation is to be preferred above one where the patient breathes spontaneously. This guarantees arterial oxygenation, as well as enabling induction of mild respiratory alkalosis by meansof hyperventilation. These factors make it even less likely that haemoglobin desaturation will occur.
c. If general anaesthesia using a technique where the patient breathes spontaneously is employed, supplemental oxygen should always be administered to elevate the inspired oxygen concentration above 30%, otherwise hypoxaemia may occur.

Postoperative

1. Oxygen must be administered postoperatively to all patients with sickle cell disease or trait until the chance of postoperative hypoxia has passed. The duration and magnitude of postoperative hypoxia after surgery carried out under general anaesthesia has been discussed in chapter 4.5.

Patients with sickle cell trait should receive oxygen for at least 4-8 hours postoperatively [see chapter 4.5].

Persons with sickle cell disease require oxygen for at least 24-48 hours postoperatively so as to guarantee erythrocyte oxygenation [see chapter 4.5].

2. If a body temperature of 35°C or lower is present in a person with sickle cell disease, mechanical ventilation with muscle relaxation and sedation should be considered until normal body temperature has been restored. This will prevent hypoxaemia due to shivering.

REFERENCES

1. Howells,T.H., et al.,(1972), Anaesthesia with sickle-cell haemoglobin: With a case report. BRITISH JOURNAL OF ANAESTHESIA, 44, 975-987.
2. Gibson,J.R.,(1987), Anesthesia for the sickle cell diseases and other hemoglobinopathies. SEMINARS IN ANESTHESIA, 6, 27-35.
3. Bay,J., et al.,(1968), Factors influencing arterial PO_2 during recovery from anaesthesia. BRITISH JOURNAL OF ANAESTHESIA, 40, 398-407.

Part 6

HAEMOSTATIC DYSFUNCTION

The anaesthetist and surgeon are sometimes confronted by a patient who has manifestations of disordered haemostasis. As an unrecognized or inadequately treated haemostatic disorder can have disastrous consequences for a patient undergoing surgery, or some invasive anaesthetic procedures, it is essential that both physicians have a sound basic knowledge of the management of the more common problems of haemostasis that can be encountered in the perioperative period.

Chapter 6.1

NORMAL HAEMOSTASIS

NORMAL HAEMOSTASIS

Haemostasis is a complex process which occurs in various phases, the vascular, platelet, coagulation and contraction phases. The proper functioning of this series of steps is essential for adequate haemostasis.

1. Vascular phase.

The injured blood vessels at first constrict due to reflex and local neural responses as well as local biochemical responses to injury. In addition to this there is local platelet release of serotonin and thromboxane-A2 which potentiates vasoconstriction. Vasoconstriction due to vascular injury lasts up to 1 hour before it relaxes.

2. Platelet phase.

Vascular damage exposes subendothelial collagen and damaged cells release adenosine diphosphate (ADP). Provided that various factors are present in the plasma, among which is von Willebrand's factor, ADP causes platelets to adhere to each other as well as to exposed subendothelial collagen within seconds after injury. These platelet aggregates form the initial haemostatic plugs in the damaged vessels. Platelets also release thromboxane-A2, serotonin, and ADP, which attract more platelets to the damaged vessels.

3. Coagulation.

Damaged tissues release tissue thromboplastins, which together with the exposure of subendothelial collagen fibers, and release of platelet factor-3 by platelets, activates both the intrinsic and extrinsic coagulation pathways. Fibrin is formed and is deposited within and around the platelet plug. Synthesis of thrombin which is necessary for fibrin formation, attracts even more platelets to the damaged region.

The end result is a haemostatic plug, initially formed of platelets, subsequently being formed by platelets embedded in a matrix of reinforcing fibrin fibers which also bind the plug to the damaged vessel walls and surrounding exposed tissues.

4. Clot contraction.

The platelet-fibrin plug subsequently contracts due to contraction of a platelet contractile protein thrombosthenin, and conversion of loose fibrin into cross-linked fibrin by factor XIII. This results in a firm haemostatic plug with a strength adequate to maintain haemostasis after vasoconstriction relaxes, exposing the haemostatic plug to the full effect of intravascular pressures.

CLINICAL CORRELATES

Platelet and vascular function

1. Efficient platelet plug formation requires stasis of the blood in which a platelet plug is forming. A continuous flow of blood out of a severed vessel removes platelets before they are firmly attached to each other, so impairing platelet plug formation at that point. Such a situation occurs when vasoconstriction of small vessels is deficient, and large vessels are not ligated or coagulated. In both situations the severed vessels continue to bleed after injury.

2. Platelet plug formation also requires that sufficient platelets be available. After efficient vasoconstriction has occurred in a severed vessel, the blood remaining in that severed vessel is the only source of platelets and coagulation factors. The quantity of platelets and coagulation factors available is therefore dependent upon the original blood concentration of these factors. Indeed it has been found that if the blood platelet concentration is $< 100{,}000$ platelets/mm^3, that the bleeding time is increased [1]. After coagulation has occurred, the platelet plus fibrin clot contracts due to the action of platelet thrombosthenin, resulting in a firm platelet/fibrin plug [2]. Clot retraction is therefore also dependent upon the quantity of platelets present in the plug, and begins to be deficient when the platelet concentration falls below 100,000 platelets/mm^3 [3]. Because of these factors, the usually accepted minimum platelet concentration for acceptable surgical haemostasis is about 50,000-100,000 platelets/mm^3 [4].

Bleeding which never stops after the initial injury is also typical of platelet dysfunction or decreased platelet concentration.

3. A practical problem sometimes arising during anaesthesia, especially during microsurgery, is that a sudden elevation of blood pressure may cause increased bleeding, which continues even when the blood pressure has been brought back down to its previous level. Presumably this is due to platelet plugs being dislodged as a result of sudden elevation of blood pressure. A subsequent lack of vasoconstriction of these vessels in which the vasoconstriction phase has already occurred and passed, means that bleeding continues.

Coagulation factor function

Fibrin formed by activation of the coagulation system reinforces the platelet plugs. The fibrin forms a matrix in which platelets and erythrocytes are embedded. The quantity of fibrin formed is a function of the coagulation factor concentration in the blood remaining in the damaged vessel. In situations where the concentration of any one or more of the coagulation factors is too low, insufficient fibrin is formed. Under these circumstances the haemostatic plug is not adequately reinforced, and upon relaxation of the vasoconstriction, or elevation of blood pressure, the haemostatic plugs are dislodged and bleeding recommences.

Because of the above, bleeding which recommences after an initial period of adequate haemostasis is typical of coagulation factor deficiency.

REFERENCES

1. Harker,L.A., Slichter,S.,(1972). The bleeding time as a screening test for evaluation of platelet function. NEW ENGLAND JOURNAL OF MEDICINE, 287, 155-159.

2. Weiss,J.W.,(1975). Platelet physiology and abnormalities of platelet function. NEW ENGLAND JOURNAL OF MEDICINE, 293, 531-541.
3. Didisheim,P.,(1967). Screening tests for bleeding disorders. THE AMERICAN JOURNAL OF CLINICAL PATHOLOGY, 47, 622-630.
4. Miller,R.D., et al.,(1971). Coagulation Defects Associated with Massive Blood Transfusions. ANNALS OF SURGERY, 174, 794-801.

Chapter 6.2

SIMPLE TESTS OF HAEMOSTATIC FUNCTION

Both the anaesthetist and surgeon should be familiar with the common tests of haemostatic function. The tests discussed in this chapter are those which are available in most modern hospitals. While these tests do not detect every haemostatic disorder, they do permit the detection and diagnosis of most problems. A haematologist should be consulted if a patient has manifestations of abnormal haemostasis despite these tests yielding normal results.

TESTS OF PLATELET FUNCTION

Platelet count

The platelet count is a reasonable measure of the adequacy of platelet function, provided that platelet function is normal. Bleeding time increases, and haemostatic plug contraction becomes increasingly deficient when the platelet count falls below 100,000 platelets/mm^3 [see chapter 6.3].

Bleeding time

Bleeding time is a measure of the function of the vasoconstriction phase, as well as the platelet phase of haemostasis. As disorders of vasoconstriction are exceedingly rare as a cause of primary haemostatic failure, the bleeding time may be taken as a test of platelet function and concentration. It is prolonged when the concentration of normally functioning platelets falls below 100,000 platelets/mm^3 [see chapter 6.3].

There are various methods of measuring the bleeding time.

1. Duke method.

This is a test which has been rendered obsolete by more accurate methods, but it is still frequently referred to. A 3 mm puncture wound is made in an earlobe, and the blood blotted from the wound every 10-15 seconds until the bleeding stops. Normal bleeding time with this technique is less than 4 minutes.

2. Ivy method.

A blood pressure cuff around the upper arm is inflated to a pressure of 40 mmHg, and three, 3 mm deep wounds are made on the dorsal aspect of the forearm. The blood is blotted from the wounds every 10-15 seconds until the bleeding stops from all wounds. The bleeding time is the average time for cessation of bleeding from all wounds. Normally this is less than 4 minutes.

3. Template bleeding time (method of Mielke et al [2]).

A plastic template is placed upon the skin surface where the bleeding time is to be determined. There is a slit allowing an incision 9 mm long and 1 mm deep to be made when using a blade inserted into a special holder. This provides a skin incision with minimum size variation. Otherwise the technique is the same as the Ivy technique, including the use of a blood pressure cuff inflated to 40 mmHg around the upper arm. The bleeding time measured with this technique is normally about 5 minutes.

Limitation of the use of bleeding time in the operating theater.

One problem frequently confusing the interpretation of the bleeding time during operation is vasoconstriction of the arm of the patient due to hypothermia. In situations where the patient is very cold and vasoconstricted, a prolonged bleeding time is certainly significant. But if the bleeding time is normal, then this need not necessarily indicate normal vascular/platelet function. The patient may still bleed abnormally from other vessels which are not so vasoconstricted.

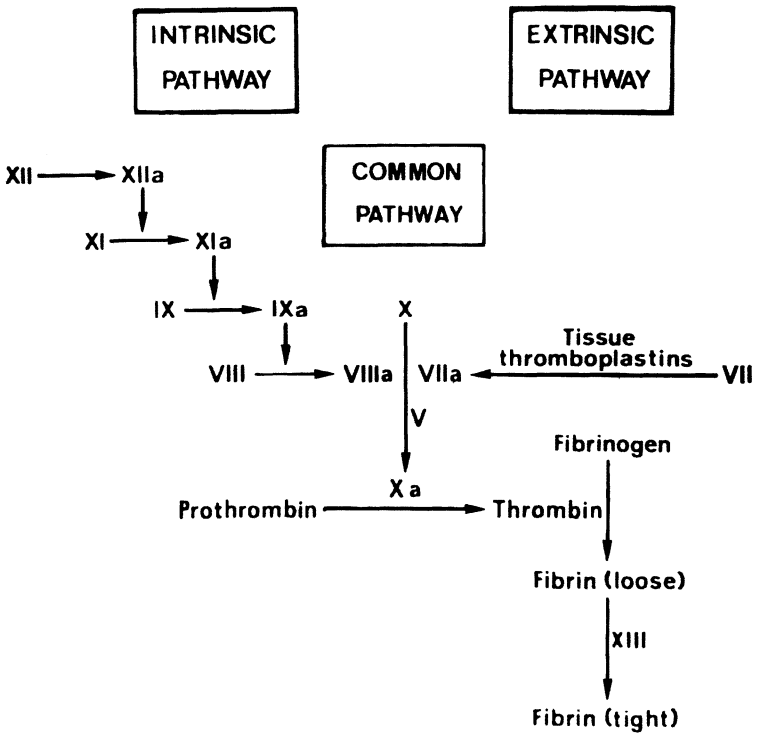

FIGURE 6.2.1. - Simplified diagram of the in-vitro coagulation pathways. This is useful when making a diagnosis on the basis of laboratory tests. The "a" suffix after the names of many of the factors means that factor is in its active form. The presence of calcium ion and phospholipids is required for many steps.

TESTS OF COAGULATION FUNCTION

The in-vitro sequence of the sequence of events occurring during coagulation is depicted in fig 6.2.1. This is not necessarily the sequence occurring during coagulation in-vivo, but this scheme does provide an aid which makes diagnosis of a coagulation disorder simpler.

Whole blood coagulation time

This is a obsolete test because the information it provides is dependent on many uncontrollable variables, in addition to which it may be normal in the presence of gross coagulation disorders. The method commonly recommended is to place freshly drawn blood into a clean glass test tube, set it aside in warmed (37°C) surroundings, and wait for the blood to clot. This normally takes 9-15 minutes.

If the coagulation time is prolonged, then it is significant. But if this test is normal, then the result is meaningless, as the coagulation time remains normal until the intrinsic and common factor pathway factor concentrations fall below 1% of normal [1,page 1057]. This test is not at all influenced by factor VII concentration.

The only other function that this test may have is to observe clot retraction. This indicates the presence of functioning platelets. However the presence of an adequate platelet concentration is better and more rapidly detected by performing a platelet count, and their function is more efficiently tested with the bleeding time.

Partial thromboplastin time (PTT) & Activated PTT (aPTT)

The PTT and the aPTT test the function of both the intrinsic and common coagulation pathways by measuring the time taken to form a fibrin clot after activation of factor XII. The aPTT is a more accurate and reproducible variant of the PTT, and is to be preferred for this reason. The test is more sensitive for deficiencies of factors VIII and IX, than the other factors. But when the concentration of any one of the other factors falls below 15-20% of the normal concentration, the PTT/aPTT is also prolonged [1,pages 1055-1056].

Despite the fact that this test is more sensitive for factors VIII and IX, patients with minimal, but sometimes haemostatically significant, degrees of hemophilia or von Willebrand's disease may have a normal PTT/aPTT.

Prothrombin time (PT)

The PT tests the function of both the extrinsic and common pathways by measuring the time taken to form a fibrin clot after activation of factor VII with a thromboplastic agent. It is more sensitive to deficiencies of factors VII and X than of the other coagulation factors. The PT is also prolonged if the concentration of any one of the other factors falls below 10% of the normal concentration [1,pages 1056 - 1057].

Thrombin time.

Preformed thrombin is added to plasma, and the time taken to form a fibrin clot is measured. Normally this is about 10-20 seconds, depending on the reagent used. The thrombin time is prolonged if the fibrinogen concentration is below 1 g/l (100 mg/100 mls). It is also prolonged by fibrin degradation products and heparin.

Fibrinogen concentration.

This the measurement of the plasma concentration of fibrinogen, normally 1.6-4.5 g/l (160-450 mg/100 mls).

Fibrin degradation products.

Fibrin degradation products are polypeptides formed by the breakdown of fibrin and fibrinogen by plasmin. Elevated concentrations usually occur in association with disseminated intravascular coagulation, as primary fibrinolysis is very rare. Primary fibrinolysis may be observed occasionally after cardiopulmonary bypass, liver cirrhosis, and prostate carcinoma.

Activated Clotting Time (ACT) [3].

The activated clotting time is a test commonly used to monitor heparin activity during cardiopulmonary bypass. It provides a very rapid estimation of the degree of intrinsic coagulation pathway inhibition by heparin. The most commonly used apparatus at the moment is the Hemochron™, a battery powered device made by the International Technidyne Corporation of New Jersy, U.S.A..

A 2.5-3 ml sample of blood is injected into a test tube containing a small magnet and powdered diatomaceous earth, (kaolin clay), and then subsequently placed in the machine. After switching the machine on, a timer built into the machine starts, and the machine spins the magnet, which stops spinning when the blood has clotted. Cessation of magnet movement is detected by the machine, which then switches itself and the timer off. The elapsed time is the activated clotting time (ACT). Clotting is initiated by activation of the intrinsic pathway by the diatomaceous earth.

The normal range for the ACT in persons who have normal coagulation function is 80-160 seconds.

REFERENCES

1. Wintrobe,M.M., et al.,(1981). "Clinical Hematology", 8th edn., pub. Lea & Febiger.
2. Mielke,C.H., et al.,(1969). The standardized normal Ivy bleeding time and its prolongation by asprin. BLOOD, 34, 204.
3. Kamath,B.S.K., Fozard,J.R.,(1980). Control of heparinisation during cardiopulmonary bypass. Experience with the activated clotting time method. ANAESTHESIA, 35, 250-256.

Chapter 6.3

MINIMALLY ACCEPTABLE PERIOPERATIVE HAEMOSTATIC PARAMETERS

Invasive procedures performed by anaesthetists and surgeons should only be carried out if the haemostatic function of the patient is such that the chance of haemorrhagic complications is minimal. This chapter attempts to provide some guidelines as to what constitutes minimally acceptable haemostatic parameters prior to surgery and invasive anaesthetic procedures.

Table 6.3.1.
Normal values for tests of haemostatic function.

PARAMETER		NORMAL VALUE
Platelet concentration		150,000-400,000/mm^3
Bleeding time	- Ivy	<5 minutes
	- Duke	<4 minutes
	- Template	<5 minutes
Prothrombin time	- Quick's one stage	11-16 seconds
Partial thromboplastin time	- Standard	68-82 seconds
	- Activated	32-46 seconds
Fibrinogen concentration		160-450 mg/100 mls (1.6-4.5 g/l)

AVERAGE NORMAL VALUES

Normal values of the various common tests of haemostatic function are set out in table 6.3.1. Only the most common tests are listed, as other tests are seldom performed except on the advice of a specialist haematologist when there is a strong but unconfirmed suspicion that a given patient has a haemostatic defect, or after an abnormality of one of the commonly performed tests is detected.

Table 6.3.2.

Platelet count and its relationship to haemostatic function for normally functioning platelets.

$>100{,}000/mm^3$	- Normal haemostasis
$<100{,}000/mm^3$	- Lengthening of bleeding time [1]
$<100{,}000/mm^3$	- Increasingly deficient clot retraction [5]
$<50{,}000\text{-}75{,}000/mm^3$	- Increased surgical bleeding [2,8]
$<50{,}000/mm^3$	- Ecchymoses and petechie [3]
$<20{,}000/mm^3$	- Increased chance of fatal haemorrhage [3]

MINIMUM PREOPERATIVE PLATELET CONCENTRATION & FUNCTION

Provided that the function of the platelets is normal, platelet caused haemostatic defects are related to the platelet concentration. From table 6.3.2. it is seen that a platelet count of more than 100,000 platelets/mm^3 is the minimum required for totally normal haemostasis, while a platelet count of under 20,000 platelets/mm^3 is associated with an increased chance of spontaneous fatal haemorrhage, e.g. cerebral haemorrhage, etc. Table 6.3.2. should only be taken as providing a guideline as to what is possible at these platelet concentrations. In the final analysis, it is the bleeding time which is the real measure of platelet function.

It should always be remembered that the patient undergoing surgery, or who has undergone trauma of some sort, is in a fundamentally different situation to someone who lies in bed, or has a minimally physically traumatic lifestyle. Bleeding from severed vessels causes loss of platelets, platelet plug formation in large numbers of severed vessels consumes platelets, and infusion of fluids and blood preparations which do not contain platelets dilutes the remaining platelets. This is not the situation in the non-traumatized or non-operated patient.

Clinical investigation has revealed that surgical bleeding is significantly increased above normal if the concentration of normally functioning platelets is less than 50,000-75,000 platelets/mm^3 [2,8]. During minor surgery, minimal amounts of platelets are lost by haemorrhage and in haemostatic plugs, and for this reason it is not unreasonable to set a minimum acceptable preoperative platelet count of 50,000 platelets/mm^3 together with a bleeding time which is less than 1.5 times normal. Major surgical procedures are different because of the expected greater blood and platelet loss, larger wound surface causing platelet consumption, and larger volumes of intravenous fluids and blood that is infused

and which dilutes the remaining platelets to a greater degree. In this situation a minimum acceptable preoperative platelet count may be set at 75,000 platelets/mm^3 together with a bleeding time less than 1.5 times normal.

Table 6.3.3.
Minimum percentage plasma concentrations (P_m) of the various coagulation proteins that are required for adequate haemostatic function in persons with a normal level of physical activity [4], and in postoperative patients [9], as well as their plasma elimination half lives ($T_{1/2e}$) [6,7].

COAGULATION FACTOR	P_m (%)	$T_{1/2e}$ (hours)
I - Fibrinogen	30-40	77-106
II - Prothrombin	20-40	72-96
V - Proaccelerin	5-20	12-36
VII - Proconvertin	10-20	5
VIII - Antihaemophilia factor	40	12
von Willebrand's factor	30	?
IX - Christmas factor	30	24
X - Stuart-Prower factor	10-20	24-60
XI - Prothrombin antecedent	20-30	48-84
XII - Hageman factor	0	?
XIII - Fibrin stabilizing factor	1-3	72-96

MINIMUM ACCEPTABLE PREOPERATIVE COAGULATION FACTOR FUNCTION

The adequacy of haemostasis is also dependent on the concentrations of the various coagulation proteins, because it is their concentration that determines the amount of fibrin formed in haemostatic plugs. Table 6.3.3 shows the minimum percentage concentrations of these factors that is required for adequate haemostasis in ambulant persons, and which at the same time are also the minimum levels of these factors required for adequate postoperative haemostasis. The pharmacokinetic elimination half lives of the various factors are also given, as this is the major determinant of the frequency with which they require to be administered to coagulation factor deficient persons.

As with the minimum platelet function and concentration, the concentration of coagulation factors required for adequate haemostasis is higher in the surgical patient than in the patient who lies in bed, or has not undergone trauma or surgery. The cause is the same as for platelets. That is, multiple severed vessels on a wound surface consume coagulation factors to make fibrin. Coagulation factors are also lost by haemorrhage, and diluted by infusions of non-coagulation factor containing plasma volume replacing fluids.

Clinical investigation has shown that surgical bleeding is significantly increased if the PT or aPTT/PTT are prolonged to more than 1.5 times normal [8]. Acceptable intraoperative haemostasis is also achieved if the concentrations of factors IX and VIII are at least 60% of the level in normal persons [9]. Postoperatively, after haemostatic plugs have formed, wound haemostasis is adequate if factor VIII and IX concentrations are as low a 30% of the concentration in normal persons [9]. These concentrations are likely to be applicable to other factors too.

Table 6.3.4.
Minimum preoperative haemostatic parameters [see text for references].

Platelet count	> 50,000 platelets/mm^3 (minor surgery) > 75,000 platelets/mm^3 (major surgery)
Bleeding time	< = 1.5 times normal
PT and/or PTT/aPTT	< = 1.5 times normal
Coagulation factor concentrations	- Intraoperative > 60% of normal concentration - Postoperative > 30% of normal concentration

CONCLUSIONS

Table 6.3.4 shows threshold values which may be used as minimum requirements for haemostatic function before most types of surgery, or invasive anaesthetic procedures may be considered possible with a minimal chance of excessive bleeding due to haemostatic dysfunction. These values should not be considered as absolute parameters to be applied to all operations, as such a use of these types of parameters is neither sensible nor practical. The nature of the surgical or anaesthetic procedure planned, the site on the body where the procedure is to occur, the desires of the surgeon, anaesthetist, and the requirements of the clinical condition of the patient should also be considered. This is illustrated using five examples.

Example 1.

The risk of serious bleeding as a result of attempts to introduce a subclavian catheter in a patient with abnormal haemostasis is considerably greater than that of inserting a central venous line through a vein in the cubital fossa. Patients in whom a subclavian catheter is to be inserted should not have haemostatic parameters that are more abnormal than those in table 6.3.4, in case catastrophic intrathoracic haemorrhage occurs. Those patients in whom a central line is to be inserted through a cubital fossa vein may have quite abnormal haemostatic function, as bleeding at this site is readily controlled.

Example 2.

The potential complications of intracranial operations performed on a patient with abnormal haemostasis are much more serious than those as a result of an operation upon a limb. No intracranial operations should be performed on patients with even slightly abnormal haemostasis, even when they satisfy the criteria in table 6.3.4.

Example 3.

Patients undergoing vascular surgery may be permitted to have haemostatic parameters which are more abnormal than those in table 6.3.4, especially if major vascular surgery is planned. This minimizes the chance of deep venous thrombosis, and of thrombus formation in vascular prostheses and anastomoses. However this is not the opinion of all vascular surgeons, and the anaesthetist and surgeon should consult with eachother as to what are to be considered acceptable haemostatic parameters in these patients.

Example 4.

No spinal or epidural anaesthesia should be administered if the haemostatic parameters are more abnormal than those in table 6.3.4. The most feared complications of these techniques are spinal epidural or subdural haematoma, which may be large enough to cause spinal cord damage. This will of course not be detected for some hours until the anaesthetists and surgeons begin to think that the spinal or epidural anaesthetic has had an overly long duration of action.

Example 5.

Elective intra-abdominal, orthopaedic, and all other forms of surgery should not be performed on patients whose haemostatic parameters are more abnormal than those in table 6.3.4.

REFERENCES

1. Harker,L.A., Slichter,S.,(1972). The bleeding time as a screening test for evaluation of platelet function. NEW ENGLAND JOURNAL OF MEDICINE, 287, 155-159.
2. Miller,R.D., et al.,(1971). Coagulation Defects Associated with Massive Blood Transfusions. ANNALS OF SURGERY, 174, 794-801.
3. Gaydos,L.A.,(1962). The quantitative relation between platelet count and hemorrhage in patients with acute leukaemia. NEW ENGLAND JOURNAL OF MEDICINE, 266, 905.
4. Ellison,N.,(1977). Diagnosis and Management of Bleeding Disorders. ANESTHESIOLOGY, 47, 171-180.
5. Didisheim,P.,(1967). Screening tests for bleeding disorders. THE AMERICAN JOURNAL OF CLINICAL PATHOLOGY, 47, 622-630.
6. Smith,J.K., Bidwell,E.,(1979). Therapeutic Materials used in the Treatment of Coagulation Defects. CLINICS IN HEMATOLOGY, 8, 183-206.
7. Wintrobe,M.M., et al.,(1981)."Clinical Hematology", 8th edn., pub. Lea & Febiger.
8. Murray,D.J., et al.,(1987), Blood replacement therapy: decreases in coagulation factors. CANADIAN JOURNAL OF ANAESTHESIA, 34, supplement, s122-s127.
9. Rudowski,W.J., et al.,(1987), Is major surgery in hemophiliac patients safe? WORLD JOURNAL OF SURGERY, 11, 378-386.

Chapter 6.4

PERIOPERATIVE MANAGEMENT OF COAGULATION FACTOR DEFICIENCIES

A severe reduction of coagulation factor concentrations results in insufficient quantities of fibrin being formed in haemostatic plugs, and so inadequate haemostasis. This chapter deals with the basic approach to, and management of, coagulation factor deficiencies in the surgical patient.

TYPES OF COAGULATION FACTOR DEFICIENCY

When considering any coagulation factor deficiency, a clear distinction should always be made between two basic categories of coagulation factor deficiencies. The acquired, or congenital coagulation factor deficiency which is present preoperatively and will also bee present postoperatively, and which is not temporary in nature. Another category is the temporary acquired deficiency, such as due to dilution of coagulation factors as a result of an infusion of large volumes of plasma replacing fluids, or administration of some drugs. This distinction is important for practical therapeutic reasons.

1. Chronic acquired, or congenital coagulation factor deficiency.

These are disorders such as von Willebrand's disease, haemophilias, or reduction of coagulation factor production as a result of severe liver disease etc. The patient may make none, or insufficient quantities of some coagulation factors. Such disorders are not temporary in nature, existing before, during and after any operation. Patients with these disorders may require life-long regular intravenous infusion of the deficient factors to maintain adequate haemostatic function.

The chronic and perioperative management of such disorders is sometimes not simple, and is usually best left in the hands of a specialist haematologist, as he is the person who manages the bleeding disorder both before and after any surgical procedure in any case.

The usual management consists of a preoperative transfusion of the deficient coagulation factors so as to elevate the plasma concentration of the deficient factors to at least 60% of the concentration in normal persons [3]. This should be sufficient to provide adequate haemostasis during the intraoperative period. The effect of the coagulation factor infusion should be checked prior to surgery by measuring the PT or aPTT/PTT, whichever is more appropriate.

Postoperatively the requirement for coagulation factors is reduced as haemostasis has already occurred in the operative wounds. However a minimum coagulation factor concentration is still necessary, or the operative wounds will recommence bleeding. The min-

imum coagulation factor concentrations required for this are given in table 6.3.3. These minimal coagulation factor concentrations must be maintained for up to a month until wound healing has occurred.

All this requires the active services of a haematologist, a laboratory capable of performing the measurements of haemostatic function required, and above all a blood bank capable of supplying the necessary quantities of coagulation factors.

2. Temporary coagulation factor deficiency.

Temporary deficiencies of coagulation factors may have a variety of causes, but they are characterized by one common factor. That is, they are temporary. Replacement of deficient coagulation factors is only required until the cause of the deficiency has disappeared, and the liver and vascular endothelium have made sufficient quantities of the deficient factors to elevate their plasma concentrations to a level at which haemostasis is adequate.

a. Massive blood transfusion.

i. Significant thrombocytopenia occurs after transfusion of about 10-15 units of blood bank ACD anticoagulated whole blood (equivalent to about one blood volume in an adult). However a deficiency of coagulation factors does not occur after transfusion of such volumes of whole blood. The PT and aPTT/PTT remain nearly normal until much more than 20 units of old ACD anticoagulated blood bank whole blood have been transfused, (i.e. more than two blood volumes) [see chapter 14.5].

ii. The situation is different for massive transfusion of packed cells, or other erythrocyte concentrates. Such concentrates are often infused suspended in crystalloid or colloid solutions. These do not provide any coagulation factors or platelets to replace those lost by haemorrhage. In this situation, clinically significant dilution of platelets and coagulation factors, and lengthening of the PTT/aPTT and PT occurs after transfusion of 10 units of such a suspension (about one blood volume in an adult) [see chapter 14.5].

Therapy in both situations consists of the administration of platelets, fresh frozen plasma or both as indicated. This may be repeated as required.

b. Massive infusion of colloidal fluids.

Coagulation disorders due to dilution of plasma proteins may occur after infusion of large amounts of plasma volume replacing fluids to replace plasma losses. In theory, such clinically significant dilution of coagulation factors is likely after more than 20-30% of the blood volume has been replaced with a solution containing no coagulation factors. If a greater volume than this is infused, the plasma concentrations of all the coagulation factors will fall below 60% of the normal level, and this is the minimum concentration of factors IX and VIII that is required for adequate intraoperative haemostasis [see chapter 6.3]. Indeed, this corresponds well with the maximum volume of dextran and albumin solutions that may be infused without causing a significant disorder of haemostasis [see chapter 14.2].

Therapy consists of an infusion of fresh frozen plasma. This restores both the plasma volume as well as all the deficient coagulation factors.

c. Effects of drugs on haemostasis.

Some drugs cause coagulation disorders, e.g. the anticoagulants and cytotoxics [see table 6.7.1, and chapter 6.6]. This is an effect that disappears when the drug concentration falls below an effective level.

Management consists of discontinuation of the drug causing the problem and waiting until the haemostatic defect has disappeared. If surgery is more urgent, an infusion of fresh frozen plasma, or specific replacement of the deficient coagulation factors is required. This may be repeated until the effect of the drug is no longer present.

Table 6.4.1.

Coagulation factor concentrations of various preparations relative to plasma. These may vary from one preparation to the other. (Plasma concentration = 1)

FACTOR	FRESH FROZEN PLASMA	CRYO-PRECIPITATE	FOUR FACTOR CONCENTRATE
I	1	7.5	0
II	0.9	0	< 10
V	0.6	0	0
VII	0.9	0	< 25
von W.	1	?	0
VIII	0.8	7.5	0
IX	0.9	0	< 25
X	0.9	0	25
XI	0.9	0	0
XII	0.9	0	0

TYPES OF COAGULATION FACTOR PREPARATIONS & THEIR INDICATIONS

1. High concentration, single coagulation factor concentrates.

Preparations containing a high concentration of a single coagulation factor are made from plasma pooled from large numbers of donors, and as such their use is associated with all the risks of this. The use of these solutions is usually only indicated in the chronic management of specific coagulation factor deficiencies. Such management is best left to a specialist haematologist, as dosage requirement and interval depend on the severity of the deficiency, and the haematologist is the physician who manages the patient both before and after surgery in any case.

2. Fresh Frozen Plasma (FFP)

The volumes of FFP required to elevate the plasma concentration of most coagulation factors to above the minimum concentrations required for haemostasis, assuming total

absence of that factor, and lack of synthesis, are very large except for factor XIII replacement. This limits the uses of FFP to situations where there is a factor XIII deficiency, and for correction of coagulation factor deficiencies during haemorrhage, or in hypovolaemic patients.

The principal indications for the use of FFP are set out below.

a. Haemorrhage.

To prevent the occurrence of a dilutional coagulation factor disorder during intraoperative blood transfusions where the volume of the blood transfusion exceeds 50% of the blood volume of the patient.

- After 21 days of storage the plasma concentrations of factors V and VIII are 20-50% of normal. 1 unit of FFP should be given per 5-10 units of whole blood transfused.
- Packed cells, and other forms of erythrocyte concentrate contain no plasma. Administer 1 unit of FFP per 2-3 units of packed cells, or erythrocyte concentrate that is transfused, when the blood volume being replaced is more than 50% of the calculated blood volume of the patient.

b. Hypovolaemia.

FFP is to be preferred as a source of coagulation factors when correcting the coagulation problems of hypovolaemic or bleeding patients. For example, a traumatized patient with a coagulation disorder and haemorrhagic shock, or a patient undergoing surgery who has significant blood loss, or a patient who is hypovolaemic as a result of plasma loss, etc.

In the above situations FFP is used to replace deficient blood and plasma volume, as well as to replace deficient coagulation factors. The volumes required are dependent upon the blood volume deficit. The haemostatic effect of the infused FFP can be determined by the appropriate tests.

3. Four factor concentrate

Because it is made from plasma pooled from a large number of donors, its use is not recommended except in emergency situations, or situations where there is no other alternative possible. Its use is sometimes associated with thrombotic complications. It replaces deficiencies of factors II, VII, IX, and X. The concentrations of the various coagulation proteins varies somewhat from one preparation to another.

4. Cryoprecipitate

This may be used to correct deficiencies of von Willebrand's factor and fibrinogen, as well as factor VIII. The dosage varies from one preparation to another.

5. Deamino-8-d-arginine vasopressin (DDAVP) [1,2]

This an analog of vasopressin which is devoid of significant vasoconstrictor activity. Administration induces vascular endothelial release of factor VIII and von Willebrand's factor. It may be used to treat patients with mild hemophilia-A (factor VIII deficiency), and von Willebrand's disease.

The dose required is 0.3-0.5 μg/kg administered via an intravenous infusion over a half hour period. The reason for the somewhat slow infusion rate is that rapid intravenous infusion of DDAVP can cause hypotension. Because its action is to induce release of factor

VIII and von Willebrand's factor from vascular endothelium, it does not work immediately. It takes about 1-2 hours before the plasma concentrations of these factors have increased sufficiently for a significant haemostatic effect to have been induced in most patients.

MONITORING OF THERAPY

The effects of any therapy of coagulation factor defects must be monitored by serial measurements with the appropriate test so that costly and potentially dangerous overtreatment may be avoided.

CAUTIONARY NOTE

1. Many plasma protein concentrates or preparations are made from pooled plasma from many donors. The greater the number of donors, the greater the chance of transmission of blood-borne viral disease to the recipient. Because of this possibility, always attempt to use a coagulation protein preparation made from the least number of donors.

- Fresh frozen plasma - 250 mls comes from 1 donor
- Cryoprecipitate - at least 4 donors per 1000 Units factor VIII activity.
- 4-Factor concentrate - many donors.
- Specific coagulation protein concentrates - many donors.

2. Patients who receive chronic therapy with coagulation factor preparations should be regularly tested for infection with Hepatitis-B and AIDS (Acquired Immune Deficiency Syndrome) viruses. This has consequences for the level of care required for medical treatment, instrument and apparatus sterilization, and nursing.

The absence of a positive test does not mean that the patient does not carry any of these viruses, and the medical attendants of these patients should always wear gloves when coming into contact with any blood from these patients.

REFERENCES

1. Mannucci,P.M., et al.,(1977). 1-deamino-8-D- arginine vasopressin: A new pharmacological approach to the management of haemophilia and von Willebrand's disease. LANCET, 1, 869-872.
2. Mannucci,P.M., et al.,(1983). Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. NEW ENGLAND JOURNAL OF MEDICINE, 308, 8-12.
3. Rudowski,W.J., et al.,(1987), Is major surgery in hemophiliac patients safe? WORLD JOURNAL OF SURGERY, 11, 378-386.

Chapter 6.5

PERIOPERATIVE MANAGEMENT OF PLATELET DISORDERS

Platelet deficiency and dysfunction are relatively common causes of abnormal perioperative haemostasis. The practical perioperative management of these disorders is usually not difficult, as the range of therapies available is limited.

PLATELET DEFICIENCY

A platelet concentration of at least 50,000-75,000 platelets/mm^3 of normally functioning platelets is required for adequate perioperative haemostasis [see chapter 6.3 for a more detailed discussion].

Platelet deficiency may has two main causes in perioperative patients.

1. Platelet deficiency due to haemorrhage and blood transfusion.

Platelet deficiency may occur as a result of gradual blood loss equivalent to one blood volume of the patient, with simultaneous replacement of the blood lost with old bank blood and plasma volume replacing fluids. This causes both loss of platelets by haemorrhage, platelet consumption by wound haemostasis, as well as dilution of the remaining platelets by transfusion of old blood and the plasma volume replacing fluids used to replace the blood volume deficit [see chapter 14.5].

Fresh blood may be used to replace blood, as well as to prevent or correct the platelet deficiency. The blood must be quite fresh as platelet function decreases to insignificance after 48-72 hours of storage [1]. Otherwise a platelet transfusion is required [see below for dosage].

2. Thrombocytopenia not due to haemorrhage or transfusion.

Thrombocytopenia may occur due to a large number of diseases and drugs, e.g. cytostatic or antirheumatic drugs. Therapy consists of waiting until the thrombocytopaenia has passed, or the effect of the bone marrow suppressing drug has disappeared. If such waiting is not possible, a platelet transfusion must be administered.

Platelet transfusions

1. Dosage of platelets.

The dosage of platelets for a platelet transfusion can be calculated using any one of the two methods presented below.

a. Infusion of platelets derived from one unit (500 mls), of donor blood raises the platelet concentration in the recipient one hour after infusion by 10,000 platelets/mm^3 per square

meter of body surface area [2]. When the total dosages are calculated for children and adults, the dosages required are the same as calculated with method b.

b. Infusion of platelets derived from 4 units of blood will usually elevate the platelet concentration of an average adult to levels sufficient for adequate surgical haemostasis. The average dosage required for the same effect in children is the platelets derived from 1-4 units of blood. The effect is checked using the bleeding time, and more is administered as required. In situations of nearly total thrombocytopenia, double the above dosages are required [9].

2. Considerations with platelet transfusions.

a. Peak function of transfused platelets usually occurs about 90 minutes after platelet transfusion, and not immediately after infusion [7].

b. The average lifespan of a platelet in the circulation is 8-10 days. After platelet transfusion, the longest time that transfused platelets are detectable in the recipient's blood is 8.1 days [8]. This agrees well with the normal platelet lifespan, as the donor platelets have ages ranging from 0-8 days. The decline of platelet concentration with time after transfusion is linear, with the concentration decreasing by one eighth of the original post-transfusion elevation of platelet concentration per day [8]. While this may be used to calculate the duration of effect of a platelet transfusion, persons who have been subjected to multiple transfusions, surgery, and severe physiological stress and disease do not have such a predictable response. For this reason monitoring of the effects of platelet transfusion is best done by regular repeated measurement of the bleeding time.

c. Patients who have had previous platelet or blood transfusions may have developed antibodies to foreign blood groups and tissue types. In these patients platelet transfusion may have little effect, as the transfused platelets may be destroyed extremely rapidly. Such patients require a transfusion of HLA-typed platelets. These platelets are less likely to be destroyed by any antibodies, will therefore last longer in the circulation, and are accordingly more likely to have the clinically desired haemostatic effect.

PLATELET DYSFUNCTION

Platelet dysfunction may also occur due to a large number of causes. In anaesthetic practice the most commonly encountered causes are anaesthetic gases, renal failure, liver failure, anti-inflammatory drugs, and cytostatic drug therapy.

Therapy.

1. Platelet transfusion is effective in most types of platelet dysfunction.

2. Deamino-8-D-arginine vasopressin (DDAVP) is worth trying in all cases of platelet dysfunction. It has certainly been shown to be effective in most cases of platelet dysfunction as a result of uremia and von Willebrand's syndrome. The dosage is 0.3-0.5 μg/kg given by intravenous infusion over 30 minutes. The relatively slow infusion rate is required because rapid intravenous infusion of DDAVP can cause hypotension. A reduction of the bleeding time is measurable 1-2 hours after administration and lasts for 8-24 hours [3,4].

3. Cryoprecipitate may be used in place of DDAVP, and has the same indications. It too is effective in most cases of uremic platelet dysfunction, and certainly in von Willebrand's syndrome. An effect is measurable in adult uremic patients by 1-12 hours after administration of cryoprecipitate derived from 10 units of donor blood, and lasts for 24-36 hours [5].

4. Dialysis will reduce the bleeding time in most patients with uremic platelet dysfunction [6].

PERIOPERATIVE MANAGEMENT

The minimum acceptable platelet concentration prior to most forms of surgery is 50,000-75,000 platelets/mm^3, together with a bleeding time of less than 6 minutes [see chapter 6.3]. This minimal platelet concentration and function must be maintained during the perioperative period until primary haemostasis is complete, that is during the operation itself, and for two days postoperatively. After two days, primary haemostasis of the operative wound is essentially complete, and the requirement for platelets is reduced.

Perioperative management of platelet disorders also obviously requires the cooperation of a haematologist, a blood bank capable of supplying the quantities of platelets required for two days, and a haematological laboratory capable of performing the necessary investigations.

MONITORING OF THERAPY

The effects of any therapy to improve platelet count and function should be carefully monitored by regular measurements of the platelet count and bleeding time. This is absolutely necessary if the therapy is intended to improve haemostatic function prior to operation, as maneuvers to improve platelet count and function are sometimes ineffective. Such monitoring spares the patient the risks and expense of further ineffective therapy, and excessive unnecessary therapy.

Bleeding time and platelet count should not be determined until at least one hour has elapsed after any therapy to improve platelet function or count has been administered. This is because transfused platelets are not optimally active until this time, and the effects of DDAVP or cryoprecipitate do not become significant until an hour or two has elapsed after administration [see above].

REFERENCES

1. Ellison,N.,(1977). Diagnosis and Management of Bleeding Disorders. ANESTHESIOLOGY, 47, 171-180.
2. Friereich,E.J.,(1966). Effectiveness of platelet transfusion in leukaemia and aplastic anemia. TRANSFUSION, 6, 50-54.
3. Mannucci,P.M., et al.,(1983). Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. NEW ENGLAND JOURNAL OF MEDICINE, 308, 812.
4. Mannucci,P.M., et al.,(1977). 1-deamino-8-D-arginine vasopressin : A new pharmacological approach to the management of haemophilia and von Willebrand's disease. LANCET, 1, 869-872.
5. Janson,P.A., et al.,(1980). Treatment of the bleeding tendency in uremia with cryoprecipitate. NEW ENGLAND JOURNAL OF MEDICINE, 303, 1318-1322.
6. Rabiner,S.F.,(1972). The effect of dialysis upon platelet function of patients with renal failure. ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 201, 234-242.
7. Slichter,S.J., Harker,L.A.,(1976). Preparation and storage of platelet concentrates. II. Storage variables influencing platelet viability and function. BRITISH JOURNAL OF HAEMATOLOGY, 34, 403-419.

8. Slichter,S.J., Harker,L.A.,(1976). Preparation and storage of platelet concentrates. I. Factors influencing the harvest of viable platelets from whole blood. BRITISH JOURNAL OF HAEMATOLOGY 34, 395-402.
9. Becker,G.A., Aster,R.H.,(1972). Platelet transfusion therapy. MEDICAL CLINICS OF NORTH AMERICA, 56, 81-94.

Chapter 6.6

ANTICOAGULANT DRUGS & SURGERY

Anticoagulant drugs may be administered to patients coming for surgery for a variety of reasons. The anaesthetist should have a practical working knowledge of the effects of these drugs and the methods of reversing their effects. There are two basic types of anticoagulant drugs in clinical use, the orally administered vitamin-K antagonists, and the heparins.

Table 6.6.1.
Commonly used oral anticoagulant drugs, their usual daily maintenance dose, and the usual duration of an anticoagulant effect after acute discontinuation of the drug [1].

DRUG	Maintenance dose (mg/day)	Duration of effect after stopping maintenance dose (days)
Dicoumarol	25-150	5-6
Warfarin	2-15	4-5
Phenprocoumon	1-4	7-14
Acenocoumarol	2-10	1.5-2
Phenindione	50-100	1-4
Diphenadione	2.5-5	15-20
Anisindione	25-250	1.5-3

ORAL ANTICOAGULANT DRUGS

Oral anticoagulant drugs are all vitamin-K antagonists, and as such depress hepatic synthesis of normally functioning molecules of factors II, VII, IX and X. Factors II, VII, IX

and X are synthesized, but their function is abnormal and they are inactive in the coagulation process.

Hepatic synthesis of normal molecules is depressed to such a degree that insufficient normal molecules are synthesized to maintain the plasma concentrations of one or more of these factors at the levels required for normal haemostasis. The rate at which an anticoagulant effect develops after administration of one of the oral anticoagulants depends on how complete the blockade of normal hepatic synthesis of factors II, VII, IX and X is, and the plasma elimination half life of the molecule with the shortest elimination half life. Of the four factors affected, it is factor VII which has the shortest elimination half life, about 5 hours [see table 6.3.3].

The test most commonly used to monitor the activity of these drugs is the prothrombin time (PT) or one of its variants, as synthesis of extrinsic pathway factors is most sensitive to the action of these drugs [see chapter 6.2]. At higher doses these drugs also cause a prolongation of the PTT/aPTT due to inhibition of common pathway factors (factors II and X), and factor IX synthesis. Clinically relevant information about the oral anticoagulants in common use is listed in table 6.6.1.

Preoperative reversal of oral anticoagulant drugs.

The effects of anticoagulant drugs should be reversed prior to surgery. Minimum haemostatic parameters required for surgery have been defined in chapter 6.3. There are various methods of reversing the effects of these drugs.

1. Discontinue the drug and wait.

If the drug is discontinued for 2-7 days prior to the planned date of operation, the effect of the drug will usually spontaneously disappear [see table 6.6.1].

2. Vitamin-K1.

If there is some haste to operate, the effect of the drug may be antagonized with vitamin-K1 given orally or parenterally at a dose of 1-5 mg depending upon the PT. This takes at least 4-6 hours to have any significant effect, as the liver must synthesize a sufficient quantity of the deficient factors to elevate the plasma concentrations to a level at which adequate haemostasis occurs.

3. Fresh frozen plasma, or whole blood.

If the operation is urgent, transfusion of whole blood or fresh frozen plasma is to be recommended in those patients who are hypovolaemic. This corrects the coagulation disorder at the same time as hypovolaemia.

4. Four-factor concentrate.

If the patient is not hypovolaemic, or bleeding, and especially if the patient cannot tolerate intravascular volume loading, four-factor concentrate is the preparation of choice if there is an indication for urgent operation. However the use of this coagulation factor preparation should be limited, as its use is associated with a risk of disease transmission and thrombotic complications.

Monitoring the effect of anticoagulant reversal.

In all cases, regular measurement of the PT is necessary to determine the efficacy of the maneuvers used to reverse the haemostatic defect. If necessary, more antagonist may then be administered.

THE HEPARINS

Heparins are a group of acidic sulphated mucopolysaccharide molecules which are synthesized in the metachromatic granules of mast cells, normally to be found in close proximity to blood vessel walls. The normal function of the heparins is to prevent activation of clotting factors. Heparin derived from animals is used for a variety of clinical purposes requiring inhibition of blood coagulation.

The action of heparin is to activate antithrombin-III, a naturally occurring protease inhibitor in the plasma. The activated forms of the coagulation factors, with the exception of fibrin, are all protease enzymes the action of each of which is to split a polypeptide off from the next inactive coagulation factor, so activating it. Activated antithrombin-III combines on a 1:1 molecular basis with the activated forms of the coagulation factors IX, X, XI, and II (thrombin), to form inactive complexes. The coagulation pathways are blocked, and clotting does not occur.

The aPTT/PTT is commonly used to monitor the effect of the heparins as it is the intrinsic clotting pathway factors which are most sensitive to the effects of the heparins.

Clinical uses of heparin.

Heparin is used for a variety of purposes in surgical and anaesthetic practice.

1. To prevent clot formation around intravascular catheters. The dosage used for this purpose is about 200 IU/day. (N.B. IU = International Unit).
2. To prevent coagulation in clamped-off blood vessels during vascular surgery. The dosage used is about 3000-5000 IU for a normal adult (40-70 IU/kg), administered intravenously prior to clamping.
3. To prevent coagulation of blood in the circulation during circulatory arrest during cardiac surgery. The dosage of heparin used here is about 200-300 IU/kg, (2-3 mg/kg).
4. Therapy of deep venous thrombosis and/or venous thromboembolism. The dosage used is about 36,000 IU/day, or 1,500 IU/hr, or 20 IU/kg/hr, administered by continuous intravenous infusion.
5. Prophylaxis of deep venous thrombosis during the perioperative period. The dosage used for the average adult is 5,000 IU administered subcutaneously 2 or 3 times per day. Note that this dose causes the PTT to be prolonged to twice normal, or more, in 10-15% of normal patients [2].
6. To keep intravascular catheters patent during radiological angiographic procedures. The total dosage of heparin used during a protracted angiogram may be surprisingly high, as much as 3,000-4,000 IU/70 kg during the whole procedure.

Heparin elimination kinetics.

Prior to any further discussion of reversal of heparin effect, a short mention of the interesting elimination kinetics of heparin is well worthwhile. This also has direct relevance to clinical practice. The heparins are substances which are eliminated almost entirely by metabolism, principally by metabolism with a saturable hepatic enzyme. Because the me-

tabolizing enzyme is saturable, this means that the larger the dose of heparin administered, the longer the elimination half life, or the slower the clearance. The equations describing the elimination kinetic parameters are shown in table 6.6.2.

Table 6.6.2.
Heparin kinetics [3, page 1689].

Volume of distribution = 58 ml/kg
Clearance (ml/min/kg) = 1/(0.65 + 0.008 x D)
$T_{(1/2)e}$ (mins) = 26 + D/3
D = heparin dosage in IU/Kg body weight.

Reversal of heparin effect

It is sometimes desirable to reverse the anticoagulant effects of the heparin administered for any of the above reasons. There are two principle methods available, waiting, or administration of protamine.

1. Waiting.

The elimination kinetics of heparin are shown in table 6.6.2. If all that is done is to wait 3-4 elimination half lives, the majority of the heparin in the body will have been eliminated, and the effect will be insignificant [see chapter 15.1]. While this is practical for lower doses of heparin, it is not practical for higher doses as the elimination half life of heparin increases with the total amount of heparin present in the body [see table 6.6.3]. Reversal of heparin effect with protamine is more practical in such cases.

2. Protamine.

Protamine is a very basic protein derived from fish sperm. Being very basic, it combines readily with the very acidic heparin molecules to form complexes which possess no anticoagulant activity. Its effect is rapid, reversal of heparin effect occurring within seconds after intravenous administration. The dosage of protamine required is calculated as below.

1-1.3 mg PROTAMINE reverses the effects of 100 IU HEPARIN

Caution should be exercised when injecting protamine intravenously. Rapid injection can cause severe hypotension and cardiovascular collapse. A given dose of protamine should always be injected slowly in fractions of the total dose.

It is common usage that surgeons and anaesthetists dose heparin in terms of milligrams. Usually 100 IU of heparin is said to be equivalent to 1 mg of heparin. As this equivalence obviously depends upon the source and purity of the heparin, such usage should

be discouraged. Dosage in terms of international units is more precise as the activity of the heparin has been determined by assay.

Table 6.6.3.
Protamine dosage for reversal of effects of an intravenous bolus dose, or infusion of heparin, and the elimination half life of the amount of heparin present in the body.

Infusion rate (IU/70 kg/day)	AMOUNT OF HEPARIN IN BODY AT TERMINATION OF ADMINISTRATION (bolus or infusion)		Heparin $T_{1/2e}$ (mins)
	(IU Heparin /70 kg)	(mg Protamine /70 kg)	
10,000	274	2.74	26
15,000	421	4.21	28
20,000	576	5.76	29
25,000	739	7.39	30
30,000	911	9.11	30
35,000	1092	10.92	31
40,000	1283	12.83	32
50,000	1700	17.0	34
	2000	20	36
	5000	50	50
	10000	100	74
	15000	150	97
	20000	200	121

Various methods of calculating the protamine dosage required in various situations are discussed below.

i. Using the Activated Clotting Time (ACT).

The ACT provides a very rapid estimation of the activity of any heparin in blood [see chapter 6.2]. The response of the ACT to heparin is linear up to an ACT of 500 seconds [4]. Because of the linear response, the dose of protamine required to reverse a given heparin effect on the ACT may be calculated using equation 1 below. This formula is derived using the observation that on average a 300 IU/kg (3 mg/kg) dosage of heparin increases the ACT from a mean of 111 seconds to 351 seconds [4].

$$\text{Protamine dose(mg/kg)} = \frac{\text{ACT(seconds)} - 110}{80} \quad \text{.....(1)}$$

ii. Single or intermittent heparin dosage.

Heparin is sometimes administered as a once only intravenous bolus during cardiac, and vascular surgical procedures, or is administered intermittently during radiological angiographic procedures. The total dosage is in general more than 40 IU/kg, resulting in an elimination half life of at least 40 minutes. Usually the requirement for reversal of the heparin arises within this time period. In such a situation, all that is required is to simply calculate the total dosage of heparin administered, and administer a dose of protamine sufficient to reverse this. If a somewhat longer time, i.e. more than 40 minutes, has elapsed, administer half the calculated protamine dose, measure the PTT/aPTT or ACT, and administer more protamine as needed.

iii. Intravenous infusion, or regular intermittent heparin administration.

The total amount of heparin in the body during a steady state intravenous infusion of heparin, or regular intermittent administration, is really quite small. This can be calculated from the kinetic parameters in table 6.6.2, and the kinetic principles outlined in chapter 15.1.

The appropriate dosages of protamine required to antagonize the heparin effect of various heparin infusion regimes, or regular intermittent dosage regimes are shown in table 6.6.3.

Monitoring of effects of reversal.

The effect of any maneuver or treatment to reverse the effects of heparin should be monitored by regular measurement of the aPTT/PTT, or at least the ACT.

REFERENCES

1. Goodman,L.S., et al.,(1975)."The Pharmacological Basis of Therapeutics", 5th edn., pub. Macmillan.
2. Gurewich,V., et al.,(1978). Hemostatic Effects of Uniform, Low-Dose Subcutaneous Heparin in Surgical Patients. ARCHIVES OF INTERNAL MEDICINE, 138, 41-44.
3. Goodman,L.S., et al.,(1985),"Goodman and Gilman's Pharmacological Basis of Therapeutics", 7th ed., pub. Macmillan.
4. Cohen,J.A.,(1984). Activated coagulation time method for control of heparin is reliable during cardiopulmonary bypass. ANESTHESIOLOGY, 60, 121-124.

Chapter 6.7

DRUGS AFFECTING HAEMOSTASIS

Many drugs used in clinical practice are capable of inducing a haemostatic defect. During the preoperative visit the anaesthetist should always consider the possibility of this when asking what medication any patient is receiving. There are a number of processes by which drugs may induce a haemostatic defect.

1. Drug induced bone marrow suppression.

Some drugs cause a thrombocytopaenia by inducing bone marrow depression. The group of drugs which by virtue of their action, nearly always cause bone marrow depression are the cytotoxic drugs. Any person who has had recent therapy with these drugs should be suspected of having a bleeding disorder until proven otherwise, as it can take 4-6 weeks for the bone marrow to recover after a course of cytostatic drugs.

2. Concentration related drug effect on haemostasis.

Drugs may affect either the function of coagulation proteins, platelet function, or both. This effect is usually related to the blood concentration of the drug. Once the drug concentration in the blood falls below a given level, the drug no longer significantly affects haemostasis. Only one drug actually has an effect on platelet function which is not concentration dependent, and that is acetylsalicylic acid. This binds irreversibly with prostaglandin synthesizing enzymes, and the effect on haemostasis lasts until sufficient new enzyme has been synthesized to replace that rendered ineffective, about 7 days. Curiously, sodium salicylate has only a temporary, concentration related effect on haemostatic function.

In general it is sufficient to discontinue most drugs for 24-48 hours for the haemostatic defect to spontaneously resolve, as the plasma drug concentration will usually have fallen below that required to cause a haemostatic defect by that time. The exceptions to this rule are those patients ingesting acetylsalicylic acid, and those persons with impaired drug elimination, e.g. the elderly, and persons with renal, hepatic or cardiac disease (see chapter 15.2).

3. Multiple drug use and haemostasis.

One drug used in normal clinical dosages may not cause a haemostatic defect, but use of more than one drug may well cause a haemostatic defect. The effects of two or more drugs may either potentiate one another, or be additive.

Table 6.7.1.
DRUGS INDUCING HAEMOSTATIC DEFECTS

DRUG	Dose at which effect occurs	Time to effect after initial dose	Duration of effect after stopping drug	References
DRUGS CAUSING INCREASED BLEEDING TIME				
ANTI-INFLAMMATORY				
Acetylsalicylic acid	300 mg	2 hrs	4-7 days	1,2
Indomethacin	50 mg	2 hrs	24-32 hrs	3,4
Naproxen	500 mg/day	?	<4 days	5
Ibuprofen	600 mg	2 hrs	<24 hrs	6
Flurbiprofen	10 mg	1 hour	<24 hrs	7
Sulindac	200 mg	?2 hrs	<24 hrs	27
Phenylbutazone	clin. dosages	?	<24 hrs	12
ANTI-MICROBIAL				
Penicillin-G	18 gm/day	<24 hrs	4 days	8,9
Ampicillin	100 mg/kg/day	15 min(iv)	>2 days	9,10
Carbenicillen	600 mg/kg/day	<24 hrs	4-12 days	11
Nitrofurantoin	431 mg	1 hr	<24 hrs	12,13
INFUSION FLUIDS				
Dextran (MW=70000)	15 ml/kg	1 hr	24 hrs	14,15
Dextran (MW=40000)	15 ml/kg	1 hr	?	15,16
Hydroxyethyl starch	15 ml/kg	1 hr	?	15,16
ANAESTHETIC DRUGS				
Halothane	0.5-2%	minutes	minutes	17,18,28
Ethanol	chronic use			19
CYTOSTATIC DRUGS				
Melphalan	clinical dosages		20	
Mitomycin	clinical dosages		21	
Mithramycin	50 μg/kg/day	6 days	5 days	22
DRUGS CAUSING INCREASED PT and/or aPTT/PTT				
VARIOUS DRUGS				
Oral anticoagulants and heparins				
Bowel sterilization and all broad spectrum antibiotics reduce intestinal vitamin-K synthesis.				
CYTOSTATIC DRUGS				
L-asparaginase	6000IU/m^2/day	3 days	5 days	23
Mithramycin	50 μg/kg/day	6 days	5 days	24,22
Adriamycin	15 mg/m^2/week	?	?	25
DRUGS CAUSING NO ABNORMAL PTT/aPTT, PT, or BLEEDING TIME				
This includes most drugs, but the ones causing most confusion are: Paracetamol [1], Sodium salicylate [2], Sulphinpyrazone [26], Dipyrimadole [26], enflurane [28], isoflurane [28], nitrous oxide [28], opiates, and gelatine solutions.				

Table 6.7.1, an explanation for the reader.

Table 6.7.1 lists common drugs known to cause defects of haemostasis in humans. The dosages mentioned are those used in the investigation reported. Usually this is the clinically used dosage, or the minimum dosage required for that effect. This table only reports the effects of these drugs on the bleeding time, prothrombin time, and partial thromboplastin time, and on **NO OTHER** haemostatic parameters. In-vitro testing may reveal abnormalities of other facets of haemostatic function, but these need not necessarily be reflected in abnormal values of these tests.

REFERENCES

1. Mielke,C.H., Britten,A.F.H.,(1970). Use of asprin or acetoaminophen in hemophilia. NEW ENGLAND JOURNAL OF MEDICINE, 282, 1270.
2. Weiss,H.J., et al.,(1968). The Effect of Salicylates on the Hemostatic Properties of Platelets in Man. JOURNAL OF CLINICAL INVESTIGATION, 47, 2169-2180.
3. de Gaetano,G., et al.,(1971). Some Effects of Indomethacin on Platelet Function, Blood Coagulation and Fibrinolysis. INTERNATIONAL JOURNAL OF CLINICAL PHARMACOLOGY, 5, 196-199.
4. Rane,A., et al.,(1978). Relation between plasma concentration of indomethacin and its effect on prostaglandin synthesis and platelet aggregation in man. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 23, 658-668.
5. Nadell,J., et al.,(1974). Effect of Naproxen and of Asprin on Bleeding Time and Platelet Aggregation. JOURNAL OF CLINICAL PHARMACOLOGY, 14, 176-182.
6. Mcintyre,B.A., et al.,(1978). Effect of ibuprofen on platelet function in normal subjects and hemophiliac patients. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 24, 616-621.
7. Nishizawa,E.E., et al.,(1973). Flurbiprofen, a new potent inhibitor of platelet aggregation. THROMBOSIS RESEARCH, 3, 577-588.
8. Andrassy,K., et al.,(1976). Penicillin-induced coagulation disorder. LANCET, 2, 1039-1041.
9. Brown,C.H., et al.,(1976). Defective PLatelet Function Following the Administration of Penicillin Compounds. BLOOD, 47, 949-956.
10. Bengmark,S., et al.,(1981). Defects in Hemostasis Produced by Antibiotics: An in vivo Study in the Rat. EUROPEAN SURGICAL RESEARCH, 13, 290-298.
11. Brown,C.H., et al.,(1974). The hemostatic defect produced by carbenicillin. NEW ENGLAND JOURNAL OF MEDICINE, 291, 265-270.
12. Holmson,H.,(1976). Classification and Possible Mechanisms of Action of Some Drugs that Inhibit Platelet Aggregation. SERIES HAEMATOLOGICA, 8, 50-80.
13. Hoener,B.A., Patterson,S.E.,(1981). Nitrfurantoin disposition. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 29, 808-816.
14. Weiss,H.J.,(1967). The effect of clinical dextran on platelet aggregation, adhesion, and ADP release in man: In vivo and in vitro studies. JOURNAL OF LABORATORY AND CLINICAL MEDICINE, 69, 37-46.
15. Alexander,B., et al.,(1975). Coagulation, hemostasis, and plasma expanders: a quarter century enigma. FEDERATION PROCEEDINGS, 34, 1429-1440.
16. Gollub,S., et al.,(1967). The bleeding tendency associated with plasma expanders. SURGERY, GYNECOLOGY & OBSTETRICS, 124, 1203-1211.
17. Dalsgaard-Nielson,J., et al.,(1981). Impaired platelet aggregation and increased bleeding time during general anaesthesia with halothane. BRITISH JOURNAL OF ANAESTHESIA, 53, 1039-1041.
18. Ueda,I.,(1971). The Effects of Volatile General Aesthetics on Adenosine Diphosphate-induced Platelet Aggregation. ANESTHESIOLOGY, 34, 405-408.
19. Haut,M.J., Cowan,D.H.,(1974). The effect of Ethanol on Hemostatic Properties of Human Blood Platelets. AMERICAN JOURNAL OF MEDICINE, 56, 22-33.
20. Klener,P., et al.,(1977). Influence of Cytotoxic Drugs on Platelet Functions and Coagulation in vivo. THROMBOSIS AND HAEMOSTASIS (Stuttgart), 37, 53-61.
21. Hashimoto,S., et al.,(1978). The Effect of Mitomycin-C on Platelet Aggregation and Adenosine 3',5'-Monophosphate Metabolism. THROMBOSIS AND HAEMOSTASIS (Stuttgart), 39, 177-185.

22. Monto,R.W., et al.,(1969). Observations on the Mechanism of Hemorrhagic Toxicity in Mithramycin (NSC 24559) Therapy. CANCER RESEARCH, 29, 697-704.
23. Ramsay,N.K.C., et al.,(1977). The effect of L-asparaginase on plasma coagulation factors in acute lymphoblastic leukemia. CANCER, 40, 1398-1401.
24. Kennedy,B.J.,(1970). Metabolic and Toxic Effects of Mithramycin During Tumor Therapy. AMERICAN JOURNAL OF MEDICINE, 49, 494-503.
25. Bick,R.L., et al.,(1976).Adriamycin and fibrinolysis. THROMBOSIS RESEARCH, 8, 467-475.
26. Packham,M.A., Mustard,J.F.,(1977). Clinical Pharmacology of Platelets. BLOOD, 50, 555-573.
27. Green,D., et al.,(1977). The effect of a new non-steroidal anti-inflammatory agent, sulindac, on platelet function. THROMBOSIS RESEARCH, 1, 283-289.
28. Fyman,P.N., et al.,(1984). Effect of volatile anaesthetics and nitrous oxide-fentanyl anaesthesia on bleeding time. BRITISH JOURNAL OF ANAESTHESIA, 56, 1197-1200.

Chapter 6.8

ASSESSMENT OF HAEMOSTATIC DISORDERS

An operation carried out on a patient with a bleeding tendency may have disastrous consequences for that patient. If the possibility of a preoperative haemostatic defect is suspected, the preoperative history and clinical examination should be directed to the elucidation of the nature, or existence of such a defect. There are various steps to follow, and these are set out below.

SUSPICION

Suspicion of the presence of a haemostatic disorder by virtue of the drugs that the patient may be using, the nature of any disease that the patient has, observation of excessive bruising, petechie etc, or the patient gives a history of excessive bleeding.

SPECIFIC ENQUIRY

A history of bleeding from minor wounds which never ceased bleeding after the initial injury, is typical of platelet deficiency, dysfunction or both [see 6.1]. Bleeding from a wound which initially ceased bleeding, and subsequently recommenced bleeding is more typical of disorders of coagulation [see 6.1].

There are some specific types of haemorrhage and disorders about which specific inquiries should be made.

1. A history of nose bleeds. If these are prolonged and sometimes involve large quantities of blood, they are significant.

2. Easy bruising, or haematoma formation as a result of normal activity or injections.

3. Excessive bleeding after dental extractions or minor cuts.

4. The occurrence of haemarthroses.

5. Diseases associated with a haemostatic disorder.
   - Liver disease. All coagulation factors with the exception of factor VIII and von Willebrand's factor are synthesized in the liver.
   - Splenomegally can cause thrombocytopenia.
   - Uremia can cause a thrombopathy.
   - Massive blood transfusion can cause factor VIII and platelet deficiency.

- Decreased vitamin K, and vitamin C intake.
- Bowel sterilization results in decreased vitamin K synthesis in the bowel, which can reduce production of vitamin-K dependent coagulation factors.
- Chronic excessive alcohol abuse may cause a thrombopathy.
- Other disorders associated with defective haemostasis, e.g. Ehlers Danlos syndrome, Rendu Osler, metastasized malignancies.

6. A family history of haemostatic disorder, and if possible their diagnosis.

7. Use of any drugs that may cause a haemostatic disorder.

CLINICAL OBSERVATION AND EXAMINATION

1. Petechie, ecchymoses, and purpura are all suggestive of platelet deficiency, dysfunction, or both.

2. Bruises or haematomas caused by trivial trauma, or even arising spontaneously, are suggestive of coagulation defects.

3. Haemarthrosis, and ankylosis resulting from a previous haemarthrosis are all suggestive of a coagulation disorder.

4. The presence of telangiectasia which may be congenital, or acquired due to liver disease.

5. Look for signs of any disease causing haemostatic disorders.

TESTS OF HAEMOSTATIC FUNCTION [see chapters 6.2 & 6.3]

1. Platelet function may be tested by measuring the bleeding time, and their quantity by the platelet count.

2. The most useful screening tests for coagulation function are the PTT/aPTT for the intrinsic pathway, and the PT for the extrinsic pathway. The fibrinogen concentration may also be measured.

3. If there is a strong suspicion of the existence of a haemostatic disorder, despite these tests yielding normal results, consult a specialist haematologist who will advise on further testing. For example, minor degrees of haemophilia, or von Willebrand's syndrome may not be detected by the above tests.

Chapter 6.9

ANAESTHESIA & SURGERY OF PATIENTS WITH KNOWN HAEMOSTATIC DISORDERS

As a general rule, no patient should be subjected to elective surgery if their haemostatic function is not within the parameters defined by table 6.3.4.

GENERAL CONSIDERATIONS

1. Consult a haematologist.

Long term management of any patient with a known haemostatic disorder is always done by a haematologist. Therefore a haematologist should always be consulted preoperatively as regards the perioperative and postoperative management of these patients.

2. Patients with platelet deficiency or function.

Platelets in sufficient quantity as well as function are required for normal surgical haemostasis. Many patients bleed slightly postoperatively, and this may continue for up to 48 hours. Because of this, arrangements must also be made to maintain adequate platelet concentration and function for two days postoperatively. The exact type of therapy depends on the nature of the platelet disorder [see chapter 6.5]. The bleeding time and platelet concentration should be monitored regularly in the perioperative period.

3. Patients with coagulation factor deficiencies.

Experience with haemophiliac patients has shown that coagulation function must remain within certain acceptable limits until wound healing has occurred. Studies of patients with haemophilia-A (factor VIII deficiency), and haemophilia-B (factor IX deficiency), who underwent surgical procedures of varying magnitudes, have shown that the intraoperative concentrations of these coagulation factors must be at least 60% of the normal concentration. Postoperatively the concentration must be maintained at least at 30% of the normal concentration until wound healing has occurred, a process which takes from 8-22 days depending on the nature of the surgery [1]. These same principles are also applicable to deficiencies of other coagulation factors. Chapter 6.4 contains a more detailed discussion of these problems.

4. Monitoring of effect of therapy.

Serial measurement of the relevant haemostatic parameters is required, so that costly and possibly risky over-treatment may be avoided, e.g. transmission of infectious diseases, allergic reactions etc.

PREOPERATIVE MANAGEMENT

1. Preoperative assessment and investigation are outlined in chapters 6.2 and 6.8.

2. If a patient about to undergo an elective surgical procedure has abnormal haemostatic function, postpone the operation until the problem has been investigated and treated. Inadequate haemostasis can result in serious, and in the worst case, lethal complications, especially in patients undergoing intracranial and spinal surgery.

3. Haemostatic dysfunction in patients who are to undergo emergency surgery should be corrected in the most effective and rapid manner possible. Treatment of specific types of disorders is dealt with in chapters 6.4 and 6.5.

4. NEVER administer drugs intramuscularly to any patient with a haemostatic defect. This may cause large intramuscular haematomas. Apart from any blood loss, the volume of blood inside some limb fascial compartments may increase the pressure inside these compartments to such a degree that fasciotomy is required to restore blood flow.

5. Percutaneous insertion of deep venous lines should only be undertaken if haemostatic function of the patients is within the limits set by table 6.3.4. Intrathoracic haemorrhage due to attempts to insert a subclavian catheter can be lethal, and are more likely to occur in patients with disordered haemostasis.

ANAESTHETIC MANAGEMENT

1. Spinal, epidural, brachial plexus, and many other forms of regional anaesthetic block should never be performed unless the results of haemostatic function testing are within the limits suggested by table 6.3.4. Epidural or intradural haematoma are the most feared complications of these forms of anaesthesia, and are obviously more likely to occur in patients with disordered haemostasis. Other perineural haematomas are also undesirable, e.g. as a result of attempts to administer a brachial plexus block.

2. General anaesthesia is to be preferred in all patients with disordered haemostasis, as general anaesthesia causes no haemorrhagic complications of itself. In fact, when general anaesthesia is used, the only contraindication to surgery is the risk of haemorrhagic complications resulting from the operation. No specific general anaesthetic technique or drugs can be recommended as being preferable. This depends on the patient, the anaesthetist, the surgeon, available drugs, and the operation to be performed.

REFERENCES

1. Rudowski,W.J., et al.,(1987), Is major surgery in hemophiliac patients safe? WORLD JOURNAL OF SURGERY, 11, 378-386.

Chapter 6.10

INTRAOPERATIVE HAEMOSTATIC DISORDERS

Occasionally a haemostatic disorder is detected intraoperatively. The disorder may be an existing unsuspected bleeding disorder, or it may have arisen intraoperatively. Regardless of the cause, diagnosis and therapy must be timely and efficient, and so the anaesthetist should be familiar with the basic diagnosis and therapy of haemorrhagic disorders occurring intraoperatively. Such knowledge is invaluable and saves time both in diagnosis and therapy. This is essential for the effective management of patients with severe life threatening intraoperative haemorrhage due to a haemostatic disorder.

DIAGNOSIS

1. Suspicion.

An intraoperative haemostatic disorder is likely when one or more of the following criteria are satisfied.

- The patient begins to bleed from wounds or puncture sites where the bleeding had initially ceased.
- The patient begins to bleed and ooze more blood than would be expected for the type and site of surgery, and no venous congestion or excessive arterial hypertension is present, nor are there any large unligated bleeding vessels.
- An experienced surgeon says that the patient is bleeding more than would be expected for that particular operation.

2. Tests.

If a haemostatic disorder is suspected, there are a few standard investigations which will provide rapid and almost certain diagnosis of its nature, if this is not already known.

- Platelet count.
- Bleeding time, (N.B. of dubious value in cold and vasoconstricted patients).
- Partial thromboplastin time (PTT/aPTT).
- Prothrombin time (PT).
- Fibrinogen concentration (optional).

The blood should preferably be taken from a region of the body in which there is no intravenous infusion. In particular, blood should never be taken from an intravenous line which is kept patent with heparin. In both cases abnormal coagulation study results may be found.

The value of the whole blood clotting time is very dubious, as has already been discussed in chapter 6.2. If the patient is cold and vasoconstricted, the value of the bleeding time is also subject to variable interpretation as has also been discussed in chapter 6.2.

Table 6.10.1 gives an outline of the diagnosis of bleeding disorders using the simple tests described above.

Some clinical problems of haemostasis are not so simple as table 6.10.1 would suggest, and in fact combined disorders do occur. Often the history, and the clinical circumstances give an indication as to the likely diagnosis of any bleeding disorder. Obviously where the diagnosis is dubious or complicated, specialist haematological help for further diagnosis and therapy is advisable.

CAUSES OF INTRAOPERATIVE HAEMORRHAGIC DISORDERS

1. Unsuspected existing bleeding disorder.

Preoperative investigation may not reveal a bleeding disorder in some patients, e.g. mild forms of von Willebrand's disease, or haemophilia. A bleeding disorder can be present that is so mild that the patient has no haemorrhagic tendency in normal life. However for surgery to be performed with clinically normal haemostasis, rather higher concentrations and function of coagulation proteins and platelets may be required [see chapter 6.3]. Blood loss, with subsequent replacement of lost volume with coagulation factor deficient infusion fluids, will exacerbate all such bleeding disorders after infusion of volumes which cause no disorder of haemostasis in those with normal haemostatic function.

2. Drugs.

Drugs ingested by the patient, or administered by the surgeon or anaesthetist may exacerbate an existing bleeding disorder, or induce a bleeding disorder.

a. The patient may ingest any of the drugs listed in table 6.7.1.
b. Subcutaneous heparin is commonly administered perioperatively to surgical patients to prevent the perioperative occurrence of deep venous thrombosis. The dosage used in adults is 5000 IU administered 2-3 times per day, the first dose being administered preoperatively. About 10-15% of patients administered such doses of heparin have a PTT that is $>=2$ times the normal value [3].
c. Heparin may be infused through an angiography catheter to prevent blood clotting in or around the catheter. If the angiogram is protracted, the total heparin dose may be significant, e.g. 3000 IU in an adult. If the angiogram is performed immediately preoperatively, a significant bleeding disorder may be present due to the heparin remaining in the circulation.
d. A haemostatic defect may occur in patients administered dextran, albumin or hydroxyethylstarch solutions [see chapter 14.2].

3. Massive blood transfusion.

Massive blood volume replacement may cause thrombocytopenia, excessively low concentrations of coagulation factors, or both. This may occur after transfusion of a volume of blood equivalent to the blood volume of the patient. A haemostatic disorder is especially likely when large volumes of packed cells suspended in fluids which contain no coagulation proteins or thrombocytes have been used for blood volume replacement [4, and see chapter 14.5].

It is always advisable to measure the platelet count, PT and aPTT/PTT after transfusion of such a volume of blood.

Table 6.10.1.
Diagnosis of intraoperative bleeding disorders.

ABNORMAL TEST RESULT	NORMAL VALUES	POSSIBLE CAUSES OF ABNORMAL RESULT
Low platelet count	150000-400000/mm^3	- DIC (<60,000/mm^3) - massive blood transfusion (more than 10-15 units) - other thrombocytopenias
Increased bleeding time	<4-5 minutes	- thrombocytopenia (see low platelet count) - thrombopathy (uremia, alcoholism, drugs, other diseases)
Increased ACT	<160 seconds	- heparin effect - gross abnormality of intrinsic clotting path, e.g. haemophilia, DIC etc.
Increased aPTT/PTT	<46 seconds	- heparin effect - massive blood transfusion - DIC - diseases such as the haemophilias
Increased PT	<16 seconds	- oral anticoagulant drug effect, e.g. coumarins. - Gross liver disease - DIC - Massive blood transfusion
Increased PT & Increased aPTT/PTT		- DIC - very high dose heparin or oral anticoagulant drugs - Massive blood transfusion
Low fibrinogen	1.6-4.5 g/l	- DIC - primary fibrinolysis (liver disease, prostate carcinoma)

4. Disseminated intravascular coagulation (DIC).

DIC may occur as a result of massive trauma, major surgery, cerebral injury, sepsis etc [2].

MANAGEMENT OF VARIOUS DISORDERS

1. Disseminated intravascular coagulation (DIC) [2].

a. DIC in bleeding patients.

Heparin is one of the most effective methods of stopping the process of DIC. But in the intraoperative situation with a patient rapidly bleeding from wounds, heparin cannot be administered to stop coagulation occurring as the patient may bleed even more rapidly. All that can be done is to attempt to minimize bleeding by replacing the deficient coagulation factors. In many cases the cause of the DIC is in itself the reason for operation, and surgery will remove the pathological process triggering it.

In such situations, therapy consists of replacement of the deficient coagulation factors with fibrinogen concentrate, fresh frozen plasma, and platelet infusions. Fresh blood may also be used in cases where the patient is bleeding rapidly, or has already lost a large amount of blood.

b. DIC in non-bleeding patients.

Some patients may have active DIC, but not be bleeding. Such a situation occurs in those patients with meningococcal meningitis, heat stroke, snake bite, malignancies, etc. Heparinization of the patient will halt the DIC. Platelets and coagulation factors may then be administered so that primary haemostasis can occur while the condition triggering the DIC can be treated.

Management of DIC usually is best done together with a specialist haematologist. Furthermore, successful management requires a blood bank capable of providing the quantities of coagulation factors needed, as well as a laboratory capable of performing the necessary tests.

2. Coagulation factor deficiency.

A person undergoing surgery loses blood, plasma, or both. The most effective therapy is an infusion of fresh plasma. This replaces both lost blood volume as well as the deficient coagulation factors. If the patient has also lost significant quantities of erythrocytes, transfusion of fresh blood is to be preferred. Fresh blood replaces all coagulation factors that have been lost, as well as the erythrocytes. An alternative to this is infusion of an erythrocyte concentrate, (e.g. packed cells), plus fresh plasma.

3. Platelet deficiency or dysfunction.

Intraoperative platelet dysfunction or deficiency is effectively treated with a platelet transfusion. Transfusion of fresh whole blood may be used for patients who have lost, or are losing large quantities of blood. This replaces both the lost blood as well as correcting the platelet deficiency [see chapter 6.5].

REFERENCES

1. Wintrobe,M.M., et al.,(1981). "Clinical Hematology", 8th edn., pub. Lea & Febiger.
2. Ellison,N.,(1977). Diagnosis and Management of Bleeding Disorders. ANESTHESIOLOGY, 47, 171-180.

3. Gurewich,V., et al.,(1978). Hemostatic Effects of Uniform, Low-Dose Subcutaneous Heparin in Surgical Patients. ARCHIVES OF INTERNAL MEDICINE, 138, 41-44.
4. Murray,D.J., et al.,(1987), Blood replacement therapy: decreases in coagulation factors. CANADIAN JOURNAL OF ANAESTHESIA, 34, suppl., s122-s123.

Part 7

ENDOCRINE DISORDERS

The anaesthetist is frequently confronted with patients with diabetes mellitus, and sometimes with patients suffering from disordered thyroid or adrenocortical function. All these are relatively common endocrinological problems, and the anaesthetist should be aware of the physiological problems caused by them, and their practical management in the perioperative period.

Chapter 7.1

DIABETES MELLITUS

Diabetes mellitus is one of the most common endocrine disorders afflicting surgical patients. It is not a benign disease as it causes significant morbidity, and is associated with a number of potentially serious problems in the perioperative period.

PROBLEMS

1. Increased mortality.

The postoperative mortality of diabetics is up to twice that of non-diabetic patients [5].

2. Depressed phagocytic function.

Phagocyte function is reduced in persons with uncontrolled diabetes, returning to normal with restoration of normoglycaemia [1].

3. Impaired wound healing.

Wound healing is deficient in patients with uncontrolled diabetes mellitus, healed wounds having less tensile strength than a comparable wound in a non-diabetic [22]. Deficient wound tensile strength is also exacerbated by the higher incidence of postoperative wound infections that occurs in diabetic patients [2,3,4].

4. Hyperglycaemia.

Anaesthesia and surgery can both cause hyperglycaemia, the level of which is in direct proportion to the degree of trauma. Hyperglycaemia may also be due to the drugs or infusion fluids used in the perioperative period. The plasma glucose concentration may rise so high that hyperglycaemic hyperosmolar non-ketotic coma may occur. Hyperglycaemic, hyperosmolar coma usually only occurs in poorly controlled diabetic patients, and only manifests when the plasma glucose is above 33 mmol/l (600 mg/100 mls), and the plasma osmolality is above 320 mosm/l [6,7,21].

5. Hypoglycaemia.

There are various possible causes of perioperative hypoglycaemia in patients with diabetes mellitus.

a. Preoperative fasting after sudden discontinuation of regular ingestion of any of the oral hypoglycaemic drugs can cause hypoglycaemia [8,9]. Hypoglycaemia due to chlorpropamide has been reported to occur up to 60 hours after the last dose of the drug [9]. This is

made more likely by the fact that oral antidiabetic drugs may have a prolonged action, especially when administered chronically, or in the presence of renal failure, e.g. chlorpropamide. Table 7.1.1 shows the elimination half lives of some of the oral hypoglycaemic drugs.

b. Hypoglycaemia may also be induced by incautious administration of insulin.

Manifestations of hypoglycaemia.

Most healthy adults experience symptoms due to hypoglycaemia when the plasma glucose concentration falls below 2-2.5 mmol/l (36-45 mg/100 mls) [29,30]. The manifestations of hypoglycaemia are those of increased sympathetic activity;

- transpiration,
- tachycardia and elevation of the blood pressure,
- pupillary dilation.
- unconsciousness in extreme hypoglycaemia.

Table 7.1.1.
Elimination half lives of some oral hypoglycaemic drugs [27].

DRUG	Elimination half life (hrs)
Acetohexamide	1.3-4.5
Chlorpropamide *	33-43
Glibomuride	8.2-8.8
Gliclazide	10
Tolbutamide	7
Glibenclamide *	5.7-10
Glipizide	4-7
Glisoxepide	20

* The elimination half lives of glibenclamide and chlorpropamide increase with prolonged use.

If these manifestations occur in a conscious patient who is not in pain, they are strongly suggestive of hypoglycaemia, and should always be treated immediately as hypoglycaemia until the plasma glucose concentration is known. However, the patient undergoing surgery under general anaesthesia, is a different matter. Manifestations of increased sympathetic

nervous activity may be due causes other than hypoglycaemia. Some of these are listed below.

- The patient may be awake due to inadequate general anaesthesia, but paralyzed due to muscle relaxants. These patients are often very anxious and have much increased sympathetic nervous activity.
- The patient may be experiencing pain due to surgery.
- The patient may be hypercarbic.
- The patient may be hypovolaemic.
- The patient may have heart failure.

The patient may be unconscious due to general anaesthesia, or heavily sedated, and cannot complain about symptoms of hypoglycaemia. Patients who have been administered ganglion blocking or ß-blocking dugs may be incapable of producing the sympathetic manifestations of hypoglycaemia.

Coma due to extreme hypoglycaemia occurs when the plasma glucose concentration is below 1.4-1.7 mmol/l (< 25-30 mg/100 mls) [12, page 1979]. Because of this especial care must be taken to ensure that the patient is normoglycaemic or hyperglycaemic, rather than hypoglycaemic during anaesthesia.

6. Osmotic diuresis.

Glycosuria occurs when the plasma glucose concentration rises above about 10 mmol/l (about 180 mg/100 mls), or when more than 17.6 mmol (320 mg), glucose appears in the glomerular filtrate per minute [11,pages 418,419]. Above this level the renal tubular glucose transport system is saturated and cannot transport any more glucose back into the body. In cases where the glomerular filtration is reasonably maintained, and there is a significant degree of surgically induced hyperglycaemia, the tubular glucose concentration may be so high that an osmotic diuresis occurs. This can cause significant hypovolaemia and electrolyte disorders.

7. Coexisting coronary and peripheral vascular disease.

Diabetic patients have a higher than normal incidence of coronary and peripheral vascular disease. "Silent" myocardial infarction also occurs more often in diabetic than in non-diabetic patients.

8. Autonomic neuropathy.

Autonomic neuropathy is a very common complication of diabetes mellitus, especially in the older diabetic patient [see chapter 8.6]. The importance of this for the anaesthetists is that the baroreflexes of diabetic patients are not as effective in maintaining haemodynamic homeostasis in comparison with those of non-diabetics. Because of this diabetic patients are more sensitive to cardiovascular depressant effects of anaesthetic drugs, and are unable to compensate as well as non-diabetics in response to blood loss, or to any degree of vasodilation. The final result of this is that they are more prone to developing hypotension in response to any of these factors.

In addition to the above, the population of post-synaptic adrenergic receptors is increased due to the neuropathy. Increased sensitivity to the effects of adrenoreceptor stimulating drugs occurs.

EFFECTS OF SURGERY AND ANAESTHESIA ON GLUCOSE METABOLISM

1. Effects of surgery on glucose homeostasis in non-diabetics.

Surgery carried out on non-diabetic patients causes the plasma glucose concentration to increase [24], and the glucose tolerance test to become abnormal [25]. The magnitude of the change in glucose metabolism is in direct proportion to the magnitude of the surgical trauma [23,24]. The cause of traumatic hyperglycaemia and glucose intolerance has been the subject of much investigation, and some of the most important changes of glucose metabolism are listed below.

a. Major trauma or surgery may increase the whole body glucose consumption by as much as three times normal, (normal basal adult glucose consumption is about 6-10 gms/hour). The magnitude of the increase of glucose consumption is directly proportional to the magnitude the trauma or surgery [25].
b. Trauma and surgery also increases the rate of glucose production from hepatic gluconeogenesis and muscle glycogenolysis [23].
c. Plasma insulin concentration does not change significantly during or after trauma [24,25].

Hyperglycaemia occurs because the rate of glucose production from muscle glycogenolysis and hepatic gluconeogenesis exceeds the rate of peripheral glucose consumption and uptake [23].

2. Effects of anaesthesia on glucose homeostasis in non-diabetics.

The effects of anaesthesia upon glucose metabolism are minor in comparison to those of trauma and surgery. But anaesthesia does have some effects upon glucose metabolism.

a. Hyperglycaemia may be exacerbated by intravenous infusion fluids such as glucose containing solutions, or Hartmann's solution (Ringer's lactate) [10].
b. The only anaesthetic drugs actually causing an elevation of blood glucose concentration are diethyl-ether [13] and halothane [26]. Adequate analgesia with opiates [26], or other techniques minimize the elevation of plasma glucose concentration simply by reducing the physiological response to trauma.
c. The use of spinal or extradural anaesthesia is associated with a minimal hyperglycaemic response to surgery in comparison with the same operation carried out under general anaesthesia [28].

3. Effect of surgery and anaesthesia in diabetic patients.

The same changes in glucose homeostasis also occur in diabetic patients, but because diabetic patients produce little to no insulin, the hyperglycaemic response to surgery, trauma, and infection is greater in magnitude than that of non-diabetic patients.

INTRAVENOUS INSULIN KINETICS AND DYNAMICS

Insulin should ideally only be administered by the intravenous route in the perioperative period, as cold and pain induced skin and muscular vasoconstriction due to surgery and anaesthesia makes insulin absorbtion from muscle and subcutaneous tissues unpredictable. Insulin should also ideally be administered by a constant intravenous infusion as this guarantees a constant plasma concentration of insulin. For this reason it is first necessary to dis-

cuss the plasma kinetics of insulin in relation to its effect, as this is important for any understanding of the rationale behind intravenous insulin infusion regimes.

The behavior of insulin may be described by the same pharmacokinetic models as drugs. Soluble insulin has a plasma elimination half life of 9-10 minutes after intravenous injection or infusion [17]. After commencing a constant intravenous infusion of insulin without an initial loading dose, the plasma insulin concentration is almost at steady state concentration by 30 minutes (=3 elimination half lives) [see chapter 15.1 for principles of intravenous drug infusions].

However plasma glucose concentration is not related to the plasma insulin concentration unless steady state conditions have been achieved, but instead is related to the interstitial fluid insulin concentration. Plasma glucose concentration changes in parallel with the interstitial fluid insulin concentration, with a lag time of less than 5 minutes. The equilibration half life of insulin in the interstitial fluid with that in the plasma is about 20 minutes [17]. This means that after starting an insulin infusion without an initial loading dose, or after changing an insulin infusion rate, that the plasma glucose concentration reaches a new steady state concentration in about 1-1.5 hours [17, see also chapter 15.1].

This is more than sufficiently rapid for adequate control of the plasma glucose concentration, making perioperative intermittent intravenous insulin dosage regimes with their attendant problems unnecessary. In addition to this, because the rapidity of onset of a desirable hypoglycaemic effect is more than sufficiently rapid for clinical purposes, an intravenous loading dose of insulin when starting an insulin infusion is also unnecessary [see chapter 15.1 for explanation of loading dose principles].

Table 7.1.2.

Thresholds for clinical manifestations of various plasma glucose concentrations, and the range of acceptable perioperative plasma glucose concentrations [see text for references].

HYPOGLYCAEMIC COMA	- 1.4-1.7 mmol/l - 25-30 mg/100 mls
SYMPTOMATIC HYPOGLYCAEMIA	- 2-2.5 mmol/l - 35-45 mg/100 mls
ACCEPTABLE PERIOPERATIVE GLUCOSE CONCENTRATIONS	**- 3.0-20 mmol/l** **- 55-350 mg/100 mls**
SIGNIFICANT OSMOTIC DIURESIS	- 15-20 mmol/l - 270-360 mg/100 mls
HYPERGLYCAEMIC COMA	- 33 mmol/l - 600 mg/100 mls

PERIOPERATIVE MANAGEMENT OF DIABETES MELLITUS

The practical anaesthetist should always remember that hypoglycaemia kills more rapidly, or is more likely to cause permanent brain and other organ damage than hyperglycaemia. A few critical plasma glucose concentrations need to be kept in mind when administering anaesthesia to the diabetic patient. These are the concentrations of glucose at which coma is likely, and that above which osmotic diuresis becomes significant. These are shown in table 7.1.2.

Because of the varying magnitude of physiological stress in the perioperative period, it is impossible to regulate the blood glucose concentration within a very narrow range. The plasma glucose concentration range generally considered acceptable in the perioperative period is one which does not cause hypoglycaemic manifestations at the lower end of the range, and which at the higher end of the range neither causes a significant osmotic diuresis nor hyperosmolar coma [see table 7.1.2 for these plasma glucose levels]. The acceptable range for plasma glucose concentration during the PERIOPERATIVE PERIOD is between 3-20 mmol/l (55-350 mg/100 mls). No extra therapeutic effort need be made to either raise or lower the plasma glucose concentration if it is within this range in the perioperative period.

Perioperative diabetes management is regulated according to the normal diabetes management of the patient. There are three categories of diabetic management, diet only, oral hypoglycaemic agents plus diet, and insulin plus diet.

1. Diet regulated diabetes mellitus.

Patients whose diabetes is managed by diet alone, only require monitoring of the plasma glucose in the perioperative period. If the glucose concentration rises above 15-20 mmol/l (270-360 mg/100 mls), then an intravenous insulin/glucose infusion regime should be commenced as described in the subsequent paragraphs.

2. Oral hypoglycaemic drug regulated diabetes mellitus.

Patients whose diabetes is managed with diet plus an oral hypoglycaemic agent require a more active regime.

a. Preoperative fast from midnight.

b. NO breakfast and NO oral hypoglycaemic medication of any sort on the day of operation.

c. At 0600 hours on the day of operation measure the plasma glucose concentration.

d. At 0800 hours on the day of operation commence an intravenous infusion of glucose 5% at a rate of 83 mls per hour (500 mls in 6 hours). Short acting (soluble) insulin is added to the glucose solution, the amount of which is determined by the 0600 hours plasma glucose concentration. The recommended rates for perioperative intravenous insulin infusions vary somewhat between authors [13,14,15,16,18], but a generally acceptable regime is set out in table 7.1.3.

It is true that a 5% glucose solution infused at a rate of 83 mls/hour only provides only about 4 gms of glucose per hour. This is less than the normal basal glucose requirement of

6-10 gms/hour for healthy adults, and the difference is even greater during surgery, as surgery increases glucose consumption. But normal glucose production, plus the increased glucose production due to a higher rate of hepatic gluconeogenesis and muscle glycogenolysis caused by surgery more than makes up for the difference.

e. Plasma glucose level should be monitored every 2-3 hours after starting an insulin glucose infusion, or changing the infusion rate. This is to allow time to achieve a new steady state interstitial fluid insulin, as well as plasma glucose concentration [see discussion on insulin kinetics]. The insulin infusion rate should be adjusted according to table 7.1.3.

Table 7.1.3.
PERIOPERATIVE INSULIN-GLUCOSE REGIME
(Insulin is added to a 5% glucose solution and infused at a rate of 500 mls/6 hours = 83 mls/hour)

0600 PLASMA GLUCOSE CONCENTRATION (mg/100 mls)	(mmol/l)	UNITS INSULIN per 500 ml Glucose 5%	INSULIN INFUSION RATE (Units/hour)
<90	<5	0	0
90-180	5-10	4-8	0.5-1.5
180-360	10-20	8-12	1.5-2.0
>360	>20	12-16	2.0-3.0

If control is inadequate with 3 units/hour, increase the dosage by 1 unit/hour steps every 2-3 hours until control is established.

f. Hypokalaemia may occur as a result of the insulin-glucose infusion, especially in situations where the glucose concentration decreases. However, routine addition of potassium to the infusion can cause hyperkalaemia in some patients [15], and so it is advisable to measure the plasma potassium concentration regularly, along with the plasma glucose, and correct any hypokalaemia as it occurs.

g. Any patient unexpectedly remaining unconscious at the end of an operation performed under general anaesthesia must be treated as having hypoglycaemic coma until proven otherwise. The plasma glucose concentration should be measured. Any insulin infusion should be stopped, and administer a glucose infusion until the plasma glucose concentration is known. The glucose infusion may be then continued or stopped depending on the plasma glucose concentration.

h. Postoperatively, the patient either continues with an insulin infusion if very sick. Or, if the postoperative course is uncomplicated, receives a regime of subcutaneous soluble insulin until normal diabetic control can be re-instituted.

3. Insulin dependent diabetes mellitus.

Insulin dependent diabetic patients may be managed very successfully in the perioperative period using the method used by the internists (Head of department Dr. J.D.M. Feuth, internist), working in the Department of Surgery of the University Hospital of Leyden, the Netherlands. Soluble (short acting) insulin has been found to have only 80% of the effect of Lente (long-acting) insulin [20, page 1525]. This may be used to calculate the total daily dose of insulin that is used in terms of a equivalent daily dose of soluble insulin using the formula below.

$$SI_e = D_{SI} + 1.25 \times D_{LI}$$

SI_e = equivalent total daily dose of soluble insulin in IU.
D_{SI} = total daily dose in IU of soluble insulin normally used by the patient.
D_{LI} = total daily dose in IU of lente insulin normally used by the patient.

The equivalent total daily dose that is so calculated is used as the initial total daily dose of soluble insulin to be administered by intravenous infusion. One quarter of this calculated daily dosage of soluble insulin is added to 500 mls of a glucose 5% solution, and infused intravenously every 6 hours (83 mls/hour). This is continued until the normal insulin regime of the patient can be recommenced. The plasma glucose level should be monitored every 2-3 hours as indicated, and the insulin infusion rate varied accordingly [see table 7.1.3]. Adjustment of the insulin infusion rate, and all other management is otherwise identical to that for patients using oral antidiabetic agents.

ANAESTHETIC MANAGEMENT

Preoperative.

1. Enquiry as to the nature of the diabetes management, and the dosages of any hypoglycaemic drugs is essential.

2. Because of the high frequency of coexisting diseases in diabetics, in particular renal dysfunction and cardiovascular disease, plasma electrolytes, haemoglobin, plasma glucose, creatinine and urea should be routinely measured preoperatively. Diabetic patients have an above normal frequency of "silent" myocardial infarction. Because of the potential risks associated with surgery performed on a patient who has had a recent myocardial infarction, all diabetic patients should have a preoperative ECG made, which is no older than one week at the date of the planned operation.

3. Specific enquiry should be made as to the presence of any possible autonomic neuropathy, which may indicate the presence of deficient baroreflexes. Autonomic neuropathy and deficient baroreflexes are common in elderly diabetics [see chapter 8.6 on baroreceptors].

4. The administration of anticholinergic, sedative or other drugs for premedication is dependent on the nature of the operation and the preferences of the anaesthetist.

Anaesthesia.

1. Because of the baroreflex deficiency which is often present, diabetic patients are more prone to develop hypotension in response to cardiodepressant drugs, vasodilation, or blood loss [see chapter 8.6]. In addition, diabetic patients have increased sensitivity to the effects of catecholamines. The result of all these changes is that anaesthesia and surgery in patients who have been diabetic for many years may be accompanied by large changes in the blood pressure in response to any or all of the above stimuli. Administration of any drug, or use of any technique should be done carefully so as to minimize the chances of this.

2. Loco-regional anaesthetic techniques are to be preferred where possible. This minimized the chances of deep venous thrombosis and exacerbation of coexisting diseases. However some caution should be exercised with spinal and epidural anaesthesia in patients with known baroreflex deficiency, as lack of effective baroreflexes means that these techniques may cause a more than usually large fall of blood pressure.

3. No special general anaesthetic technique can be recommended, except that deep anaesthesia with adequate suppression of stress responses minimizes the hyperglycaemia response to surgery. Anaesthesia itself, (except for ether and chloroform anaesthesia), has only a minor hyperglycaemic effect in comparison with the effect of surgery [13].

4. Do not administer glucose containing intravenous solutions unless they are administered together with insulin, or are required for therapy of hypoglycaemia, as excessive degrees of hyperglycaemia may occur. The use of Ringer's lactate solution (Hartmann's solution) is also not advisable as it causes a greater degree of hyperglycaemia in diabetic patients that in non-diabetic patients [10].

Postoperative.

1. Continue to regularly monitor the plasma glucose concentration, and as necessary adjust the insulin infusion rate.

2. Once the patient is able to orally ingest fluids and food, he may resume his normal diet and diabetic regime.

3. The old "sliding-scale" technique is still frequently used, although mainly in the postoperative period. The system consists of regular testing of the urine with glucose testing tablets or strips every 4-6 hours, followed by administration of a subcutaneous dose of soluble insulin according to the glucose concentration measured. If the concentration of glucose in the urine is;

- 1+ = no insulin need be administered,
- 2+ = administer 5 units insulin subcutaneously,
- 3+ = administer 10 units insulin subcutaneously,
- 4+ = administer 15 units insulin subcutaneously [19].

This method of postoperative diabetic control assumes a normal renal glucose threshold, and makes the assumption that the last urine sample is an accurate reflection of the plasma glucose concentration at that time. Neither of these assumptions is true in patients with longstanding diabetes mellitus. In these patients the renal glucose transport is frequently abnormal.

REFERENCES

1. Bagdade,J.D., et al.,(1972), Reversible abnormalities in phagocytic function in poorly controlled diabetic patients. AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 263, 451-456.
2. Cruse,P.J.E., Foord,R.,(1973), A Five Year Prospective Study of 23,649 Surgical Wounds. ARCHIVES OF SURGERY, 107, 206-210.
3. Najarian,J.S., et al.,(1977), Kidney transplantation for the uremic diabetic patient. SURGERY GYNECOLOGY & OBSTETRICS, 144, 682-690.
4. Keighly,M.R.B., et al.,(1984), Influence of diabetes on mortality and morbidity following operations for obstructive jaundice. ANNALS OF THE ROYAL COLLEGE OF SURGEONS OF ENGLAND, 66, 49-51.
5. Alieff, von A.,(1969), Das Risiko chirurgischer Eingriffe beim Diabetiker. ZENTRALBLATT FUR CHIRURGIE, 26, 857-860.
6. Wulfson,H.D., Dalton,B.,(1974), Hyperosmolar Hyperglycemic Nonketotic Coma in a Patient Undergoing Emergency Cholecystectomy. ANESTHESIOLOGY, 41, 286-290.
7. Larson,C.P.,(1974), Hyperosmolar Hyperglycemic Nonketotic Coma, a Cause of Delayed Recovery from Anesthesia. ANESTHESIOLOGY, 41, 284-285.
8. Schen,R.J.,(1973), Chlorpropamide: dangerous hypoglycaemia in old age? LANCET, 1, 1121.
9. Schen,R.J., Khazzam,A.S.,(1975), Postoperative hypoglycaemic coma associated with chlorpropamide. BRITISH JOURNAL OF ANAESTHESIA, 47, 899-900.
10. Thomas,D.J.B., Alberti,K.G.M.M.,1978), Hyperglycaemic effects of Hartmann's solution during surgery in patients with maturity onset diabetes mellitus. BRITISH JOURNAL OF ANAESTHESIA, 50, 185-187.
11. Guyton,A.C.,(1981),"Textbook of Medical Physiology", 6th edn., pub. W.B.Saunders Co.
12. Isselbacher,K.J., et al.,(1980),"Harrison's Principles of Internal Medicine", 9th edn.,pub. McGraw-Hill.
13. Alberti,K.G.M.M., Thomas,D.J.B.,(1979), The management of diabetes during surgery. BRITISH JOURNAL OF ANAESTHESIA, 51, 693-710.
14. Thomas,D.J.B., et al.,(1984), Insulin-dependent diabets during the peri-operative period. ANAESTHESIA, 39, 629-637.
15. Bowen,D.J., et al.,(1984), Insulin-dependent diabetic patients during surgery and labour. ANAESTHESIA, 39, 407-411.
16. Clark,R.B., et al.,(1982), Continuous Insulin Infusion is a Preferred Method for Managing Diabetics. ANESTHESIOLOGY, 56, 332-333.
17. Sherwin,R.S., et al.,(1974), A Model of the Kinetics of Insulin in Man. JOURNAL OF CLINICAL INVESTIGATION, 53, 1481-1492.
18. Miller,R.D., et al.,(1981),"Anesthesia", pub. Churchill Livingstone, pages 22 and 23.
19. Steinke,J.,(1970), Management of Diabetes Mellitus and Surgery. NEW ENGLAND JOURNAL OF MEDICINE, 282, 1472-1474.
20. Goodman,L.S., et al.,(1975),"The Pharmacological Basis of Therapeutics", 5th edn., pub. Macmillan.
21. Fulop,M., et al.,(1973), Ketotic hyperosmolar coma. LANCET, 1, 635-639.
22. Goodson,W.H., Hunt,T.K.,(1977), Studies of Wound Healing in Experimental Diabetes Mellitus. JOURNAL OF SURGICAL RESEARCH, 22, 221-227.
23. Long,C.L., et al.,(1971), Carbohydrate metabolism in man: effect of elective operations and major injury. JOURNAL OF APPLIED PHYSIOLOGY, 31, 110-116.
24. Clarke,R.S.J., et al.,(1970), The influence of anaesthesia and surgery on plasma cortisol, insulin and free fatty acids. BRITISH JOURNAL OF SURGERY, 42, 295-299.
25. Allison,S.P., et al.,(1969), Some effects of anaesthesia and surgery on carbohydrate and fat metabolism. BRITISH JOURNAL OF ANAESTHESIA, 41, 588-593.
26. Hall,G.M., et al.,(1978), Substrate mobilization during surgery. A comparison between halothane and fentanyl anaesthesia. ANAESTHESIA, 33, 924-930.

27. Balant,L.,(1981), Clinical pharmacokinetics of sulphonylurea hypoglycaemic drugs. CLINICAL PHARMACOKINETICS, 6, 215-241.
28. Lund,J., et al.,(1986), Effect of extradural analgesia on glucose metabolism and gluconeogenesis. BRITISH JOURNAL OF ANAESTHESIA, 58, 851-857.
29. Johnson,D.D., et al.,(1980), Reactive hypoglycaemia. JOURNAL OF THE AMERICAN MEDICAL AS SOCIATION, 243, 1275-1278.
30. Fajans,S.S., Floyd,J.C.,(1976), Fasting hypoglycaemia in adults. NEW ENGLAND JOURNAL OF MEDICINE, 294, 766-772.

Chapter 7.2

HYPERTHYROIDISM AND "THYROID STORM"

SOME ASPECTS OF THE PHYSIOLOGY OF THYROID HORMONES

Prior to considering the relationship of hyperthyroidism to anaesthesia and surgery, a brief review of the relevant aspects of the physiology and metabolism of the thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), is of value.

T_4 acts like a prohormone in that it is 5-10 times less active than its metabolic product, T_3 [5]. T_3 acts by binding with specific receptors in the nuclei of cells sensitive to the effects of T_3. The tissues most sensitive to the effects of thyroid hormones are also those with the highest concentrations of nuclear T_3 receptors. These tissues are the anterior pituitary, brain, kidney, liver, and myocardium [4]. T_3 binds with the receptors in the cell nuclei, stimulates ribonucleic acid (RNA) synthesis, and subsequently protein synthesis. Because of this the effects of the thyroid hormones only begin to manifest several hours after administration.

About 80% of the conversion of T_4 to T_3 takes place outside the thyroid gland. This conversion is subject to control by various other hormones, such as catecholamines and glucocorticoid hormones.

1. Catecholamines increase the rate of conversion of T_4 to T_3 [1]. In man it has been shown that this is regulated to some degree by ß2-adrenoreceptors. ß2, but not ß1-adrenoreceptor blockade in man partially blocks the conversion of T_4 to T_3, and decreases the plasma concentration of T_3 by 13-30%, but has no effect on T_4 concentration [2].

2. Glucocorticoid hormone administration in normal pharmacological dosages reduces T_4 secretion, thereby decreasing the plasma concentration of T_4, in addition to partially inhibiting its conversion to T_3. This causes the plasma T_3 concentration to fall [3].

PROBLEMS DUE TO HYPERTHYROIDISM

1. Clinical manifestation of hyperthyroidism.

In one series [18], the frequency of symptoms and signs observed in hyperthyroid patients were as listed in table 7.2.1.

2. Hyperthermia.

Hyperthyroidism elevates the body temperature by raising the metabolic rate of most tissues, and with this, the whole body oxygen consumption too. "Uncoupling of mitochondrial oxidative phosphorylation" is not, as was previously thought, the cause of the increased metabolic rate, as hyperthyroidism increases the intracellular production and

utilization of adenosine triphosphate (ATP) [6]. About 40% of the increased tissue heat production is due to elevated activity of the membrane sodium-potassium pump [6].

Both anaesthesia and surgery elevate the plasma concentrations of thyroid hormones [7,8,9], as may psychological stress [10,11]. This can cause the body temperature to rise, typically 5 or more hours after the initial stimulus [11].

Table 7.2.1.
Frequency of the most common symptoms and signs in hyperthyroidism [18].

SYMPTOMS		SIGNS	
Nervousness	9%	Tachycardia	100%
Increased sweating	91%	Tremor	97%
Heat sensitivity	89%	Eye signs	71%
Palpitations	89%	Atrial fibrillation	10%
Easy fatigability	88%		
Weight loss	81%		
Tachycardia	82%		
Dyspnea	5%		
Muscular weakness	70%		

3. Increased sensitivity to catecholamines.

Many of the manifestations of hyperthyroidism such as peripheral tremor, increased sweating, and tachycardia are the same as those due to increased sympathetic nervous system activity. But neither the plasma concentrations, nor the secretion rates of either noradrenaline [12], or adrenaline [13], are increased in hyperthyroidism in man.

However there is evidence for increased sensitivity to the effects of catecholamines and sympathetic nervous stimulation. Thyroid hormones increase myocardial ß-adrenoreceptor concentrations, as well as increasing the activity of myocardial adenyl cyclase, the enzyme coupled to ß-adrenoreceptors [14]. Simultaneously hyperthyroidism decreases the concentration of vascular α-adrenoreceptors [14]. This would indicate that an increased sensitivity to the ß-adrenergic effects of catecholamines should be observed. This has never been consistently observed in hyperthyroid humans [15]. The most positive evidence that hyperthyroidism does cause increased sensitivity to catecholamines, and normal resting levels of sympathetic nervous stimulation, is provided by the effects of the ß-adrenoreceptor blocking drugs. Propranolol, a non-specific ß1 as well as ß2-adrenoreceptor blocking drug, reduces hyperthyroidism caused tachycardia and psychomotor symptoms within 2-10 minutes after intravenous injection [16]. While it is true that propranolol also decreases the conversion of T_4 to T_3, this cannot be the explanation for the effect on the tachycardia and other manifestations of increased sympathetic nervous activity, as the ef-

fects of a decreased concentration of T_3 takes several hours to manifest by virtue of its mode of action.

In conclusion it may be stated that increased sensitivity to catecholamines does occur in hyperthyroidism.

4. Cardiovascular function.

Hyperthyroid patients have what is commonly called a "hyperkinetic" circulation. Tachycardia occurs in 100% of hyperthyroid patients [18], the cardiac output and contractility are increased, and the systemic vascular resistance is decreased [19,20,21]. The altered cardiac function is in part due to the increased catecholamine sensitivity, (increased ß-adrenoreceptor numbers), and also due to the other effects of thyroid hormones on the myocardium.

Hyperthyroidism can have other effects upon the heart. Atrial fibrillation occurs in about 10% of all hyperthyroid patients [18]. Those with coronary artery disease may develop angina pectoris as a result of the increased cardiac work due to the changes mentioned above. Patients with marginal myocardial function may develop heart failure for the same reasons.

The decreased systemic vascular resistance is most likely due to the combination of increased ß-adrenoreceptor, together with decreased α-adrenoreceptor concentrations, as well as hyperthermia.

5. Muscle weakness [17].

Electromyographic abnormalities are found in about 90% of hyperthyroid patients. About 32-100% of hyperthyroid patients complain of muscle weakness, and 60-100% actually have clinical muscle weakness. The weakness is typically confined to the shoulder and hip muscles, and difficulty is experienced in rising from a squatting position, and climbing steps.

The cause is thought to be due to thyrotoxic inhibition of muscle phosphocreatine kinase. Less creatine phosphate is synthesized in the muscle cells, and the intracellular ATP concentration is decreased. A lower muscle cell ATP concentration means that less ATP is available for muscle contraction, and so muscle weakness occurs.

EFFECTS OF ANXIETY, ANAESTHESIA AND SURGERY

The human thyroid gland is innervated by adrenergic sympathetic fibers arising from the cervical ganglia. Stimulation of these fibers in animal experiments increases thyroid hormone secretion rate [22]. The mechanism by which both surgical and anaesthetic procedures cause the thyroid hormone concentrations or activity to increase is most likely by increasing the sympathetic nervous system activity. This stimulates release of more thyroid hormone, and elevated plasma catecholamine concentrations accelerates the conversion of T_4 to T_3.

1. Effect of anxiety.

There is some clinical evidence that preoperative anxiety can precipitate thyrotoxic hyperthermia in hyperthyroid persons [11]. This is not surprising as anxiety increases sympathoadrenal activity, increasing plasma catecholamine secretion rate and concentrations [23], as well as increasing thyroid hormone secretion. Conversion of T_4 to T_3 is increased by catecholamines.

2. Effect of anaesthesia.

Diethyl-ether [9], halothane [24], and isoflurane [7] anaesthesia all increase the plasma T_4 concentrations significantly. Spinal [25], thiopentone [9], and methoxyflurane [24] anaesthesia do not cause the plasma concentration of T_4 to rise.

3. Effect of surgery, trauma.

Surgical procedures such as thyroid surgery [8], so-called "minor" surgical procedures such as appendectomy and inguinal herniorrhaphy, and certainly major surgical procedures all cause the plasma T_4 concentration to rise [7,9,24].

MANAGEMENT OF HYPERTHYROIDISM

Pharmacological therapy is the principal method of treatment of hyperthyroidism. Therapy of hyperthyroid patients has varying aims.

1. To treat the patient chronically until the condition causing hyperthyroidism undergoes spontaneous remission.

2. To render a patient euthyroid prior to surgery.

3. Acute treatment of the effects of thyrotoxicosis.

1. Chronic treatment.

This is usually done with one of a variety of antithyroid drugs.

- Propylthiouracil, 100-200 mg every 8 hours.
- Methimazole, 30-60 mg once a day.
- Carbimazole, 2-10 mg once a day.

It usually takes 3-12 weeks of treatment with any of these drugs before the patient becomes euthyroid. Of the above drugs, propylthiouracil has the added advantage that it blocks the peripheral conversion of T_4 to T_3. This is not a property shared by the other antithyroid drugs.

2. Preparation of the patient for surgery.

a. Preparation for elective operation.

The patient is rendered euthyroid with one of the above antithyroid drugs. In addition to the antithyroid drugs, 60 mg of potassium iodide is administered every 8 hours for 7-10 days prior to the planned date of surgery. This further reduces the thyroid hormone production, and also the vascularity of the gland [10].

b. Rapid preoperative preparation.

A more rapid method of preoperative preparation has been described [8]. The hyperthyroid patient is given propranolol 80 mg, and potassium iodide 60 mg every 8 hours for 10 days prior to the planned date of surgery. This method should really only be employed in those cases where surgery must be performed relatively rapidly on a patient with untreated hyperthyroidism.

c. Preparation for emergency operation.

Patients whose hyperthyroidism is uncontrolled, but who must undergo an emergency operation, should have the hyperthyroid manifestations controlled before surgery is commenced [10]. Management is identical to that for control of clinical manifestations and thyrotoxic crisis.

3. Treatment of clinical manifestations.

Treatment of the clinical manifestations of hypothyroidism has two aspects, reduction of hyperthermia, and cardiovascular manifestations, as well as reducing the secretion of T_4 and blocking its conversion to T_3.

a. Reduction of sympathetic overactivity.

Propranolol should be administered intravenously at a rate of 1 mg per minute until the pulse rate drops below 100 beats/minute, and the other manifestations of increased sympathetic nervous system activity are reduced. The effect of propranolol manifests within minutes. Subsequently an infusion of propranolol should be commenced at a rate of 1-3 mg/hour [16]. Propranolol also partially blocks the conversion of T_4 to T_3 [see above].

b. Decrease release of T_4 and conversion of T_4 to T_3.

Hydrocortisone should be administered intravenously at a dosage of 100-200 mg every 8 hours. This reduces both the T_4 secretion rate, as well as partially inhibiting conversion of T_4 to T_3 [see above].

If feasible, propylthiouracil may be administered orally every 8 hours at a dosage of 100-200 mg every 8 hours. Propylthiouracil blocks both the secretion of T_4 and blocks the conversion of T_4 to T_3.

PREOPERATIVE ASSESSMENT

1. No hyperthyroid patient should be allowed to undergo elective surgery until the hyperthyroidism has been controlled and the patient rendered euthyroid.

The patient who has been rendered euthyroid has a perioperative morbidity and mortality similar to normal patients undergoing the same operation.

2. Preoperative assessment of the absence or presence of hyperthyroidism is essentially clinical, based upon the clinical manifestations of the disease. Of all the clinical manifestations, the resting pulse rate is the best indicator. A resting pulse rate of more than 100 beats/minute should be taken as evidence of inadequately controlled hyperthyroidism, in a hyperthyroid person.

ANAESTHETIC MANAGEMENT

The clinically euthyroid patient may be managed the same as any normal patient. Anaesthetic management of patients with existing or inadequately controlled hyperthyroidism, is directed towards minimizing the chance of the development of acute thyrotoxicosis. This requires that any perioperative sympathoadrenal response be blunted as much as possible.

Premedication.

1. This should provide sufficient sedation, analgesia, or both, as required to prevent any preoperative anxiety or pain caused elevation of sympathoadrenal activity. The choice of drugs to use for this purpose is individual and depends also upon the clinical circumstances.

2. Atropine and anticholinergic drugs should not be administered as this causes a relative increase of sympathetic nervous system activity [26].

Anaesthesia.

1. Regional anaesthesia.

Surgery conducted under regional anaesthesia with adequate sedation causes minimal to no elevation of thyroid hormone activity, and is to be recommended where appropriate. Because of the increased cardiovascular sensitivity to catecholamines, and the increased T_4 release that they may cause, caution should be used during administration of any vasoconstrictor catecholamines which also possess ß-adrenoreceptor activity.

2. General anaesthesia.

There are some factors which must be considered when general anaesthesia is required.

a. Controlled ventilation is to be preferred as this guarantees tissue oxygenation in the presence of increased oxygen consumption and possible myopathic respiratory muscle weakness.
b. The elimination rate of most anaesthetic drugs is most likely to be increased in direct proportion to the elevation of cardiac output. This means that most drugs administered will have a shorter duration of action than normal, and that while the same dosages of any given drug will still be required, the dosage interval will be shorter [see chapter 15.2].
c. Induction of anaesthesia should preferably be done with thiopentone, as the use of this drug blunts any elevation of the plasma T_4 concentration. But because of the increased cardiac output in hyperthyroid patients, the induction dosage is increased, and the sleep time is reduced, in proportion to the elevation of cardiac output [27]. Ketamine should not be used as this causes an increase of sympathetic nervous system activity, and so in theory may actually exacerbate hyperthyroidism.
d. The induction time with volatile anaesthetic agents is increased in direct proportion to the elevation of cardiac output. As the peripheral distribution is rapid, the partial pressure of the gas in the central blood volume does not rise as rapidly as usual. The minimum alveolar concentration (MAC) of anaesthetic gases is relatively unaffected by hyperthyroidism [28], but is increased in direct proportion to any elevation of body temperature [29]. No volatile agent that elevates the plasma concentration of thyroid hormones should be used [see above].
e. The significance of the muscle weakness in relation to muscle relaxant drug use is unclear. On a practical level, significant muscle weakness, plus the effects of respiratory depressant drugs, as well as the residual effects of any muscle relaxant drugs, may cause postoperative respiratory failure. Muscle relaxants should therefore be administered only on clinical indication.Tubocurarine has much to recommend it as a muscle relaxant drug for use in hyperthyroid patients, because of the ganglion blockade it induces with clinically used dosages [see chapter 2.1].

Postoperative.

Clinically hyperthyroid patients should all be sent to an intensive care unit for both observation, and if required, effective management of any thyrotoxic crisis. Patients with severe thyrotoxic myopathy may require mechanical ventilation.

THYROID "STORM" OR "CRISIS"

Thyroid "storm" or "crisis" is the name given to an acute potentially lethal severe exacerbation of thyrotoxic manifestations in an already hyperthyroid patient. The precipitating stimulus is often an infection, usually respiratory, anaesthesia, trauma, surgery, vigorous palpation of a thyrotoxic gland, or acute withdrawal of antithyroid therapy [10,11]. There is also some clinical evidence that it may be triggered by psychological stress too [11].

The mortality of this syndrome in the past when it was only treated with iodine was about 60-70% [10]. This high mortality has been reduced to about 20% by current therapy with propranolol, corticosteroids and antithyroid drugs [16].

Typically the manifestations begin about 5-18 hours after the initial stimulus and last on average about 3 days [10], or until death occurs.

Diagnosis.

This is primarily a clinical diagnosis, based upon clinical suspicion of the likelihood of the syndrome occurring, combined with the rapid onset of the symptoms of profuse sweating, tachycardia, and elevation of body temperature. A differentiation must be made between this syndrome and that of anaesthetic induced malignant hyperpyrexia. This differentiation is also clinical, based upon the possible presence of a family history of malignant hyperthermia, preoperative hyperthyroidism, and the presence or absence of muscular rigidity which occurs in 70% of cases of malignant hyperpyrexia. If the patient has known preoperative hyperthyroidism, then exacerbation of thyrotoxic manifestations is by far the most likely diagnosis.

Management.

Management consists of general supportive measures and specific pharmacological treatment to block the manifestations of hyperthyroidism, the secretion of T_4 and the conversion of T_4 to T_3.

1. General and supportive management.

a. Terminate any operation as rapidly as possible.
b. Administer 100% oxygen. If the patient is under anaesthesia, mechanically ventilate the patient.
c. Administer intravenous fluids to prevent dehydration and hypovolaemia. The best solution to use for this purpose is a glucose-saline mixture, as fluid is lost by both increased respiratory water loss (pure water), and by increased sweating (water and sodium chloride).
d. The patient should be cooled. Remove all coverings from the patient. Apply ice packs to both groins and axillae. Sponge the body with cold water.

2. Pharmacological treatment [16].

The pharmacological therapy of acute thyrotoxic manifestations essentially consists of suppression of the manifestations of hyperthyroidism, so as to maintain life until an-

tithyroid medication has reduced the plasma and tissue concentrations of T_4 and T_3 to normal.

a. Propranolol is the drug of choice, and rapid administration is life saving. The pulse rate and other peripheral manifestations of thyrotoxicosis decrease within 2-10 minutes after intravenous administration of propranolol. It should be administered at a rate of 1 mg/minute to a total dose of 2-10 mg, or until the pulse rate decreases below 100 beats/minute. Subsequently an intravenous infusion of propranolol should be started at a rate of 1-3 mg/hour to maintain ß-adrenergic blockade. The mechanism of its action is twofold, blockade of ß-adrenoreceptors, and a degree of inhibition of the conversion of T_4 to T_3.

b. Cortisol or hydrocortisone should be administered at a dosage of 100-200 mg every 8 hours. After the thyrotoxic symptoms have subsided, the dosage is gradually reduced. The reason for the administration of cortisol is not so much that acute adrenocortical insufficiency may occur, but because of the effects of cortisol upon thyroid hormone homeostasis. Glucocorticoid hormones decrease the secretion rate of thyroid hormones, as well as causing a degree of inhibition of conversion of T_4 to T_3.

c. Propylthiouracil should be administered orally or through a nasogastric tube at a dosage of 100-200 mg every 8 hours, and this dosage maintained until remission of hyperthyroidism, or definitive treatment occurs. In addition to inhibiting T_4 production by the thyroid gland, propylthiouracil blocks the peripheral conversion of T_4 to T_3, a property not shared by carbimazole or methimazole. The plasma T_3 concentration is reduced by 50% one day after starting propylthiouracil administration at this dosage [NOTE: This corresponds well with the $T_{1/2e}$ of T_3 = 24 hours].

d. No sooner than at least one hour after administration of propylthiouracil has been commenced, 1 gm of sodium iodide should be administered every 8 hours for 7-10 days. This further decreases T_4 production.

REFERENCES

1. Galton,V.A.,(1965), Thyroid hormone-catcholamine interrelationships. ENDOCRINOLOGY, 77, 278-284.
2. Nilsson,R., et al.,(1979), Non-selective and selective beta-1 adrenoreceptor blocking agents in the treatment of hyperthyroidism. ACTA MEDICA SCANDINAVICA, 206, 21-25.
3. Williams,D.E., et al.,(1975), Acute effects of corticosteroids on thyroid activity in Graves' disease. JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOL ISM, 41, 354-361.
4. Oppenheimer,J.H.,(1975), Initiation of thyroid hormone action. NEW ENGLAND JOURNAL OF MEDICINE, 292, 1062-1068.
5. Burman,K.D.,(1978), Recent developments in thyroid hormone metabolism: Interpretation and significance of measurements of reverse T_3,3 3'T2, and thyroglobulin. METABOLISM, 27,615-630.
6. Edelman,I.S.,(1974), Thyroid thermogenesis. NEW ENGLAND JOURNAL OF MEDICINE, 290, 1303-1308.
7. Oyama,T., et al.,(1975), Effects of isoflurane anaesthesia and surgery on thyroid function in man. CANADIAN ANAESTHETISTS' SOCIETY JOURNAL, 22, 474-477.
8. Feek,C.M., et al.,(1980), Combination of potassium iodide and propranolol in preparation of patients with Graves' disease for thyroid surgery. NEW ENGLAND JOURNAL OF MEDICINE, 302, 883-885.
9. Oyama,T., et al.,(1972), Effect of ether, thiopentone anaesthesia and surgery on plasma thyroid stimulating hormone (TSH) in man. BRITISH JOURNAL OF ANAESTHESIA, 44, 841-844.
10. Steling,L.C.,(1974), Anesthetic management of the patient with hyperthyroidism. ANESTHESIOLOGY, 41, 585-595.

11. Peter,K.R., et al.,(1981), Malignant hyperthyroidism or malignant hyperthermia? ANESTHESIA AND ANALGESIA, 60, 613-615.
12. Coulombe,P., et al.,(1977), Catecholamine metabolism in thyroid disease. II. Norpinephrine secretion rate in hyperthyroidism and hypothyroidism. JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, 44, 1185-1189.
13. Coulombe.P., et al.,(1976), Catecholamine metabolism in thyroid diseases. I. Epinephrine secretion rate in hyperthyroidism and hypothyroidism. JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, 42, 125-131.
14. Bilezikian,J.P., Loeb,J.N.,(1983), The influence of hyperthyroidism and hypothyroidism on alpha- and beta-adrenergic receptor systems and adrenergic responsiveness. ENDOCRINE REVIEWS, 4, 378-388.
15. Aoki,V.S., et al.,(1972), Studies of the reputed augmentation of the cardiovascular effects of catecholamines in patients with spontaneous hyperthyroidism. JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPY, 181, 362-368.
16. Mackin,J.F., et al.,(1974), Thyroid storm and its management. NEW ENGLAND JOURNAL OF MEDICINE, 291, 1396-1398.
17. Ramsay,I.,(1968), Thyrotoxic muscle disease. POSTGRADUATE MEDICAL JOURNAL, 44, 385-397.
18. Williams,R.H.,(1946), Thiouracil treatment of thyrotoxicosis. JOURNAL OF CLINICAL ENDOCRINOLOGY, 6, 1-22.
19. Parisi,A.F., et al.,(1974), The short cardiac pre-ejection period. An index to thyrotoxicosis. CIRCULATION, 49, 900-904.
20. Pietras,J., et al.,(1972), Cardiovascular response in hyperthyroidism. ARCHIVES OF INTERNAL MEDICINE, 129, 426-429.
21. Groot,W.J. de.,(1966), Hyperthyroidism as a high cardiac output state. AMERICAN HEART JOURNAL, 64, 489.
22. Melander,A., et al.,(1977), Influence of the sympathetic nervous system on the secretion and metabolism of thyroid hormone. ENDOCRINOLOGY, 101, 1228-1237.
23. Ward,M.M., et al.,(1983) Epinephrine and norepinephrine responses in continuously collected human plasma to a series of stressors. PSYCHOSOMATIC MEDICINE, 45, 471-486.
24. Oyama,T., et al.,(1972), Effects of Halothane, methoxyflurane anaesthesia and surgery on plasma thyroid stimulating hormone (TSH) levels in man. ANAESTHESIA, 27, 2-8.
25. Oyama,T., Matsuki,A.,(1971), Serum levels of thyroxine in man during spinal anesthesia and surgery. ANESTHESIA AND ANALGESIA, 50, 309-313.
26. Shutt,L.E., Bowes,J.B.,(1979), Atropine and hyoscine. ANAESTHESIA, 34, 476-490.
27. Christensen,J.H., et al.,(1982), Pharmacokinetics and pharmacodynamics of thiopentone. A comparison between young and elderly patients. ANAESTHESIA, 37, 398-404.
28. Badad,A.A., Eger,E.I.,(1968), The effects of hyperthyroidism on halothane and oxygen requirements in dogs. ANESTHESIOLOGY, 29, 1087-1093.
29. Steffey,E.P., Eger,E.I.,(1974), Hyperthermia and halothane MAC in the dog. ANESTHESIOLOGY, 41, 392-396.

Chapter 7.3

HYPOTHYROIDISM

The manifestations of hypothyroidism are usually insidious in onset, and unless the deficiency is gross, the manifestations are easily mistaken for many other disorders.

PROBLEMS

1. Mortality due to hypothyroidism.

The most extreme form of hypothyroidism is hypothyroid coma, which in the early 1960's was associated with a mortality rate of about 80%, mainly due to infection and circulatory collapse [26].

2. Hypothermia.

About 89% of hypothyroid patients complain of cold sensitivity [1]. This is due to a reduced metabolic rate, as a result of which body temperature is less easily maintained especially in cool environments or exposure such as occurs during under anaesthesia in a cool operating theater [2].

A body temperature below 32°C is associated with an increasing chance of atrial fibrillation, while a body temperature below 30°C is associated with an increased chance of ventricular fibrillation [24]. Below 30°C the level of consciousness is decreased, and below 26°C most humans are unconsciousness [19,24, see also table 8.1.2].

Under anaesthesia the body temperature often falls despite active measures taken to maintain the temperature, and this is even more so in hypothyroid patients [2].

3. Fluid and electrolyte balance.

Hyponatraemia frequently occurs in hypothyroidism [4]. This is thought to be partly due to impaired renal water excretion relative to sodium excretion [5].

In spite of the elevation of the total body and extracellular water volumes, the plasma volume is reduced 10-24% below normal [3].

Hypovolaemia contributes to the severe cardiovascular depression that can occur in hypothyroid patients during induction of general anaesthesia [2, and see chapter 14.4]

4. Myopathy.

The most well known muscular manifestation of hypothyroidism is the delayed relaxation of the deep tendon reflexes. About 90% of hypothyroid patients complain of muscular weakness, in addition to which, some patients complain of stiffness and aching of muscles [1].

The above correlates well with the pathological changes. The stiffness most likely being due to the known increased interstitial water content due to myxoedema. Slowing of

muscular contraction speed is in agreement with the observation that type-II muscle fibers are atrophied in hypothyroid patients [6]. Human muscle is composed of various fiber types, type-I which has a slow contraction velocity and predominantly aerobic metabolism, and type-II which has a greater contraction velocity and can function anaerobically for short periods of time [7]. Atrophy of type-II fibers implies that the contractile speed of the muscles so affected will decrease. The significance of the muscle weakness is uncertain as regards the muscle relaxant drugs, but muscle weakness in combination with the residual effects of muscle relaxant drugs, further exacerbated by the respiratory depressant effects of anaesthetic drugs, may cause postoperative respiratory failure.

5. Cardiovascular problems.

Hypothyroidism is associated with major cardiovascular and haemodynamic alterations. Cardiac output, and stroke volume are reduced [8], as is the myocardial contractility [9], and the systemic vascular resistance is increased.

Myocardial cellular function is profoundly affected, a pericardial effusion is present in 30% of patients, cardiomegally in 36%, and a low voltage ECG is present in 30% [10]. There is also a high incidence of coronary vascular disease due to the frequent occurrence of hypercholesterolaemia in hypothyroidism. As well as all the above, there are the added problems of hypothermia induced arrhythmias, and a decreased blood volume. Adrenoreceptor numbers and concentrations are also changed by hypothyroidism. Myocardial and peripheral vascular ß-adrenoreceptor concentrations are reduced as is the myocardial α-adrenoreceptor concentration [11].

There is a baroreceptor mediated elevation of sympathoadrenal activity in response to reduced blood volume, and cardiac output. This explains the increased rate of noradrenaline synthesis and the elevation of plasma noradrenaline concentration observed in hypothyroid patients [13]. The systemic vascular resistance is increased as a result of the elevated plasma noradrenaline concentration and increased sympathetic nervous activity.

Anaesthetic drugs exacerbate the existing cardiovascular depression [see chapter 2.1], and this together with the reduced catecholamine sensitivity, reduced response to sympathetic baroreflexes, and a reduced blood volume, make hypotension likely during anaesthesia.

6. Baroreceptor reflexes.

Baroreflex efficacy is reduced by hypothyroidism [14]. This is evidently not due to a reduction of sympathoadrenal activity, as the noradrenaline synthesis rate and plasma concentration are increased [13]. Reduction of efficacy of baroreflexes is evidently due to the reduction of the adrenoreceptor concentrations. Because of these changes, hypotension occurs readily as a result of administration of anaesthetic drugs, and intermittent positive pressure ventilation [see also chapter 8.6].

7. Respiratory function.

Pulmonary function tests are unchanged by hypothyroidism, but respiratory responses to both hypoxaemia and hypercapnia are depressed [15]. Actual respiratory failure due to depression of the hypoxic and hypercapnic respiratory drives has only been described to occur when other disorders were also present, such as respiratory depressant anaesthetic drugs, obesity, lung disease, or a decreased level of consciousness, etc [15].

8. Adrenocortical function.

The cortisol response to hypoglycaemia, and possibly other stimuli, is depressed in hypothyroid patients. But the response of hypothyroid patients to adrenocorticotrophic hormone (ACTH) is normal [18].

Surgery, trauma and infection increase the requirement for corticosteroid hormones, and their production increases. But patients whose adrenocortical response to these stimuli is depressed by hypothyroidism may require perioperative corticosteroid hormone supplements.

9. Altered drug kinetics and dynamics.

A reduction of cardiac output reduces renal and hepatic perfusion, as well as decreasing perfusion of other organs. In addition to this, the plasma volume is also reduced. These alterations profoundly affect the duration of action of any drug, as well as the dosage required for a given effect. The effects of these changes are extensively discussed in chapter 15.2.

ASSESSMENT OF HYPOTHYROIDISM

The anaesthetist should always be aware of the possibility of the occurrence of hypothyroidism, especially in persons who have ceased taking thyroid hormone replacement therapy, those with goiter, and those with unexplained hypercholesterolaemia or hyponatraemia.

The severity of hypothyroidism is based upon clinical manifestations as well as measurement of the thyroid hormone concentrations and is commonly classified as below [17]. This classification has practical clinical significance as it may be used to determine the relative anaesthetic and surgical risk.

1. Subclinical hypothyroidism.

The patients in this group have no clinical manifestations, have normal plasma T_4 and T_3 concentrations, but do have an elevated plasma thyroid stimulating hormone (TSH) concentration. The risk of surgery and anaesthesia in this group of patients is the same as that for normal patients undergoing the same operation.

2. Mild hypothyroidism.

This group consists of patients with mild symptoms who have plasma T_3 and T_4 concentrations which are slightly below normal, and an elevated TSH concentration. Anaesthesia and surgery in these patients carries only a slightly increased risk.

3. Overt hypothyroidism.

This is the full clinical syndrome of hypothyroidism with low plasma concentrations of the thyroid hormones and an elevated TSH concentration. These patients have a high mortality and morbidity if they undergo anaesthesia and surgery without preoperative correction of their hypothyroidism.

The only exception to this rule are those hypothyroid patients with severe coexisting coronary vascular disease. It is recommended that these patients at first undergo a coronary revascularization procedure prior to any administration of thyroid hormones. Increasing the metabolic rate of these patients by administering thyroid hormones elevates the myocardial oxygen consumption. If there is severe coronary vascular disease, the coronary vessels

may be too narrow to permit the increased blood flow required for increased cardiac output, and myocardial ischaemia, sometimes with fatal consequences can occur [22].

MANAGEMENT OF HYPOTHYROIDISM

Except in patients whose hypothyroidism is due to iodine deficiency, the only therapy possible for hypothyroidism is regular substitution of the deficient thyroid hormones. Both L-T_4 and/or L-T_3 may be used. The pharmacokinetic properties of these two thyroid hormones are relevant to any discussion of substitution therapy [see table 7.3.2].

1. L-Triiodothyronine.

T_3 is the most active form of the thyroid hormones, T_4 being much less active. The normal oral dosage of T_3 is about 25 μg once per day, which is in good agreement with the kinetic data presented in table 7.3.1.

There are a number of disadvantages associated with its use for the purposes of regular substitution of thyroid hormone deficiency.

a. Because it is the active form of the thyroid hormones, a reduction of plasma concentration below normal causes hypothyroidism within a short time.
b. Due to its relatively short pharmacokinetic elimination half life of 24 hours, even missing one daily dose causes the plasma T_3 concentration to fall significantly.
c. T_3 is the most active form of the thyroid hormones, as well as being the most rapidly active form too. Once administered, its plasma and tissue concentration is only dependent on the amount given. This means that an excessively large dose of T_3 is likely to have a more toxic effect than an excessively large dose of T_4.

2. L-Thyroxine.

This is the preparation most commonly used for oral substitution of thyroid hormone deficiency. The dosage most commonly used for adults is about 100-150 μg taken orally once per day, which is in good agreement with the kinetic data in table 7.3.1.

When therapy is instituted with oral T_4 without an initial loading dose, it takes about 3-4 elimination half lives before a steady state plasma concentration is achieved, in this case about 3 weeks [see chapter 15.1 on pharmacokinetics]. Normal cardiac function [9], and respiratory responses to hypercarbia as well as hypoxaemia [15], are restored by 2-4 weeks after initiation of regular substitution of thyroid hormone deficiency with T_4.

The use of T_4 is attended with a number of advantages.

a. The long pharmacokinetic elimination half life of T_4 means that the regular dosage may be missed for a number of days before the plasma concentration falls significantly. Such a drop of plasma T_4 concentration has few consequences, as it is the product of T_4 metabolism, T_3 which is the active hormone. The conversion rate of T_4 to T_3 is regulated such that the plasma T_3 concentration can be maintained at normal levels despite a low plasma concentration of T_4 [21].
b. Because the conversion of T_4 to T_3 is regulated by the T_3 plasma concentration, the plasma concentration of T_3 fluctuates much less during T_4 substitution therapy than during T_3 substitution, and excessive plasma T_3 concentrations do not often occur [21].

3. Intravenous thyroid hormone replacement.

Intravenous thyroid hormone replacement is only recommended in situations where the patient is unable to ingest oral medication, or in situations where the intestinal absorbtion is likely to be minimal or very erratic. These two situations only occur in comatose, or imminently comatose hypothyroid patients. The same principles are followed as with any regular intravenous drug regime, first administer a loading dose, and subsequently all that is required is a maintenance dosage [see chapter 15.1 on pharmacokinetics].

The intravenous dosages may readily be calculated from the kinetic parameters in table 7.3.1.

T_4 loading dose = 780 μg, T_4 maintenance dose = 86 μg/day
*T_3 loading dose = 50 μg, T_3 maintenance dose = 30 μg/day
(* this loading dose may cause acute hyperthyroidism and sudden death)

Table 7.3.1.
Kinetic parameters and normal plasma concentrations of T_4 and T_3 in adults [20].

HORMONE	$T_{1/2e}$ (days)	V_d (liters)	Cl (l/day)	Normal plasma concentration (μg/l)
T_4	6.2	9.1	1.02	86
T_3	1	40	26.0	1.28

$T_{1/2e}$ = pharmacokinetic elimination half life.
V_d = pharmacokinetic volume of distribution.
Cl = whole body clearance.

a. Thyroxine.

In practice, adminstration of 500-750 μg T_4 to an adult will replenish totally depleted peripheral T_4 stores, and 100-200 μg per day is enough to replace the T_4 lost by elimination from the body [18] It takes at least a day before an increased plasma concentration of T_3 is measurable after starting therapy with T_4 [18]. This corresponds with the observation that no increase of the basal metabolic rate is measurable until 1-2 days after acute intravenous T_4 administration in hypothyroid patients, and that the peak effect is not observed until after about 10 days [18,23].

b. Triiodothyronine.

Acute intravenous administration of 1 μg of T_3 to hypothyroid patients causes a measurable increase of pulse rate and temperature after about 4-6 hours, and the basal metabolic rate rises to normal by 24 hours, with a maximum effect by 1-2 days [23]. It is recommended that the initial intravenous dosage be only 1-5 μg. The theoretically calculated loading dosage has been found in practice to be too high, as a sudden increase in myocardial work may precipitate angina pectoris [22]. Death has been reported due to myocardial ischaemia after a single intravenous dosage of 50 μg of T_3 [26].

c. Corticosteroid hormones.

In addition to the administration of thyroid hormone(s), the comatose hypothyroid patient, especially one coming for surgery, requires extra corticosteroid hormones. The recommended dosage is 100-200 mg of hydrocortisone or equivalent every 8 hours. This is necessary because the adrenocortical response to many physiological stimuli is reduced in hypothyroidism [18], while the requirement for corticosteroids is increased by surgery, and all other types of injury.

ANAESTHETIC MANAGEMENT

Preoperative [25,26,2].

1. The hypothyroid patient rendered euthyroid with an adequate dosage of thyroid hormones has essentially the same risk of perioperative complications as a normal patient for any given non-thyroid operation. It is the overtly hypothyroid patient who is at risk, [see clinical classification of hypothyroidism in this chapter].

2. No hypothyroid patient should be accepted for anaesthesia and surgery for an elective surgical procedure. Any such operation should be postponed for at least a month to allow the effects of the thyroid hormone substitution to restore cardiac pulmonary, hormonal and muscular function to normal, or near normal. An important exception to this rule is the hypothyroid patient with severe coronary vascular disease. These patients may develop lethal, or life threatening myocardial ischaemia if they are administered thyroid hormones before coronary artery bypass grafting has been performed [22].

3. If a hypothyroid patient presents for emergency surgery, no time can be lost waiting for euthyroidism to be restored. The most that can be done is to administer corticosteroid supplements, and administer anaesthesia as described below. As regards the administration of thyroid hormones, these are not effective in the short period of time that most operations last, and so their administration may be left in the hands of an endocrinologist in the postoperative period. In fact if the patient also has coronary ischaemia as well as hypothyroidism, the administration of thyroid hormones is dangerous [22].

4. Because of the much increased sensitivity to most drugs, as well as the chance of increased depression of an already compromised cardiopulmonary system, no sedative or opiate drugs should be administered to hypothyroid patients prior to any operation.

Anaesthesia [25,26,2].

During anaesthesia the two main problems are the respiratory and cardiovascular changes induced by hypothyroidism.

1. Loco-regional anaesthesia.

Loco-regional anaesthetic techniques are to be preferred where possible. These cause the least cardiopulmonary depression. Care should be taken with the administration of spinal or epidural anaesthesia, as the depression of baroreflex efficacy may result in these techniques causing profound hypotension which may be difficult to reverse with catecholamines, due to the reduced responsiveness to these drugs.

2. General anaesthesia.

Administration of general anaesthesia to overtly hypothyroid patients is fraught with hazard for the patient, mainly due to diminished cardiovascular reserves. There are some aspects relating to the administration of general anaesthesia to hypothyroid patients that deserve special mention.

a. Hypothyroidism depresses myocardial function, and reduces the efficacy of the baroreflexes. Severe and potentially lethal changes of haemodynamic status may not manifest as clearly as with euthyroid patients. A pulmonary artery catheter for measurement of cardiac output, systemic vascular resistance, and pulmonary arterial as well as pulmonary arterial wedge pressure is essential, so that replacement of blood volume deficits, as well as administration of inotropic drugs is able to be more effectively managed. Indirect blood pressure measurement techniques are inaccurate in the presence of vasoconstriction which is a feature of hypothyroidism. Direct intra-arterial blood pressure measurement is required to overcome this problem.
b. Controlled ventilation is necessary because of the decreased responsiveness to hypoxaemia and hypercarbia, plus muscle weakness due to hypothyroidism, plus the effects of general anaesthetic drugs, which further reduces both the hypoxic and hypercarbic responses.
c. The reduced basal metabolic rate as well as cardiac output mean that carbon dioxide production is reduced. End-tidal capnography or regular arterial blood gas sampling are required, so that the respiratory minute volume may be adjusted to minimize the tendency to extreme hypocarbia.
d. Induction of anaesthesia should be done with drugs causing minimal cardiovascular depression [see chapter 2.1]. Of the drugs available, ketamine is the drug of choice, with etomidate the drug of second choice.
e. All volatile anaesthetic drugs cause myocardial depression, and should not be used if possible [see chapter 2.1].
f. Opiates as well as muscle relaxant drugs normally cause minimal haemodynamic depression, and may be used as usual. The only exceptions are tubocurarine, and metocurine. These exert a ganglion blocking effect in clinically used dosages, and may cause hypotension [see chapter 2.1].

3. Glucocorticoid drugs should be administered as the adrenal cortical responsiveness is diminished in hypothyroidism, and surgery may precipitate acute hypoadrenocorticism. Administer 100 mg hydrocortisone every 6 hours. Postoperatively use the perioperative corticosteroid supplementation regime in table 7.5.1.

Postoperative.

1. Postoperatively the patient should be admitted to an intensive care until normal body temperature and haemodynamics have returned.

2. Patients with excessive muscle weakness, or respiratory depression, may require mechanical ventilation until full muscle strength and normal respiratory control have returned.

REFERENCES

1. Wilson,J.D., Foster,D.W., editors.,(1985),"Williams Textbook of Endocrinology", 7th edition, pub. W.B.Saunders Co., U.S.A.
2. Kim,J.M., Hackman,L.,(1977), Anesthesia for untreated hypothyroidism. Report of three cases. ANESTHESIA AND ANALGESIA, 56, 299-302.
3. Aikawa,J.K.,(1956), The nature of myxedema: Alterations in the serum electrolyte concentrations and radiosodium space and in the exchangeable sodium and potassium contents. ANNALS OF INTERNAL MEDICINE, 44, 30-39.
4. Shalev,O., et al.,(1979), Hyponatremia in myxedema: A suggested therapeutic approach. ISRAELI JOURNAL OF THE MEDICAL SCIENCES, 15, 913-916.
5. Emmanouel,D.S., et al.,(1974), Mechnism of impaired water secretion in the hypothyroid rat. JOURNAL OF CLINICAL INVESTIGATION, 54, 926-934.
6. McKeran,P.O., et al.,(1975), Muscle fiber type changes in hypothyroid myopathy. JOURNAL OF CLINICAL PATHOLOGY, 28, 659-663.
7. Close,R.I.,(1972), Dynamic properties of mammalian skeletal muscles. PHYSIOLOGICAL REVIEWS, 52, 129-197.
8. Campbell,J.A.,(1958), A correlation of clinical and hemodynamic studies in patients with hypothyroidism. JOURNAL OF CLINICAL INVESTIGATION, 37, 502-510.
9. Crowley,W.F., et al.,(1977), Noninvasive evaluation of cardiac function in hypothyroidism. Response to gradual thyroxine replacement. NEW ENGLAND JOURNAL OF MEDICINE, 296, 1-6.
10. Keber,R.E., Sherman,B.,(1975), Echocariographic evaluation of pericardial effusion in myxedema. Incidence and biochemical and clinical correlations. CIRCULATION, 52, 823-827.
11. Bilezikian,J.P., Loeb,J.N.,(1983), The influence of hyperthyroidism and hypothyroidism on alpha- and beta-adrenergic receptor systems and adrenergic responsiveness. ENDOCRINE REVIEWS, 4, 378-388.
12. Stoffer,S.F., et al.,(1973), Plasma catecholamines in hypothyroidism and hyperthyroidism. ENDOCRINOLOGY AND METABOLISM, 36, 587-589.
13. Coulombe,P., Dassault,J.H.,(1977), Catecholamine metabolism in thyroid disease. II. Norepinephrine secretion rate in hyperthyroidism and hypothyroidism. JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, 44, 1185-1189.
14. McBrien,D.J., Hindle,W.,(1963), Myxoedema and heart failure. LANCET, 1, 1066-1068.
15. Zwillich,C.W., et al.,(1975), Ventilatory control in myxedema and hypothyroidism. NEW ENGLAND JOURNAL OF MEDICINE, 292, 662-665.
16. Christensen,J.H., et al.,(1982), Pharmacokinetics and pharmacodynamics of thiopentone. A comparison between young and elderly patients. ANAESTHESIA, 37, 398-404.
17. Evered,D.C., et al.,(1973), Grades of hypothyroidism. BRITISH MEDICAL JOURNAL, 1, 657-662.
18. Ridgway,E.C., et al.,(1972), Acute metabolic responses in myxedema to large doses of intravenous L-thyroxine. ANNALS OF INTERNAL MEDICINE, 77, 549-555.
19. McNicol,M.W., Smith,R.,(1964), Accidental hypothermia. BRITISH MEDICAL JOURNAL, 1, 19-21.
20. Chopra,I.J.,(1976), An assessment of daily production and significance of thyroid secretion of 3,3'5'-triiodothyronine (reverse T_3) in man. JOURNAL OF CLINICAL INVESTIGATION, 58, 32-40.
21. Larsen,P.R., et al.,(1981), Relationships between circulating and intracellular thyroid hormones. Physiological and clinical implications. ENDOCRINE REVIEWS, 2, 87-102.
22. Paine,T.D., et al.,(1977), Coronary arterial surgery in patients with incapacitating angina pectoris and myxedma. AMERICAN JOURNAL OF CARDIOLOGY, 40, 226-231.
23. Blackburn,C.M., et al.,(1954), Calorigenic effects of single intravenous doses of L-triiodothyronine and L-thyroxine in myxedematous persons. JOURNAL OF CLINICAL INVESTIGATION, 819-824.
24. Swan,H.,(1973), Clinical hypothermia: A lady with a past and some promise for the future. SURGERY, 73, 736-758.

25. Murkin,J.M.,(1982), Anesthesia and hypothyroroidism: A review of thryoxine physiology, pharmacology, and anesthetic implications. ANESTHESIA AND ANALGESIA, 61, 371-383.
26. James,M.L.,(1970), Endocrine disease and anaesthesia. A review of anaesthetic management in pituitary, adrenal and thyroid diseases. ANAESTHESIA, 25, 232-252.

Chapter 7.4

HYPERADRENOCORTICISM

The syndrome of hyperadrenocorticism is produced by synthesis of, or exogenous administration of corticosteroids in excess of physiological requirements. Another name for this syndrome is "Cushing's syndrome", although this may really only be applied due to hyperadrenocorticism due to an adrenocorticotropic hormone secreting pituitary adenoma.

Hyperadrenocorticism may be due to one of two causes.

1. Increased glucocorticoid production.

The basal production of cortisol by the average adult is about 20 mg/day. Glucocorticoid poduction rate is increased by physiological stress, or an increased metabolic rate [1]. Increased adrenocortical glucocorticoid production may also be due to a primary tumor of the adrenal cortex, ACTH secreting adenomas of the pituitary, etc.

2. Glucocorticoid administration.

If a daily dosage of more than 20 mg hydrocortisone (cortisol), or an equivalent dosage of another glucocorticoid hormone is administered, the manifestations of hyperadrenocorticism will occur, as the amount of glucocorticoid is in excess of requirements. The severity of the manifestations are directly related to the daily glucocorticoid dosage. The relative potencies of the various glucocorticoid preparations available are listed in table 7.4.1.

PROBLEMS DUE TO HYPERADRENOCORTICISM

The problems due to hyperadrenocorticism may manifest within hours after induction of this metabolic condition, e.g. by administration of glucocorticoids [10].

Cushing's syndrome as described in the medical texts only manifests after some weeks or months of hyperadrenocorticism. The manifestations typically consist of wasting of the arms and legs, increased fat deposition on the trunk, face and neck, muscle weakness, osteoporosis, hypertension, hyperglycaemia, and atrophic thin skin with striae.

1. Hyperglycaemia.

A diabetic glucose tolerance curve is observed in 90% of patients with hyperadrenocorticism [2]. This is due to a number of factors.

Peripheral tissue uptake of glucose is inhibited, and liver gluconeogenesis is increased by glucocorticoid hormones. This is further exacerbated by inhibition of muscle, bone and connective tissue protein synthesis. As a result of decreased protein synthesis more amino acids are available for gluconeogenesis [3, page 1255].

Table 7.4.1.
Relative potencies of glucocorticoid hormones. (Data derived from [2].)

GLUCOCORTICOID HORMONE	POTENCY RELATIVE TO HYDROCORTISONE
Cortisone	0.8
HYDROCORTISONE (Cortisol)	**1**
Prednisone	4
Prednisolone	4
Methylprednisolone	5
Triamcinolone	5
Paramethasone	10
Beclomethasone	25
Dexamethasone	27
Betamethasone	33

2. Skeletal muscle weakness.

Most patients have skeletal muscle weakness, particularly of the quadriceps muscles [2].

Cortisol inhibits protein synthesis in skeletal muscle [3, page 1255]. This causes wasting of skeletal muscle. In addition, to this, skeletal muscle uptake of glucose is decreased. These two factors combine to diminish the amount of muscle, and to diminish the substrate supply to skeletal muscle. Both factors may cause the muscle weakness observed.

The relevance of hyperadrenocorticism induced muscle weakness to anaesthetic practice is uncertain. Nondepolarizing muscle relaxant effects are unchanged 30 minutes after acute injection of high dosages of glucocorticoid hormones, and there is evidence suggestive of actual antagonism of nondepolarizing muscle relaxant drugs by glucocorticoid hormones, in that both synthesis and release of acetylcholine are enhanced by glucocorticoid drugs [8]. For practical purposes all that may be said is that if muscle weakness is present, then muscle relaxant drugs should be used with caution as they are likely to have a greater effect than usual.

3. Fluid and electrolyte disturbances.

Corticosteroid hormones cause renal retention of sodium ion, and bicarbonate ion, while potassium and chloride are excreted in increased quantities. Because renal sodium excretion is decreased, water is retained, and the extracellular fluid volume increases.

4. Cardiovascular problems.

Chronic hyperadrenocorticism reduces the cardiac ß-adrenoreceptor concentration [9], while the sensitivity of at least the non-cardiac ß-adrenoreceptors is enhanced by glucocorticoid hormones [10].

The net effect of increased peripheral vascular adrenoreceptor sensitivity to catecholamines, and the increased extracellular fluid volume, is that hypertension is common in persons with chronic hyperadrenocorticism.

5. Wound strength.

Glucocorticoid hormones affect wound healing by retarding wound contraction and epithelialization [4]. Tensile strength of wounds is also decreased as a result of excessive glucocorticoid hormone administration [2]. The mechanism of these effects is not clear as glucocorticoid hormones injected into human scar and keloid tissue do not depress the rate of collagen synthesis. This is only depressed by massive doses of glucocorticoid hormones [4]. But injection of glucocorticoid hormones into wound tissue does reduce scar and keloid size, as well as making these tissues softer. A part explanation for these observations may be that the collagen content in scar or keloid tissue is reduced due to increased collagen breakdown, caused by increased tissue collagenase activity induced by glucocorticoid hormones [4].

6. Wound, and other infections.

The incidence of both secondary and opportunistic infections is greatly increased in patients with hyperadrenocorticism [2,4]. The surgical wound infection rate in patients taking more than 40 mg of hydrocortisone per day, or equivalent, is at least twice that of patients without hyperadrenocorticism [2,5].

7. Gastrointestinal ulceration [2].

Gastrointestinal ulceration associated with corticosteroid administration has been described as occurring from the oesophagus to the colon. Patients with rheumatoid arthritis who have received glucocorticoid hormones for a month or more, have been reported to have a frequency of gastroduodenal ulceration of 10-30%. Pain due to corticosteroid induced ulceration is reported as being less in intensity than that due to ulceration induced by causes other than corticosteroid drugs. This latter is probably due to the well known anti-inflammatory effect of these hormones.

Stressful surgery or trauma can both induce gastroduodenal ulceration. Acute or chronic administration of glucocorticoids only serves to exacerbate this problem.

PREOPERATIVE ASSESSMENT

The known problems associated with hyperadrenocorticism must be looked for, and as indicated, treated. Particular points to carefully assess are listed below.

1. The presence of any infection in a patient with hyperadrenocorticism is a relative contraindication to any elective surgery, as immune response is already depressed by hyperadrenocorticism, in addition to which surgery is also known to depress immune responses [6].

2. Hypertension should managed according to the guidelines in chapter 2.6.

3. Hyperglycaemia should be managed as for diabetes mellitus [see chapter 7.1].

4. Electrolyte disorders, particularly hypokalaemia, should be corrected prior to any elective surgery.

5. Either antacids or cimetidine should be administered perioperatively to reduce the chance of perioperative peptic ulceration.

ANAESTHETIC MANAGEMENT

Preoperative.

1. There is no absolute contraindication to the administration of anaesthesia to any patient with hyperadrenocorticism, unless it is any of the associated medical problems which is out of control.

2. There is no absolute contraindication to the administration of any drug. Any drugs for premedication may be administered according to the preferences of the anaesthetist and the requirements imposed by various associated disorders.

Anaesthesia.

1. No particular anaesthetic technique can be recommended. Any technique that is used should be adjusted according to the associated medical problems, i.e. hyperglycaemia, hypertension etc.

2. If general anaesthesia is to be used, a technique employing controlled ventilation is advisable in the presence of excessive body weight, abnormal thoracic anatomy, and skeletal muscle weakness. Some caution should be employed with neuromuscular blocking drugs if the patient has significant muscle weakness.

Postoperative.

1. Because of the numerous associated medical problems, and potential postoperative medical and surgical problems, it is advisable that patients with significant hyperadrenocorticism be admitted to an intensive care unit postoperatively.

2. Those patients with thoracic abnormalities, significant obesity, or severe muscle weakness may require mechanical ventilation postoperatively, especially when the surgery was in the thorax or upper abdomen. These latter two locations are associated with a greater degree of postoperative hypoxaemia than limb or lower abdominal surgery [7].

3. Patients undergoing bilateral adrenalectomy or hypophysectomy for treatment of hyperadrenocorticism should receive supplemental corticosteroids, beginning intraoperatively [see table 7.5.1].

REFERENCES

1. Byyny,R.L.,(1976) Withdrawal from glucocorticoid therapy. NEW ENGLAND JOURNAL OF MEDICINE, 295, 30-32.

2. Diethelm,A.G.,(1977), Surgical management of complications of steroid therapy. ANNALS OF SURGERY, 185, 251-263.
3. White,A., et al.,(1978),"Principles of Biochemistry", 6th editionn, published McGraw-Hill Kogkusha Ltd.
4. Cohen,K., et al.,(1977), Effect of corticosteroids on collagen synthesis. SURGERY, 82, 15-20.
5. Engquist,A., et al.,(1974), Incidence of postoperative complications in patients subjected to surgery under steroid cover. ACTA CHIRURGICA SCANDINAVICA, 140, 343-346.
6. Walton,B.,(1978), Anaesthesia, surgery, and immunology. ANAESTHESIA, 33, 322-348.
7. Kitamura,H., et al.,(1972), Postoperative hypoxaemia: the contribution of age to the maldistribution of ventilation. ANESTHESIOLOGY, 36, 244-252.
8. Schwartz,A.E..,(1986), Acute steroid therapy does not alter nondepolarizing muscle relaxant effect in humans. ANESTHESIOLOGY, 65, 326-327.
9. Abrass,I.B., Scarpace,P.J.,(1981), Glucocorticoid regulation of myocardial myocardial beta-adrenergic receptors. ENDOCRINOLOGY, 108, 977-980.
10. Ellul-Micallef,R., Fenech,F.F.,(1975), Effect of intravenous prednisolone in asthmatics with diminished adrenergic responsiveness. LANCET, 2, 1269-1271.

Chapter 7.5

HYPOADRENOCORTICISM

Glucocorticoid hormones are facilitatory hormones which are required for normal function of other hormones, e.g. catecholamines, antidiuretic hormone etc. For this reason, deficiency of glucocorticoid hormones, or hypoadrenocorticism, is associated with abnormal function of multiple organ systems.

PROBLEMS DUE TO HYPOADRENOCORTICISM

1. Mortality and morbidity.

Prior to the advent of glucocorticoid substitution therapy, the mortality of surgical procedures carried out on patients with Addison's disease was about 78% [4]. Glucocorticoid substitution therapy has brought about a dramatic reduction of mortality.

Hypotension and shock have been reported to occur after operations in patients whose long term glucocorticoid supplementation was abruptly stopped prior to surgery. However this does not invariably occur, and in fact has not been reported to occur at all in more recent investigations [6,3]. This raises the possibility that any such hypotension observed in early series was more likely to have been due to hypovolaemia than any other cause.

2. Fluid and electrolyte problems.

Renal tubular sodium ion resorbtion is decreased and hyponatraemia is observed in about 88%, while potassium excretion is decreased causing hyperkalaemia in about 64% of patients with hypoadrenocorticism [14].

Water excretion is increased, which together with a reduction of total body sodium content reduces the extracellular fluid volume (ECFV), and also the plasma volume. In experimental animals the plasma volume may be reduced as much as 30%, and blood volume may be 17% below normal volumes [8].

3. Hypoglycaemia.

Hypoglycaemia occurs in about 50% of patients with adrenal cortical insufficiency [14].

Hepatic and muscle glycogen stores are reduced and hepatic gluconeogenesis is decreased, both of which combine to reduce hepatic glucose production [12 page 1255]. Because glucose production is lower than normal, the insulin requirement is reduced, which means that the hypoglycaemic effect of a given dose, or quantity, of insulin is enhanced. This accounts for the increased insulin sensitivity which occurs in these patients.

Reduced muscle and hepatic glucose production reduce tissue glucose supplies, making hypoglycaemia likely during a period of fasting. Patients with adrenal cortical insufficiency should never be permitted to undergo prolonged preoperative fasting without an intravenous infusion of a glucose solution.

4. Cardiovascular problems.

About 88% of patients with adrenal cortical insufficiency are hypotensive [14]. Deficiency of glucocorticoid hormones reduces both myocardial contractility and cardiac output [8], as well as depressing vascular responses to catecholamines [8,9,10,11].

Glucocorticoid hormones are required for the action of the catecholamines. Hypoadrenocorticism is associated with reduced myocardial responsiveness to catecholamines, despite an increased concentration of myocardial ß-adrenoreceptors [15]. This is in part explained by two factors.

a. Glucocorticoids enhance the vascular response to catecholamines either by blocking catechol-O-methyltransferase, or by enhancing receptor affinity to catecholamines [17].
b. Cortisol is required for adrenal medullary synthesis of adrenaline. Hypoadrenocorticism is associated with a reduced plasma concentration of adrenaline, as cortisol deficiency reduces phenylethanolamine-N-methyltransferase activity, so inhibiting conversion of noradrenaline to adrenaline [16]. This may increase ß-adrenoreceptor numbers.

Despite reduced vascular sensitivity to catecholamines, the systemic vascular resistance is increased in adrenal cortical insufficiency [8]. This is possibly due increased baroreflex activity secondary to a reduction of cardiac output and blood pressure.

5. Muscular weakness.

Muscular weakness and easy fatigability are observed in all patients with adrenocortical insufficiency, while muscle pains occur in 13% [14]. There is no single cause of the muscle weakness. Some possible causes are listed below.

a. Insufficient available glucose in muscle fibers due to the reduced muscle glycogen content.
b. Decreased hepatic glucose production which reduces glucose supply to muscle fibers.
c. Skeletal muscle protein synthesis is decreased, reducing the mass of functioning muscle tissue.

The significance of the muscle weakness in relation to the use of neuromuscular junction blocking drugs uncertain. In general it is better to avoid administering any drugs which will increase muscle weakness in patients whose skeletal muscles are already weakened. Residual curarization, plus reduction of hypoxic and hypercarbic respiratory drives by anaesthetic drugs, may be just enough to cause respiratory failure in such patients.

6. Pharmacokinetic changes.

These are likely, due to the reduced cardiac output and ECFV [see chapter 15.2]. These changes explain the increased sensitivity of patients with hypoadrenocorticism to the cardiovascular depressant and sedative effects of anaesthetic drugs.

EFFECTS OF TRAUMA, SURGERY ON ADRENAL CORTICAL FUNCTION

Trauma, surgery, infection and physical exertion all increase adrenal cortical production and secretion of glucocorticoid hormones. The amount secreted varies according to the degree of physiological stress.

1. Basal cortisol secretion rate in adults is about 20 mg per day [2].

2. Minor surgery, e.g. inguinal herniorrhaphy, cataract extraction etc, causes the cortisol secretion rate to be elevated transiently for 24 hours to about 50-65 mg per day [5].

3. Major surgery, e.g. major abdominal, orthopedic, thoracic operations, causes the cortisol secretion rate to be elevated for 1.5-3 days to about 75-250 mg per day [2,5].

PERIOPERATIVE GLUCOCORTICOID SUPPLEMENTATION

During the perioperative period, and during times of physiological stress, the glucocorticoid requirement of the body is increased. Patients whose pituitary or adrenocortical response to surgical stress is insufficient are unable to produce the quantities of glucocorticoid hormones required, and a degree of hypoadrenocorticism with all its consequences occurs. To prevent this occurring such patients should receive perioperative glucocorticoid supplementation. The categories of patients requiring such supplementation are listed below.

1. Those with failure of pituitary secretion of ACTH.

2. Those with primary adrenocortical failure.

3. Patients who are regularly administered drugs suppressing glucocorticoid synthesis such as metapyrone or an etomidate infusion. Etomidate even significantly suppresses glucocorticoid synthesis even after a single intravenous dose such as used for induction of anaesthesia [1].

4. The daily basal cortisol production is about 20 mg per day [2]. Administration of exogenous glucocorticoids at daily dosages greater than this causes suppression of adrenocortical glucocorticoid synthesis [2]. Pituitary-adrenocortical dysfunction occurs after one month of such therapy, and manifests as loss, or blunting of the normal elevation of glucocorticoid hormone plasma concentrations in response to surgery [3]. Return of normal pituitary and adrenocortical function after discontinuation of chronic suppressant dosages of glucocorticoid hormones takes up to nine months [2].

Glucocorticoid supplementation is therefore required in all patients who have stopped taking regular glucocorticoid hormone drugs within 9 months of the planned surgical procedure, where the daily dose was equivalent to more than 20 mg of hydrocortisone per day, and the glucocorticoid was taken for at least one month [2].

5. Patients receiving long term glucocorticoid supplementation.

PERIOPERATIVE GLUCOCORTICOID SUPPLEMENTATION REGIMES

Various schemes have been proposed for perioperative glucocorticoid supplementation. These are shown in table 7.5.1.

ANAESTHETIC MANAGEMENT

The discussion that follows deals only with patients who are diagnosed or suspected of having adrenocortical insufficiency, but whose surgery cannot be delayed for adequate investigation and preoperative treatment. Patients with adrenocortical insufficiency who receive adequate glucocorticoid replacement therapy have almost the same mortality and morbidity as any normal person undergoing the same operation.

Preoperative.

1. No patient with hypoadrenocorticism should be permitted to undergo elective anaesthesia and surgery without adequate preoperative glucocorticoid supplementation and restoration of the circulating blood volume. The mortality associated with anaesthesia and surgery is about 78% in untreated patients [4].

2. No sedative or opiate drugs should be administered preoperatively, as the patient may be abnormally sensitive to the haemodynamic and central nervous system depressant effects of these drugs.

3. The first priority is to administer a glucocorticoid hormone. The most rapidly effective is hydrocortisone administered intravenously, an effect being observed within an hour. But even glucocorticoids such as prednisolone [18], and methylprednisolone [7], may be used as they also have a measurable effect within 60 minutes after intravenous administration.

An appropriate dosage of hydrocortisone is about 100 mg administered intravenously every 6-8 hours [2], followed up postoperatively with regular supplementation.

4. Plasma glucose concentration should be measured regularly in the perioperative period. Hypoglycaemia may be prevented with an intravenous infusion of a glucose solution.

5. Measure the plasma electrolyte concentrations regularly in the perioperative period and treat hyperkalaemia.

Anaesthesia.

1. Intensive haemodynamic monitoring should be used to assist management of the haemodynamic problems due to the combination of hypovolaemia, decreased cardiac output secondary to negative inotropy and hypovolaemia, as well as the increased systemic vascular resistance.

A pulmonary artery catheter, arterial line, as well as an urinary catheter should be inserted. If a pulmonary artery catheter is not available, then minimal monitoring consists of central venous pressure monitoring and a urinary catheter for urinary output measurement.

2. Regional anaesthetic techniques such as spinal or epidural anaesthesia are relatively contraindicated because of the haemodynamic problems. Other loco-regional anaesthetic techniques are not contraindicated.

Table 7.5.1.
GLUCOCORTICOID SUPPLEMENTATION REGIMES

MINOR SURGERY
(e.g. uterine curettage, inguinal hernia etc) [5]

Morning of operation	Usual glucocorticoid therapy.
Induction of anaesthesia	25 mg hydrocortisone or equivalent i.v. at induction.
Postoperative	Normal glucocorticoid supplementation. If oral drug ingestion is impossible, then use regime for major surgery.

MAJOR SURGERY [5,6].

Morning of operation	Usual glucocorticoid therapy.
Induction of anaesthesia	25 mg hydrocortisone or equivalent i.v. at induction.
Postoperative	100 mg hydrocortisone or equivalent i.v. or i.m. per 24 hours until oral drug ingestion is again possible Thereafter the normal glucocorticoid regime should be recommenced.

HIGH DOSE REGIME
(An alternative to the above scheme)

Perioperative day number	I.V. Infusion (Hydrocortisone)	I.M. Cortisone acetate Morning	Afternoon
0	200 mg	100 mg	50 mg
1	150 mg	50 mg	50 mg
2	100 mg	50 mg	50 mg
3	50 mg	50 mg	-

The patient's usual glucocorticoid regime may be resumed on the fourth postoperative day.

3. General anaesthesia using controlled ventilation is to be preferred for most operations. This guarantees adequate oxygenation in the face of possible muscle weakness and a reduced cardiac output. In addition, the depth of anaesthesia may be rapidly varied at will. No recommendations can be made as to the particular drugs to use, except to recommend that drugs known to cause significant cardiovascular depression should be avoided see chapter 2.1].

4. Inotropic and vasodilator drugs may be required to maintain cardiac output and arterial blood pressure until normovolaemia is restored, and the hydrocortisone increases the cardiac output.

Postoperative.

Patients who were glucocorticoid deficient at the time of operation, are still in a critical condition postoperatively. They should be admitted to an intensive care unit for further management of their problems until physiological stability has returned.

REFERENCES

1. Wagner,R., White,P.F.,(1984), Etomidate inhibits adrenocortical function in surgical patients. ANESTHESIOLOGY, 61, 647- 651.
2. Byyny,R.L.,(1976), Withdrawal from glucocorticoid therapy. NEW ENGLAND JOURNAL OF MEDICINE, 295,30-32.
3. Kehlet,H. et al.,(1974), Plasma catecholamine concentrations during surgery in unsupplemented glucocorticoid-treated patients. BRITISH JOURNAL OF ANAESTHESIA, 46, 73-77.
4. Diethelm,A.G.,(1977), Surgical managemnt of complications of steroid therapy. ANNALS OF SURGERY, 185, 251-263.
5. Kehlet,H.,(1975), A rational approach to dosage and preparation of parenteral glucocorticoid substitution therapy during surgical procedures. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 19, 260-264.
6. Symreng,T., et al.,(1981), Physiological cortisol substitution of long-term steroid-treated patients undergoing major surgery. BRITISH JOURNAL OF ANAESTHESIA, 53, 949-953.
7. Littenberg,B., Gluck,E.H.,(1986), A controlled trial of methylprednisolone in the emergency treatment of acute asthma. NEW ENGLAND JOURNAL OF MEDICINE, 314, 150-152.
8. Webb,W.R. et al.,(1965), Cardiovascular responses in adrenal insufficiency. SURGERY, 58, 273-282.
9. Filippis,V. de., et al.,(1964) Hormonal influence on vascular reactivity. BIBL. ANAT., 7, 510-516.
10. Reis,D.J.,(1960), Potentiation of the vasoconstrictor action of topical norepinephrine on the human bulbar conjunctival vessels after topical application of certain adrenocortical hormones. JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, 20, 446-456.
11. Yard,A.C., Kadowitz,P.J.,(1972), Studies on the mechanism of hydrocortisone potentiation of vasoconstrictor responses to epinephrine in the anesthetized animal. EUROPEAN JOURNAL OF PHARMACOLOGY, 20, 1-9.
12. White,A., et al.,(1978), "Principles of Biochemistry", 6th edition, published McGraw-Hill Kogakusha.
13. Isselbacher,K.J., et al.,(1981), "Harrison's Principles of Internal Medicine", 9th edition, published McGraw-Hill.
14. Nerup,J.,(1974), Addison's disease - clinical studies. A report of 108 cases. ACTA ENDOCRINLOGICA, 76, 127-141.
15. Abrass,I.B., Scarpace,P.J.,(1981), Glucocorticoid regulation of myocardial beta-adrenergic receptors. ENDOCRINOLOGY, 108, 977-980.
16. Phorecky,L.A., Wustman,R.J.,(1971), Adrenocortical control of epinephrine synthesis. PHARMACOLOGICAL REVIEWS, 23, 1-35.
17. Kalsner,S.,(1969), Mechanism of hydrocortisone potentiation of responses to epinephrine and norepinephrine in rabbit aorta. CIRCULATION RESEARCH, 24, 383-395.
18. Ellul-Micallef,R., Fenech,F.F.,(1975), Effect of intravenous prednisolone in asthmatics with diminished adrenergic responsiveness. LANCET, 2, 1269-1271.

Part 8

NEUROLOGICAL DISORDERS

The prime function of the anaesthetist is to block the functioning of the central nervous system, or the peripheral nervous system, or both, so as to make surgery possible. In order that this may be done with minimum chance of damaging the patient, there are two aspects of nervous system function relevant to anaesthesia which must be considered.

1. Anaesthetic management in general, and anaesthetic management of patients with disorders of the nervous system in particular, is made simpler by a sound knowledge of the ohysiological limits within which normal central nervous system function is maintained.

2. Some patients may have neurological disorders which may be exacerbated by anaesthesia or surgery, or affect the surgical or anaesthetic management of the patient.

Chapter 8.1

CEREBRAL FUNCTION & ABNORMAL PHYSIOLOGY

Knowledge of the physiological extremes within which consciousness and normal cerebral function are maintained is of vital importance to the practicing anaesthetist.

The maintenance of normal cerebral function is dependent on a large number of physiological variables. The discussion below focusses on each of the principal variables individually, and the threshold for normal cerebral function is given for that variable alone. Some patients will have abnormalities of more than one of these variables. In such situations, lesser degrees of abnormality of each individual variable combine to induce abnormal cerebral function

All studies cited and values given below are from human studies unless otherwise stated.

CEREBRAL BLOOD FLOW (CBF)

The normal CBF in humans is 54 mls/100 gms/minute. Symptoms and manifestations of cerebral ischaemia, including diminished level of consciousness, occur in conscious humans when the CBF falls below 31 mls/100 gms/minute [23]. Cortical electrical function as shown by the electroencephalogram is abolished when the CBF is about 11-19 mls/100 gms/minute [1]. Total cessation of CBF as occurs after acute bilateral carotid artery occlusion, or due to circulatory arrest, causes loss of consciousness in humans by 6-7 seconds, and permanent brain damage when prolonged more than 3 minutes [24]. The influence of CBF on cerebral function is discussed in more detail in chapter 2.7 on hypotension.

BLOOD PRESSURE

CBF is not measured routinely in current clinical practice, and any clinical decision as to the adequacy of the CBF is based on the level of consciousness and the arterial blood pressure. CBF is a function of the cerebral perfusion pressure (CPP), which may be calculated approximately using equation 1 below. The CBF is normally autoregulated in the MABP range of 60 to 130-150 mmHg in adults.

$$\mathbf{CPP = MABP - ICP} \quad \text{.....(1)}$$

ICP = mean intracranial pressure, assuming that the ICP is slightly less than, or equal to, the intracranial venous pressure (normal ICP = 5-13 mmHg).
MABP = mean arterial blood pressure, which can be measured, or calculated using the equation in table 2.0.1.

1. Hypertension.

The effect of hypertension is to increase cerebral blood flow, especially when the blood pressure rises above the upper autoregulation limit. Once this limit is exceeded, the constrictor response to increasing blood pressure is lost, and the CBF as well as cerebral capillary pressures are directly proportional to the blood pressure. A consequence of increased cerebral capillary pressures is that the flow of water from the capillaries into the cerebral interstitium is increased [see chapter 14.1]. The capillary endothelium is also exposed to elevated intravascular pressures, which if high enough will damage the cerebral capillary endothelium, causing plasma to leak into the interstitium [3,6]. Interstitial oedema may occur due to the first effect, and certainly will occur as a result of damaged capillary endothelium. Acute hypertensive encephalopathy is due to cerebral oedema caused by either of these two mechanisms [see also chapter 2.6 on hypertension].

CBF in normotensive adults is normally autoregulated in the pressure range 60 to 130-150 mmHg. The CBF in chronically hypertensive adults may have an upper autoregulation limit which is higher [2,4].

An MABP of 130-150 mmHg, the upper autoregulation limit, may be considered a safe maximum blood pressure in normotensive persons.

2. Hypotension.

If the MABP is lower than the lower CBF autoregulation limit, the cerebral blood vessels are maximally dilated, and the CBF is directly proportional to the CPP. Clinical experience with patients undergoing hypotensive anaesthesia has shown that the chance of cerebral damage increases if the systolic blood pressure is lower than 80 mmHg [5]. More exact investigations carried out on awake human volunteers have shown that the MABP at which clinical manifestations of cerebral ischaemia become increasingly likely is directly related to the resting MABP prior to any hypotensive episode [23]. This threshold MABP, or "safe" MABP is given by equation 2 below [see also chapter 2.7 on hypotension for a more detailed discussion, and fig 2.7.2].

$$\text{"Safe MABP"(mmHg)} = 20 + \frac{\text{Resting MABP}}{2} \quad \text{.....(2)}$$

ARTERIAL OXYGEN PARTIAL PRESSURE (P_aO_2)

1. Hypoxaemia.

It has been found that CBF remains relatively constant with decreasing P_aO_2 until the P_aO_2 drops below 6.7 kPa (50 mmHg), below which the CBF increases with decreasing P_aO_2 [18].

The level of consciousness is directly related to the degree of hypoxaemia [see also table 13.2.1]. The lowest P_aO_2 compatible with consciousness in chronically hypoxaemic, hypercarbic patients is 2.7-3.3 kPa (20-25 mmHg) [8]. Unconsciousness occurs in normal persons when the P_aO_2 is acutely reduced below 3.3-4 kPa (25-30 mmHg) [9,10]. Slowing of the EEG due to cerebral hypoxia occurs when the cerebral venous PO_2 falls below 2.8 kPa (21 mmHg) [13], but this level of hypoxia does not appear to cause permanent cerebral damage in persons with a normal haemoglobin and cardiac output [also see chapter 13.2].

2. Hyperoxaemia.

Increasing the P_aO_2 above normal does not significantly alter the CBF. If the P_aO_2 is 80 kPa (600 mmHg) the CBF only decreases by about 13% below that at a normal P_aO_2 [16]. No alteration of consciousness occurs with increasing P_aO_2.

Table 8.1.1.
PHYSIOLOGICAL LIMITS OF NORMAL CEREBRAL FUNCTION

Patients who have values of these parameters above or below these threshold values are likely to have a decreased level of consciousness, or are at increased risk of developing brain damage.

PARAMETER	MINIMUM VALUE	MAXIMUM VALUE
CBF	30 mls/100 gms/min	none
MABP (normal ICP)	20 + ((Resting MABP)/2)	130-150 mmHg
P_aO_2	4 kPa (30 mmHg)	?
P_aCO_2 (normal ICP)	4 kPa (30 mmHg)	10 kPa (75 mmHg)
pH (of CSF)	7.25	7.47
Plasma glucose concentration	1.7 mmol/l (30 mg/100 ml)	33 mmol/l (600 mg/100 ml)
Plasma [Na]	125 mmol/l	150 mmol/l
Plasma osmolality	265 mosm/kg	320 mosm/kg
Temperature	26-30°C	41°C

ARTERIAL CARBON DIOXIDE PARTIAL PRESSURE (P_aCO_2)

CBF varies in direct proportion to any change of P_aCO_2 [see figure 8.1.1]. Acute elevation of the P_aCO_2 causes vasodilation, and an acute reduction of the P_aCO_2 causes cerebrovascular vasoconstriction. In the P_aCO_2 range of 2.7-6.7 kPa (20-50 mmHg), the CBF increases about 1 ml/100 gms/minute per 1 mmHg increase of P_aCO_2, and above this P_aCO_2, the increase is no longer linear [16]. Maximal vasodilation in response to acute elevation of P_aCO_2 occurs at a P_aCO_2 of 10.7-16 kPa (80-120 mmHg) [17]. Maximal vasoconstriction in response to an acute reduction of the P_aCO_2 occurs at a P_aCO_2 of 2.7 kPa (20 mmHg) [12].

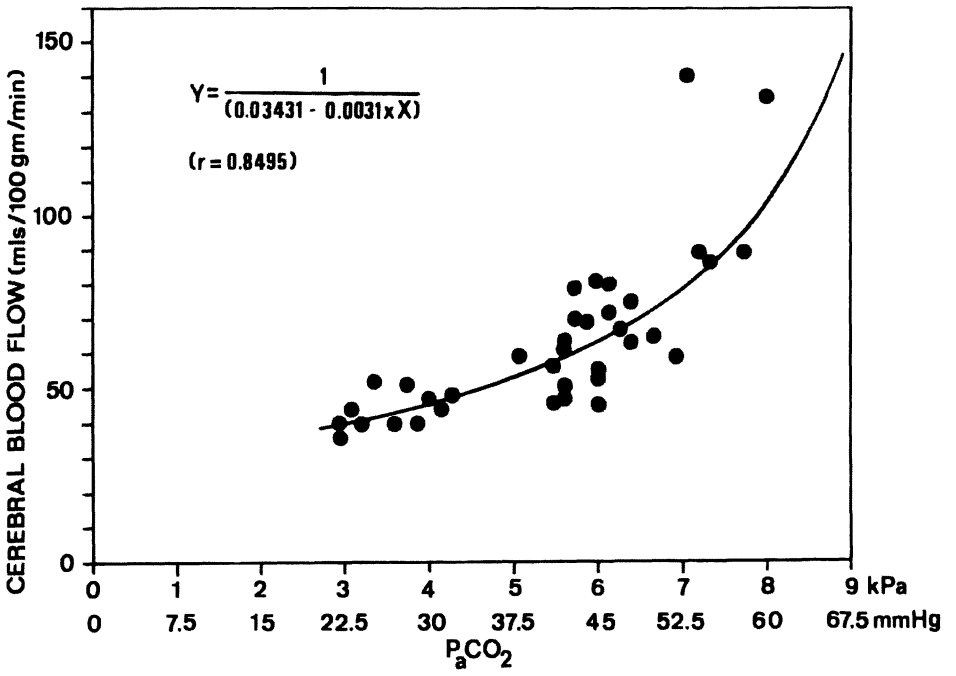

FIGURE 8.1.1. - The relationship between the cerebral blood flow and the P_aCO_2 is shown for healthy conscious young men in the P_aCO_2 range 2.9-8 kPa [11,16].

1. Hypercarbia.

Extreme hypercarbia causes loss of consciousness, ("carbon dioxide narcosis"). The threshold of unconsciousness for chronically hypercarbic persons is a P_aCO_2 above 10 kPa (75 mmHg) [8]. This does not mean that all persons are unconscious at this P_aCO_2, but that the percentage of persons that are unconscious increases in direct proportion to the P_aCO_2 above a P_aCO_2 greater than 10 kPa (75 mmHg).

2. Hypocarbia.

Healthy young volunteers who actively hyperventilated, or were passively hyperventilated, experienced symptoms ranging from carpopedal spasm, clouded consciousness, to unconsciousness when the P_aCO_2 was 4.1 kPa (31 mmHg), or lower [11]. If acute hyperventilation reduces the P_aCO_2 below 4.16 kPa (31.2 mmHg), slowing of the EEG occurs [13]. This is possibly due to cerebral hypoxia secondary to cerebral vasoconstriction. If the P_aCO_2 acutely falls below 2.7 kPa (20 mmHg), increased cerebral lactate production occurs, either due to increased lactate production secondary to the acute respiratory alkalosis [see chapter 13.3], or due to anaerobic brain metabolism caused by cerebral vasoconstriction [14,15].

During anaesthesia with controlled ventilation, the CBF is directly related to the arterial PCO_2 [25], the relationship being described by the regression equation below.

$$\text{CBF(mls/100 gms/min)} = 0.87 \times P_aCO_2\text{(mmHg)} + 4.5 \quad .....(3)$$

OR

$$\text{CBF(mls/100 gms/min)} = 6.53 \times P_aCO_2\text{(kPa)} + 4.5 \quad .....(3)$$

ACID BASE BALANCE

1. Acute plasma pH changes.

The CBF increases with decreasing arterial pH. It increases 9 mls/100 gms/minute per 0.1 reduction of the pH during respiratory acidosis in the pH range of 7.4-7.3. During acute respiratory alkalosis the CBF decreases 1 ml/100 gms/minute per 0.1 increase of pH in the pH range 7.4-7.6 [16].

Unconsciousness may occur during acute respiratory alkalosis when the P_aCO_2 is lower than 4.1 kPa [see above].

2. Chronic changes of cerebrospinal fluid pH.

Chronic changes of the cerebrospinal fluid (CSF) pH may also be associated with disordered consciousness. The level of consciousness then correlates better with the pH of the CSF, and NOT with that of the plasma [19]. Drowsiness or stupor occur when the CSF pH falls to 7.25 and lower, and coma occurs at lower pH levels [19,20].

A reduced level of consciousness is likely when the CSF pH is chronically elevated above 7.47 [20].

PLASMA SODIUM CONCENTRATION

If the plasma sodium concentration rises above 150 mmol/l, or falls below 125 mmol/l within a 24 hour time period, an extracellular fluid osmolality related reduction of the level of consciousness occurs, [see chapter 12.1 on hyponatraemia and 12.2 on hypernatraemia for a detailed discussion].

PLASMA GLUCOSE CONCENTRATION

Hypoglycaemic coma occurs when the plasma glucose concentration is lower than 1.4-1.7 mmol/l (25-30 mg/100ml), and hyperosmolar hyperglycaemic coma occurs when the plasma glucose rises above 33 mmol/l (600 mg/100ml) [see chapter on 7.1 on diabetes mellitus].

PLASMA OSMOLALITY

Plasma osmolality normally varies between 280-300 mosm/kg. Hyperosmolar coma occurs when the plasma osmolality is > 320 mosm/kg [see chapter 12.2 on hypernatraemia, as well as chapter 7.1 on diabetes mellitus].

An altered level of consciousness is likely when the plasma osmolality falls acutely below 265 mosm/kg [see chapter 12.1 on hyponatraemia].

TEMPERATURE

Extremes of body temperature will alter the level of consciousness as well as body function. Table 8.1.2 shows the relationship of the level of consciousness to the body temperature.

Table 8.1.2.
Relationship of the level of consciousness to body temperature in humans.

26°C	Most persons are unconscious [21,22,27]
30°C	Threshold for reduced level of consciousness [21,22,27]
37°C	**NORMAL**
39°C	Threshold for occurrence of delirium [28]
41°C	Level of consciousness is reduced [26]
>42°C	Death is likely [26]

REFERENCES

1. Trojaborg,W., Boysen,G.(1973). Relation between EEG, regional cerebral blood flow and internal carotid artery pressure during carotid endarterectomy. ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY, 34, 61-69.
2. Smith,A.L., Wollman,H.(1972). Cerebral Blood Flow and Metabolism. ANESTHESIOLOGY, 36, 378-400.
3. Johansson,B.(1974). Blood-brain barrier dysfunction in acute arterial hypertension with papaverine-induced vasodilatation. ACTA NEUROLOGICA SCANDINAVICA, 50, 573-580.
4. Langfitt,T.W.(1974). Cerebral circulation and metabolism. JOURNAL OF NEUROSURGERY, 40, 561-576.
5. Nilsson,O.B., Vinnars,E.(1957). Investigation of cerebral damage following induced hypotension. BRITISH JOURNAL OF ANAESTHESIA, 29, 146-150.
6. Johansson,B., et al.(1974). On the Pathogenesis of Hypertensive Encephalopathy. CIRCULATION RESEARCH, 34, suppl. I, 167-171.
7. Fox,E.J., et al.(1977). Complications Related to the Pressor Response to Endotracheal Intubation. ANESTHESIOLOGY, 47, 524-525.
8. Refsum,H.E.(1963). Relationship between state of consciousness and arterial hypoxaemia and hypercapnia in patients with pulmonary insufficiency, breathing air. CLINICAL SCIENCE, 25, 361-367.
9. Horvath,S.M., et al.(1943). Effects on man of severe oxygen lack. AMERICAN JOURNAL OF PHYSIOLOGY, 138, 659-668.
10. Lambertson,C.J.,et al.(1952). Relationship of Oxygen Tension to Hemoglobin Oxygen Saturation in the Arterial Blood of Normal Men. JOURNAL OF APPLIED PHYSIOLOGY, 4, 873-885.
11. Kety,S.S., Schmidt,C.F.(1946). The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men. JOURNAL OF CLINICAL INVESTIGATION, 25, 107-119.

12. Wollman,H., et al.(1968). Effects of extremes of respiratory and metabolic alkalosis on cerebral blood flow in man. JOURNAL OF APPLIED PHYSIOLOGY, 24, 60-65.
13. Gotoh,F., et al.(1965). Cerebral Effects of Hyperventilation in Man. ARCHIVES OF NEUROLOGY, 12, 410-423.
14. Alexander,S.C., et al.(1968). Cerebral carbohydrate metabolism of man during respiratory and metabolic alkalosis. JOURNAL OF APPLIED PHYSIOLOGY, 24, 66-72.
15. Alexander,S.C., et al.(1965). Cerebral Carbohydrate Metabolism During Hypocarbia in Man. ANESTHESIOLOGY, 26, 624-632.
16. Kety,S.S., Schmidt,C.F.(1948). The effects of altered tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. JOURNAL OF CLINICAL INVESTIGATION, 27, 487-492.
17. Reivich,M.(1964). Arterial PCO_2 and cerebral hemodynamics. AMERICAN JOURNAL OF PHYSIOLOGY, 206, 25-35.
18. Kogure,K., et al.(1970). Mechanisms of cerebral vasodilatation in hypoxia. JOURNAL OF APPLIED PHYSIOLOGY, 29, 223-229.
19. Posner,J.B., Plum,F.(1967). Spinal-fluid pH and neurologic symptoms in systemic acidosis. NEW ENGLAND JOURNAL OF MEDICINE, 277, 605-613.
20. Posner,J.B., et al.(1965). Acid-Base Balance in Cerebrospinal Fluid. ARCHIVES OF NEUROLOGY, 12, 479-496.
21. McNicol,M.W., Smith,R.(1964). Accidental Hypothermia. BRITISH MEDICAL JOURNAL, 1, 19-21.
22. Swan,H.(1973). Clinical hypothermia: A lady with a past and some promise for the future. SURGERY,73, 736-758.
23. Finnerty,F.A., et al.(1954). Cerebral hemodynamics during cerebral ischemia induced by acute hypotension. JOURNAL OF CLINICAL INVESTIGATION, 33, 1227-1232.
24. Rossen,R., et al.(1943). Acute arrest of cerebral circulation in man. ARCHIVES OF NEUROLOGY AND PSYCHIATRY, 50, 510-528.
25. Wollman,H., et al.(1965). Cerebral circulation during general anaesthesia and hyperventilation in man. Thiopentone induction to nitrous oxide and d-tubocurarine. ANESTHESIOLOGY, 26, 329-334.
26. Shibolet,S., et al.,(1967), Heat stroke: Its clinical picture and mechanism in 36 cases. QUARTERLY JOURNAL OF MEDICINE, 36, 525-548.
27. Fay,T., Smith,G.W.,(1941), Observations on reflex responses during prolonged periods of human refrigeration. ARCHIVES OF NEUROLOGY & PSYCHIATRY (CHICAGO), 45, 215-222.
28. Ebaugh,F.G., et al.,(1936), Delerious episodes associated with artificial fever. A study of 200 cases. AMERICAN JOURNAL OF PSYCHIATRY, 93, 191-217.

Chapter 8.2

CLASSIFICATION OF LEVEL OF CONSCIOUSNESS

A system of classification of the level of consciousness that is relatively observer independent is of great clinical utility in following the progression of neurological diseases where the level of consciousness is impaired. Two systems are in common clinical use.

1. SUBJECTIVE ASSESSMENT

One commonly employed classification of the level of consciousness is set out below [1, pages 114-115].

I. Conscious.

The patient is normally conscious and oriented, as well as having normal spontaneous speech, intellectual activity and movement.

II. Drowsy/Confused.

The patient is inattentive, may not manifest any spontaneous activity or speech. When stimulated he will react appropriately both with speech and/or movement. May be disoriented but can carry out simple commands.

III. Asleep.

The patient is asleep unless stimulated, being accessible to verbal stimulation or touch, but when awake is usually disoriented.

IV. Stupor.

The patient is not conscious unless stimulated. Manifests no spontaneous behavior, except for twitching, stereotyped or other automatic or abnormal movements. Responds only minimally to shouting or light pain stimuli.

V. Coma.

The patient is unconscious. Only reflex activity is present which maintains respiration and the circulation. The patient responds neither to intense pain, nor verbal stimuli.

The above classification is not observer independent, as the definition of each level of consciousness is based upon evaluation of observations and responses which are subject to wide variation in interpretation between different observers. This is unsatisfactory for

the purpose of accurately monitoring the clinical progress of patients whose level of consciousness may be assessed by a number of nurses or physicians.

Table 8.2.1.
GLASGOW COMA SCALE

Eye opening	
4. Spontaneous	
3. To speech	If eyes are closed by swelling,
2. To pain	then add "C" to this score.
1. None	
Best verbal response	
5. Oriented	
4. Confused	If patient has an endotracheal
3. Inappropriate	tube in place add a "T" to score.
2. Incomprehensible	
1. None	
Best motor response	
6. Obeys commands	
5. Localizes pain	
4. Withdraws from pain	
3. Flexion to pain	
2. Extension to pain	
1. None	

2. GLASGOW COMA SCALE

A more satisfactory method of classification is the Glasgow Coma Scale [2,3]. This is otherwise known as the EMV scale, "E" standing for the ocular responses, "M" for the motor responses, and "V" for verbal responsiveness.

The level of consciousness is classified according to the best ocular, motor, and verbal responses to an administered stimulus. The stimuli applied range from nothing, to pain. The responses are either present or not, and are not easily capable of ambiguous or subjective interpretation. The score obtainable varies from 3 to a maximum of 15. The scoring system is shown in table 8.2.1.

The EMV (or Glasgow Coma Scale) has found universal acceptance by virtue of relative observer independence. It also correlates well with morbidity and mortality after head trauma, the results of one series dealing with head injury patients being set out in table 8.2.2.

Table 8.2.2.
Neurological outcome related to best EMV score in the first 24 hours after injury [4].

Best EMV score in first 24 hours after head injury	% Patients dead or vegetative 6 months after head injury
3,4,5	82
6,7	48
8+	23

REFERENCES

1. Isselbacher,K.J., et al.(1981)."Harrison's Principles of Internal Medicine", 9th edn., pub. McGraw-Hill.
2. Teasdale,G.(1976). Assessment of head injuries. BRITISH JOURNAL OF ANAESTHESIA, 48, 761-766.
3. Gelb,A.W., et al.(1984). The anaesthetist and the head-injured patient. CANADIAN ANAESTHETISTS' SOCIETY JOURNAL, 31, 98-108.
4. Jennett,B., et al.(1980). Treatment for severe head injury. JOURNAL OF NEUROLOGY, NEUROSURGERY, AND PSYCHIATRY, 43, 289-295.

Chapter 8.3

RAISED INTRACRANIAL PRESSURE

Anaesthetic management of patients with elevated intracranial pressure (ICP) requires care, planning and thought about the consequences of every maneuver performed.

PROBLEMS DUE TO ELEVATED ICP

The manifestations of acutely raised ICP are well known, consisting of altered level of consciousness, vomiting, slowing of the pulse rate and respiration, together with elevation of the blood pressure. These manifestations occur to a lesser degree in patients in whom the ICP has risen slowly [2].

1. Reduced cerebral blood flow.

Aside from any alteration of consciousness, and the changes in cardiopulmonary physiology, the main problem, and the greatest threat to life is the reduction of cerebral blood flow (CBF) due to the raised ICP. CBF is a function of the cerebral perfusion pressure (CPP). The CPP itself is the difference between the mean arterial blood pressure and the intracranial pressure, as the cerebral venous pressure in normovolaemic persons is maintained at a value equal to, or slightly greater than the ICP. This also applies to those with elevated ICP too [22], and so the CPP may be expressed by the formula below for most situations.

$$\mathbf{CPP = MABP - ICP}$$

MABP = mean arterial blood pressure [see table 2.0.1].
ICP = mean intracranial pressure. The normal human ICP = 5-13 mmHg.

Provided that the MABP is greater than the ICP, some cerebral perfusion will occur, although a CPP of at least 30-40 mmHg is necessary to provide a normal CBF in normovolaemic persons [also see chapter 2.7 on hypotension]. However in persons with elevated ICP who are administered hypotensive or anaesthetic drugs, or who are hypovolaemic, the cerebral venous pressure may fall below the ICP. In such a situation the cerebral blood flow ceases because the tissue pressure inside the affected brain closes the intracerebral veins. This is probably one of the main reasons for the high mortality of patients with traumatically elevated ICP, those with an ICP in the range 41-80 mmHg having

a mortality of about 79%, while the mortality of persons with an ICP of 21-40 mmHg is about 29% [22].

2. Altered level of consciousness.

A reduction of the level of consciousness is always associated with decreased efficacy of laryngeal reflex activity, with an increased risk of aspiration of oropharyngeal contents.

3. Respiratory dysfunction.

A variety of abnormal respiratory rhythms may occur as a result of elevation of the ICP. Some of these rhythms are dysfunctional, in that alveolar ventilation is inadequate to sufficiently oxygenate the blood. Elevation of the ICP may also cause other respiratory problems.

a. Abnormal respiratory rhythm.

i. Apnea. This may be a result of cerebral herniation through the tentorium or foramen magnum [10].
ii. Cheyne-Stokes respiration may be a result of metabolic derangements, drug effects, or bilateral internal capsule lesions [11].
iii. Apneustic breathing. This a respiratory pattern characterized by a slow respiratory frequency, with a very prolonged end-inspiratory pause. This may be a result of severe hypoxaemia, hypoglycaemia, or pontine damage [12].
iv. Ataxic breathing. This is a totally irregular respiratory pattern which is caused by medullary lesions [13]. These patients are insensitive to the effects of P_aCO_2, and as a result are very sensitive to the effects of any drug capable of depressing respiration.
v. Central neurogenic hyperventilation. This is pathologically increased hyperventilation secondary to generalized cerebral damage [14].

b.Neurogenic pulmonary oedema.

Neurogenic pulmonary oedema may occur. This is discussed more fully in chapter 8.4.

4. Altered cardiac rhythm.

The cardiac rhythm may be affected by increased ICP. Both atrial and ventricular arrhythmias may occur. Bradycardia is one of the most frequently observed arrhythmias. It is vagally mediated, and is due to either baroreceptor reflex activity secondary to arterial hypertension, the effects of cerebral hypoxia, or the mechanical effects of the lesion causing elevation of the ICP on the brainstem.

5. Arterial hypertension.

Arterial hypertension frequently, although not always occurs as a consequence of elevated ICP. The cause is either the mechanical effects of the lesion causing the elevated ICP on the brainstem, brainstem hypoxia, or both.

6. Arterial hypotension.

Some patients not only have an elevated ICP, but may also be hypovolaemic. Hypovolaemia may be a result of haemorrhage, or may be due to vomiting caused by chronic or acute elevation of the ICP. The risk of brain damage as a result of hypotension secondary to hypovolaemia is very real. In such situations hypotension may reduce the CPP below what is required for adequate perfusion of the brain, and hypoxic cerebral damage occurs.

MANEUVERS TO REDUCE ELEVATED INTRACRANIAL PRESSURE

1. Elevation of the head.

Elevation of the head above the level of the heart reduces the intracerebral blood volume and the ICP falls within seconds [2].

2. Controlled respiration with hyperventilation.

Controlled respiration with hyperventilation causes cerebral vasoconstriction which reduces the cerebral blood volume and the ICP [2]. This is one of the situations where reduction of the P_aCO_2 below 4 kPa (30 mmHg) is permissable, as the increase in CBF due to a raised CPP more than compensates for the vasoconstriction that is induced [2]. Reduction of the ICP, provided it is not associated with a reduction of the MABP increases the CBF.

3. Prevention of coughing, straining, etc.

Coughing, straining, elevation of intrathoracic pressure, and raised intra-abdominal pressure, all elevate the ICP by increasing the cerebral venous pressure. This may be prevented and treated by administration of adequate dosages of neuromuscular blocking drugs [2], and by deep anaesthesia.

4. Diuretic therapy.

Diuretic drugs may also be used to reduce the ICP. However they only reduce the ICP for a relatively short period of time. There are two groups of diuretics which are used to reduce the ICP, the osmotic, and the "loop" diuretics.

a. Osmotic diuretics.

Of the various osmotic diuretic drugs used, hypertonic urea, sorbitol, and mannitol, mannitol has the fewest disadvantages.

Mannitol crosses the intact blood brain barrier to a very minor degree, and significantly reduces the ICP in normal, traumatized and diseased brain [15,16]. It does this by osmotic reduction of the interstitial fluid volume (ISFV) in regions of normal brain. Mannitol does not reduce the volume of regions of brain where the blood-brain-barrier is damaged, as it diffuses readily into the interstitium of traumatized regions through the damaged capillary endothelium [see chapter 14.3]. As no osmotic pressure gradient exists across the capillary endothelium of damaged tissue, no reduction of the interstitial oedema in these regions occurs. A "rebound" elevation of ICP may occur once enough mannitol has been eliminated from the body to reduce the plasma mannitol concentration below the mannitol concentration in the interstitium of damaged regions of brain. Water then diffuses into the interstitium of the damaged regions, increasing the ISFV there, and elevating the ICP. This is the "rebound" effect of mannitol. It also occurs with other osmotic diuretics too.

The reduction of the ICP due to repeat doses of mannitol is less than that due to the initial dose, especially in patients with traumatic elevation of the ICP. This is due to mannitol from previous doses which has diffused into the cerebral interstitium, especially of the damaged regions. Interstitial mannitol reduces the plasma-interstitium colloid osmotic pressure gradient generated by the repeat dose, so decreasing the degree of ISFV, and ICP reduction able to be achieved.

The dosage of mannitol required for significant reduction of ICP is about 0.5-1 gm/kg body weight. A maximum reduction of ICP occurs by 20 minutes after intravenous infusion of mannitol, simultaneously with the onset of diuresis, although diuresis itself is not the cause of the ICP reduction [16,17].

The rate of any mannitol infusion should be limited so that the total dosage is administered over a minimum time period of 15 minutes, as rapid intravenous infusion of mannitol is not without undesirable effects. Within 15 minutes after a rapid intravenous administration of a total dose of 1-2 gm/kg of mannitol, the plasma sodium concentration is decreased by 10 mmol/l, the blood volume increased by 43%, and the plasma osmolality increased by 23 mosm/l [18]. After 45-60 minutes the blood volume has returned to normal, but the plasma osmolality remains increased, and the plasma sodium remains low [18]. Such a large increase of blood volume can precipitate acute heart failure, and extreme hyponatraemia may occur. In addition to these effects, a rapid infusion of mannitol at a rate greater than 1-1.2 gm/70 kg/sec, to a total dosage of 0.25 gm/kg, can reduce the mean arterial blood pressure by up to 25 mmHg in patients whose cardiac output cannot increase sufficiently to compensate for the reduction of systemic vascular resistance that a mannitol infusion induces [19]. Large amounts of mannitol administered over a period of days, (>200 gms/day), can cause acute renal failure due to damage of proximal and distal renal tubular cells [20].

b. Diuretic drugs.

Diuretic drugs also reduce the ICP. The most commonly used diuretic drug for reducing the ICP is frusemide. Frusemide in a dosage of 1 mg/kg also reduces the ICP, but to a lesser degree than 1 gm/kg mannitol [16]. Here too, the maximum reduction of ICP occurs coincidentally with the peak diuresis, which occurs about 20-40 minutes after intravenous administration of an intravenous bolus of frusemide [17]. Frusemide also potentiates the effects of the osmotic diuretics [16].

Diuretic drugs should never be used in patients who are already hypovolaemic, or suspected to be so, as the CPP may be reduced to dangerously low levels if the blood volume falls even further.

5. Glucocorticoid hormones.

The use of glucocorticoid hormones such as dexamethasone to reduce ICP is controversial. They certainly do reduce ICP in those patients with brain oedema due to tumors, but there is little evidence that they reduce the ICP in patients with raised ICP due to traumatic or hypoxic injury [4].

6. Ventricular drainage.

Drainage of the ventricles is very effective in reducing elevated ICP.

7. Etomidate.

Etomidate, administered either as an intravenous bolus at a dose of 0.3 mg/kg, or as an intravenous infusion at a rate of 50-100 μg/kg/min significantly reduces elevated ICP without reducing the arterial blood pressure. The effect of this is a reduction of the ICP while at the same time the CPP is maintained or actually increased [8].

ANAESTHETIC MANAGEMENT

Preoperative.

1. No patient with an elevated ICP should receive sedative, opiate or other drugs preoperatively if they are breathing spontaneously. The opiates, benzodiazepines and barbiturates all cause a degree of respiratory depression, and may cause the already elevated ICP to rise

Table 8.3.1.
EFFECTS OF VARIOUS DRUGS ON BRAIN
(During controlled ventilation with constant P_aCO_2, and so does NOT apply to spontaneously breathing patients [2,8,9]).

DRUG	MABP	ICP	CPP	CBF	$CMRO_2$
THIOPENTONE	↓↓↓	↓↓↓	↓↓↓	↓↓	↓↓
ETOMIDATE	↓/0	↓↓↓	0/↑	↓↓	↓↓
KETAMINE	↓/↑	↑↑↑	↓↓↓	↑↑	0
FENTANYL	0	↓	↓	↓	↓
MORPHINE	↓	↓	↓	↓	↓
VOLATILE ANAESTHETICS	↓	↑↑↑	↓↓↓	↑↑↑	↓↓↓

$CMRO_2$ = cerebral oxygen consumption per unit time.
"↑" = increase; "↓" = decrease; "0" = no change.

even further due to elevation of the P_aCO_2. This reduces tissue oxygenation even further in situations where this is marginal.

2. Preoperative reduction of elevated blood pressure may cause cerebral ischaemia in those patients whose ICP is extremely elevated. No attempt should be made to reduce the blood pressure in patients in whom a raised ICP is suspected.

Anaesthesia.
1. The basic principle of anaesthetic management of any patient with elevated ICP is to maintain a CPP at which the brain remains viable. This usually can be translated to mean that the intraoperative blood pressure should be maintained at the preoperative level until craniotomy has reduced the ICP. The reason for using the preoperative blood pressure as a measure of the adequacy of cerebral perfusion is simple. If the person was conscious to some degree, then the cerebral perfusion at that blood pressure was compatible with brain viability, and so this blood pressure is a known blood pressure at which the brain is viable.

The reflex elevation of blood pressure occurring as a result of elevation of ICP is a reflex response which maintains the CPP at a level which is compatible with the absence of brain ischaemia, and is called the Cushing reaction [1, pages 253-254]. A reduction of the blood pressure below preoperative levels by either induction of anaesthesia or premedication should never be permitted in this situation, as it may reduce the blood pressure below that which is necessary to prevent cerebral hypoxia. Blood pressure reduction may only be permitted to occur after the dura has been opened during a craniotomy, because then the

ICP is equal to atmospheric pressure, EXCEPT in situations where the brain is bulging out of the opening in the dura. In the latter situation, the ICP is obviously still elevated.

For this reason it is always essential to have a vasoconstrictor drug immediately available during any anaesthetic procedure carried out on a patient with an elevated ICP, e.g. ephedrine, phenylephrine etc. If induction of anaesthesia or hypovolaemia causes the blood pressure to drop significantly below the preoperative level, administration of a vasoconstrictor to elevate the blood pressure to near the preoperative level, e.g. 5-10 mg ephedrine, will increase the blood pressure, CPP, and CBF within less than a minute [4,21, see also chapter 2.2]. It usually requires more time than this to raise the blood pressure and CPP with even a rapid infusion of intravenous fluids, and significant cerebral ischaemia may occur in patients with an extremely high ICP during this time.

2. Anaesthesia should never be induced in a hypovolaemic patient who has a raised ICP. Hypovolaemia should be treated prior to induction. Induction of anaesthesia under these circumstances is extremely hazardous for the patient, as all general anaesthetic drugs, including ketamine, further reduce the cardiac output, and blood pressure in hypovolaemic patients [see chapter 14.4].

3. Loco-regional anaesthesia.

If there is some suspicion that the ICP may be elevated never use a regional anaesthetic technique where a needle can puncture the dura, either intentionally or by accident. Therefore NO spinal or epidural anaesthesia should be attempted in patients with raised ICP. Both can cause a significant CSF leak. A reduction of the extracranial cerebrospinal fluid pressure may cause herniation of brain through the falx cerebri, tentorium cerebelli, or foramen magnum in patients with supratentorial or infratentorial elevation of the ICP.

4. General anaesthesia.

Induction and maintenance of general anaesthesia in patients with raised ICP should only be carried out by persons who have a sound understanding of the possible effects of general anaesthetic drugs and techniques on cerebral perfusion. A few minutes of cerebral circulatory arrest is sufficient to cause severe cerebral damage. The main points to remember when administering general anaesthesia to patients with elevated ICP are discussed below.

a. Respiration should always be controlled so that oxygenation can be guaranteed in the face of abnormal respiratory control. Use of a cuffed endotracheal tube ensures that no pulmonary aspiration of gastric contents can occur, and a muscle relaxant drug to paralyze the peripheral muscles prevents active vomiting.
b. Laryngoscopy for endotracheal intubation can cause the ICP to increase by up to 88 mmHg above preoperative levels [5]. This further elevates the ICP in patients with an already elevated ICP, with all the possible consequences of this. Administration of lignocaine intravenously at a dosage of 1.5 mg/kg 1 minute prior to laryngoscopy significantly reduces elevation of ICP due to laryngoscopy [6], as does intravenous administration of 5 μg/kg of fentanyl 3-5 minutes prior to laryngoscopy [7].
c. Drugs used for induction and maintenance of anaesthesia should be those which cause minimal cardiovascular depression [see chapter 2.1], and minimal reduction of the CPP [see table 8.3.1].

d. Drugs such as etomidate, and thiopentone reduce the ICP in normocapnic or hypocapnic patients by causing cerebral vasoconstriction. They decrease both the CBF and ICP, as well as reduce the cerebral metabolic rate [2], and so are the drugs of choice for induction of anaesthesia in patients with raised ICP. Etomidate can also be used intermittently in intravenous boluses of 5-20 mg to temporarily reduce the ICP if this is indicated.
e. Preferred muscle relaxants are pancuronium, alcuronium, or vecuronium, because they cause the least alterations of systemic haemodynamics [see chapter 2.1]. Suxamethonium should not be used, as it can cause a significant increase of ICP [2].
f. Any opiate may be used, as none of them adversely affect the ICP in the patient whose ventilation is controlled, unless they significantly reduce the blood pressure [see chapter 2.1]. Administration of opiates to spontaneously breathing patients with elevated ICP is contraindicated as this further elevates the ICP due to hypercapnia secondary to respiratory depression.
g. Use volatile anaesthetics only when the skull and dura are open, and the patient is hyperventilated. All volatile anaesthetics are powerful cerebral vasodilators, increasing the intracranial blood volume and the ICP [2].

5. The maintenance of stable haemodynamics, and the restoration or maintenance of normovolaemia should always be the aim of any intravenous fluid therapy in patients with raised ICP. Intravenous fluid therapy is aimed at maintaining the blood volume, as well as the protein and electrolyte composition of the extracellular fluid as near normal as possible. In this way the brain cells only swell due to cell membrane damage, and not due to a hypoosmolar extracellular fluid composition [see chapter 12.1 on hyponatraemia]. Maintenance of the plasma colloid osmotic pressure also ensures that the interstitial fluid volume in undamaged regions of the brain will not increase due to a low plasma colloid osmotic pressure [see chapter 14.1].

Maintain vascular filling pressures at the lower limit of normal, e.g. a CVP of 5 cm H_2O, or a PCWP = 5 mmHg. This minimizes the amount of fluid that flows into the interstitium of normal and damaged regions of brain, reducing the likelihood of iatrogenic exacerbation of the raised ICP [see chapters 14.1 and 14.3 for a more detailed discussion of the effects of trauma on fluid balance].

Postoperative.

1. All patients with an elevated ICP should go to an intensive care postoperatively for monitoring, and for further therapy.

2. If the patient is comatose, or has an EMV score of 7 or less. The patient should be mechanically ventilated until consciousness returns.

REFERENCES

1. Guyton,A.C.(1981)."Textbook of Medical Physiology", 6th edn., pub. W.B.Saunders.
2. Messick,J.M., et al.(1985). Principles of Neuroanesthesia for the Non-neurosurgical Patient with CNS Pathophysiology. ANESTHESIA AND ANALGESIA, 64, 143-174.
4. Gelb,A.W., et al.(1984). The anaesthetist and the head-injured patient. CANADIAN ANAESTHETISTS' SOCIETY JOURNAL, 31, 98-108.
5. Shapiro,H.M., et al.(1972). Acute Intracranial Hypertension in Neurosurgical Patients: Mechanical and Pharmacologic Factors. ANESTHESIOLOGY, 37, 399-405.

6. Hamill,J.F., et al.(1981). Lidocaine before Endotracheal Intubation: Intravenous or Laryngotracheal? ANESTHESIOLOGY, 55, 578-581.
7. White,P.F., et al.(1982). A Randomized Study of Drugs for Preventing Increases in Intracranial Pressure during Endotracheal Intubation. ANESTHESIOLOGY, 57, 242-244.
8. Schulte am Esch,J., et al.(1978). The Influence of Intravenous Anaesthetic Agents on Primarily Increased Intracranial Pressure. ACTA NEUROCHIRURGICA, 45, 15-25.
9. Renou,A.M., et al.(1978). Cerebral blood flow and metabolism during etomidate anaesthesia in man. BRITISH JOURNAL OF ANAESTHESIA, 50, 1047-1051.
10. Miller,J.D., Sullivan,H.G.(1979). Severe intracranial hypertension. INTERNATIONAL ANESTHESIOLOGY CLINICS, 17, 19-75.
11. Brown,H.W., Plum,F.(1961). The neurologic basis of Cheyne-Stokes respiration. AMERICAN JOURNAL OF MEDICINE, 30, 849-860.
12. Plum,F. Alvord,E.C.(1964). Apneustic breathing in man. ARCHIVES OF NEUROLOGY, 10, 101-112.
13. Plum,F., Swanson,A.G.(1958). Abnormalities in the central regulation of respiration in acute and convalescent poliomyelitis. ARCHIVES OF NEUROLOGY AND PSYCHIATRY, 80, 267-285.
14. Plum,F., Swanson,A.G.(1959). Central neurogenic hyperventilation in man. ARCHIVES OF NEUROLOGY AND PSYCHIATRY, 81, 535-549.
15. James,H.E., et al.(1977). Treatment of intracranial hypertension. Analysis of 105 consecutive recordings of intracranial pressure. ACTA NEUROCHIRURGICA, 36, 189-200.
16. Cottrell,J.E., et al.(1977). Furosemide and mannitol induced changes in intracranial pressure and serum osmolality and electrolytes. ANESTHESIOLOGY, 47, 28-30.
17. Jarnberg,P-O., et al.(1978). Acute effects of furosemide and mannitol on renal function in the early postoperative period. ACTA ANAESTHESIOLGICA SCANDINAVICA, 22, 173-183.
18. Rudehill,A., et al.(1983). Effects of mannitol upon blood volume and central hemodynamics in patients undergoing cerebral aneurism surgery. ANESTHESIA AND ANALGESIA, 62, 875-880.
19. Cote,C.J., et al.(1979). The hypotensive response to rapid intravenous administration of hypertonic solutions in man and in the rabbit. ANESTHESIOLOGY, 50, 30-35.
20. Goldwasser,P., Fotino,S.(1984). Acute renal failure following massive mannitol infusion. ARCHIVES OF INTERNAL MEDICINE, 144, 2214-2216.
21. Mutch,W.A.C., Ringaert,K.R.A.,(1987), Effects of haemorrhage and phenylephrine on cerebral blood flow in rats during isoflurane anaesthesia. CANADIAN JOURNAL OF ANAESTHESIA, 34, supplement, s106-s107.
22. Miller,J.D.,(1985), Head injury and brain ischaemia - implications for therapy, BRITISH JOURNAL OF ANAESTHESIA, 57, 120-129.

Chapter 8.4

HEAD INJURY

Management of the head injured patient is a matter of teamwork requiring the skills of various specialists, neurologist, neurosurgeon, general surgeon, orthopedic surgeon, anaesthetist and others.

PROBLEMS DUE TO HEAD INJURY [1,2]

It is unusual to encounter a patient with an isolated head injury. Usually a head injury is associated with other injuries.

1. Skeletal.

i. Skull, maxillofacial, and cervical spine fractures.
ii. Fractures of other bones with their associated blood loss.
iii. Spinal injuries and fractures.

2. Neurological.

Brain damage and death may occur due to the direct effects of trauma, and the secondary effects of swelling and hypoxaemia.

3. Cardiopulmonary effects.

a. Hypoxaemia.

i. Due to rib, thoracic, or spinal injury.
ii. Due to lung contusion, and adult respiratory distress syndrome.
iii. Abnormal respiratory pattern, apnea, hyperventilation, apneustic respiration, ataxic respiration and Cheyne-Stokes respiration [see chapter 8.3].
iv. Neurogenic lung oedema may occur due to capillary endothelial damage. Head injury may initially cause such massive sympathetic stimulation that the pulmonary arterial, capillary, and venous pressures are elevated to such a degree that pulmonary capillary endothelium is damaged. Plasma then leaks into the pulmonary interstitium and alveoli unhindered by a functioning capillary endothelial barrier. Because endothelial injury lasts until cellular and basement membrane healing has occurred, such lung oedema continues long after the sympathetic stimulation that caused it has ceased [3,4].
v. Airway obstruction may occur due to faciomaxillary injury, or the tongue. This is made more likely by a decreased level of consciousness which diminishes protective airway reflexes. These maintain airway patency as a result of stimulation by hypoxaemia and hypercarbia. Both hypoxaemic and hypercarbic responses are also depressed in unconscious persons.

vi. Aspiration of gastric contents and blood. This is made more likely by vomiting due to raised intracranial pressure combined with reduced efficacy of upper airway reflexes caused by a decreased level of consciousness.

b. Circulatory effects.

i. A significant proportion of the blood volume may have been lost due to wounds and fractures. If hypotension occurs as a result of hypovolaemia, the CPP may fall below 30-40 mmHg, the minimum level required for adequate cerebral perfusion [see chap. 8.3].

ii. Hypertension may occur during periods of elevated ICP, i.e. the Cushing response [5]. However this response cannot be relied upon to maintain an adequate CBF in hypovolaemic patients with an elevated ICP, and certainly cannot be relied on to maintain the CPP if general anaesthesia is administered to hypovolaemic and even to normovolaemic patients.

c. Cardiac effects [5].

i. Vagally mediated bradycardia may occur.

ii. A variety of cardiac arrhythmias may occur in association with raised ICP, ranging from atrial to ventricular arrhythmias, and even atrioventricular block.

iii. ECG changes of myocardial ischaemia may occur, even ECG signs of myocardial infarction.

4. Haematological effects.

Brain contains a high concentration of tissue thromboplastins. Sufficient quantities may be released by massive trauma to initiate disseminated intravascular coagulation.

5. Endocrine effects.

a. Hypothalamic or pituitary damage can cause diabetes insipidus, or inappropriate ADH secretion. Other forms of hypothalamic or pituitary dysfunction may also occur.

b. Damage to the hypothalamus may also cause disordered temperature regulation.

c. Nonketotic hyperglycaemic coma may occur in patients with diabetes mellitus, due to the hyperglycaemic response to severe trauma.

ASSESSMENT OF THE PATIENT WITH A HEAD INJURY

1. Use the EMV score, or alternatively, a much simpler system of classification as shown in table 8.4.1 may be used [8].

2. Upon arrival of the patient in the emergency department, arterial blood should be immediately be withdrawn for arterial blood gas analysis as well as measurement of haemoglobin and electrolyte concentrations. Clinically assess the adequacy of the respiratory function, in addition to the neurological status, the presence of other injuries, and the magnitude of any blood loss.

Table 8.4.1.
SIMPLE CLINICAL ASSESSMENT OF HEAD INJURY SEVERITY [8]

Class 1.	Patient in coma. May have open head wounds and/or paralysis.
Class 2.	Patients with a reduced level of consciousness, but not comatose.
Class 3.	Patients who have had a short period of unconsciousness, after which they are well oriented in time, place, and person, and in addition have no obvious brain damage or paralyses.

FACTORS AND TREATMENT AFFECTING SURVIVAL AFTER HEAD INJURY

Survival, and quality of survival after head injury have been extensively studied. The neurological outcome is related both to the clinical condition of the patient and the treatment administered.

1. Factors affecting survival.

a. Hypotension, defined as a systolic arterial blood pressure less than 90 mmHg, doubles the mortality associated with severe head injury [10].

b. Percentage survival is directly related to the degree of elevation of the ICP. Mortality is about 19% in patients with severe head injury but with a normal ICP, and rises to about 79% in patients whose ICP is elevated between 41-80 mmHg [10].

2. Treatments affecting survival, and quality of survival [9].

a. Administration of a glucocorticoid hormone, e.g. dexamethasone, does not affect the neurological outcome, however high doses of glucocorticoids themselves may cause problems [see chapter 7.4]

b. The use of osmotic diuretics significantly improves neurological outcome.

c. Cranial decompression significantly improves the neurological outcome.

d. Rapid and early endotracheal intubation/tracheostomy improves the neurological outcome.

e. Early institution of mechanical ventilation in patients with abnormal respiratory function significantly improves the neurological outcome.

INITIAL MANAGEMENT OF PATIENTS WITH HEAD INJURY

The primary resuscitative measures of any patient with a head injury are treatment of hypoxaemia and hypovolaemia.

1. Hypoxaemia.

Hypoxaemia should always be aggressively treated, and a "safe airway" should be ensured. Patients with an EMV score of 6-7 or less, or who fall into class-1 of table 8.4.1, require immediate endotracheal intubation and mechanical ventilation. Any patient with an abnormal respiratory pattern, who is cyanosed, unconscious, or is vomiting while the level of consciousness is reduced, should be intubated immediately, and mechanically ventilated, to ensure both a "safe airway" and adequate oxygenation.

2. Hypovolaemia.

Hypovolaemia must always be rapidly and aggressively treated in all patients with head injury. Hypotension secondary to blood or plasma loss may cause cerebral ischaemia if the ICP is elevated above the intracerebral capillary pressure.

A vasoconstrictor drug should be administered to elevate the blood pressure to acceptable levels during acute hypotensive episodes in hypovolaemic head injured patients. This will maintain CPP and CBF at an acceptable level until normovolaemia and an acceptable blood pressure have been restored by an intravenous infusion. It usually takes less than a minute for a vasoconstrictor to act, while it may take some minutes for even a rapid intravenous infusion to elevate the blood pressure significantly. Significant cerebral damage can occur within this time. It should be emphasized that administration of a vasoconstrictor is no substitute for restoring a normal blood volume, and in fact is very bad therapy for hypovolaemic shock as it reduces blood flow to most other organs, but it does increase CBF during hypovolaemia [11, see also chapter 2.2]. Restoration of normovolaemia should be done simultaneously with administration of the vasoconstrictor. All that the vasoconstrictor does is protect cerebral function while normovolaemia is restored, as the ability of the brain to survive ischaemia and hypoxia is much less than that of all other organs in the body. Elevation of the arterial blood pressure with a vasoconstrictor has the extra benefit of increasing coronary vascular flow too.

3. Osmotic diuretics.

If the patient has clinical signs of markedly elevated ICP, and some time is expected to elapse before any surgery is likely to take place, administer mannitol intravenously at a dosage of 0.5-1 gm/kg to temporarily reduce the ICP to a lower level.

4. Check for cervical spinal injury.

All patients with a head injury must be assumed to have cervical spinal injury until proven otherwise by cervical spinal X-rays. Cervical injury is the primary cause of death in 3% of patients with head injury [7].

ANAESTHETIC MANAGEMENT

Preoperative.

1. No sedative drugs or opiates should be administered preoperatively. They may reduce the CBF or cloud the clinical neurological picture.

2. Insert a large bore intravenous infusion prior to inducing anaesthesia. Hypotension after induction may make this impossible in hypovolaemic patients.

3. Replace any blood volume deficit prior to administration of any anaesthetic drugs. Reduction of the arterial blood pressure in the presence of an elevated ICP may reduce the CPP and CBF to lethally low levels [see table 2.7.2].

Anaesthesia.

All head injured patients must be presumed to have raised ICP as a result of their injury, REGARDLESS of whether they are conscious or not. Anaesthetic management is otherwise the same as for patients with elevated ICP. Any technique used must be adjusted for the presence of any associated trauma. In fact most patients with head injury who undergo an operation, are operated for the associated injuries, rather than for neurological problems [6]. Injury to the central nervous system is usually not amenable to surgical correction, except for haematomas, depressed skull fractures, bleeding vessels etc.

2. No spinal or epidural anaesthesia should be administered in the presence of a possibly elevated ICP. Any other loco-regional anaesthetic technique is permissable.

3. General anaesthesia is to be preferred for any surgical procedure. There are a few points which should be kept in mind when administering general anaesthesia to a head injured patient.

a. A technique using endotracheal intubation and controlled ventilation is required. This ensures oxygenation, a cuffed endotracheal tube prevents pulmonary aspiration of possible regurgitated gastric contents, and hyperventilation will reduce the intracranial pressure.
b. Endotracheal intubation should be carried out with due care for the effects it may have upon the ICP [see chapter 8.3], and also with due consideration for the possible presence of a full stomach. Care must also be taken with movement of the head and neck during endotracheal intubation in case cervical spine injury is present.
c. Anaesthetic drugs should be selected that cause minimum cardiovascular depression, while reducing the ICP [see chapter 2.1, and table 8.3.1]. Etomidate is the drug of choice for induction, pancuronium or vecuronium for muscle relaxation and endotracheal intubation, and fentanyl is the opiate of choice.

Postoperative.

1. Those patients requiring endotracheal intubation and ventilation prior to operation should be ventilated postoperatively in an intensive care unit.

2. All head injury patients who are comatose postoperatively should be mechanically ventilated in an intensive care unit until their neurological status improves.

REFERENCES

1. Stulken,E.H., et al.(1985). Anesthetic Management of Head Trauma. SEMINARS IN ANESTHESIA, 4, 154-161.
2. Gelb,A.W., et al.(1984). The anaesthetist and the head-injured patient. CANADIAN ANAESTHETISTS' SOCIETY JOURNAL, 31, 98-108.
3. Ducker,T.B.(1968). Increased Intracranial Pressure and Pulmonary Edema. Part 1: Clinical Study of 11 Patients. JOURNAL OF NEUROSURGERY, 28, 112-117.

4. Ducker,T.B., Simons,R.L.(1968). Increased Intracranial Pressure and Pulmonary Edema. Part 2: The Hemodynamic Response of Dogs and Monkeys to Increased Intracranial Pressure. JOURNAL OF NEUROSURGERY, 28, 118-123.
5. Messick,J.M., et al.(1985). Principles of Neuroanesthesia for the Non-Neurosurgical Patient with CNS Pathology. ANESTHESIA AND ANALGESIA, 64, 143-174.
6. Pfenninger,E., Ahnefeld,F.W.,(1983). Narkosefuhrung beim polytraumatisierten Patienten mit assoziertem Schädel-Hirn Trauma. DER ANAESTHESIST, 32, 191-199.
7. Sefrin,P., et al.(1980). Konsequenzen fur die Primarversorgung von Notfallpatienten aus einer propektiven Studie an 106 tödlichen Verlaufen. DER ANAESTHESIST, 29, 667-672.
8. Alphen,H.A.M. van, Braakman,R.(1985). Guidelines for the treatment of patients with severe traumatic brain damage. NEDERLANDSE TIJDSCHRIFT VOOR DE GENEESKUNDE, 129, 645-649.
9. Jennett,B., et al.(1980). Treatment for severe head injury. JOURNAL OF NEUROLOGY, NEUROSURGERY, AND PSYCHIATRY, 43, 289-295.
10. Miller,J.D.(1985). Head injury and brain ischaemia - implications for therapy. BRITISH JOURNAL OF ANAESTHESIA, 57, 120-129.
11. Mutch,W.A.C., Ringaert,K.R.A.,(1987), Effects of haemorrhage and phenylephrine on cerebral blood flow in rats during isoflurane anaesthesia. CANADIAN JOURNAL OF ANAESTHESIA, 34, supplement, s106-s107.

Chapter 8.5

DISORDERS AFFECTING NEUROMUSCULAR FUNCTION

Neuromuscular function may be affected by a large variety of diseases, metabolic disorders and drugs. While disorders of neuromuscular function do not occur very frequently, they are encountered regularly.

ELECTROLYTE DISORDERS

1. Disorders of potassium balance.

Clinical muscle weakness occurs when the plasma potassium concentration is lower than 2.5 mmol/l [1]. Hyperkalaemia is also associated with muscle weakness, which occurs when the plasma potassium concentration is 7.2 mmol/l and higher [2,3]. A more extensive discussion of disorders of potassium homeostasis is to be found in chapters 12.3 and 12.4.

In-vitro investigation has shown that hypokalaemia is associated with increased sensitivity to non-depolarizing muscle relaxants, while hyperkalaemia antagonizes the effects of these drugs [4]. The same has been found clinically for hypokalaemia, but the situation is less clear for hyperkalaemia. Hyperkalaemia itself also causes muscle weakness, which is likely to be potentiated by muscle relaxant drugs, although the duration of their effect may be reduced by the effects of potassium on the neuromuscular junction [see chapter 12.4].

2. Disorders of calcium balance.

If the total plasma calcium concentration is below 1.75 mmol/l, tetany and other symptoms of hypocalcaemia are likely [5,6], and if it is above 3 mmol/l muscle weakness may occur [7]. A more extensive discussion of disorders of calcium homeostasis may be found in chapters 12.5 and 12.6.

In-vitro studies show that the dosage of a non-depolarizing muscle relaxant required to produce a given degree of muscle relaxation is directly proportional to the extracellular calcium ion concentration [4]. One of the reasons for this is that calcium entry into cholinergic nerve terminals during depolarization is required for the release of acetylcholine [4,8]. Despite the fact that hypocalcaemia does cause tetany, it is likely that the sensitivity to non-depolarizing drugs is increased in this condition. Hypercalcaemia can cause clinically significant skeletal muscle weakness itself, but despite this, the effect of non-depolarizing muscle relaxants are reduced [see chapter 12.6].

3. Disorders of magnesium balance.

Plasma magnesium concentration is normally in the range 0.8-1.3 mmol/l. Hypermagnesaemia can cause muscle weakness. It does this by inhibiting the release of acetylcholine from cholinergic nerve terminals, so inducing a neuromuscular block. The effect of the

neuromuscular block so produced is to greatly enhance sensitivity to both depolarizing as well as nondepolarizing neuromuscular blocking drugs [9]. Administration of calcium intravenously reverses the effects of hypermagnesaemia. The usual dose of calcium for an adult is 0.5-1 gm/70 kg of calcium chloride or gluconate [9].

DISEASES AND MYOPATHIES

1. Various non-specific myopathies.

Clinical muscle weakness and myopathies may be caused by non-neurological disorders such as diabetes mellitus, glucocorticoid hormone use and alcohol abuse.

If a patient has clinically evident muscle weakness, any neuromuscular junction blocking drug should be used with caution, as their action may be potentiated by the existing muscle weakness.

2. Autoimmune inflammatory diseases.

This includes such diseases as polymyositis, dermatomyositis, systemic lupus erythematosis, polyarteritis nodosa. These conditions may be associated with easy fatigability. The muscle weakness associated with these disorders may decrease after administration of neostigmine [10].

Here too, caution should be exercised when muscle relaxant drugs are administered to patients with clinical muscle weakness.

3. Thyroid diseases.

Both hyperthyroidism as well as hypothyroidism are associated with clinical muscle weakness [11,12, see also chapters 7.2 and 7.3 for a more extensive discussion].

Hyperthyroid patients have decreased responsiveness to suxamethonium due to an increased plasma cholinesterase concentration [13]. The responses to non-depolarizing muscle relaxants are normal in both hyperthyroid as well as hypothyroid patients. But, as with other non-specific myopathies, muscle relaxants should be used with caution in such patients, as their effect may be potentiated by the existing muscle weakness.

4. Dennervation myopathy.

After dennervation due to either an upper motor neurone lesion or peripheral nerve damage, there is an increase in the number of postsynaptic acetylcholine receptors at the neuromuscular junctions of the paralyzed muscles. In addition to this, the whole muscle cell membrane of the paralyzed muscles becomes more sensitive to acetylcholine [14].

Due to increased sensitivity to acetylcholine, plus increased numbers of muscle acetylcholine receptors, the effect of non-depolarizing muscle relaxants on paralyzed muscles is reduced both in duration as well as degree of neuromuscular block achieved [15]. Because of this, any repeat dosage of these drugs should be administered on the basis of information derived from non-paretic muscles whose response to these drugs is normal.

Use of depolarizing muscle relaxants in patients with either an upper or lower motor neurone lesion is associated with a larger than usual plasma potassium concentration increase. In some patients the plasma potassium concentration may actually be dangerously increased after suxamethonium administration. Increased potassium release in response to suxamethonium and other depolarizing relaxants occurs for a period of 8 days to 9 months after dennervation [14].

5. Various neurological disorders.

Diseases such as von Recklinghausen's disease, multiple sclerosis, poliomyelitis, syringomyelia and amyotrophic lateral sclerosis may cause combinations of upper as well as lower motor neurone lesions.

The actual effects of any muscle relaxants used are dependent on how extensive any lesions are, and how recently they occurred, [see paragraph 4. of this chapter].

6. Eaton-Lambert syndrome.

These patients are very sensitive to both depolarizing and nondepolarizing neuromuscular blocking agents. 4-aminopyridine reduces the muscle weakness. See chapter 4.11 on primary lung tumors for a more extensive discussion.

7. Myasthenia gravis.

This is a disease caused by a decreased number of acetylcholine receptors at the motor end plate. The easy fatigability and muscle weakness are reversible with acetylcholinesterase blocking drugs such as neostigmine etc.

Typically these patients have an extreme sensitivity to the effects of nondepolarizing muscle relaxants [10]. The reaction of myasthenic patients to depolarizing relaxants such as suxamethonium is somewhat different. Resistance to depolarization occurs at a dosage of 0.5 mg/kg, while no such resistance is present at a dose of 1 mg/kg, but the duration of the depolarization block is longer than normal. In addition to this, suxamethonium also causes a non-depolarizing block ("phase-II block") in all myasthenic patients, an effect which may last for up to 30 minutes [22].

All patients with myasthenia gravis should be admitted to an intensive care unit postoperatively for intensive respiratory monitoring, and if indicated, mechanical ventilation until the effects of anaesthetic drugs have passed.

8. Myotonic dystrophy

Patients with dystrophic disorders such as dystrophica myotonica, present the anaesthetist with a number of problems, including muscle weakness, cardiomyopathy, and sensitivity to the effects of sedative and hypnotic drugs [16].

Sedative, hypnotic and anaesthetic drugs exert a number of effects in these patients.

a. The patients are more sensitive to the respiratory depressant effects of these drugs, which makes controlled ventilation mandatory for these patients during general anaesthesia.
b. Central nervous system depression due to hypnotic, sedative drugs is more pronounced than for normal persons. This means that the dosages of all these drugs should be reduced.
c. The existing myocardopathy is greatly exacerbated by myocardial depression due to anaesthetic drugs, and so they produce a more pronounced degree of cardiovascular depression than is usual [17].

All anaesthetic, sedative, and hypnotic drugs should be used with caution in these patients. Drugs should be chosen that exert only a minimal degree of cardiovascular depression [see chapter 2.1], and which have a short elimination half life so that any central nervous system or haemodynamic effect is only of relatively short duration [see appendix-A].

Acetylcholinesterase blocking drugs such as neostigmine [16], and depolarizing muscle relaxants such as suxamethonium [18], can cause a persistent generalized muscle

spasm which lasts the duration of the drug effect [16]. Such generalized spasm may make ventilation and endotracheal intubation impossible. The response of these patients to non-depolarizing neuromuscular blocking agents is normal [18,19]. Postoperative hypothermia may also cause generalized muscle spasm [16].

Patients with these disorders should be placed in an intensive care unit postoperatively for respiratory monitoring and mechanical ventilation, until muscle strength and reflexes have returned to normal.

9. Progressive muscular dystrophy (e.g. Duchenne).

Patients with progressive muscular dystrophies may have a cardiomyopathy, in addition to general immobility due to muscle weakness which also causes a degree of respiratory insufficiency and skeletal deformity [20].

General anaesthetic agents and administration of hypnotic drugs can cause further respiratory depression due to muscle relaxation, or central nervous system depression. Because of this controlled ventilation is always required during general anaesthesia.

The circulatory depressant effects of cardiodepressive drugs are exacerbated by any cardiomyopathy present. All drugs must be chosen and administered with caution, and preferably only drugs which cause minimal cardiovascular depression should be used [see chapter 2.1].

Depolarizing muscle relaxant drugs can induce myoglobinuria by causing rhabdomyolysis [20]. Suxamethonium may be associated with the occurrence of delayed respiratory insufficiency due to delayed onset of severe muscle weakness several hours after apparently good recovery from the anaesthetic during which it was administered [20].

Patients with muscular dystrophy also may be at risk of developing malignant hyperpyrexia. Some patients develop elevated temperatures, metabolic acidosis, and myoglobinuria after suxamethonium or halothane has been used during anaesthesia [20]. The use of suxamethonium or any other depolarizing neuromuscular blocking drugs should be avoided.

Postoperative admission to an intensive care unit is advisable after general anaesthesia for respiratory function monitoring, and mechanical ventilation if indicated.

ANAESTHETIC CONSIDERATIONS

The anaesthetist should always consider a number of factors when planning anaesthesia for any patient with any disorder affecting neuromuscular function.

1. General considerations.

General anaesthetic drugs usually exacerbate muscle weakness, in addition to reducing both the hypoxic and hypercapnic respiratory drives. These factors, combined with hypoventilation due to wound pain from thoracic or upper abdominal surgery may precipitate respiratory failure. Accordingly a number of precautions must be taken in the perioperative period to minimize the chances of hypoxic injury due to such effects.

a. Always make arrangements for possible postoperative mechanical ventilation in an intensive care unit.
b. Preoperative respiratory function tests must be performed so as to have an exact measure of the normal pulmonary parameters of that patient. These are used as a target to which to strive in the postoperative period.

c. Perioperative spirometry should be performed regularly. This is mainly to measure vital capacity to assess if ventilatory support is required. If the perioperative vital capacity is less than 15 mls/kg body weight mechanical ventilation is required [21, see normal values in table 4.4.1].

2. Type of anaesthesia.

a. Locoregional anaesthesia.

Assess whether loco-regional anaesthesia is possible for the planned operation. Regional anaesthesia has minimal effects on neuromuscular function, and may spare the patient admission into an intensive care unit for respiratory monitoring or mechanical ventilation.

b. General anaesthesia.

General anaesthetic drugs usually exacerbate muscle weakness, in addition to reducing the hypoxic and hypercapnic respiratory drives. These factors mean that the range of general anaesthetic techniques is restricted.

i. The patients should always be mechanically ventilated to ensure oxygenation in despite weakened respiratory muscles, and reduction of hypoxic and hypercarbic drives, all of which are exacerbated by anaesthetic drugs.

ii. If neuromuscular junction blocking drugs are used, due consideration of the type of neuromuscular disorder should be made when selecting a drug. Their effect should be monitored so that overdosage of patients who may be exceptionally sensitive to their effects may be prevented. Repeat dosages of any of these drugs should only be administered according to clinical indication, i.e. the patient moves, muscles are obviously vigorously contracting, etc. Otherwise a peripheral nerve stimulator should be used to decide whether a repeat dose is required.

iii. A good choice of general anaesthetic technique in patients without any cardiomyopathy, or in whom malignant hyperpyrexia is unlikely, is controlled ventilation of the patient using a volatile anaesthetic agent as the sole anaesthetic drug. This technique has the advantage that once the anaesthetic gas has been eliminated from the body, that the residual neuromuscular and respiratory effects of the anaesthetic are almost non-existent.

REFERENCES

1. Vaughan,R.S., Lunn,J.N.(1973). Potassium and the anaesthetist. ANAESTHESIA, 28, 118-131.
2. Bell,H., et al.(1965). Hyperkalemic Paralysis Due to Adrenal Insufficiency. ARCHIVES OF INTERNAL MEDICINE, 115, 618-620.
3. Finch,C.A., et al.(1946). Clinical Syndrome of Potassium Intoxication. AMERICAN JOURNAL OF MEDICINE, 1, 337-352.
4. Waud,B.E., Waud,D.R.(1980). Interaction of calcium and potassium with neuromuscular blocking agents. BRITISH JOURNAL OF ANAESTHESIA, 52, 863-866.
5. McMahon,M.J., et al.(1978). The nature of hypocalcaemia in acute pancreatitis. BRITISH JOURNAL OF SURGERY, 65, 216-218.
6. Drop,L.J., Miller,E.V.(1980). Biochemical Alterations during Tetany. ANESTHESIOLOGY, 52,82-83.
7. O'Dorisio,T.M., (1978). Hypercalcaemic crisis. HEART & LUNG, 7, 425-434.
8. Standaert,F.G.(1982). Release of transmitter at the neuromuscular junction. BRITISH JOURNAL OF ANAESTHESIA, 54, 131-145.
9. Ghoneim,M.M., Long,J.P.(1970). The Interaction between Magnesium and other Neuromuscular Blocking Agents. ANESTHESIOLOGY, 32, 23-27.
10. Ali,H.H., Savarese,J.J.(1976). Monitoring of Neuromuscular Function. ANESTHESIOLOGY, 45, 216-249.

11. Murkin,J.M.(1982). Anesthesia and Hypothyroidism: A Review of Thyroxine Physiology, Pharmacology, and Anesthetic Implications. ANESTHESIA AND ANALGESIA, 61, 371-383.
12. Stehling,L.C.(1974). Anesthetic Management of the Patient with Hyperthyroidism. ANESTHESIOLOGY, 41, 585-595.
13. Whittaker,M.(1980). Plasma cholinesterase variants and the anaesthetist. ANAESTHESIA, 35, 174-197.
14. Fraser,A., Edmonds-Seal,J.(1982). Spinal cord injuries: A review of the problems facing the anaesthetist. ANAESTHESIA, 37, 1084-1098.
15. Moorthy,S.S., Hilgenberg,J.C.(1980). Resistance to Non-depolarizing Muscle Relaxants in Paretic Upper Extremities of Patients with Residual Hemiplegia. ANESTHESIA AND ANALGESIA, 59, 624-627.
16. Mudge,B.J., et al.(1980). Perioperative hazards in myotonic dystrophy.ANAESTHESIA, 35, 492-495.
17. Meyers,M.B., Barash,P.G.(1976). Case History Number 90: Cardiac Decompensation During Enflurane Anesthesia in aPatient with Myotonia Atrophica. ANESTHESIA AND ANALGESIA,55, 433-435.
18. Mitchell,M.M., et al.(1978). Myotonia and Neuromuscular Blocking Agents. ANESTHESIOLOGY, 49, 44-48.
19. Stirt,J.A., et al.(1985). Atracurium in a Child With Myotonic Dystrophy. ANESTHESIA AND ANALGESIA, 64, 369-370.
20. Smith,C.L., Bush,G.H.(1985). Anaesthesia and progressive muscular dystrophy. BRITISH JOURNAL OF ANAESTHESIA, 57, 1113-1118.
21. Feeley,T.W., Hedley-Whyte,J.(1975). Weaning from controlled ventilation and supplemental oxygen. NEW ENGLAND JOURNAL OF MEDICINE, 292, 903-906.
22. Wainright,A.P., Brodrick,P.M.,(1987), Suxamethonium in myasthenia gravis. ANAESTHESIA, 42, 950-957.

Chapter 8.6

BARORECEPTOR REFLEXES & ANAESTHESIA

The autonomic nervous system is of vital importance in the maintenance of cardiovascular homeostasis. Autonomic nervous system dysfunction or neuropathy, especially baroreceptor reflex deficiency, has a profound effect on the reaction of the body to anaesthesia, trauma, and surgery.

BARORECEPTOR REFLEXES

The function of the baroreflexes is to maintain adequate blood pressure and cardiac output in the face of changing degrees of vascular filling and vasoconstriction [15,18]. The efferent loop of the baroreflexes is the autonomic nervous system, and this affects systemic haemodynamic function by varying the myocardial contractility, heart rate (**HR**), stroke volume (**SV**) and systemic vascular resistance (**SVR**). These three factors are related as is shown by the formula below.

$$\textbf{MABP} = \textbf{HR} \times \textbf{SV} \times \textbf{SVR}$$

[see table 2.0.1 for method of calculation of **MABP**].

The most important functions of the baroreflexes are listed below.

1. Response to hypovolaemia.

Hypovolaemia reduces intravascular and intracardiac pressures, activating baroreflex activity. The effector side of the baroreflexes is the autonomic nervous system which increases the heart rate, myocardial contractility, and elevates the systemic vascular resistance. This response maintains mean arterial blood pressure and cardiac output until the blood volume is reduced by about 15% or more below its normal volume [see chapter 14.4 on hypovolaemia].

2. Response to vasoconstrictor drugs.

Administration of a vasoconstrictor drug to normovolaemic patients elevates intravascular pressures and causes a baroreflex mediated bradycardia which reduces the cardiac output [see table 2.2.1].

3. Response to vasodilator drugs.

Vasodilator drugs decrease intravascular pressures and cause a baroreceptor mediated elevation of heart rate. This response increases cardiac output and maintains arterial blood pressure.

4. Positive inotropic effect.

Baroreflexes increase sympathetic nervous system activity, which has a positive inotropic effect, increasing myocardial contractility and stroke volume for a given degree of vascular filling.

Table 8.6.1.
Cardiovascular actions of the autonomic nervous system.

ORGAN	SYMPATHETIC (Action and receptor types)	PARASYMPATHETIC
HEART		
	Tachycardia (β1)	Bradycardia (muscarinic)
	Positive inotropy (β1)	Negative inotropy (muscarinic)
	Increased automaticity (β1)	Decreased automaticity (muscarinic)
BLOOD VESSELS		
Coronary	Dilation (β1) Constriction (α1)	Dilation (muscarinic)
Pulmonary	Dilation (β2) Constriction (α1)	Dilation (muscarinic)
Systemic (veins and arteries)	Dilation (β2) Constriction (α1)	Dilation (muscarinic)

PERIPHERAL NEUROANATOMICAL SUBSTRATE OF BAROREFLEXES

The afferent as well as efferent limbs of the baroreflexes are mediated by nerve fibers in the autonomic nervous system.

1. Afferent fibers of the baroreceptor reflexes.

a. Activation of afferent fibers.

Some of the fibers in autonomic nerves are baroreceptor afferent fibers. These originate in stretch receptors located in large veins, arteries, pulmonary vessels, cardiac atria and ventricles. These stretch receptors are stimulated by stretching of the fibers in the walls of the structures in which they are present. This occurs under a number of conditions.

i. Hypovolaemia reduces pressures in the cardiovascular system. Stretch receptor fibers are not stretched, or stimulated as normal, and the baroreflexes are activated. Hypervolaemia has the reverse effect.
ii. Administration of vasodilator drugs has the same effects as hypovolaemia, a reduction of the tension on stretch receptors in the walls of the cardiac chambers. Vasoconstrictor drugs have the reverse effect.
iii. Intermittent positive pressure ventilation, especially when combined with positive end expiratory pressure, compresses the cardiac chambers and large intrathoracic vessels, tending to collapse them. This reduces the degree of stretch in the stretch receptors in the walls of these structures, and activates the baroreflexes.

b.Locations of stretch receptor fibers.

Some knowledge of the anatomical locations of the stretch receptors is of use in predicting the effects of various maneuvers or operations. An example of this is that of patients who have undergone carotid endarterectomy. Postoperatively these patients frequently develop a very high arterial blood pressure. This is thought to be due to surgical destruction of carotid baroreceptor nerves, producing an effect similar to the lack of stimulation of these nerves by hypovolaemia.

The precise anatomical locations of baroreflex afferent fibers are listed below.

i. At the junctions of the superior and inferior vena cava with the right atrium.
ii. At the junctions of the pulmonary veins with the left atrium.
iii. The left ventricle.
iv. Pulmonary artery and pulmonary vein.
v. Arterial baroreceptor locations [18].

- In the aortic arch at the origins of the brachiocephalic artery and left subclavian artery, (vagus nerves).
- In the brachiocephalic artery at its bifurcation into the right carotid and subclavian arteries.
- In the carotid sinuses which are found at the bifurcation of the carotid arteries into the internal and external carotid arteries, (glossopharyngeal nerves).
- Along both common carotid arteries.

2. Efferent component of the baroreceptor reflexes.

The efferent loop of the baroreflexes are the sympathetic and parasympathetic fibers of the autonomic nervous system. Cardiovascular actions of the autonomic nervous system are listed in table 8.7.1.

CAUSES OF BAROREFLEX DYSFUNCTION

Most conditions causing dysfunction of the autonomic nervous system also cause depressed baroreflex function.

1. Age.

The efficacy of the baroreflexes declines with advancing age. Most of the age related function decrease has occurred by 50-60 years of age [1].

2. Disease.

a. Congenital diseases.

Congenital diseases such as familial dysautonomia and other inherited autonomic nervous system disorders are associated with abnormal baroreflexes.

b. Central nervous system disorders.

Diseases such as syringomyelia, multiple sclerosis, tabes dorsalis, and subacute combined sclerosis can all affect autonomic nervous system and baroreflex function.

c. Diabetes mellitus.

About 20-30% of elderly diabetic patients have some degree of autonomic neuropathy and deficient baroreflex function [2].

d. Hypertension.

Chronic arterial hypertension is frequently associated with deficient baroreflex function [3,4].

e. Hypothyroidism.

Most, if not all, clinically myxedemic patients have deficient baroreflexes [26].

f. Heart failure.

Patients with chronic heart failure have a reduced heart rate response to sympathetic stimulation and physical exertion [28,29]. That is, they have deficient baroreflex function.

3. Drugs.

Most drugs currently employed for the treatment of arterial hypertension inhibit or block the function of one or more parts of the sympathetic nervous system. Some of these drugs, e.g. the ß-adrenoreceptor blocking drugs, alpha-methyldopa, ganglion blockers, reserpine, labetalol, and prazocine [5], have all been shown to depress baroreflex function.

4. Anaesthetic drugs.

Most drugs used for general anaesthesia depress baroreflex function. This is either due to a non-specific central nervous system depression or ganglion blockade.

a. Hypnotic drugs.

Thiopentone [6], althesin [8], diazepam [9,10], and midazolam [10] all depress baroreflex function in humans, an effect also observed as a result of methohexital administration to cats [7], and pentobarbital to dogs [15]. Baroreflex depression is most likely a property common to all hypnotic drugs due to the central nervous system depression

they cause. One exception is ketamine which actually increases central nervous system activity, in addition to increasing the plasma noradrenaline concentration [11].

b. Anaesthetic gases.

Nitrous oxide [12], halothane [13], isoflurane [14], and enflurane [12], have all been shown to depress baroreflex function in humans. This may be a property common to all general anaesthetic gases because of the central nervous system depression that they cause. One exception to this rule may well be diethyl-ether which actually increases sympathetic nervous activity, elevating the plasma noradrenaline concentration in direct proportion to the diethyl-ether concentration administered [16].

c. Muscle relaxant drugs.

In addition to the neuromuscular junction blockade which is the reason for using these drugs, some of these drugs also can cause a degree of autonomic nervous system ganglionic blockade.

D-tubocurarine produces a clinically significant degree of autonomic ganglionic blockade which is maximal at a dosage within the usual clinical range of about 0.5 mg/kg body weight [17]. It is the muscle relaxant drug causing the greatest degree of ganglionic blockade. A related drug metocurine produces a lesser degree of blockade [17].

Gallamine, alcuronium, pancuronium, atracurium, and vecuronium cause no significant degree of ganglionic blockade when used in clinically employed dosages [17]. In contrast to the above, suxamethonium, a depolarizing neuromuscular junction blocking drug, is a weak ganglionic stimulant [17].

d. Opiates.

Little to no investigation has been performed on the effects of opiates on baroreflex function.

DIAGNOSIS OF DEPRESSED BARORECEPTOR FUNCTION [27]

Diagnosis is based on clinical suspicion which may then be confirmed by a variety of simple clinical tests that the anaesthetist may carry out at the bedside to confirm the diagnosis.

1. Clinical suspicion and history.

If a person is elderly, or has any disease associated with defective baroreflex function, then the anaesthetist should suspect some degree of baroreflex dysfunction.

Specific enquiry as to symptoms which are typical manifestations of deficient baroreflexes should be made. Enquire as to the occurrence of;

- syncope or dizziness while straining on the toilet,
- postural, or orthostatic hypotension, postural syncope,
- persistent tachycardia or bradycardia,
- peripheral oedema.

2. Tests of parasympathetic function.

Cardiac parasympathetic fibers control the beat-to-beat regulation of heart rate, i.e. the R-R interval. The simplest test of abnormal parasympathetic function is to look for the presence of sinus arrhythmia.

Normally the heart rate varies during the respiratory cycle. But the heart rate of persons with deficient baroreflexes does not vary, or varies only minimally. In normal persons, the variation of heart rate is most pronounced during slow inspiration and expiration. The variation in heart rate may be detected by feeling the pulse, or better yet, observing the ECG during several slow respirations. At a respiratory rate of six breaths per minute, a 15 beats/minute variation of heart rate is normal. A heart rate variation of less than 10 beats/minute is abnormal.

3. Tests of sympathetic function.

Regrettably sympathetic nervous system function cannot be tested separately. But tests of integrated cardiovascular responses in which the sympathetic nervous system reflexes play an essential role are possible.

One such test is the lying-to-standing blood pressure and heart rate changes. The patient rests in bed for some time and then is requested to stand. Prior to standing, and immediately after standing, both the systolic blood pressure and the heart rate are measured. Normally the systolic blood pressure falls less than 30 mmHg. Changes greater than this cause clinical symptoms, and are indicative of deficient baroreflex function. Immediately on standing the heart rate increases. This does not occur in patients with deficient baroreceptor reflexes. Heart rate changes may be measured with a finger on the pulse, but ECG monitoring is more accurate.

PROBLEMS DUE TO DEPRESSED BAROREFLEX FUNCTION

1. Reaction to position changes.

Sudden alterations of body position, e.g. from lying to standing, as well as some positions such as prolonged standing, or the antitrendelenberg position, can cause hypotension in persons with deficient baroreflex function. As is to be expected by the above discussion, general anaesthesia further exacerbates this problem.

2. Reaction to hypovolaemia.

Hypovolaemia reduces the pressure in all parts of the cardiovascular system. Normally this causes a baroreflex mediated increase of heart rate, myocardial contractility, and systemic vascular resistance, all of which tends to maintain a normal arterial blood pressure and cardiac output [18]. Canine experiments have shown that the reduction of blood pressure with increasing percentage loss of circulating blood volume is three times greater in dogs whose carotid and aortic baroreceptors are denervated, than in dogs in whom the receptor innervation is intact [15]. This correlates well with the clinical observation that patients with deficient baroreflex function or autonomic neuropathy tolerate hypovolaemia poorly, becoming hypotensive at a smaller percentage circulating volume deficit than normal patients. General anaesthesia further exacerbates this problem.

3. Reaction to spinal and epidural anaesthesia.

Both epidural and spinal anaesthesia cause autonomic afferent and efferent nervous blockade in the segments blocked by the regional anaesthetic technique

employed. Vasodilation in the blocked region increases the volume of the vascular system relative to the blood volume, causing a relative hypovolaemia [see chapter 14.4]. Because of the relative hypovolaemia, plus the loss of the ability to constrict the blood vessels in the blocked region of the body, patients under spinal and epidural anaesthesia become more hypotensive for a given degree of blood loss than patients who do not undergo such an anaesthetic technique [see chapter 14.4].

Patients with deficient baroreflexes may be expected to develop a more profound hypotension in response to these forms of anaesthesia, as neither the vascular resistance in the unblocked regions of the body, nor the heart rate can be elevated sufficiently to maintain the arterial blood pressure by the remaining defective baroreflex function.

4. Reaction to general anaesthetic drugs.

Most general anaesthetic drugs depress the baroreflexes. Administration of any such drugs will of course exacerbate any existing baroreflex deficit. Clinically this is observed as a rather more pronounced drop of blood pressure due to general anaesthesia than would normally occur, together with a minimal change in heart rate during events likely to produce this, e.g. hypovolaemia, induction of anaesthesia, pain etc.

5. Reaction to controlled ventilation.

Controlled ventilation using intermittent positive pressure ventilation (IPPV), causes a reversal of the normal pattern of venous return. During spontaneous respiration venous return is greatest during inspiration, as this is the time when the intrathoracic pressure is lowest. Cardiac output is highest at the beginning of expiration when the intrathoracic pressure increases left atrial filling by forcing blood out of the pulmonary vessels.

IPPV reverses this pattern. Most venous return occurs during expiration as it is at this time that the intrathoracic pressure is at its lowest during the respiratory cycle, and the peak cardiac output occurs at the beginning of inspiration [19]. Cardiac output during IPPV is lower than that occurring during spontaneous respiration, the output being inversely proportional to the respiratory minute volume [20]. The reason is simple. IPPV elevates the mean intrathoracic pressure, and this reduces venous return. The greater the minute volume, the greater the mean intrathoracic pressure, and so the less the venous return, and hence cardiac output. Continuous positive pressure ventilation (CPPV), that is IPPV with positive end expiratory pressure (PEEP), decreases the cardiac output even further, cardiac output being inversely proportional to the level of PEEP applied [21,22,23].

Venous return during IPPV is maintained by venous constriction. During inspiration, blood accumulates in the veins, as entry into the thorax is limited by elevated intrathoracic pressure. The veins distend elastically, and the intravenous pressure rises. During expiration the veins empty like full balloons, forcing the blood into the thorax. The rate of rise of venous pressure, and the pressure attained is a function of the venous constrictor tone. If there is a degree of venous constriction, the elevation of intravenous pressure per unit volume of blood entering the veins will of course be high. During IPPV, venous constrictor tone is elevated. This is because the elevated intrathoracic pressure decreases intrathoracic vascular and cardiac transmural pressure gradients, reducing the degree of stretch of the baroreceptors, increasing afferent baroreceptor fiber activity, which causes venous constriction. The latter enhances venous return, so that it is maintained during IPPV.

Loss of this manifestation of the baroreflexes (sometimes called the "Valsalva reflex"), causes hypotension and low cardiac output in affected patients when IPPV is commenced. This occurs in all those whose baroreflexes have been inhibited by massive drug overdosage,

those with deficient baroreflexes due to disease, patients who have been administered vasodilator drugs, extremely deep general anaesthesia, etc.

6. Reaction to vasoactive drugs.

The normal baroreflex response to administration of vasodilator drugs is to cause a tachycardia, and the reverse occurs after administration of vasoconstrictors. These effects are modified by administration of sympathetic nervous system blocking drugs, and disorders affecting the autonomic nervous system.

Sympathetic dennervation, sympathetic nervous system degeneration, or administration of drugs which block the release of noradrenaline from the sympathetic nerve terminals (e.g. guanethidine, reserpine, alpha-methyldopa etc), causes the concentration of postsynaptic adrenergic receptors to increase [24]. Hypersensitivity to the effects of adrenoreceptor stimulating drugs occurs in situations where the number of postsynaptic adrenergic receptors is increased, but not blocked by any drug. This accounts for the greater response of hypertensive [25] and diabetic patients to catecholamines, in particular to vasoconstrictors.

ANAESTHETIC MANAGEMENT

Preoperative.

1. The anaesthetist should always suspect the presence of deficient baroreflexes in susceptible categories of patients.

2. Correct any preoperative hypovolaemia. This will exacerbate the deleterious haemodynamic effects of existing baroreflex function deficits.

Anaesthesia.

1. Maintain normovolaemia.

2. Spinal and epidural anaesthesia should only be administered on indication, as these two regional anaesthetic techniques will cause a greater than usual degree of hypotension in patients with deficient baroreflexes. Other forms of regional anaesthesia are not contraindicated.

3. Some points are worthy of mention when considering general anaesthesia of patients with deficient baroreflexes.

a. IPPV, and especially PEEP, may cause hypotension. For this reason, use low ventilation pressures, so as to minimally impede venous return.
b. Only use drugs which cause minimal cardiovascular depression [see chapter 2.1].

4. Administer vasoconstrictor or inotropic drugs as required.

Postoperative.

Postoperative care depends on the nature of the surgery performed and the condition of the patient.

REFERENCES

1. Duke,P.C., et al.(1976). The effects of age on baroreceptor reflex function in man. CANADIAN ANAESTHETISTS' SOCIETY JOURNAL, 23, 111-124.
2. Clarke,B.F., et al.(1979). Diabetic autonomic neuropathy. DIABETOLOGIA, 17, 195.
3. Sleight,P.(1979). Reflex control of the heart. AMERICAN JOURNAL OF CARDIOLOGY, 44, 889-894.
4. Mancia,G., et al.(1979). Control of blood pressure by carotid sinus baroreceptors in human beings. AMERICAN JOURNAL OF CARDIOLOGY, 44, 895-902.
5. Mancia,G., et al.(1980). Methyldopa and neural control of the circulation in essential hypertension. AMERICAN JOURNAL OF CARDIOLOGY, 45, 1237-1243.
6. Joyce,J.T. et al.(1983). Effect of thiopentone induction on sympathetic activity. ANESTHESIOLOGY, 59, 19-22.
7. Skovsted,P., et al.(1970). The effects of short-acting barbiturates on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. ANESTHESIOLOGY, 33, 10-18.
8. Jones,D.F., Prys-Roberts,C.(1983). Baroreflex effects of althesin infusions to supplement nitrous oxide anaesthesia in man. BRITISH JOURNAL OF ANAESTHESIA, 55, 849-853.
9. Kotrly,K.J., et al.(1984). Baroreceptor reflex control of heart rate during morphine sulphate, diazepam, N_2/O_2 anesthesia in humans. ANESTHESIOLOGY, 61, 558-563.
10. Marty,J., et al.(1986). Effects of diazepam and midazolam on baroreflex control of heart rate and sympathetic activity in humans. ANESTHESIA AND ANALGESIA, 65, 113-119.
11. Baraka,A., et al.(1973). Catecholamine levels after ketamine anesthesia in man. ANESTHESIA AND ANALGESIA, 52, 198-200.
12. Morton,M., et al.(1980). Baroreflex control of heart rate in man awake and during enflurane and enflurane - nitrous oxide anesthesia. ANESTHESIOLOGY, 52, 221-223.
13. Duke,P.C., Trosky,S.(1980). The effect of halothane with nitrous oxide on baroreflex control of heart rate in man. CANADIAN ANAESTHETISTS' SOCIETY JOURNAL, 27, 531-534.
14. Kotrly,K.J., et al.(1984). Baroreceptor control of heart rate during isoflurane anesthesia in humans. ANESTHESIOLOGY, 60, 173-179.
15. Vatner,S.F., Braunwald,E.(1975). Cardiovascular control mechanisms in the conscious state. NEW ENGLAND JOURNAL OF MEDICINE, 293, 970-976.
16. Black,G.W., et al.(1969). Circulatory catecholamines and some cardiovascular, respiratory, metabolic and pupillary responses during diethyl-ether anaesthesia. ANAESTHESIA, 24, 168.
17. Bowman,W.C.(1982). Non-relaxant properties of neuromuscular blocking drugs. BRITISH JOURNAL OF ANAESTHESIA, 54, 147-160.
18. Kircheim,H.R.(1976). Systemic arterial baroreceptor reflexes. PHYSIOLOGICAL REVIEWS, 56, 100-176.
19. Jardin,F., et al.,(1983), Cyclic changes in arterial pulse during respiratory support. CIRCULATION, 68, 266-274.
20. Prys-Roberts,C., et al.(1968). Hemodynamics and alveolar-arterial PO_2 differences at varying P_aCO_2 in anaesthetized man. JOURNAL OF APPLIED PHYSIOLOGY, 25, 80-87.
21. Kumar,A., et al.(1970). Continuous positive pressure ventilation in acute respiratory failure. Effects on hemodynamics and lung function. NEW ENGLAND JOURNAL OF MEDICINE, 283, 1430-1436.
22. Elbuns,R.C., et al.(1974) > Clinical hemodynamic and respiratory responses to graded positive end-expiratory pressure. SURGICAL FORUM, 25, 226-229.
23. Colgan,F.J., Marocco,P.P.(1972). The cardiorespiratory effects of constant and intermittent positive pressure breathing. ANESTHESIOLOGY, 36, 444-448.
24. Maze,M.(1981). Clinical implications of membrane receptor function in anesthesia. ANESTHESIOLOGY, 55, 160-171.
25. Goldstein,D.S., et al.(1982). Comparison of techniques for measuring baroreflex sensitivity in man. CIRCULATION, 66, 432-439.
26. McBrien,D.J., Hindle,W.(1963). Myxoedema and heart failure. LANCET, 1, 1066-1068.
27. Campbell,I.W., et al.,(1980), The quantification of diabetic autonomic neuropathy and its clinical significance. In "New Approaches to Insulin Therapy", edited Irsigler,K., et al, published MTP Press Ltd, pages 425-436.
28. Rutenberg,H.L., Spann,J.F.,(1973), Alterations of cardiac sympathetic neurotransmitter activity in congestive cardiac failure. AMERICAN JOURNAL OF CARDIOLOGY, 32, 472-480.
29. Zelis,R., et al.,(1973), Peripheral circulatory control mechanisms in congestive heart failure. AMERICAN JOURNAL OF CARDIOLOGY, 32, 481-490.

Part 9

RENAL DYSFUNCTION

Abnormal renal function can profoundly affect the reaction of a patient to surgery and anaesthesia. However nothing can be done to cure existing renal dysfunction in the perioperative period, but much can be done to prevent further deterioration of renal function, and to minimize the detrimental effects of anaesthesia and surgery on renal function.

This section discusses those aspects of renal dysfunction which are relevant to perioperative management.

1. Clinical assessment of renal function.

2. Effects of surgery and anaesthesia on renal function.

3. Recognition and management of imminent, or developing renal dysfunction.

4. Perioperative management of the patient with existing renal failure.

Chapter 9.1

ASSESSMENT OF RENAL FUNCTION

A good working knowledge of the clinical assessment of renal function is of considerable use for effective perioperative management of patients with renal disease. Renal function is usually assessed by measurement of urine output, specific gravity, and osmolality, as well as plasma creatinine and urea concentrations and clearances.

URINE OUTPUT

The main function of kidneys is to eliminate non-volatile waste products from the body by excreting them in aqueous solution. The normal adult human urine output is about 1500 mls/day, which for the "average" adult is a urine production of about 70+ mls/hour, or about 1+ ml/kg/hour. Oliguria is defined as a urine production less than 0.5 ml/kg/hour.

Urinary water loss is minimized by renal concentration of urinary solutes. As urine cannot be infinitely concentrated, a given daily urinary solute load can only be excreted in a minimum volume of urine. If the daily urine volume is less than the minimum required to excrete this solute load, these solutes accumulate in the body, (principally ammonium chloride, urea, uric acid, sodium chloride, potassium chloride, and creatinine). The maximum urinary concentration possible for most persons with normal renal function is 1400 mosm/l, and so the minimum daily volume of urine required to excrete a given daily urine solute load is given by equation 1 [8].

$$\underset{\text{(mls/day)}}{\text{Minimum urine output}} = 0.714 \times \underset{\text{(mosm/day)}}{\text{Solute production}} \quad \text{...(1)}$$

The average daily solute production and associated minimum daily urine volume for "average adults" under various conditions are shown in table 9.1.1. This table also shows the considerable reduction of urinary solute production caused by rest and fasting. In addition it shows the efficacy of glucose ingestion in reducing protein metabolism, and hence in reduction of the production of the products of protein catabolism, (urea, ammonia), which are all excreted in the urine. However it should be noted that the "protein sparing" effect of glucose infusions is absent after major surgery, trauma or sepsis [9,10].

A daily urine production of 500 mls/day (20 mls/hour) is usually considered a minimum diuresis for adults who have undergone major surgery or trauma, and who are septic.

Table 9.1.1.
Average daily solute production and minimum urine production for "average" adults under various circumstances [8].

	Solute production (mosm/day)	Minimum urine volume (mls/day)
Average activity level, diet, and water intake	1200	860
Resting, no food, and only water to drink	730	520
Resting, no food but for 100 gms glucose/day, plus water to drink	312	223

URINE SPECIFIC GRAVITY & OSMOLALITY

The specific gravity (SG) of urine gives a measure of the total amount of solute in the urine. In the normal adult the urine SG may vary between 1.003 to 1.040 gm/ml urine.

The urine osmolality is also a measure of the total solute content of the urine, the normal range being between 900 - 1400 mosm/l urine.

The urine osmolality and SG are related, and urine osmolality may be calculated approximately from the SG using equation 2 [1].

$$\text{Urine Osmolality(mosm/l)} = \frac{1000 \times [\text{SG(gm/ml)} - 1]}{0.0318} \quad \text{.....(2)}$$

There is a diurnal variation in the rate of urine production, more urine being produced when awake than when asleep. A diurnal variation of the urinary SG and osmolality also occurs, both increasing when the urine production falls, and vice versa.

A typical feature of renal failure is loss of the ability to concentrate urine. Because of this there is no diurnal change in urinary concentration, and the urine that is produced has the same SG and osmolality as deproteinated plasma. The SG in persons with renal failure remains constant at about 1.010 g/ml, and the osmolality at about 281-297 mosm/l.

CREATININE AND UREA CONCENTRATIONS AND CLEARANCES

1. Urea [2].

Urea enters the urine in the glomerular filtrate. There is usually a constant fractional absorbtion of urea in the tubules. Accordingly the plasma urea concentration provides some idea of the glomerular function. But the renal handling of urine varies, fractional tubular urea resorbtion varies with renal disease, and the urine production. Because urea is one of the end products of protein metabolism and is synthesized in the liver, severe liver disease results in a diminished urea production, and a low plasma urea concentration. Low dietary intake of proteins also causes the plasma urea concentration to be low.

This places a number of limitations on the use of urea as a measure of renal function. While plasma urea concentration does correlate reasonably well with the presence of uraemic encephalopathy symptoms, it does not always give an accurate idea of the renal function. The same considerations apply to the urea clearance.

2. Creatinine.

Creatinine is a product of creatine phosphate metabolism in muscle. The production of creatinine is relatively constant and is minimally dependent upon the level of muscular activity or protein intake and catabolism. But creatinine production is directly related to the muscle mass, muscular persons having a higher plasma creatinine concentration than non-muscular [2].

a. Plasma creatinine concentration.

Excretion of creatinine is almost exclusively through the glomeruli, with only minimal tubular secretion occurring, and no absorbtion. The plasma concentration under STEADY STATE CONDITIONS is therefore a true reflection of the balance between creatinine production and the glomerular filtration rate. Under these conditions, a halving of glomerular filtration rate is associated with a doubling of the plasma creatinine concentration [2].

Plasma creatinine concentration is not a true reflection of glomerular function under some common clinical circumstances.

- During acute change of glomerular function the plasma creatinine concentration does not correlate well with the reduction of glomerular filtration, as it takes time for a new equilibrium between production and excretion to occur [2,3].
- Plasma creatinine concentration is also not a true reflection of glomerular function in the wasted, elderly, bedridden patient. The plasma creatinine concentration may be normal, despite quite abnormal glomerular function, as the muscle mass of these patients is so reduced that only small amounts of creatinine are produced.

b. Creatinine clearance.

For the above reasons, the creatinine clearance is the better estimate of glomerular filtration rate. Because of the inaccuracy and sometimes difficulties associated with the collection of the urine required for determination of the endogenous creatinine clearance, formulae have been devised for calculation of the creatinine clearance from the plasma creatinine concentration. These formulae are obviously only valid under steady state conditions with relatively constant glomerular function. One such formula is equation 3. This

formula is for calculation of the creatinine clearance in males, the value for females being 15% less than that calculated for males [4].

$$Cr_C = \frac{(140 - AGE) \times WEIGHT}{0.814 \times [Cr]_P} \quad .....(3)$$

Normal range for creatinine clearance is 80-120 mls/minute.
Cr_C = Urinary creatinine clearance in mls/minute.
$[Cr]_P$ = plasma creatinine concentration in mmol/l.
AGE = age of patient in years.
WEIGHT = body weight of patient in kg.

ASSESSMENT OF RENAL FUNCTION IN ACUTE SITUATIONS

The situation frequently arises during the management of acutely ill patients that it is desirable to rapidly assess the degree of any possible renal function impairment.

1. Urine production.

In present day clinical practice the urine production rate is used as the cardinal indicator of hour to hour changes of renal function. But this is not always accurate, as non-oliguric renal failure is a well recognized clinical entity. Clinical studies have shown that about 40% of patients with acute renal failure due to trauma, rhabdomyolysis, hypovolaemic hypotension, low cardiac output, or postoperative renal failure, have non-oliguric renal failure [5,6]. Obviously, while oliguria and anuria are good indicators when present, the absence of oliguria does not mean that the renal function is not impaired.

2. Plasma urea and creatinine concentrations.

At least one day must elapse before any significant elevation of either the plasma creatinine or urea occurs as a result of sudden total loss of renal function. It is obvious that relying on these parameters is of no use in acute situations where it is desired to measure the change of renal function on a nearly hour-to-hour basis.

3. Creatinine clearance.

Of the tests mentioned above, only the 1-2 hour creatinine clearance provides a rapid and accurate measure of glomerular function [7]. The performance of a 1-2 hour creatinine clearance does require that the patient have a urinary catheter in-situ for accurate urine collection. Creatinine clearance is then calculated using the usual formula for urinary creatinine clearance, equation 4.

$$Cr_C = \frac{[Cr]_U \times V_U}{[Cr]_P \times Time} \quad .....(4)$$

Normal creatinine clearance is 80-120 mls/minute.
Cr_C = urinary creatinine clearance in mls/minute.
$[Cr]_U$ = urinary creatinine concentration in mmol/l.

$[Cr]_P$ = plasma creatinine concentration in mmol/l.
Time = duration of urine collection in minutes.
V_U = volume of urine sampled in the collection time in mls.

REFERENCES

1. Mertz,D.P.,(1963), Untersuchungen uber den Harnkonzentrierungsmechanismus wahrend Hydropenie. ZEITSCHRIFT FUR KLINISCHE MEDIZIN, 157, 517-528.
2. Kassirer,J.P.(1971). Clinical evaluation of kidney function - glomerular filtration. NEW ENGLAND JOURNAL OF MEDICINE, 285, 385-389.
3. Enger,E., Blegen,E.M.,(1964). The relationship between endogenous creatinine clearance and serum creatinine in renal failure. SCANDINAVIAN JOURNAL OF CLINICAL & LABORATORY INVESTIGATION. 16, 273-280.
4. Cockroft,D.W., Gault,M.H.(1976). Predicition of creatinine clearance from serum creatinine. NEPHRON, 16, 31-41.
5. Anderson,R.J., et al.,(1977), Nonoliguric acute renal failure. NEW ENGLAND JOURNAL OF MEDICINE, 296, 1134-1138.
6. Shin,B., et al.,(1979), Postoperative renal failure in trauma patients. ANESTHESIOLOGY, 51, 218-221.
7. Shin,B., et al.,(1986), Creatinine clearance for early detection of post-traumatic renal dysfunction. ANESTHESIOLOGY, 64, 605-609.
8. Gamble,J.L., Butler,A.M.,(1944), Measurement of the renal water requirement. TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, 58, 157-161.
9. Blackburn,G.L., et al.(1973), Protein sparing therapy during periods of starvation with sepsis or trauma. ANNALS OF SURGERY, 177, 588-594.
10. Freeman,J.B., et al.(1977), The current status of protein sparing. SURGERY, GYNECOLOGY & OBSTETRICS, 144, 843.

Chapter 9.2

EFFECTS OF ANAESTHESIA AND SURGERY ON RENAL FUNCTION

Both anaesthesia and surgery may have a marked effect on renal function. These effects may adversely affect renal function, and must be taken into account when administering anaesthesia to patients with already compromised, or threatened renal function. Every effort must be made to prevent further deterioration of renal function, or renal failure.

EFFECTS OF TRAUMA AND SURGERY

1. Redistribution of blood flow.

Trauma, surgery, and hypovolaemia all increase sympathetic nervous system activity which causes a redistribution of intrarenal blood flow. While the total renal blood flow may decrease or remain the same, blood flow to the cortical regions decreases relative to the medullary blood flow [1,2]. This is called "cortico-medullary shunting" [2]. Cortical nephrons constitute about 60% of the nephrons, and have short loops of Henle. They are not able to concentrate urine to the same degree as the juxtamedullary nephrons which have long loops of Henle and vasa rectae which extend deep into the renal papillae. Accordingly the result of a relative decrease of cortical blood flow is a reduction of urine output and sodium retention. Evidence that perioperative sodium retention is most likely to be due to increased sympathetic nervous system activity, is provided by the fact that perioperative sodium, but not water retention, is reversed by epidural anaesthesia sufficient to block the renal sympathetic nerves which arise from thoracic spinal roots T_{10}-T_{12} [2].

2. Hormonal secretion.

a. Increased adrenal hormone secretion.

Trauma and surgery increase adrenal secretion of glucocorticoids, aldosterone, and catecholamines. The net effect of this is sodium and water retention with increased potassium excretion.

b. Antidiuretic hormone (ADH) secretion.

Trauma and surgery greatly increases the secretion of ADH, an effect which is unrelated to the presence or absence of hypovolaemia, as it is unable to be influenced even with relatively large degrees of fluid loading [3]. Increased ADH secretion causes retention of water only. Some proof that perioperative water retention is hormonally caused, most likely due to the increased ADH secretion, is furnished by the observation that perioperative water retention is unable to be reversed with epidural anaesthesia sufficient to block the renal sympathetic nerves and reverse perioperative sodium retention [2].

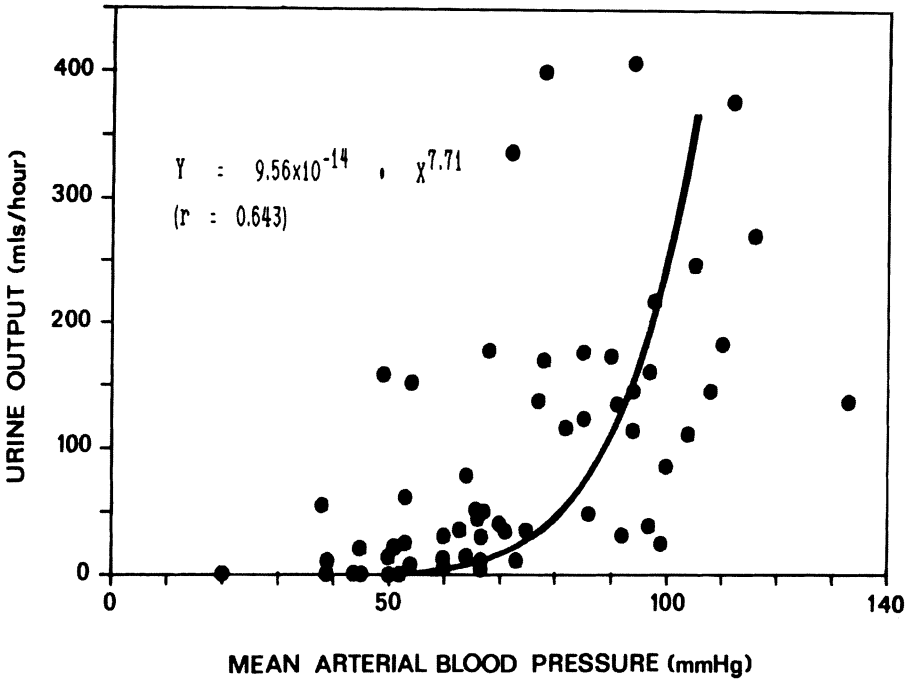

FIGURE 9.2.1. - Urine output is related to the mean arterial blood pressure in normal patients, head injured patients, hypovolaemic patients, and patients in cardiogenic shock. The data are derived from Lauson,H.D., et al.,(1944) [4], and Mir,M.A., et al.,(1974) [19].

3. Hypotension, hypovolaemia, & renal circulatory arrest.

Urine output is directly related to the glomerular filtration rate. This in turn is a function of the glomerular filtration pressure, i.e. the pressure difference between the glomerular capillaries and Bowman's capsule.

$$P_{GF} = P_{GC} - P_{BC} - COP$$

P_{GF} = glomerular filtration pressure in mmHg.
P_{GC} = mean glomerular capillary pressure in mmHg.
P_{BC} = Bowman's capsule pressure in mmHg.
COP = colloid osmotic pressure in mmHg.

As the human COP is normally about 25 mmHg and the Bowman's capsular pressure is estimated to be about 10-15 mmHg [9], glomerular filtration and urine production in humans will theoretically cease at a mean blood pressure of about 40 mmHg, and will increase in direct proportion to any increase of blood pressure above this. Indeed it has been found that urine output in humans ceases when the mean arterial blood pressure (MABP)

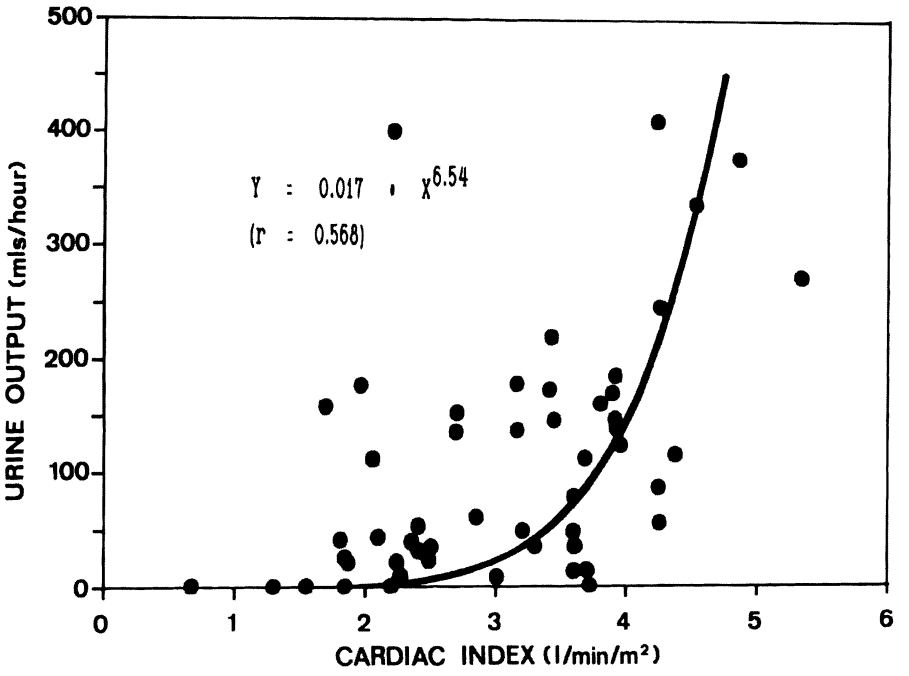

FIGURE 9.2.2. - Urine output is related to the cardiac index of normal patients, head injured patients, and patients with hypovolaemia of varying degrees. The data are derived from Lauson, H.D., et al.,(1944) [4].

falls below 40-50 mmHg, or the cardiac index falls below 1.8 l/min/m^2 [4]. Urine output increases in direct proportion to the blood pressure above an MABP of 45 mmHg, or a cardiac index above 1.8 l/min/m^2 [4]. These relationships are shown in figures 9.2.1 and 9.2.2.

Human kidneys can tolerate a period of at least 30 minutes of normothermic circulatory arrest, (warm ischaemia), without any significant permanent functional impairment [5, see figure 9.2.3], or permanent pathological changes [17]. If renal ischaemia is prolonged more than 30 minutes, the chance of renal failure increases with increasing ischaemia time [17].

In the opinion of the author, prolonged hypotension lasting more than an hour, with an MABP less than 45-50 mmHg, or the cardiac output reduced below 1.8 l/min/m^2 is very likely to cause acute renal failure. Support for this contention is not to be found in human research. But some supportive evidence is provided by canine renal transplant investigations, where kidneys removed from dogs subjected to normothermic hypovolaemic hypotension at an MABP of 50 mmHg for a period of one hour prior to nephrectomy were unable to be successfully transplanted. But kidneys removed from dogs whose MABP due to hypovolaemic hypotension prior to nephrectomy was 60 mmHg were able to be successfully transplanted [6].

It should be carefully noted by the reader that the hypotension that has been discussed up till now in this section is due to hypovolaemia or circulatory shock. Cardiac output is

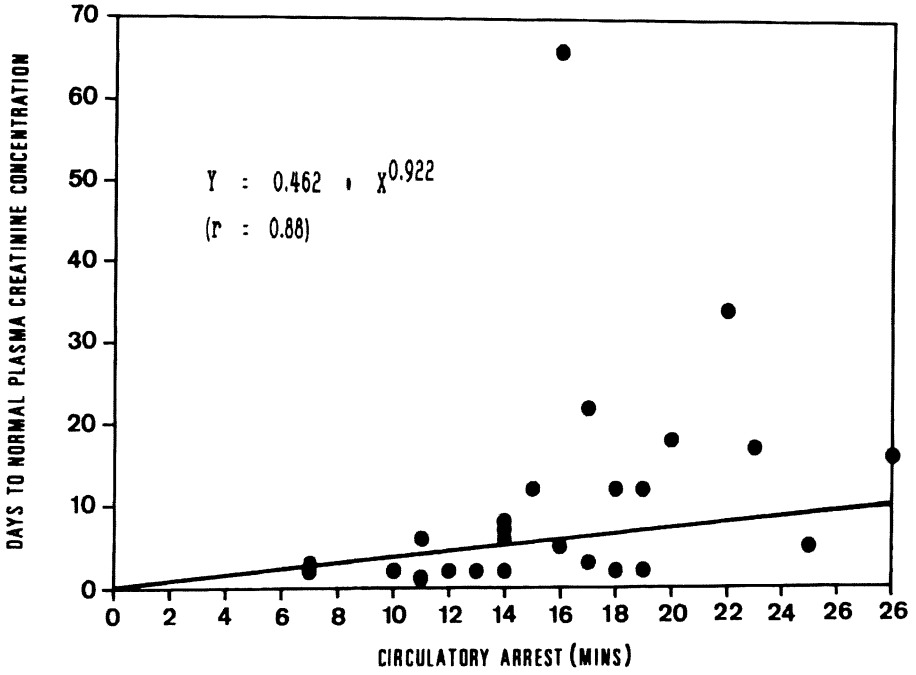

FIGURE 9.2.3. - Number of days required for the plasma creatinine concentration of renal transplantation recipients to normalize, related to the number of minutes of normothermic circulatory arrest to which the donor kidneys were exposed. The data are from Hartley,L.C.J., et al.,(1971) [5].

decreased below normal in both of these conditions. Pharmacologically induced controlled hypotension during anaesthesia is quite different, as the cardiac output is well maintained, and may even be increased above normal [see chapter 2.7]. This is also confirmed by the finding that postoperative renal function in healthy young adults is unimpaired by profound sodium nitroprusside induced hypotension down to arterial pressures as low as 40/25 mmHg for periods of 1 to 3 hours [18]. Therefore when considering the effects of hypotension on renal function, the prime consideration is whether the condition causing hypotension is associated with a reduction of cardiac output.

Table 9.2.1. shows these critical physiological thresholds below or above which renal damage or failure may occur.

EFFECTS OF ANAESTHESIA

These are twofold, one the neuroendocrine effects, and two, the nephrotoxic effects of anaesthetic drugs.

Table 9.2.1.
Critical physiological thresholds which if exceeded may cause, or be a manifestation of, renal damage or failure. [see text for references]

Urine production < 0.3 mls/kg/hour
Cardiac index < 1.8 liters/m^2/minute
MABP < 40-50 mmHg for more than 60 minutes (For hypotension due to shock or hypovolaemia)
Renal circulatory arrest (37°C) > 30-60 minutes

1. Neuroendocrine and Cardiovascular effects.

a. Normotensive general anaesthesia.

Normotensive general anaesthesia has minimal effects on urine output and electrolyte excretion, while surgery always has a profound effect, as has been shown by fluid loading experiments with human subjects under anaesthesia, prior to, and during surgery [7].

Despite the above, renal blood flow is reduced to a greater or lesser degree by general anaesthesia, renal blood flow decreasing as much as 50-70% during deep diethyl-ether or cyclopropane anaesthesia, while anaesthesia using a muscle relaxant-opiate-mechanical ventilation technique causes less renal blood flow depression [1].

b. Spinal or epidural anaesthesia.

Spinal or epidural anaesthesia which blocks the renal sympathetic nerves which arise from T_{10}-T_{12}, blocks sodium retention due to surgery or trauma, but not the water retention [2]. Perioperative water retention is mainly due to ADH secretion [see previous paragraphs].

c. Effects of controlled ventilation.

Controlled ventilation without PEEP causes NO change of renal function. But IPPV with PEEP of 10 cm H_2O may reduce the cardiac output by 15% of the control value prior to PEEP, the glomerular filtration rate by 19%, and the urine output by 34%. PEEP also significantly increases the plasma concentrations of renin, aldosterone, and ADH [8]. Discontinuation of PEEP reverses these changes.

d. Hypotension during anaesthesia.

Urine output is directly proportional to the MABP, and when the MABP falls below 40-50 mmHg urine output ceases [see above]. Controlled hypotension in normovolaemic patients under general anaesthesia also reduces the renal blood flow [16]. For a more

detailed discussion see chapter 2.7 on hypotension and also the paragraphs on hypotension during surgery in this chapter.

2. Nephrotoxic effects.

Nephrotoxic effects of anaesthesia are primarily due to fluoride ion produced by metabolism of fluorinated hydrocarbon anaesthetic agents. Fluoride ion produces a polyuric renal insufficiency characterized by hypotonic urine due to loss of tubular concentrating ability, and a lack of response to ADH [10,11]. The threshold plasma concentration of inorganic fluoride ion required to produce this type of renal damage is about 33.6-40 mmol/l in humans [10,12].

a. Methoxyflurane.

A total dose of more than 2.5 MAC hours causes clinical manifestations of fluoride nephrotoxicity due to metabolism of a large percentage of the total administered dose of methoxyflurane [10].

b. Enflurane.

One of the products of enflurane metabolism is inorganic fluoride ion. Administration of a total dose of 2 MAC hours of enflurane results in a peak inorganic fluoride concentration after 2 hours of 17.4 mmol/l [13], while anaesthesia with a total enflurane dosage of 9.6 MAC hours results in a peak fluoride ion concentration 6 hours after anaesthesia of 33.6 mmol/l [12].

Liver enzyme inducing drugs such as isoniazid can increase the percentage of enflurane metabolized to such a degree, that nephrotoxic plasma fluoride ion concentrations may be developed, which can cause slight renal dysfunction [14].

c. Halothane.

Metabolism of halothane also produces inorganic fluoride ion, but the plasma concentrations produced even after a total dose of 13.7 MAC hours in man are not sufficient to impair renal function [12], even when the patients are obese, and the metabolism of halothane is increased [15].

d. Other anaesthetic drugs.

Other drugs used in anaesthesia have no specific nephrotoxic effects.

REFERENCES

1. Larson,C.P., et al.,(1974), Effects of anesthetics on cerebral, renal, and splanchnic circulations. ANESTHESIOLOGY, 41, 169-181.
2. Bevan,D.R.(1973). The Sodium Story: Effects of Anaesthesia and Surgery on Intrarenal Mechanisms Concerned With Sodium Homeostasis. PROCEEDINGS OF THE ROYAL SOCIETY OF MEDICINE, 66, 1215 -1220.
3. Sinnatamby,C., et al.(1974). Antidiuretic hormone response to high and conservative fluid regimes in patients undergoing operation. SURGERY, GYNECOLOGY & OBSTETRICS, 139, 715-719.
4. Lauson,H.D., et al.(1944). The renal circulation in shock. JOURNAL OF CLINICAL INVESTIGATION, 23, 381-402.
5. Hartley,L.C.J., et al.(1971). Kidney peservation for transportation: Function of 29 human-cadaver kidneys preserved with an intracellular perfusate. NEW ENGLAND JOURNAL OF MEDICINE, 285, 1049-1052.
6. Grundmann,R., et al.(1981). Effect of hypotension on the results of kidney storage and the use of dopamine under these conditions. TRANSPLANTATION, 32, 184-187.

7. MacKenzie,A.J., Donald,J.R.(1969). Urine Output and Fluid Therapy during Anaesthesia and Surgery. BRITISH MEDICAL JOURNAL, 3, 619-622.
8. Annat,G., et al.(1983). Effect of PEEP Ventilation on Renal Function, Plasma Renin, Aldosterone, Neurophysins and Urinary ADH, and Prostaglandins. ANESTHESIOLOGY, 58, 136-141.
9. Renkin,E.M., Robinson,R.R.,(1974), Glomerular filtration. NEW ENGLAND JOURNAL OF MEDICINE, 290, 785-792.
10. Mazze,R.I., Cousins,M.J.(1973). Renal toxicity of anaesthetics: With specific reference to the nephrotoxicity of methoxyflurane. CANADIAN ANAESTHETISTS' SOCIETY JOURNAL, 20, 64-80.
11. Roman,R.J., et al.(1977). Renal Tubular Site of Action of Fluoride in Fischer 344 Rats. ANESTHESIOLOGY, 46, 260-264.
12. Mazze,R.I., et al.(1977). Inorganic Fluoride Nephrotoxicity: Prolonged Enflurane and Halothane Anesthesia in Volunteers. ANESTHESIOLOGY, 46, 265-271.
13. Jarnberg,P.O., et al.(1979). Fluoride Kinetics and Renal Function During Enflurane Anesthesia. ACTA ANAESTHESIOLOGICA SCANDINAVICA, suppl. 71, 20-23.
14. Mazze,R.I., et al.(1982). Isoniazid-induced Enflurane Defluorination in Humans. ANESTHESIOLOGY, 57, 5-8.
15. Bentley,J.B., et al.(1982). Halothane Biotransformation in Obese and Nonobese Patients. ANESTHESIOLOGY, 57, 94-97.
16. Birch,A.A., Boyce,W.H.,(1977), Changing renal blood flow following sodium nitroprusside in patients undergoing nephrolithotomy. ANESTHESIA AND ANALGESIA, 56, 102-109.
17. Rosetti,S.R.,(1983), Impact of acute ischemia on human kidney. In "International Perspectives in Urology", volume 8, Marberger,M., Dreikorn,K. editors, published Williams & Wilkins, Baltimore/London, pages 21-35.
18. Simpson,P., et al.,(1976), Electrocardiographic studies during hypotensive anaesthesia using sodium nitroprusside. ANAESTHESIA, 31, 1172-1178.
19. Mir,M.A., et al.,(1974), Clinical appraisal of shock following acute myocardial infarction. CARDIOLOGY, 59, 69-82.

Chapter 9.3

THREATENED RENAL FAILURE

Renal function may be threatened by a variety of disorders. If the potential threat is not recognized in time and corrective measures taken, acute renal failure with all its consequences may occur.

SOME CAUSES OF ACUTE RENAL FAILURE

Some common causes of acute renal failure are listed below.

- Critical levels in table 9.2.1 have been exceeded.
- Postoperative - due to hypovolaemia.
- Failure of transplanted kidney.
- Toxin or drug induced.
- Traumatic and nontraumatic rhabdomyolysis.
- Septicaemia.
- Prolonged hypovolaemia and/or decreased cardiac output.
- Massive haemolysis.
- Hypercalcaemia.
- Hepatic failure.

RECOGNITION OF THREATENED RENAL FAILURE

Diagnosis of threatened renal failure is at first by clinical suspicion, subsequently confirmed by observation and laboratory tests.

1. The patient has a disorder which may cause renal failure.

All patients with any of the problems listed above are potential candidates for developing renal failure. They should be monitored carefully.

2. The presence of oliguria or anuria.

The development of oliguria, despite normovolaemia, or even hypovolaemia may indicate that renal failure is developing. But this is not always accurate. Oliguria or anuria may occur due to a variety of causes.

- Low cardiac output.
- Induced, or pathologically low blood pressure.
- Hypovolaemia.

- Increased ADH secretion due to surgery or trauma.

Some patients are oliguric because of excessive antidiuretic hormone excretion. This may be recognized by a simple test that may be performed in normovolaemic or hypervolaemic patients. Intravenous administration of about 10-20 mg of frusemide to a normovolaemic or hypervolaemic adult will induce a large diuresis if the cause of oliguria is not renal failure. But this low dose of frusemide will induce only a minimal diuresis in hypovolaemic patients, or those who are developing renal failure.

3. Two hour creatinine clearance.

The two hour creatinine clearance is the most accurate method of diagnosis of acute renal dysfunction. If all other indications of renal dysfunction are dubious, this will provide a definite result as to whether the clinical suspicion of acute renal dysfunction is indeed justified.

MANAGEMENT OF THREATENED RENAL FAILURE

Any patient with threatened renal failure should be aggressively treated in order to minimize or prevent renal failure. Even if these measures do not avert the occurrence of acute renal failure, they may at least prevent the renal failure being of the oliguric type [16]. Oliguric renal failure is associated with both a higher mortality and morbidity than non-oliguric renal failure [1,16], and is therefore well worth preventing if possible.

The management of threatened renal failure may be divided into various facets, each directed at treating one or more of the lesions causing renal failure.

1. Increase renal blood flow.

Increasing renal blood flow improves renal parenchymal oxygenation. Renal blood flow may be elevated by increasing the arterial blood pressure, cardiac output, or both. This is done by treating the cause of the haemodynamic disorder such as, anaesthesia induced hypotension, other forms of drug induced hypotension, hypovolaemia, and cardiogenic and neurogenic shock. In all cases the final result aimed at is restoration of the cardiac output and normal arterial blood pressure.

2. Increasing urine output.

Elevation of the urine output means that the renal tubular flow is also increased. This has the theoretical, and perhaps even actual benefit, of flushing potentially toxic or damaging substances in the tubules out of the kidneys. In addition, the intra-tubular concentrations of these substances is reduced as a result of the increased urine volume with which they are mixed.

The first priority in restoring or increasing urine production, is to correct any haemodynamic disorder. This will usually reverse any oliguria that may be present. Dehydration, hypovolaemia, and low cardiac output should be treated appropriately. In cases where the blood pressure is reduced due to neurogenic shock, spinal or epidural anaesthesia or vasodilator drugs, treatment consists of administration of a vasoconstrictor drug.

If no haemodynamic disorder is present, or has been corrected, and oliguria persists, a diuretic is indicated. The range of suitable drugs is limited, consisting of mannitol, a loop diuretic or both. Low dosage dopamine may also be administered.

a. Loop diuretics.

The most commonly employed diuretic of this type is frusemide. Loop diuretics inhibit the sodium-potassium-chloride (Na-K-2Cl), transport system in the loops of Henle. This transport system accounts for up to 25% of the oxygen consumption of the kidney [2]. It has been theorized that administration of loop diuretics in adequate dosages, e.g. frusemide 40 mg/70 kg i.v., may reduce renal oxygen requirements enough for a kidney with reduced blood flow to survive a greater degree and duration of hypoxia without acute renal failure occurring [2].

During the development phase of acute renal failure, or if the development of renal failure is thought likely, frusemide is indicated for the treatment of oliguria. But the patient must neither be hypovolaemic, nor have a low cardiac output, as a diuresis will only exacerbate these disorders.

Frusemide does not modify the course of established acute renal failure, even when administered intravenously in doses of up to 6 mg/kg body weight [3]. Even when infused directly into a renal artery of patients with established acute renal failure, frusemide has no effect on total renal blood flow, its distribution, or the urine output [4].

b. Mannitol.

Mannitol is an osmotic diuretic. When administered to adults with normal renal function in a dose of 0.25-1.0 g/kg, it causes an increase of renal blood flow secondary to renovascular dilation as well as elevation of the cardiac output and blood pressure [5,8]. A pronounced diuresis occurs which is maximal by up to 20-40 minutes after commencing rapid intravenous administration of mannitol [5]. Besides the beneficial local renal haemodynamic effects, mannitol has many advantages when used in the management of threatened, or developing renal failure.

Administration of mannitol increases the blood volume, central vascular pressures, and the cardiac output. These changes reach their maximum towards the end of a rapid intravenous infusion, after which they rapidly decline in magnitude after discontinuation of the infusion [6,7].

Mannitol administered intraoperatively during human renal transplantation improves the function of the transplanted kidney, as well as reducing the incidence of acute postoperative failure of the transplant [9]. This is probably due to the demonstrated preservation of mitochondrial and cellular function by mannitol when administered prior to ischaemic injury [10]. The exact mechanism of this preservation of mitochondrial function is unclear, but such an effect makes the use of mannitol for prophylactic prevention of ischaemic renal failure desirable. The dosage appropriate for this is between 0.25-1.0 g/kg.

However administration of mannitol does sometimes have deleterious effects. Mannitol always causes a degree of hyponatraemia, the plasma sodium concentration dropping from 132 to 121 mmol/l after an intravenous infusion of 12.5 gms mannitol to an adult who is able to excrete the administered dose of mannitol. Caution should be exercised when considering administration of mannitol to normovolaemic persons who are oliguric or anuric due to actual renal damage. Hypervolaemia, hyponatraemia and hyperosmolar plasma occur if the mannitol is unable to be excreted because of existing renal damage [11]. Renal failure can be caused by regular administration of about 400+ gms mannitol per day [12].

In conclusion, mannitol appears to be the ideal drug for both promoting diuresis and minimizing ischaemic renal damage when administered at a dosage of 0.25-1.0 g/kg to normovolaemic or hypovolaemic patients. But administration of mannitol to an oliguric hyper-

volaemic patient may cause acute circulatory overloading, and a loop diuretic is more appropriate in these patients.

c. Dopamine.

Dopamine in a dosage range of 2-7 μg/kg/min elevates the renal blood flow both by dilation of renal vasculature and increasing the cardiac output [13]. The result of these two effects, plus perhaps some as yet undefined effect upon the renal tubules, is to cause a diuresis [14]. When administered in the above dosage range to patients undergoing renal transplantation, dopamine has also been demonstrated to reduce the chance of acute failure occurring in the transplanted kidney [15].

The indications for dopamine are as an ajuvant to frusemide or mannitol, and as an inotropic drug for oliguric normovolaemic patients with low cardiac output.

3. Depression of renal metabolism.

Renal metabolism may be depressed by depression of whole body metabolism, but this also slows any recovery process too. The so called "loop" diuretics, such as frusemide, ethacrynic acid and bumetanide reduce renal oxygen consumption by up to 25% by inhibition of the Na-K-2Cl transport system. This does not affect any healing processes, and so makes it more likely in theory that affected kidneys will survive any ischaemic episode [2].

ANAESTHETIC MANAGEMENT

Any patient likely to develop acute renal failure should be intensively monitored so that rapid and effective measures may be taken at the least suspicion that renal failure may be developing. Monitoring should consist of continuous measurement of urine output using a urinary catheter, and the appropriate haemodynamic monitoring.

Anaesthesia.

Any form of anaesthesia appropriate for the patient and type of surgery may be used. Avoid the use of drugs which may have nephrotoxic effects [see chapter 9.2], or cause excessive cardiovascular depression [see chapter 2.1].

REFERENCES

1. Anderson,R.J., et al.,(1977), Nonoliguric acute renal failure. NEW ENGLAND JOURNAL OF MEDICINE, 296, 1134-1138.
2. Feig,P.U.,(1986), Cellular mechanism of action of loop diuretics: Implications for drug effectiveness and adverse effects. AMERICAN JOURNAL OF CARDIOLOGY, 57, 14a-19a.
3. Kleinknecht,D., et al.,(1976), Furosemide in acute oliguric renal failure. A controlled trial. NEPHRON, 17, 51-58.
4. Epstein,M., et al.,(1975), Effect of intrarenal furosemide on renal function and intrarenal hemodynamics in acute renal failure. AMERICAN JOURNAL OF MEDICINE, 58, 510-516.
5. Jarnberg,P-O., et al.,(1978), Acute effects of furosemide and mannitol on renal function in the early postoperative period. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 22,173-183.
6. Jarnberg,P-O.,(1978), Acute effects of furosemide and manitol on central hemodynamics in the early postoperative period. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 22, 184-193.
7. Rudehill,A., et al.,(1983), Effects of mannitol on blood volume and central hemodynamics in patients undergoing cerebral aneurism surgery. ANESTHESIA AND ANALGESIA, 62, 875-880.
8. Johnston,P.A., et al.,(1981), Prostaglandins mediate the vasodilatory effect of mannitol in the hypoperfused rat kidney. JOURNAL OF CLINICAL INVESTIGATION, 68, 127-133.

9. Roland,G.W.L., et al.,(1985), Prevention of acute tubular necrosis in cadaveric kidney transplantation by the combined use of mannitol and moderate hydration. ANNALS OF SURGERY, 201, 246-251.
10. Schrier,R.W., et al.,(1984), Protection of mitochondrial function by mannitol in ischemic acute renal failure. AMERICAN JOURNAL OF PHYSIOLOGY, 247, F365-F369.
11. Berry,A.J., Peterson,M.L.,(1981), Hyponatremia after mannitol administration in the presence of renal failure. ANESTHESIA AND ANALGESIA, 60, 165-167.
12. Goldwasser,P., Fotino,S.,(1984), Acute renal failure following massive mannitol infusion. Appropriate response of tubulo-glomerular feedback? ARCHIVES OF INTERNAL MEDICINE, 144, 2214-2216.
13. Goldberg,L.I.,(1972), Cardiovascular and renal actions of dopamine: Potential clinical applications. PHARMACOLOGICAL REVIEWS, 24, 1-29.
14. Hilberman,M., et al.,(1984), The diuretic properties of dopamine in patients after open-heart operation ANESTHESIOLOGY, 61, 489-494.
15. Grundmann,R., et al.,(1981), Effect of hypotension on the results of kidney storage and the use of dopamine under these circumstances. TRANSPLANTATION, 32, 184.
16. Shin,B., et al.,(1979), Postoperative renal failure in trauma patients. ANESTHESIOLOGY, 51, 218-221.

Chapter 9.4

RENAL FAILURE

Renal failure may either be acute or chronic. The problems due to both forms of renal failure are similar, except that patients with chronic renal failure have also developed the long term problems of renal failure. The problems associated with renal failure are due to loss of the various functions of the kidney. The most important consequences for perioperative management are listed below.

1. Minimal, or no ability to excrete a given solute load.
2. Patients with oliguric renal failure are unable to excrete a water load.
3. Loss of the metabolic and hormone producing functions of the kidney such as;
   a. production of renal erythropoietic factor which is required for activation of erythropoietin,
   b. production of renin,
   c. regulation of acid-base homeostasis,
   d. hydroxylation of 25-hydroxycholecalciferol into 1,25-dihydroxycholecalciferol which is required for intestinal calcium absorbtion, etc.

The problems due to renal failure which affect anaesthetic practice and perioperative management are discussed in the rest of this chapter.

PROBLEMS DUE TO RENAL FAILURE

1. Abnormal fluid balance.

Patients with oliguric renal failure are unable to eliminate more water per day than is permitted by their maximal urine output, respiratory, sweat and insensible water loss, and this predisposes to the development of hypervolaemia. Because of this, oliguric renal failure is associated with a significantly higher incidence of pulmonary oedema than is non-oliguric renal failure [1].

Both oliguric and non-oliguric renal failure patients are at risk of hypovolaemia due to excessively strict water restriction.

Both groups of patients may be subject to regular dialysis. Dialysis can cause profound fluid shifts in the body, either hypervolaemia or hypovolaemia may occur.

Because of the difficulties in maintaining normovolaemia, especially when large fluid compartment shifts occur during major surgery, monitoring of central vascular filling pressures with either a central venous or pulmonary artery catheter is required. Use of such monitoring enables efficient blood and fluid replacement to be carried out, and minimizes the risk of either hyper- or hypovolaemia. Maintenance of normovolaemia in the periopera-

tive period is essential, as hypovolaemia will cause further deterioration of remaining renal function in some patients.

2. Hyperkalaemia.

Hyperkalaemia is common in patients with renal failure because of reduced ability to excrete a given potassium load, although it is more common in patients with oliguric renal failure than in those with non-oliguric failure [1]. This is not surprising, as if some urine production is possible, even urine that is not concentrated will remove some potassium from the body.

The main problem due to hyperkalaemia is cardiac arrhythmias. ECG manifestations of hyperkalaemia such as "peaking" of the T-wave occur when the plasma potassium concentration is acutely elevated above 5.5 mmol/l. The potassium concentration corresponding with maximal myocardial excitability is thought to be about 6 mmol/l, the myocardial excitability decreasing at concentrations above and below this [2]. A differentiation should always be made between acute, (developing over minutes to hours), and chronic hyperkalaemia, (developing over days). Acute hyperkalaemia is much more likely to cause cardiac arrhythmias than chronic hyperkalaemia [2]. The other effects of hyperkalaemia and its therapy are discussed fully in chapter 12.4 on hyperkalaemia.

Administration of a dose of 1-2 mg/kg of suxamethonium to normokalaemic healthy patients causes the plasma potassium to rise by about 0.35-1.0 mmol/l [3]. The same dosage of suxamethonium administered to normokalaemic patients with renal failure causes the plasma potassium to rise no more than in normal persons, and use of this drug is therefore not contraindicated in this group of patients [4]. But suxamethonium is contraindicated in all patients with preoperative hyperkalaemia, as the elevation of the potassium concentration that it induces may be sufficient to cause dangerous cardiac arrhythmias.

Other muscle relaxant drugs do not affect the plasma potassium concentration. But an elevated plasma potassium concentration, in the presence of normocalcaemia and normomagnesaemia may reduce the activity of nondepolarizing muscle relaxant drugs [5, and see chapter 12.4].

3. Hypocalcaemia.

Hypocalcaemia is common during renal failure, especially if the patient is inadequately treated. One of the principal reasons for this is deficient of renal conversion of dietary vitamin-D to 1,25-dihydroxycholecalciferol which is the form of this vitamin necessary for intestinal absorbtion of calcium.

Clinical manifestations of hypocalcaemia, such as tetany, or positive Chvostek's sign or Trousseau's sign, occur when the total plasma calcium concentration is lower than 1.75 mmol/l. See chapter 12.5 for a more detailed discussion on hypocalcaemia.

Hypocalcaemia potentiates the effects of the nondepolarizing muscle relaxants, as calcium ion is required for the release of acetylcholine into skeletal muscle neuromuscular junctions [5].

4. Hypermagnesaemia.

Hypermagnesaemia occurs commonly in untreated, or inadequately treated, patients with renal failure. Magnesium ion inhibits the release of acetylcholine at the neuromuscular junction, decreases the response to acetylcholine at the motor end plate, and depresses muscle cell membrane excitability. The net result of all this is that hypermagnesaemia potentiates the action of both nondepolarizing as well as depolarizing muscle relaxants, al-

though the effect of the nondepolarizing relaxants are potentiated to a greater degree than that of the depolarizing relaxants [6].

Treatment of the neuromuscular effects of hypermagnesaemia is to administer 0.5-1 gm of calcium gluconate or chloride intravenously.

5. Metabolic acidosis.

One of the functions of the kidneys is maintaining acid-base homeostasis. A moderate degree of metabolic acidosis occurs frequently in persons with chronic renal failure. Some respiratory compensation always occurs, which minimizes the degree of this metabolic acidosis.

Correction of mild acidosis is unnecessary, and even undesirable, for a number of reasons.

a. Administration of sodium bicarbonate may precipitate hypervolaemia in anuric or oliguric patients.

b. Many chronic renal failure patients are severely anaemic. Tissue oxygenation is maintained by elevation of the cardiac output, and right-shifting of the oxyhaemoglobin dissociation curve by both acidosis and elevation of the erythrocyte 2,3-diphosphoglycerate concentration. Correction of acidosis causes left-shifting of the oxyhaemoglobin dissociation curve, decreasing tissue oxygen delivery [see chapters 5.1 and 13.2].

6. Hyperuricaemia.

Hyperuricaemia occurs due to a reduced ability to excrete uric acid. Severe prolonged hyperuricaemia may cause symptomatic gout. Dialysis is effective in removing uric acid from the blood.

7. Hypertension.

Hypertension is a very common in patients with chronic renal failure. Severe chronic hypertension causes further deterioration of any remaining renal function, in addition to the other problems associated with hypertension [see chapter 2.6 on hypertension].

8. Anaemia.

Patients with chronic renal failure often have quite extreme degrees of anaemia. The anaemia is normochromic and normocytic, the red cell life span is only slightly decreased, and the reticulocyte count is normal, indicating that the red cell production rate is not increased by the anaemia. There are various causes of anaemia in chronic renal failure.

a. Low erythropoietin levels.
b. Slow iron incorporation into red cells.
c. The effect of uraemia on red cell production.
d. Loss of blood by haemodialysis.
e. Some patients have a degree of haemolysis.

Anaemia reduces the oxygen carrying capacity of the blood, and as a result peripheral oxygen transport is only able to be maintained by some of the factors listed below [see chapter 5.1 on anaemia].

a. Acidaemia causing right-shifting of the oxygen-haemoglobin dissociation curve,
b. Increased red cell 2,3-diphosphoglycerate concentration causing right-shifting of the oxygen-haemoglobin dissociation curve,
c. Increased cardiac output.

Provided that anaemia remains asymptomatic, no blood transfusion need be administered [see chapter 5.1 on anaemia]. Another reason for limiting the number of blood transfusions is the fact that all patients with chronic renal failure in western countries are potential candidates for renal transplantation. Blood transfusion increases the chance that they will develop antibodies to foreign tissue types, and so increases the chance that they may reject a transplanted kidney. In addition to this, blood transfusion is only of temporary benefit, the elevation of the haemoglobin being only of short duration, disappearing once the transfused red cells reach the end of their lifespan.

9. Cardiac problems.

These are secondary to all the above problems.

a. Cardiac arrhythmias due to hyperkalaemia, myocardial ischaemia, heart failure.

b. Heart failure due to hypertension, hypervolaemia, and coronary vascular disease, all of which are exacerbated by anaemia.

c. Myocardial ischaemia which may be exacerbated by hypervolaemia, hypertension, heart failure, and anaemia.

d. Cardiac output is increased in many patients with chronic renal failure. This is mainly due to chronic anaemia, as well as slight metabolic acidosis. Arteriovenous shunts which have been formed for haemodialysis also increase the cardiac output.

10. Haemostatic disorder.

Uraemic patients may develop a bleeding tendency due to platelet dysfunction [7,8]. This usually manifests in those patients with marked elevation of plasma urea and creatinine, and whose creatinine clearance is less than 20-25% of normal.

The bleeding time should be measured in all uraemic patients prior to surgery. Uraemic thrombopathy may be reversed by infusion of cryoprecipitate [8], intravenous infusion of deamino-8-D-arginine vasopressin (DDAVP) at a dosage of 0.3 μg/kg body weight [7], by haemodialysis [7,8], or simply by a platelet transfusion [see chapter 6.5 for more detailed information on the treatment of platelet disorders].

11. Altered kinetics of anaesthetic drugs.

The pharmacokinetics of many anaesthetic drugs are changed by renal failure, especially chronic renal failure.

a. Reduced protein binding.

The protein binding of many drugs is reduced in chronic renal failure due to both the metabolic acidosis, and the reduced plasma albumin concentration. Reduced protein binding of drugs has a number of implications [also see chapter 15.2].

i. Increased free drug concentration for a given dose of a drug, with as a result the same effect is achieved with a lower dose.
ii. Increased free drug concentration of a drug eliminated predominantly through the liver means that drug will be more rapidly eliminated in a patient with renal failure, as the drug enters the liver parenchyma more readily.
iii. Increased volume of distribution, as more of the drug can leave the circulation.

The changes in protein binding for some anaesthetic drugs are shown in table 9.4.1.

Table 9.4.1.
Percentage changes in anaesthetic drug kinetics induced by renal failure, compared with the kinetics of the same drug in healthy control patients in the same study.

DRUG	URINE	FREE	V_d	$T_{1/2e}$	Cl
Thiopentone [10]	1	-6*	+143*	+81*	+26
Pentobarbitone [11]	1	-11*	-6	-20	+17
Morphine [12]	11		-33	-9	-10
Alfentanil [13]	0.4	-3*	+67*	-21	+94*
Gallamine [20]	>70		+433*	+475*	-80*
Alcuronium [14]	80			+470*	
Tubocurarine [21]	45			+43	
Pancuronium [15]	40		+60*	+390*	-72*
Vecuronium [16]	15		+23	+22	-29
Atracurium [17]	0		-23*	0	-18
Neostigmine [18]	67		+14	+127*	-53*
Pyridostigmine[19]	80		-10	+238*	-75*

URINE = percentage of total dose unchanged drug excreted in the urine per 24 hours.
FREE = percentage change in plasma non-protein bound drug concentration.
V_d = percentage change of distribution volume.
$T_{1/2e}$ = percentage change of elimination half life.
Cl = percentage change of drug clearance.
"+" = increase. "-" = decrease.
"*" = significant at 0.05 level in the study quoted.

b. Altered distribution kinetics.

The distribution kinetics of drugs may be changed in patients with chronic renal failure due to the elevated cardiac output secondary to anaemia. This increases the rate at which a drug is cleared from the central circulation. As the induction dosage of any hypnotic induction agent is directly proportional to the cardiac output [9], one would expect that the induction dosage of these drugs would increase in chronic renal failure. This has not been demonstrated in the case of thiopentone [10], presumably because the plasma free fraction of thiopentone is increased in renal failure. The same may be true of other drugs too.

c. Altered elimination kinetics.

The elimination half lives of drugs whose elimination is principally due to excretion in unchanged form by the kidney are increased. This is particularly true for some of the nondepolarizing muscle relaxant drugs such as gallamine alcuronium and d-tubocurarine [see table 9.4.1].

ANAESTHETIC MANAGEMENT

Preoperative.

1. Delay any elective surgery until the patient is in as good a physical condition as possible.

2. Correct any electrolyte disorders, especially hyperkalaemia. Chronic hyperkalaemia is tolerated better than acute hyperkalaemia. For a more detailed discussion on the management of hyperkalaemia see chapter 12.4.

3. The bleeding time should always be measured preoperatively in uraemic patients. Uraemic thrombopathy must be treated prior to any surgery. This may require platelet transfusions, cryoprecipitate infusion, deamino-8-D-arginine vasopressin, or dialysis to correct the problem [see chapter 6.5].

4. Treat excessive hypertension prior to any elective operation [see chapter 2.6 on hypertension].

5. Preoperative dialysis may be required to correct many of the disorders above.

6. Premedication with sedative or anticholinergic drugs is not contraindicated in the patient with renal failure, except for the most desperately ill patients.

Anaesthesia.

1. Maintain normal blood pressure and cardiac output so that the renal blood flow does not decrease in patients with some remaining renal function. Preservation or restoration of normal haemodynamics by maintaining or restoring normovolaemia is of the utmost importance in maintaining renal blood flow. Reduced renal blood flow means decreased renal oxygenation, which will exacerbate any existing renal dysfunction.

2. Adequate monitoring is required. Central venous pressure measurement is of value in regulating perioperative fluid balance and maintaining normovolaemia in patients undergoing renal transplantation, or with threatened renal function. Pulmonary artery catheterization for measurement of systemic cardiac output, systemic vascular resistance,

as well as pulmonary vascular pressures is required for patients whor have severe cardiovascular disease in addition to renal failure. A urinary catheter is necessary for regular measurement of the urine output in all patients.

Monitoring itself, does nothing except provide a measurement of some physiological parameters. But effective use of the information gained by monitoring enables effective therapy of the fluid balance problems of patients with existing or threatened renal failure.

3. Loco-regional anaesthesia.

Loco-regional anaesthesia is to be preferred where possible, as it causes minimal metabolic or cardiorespiratory changes. Bleeding time should be less than 6 minutes to ensure minimum haemorrhagic complications from any regional anaesthetic block [see chapter 6.3 for haemostatic requirements].

4. General anaesthesia.

There are some factors which must be considered whenever administering general anaesthesia to any patient with chronic or acute renal failure.

a. If the patient is severely anaemic or acidaemic, a general anaesthetic technique where the patient breathes spontaneously is contraindicated. Tissue oxygenation is already compromised by anaemia, and the respiratory depressant actions of all general anaesthetic agents will further exacerbate this, in addition to exacerbating any metabolic acidosis. Because of these problems, controlled ventilation is required for uraemic, or metabolically "sick" patients if general anaesthesia is thought necessary.
b. This raises the question of what drugs are appropriate. The answer is simple. Any drug may be used to provide anaesthesia for anephric patients, or patients with impaired renal function. The only requirement is that the dose of the drug(s) be sufficient for the purpose desired, and that any further dosages be administered on indication alone. In general it is better to employ drugs whose elimination does not depend upon renal excretion of the unchanged drug. Another problem may arise due to accumulation of active breakdown products that are excreted through the kidneys, but this will only manifest after administration of large total doses.
c. Any induction agent may be used. The sleep doses of these drugs is probably not altered by renal failure. In the case of thiopentone sleep dose the sleep dose is not altered significantly by renal failure [3].
d. Opiates are mostly excreted in the metabolized form. From the few data available on the kinetics of opiates in chronic renal failure, it is apparent that neither the volume of distribution, nor the elimination half life of morphine or alfentanil are changed by renal failure. This means that these drugs may be used in the same way as for healthy patients. One exception may be pethidine, which has an active metabolite norpethidine which is excreted predominantly in the urine.
e. The kinetics of the non-depolarizing muscle relaxants are changed by renal failure. Exceptions to this rule are vecuronium and atracurium. The distribution volumes of these relaxants are the same as in healthy persons, but the elimination half lives of these drugs are prolonged due to a reduction of renal drug clearance. This is hardly surprising as most of the non-depolarizing muscle relaxants undergo minimal hepatic metabolism, and the active drug is eliminated predominantly by excretion in the urine [see table 9.4.1 and appendix-A]. The practical clinical implication of these changes are that the normal doses, and repeat doses of these drugs are required for any given degree of muscle

relaxation, but the dosage intervals should be increased because elimination is slower. Excessive accumulation of these drugs may be prevented by only administering repeat doses according to clinical requirements, or using a peripheral nerve stimulator. Drugs such as vecuronium or atracurium should be used preferentially during anaesthesia because their elimination kinetics are not altered by renal failure, most of the administered dose being metabolized. The elimination half lives of neostigmine and pyridostigmine are also lengthened by renal failure. The increase is in proportion to that seen with the muscle relaxants. This lessens the chance of recurarisation after reversal of non-depolarizing block with these drugs.

f. Volatile anaesthetic agents are valuable ajuvants to anaesthesia using controlled ededed-ventilation. The requirement for muscle relaxant drugs is decreased, as is the requirement for opiates. In addition they are principally excreted via the lungs. The only volatile anaesthetic consistently associated with renal failure is methoxyflurane which is no longer available. Enflurane, even though it may be associated with the development of slight renal dysfunction when a total dosage of more than 9.6 MAC hours is administered [see chapter 9.2], has been used without problem as a supplement for anaesthesia for renal transplantation in total doses of up to 7.5 MAC hours [23]. The use of halothane and isoflurane have never been associated with renal function impairment due to fluoride ion production. The metabolism of other anaesthetic agents such as trichloroethylene, diethyl-ether, and cyclopropane produces no fluoride ion.

Postoperative.

Patients with renal failure should be admitted to an intensive care unit postoperatively after all but the most minor operations.

REFERENCES

1. Shin,B., et al.,(1979), Postoperative renal failure in trauma patients. ANESTHESIOLOGY, 51, 218-221.
2. Surawicz,B.,(1967), Relationship bewteen electrocardiogram and electrolytes. AMERICAN HEART JOURNAL, 73, 814-834.
3. Vaughan,R.S., Lunn,J.N.,(1973), Potassium and the anaesthetist. ANAESTHESIA, 28, 118-131.
4. Miller,R.D., et al.,(1972), Succinylcholine-induced hyperkalemia in patients with renal failure? ANESTHESIOLOGY, 36, 138-141.
5. Waud,B.E., Waud,D.R.,(1980), Interaction of calcium and potassium with neuromuscular blocking agents. BRITISH JOURNAL OF ANAESTHESIA, 52, 863-865.
6. Ghoneim,M.M., Long,J.P.,(1970), The interaction between magnesium and the neuromuscular blocking agents. ANESTHESIOLOGY, 32, 23-27.
7. Mannucci,P.M., et al.,(1983), Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. NEW ENGLAND JOURNAL OF MEDICINE, 308, 8-12.
8. Janson,P.A., et al.,(1980), Treatment of the bleeding tendency in uremia with cryoprecipitate. NEW ENGLAND JOURNAL OF MEDICINE, 303, 1318-1322.
9. Christensen,J.H., et al.,(1982), Pharmacokinetics and pharmacodynamics of thiopentone: A comparison between young and elderly patients. ANAESTHESIA, 37, 398-404.
10. Christensen,J.H., et al.,(1983). Pharmacokinetics and pharmacodynamics of pentothal in patients undergoing renal transplantation. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 27, 513-518.
11. Reidenberg,M.M., et al.,(1976), Pentobarbital elimination in patients with poor renal function. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 20, 67-71.
12. Aitkenhead,A.R., et al.,(1984), Pharmacokinetics of single dose i.v. morphione in normal volumteers and patients with end-stage renal failure. BRITISH JOURNAL OF ANAESTHESIA, 56, 813-819.
13. Sear,J.W., et al.,(1986), Disposition of alfentanil in patients with chronic renal failure. BRITISH JOURNAL OF ANAESTHESIA, 58, 812P.

14. Raaflaub,J.von., Frey,P.,(1972). Zur Pharmacokinetiek von Dially-nortoxiferin beim Menschem. ARTZNEIMITTELFORSCHUNG, 22, 73-78.
15. McLeod,K., et al.,(1976), Pharmacokinetics of pancuronium in patients with normal and impaired renal function. BRITISH JOURNAL OF ANAESTHESIA, 48, 341-345.
16. Fahey,M.R., et al.,(1981), Pharmacokinetics of ORG NC45 (Norcuron) in patients with and without renal failure. BRITISH JOURNAL OF ANAESTHESIA, 53, 1049-1053.
17. Ward,S., Neill,E.A.M.,(1983), Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). BRRITISH JOURNAL OF ANAESTHESIA, 55, 1169-1172.
18. Cronnelly,R., et al.,(1979), Renal function and the pharmacokinetics of neostigmine in anesthetized man. ANESTHESIOLOGY, 51, 222-226.
19. Cronnelly,R., et al.,(1980), Pyridostigmine kinetics with and without renal function. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 28, 78-81.
20. Ramzan,M.I., et al.,(1981), Gallamine disposition in surgical patients with chronic renal failure. BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, 12, 141-147.
21. Miller,R.D., et al.,(1977), The pharmacokinetics of d-tubocurarine in man with and without renal failure. JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, 202, 1-7.
22. Christensen,J.H., et al.(1980). Pharmacokinetics of thiopentone in a group of young women and a group of young men. RITISH JOURNAL OF ANAESTHESIA, 52, 913-917.
23. Temmerman,P. de, Gibomont,P.(1979). Enflurane in Renal Transplantation: Report of 375 Cases. ACTA ANAESTHESIOLOGICA SCANDINAVICA, suppl. 71, 24-31.

Part 10

HEPATIC DYSFUNCTION

Hepatic dysfunction can profoundly affect the response of the body to surgery and anaesthesia. As with renal dysfunction, the perioperative period is too short to effect a cure of any hepatic disorder. But the anaesthetist can ensure that existing hepatic dysfunction is not exacerbated by surgery or anaesthesia, and that perioperative problems due to hepatic dysfunction are minimized.

Chapter 10.1

ASSESSMENT OF LIVER FUNCTION

Patients with severely disordered hepatic function, either due to hepatocellular or obstructive icterus, have a high postoperative mortality and morbidity [1,2,3,4]. This may be minimized by appropriate perioperative management which is based on accurate assessment of the magnitude and type of hepatic dysfunction. The magnitude and type of hepatic dysfunction is related to a number of perioperative problems.

- It is directly related to perioperative morbidity and mortality.
- It determines the most appropriate surgical procedures, and the perioperative management.
- It determines the most appropriate anaesthetic management as well as perioperative monitoring.

TESTS USED FOR INVESTIGATION OF LIVER DISEASE

1. Tests of hepatocellular damage.

Intracellular enzymes leak from damaged liver cells, and elevate plasma concentrations of hepatocellular enzymes. The elevation of hepatic enzyme concentrations not only indicates hepatic damage, but the particular enzymes released also indicate the site of hepatic damage too.

a. Hepatocellular enzymes.
- Transaminases.
- Lactate dehydrogenase.

b. Cells lining the bile canaliculi.
- Alkaline phosphatase
- 5-nucleotidase.

Elevated plasma concentrations of these enzymes indicates active hepatocellular damage occurring at that time, otherwise no hepatocellular enzymes would be leaking into the blood. Some patients with severe hepatic disease, but no active hepatocellular destruction, and with no biliary obstruction, may have normal plasma concentrations of these enzymes as no destruction of liver cells is occurring at that time. This latter situation does not mean that hepatic function in this group of patients is normal.

Except for 5-nucleotidase, none of these enzymes are specific to the liver, and elevated plasma concentrations of these enzymes may also indicate other disease too. As usual, the clinical picture must also be taken into account.

2. Tests of hepatocellular function.

The liver has a vast range of metabolic functions which are essential for the normal functioning of the body. Abnormalities of these functions also give an idea of the degree of hepatic dysfunction.

a. Conjugating ability.

The liver has the ability to form conjugated water soluble compounds which are more easily excreted in urine or bile. Reduced hepatic conjugating ability is indicated by;

i. decreased plasma concentration of conjugated bilirubin
ii. reduced bromsulphthalein elimination.

b. Synthetic function.

The liver synthesizes a large range of substances. A reduced plasma concentration, or production rate of any of these indicates decreased hepatic synthetic capability, e.g,

i. Decreased plasma albumin concentration.
ii. Elevated prothrombin time, or decreased plasma fibrinogen concentration indicate reduced hepatic coagulation protein synthesis.
iii. Decreased plasma cholinesterase concentration.
iv. Decreased plasma urea concentration.

TYPE OF LIVER DISEASE

It is essential to differentiate between hepatocellular and obstructive icterus as they are associated with some different problems and a different prognosis. One of the main differences is that patients with obstructive icterus, also have a 50% incidence of systemic endotoxaemia due to reduction of the effects of bile salts on the intestinal flora [1,2]. Patients with endotoxaemia have a considerably increased chance of developing perioperative hypotension, and as a result postoperative renal dysfunction [1,2]. Surgery for the relief of obstructive jaundice is therefore not surprisingly associated with a high mortality [2].

Tests useful in differentiating cholestatic liver disease from hepatocellular disease are listed below, and further expanded in table 10.1.1.

a. An elevated plasma conjugated bilirubin concentration relative to unconjugated bilirubin in the presence of elevated total plasma bilirubin concentration indicates cholestasis is more likely.
b. Decreased urinary urobilinogen concentration. Urobilinogen is a product of intestinal bacterial metabolism of bilirubin. Some urobilinogen is absorbed by the bowel and subsequently excreted in the urine. A decreased urinary urobilinogen is indicative of cholestatic liver disease.
c. Increased plasma concentrations of enzymes produced by cells lining the biliary ducts indicates that cholestatic liver disease is more likely, i.e. alkaline phosphatase and 5-nucleotidase. 5-nucleotidase is an enzyme that is mainly synthesized in the liver and is a

more specific test for liver disease than is alkaline phosphatase, which is produced by bones and intestines as well as liver.

d. Elevation of hepatocellular enzyme concentrations, e.g. the transaminases, relative to the concentrations of alkaline phosphatase and 5-nucleotidase, indicates that hepatocellular disease is more likely.

Table 10.1.1.
Differences between cholestatic and hepatocellular jaundice.

	CHOLESTATIC JAUNDICE	HEPATOCELLULAR JAUNDICE
FAECES		
Steatorrhoea	↑	↑/↓
URINE		
Urobilinogen	↓	↑/↓
Bilirubin	↑	↑
BLOOD		
Total bilirubin	↑	↑
Conjugated bilirubin	↑	↑/N
Unconjugated bilirubin	↑/N	↑
Transaminases	↑/N	↑
Alkaline phosphatase	↑	↑/N
5-nucleotidase	↑	↑/N

"↑" = increased or present
"↓" = decreased or absent
"N" = normal.

ASSESSMENT OF SURGICAL RISK

The necessity for any surgery should be reviewed with regard to the high mortality associated with surgery performed on patients with severe liver disease. Perioperative mortality associated with laparotomy performed on patients with severe liver disease is high, varying between 25-80% [2,3,4], the mortality being greater in those with inflammatory hepatocellular liver disease [3].

Various functional classifications of liver disease have been devised, and the classification correlated with surgical morbidity and mortality. The two main systems are those of Child [5, table 10.1.2], and Pugh et al [4, table 10.1.3]. The classification of Child is rather

more subjective than that of Pugh, but is easier to use. The author has added steatorrhoea to these assessments, as this is a factor associated with endotoxaemia in 50% of patients with cholestasis. The problems caused by each of the factors in tables 10.1.2 and 10.1.3 are discussed in the chapter on impaired liver function [chapter 10.3]. Only patients falling into group A of either classification should be considered for elective surgery. As for patients in groups B and C, the possible risks of abstaining from any operation should be weighed carefully against the possible risks of any operation planned.

Table 10.1.2.
Classification of hepatic function according to Child [5].

PARAMETER	Class A	Class B	Class C
Serum Bilirubin (mmol/l)	40	40-50	50
Serum Albumin (g/l)	>35	30-35	<30
Ascites	none	easily controlled	poorly controlled
Steatorrhoea *	none	present	present
Neurological disorder	none	minimal	advanced coma
Nutritional status	excellent	good	wasting
OPERATIVE RISK	**GOOD**	**MODERATE**	**POOR**

* Steatorrhoea has been added by the author as an extra high risk factor.

Table 10.1.3.
Classification of hepatic reserve according to Pugh et al [4].

PARAMETER	Points scored for each abnormality		
	1	2	3
Encephalopathy grade [6]	none	1 or 2	3 or 4
Ascites	absent	slight	moderate
Serum bilirubin (mmol/l)	25	25-40	40+
Serum albumin (g/l)	>35	28-35	<28
Relative prolongation of Prothrombin Time	1-4	4-6	>6

Class A = score of 5 - 6 = Low risk
Class B = score of 7 - 9 = Moderate risk
Class C = score of 10 - 15 = High risk

REFERENCES

1. Bailey,M.E.,(1976), Endotoxin, bile salts and renal function in obstructive jaundice. BRITISH JOURNAL OF SURGERY, 63, 774-778.
2. Cahill,C.J.,(1983), Prevention of postoperative renal failure in patients with obstructive jaundice - the role of bile salts. BRITISH JOURNAL OF SURGERY, 70, 590-595.
3. Powell-Jackson,P., et al.,(1982), Adverse effects of exploratory laparotomy in patients with unsuspected liver disease. BRITISH JOURNAL OF SURGERY, 69, 449-451.
4. Pugh,R.N.H., et al.,(1973), Transection of the oesophagus for bleeding oesophageal varices. BRITISH JOURNAL OF SURGERY, 60, 646-649.
5. Child,C.G.,(1966), The liver and portal hypertension. In "Major Problems in Clinical Surgery", Volume 1, editor Child,C.G., published W.B.Saunders.
6. Trey,C., et al.,(1966), Treatment of hepatic coma by exchange blood transfusion. NEW ENGLAND JOURNAL OF MEDICINE, 274, 473.

Chapter 10.2

EFFECTS OF ANAESTHESIA AND SURGERY ON THE LIVER

Both anaesthesia as well as surgery may have profound effects on hepatic function.

EFFECTS OF SURGERY ON HEPATIC FUNCTION

Except for the obvious effects of hepatic surgery or trauma on liver function, the main effect of surgery on hepatic function is due to a reduction of hepatic blood flow. The liver is an unusual organ in that it derives its blood from two sources, about 70% of the blood entering the liver comes from the portal vein, with the remaining blood coming from the hepatic artery.

Surgery and trauma affect hepatic function is two ways.

1. Sympathetic nervous system activity.

Vessels in the regions drained by the portal vein, i.e. the splanchnic circulation, have a rich sympathetic nervous innervation. Increased sympathetic nervous activity reduces splanchnic blood flow. As 70% of the blood entering the liver comes from the splanchnic vascular bed, a reduction of splanchnic blood flow also means a reduction of hepatic blood flow. In addition to this, the liver itself has a sympathetic nervous innervation which also controls hepatic blood flow to some degree.

Both surgery and trauma increase sympathetic nervous activity, and reduce splanchnic as well as hepatic blood flow.

2. Haemorrhage.

Haemorrhage increases the systemic vascular resistance, reduces the cardiac output, and if the volume of haemorrhage is great enough, decreases the arterial blood pressure too [see chapter 14.4 on hypovolaemia].

Hypotension, regardless of whether it is pharmacologically induced, or whether it is caused by haemorrhage, reduces the hepatic blood flow [3]. Blood loss of up to 17% of blood volume in healthy adults causes no significant change of cardiac output or blood pressure, but does significantly reduce splanchnic blood volume and hepatic venous pressure, as well as decreasing indocyanine green dye clearance [4]. Indocyanine green dye clearance is a function of hepatic blood flow and metabolism, and a reduction implies that the clearance of drugs primarily eliminated by hepatic metabolism is also reduced [17].

EFFECTS OF ANAESTHESIA ON HEPATIC FUNCTION

Anaesthesia may affect hepatic function in a number of ways.

- Effects of anaesthetic technique on hepatic haemodynamics.
- Effects of anaesthetic drugs on hepatic haemodynamics.
- Effects of drugs on hepatocellular function, e.g. toxicity.

1. Effect of anaesthetic technique on hepatic haemodynamics.

a. Spinal or epidural anaesthesia.

Both spinal and epidural anaesthetic techniques reduce splanchnic vascular resistance, pressure and flow [1,2]. The cause is usually hypotension in combination with a cardiac output that does not increase in proportion to the reduction of systemic and splanchnic vascular resistances. This situation is reversed by administering ephedrine, which has both ß- as well as α-adrenoreceptor stimulating effects, which increases both cardiac output and systemic vascular resistance, as well as splanchnic blood pressure, resistance and flow [1].

b. Intermittent positive pressure ventilation (IPPV).

Inferior vena caval as well as portal blood flow are reduced, and portal vascular resistance and pressure are increased during IPPV. This is especially so when large tidal volumes are used [5], during hyperventilation [6], and when positive end expiratory pressure (PEEP) is applied [7]. The same changes also occur in the hepatic circulation [6].

c. Hypercarbia and hypocarbia.

Hypercarbia increases the splanchnic vascular resistance, and decreases the hepatic blood flow [8], while hepatic blood flow is apparently unrelated to hypocarbia [6].

d. Controlled hypotension.

Controlled hypotension reduces hepatic and splanchnic blood flow regardless of the techniques or drugs used [3].

2. Effects of anaesthetic drugs on hepatic haemodynamics.

Drugs used in anaesthesia may in themselves affect splanchnic and hepatic haemodynamics.

a. Induction agents.

Thiopentone, ketamine and etomidate cause a dose related reduction of liver blood flow. This is related to a reduction of cardiac output, as well as being caused by a local vasoconstrictor effect of these drugs, as is shown by an elevation of the mesenteric and hepatic vascular resistances in experimental animals [9].

b. Muscle relaxants.

The effects of these on hepatic and splanchnic haemodynamics has not been well investigated.

c. Opiates.

Provided that hypoxaemia and hypercarbia are prevented with controlled ventilation, opiates increase splanchnic, and presumably liver blood flow [10].

d. Anaesthetic gases.

Cyclopropane [2,12], and methoxyflurane [2], both reduce hepatic blood flow by reducing the cardiac output, as well as by inducing local hepatic vasoconstriction.

Halothane [2,9,12], and enflurane [11], decrease the liver blood flow, as well as hepatic and splanchnic vascular resistances. The reduction of liver blood flow is in direct proportion to the reduction of cardiac output caused by these drugs [9].

3. Effects of anaesthetic drugs on hepatocellular function.

Hepatocellular dysfunction usually manifests by an elevation of plasma concentrations of hepatocellular enzymes. The frequency with which abnormal liver function tests occur after anaesthesia is not only related to the drugs used, but also to other factors, such as age, sex, body build, and regular ingestion of drugs inducing drug metabolizing enzymes.

There are a number of ways in which anaesthetic drugs may affect hepatocellular function.

- A direct hepatotoxic effect of the drug itself.
- Hepatotoxic effect of the drug metabolites.
- Induction of hepatocellular damage due to hypoxaemia secondary to respiratory depression.

a. Induction agents.

Single bolus doses or infusions of drugs in normal clinical dosages such as etomidate, althesin and profolol appear to cause minimal to no increase of the plasma concentrations of liver enzymes [9]. Administration of thiopentone and ketamine have been associated with postoperative increased plasma concentrations of liver enzymes [9].

b. Muscle relaxant drugs.

Few, or no investigations have been performed on the effects of muscle relaxant drugs on hepatocellular function. As large numbers of studies have been performed with other drugs, and muscle relaxants were also administered during these studies, it is perhaps not unreasonable to assume that as nothing has been found up till now, muscle relaxant drugs have minimal effects on hepatocellular function.

c. Opiates.

Opiates decrease splanchnic and liver blood flow in spontaneously breathing animals due to hypoxaemia secondary to respiratory depression. Hypoxia can cause liver damage if severe enough. These changes do not occur in animals whose ventilation is controlled, and in whom hypoxaemia does not occur [10].

d. Anaesthetic gases.

It has been consistently observed for many years that the use of most anaesthetic gases is associated with postoperative elevation of the plasma concentrations of hepatic enzymes. This is particularly so after repeat anaesthetics.

It is the halogenated anaesthetic vapors which are most frequently associated with postoperative disorders of liver function. Of the three halogenated anaesthetics in common clinical use, (halothane, enflurane, and isoflurane), it is halothane that causes the highest incidence of abnormal liver enzyme concentrations after single or repeat anaesthetics [13,14]. After a second repeat anaesthetic within a six month period with the above three

agents, the frequency with which abnormal liver enzyme concentrations are measured within plasma is 27% for halothane, 12% for enflurane and 0% for isoflurane [13,14].

In the case of halothane, obese persons are more likely to have abnormal liver function tests after repeat anaesthesia [15]. This is due to the increased metabolism of halothane occurring in obese patients [16], presumably due to the slower elimination of these drugs as a result of larger than usual quantities of vapor being stored in fat tissue. This suggests that one or more halothane breakdown products is hepatotoxic.

PRACTICAL IMPLICATIONS

It is obvious from this brief review, that it is hypoxaemia and reduction of the hepatic blood flow that are the two factors most likely to cause perioperative impairment of liver function. Drug induced hepatocellular dysfunction is less likely, but certainly may occur after use of some anaesthetic vapors.

REFERENCES

1. Greitz,T., et al.,(1984), Effects of ephedrine on hemodynamics and oxygen consumption in the dog during high epidural block with special reference to the splanchnic region. ANESTHESIA AND ANALGESIA, 28, 557-562.
2. Larson,C.P., et al.,(1974), Effects of anesthetics on cerebral, renal, and splanchnic circulations. Recent developments. ANESTHESIOLOGY, 41, 169-181.
3. Strunin,L.,(1975), Organ perfusion during controlled hypotension. BRITISH JOURNAL OF ANAESTHESIA, 47, 793-798.
4. Price,H.L., et al.,(1966), Hemodynamics and metabolic effects of hemorrhage in man with particular reference to the splanchnic circulation. CIRCULATION RESEARCH, 18, 469-474.
5. Cooperman,L.H., et al.,(1968), Splanchnic circulation during nitrous oxide anesthesia and hypocarbia in normal man. ANESTHESIOLOGY, 29, 254-258.
6. Johnson,E.E.,(1975), Splanchnic hemodynamic response to passive hyperventilation. JOURNAL OF APPLIED PHYSIOLOGY, 38, 156-162.
7. Johnson,E.E., Hedley-Whyte,J.,(1972), Continuous positive pressure ventilation and portal flow in dogs with pulmonary oedema. JOURNAL OF APPLIED PHYSIOLOGY, 33, 385-389.
8. Epstein,R.M., et al.,(1961), The effect of hypercapnia on estimated hepatic blood flow, circulating splanchnic blood volume, and hepatic sulfobromthalein clearance during anaesthesia in man. JOURNAL OF CLINICAL INVESTIGATION, 40, 592.
9. Sear,J.W.,(1986), Toxicity of i.v. anaesthetics. BRITISH JOURNAL OF ANAESTHESIA, 59, 24-45.
10. Duthie,D.J.R., Nimmo,W.S.,(1987), Adverse effects of opoid analgesic drugs. BRITISH JOURNAL OF ANAESTHESIA, 59, 61-77.
11. Andreen,M., Irestedt,I.,(1979), Effects of Enflurane on splanchnic circulation. ACTA ANAESTHESIOLOGICA SCANDINAVICA, suppl. 71, 48-51.
12. Price,H.L., et al.,(1966), Can general anesthetics produce splanchnic visceral hypoxia by reducing regional blood flow? ANESTHESIOLOGY, 27, 24-32.
13. Johnston,S.B., et al.(1979). Liver Function Following Repeated Anaesthesia: Method of Study and Interim Results. ACTA ANAESTHESIOLOGICA SCANDINAVICA, suppl. 71, 12-14.
14. Eger,E.I.(1981). Isoflurane: A Review. ANESTHESIOLOGY, 55, 559-576.
15. Dundee,J.W., et al.(1980), The influence of obesity on liver dysfunction following repeated administrations of halothane and enflurane. In "Enflurane. Selected proceedings of the Seventh World Congress of Anesthesiology", editor Bennetts, F.E., Hamburg, pub. Excerpta Medica, pages 55-60.
16. Bentley,J.B., et al.(1982). Halothane Biotransformation in Obese and Nonobese Patients. ANESTHESIOLOGY, 57, 94-97.
17. Chauvin,M., et al.,(1986), The influence of hepatic plasma flow on alfentanil plasma concentration plateaus achieved with an infusion model in humans: Measurement of the hepatic extraction coefficient. ANESTHESIA AND ANALGESIA, 65, 999-1003.

Chapter 10.3

IMPAIRED LIVER FUNCTION

Hepatic dysfunction is a multisystem disorder, for the liver is an organ whose proper functioning is vital for the function of the whole body. The functional reserve capacity of the liver is enormous. If only 10% of normal liver tissue is left after a major partial hepatic resection in humans, this is sufficient to sustain life, in addition to which full regeneration of the liver mass occurs after four months [1]. However despite this massive functional reserve, surgery performed on patients with severe liver disease is associated with a high mortality [see chapter 10.1].

Reduction of the associated morbidity and mortality is only possible by means of a thorough understanding of the problems caused by liver dysfunction and their management. The problems of most concern to the anaesthetist and surgeon are discussed below.

PROBLEMS

1. Deficient wound healing.

The rate of wound healing is reduced, and the strength of the healed wound is also reduced in patients with liver dysfunction. In the past this was attributed to the effects of hyperbilirubinaemia. But multivariate analysis of the clinical circumstances of 373 patients in one study has shown that deficient wound healing is not related to hyperbilirubinaemia, but is related to the other problems associated with liver disease, such as concurrent infection, poor nutritional status, etc [2].

2. Decreased hepatic protein synthesis.

Nearly all plasma proteins are synthesized in the liver. Hepatocellular dysfunction causes the plasma concentrations of these proteins to fall because of;

- reduced synthesis,
- insufficient dietary amino acid intake,
- loss of plasma proteins into ascites fluid.

a. Hypoalbuminaemia.

Hypoalbuminaemia occurs as a result of severe liver disease. This has a number of effects.

i. Many drugs are bound to albumin. Hypoalbuminaemia means that the percentage protein binding of many drugs is less than normal with all the consequences of this [see table 10.3.1, and chapter 15.2].

ii. Albumin is the plasma protein which exerts the greatest part of the plasma colloid osmotic pressure. Hypoalbuminaemia exacerbates ascites and oedema formation. Clinically evident peripheral oedema occurs when the plasma colloid osmotic pressure falls below 15 mmHg, or the plasma albumin concentration is lower than 20 gm/l [see chapter 14.1]

b. Plasma cholinesterase.

Plasma cholinesterase is synthesized in the liver. Severe hepatocellular disease reduces the plasma cholinesterase concentration [3]. The action of drugs such as suxamethonium and propanidid, which are metabolized by plasma cholinesterase, are likely to be prolonged in severe liver dysfunction.

c. Coagulation proteins.

All coagulation proteins are synthesized in the liver, with the exception of factor VIII and von Willebrand's factor which are synthesized by vascular endothelial cells.

Because the concentration of factor VIII is relatively unaffected by liver disease, the partial thromboplastin time is not a good test of a deficiency of coagulation proteins. But the prothrombin time is a good single test, as it relies entirely upon coagulation factors synthesized in the liver, [see chapter 6.2 on simple tests of haemostatic function].

Deficient coagulation protein synthesis is one of the causes of abnormal haemostatic function in patients with liver disease.

3. Reduced metabolic function.

The liver performs a vast range of metabolic functions which are required for the normal functioning of the body, e.g.amino acid metabolism, glucose homeostasis, and hormone metabolism.

a. Hormone metabolism.

Insulin, oestrogen, aldosterone, glucocorticoids are some of the hormones that are inactivated by the liver. Severe hepatocellular disease can cause the plasma concentrations of these hormones to rise due to decreased hepatic clearance of these hormones.

i. About half the insulin produced by the pancreas is eliminated in the first pass through the liver. The average adult human insulin production rate is about 1-2 IU/hour, while the amount reaching the systemic circulation is about 0.5 IU/hour [4]. Severe hepatocellular disease, by reducing insulin clearance may cause hyperinsulinaemia.
ii. Decreased aldosterone metabolism may cause sodium and water retention.
iii. Reduced glucocorticoid hormone breakdown causes the usual effects of hypercorticism, such as thin atrophic skin, striae, etc.

b. Glucose metabolism.

Either hyperglycaemia or hypoglycaemia may occur as a result of severe liver disease.

i. Hyperglycaemia occurs frequently in patients with liver disease, often being associated with glucose intolerance, insulin resistance, and hyperinsulinaemia.
ii. Hypoglycaemia does not often occur as a result of liver disease. It usually only occurs in situations where the liver glycogen reserves are depleted. Reduction of hepatic glycogen

stores decreases the rate of hepatic gluconeogenesis. This may be exacerbated by alcohol ingestion which also inhibits hepatic gluconeogenesis.

c. Lactate metabolism.

The average 70 kg adult produces about 1200-1500 mmol lactate per day, (about 50-63 mmol/hour). Lactate is produced by the skin, skeletal muscle, erythrocytes, brain and intestines. The liver metabolizes about 60% of this, and the kidney the remaining 40%. Glucose is the product of hepatic and renal lactate metabolism [7,29]. The liver has a large reserve metabolic capacity, being able to metabolize up to two to four times the normal daily lactate production, i.e. up to 120-240 mmol/ hour [29].

Very rapid infusion of lactate containing infusion fluids in patients with severe hepatic insufficiency may theoretically cause accumulation of lactate, but only if the infusion rate is very high, or if hepatic function is very severely compromised. For example, Ringer's lactate (Hartmann's solution) is commonly infused in the perioperative period, and contains 29 mmol/l of sodium lactate. Rapid infusion of this is unlikely to cause acidosis as the pH of this solution is between 6-8, and infusion rates of more than one liter per hour would be required, (liver is normally able to metabolize 120-240 mmol of lactate/hour, and the kidneys also can metabolize lactate too). Experimental infusion of lactate into healthy dogs for some hours at rates sufficient produce acidosis produces no detrimental haemodynamic effects [29], so even if a lactic acidaemia were to be produced by infusion of lactate containing fluids, it would have no immediate consequences. A delayed alkalosis is the usual consequence of peroperative infusion of large amounts of sodium lactate containing solutions into human patients [7, see also chapter 13.3].

4. Decreased drug metabolism.

The liver is the principal drug metabolizing organ of the body, converting many foreign substances such as drugs into water soluble products able to be excreted in bile or urine.

a. Drug elimination.

Decreased drug metabolizing ability has profound consequences on the kinetics of dugs principally eliminated by the liver. The effects of severe hepatic disease on the kinetics of some drugs used in anaesthesia are listed in table 10.3.1.

b. Sodium citrate.

Sodium citrate is the anticoagulant used most commonly in blood bank blood. Citrate is principally metabolized in the liver. Normally it takes a healthy normothermic human adult about 10 minutes to metabolize the sodium citrate contained in 500 mls of bank blood (1.7-2.5 gms of disodium citrate) [5]. When citrate anticoagulated blood is infused at a rate greater than 120 mls/minute in a normothermic adult, hypotension due to citrate intoxication may occur [6]. Citrate intoxication may possibly occur at lower infusion rates in patients with impaired hepatic function [see also chapter 13.3 on acid base balance].

5. Portal hypertension.

Portal hypertension is caused by obstruction of portal venous flow due to abnormal hepatic anatomy, e.g. as in cirrhosis. It causes a number of problems of concern to both surgeons and anaesthetists.

a. Collateral vascular channel development.

Collateral vascular channels develop because of obstruction to portal blood flow. These may give rise to haemorrhoids, oesophageal varices, and abdominal wall varices. These varices may bleed. The magnitude of the haemorrhage may vary from minor chronic blood loss causing a chronic anaemia, to massive lethal haemorrhage. The latter usually only occurs as a result of bleeding from oesophageal varices.

b. Portosystemic shunting.

Blood flowing through portosystemic collateral vascular channels bypasses the liver. Substances absorbed from the bowel are not metabolized or removed by the liver, and these can cause or exacerbate hepatic encephalopathy. Regrettably the precise nature of these substances is as yet unknown.

c. Congestive splenomegally.

Portal hypertension may cause congestive splenomegally. This can give rise to the syndrome of hypersplenism, consisting of anaemia, leukopaenia, or thrombocytopaenia. Thrombocytopaenia will contribute to, or cause a bleeding tendency.

d. Ascites formation.

Elevated portal venous pressure means that splanchnic capillary pressure is also elevated. Elevated splanchnic capillary pressures may exacerbate or cause ascites, especially in the presence of hypoalbuminaemia.

6. Ascites.

Ascites is one of the major problems associated with the surgical management of the patient with hepatic insufficiency, especially in those patients coming for intra-abdominal surgery.

The electrolyte composition of ascites fluid is the same as that of plasma or extracellular fluid, but the protein content varies from 1 to 38 gm/l, (normal plasma total protein concentration = 55-80 gm/l). The variability of the total protein concentration in ascites fluid is readily explained by variation in the rate of loss of intravascular fluid into splanchnic interstitium and ascites fluid. Elevation of splanchnic venous pressures increases both the hepatic [8] and intestinal [9] lymph/capillary protein concentration ratios. This means that increasing splanchnic venous pressure elevates the concentration of protein in both hepatic lymph and ascites fluid.

A rough idea of the magnitude of the forces driving fluid into the splanchnic interstitium and the peritoneal cavity is given by the equation below. This is a modification of the Starling equation simplified for didactic purposes. The rate of ascites formation is directly proportional to the splanchnic capillary filtration pressure.

$$P_F = [P_C - P_{IA}] - [COP_p - COP_i]$$

P_F = splanchnic capillary filtration pressure in mmHg.
P_C = mean splanchnic capillary pressure in mmHg.
P_{IA} = intra-abdominal pressure in mmHg.
COP_p = plasma colloid osmotic pressure in mmHg.
COP_i = colloid osmotic pressure of peritoneal interstitial tissue in mmHg.

If the capillary filtration pressure is greater than zero, ascites formation will occur. It is apparent that ascites fluid formation continues until $P_C <= P_{IA} + [COP_p - COP_i]$. Laparotomy and drainage of ascites reduce the P_{IA}, and the rate of ascites formation may actually increase, and remain elevated until the abdomen is closed or drainage of ascites is stopped. The volume of fluid lost in ascites may be considerable, and when one considers that ascites fluid has an electrolyte composition the same as that of extracellular fluid, as well as a relatively high protein concentration, it is obvious that a large loss of ascites fluid constitutes a considerable loss of extracellular fluid and plasma volume.

Ascites fluid continues to form postoperatively until $P_C <= P_{IA} + [COP_p - COP_i]$ again. Careful monitoring and fluid replacement must continue postoperatively until the rate of ascites formation has decreased to a level that is relatively "normal" for that patient. If the fluid volume lost as ascites is not replaced, hypovolaemia will occur. This must be aggressively treated as the degree of hypovolaemia may be so extreme in some patients that lethal hypovolaemic shock occurs.

Lost ascites fluid should be replaced with fluid with a similar electrolyte and protein content as the ascites fluid, or hypoproteinaemia and electrolyte disorders will also occur. Because it is frequently difficult to accurately measure the volume of fluid lost as ascites, central venous pressure monitoring is often required for accurate guidance of fluid replacement.

Another problem occurring with massive ascites is restriction of diaphragmatic movement to such a degree that hypoxaemia occurs.

7. Haemostatic disorders.

Haemostatic defects are common in patients with severe hepatocellular disease. There are various causes for this.

a. Decreased synthesis of all coagulation factors, with the exception of factor VIII and von Willebrand's factor which are produced by vascular endothelial cells.
b. Decreased clearance of activated coagulation factors.
c. Increased destruction of coagulation factors due to disseminated intravascular coagulation, or localized intravascular coagulation, e.g. due to hepatic cell necrosis or fibrinogenolysis.
d. Thrombocytopaenia may occur due to hypersplenism secondary to portal hypertension or as a result of disseminated intravascular coagulation.
e. Platelet dysfunction may occur due to chronic ethanol abuse.

All patients with hepatic insufficiency should be suspected of having a haemostatic disorder until proven otherwise. Haemostatic function should always be investigated preoperatively. Suitable tests which will detect most of the problems are the platelet count, bleeding time, prothrombin time, partial thromboplastin time, and the fibrinogen concentration.

8. Hepatic encephalopathy.

Patients with severe hepatic insufficiency may have a degree of encephalopathy varying from slight neurological disorder to coma. The effects of sedative or hypnotic drugs are potentiated by the central nervous system depression due to the encephalopathy. In addition to this, patients with encephalopathy are at an increased risk of aspiration of gastric contents because of depression of protective laryngeal reflexes.

9. Obstructive jaundice.

Bile salts are essential for maintenance of the normal chemical and bacteriological composition of the intestinal contents. Due to their detergent action they have a bactericidal/bacteriostatic function and prevent the absorbtion of any significant quantities of bacterial endotoxins [11].

Reduced amounts of bile salts enter the bowel during obstructive or severe hepatocellular jaundice. Because of this, about 50% of patients with obstructive jaundice have a demonstrable systemic endotoxaemia as a result of endotoxin absorbtion from the intestine, and the presence of endotoxaemia is directly related to the occurrence of postoperative renal dysfunction [10,11]. Renal failure is a major cause of death in patients undergoing surgery for relief of obstructive jaundice, the mortality being in the order of 25-80% [11]. Steatorrhoea is therefore an indicator of an increased likelihood of increased perioperative morbidity and mortality.

Oral administration of sodium deoxycholate for 48 hours prior to any surgery has been shown to prevent the occurrence of postoperative endotoxaemia and renal failure [11].

10. Hyperbilirubinaemia.

Hyperbilirubinaemia has a number of detrimental physiological effects.

a. Reduction of the contractility of smooth muscle.

Bile salts reduce the contractile response of vascular smooth muscle to noradrenaline, tyramine and angiotensin-II [12]. Increased plasma concentrations of bile salts have been shown to reduce the systemic vascular resistance in animal studies, and may be the cause of the reduction of systemic vascular resistance in hyperbilirubinaemic humans too [12].

b. Decreased myocardial contractility.

Myocardial contractility is depressed by hyperbilirubinaemia [14]. This is presumably in part due to a reduced responsiveness of jaundiced myocardium to ß-sympathomimetic stimulation [13].

c. Cytotoxicity.

High concentrations of bile salts are toxic to some tissues, the most well known examples being kernicterus and renal medullary damage which occur in infants. The mechanism of the cytotoxicity is uncertain, but high concentrations of bile salts have been shown to inhibit ATPase activity, oxygen uptake, and protein synthesis in rat small intestine [12].

11. Cardiovascular effects of hepatic insufficiency.

From the preceding discussion, it is obvious that there are many factors in patients with hepatic insufficiency which can affect systemic haemodynamics.

a. Systemic vascular resistance.

The systemic vascular resistance is reduced in severe hepatic disease due to reduced vascular smooth muscle responsiveness to both circulating vasoactive substances, as well as to sympathetic nervous stimulation [10,12].

b. Cardiac output.

The cardiac output of most patients with hepatic dysfunction is elevated above normal, regardless of whether the dysfunction is cholestatic or hepatocellular in origin [12,32,14]. This is due to a reduction of the systemic vascular resistance as a result of which the cardiac output reflexly increases, despite reduced myocardial contractility [12,14,32, see above].

c. Hypotension.

Hypotension occurs frequently in patients with severe liver dysfunction. There are a number of reasons for this [12].

i. The elevation of cardiac output in response to a reduction of systemic vascular resistance is not sufficient to maintain the arterial blood pressure.
ii. Hypovolaemia due to loss of fluid into ascites.
iii. Blood loss from bleeding oesophageal varices, etc.
iv. Endotoxaemia.

12. Renal dysfunction.

Postoperative renal failure occurs in 3-50% of patients who have undergone an operation on to relieve obstructive jaundice, and is associated with a high mortality [11]. The old term "hepato-renal syndrome" is merely a single name for a large variety of disorders which may cause renal failure in patients with severe liver disease. Some of these disorders are listed below.

a. About 50% of patients with obstructive jaundice have a demonstrable systemic endotoxaemia, the presence of which is directly related to the occurrence of postoperative renal dysfunction [10,11]. Endotoxaemia induces renal failure by inducing hypotension.
b. Hypovolaemia may occur due to bleeding from oesophageal varices, or loss of ascites fluid. Hypovolaemia will cause renal dysfunction if the blood pressure and or cardiac output are sufficiently reduced.
c. Hypotension may occur due to an excessive reduction of the systemic vascular resistance without a corresponding elevation of cardiac output.
d. High concentrations of bile salts may have a direct toxic effect on renal cells.
e. Oliguria may occur due to the combination of elevated sympathetic nervous system activity, together with increased plasma concentrations of aldosterone, angiotensin-II and antidiuretic hormone which can occur in patients with severe hepatocellular dysfunction [15].

Because of the high postoperative mortality associated with renal failure combined with hepatic dysfunction, all jaundiced patients coming for surgery should be subjected to a monitoring, fluid and diuretic therapy regime appropriate for a patient with threatened renal function [see chapter 9.3].

13. Hypoxaemia.

There are various causes of hypoxaemia in patients with severe liver disease.

a. Massive ascites restricting normal respiratory movement of the diaphragm.
b. Endotoxaemia causing intrapulmonary shunting.

c. Pulmonary oedema.
d. Pulmonary infection.

Arterial blood gases should be measured perioperatively in all jaundiced patients.

Table 10.3.1.
Percentage changes of the kinetics of some anaesthetic drugs induced by severe hepatic dysfunction, compared with the kinetics of the same drugs administered to healthy controls in the same study.

DRUG	METAB	FREE	V_d	$T_{1/2e}$	Cl
Thiopentone [16]	most	+74*	+34	+34	+11
Hexobarbitone [17]	43		+10	-5	+12
Etomidate [18,19]	90	+74*	+140*	+158*	0
Morphine [20]	>49	+20	-27	-12	-6
Pethidine [21]	>13		-6	+68*	-36
Pentazocine [21]	>75		-14	+72*	-45*
Phenoperidine [22]	98		-12	+51	-34
Fentanyl [23]	77		+16	+16	+4
Alfentanil [28]	most		+10	+125	-48
Gallamine [24]	0		+20*	+19	0
Tubocurarine [25]	small	+27			
Pancuronium [25,26]	20	-12	+49*	+82*	-22*
Vecuronium [25,30]	<3	+8	0	+69*	-45*
Atracurium [27]	93		+30*	+5	+23

METAB = % drug dose metabolized per 24 hours in normal persons.
FREE = % change in the non-protein bound plasma drug concentration.
V_d = % change in the volume of distribution.
$T_{1/2e}$ = % change in the elimination half life.
Cl = % change in the plasma clearance.
"+" = increase.
"-" = decrease.
"*" = significant to a probability level of at least 0.05 in the study cited.

14. Altered drug kinetics.

Hepatic dysfunction has a profound effect on drug kinetics, affecting both the distribution and elimination of drugs. These changes are of direct relevance to the clinical use of anaesthetic drugs. Table 10.3.1 shows some of the changes in the kinetics of some anaesthetic drugs which are caused by hepatic disease.

a. Altered distribution kinetics.

Most patients with obstructive or hepatocellular jaundice have a cardiac output that is elevated above normal. Because of this, the redistribution of drugs after intravenous injection or inhalation is more rapid [see chapter 15.2].

b. Reduced protein binding.

Reduced plasma albumin concentrations mean that the plasma protein binding of many drugs is reduced, and as a consequence the volume of distribution increases because more drug can diffuse out of the capillaries [see chapter 15.2].

The percentage plasma free drug concentration of thiopentone and etomidate are increased in direct proportion to the reduction of the plasma albumin concentration in patients with hepatic disease [16,19]. Because the free fraction of these drugs are increased, the sleep dosages of these anaesthetic induction agents are, in theory, reduced. But against this, the cardiac output is increased above normal in patients with hepatic dysfunction, and this increases the sleep dosage [31]. The result is that the sleep dosage is the same as for normal patients [16], with the exception of those patients with encephalopathy who are more sensitive to the effects of sedative and hypnotic drugs.

c. Altered elimination kinetics.

As can be seen in table 10.3.1, the elimination of many drugs is slowed, either because the hepatic clearance of the drug is reduced, the volume of distribution is increased, or both.

ANAESTHETIC MANAGEMENT

Preoperative

1. The preoperative investigations that should be performed on patients with severe hepatic dysfunction are listed below.

a. Chest X-Ray to check for the presence of any pulmonary infection, the presence of pulmonary oedema, or both.
b. Arterial blood gases to detect hypoxaemia.
c. Haemoglobin concentration. The patient may be anaemic due to either hypersplenism, haemorrhage etc.
d. Haemostatic function screen, including bleeding time, platelet count, partial thromboplastin time, prothrombin time, and possibly the fibrinogen concentration.
e. Plasma creatinine and urea concentrations, and if indicated the creatinine clearance.
f. Plasma bilirubin concentration. This gives one measure of the functional severity of the liver failure.
g. Plasma electrolyte concentrations.
h. Plasma protein concentrations. If the albumin concentration is low, pulmonary and peripheral oedema will occur at lower intravascular pressures.
i. Test for Australia antigen, i.e. Hepatitis-B antigen, as indicated.

2. Administration of drugs for preoperative sedation, as well as anticholinergic drugs should only be done according to the clinical indications for these drugs, not as a routine.

Anaesthesia.

Anaesthetic management is directed towards;

- restoring or maintaining normovolaemia, with normal electrolyte, protein and haemoglobin concentrations,
- prevention of renal failure,
- use of anaesthetic drugs so that there is minimal postoperative respiratory depression,
- maintenance of hepatic perfusion, and oxygenation,
- maintenance of normocapnia.

1. All patients with severe degrees of hepatic dysfunction (classes B and C of the Pugh or Child classification systems), must be maximally monitored in the perioperative period so that the results of any therapy to restore or maintain normovolaemia and adequate oxygenation may be checked, and therapy adjusted as needed.

Ideally a pulmonary artery catheter and direct intra-arterial blood pressure monitoring should be used in class "C" patients. A urinary catheter is also required, as an optimal diuresis must be maintained to minimize the chances of postoperative renal dysfunction.

Patients in classes A and B require at least monitoring of the urine output and central venous pressure.

2. Because of the high risk and associated mortality of renal failure in class B and C patients, fluid therapy and monitoring should be the same as for any patient with threatened renal failure.

3. Loco-regional anaesthesia.

Because of the haemodynamic changes, as well as the changes in blood volume due to severe hepatic insufficiency, epidural and spinal anaesthesia may be associated with a more profound drop in blood pressure than normal. The use of all other loco-regional anaesthetic techniques is most likely to be associated with a lower morbidity and mortality than general anaesthesia. Prior to the use of any of these techniques, the haemostatic parameters should be within an acceptable range as discussed in chapter 6.3.

4. General anaesthesia.

General anaesthesia is advisable for seriously ill patients who are to undergo any form of major surgery. The main reason for this is the easy control over ventilation, systemic vascular resistance and cardiac output that is possible. The same applies to patients with liver dysfunction. There are some aspects relating to the administration of general anaesthesia in patients with severe hepatic dysfunction (functional classes B and C), which are worthy of mention.

a. The ventilation of the patient should be controlled so as to minimize the chance of hypoxaemia due to pressure on the diaphragm from ascites, upper abdominal operative procedures etc. In addition the chance of hypoxic hepatocellular damage is minimized, and normocapnia can be easily maintained.

b. Any induction agent may be used, so long as the arterial blood pressure and cardiac output due not fall excessively. A prolonged elimination half life is no reason not to use any particular induction agent as the termination of the action of anaesthetic induction agents administered as a single intravenous bolus is by redistribution within the body, and not by elimination. Selection of an appropriate induction agent is on haemodynamic criteria, the drug causing least cardiovascular depression being the most appropriate in the severely ill patient [see chapter 2.1].
c. The elimination half lives of many of the most commonly used non-depolarizing muscle relaxants are prolonged by hepatic dysfunction. From table 10.3.1 it is seen that the volumes of distribution of these drugs are increased, as are their elimination half lives. This has consequences for the administration of these drugs. As the plasma concentration at which a relaxant has a given effect is unchanged by liver disease, larger initial and repeat dosages than usual of a given muscle relaxant must be given to achieve the same effect. As the elimination half lives are increased, the dosage interval between any repeat dosages is longer than in patients without liver dysfunction. It is preferable to administer repeat dosages of these drugs according to clinical requirements, or using a peripheral nerve stimulator to monitor neuromuscular transmission.
d. Many opiates have a prolonged elimination half life in patients with hepatic cirrhosis. This is due to decreased clearance rather than any alteration of the distribution volume. The implications for administration of these drugs is that the normal initial and repeat dosages may be given, but that the interval between repeat dosages is likely to be longer than in a patient with normal hepatic function.
e. The use of many anaesthetic gases is associated with a high incidence of postoperative elevation of the concentrations of hepatic enzymes, [see chapter 10.2]. For this reason it is best to avoid the use of drugs such as halothane and enflurane as their use may exacerbate existing hepatic dysfunction.

5. Fluid therapy.

The aim of perioperative fluid therapy is to restore, or to maintain normovolaemia. The normal volumes of replacement fluids should be administered perioperatively, plus an extra volume to replace any losses of extracellular fluid due to ascites formation. As the rate of formation of ascites fluid may be quite large, hypovolaemic hypotension may occur if losses of ascites fluid are not aggressively managed perioperatively. Determination of the volumes of fluid required is difficult, and can only be done by infusion of the appropriate fluids to replace ascites losses until acceptable haemodynamics and urine output have been achieved.

Postoperative.

Patients with classes B and C hepatic dysfunction should be routinely admitted into an intensive care unit postoperatively for monitoring and therapy of hypovolaemia and hypoxaemia.

REFERENCES

1. Davidson,C.S., et al.,(1969), Sustaining life during fulminant hepatic failure. ANNALS OF INTERNAL MEDICINE, 71, 415-418.
2. Armstrong,C.P., et al.,(1984), Wound healing in obstructive jaundice. BRITISH JOURNAL OF SURGERY, 71, 267-270.
3. Whittaker,M.(1980). Plasma cholinesterase variants and the anaesthetist. ANAESTHESIA, 35, 174-197.

4. Sherwin,R.S., et al.,(1974), A model of the kinetics of insulin in man. JOURNAL OF CLINICAL INVESTIGATION, 53, 1481-1492.
5. Denlinger,J.K., et al.(1976). Hypocalcaemia during rapid blood transfusion in anaesthetized man. BRITISH JOURNAL OF ANAESTHESIA, 48, 995-1000.
6. Denlinger,J.K., Nahrwold,M.L.(1976). Cardiac Failure Associated with Hypocalcemia. ANESTHESIA AND ANALGESIA, 55, 34-36.
7. Cohen,R.D., Simpson,R.,(1975), Lactate metabolism. ANESTHESIOLOGY, 43, 661-673.
8. Granger,D.N., et al.,(1979), Permselectivity of cat liver blood-lymph barrier to endogenous macromolecules GASTROENTEROLOGY, 77, 103-109.
9. Granger,D.N., Taylor,A.E.,(1980), Permeability of intestinal capillaries to endogenous macromolecules. AMERICAN JOURNAL OF PHYSIOLOGY, 238, H457-H464.
10. Bailey,M.E.,(1976), Endotoxin, bile salts and renal function in obstructive jaundice. BRITISH JOURNAL OF SURGERY, 63, 774-778.
11. Cahill,C.J.,(1983), Prevention of portoperative renal failure in patients with obstructive jaundice - the role of bile salts. BRITISH JOURNAL OF SURGERY, 70, 590-595.
12. Green,J., et al.,(1986), Jaundice, the circulation and the kidney. NEPHRON, 37, 145-152.
13. Binah,O., et al.,(1985), Obstructive jaundice blunts myocardial contractile response to isoproterenol: A clue to the susceptability of jaundiced patients to shock? CLINICAL SCIENCE, 69, 647-653.
14. Green,J., et al.,(1986), The "jaundiced heart": A possible explanation for postoperative shock in obstructive jaundice. SURGERY, 100, 14-19.
15. Schrier,R.W., et al.,(1983), Disturbed volume homeostasis in patients with cirrhosis of the liver. KIDNEY INTERNATIONAL, 23, 303-311.
16. Pandele,G., et al.(1983). Thiopental Pharmacokinetics in Patients with Cirrhosis. ANESTHESIOLOGY, 59, 123-126.
17. Richter,E., et al.(1980). Disposition of Hexobarbital in Intra- and Extrahepatic Cholestasis in Man and the Influence of Drug Metabolism Inducing Agents. EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, 17, 197-202.
18. Sear,J.W.,(1983), General kinetic and dynamic principles and their application to continuous infusion anaesthesia. ANAESTHESIA, supplement, 38, 10-25.
19. Carlos,R., et al.,(1979), Plasma protein binding of etomidate in patients with renal failure or hepatic cirrhosis. CLINICAL PHARMACOKINETICS, 4, 144-148.
20. Rashmi,V., et al.,(1981) Normal metabolism of morphine in cirrhosis. GASTROENTEROLOGY, 81, 1006-1011.
21. Neal,E.A., et al.(1979). Enhanced bioavailability and decreased clearance of analgesics in patients with cirrhosis. GASTROENTEROLOGY, 77, 96-102.
22. Isherwood,C.N., et al.(1984). Elimination of phenoperidine in liver disease. BRITISH JOURNAL OF ANAESTHESIA, 56, 843-847.
23. Haberer,J.P., et al.(1982). Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. BRITISH JOURNAL OF ANAESTHESIA, 54, 1267-1269.
24. Ramzan,I.M., et al.(1981). Pharmacokinetics and Pharmacodynamics of Gallamine Triethiodide in Patients with Total Biliary Obstruction. ANESTHESIA AND ANALGESIA, 60, 289-296.
25. Duvaldestin,P., Henzel,D.(1982). Binding of tubocurarine, pancuronium, and ORG-NC45 to serum proteins in normal man and in patients with cirrhosis. BRITISH JOURNAL OF ANAESTHESIA, 54, 513-516.
26. Duvaldestin,P., et al.(1978). Pancuronium pharmacokinetics in patients with liver cirrhosis. BRITISH JOURNAL OF ANAESTHESIA, 50, 1131-1135.
27. Ward,S., Niell,E.A.M.(1983). Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). BRITISH JOURNAL OF ANAESTHESIA, 55, 1169-1172.
28. Hug C.C., Chaffman M.(1984). "Alfentanil :Pharmacology and Uses in Anaesthesia",pub. ADIS Press, New Zealand, page 14.
29. Park,R., Arueff,A.I.,(1983), Lactic acidosis: Current concepts. CLINICS IN ENDOCRINOLOGY AND METABOLISM, 12, 339-359.
30. Lebrault,C., et al.,(1986), Pharmacokinetics and pharmacodynamics of vecuronium in patients with cholestasis. BRITISH JOURNAL OF ANAESTHESIA, 58, 983.
31. Christensen,J.H., et al.(1982). Pharmacokinetics and pharmacodynamics of thiopentone: A comparison between young and elderly patients. ANAESTHESIA, 37, 398-404.
32. Siegel,J.H., et al.,(1974), Hyperdynamic states and the physiologic determinants of survival in patients with cirrhosis and portal hypertension. ARCHIVES OF SURGERY, 108, 282-292.

Part 11

GASTROINTESTINAL FUNCTION

Gastrointestinal function, and the effects of anaesthesia and surgery are frequently of limited interest to many anaesthetists, however they are of direct relevance to everyday anaesthetic practice. The problems most relevant to anaesthetic practice that are discussed are;

1. The duration of the preoperative fast.

2. The problems presented by the patient with a full stomach.

3. Postoperative nausea and vomiting.

4. How soon after surgery can the patient resume oral fluids and food.

5. The necessity for a nasogastric tube.

Chapter 11.1

THE PREOPERATIVE FAST

Anaesthesia and sedation depress or block the functioning of protective upper airway reflexes, making pulmonary aspiration of vomited or regurgitated gastric contents likely. This is a complication of anaesthesia feared by both anaesthetists and surgeons alike. For this reason patients are fasted preoperatively in the hope that the stomach is completely empty, or at least that the volume of gastric contents is minimal, prior to induction of general anaesthesia or administration of sedative drugs during regional anaesthetic techniques.

The generally accepted time period that the patient should remain without food or drink prior to induction of general anaesthesia is 4 hours or more. However the necessity for such a long preoperative fast has recently been the subject of some investigation and review [1,2,3,4,5]. The conclusion to be drawn from all recent studies is that gastric emptying for a light meal, such as tea and toast, is essentially complete within 2-4 hours in patients who are NOT SICK OR ANXIOUS [1]. But this is obviously not applicable to everyone as the rate of gastric emptying varies from one patient to another, and is influenced by a number of factors such as disease, drugs and psychological factors [see also chapter 11.2].

FACTORS RETARDING GASTRIC EMPTYING

1. Psychological.

a. Preoperative anxiety or terror [4,13].
b. Severe depression.

2. Type of food.

a. Liquids pass through the stomach more rapidly than solids.
b. Fatty foods pass through the stomach more slowly than non-fatty foods.
c. Antacids pass slowly through the stomach.

3. Gastrointestinal disease.

a. Mechanical stenosis, due to oesophageal stenosis, pyloric stenosis, bowel obstruction, etc.
b. Functional defects such as achalasia of the oesophagus, gastric atony, bowel obstruction, etc.
c. Intra-abdominal sepsis of any sort retards intestinal and gastric motility.

4. Coexisting disease or variations of normal physiology.

a. Fractures of bones will usually stop or retard gastric emptying.
b. Severe pain.
c. Pregnancy, and especially labor [4,14].

5. Drugs.

a. Glycopyrrolate, but not atropine retards gastric emptying.
b. Opiates retard gastric emptying. This effect may be reversed with naloxone.
c. Antidepressant retard intestinal motility by virtue of their anticholinergic action, e.g. amitryptaline, doxepin etc.
d. Alcohol in large quantities.

Table 11.1.1.

Effects of fasting on the plasma glucose concentration in children and adults. This table gives the results of a number of investigations, giving the mean glucose concentration measured at the end of the period of fasting mentioned, and the percentage of persons with significant hypoglycaemia.

	Duration of fast (hours)	Mean plasma glucose concn. (mmol/l)	% patients with glucose < 3 mmol/l
ADULTS [9]			
(Healthy)			
males (N = 12)	24	4.35	0
females (N = 44)	24	3.2	2.5
CHILDREN [6,10]			
(Healthy)			
ages 0-1 yrs (N = 37)	4	4.45	2.7
ages 1-4 yrs (N = 24)	13	54.1	0
ages 4 + yrs (N = 22)	13	3.96	0
CHILDREN [6]			
(Underweight)			
ages 0-5 yrs (N = 32)	4	3.6-4.1	31

N.B. Normal plasma glucose concentration is between 3.5-5.5 mmol/l. Hypoglycaemia is significant and often symptomatic when the plasma concentration falls below 2-2.5 mmol/l (35-45 mg/100 mls) in adults [11,12], and in children when it is below 3 mmol/l (55 mg/100 mls) [6].

PROBLEMS DUE TO FASTING

1. Fasting is unpleasant.

Both adults and children find that a protracted preoperative fast is unpleasant.

2. Increased blood viscosity.

Blood viscosity in adults increases significantly after a 24 hour, but not after a 12 hour fast [7]. The increased viscosity is due to haemoconcentration. However, while blood viscosity is undoubtedly increased, the physiological effects are negligible as the increase is only slight.

3. Hypoglycaemia.

The manifestations of anxiety and hypoglycaemia are similar, consisting principally of the manifestations of increased sympathetic nervous system activity, such as anxiety or agitation together with a tachycardia, elevation of the arterial blood pressure and sweating. Because these manifestations are rather non-specific, no real diagnosis of their cause can be made unless the plasma glucose concentration has been measured.

The results of various studies of plasma glucose concentrations resulting from preoperative fasting are presented in table 11.1.1. It is apparent from this table that the group of patients most likely to develop symptomatic hypoglycaemia are underweight children under 5 years old fasted for longer than 4 hours [6]. Healthy infants under one year old, and women may also develop fasting hypoglycaemia but this is less likely than for underweight children.

It is quite likely that the more rapid onset of fasting hypoglycaemia in underweight children is due to reduced glycogen reserves [6]. Undernourished adults also have reduced muscle and liver glycogen reserves too, and this group of patients is also prone to fasting hypoglycaemia [12].

ANAESTHETIC CONSEQUENCES AND GUIDELINES

1. A minimum 4 hour fasting period is not unreasonable prior to an elective operation on a normally healthy patient. Even if this is rather longer than necessary for some patients, anxious patients require somewhat longer for "complete" gastric emptying to occur, and most patients are anxious to a greater or lesser degree prior to surgery.

2. Consider any patient who has any of the factors retarding gastric emptying as having an increased, or definite risk of having a non-empty stomach. The anaesthetist should be especially suspicious that the stomach is not empty in the categories of patients listed below.

a. The drunken patient, especially one who has fractured bones.
b. The terrified, anxious patient may be regarded as a patient with a stomach containing a greater volume of fluid than a non-anxious patient coming for the same operation.
c. A patient who has undergone major trauma is a patient with a potentially full stomach, despite the fact that some hours may have elapsed between the trauma and induction of anaesthesia.
d. A patient without a nasogastric tube in-situ who comes for re-operation within 24 hours after a previous operation should be regarded as a patient with a potentially full stomach. Significant volumes of gastric fluid as well as saliva may have accumulated.

e. Those patients who have been administered opiates or anticholinergic drugs prior to surgery while the stomach was not empty. These drugs retard gastric emptying still further, increasing the chance that a significant volume of gastric contents is present at induction of anaesthesia. However opiates should never be denied patients who are in severe pain because of the retardation of gastric motility that they cause. Humanity requires that they be administered, and the risk presented by the likelihood of an increased volume of gastric contents is minimized by adjusting the type of anaesthesia, or induction technique.

3. Children under one year of age should be permitted to drink some liquid feed 4 hours before induction of anaesthesia, e.g. a milk, or a glucose solution etc. This is certainly necessary for all underweight children under the age of 5 years, as all underweight children are especially likely to develop hypoglycaemia if fasted, even for a period of 4 hours [see table 11.1.1].

4. Adults whose operation is planned for the afternoon, should be permitted a light breakfast, e.g. tea and toast etc. Underweight undernourished adults should have an intravenous glucose 5% infusion inserted preoperatively to prevent fasting hypoglycaemia.

5. Oral premedication should be administered at least 1.5-2 hours preoperatively, as gastric absorbtion may be delayed by anxiety. Gelatine capsules and aqueous solutions of dugs are more rapidly absorbed than are tablets. The small amount of fluid required for ingestion of these oral medicaments, usually about 20 mls, is very rapidly absorbed. In addition to this, 20 mls is no more in volume than is what is normally present in the stomach after fasting.

MANAGEMENT OF THE PATIENT WITH A "FULL" STOMACH

If there is a possibility of a patient having a full stomach, that is a stomach with a greater than normal volume of intragastric contents, then measures must be taken to minimize the chance of aspiration of the gastric contents during anaesthetic induction.

1. Decrease the volume of gastric contents.

The gastric contents of any patient with a suspected full stomach should be emptied as much as possible prior to induction of anaesthesia by means of gastric suction. After the stomach has been emptied as much as is possible, the gastric tube should be removed prior to induction of anaesthesia, as a nasogastric tube renders the oesophageal sphincters incompetent, and permits regurgitation of stomach contents alongside the nasogastric tube. Prior to its removal, an antacid solution should be introduced into the stomach through the tube so as to increase the pH of the contents above 2.5 [see below].

2. Decrease the acidity of the gastric contents.

Gastric acidity may be reduced using any one of a variety of antacid solutions. Increasing the pH of the gastric contents has two effects. The tone of the lower oesophageal sphincter is increased which makes regurgitation of gastric contents less likely [8]. In addition, if the pH of the gastric contents are increased above 2.5, pulmonary damage due to aspiration of gastric contents is reduced [5]. Effective dosages for adults are given below.

- Magnesium trisilicate mixture B.P.C. 20 mls. This maintains the gastric pH above 2.5 for about 2 hours [5].
- Sodium citrate solution (0.3 mmol/l) 20-30 mls. This also maintains the gastric pH above 2.5 for about 2 hours [5].

3. Anaesthetic technique.

a. General anaesthesia.

If general anaesthesia is indicated, use a rapid intravenous induction sequence for induction of anaesthesia ("Crash induction"), with cricoid pressure to minimize the chance of regurgitation of gastric contents. Insertion of a cuffed endotracheal tube and positive pressure ventilation will minimize the chance of aspiration. Maintenance of anaesthesia may otherwise be done using any drugs deemed appropriate.

After the operation the endotracheal tube should only be removed when the patient is sufficiently awake with enough muscle power, and reflexes to protect his airway against aspiration of gastric contents should he vomit or regurgitate.

b. Regional anaesthesia.

There is no contraindication to regional anaesthesia if this is an appropriate technique for the patient and procedure planned. However the patient should not be excessively sedated, as a sleeping sedated patient cannot protect his airway adequately against possible aspiration of gastric contents.

REFERENCES

1. Miller,M., et al.(1983). Gastric contents at induction of anaesthesia. Is a 4-hour fast necessary? BRITISH JOURNAL OF ANAESTHESIA, 55, 1185-1188.
2. Todd, J.G., Nimmo, W.S.(1983). Effect of premedication on drug absorbtion and gastric emptying. BRITISH JOURNAL OF ANAESTHESIA, 55, 1189-1193.
3. Clark, J.M., Seager, S.J.(1983). Gastric emptying following premedication with glycopyrrolate or atropine. BRITISH JOURNAL OF ANAESTHESIA, 55, 1195-1199.
4. Nimmo, W.S.(1984). Effect of anaesthesia on gastric motility and emptying. BRITISH JOURNAL OF ANAESTHESIA, 56, 29-36.
5. Morgan,M.(1984). Control of intragastric pH and volume. BRITISH JOURNAL OF ANAESTHESIA, 56, 47-57.
6. Payne,K., Ireland,P.(1984). Plasma glucose levels in the peri-operative period in children. ANAESTHESIA, 39, 868-872.
7. Aronson,H.B., et al.(1980). Blood viscosity and the overnight fast. CANADIAN ANAESTHETISTS' SOCIETY JOURNAL, 27, 550-551.
8. Cotton,B.R., Smith,G.(1984), The lower oesophageal sphincter and anaesthesia. BRITISH JOURNAL OF ANAESTHESIA, 56, 37-46.
9. Merimee,T.J., Tyson,J.E.,(1974), Stabilization of plasma glucose during fasting. Normal variations in two studies. NEW ENGLAND JOURNAL OF MEDICINE, 291, 1275-1278.
10. Jensen,B.H., et al.,(1982), Preoperative starvation and blood glucose concentrations in children undergloing inpatient and outpatient surgery. BRITISH JOURNAL OF ANAESTHESIA, 54, 1071-1074.
11. Johnson,D.D., et al.,(1980), Reactive hypoglycaemia. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 243, 1151-1155.
12. Fajans,S.S., Floyd,J.C.,(1976), Fasting hypoglycaemia in adults. NEW ENGLAND JOURNAL OF MEDICINE, 294, 766-772.
13. Simpson,K.H., Stakes,A.F.,(1987), Effect of anxiety on gastric emptying in preoperative patients. BRITISH JOURNAL OF ANAESTHESIA, 59, 540-544.
14. Lewis,M., Crawford,J.S.,(1987), Can one risk fasting the obstetric patient for less than 4 hours? BRITISH JOURNAL OF ANAESTHESIA, 59, 312-314.

Chapter 11.2

EFFECTS OF SURGERY & ANAESTHESIA ON GASTROINTESTINAL FUNCTION

Gastrointestinal motility and function is regulated by centrally as well as locally mediated neural and hormonal factors. There is both a parasympathetic as well as sympathetic nervous innervation of the gastrointestinal tract. But this appears to only have a modulatory function as dennervation does not alter normal spontaneous gastrointestinal activity. Gastrointestinal activity is also regulated by a large number of local and systemic hormones [1]. All these regulatory and control mechanisms are affected by surgery and anaesthesia, which can have a profound effect on gastrointestinal function.

EFFECTS OF TRAUMA AND SURGERY

"Postoperative ileus" is a well recognized syndrome in clinical surgical practice. It usually manifests as an inability to absorb oral fluids or solids, as evidenced by nausea, vomiting and abdominal distension when food and drink are administered too soon postoperatively. For this reason postoperative fasting and nasogastric drainage are commonly employed to prevent fluid accumulating in the stomach.

1. Effect of increased sympathetic activity.

The causes of "postoperative ileus" are not well defined, but the autonomic nervous system is certainly involved. Pain and surgery increase sympathetic nervous activity, and this is known to depress gastrointestinal activity. Blockade of abdominal sympathetic afferent and efferent activity with epidural anaesthesia has been shown to prevent the depression of gastric motility resulting from intra-abdominal operations such as cholecystectomy [3] or hysterectomy [5], although it does not prevent the depression of colonic activity resulting from cholecystectomy [4]. These somewhat variable results show that while the sympathetic nervous system certainly plays an important role in the pathogenesis of postoperative ileus, it is not the only factor.

2. Effect of altered gastrointestinal hormone concentrations.

Gastrointestinal hormone concentrations are also affected by trauma and surgery. An example of this is the effect of surgery on "motilin", a gastrointestinal hormone. The plasma motilin concentration falls immediately on commencing surgery, and simultaneously gastrointestinal activity is depressed. Recovery of gastrointestinal function occurs simultaneously with the spontaneous restoration of normal plasma motilin concentrations [6].

Conclusions.

It is apparent from this small review that trauma and surgery significantly affects the neuro-endocrine physiology of the gastrointestinal tract, the final result of which is to depress gastrointestinal propulsive activity.

REGIONS OF THE GASTROINTESTINAL TRACT AFFECTED BY SURGERY

Many studies have been performed to define those sections of the gastrointestinal tract most sensitive to the effects of surgery, and to define approximately how long such effects last. These studies all show that spontaneous electrical, contractile and propulsive activity of the gastrointestinal tract are depressed by surgery, and the depression of activity extends into the postoperative period [7,8,9,10].

1. Regions of gastrointestinal tract most affected by surgery.

Gastrointestinal activity is depressed by all forms of surgery, but it is depression of spontaneous gastric emptying that causes the intolerance of food and fluids in the beginning of the postoperative period [7,8]. Studies of patients undergoing various types of surgery all show that spontaneous activity of the small intestine is minimally depressed, and may continue even during major surgery. The small intestine is the first section of the gastrointestinal tract to recover its spontaneous contractile and prōpulsive activity, and subsequently the stomach. The colon is the section of the bowel which recovers last of all. It may take up to 3-5 days before any faeces or flatus are passed after major intra-abdominal surgery [7]. Animal studies have confirmed this pattern [9,10,18], and have shown that it is the sigmoid colon which is the last section of the gastrointestinal tract to regain normal spontaneous activity [10].

2. Effect of site of operation on gastrointestinal depression.

The site of operation influences the duration of any postoperative depression of gastrointestinal contractility. Spontaneous gastric propulsive activity is depressed in nearly all patients postoperatively, regardless of the site of operation. However gastric motility recovers more rapidly in patients whose operation is extraperitoneal rather than in those undergoing intraperitoneal operations [7].

3. Effect of magnitude of operation on gastrointestinal depression.

Human studies show that there is a relationship between the magnitude of an operation and the duration of postoperative gastrointestinal depression [6,7,2]. Gastric emptying is normal shortly after light general anaesthesia for minor procedures such as cystoscopy [2]. Gastric motility has also been found to be normal within 24 hours in 62% of patients undergoing extraperitoneal procedures, while it is normal in only 40% of patients who have undergone major intraperitoneal surgery [7].

EFFECTS OF ANAESTHESIA

Anaesthetic procedures are minimally traumatic, and as a consequence, the gastrointestinal effects of anaesthesia are those of the drugs employed.

1. Sedative/hypnotic drugs.

Diazepam has no effect on the rate of gastric emptying [13,14]. Thiopentone increases the electrical activity and the motility of the duodenum and jejunum, but not the stomach or ileum [16]. Neither ketamine nor althesin affect gastric emptying [12].

In practice it may be expected that none of the sedative/hypnotic drugs used in anaesthesia significantly depress gastrointestinal function in the postoperative period.

2. Anticholinergic drugs.

Anticholinergic drugs have a pronounced effect on gastrointestinal function, reducing the rate of secretion from the mucosal glands, as well as decreasing gastric, small and large intestinal motility in normal therapeutic dosages [15]. For example a dose of 0.8 mg atropine is more than sufficient to block the propulsive activity of the human colon [15].

3. Anaesthetic gases.

The volatile anaesthetic gases, diethyl-ether, chloroform, cyclopropane and halothane depress spontaneous gastrointestinal activity in a dose related manner, the effect disappearing when the drugs are no longer present at anaesthetic concentrations within the body [12].

Nitrous oxide diffuses rapidly through biological membranes, increasing the volume and pressure within any closed gas containing cavity in the body. This is because the usual gases present in these cavities diffuse into the blood much less rapidly than nitrous oxide diffuses into the cavity. Nitrous oxide diffuses through biological membranes 34 times more rapidly than nitrogen. The result of all this is that the gastrointestinal tract becomes distended with gas, mainly nitrous oxide, during the course of a long operation. Canine experiments show that the maximum degree of gastrointestinal distension is achieved after 200 minutes (3.4 hours) of inspiring a 70% nitrous oxide - 30% oxygen mixture [17]. Such gaseous distension can cause the volume of the intestines to be so great that closing the abdomen after prolonged intra-abdominal surgery is very difficult. This is a problem commonly encountered by many anaesthetists and surgeons.

4. Opiates.

Opiates are frequently used during the perioperative period. Administration of any opiate depresses the electrical activity of the stomach as well as that of the small intestine [3]. The rate of gastric emptying is also slowed [8,13,14], as is small and large intestinal propulsive activity [12].

In addition to the above effects, morphine, and other opiates, with the exception of pethidine, increase intraluminal gastrointestinal pressures by causing uncoordinated intestinal contractions [12].

5. Muscle relaxant drugs.

These drugs do not appear to affect gastrointestinal motility.

6. Anticholinesterases.

Drugs such as neostigmine and other anticholinesterases are used to reverse the effects of anticholinergic drugs. Neostigmine increases gastrointestinal propulsive activity as well as increasing the intraluminal intestinal pressures. Intraluminal pressures of up to 75 mmHg have been measured after administration of 0.25 mg neostigmine intravenously [12], and use of these drugs may be associated with a higher frequency of leakages of intestinal

anastomoses. Atropine and anaesthetic concentrations of halothane reduce these effects somewhat [12].

7. Regional anaesthesia.

Regional anaesthetic techniques such as epidural anaesthesia increase gastrointestinal motility, and inhibit surgery induced reduction of gastric, but not colonic emptying [3,4,5].

CLINICAL CONSEQUENCES

The clinical consequences of all the above are mainly related to postoperative surgical management rather than anaesthetic management, as the effects of anaesthesia as such are temporary. Some clinically relevant consequences are listed below.

1. Time to resumption of oral fluids and food.

a. Minor elective surgery.

Minor elective operative procedures performed under general anaesthesia such as cystoscopy or uterine curettage have no significant effect on gastric or intestinal function. Patients who have undergone such procedures may be permitted to drink as soon as consciousness and airway reflexes have returned to normal.

b. Non-abdominal surgery.

Procedures which are extraperitoneal, and of the order of magnitude of an inguinal herniorrhaphy, sympathectomy, excision of herniated lumbar intervertebral discs, or less, may reduce gastric emptying for 8-24 hours postoperatively. Patients who have undergone uncomplicated surgical procedures of this order of magnitude under general anaesthesia should only be permitted to cautiously resume ingestion of oral fluids about 8 hours postoperatively.

c. Intra-abdominal surgery.

Intra-abdominal operations retard the rate of gastric emptying for a period of at least 24 hours in most patients, regardless of the magnitude of the procedure. Colonic motility may be depressed for up to 3-5 days postoperatively. If the operation is greater in magnitude than a cholecystectomy, then insertion of a nasogastric tube is desirable to prevent possible excessive postoperative accumulation of fluid in the stomach secondary to prolonged gastric atony.

Oral fluid intake may be gradually resumed once there is auscultatory evidence of intestinal activity, together with evidence of minimal gastric retention measured one hour after administration of test doses of 50-100 mls of water into the stomach through the nasogastric tube.

2. Effects of postoperative drugs.

Postoperative administration of opiates slows the return of normal gastrointestinal motility, slowing the return to normal oral ingestion of fluids.

3. Administration of oral medications.

Oral medications cannot be administered until gastric motility has returned. This means that some patients will have to miss their usual medication for about 8-24 hours at

least. If any drugs must be given, then they should be administered by suppository, intramuscularly, or by intravenous infusion.

REFERENCES

1. Scratcherd,T., Grundy,D.(1984), The physiology of gastrointestinal motility and secretion. BRITISH JOURNAL OF ANAESTHESIA, 56, 3-18.
2. Nimmo,W.S.,(1984), Effect of anaesthesia on gastric motility and emptying. BRITISH JOURNAL OF ANAESTHESIA, 56,29-36.
3. Gelman,S., et al.,(1977), Electroenterography after cholecystectomy. The role of high epidural anaesthesia. ARCHIVES OF SURGERY, 112, 580-583.
4. Wallin,G., et al.,(1986), Failure of epidural anaesthesia to prevent postoperative paralytic ileus. ANESTHESIOLOGY, 65, 292-297.
5. Nimmo,W.S., et al.,(1978), Gastric emptying following hysterectomy with extradural anaesthesia. BRITISH JOURNAL OF ANAESTHESIA, 50, 559-561.
6. Rennie,J.A., et al.,(1980), Neural and humoral factors in postoperative ileus. BRITISH JOURNAL OF SURGERY, 67, 694-698.
7. Nachlas,M.M., et al.,(1972), Gastrointestinal motility studies as a guide to postoperative management. ANNALS OF SURGERY, 175, 510-522.
8. Ingram,D.M., Sheiner,H.J.,(1981), Postoperative gastric emptying. BRITISH JOURNAL OF SURGERY, 68, 572-576.
9. Graber,J.N., et al.,(1982), Relationship of duration of postoperative ileus to extent and site of operative dissection. SURGERY, 92, 87-92.
10. Woods,J.H., et al.,(1978), Postoperative ileus: A colonic problem? SURGERY, 84, 527-533.
11. Marsh,R.H.K., et al.,(1983), Gastric emptying and drug absorbtion before and after surgery. BRITISH JOURNAL OF ANAESTHESIA, 55, 242P.
12. Aitkenhead,A.R.,(1984), Anaesthesia and bowel surgery. BRITISH JOURNAL OF ANAESTHESIA, 56, 95-101.
13. Todd,J.G., Nimmo,W.S.,(1983), Effect of premedication on drug absorbtion and gastric emptying. BRITISH JOURNAL OF ANAESTHESIA, 55, 1189-1193.
14. Shah,M., et al.,(1984), Effect of premedication with diazepam, morphine or nalbuphine on gastrointestinal motility after surgery. BRITISH JOURNAL OF ANAESTHESIA, 56, 1235-1238.
15. Innes,I.R., Nickerson,M.,(1975), Atropine, scopolamine, and related antimuscarinic drugs. In "The Pharmacological Basis of Therapeutics", 5th edn., editors Goodman,L.S., Gilman,A., published Macmillan, pages 515-532.
16. Healy,T.E.J., et al.,(1981), Effect of some i.v. anaesthetic agents on canine gastrointestinal motility. BRITISH JOURNAL OF ANAESTHESIA, 52, 229.
17. Munson,E.S.,(1974), Transfer of nitrous oxide into body air cavities. BRITISH JOURNAL OF ANAESTHESIA, 46, 202-209.
18. Carmichael,M.J., et al.,(1977), Effect of abdominal surgery on intestinal myoelectric activity in the dog. AMERICAN JOURNAL OF SURGERY, 133, 34-38.

Chapter 11.3

NAUSEA AND EMESIS

Nausea and vomiting are sometimes unpleasant and troublesome accompaniments to surgery, anaesthesia, or the use of some drugs.

Nausea is defined as the desire or tendency to vomit. Vomiting should always be carefully be differentiated from regurgitation. Regurgitation is the passive reflux of gastric contents through a relaxed oesophagus and oesophageal sphincters. Vomiting is an active process, consisting of the simultaneous closure of the glottis, elevation of the soft palate to close the nasal cavity, relaxation of oesophageal sphincters, contraction of the pylorus, and a powerful synchronous contraction of the diaphragm and abdominal muscles. The end result of all these changes is the forceful expulsion of gastric contents into the oropharynx.

Table 11.3.1.
Known neurotransmitter receptors in nuclei involved in nausea and vomiting [1].

Vomiting center	- Histamine-H_1 - Acetylcholine-muscarinic
Chemoreceptor trigger zone	- Dopamine-D_2
Vestibular center	- Histamine-H_1

CONTROL OF NAUSEA & EMESIS

The act of vomiting itself is controlled from the vomiting center, which consists of a bilateral nucleus situated deep in the medulla at the level of the dorsal motor nucleus, near the tractus solitarius.

1. There is also a chemoreceptor trigger zone which is able to trigger vomiting. This is also a bilateral structure, located in the surface of the medulla in the floor of the fourth ventricle at the level of the area postrema.

2. Rapidly changing motion may also trigger vomiting. This is mediated via the lateral vestibular nuclei.

3. Unpleasant psychic stimuli may also trigger vomiting. The neurological pathways initiating vomiting in these cases is unknown.

4. Direct gastric irritation may initiate vomiting.

Some progress has been made in identifying some of the neurotransmitters and their receptors in the various nuclei involved in nausea and vomiting. These are shown in table 11.3.1.

PROBLEMS DUE TO NAUSEA AND VOMITING

Perioperative, and especially postoperative nausea and emesis may adversely affect the result of an operative procedure, quite apart from the fact that it is exceedingly unpleasant for the affected person. These problems fall into three categories.

1. Pulmonary aspiration.

Pulmonary aspiration of gastric contents may occur. This is especially likely to occur in patients with a reduced level of consciousness due to sedation, and during or after general anaesthesia. A reduced level of consciousness due to sedation and general anaesthesia diminishes the efficacy of protective laryngeal and pulmonary reflexes. These reflexes consist of closure of the larynx and cessation of spontaneous respiration in response to stimulation of the nasal and respiratory mucosa.

The elderly are especially prone to pulmonary aspiration, as age is accompanied by a progressive decrease in the efficacy of these protective airway reflexes [2], and this is only exacerbated by general anaesthesia and sedation.

2. Forceful contraction of abdominal musculature.

Vomiting causes forceful contractions of the abdominal muscles, and this, coupled with the associated contraction of the diaphragm may cause the intra-abdominal pressure to rise to such a degree that abdominal wall sutures may either tear out, or become unknotted. In such cases abdominal wound dehiscence, or incisional hernias may occur.

3. Raised venous pressure.

The act of vomiting elevates the venous pressure considerably. Such elevation of the venous blood pressure can cause postoperative problems in those patients who have undergone intraocular operations. The chance of vitreous haemorrhage may well be increased by repeated vomiting after a procedure such as intracapsular lens extraction.

Table 11.3.2.
Percentage frequency of postoperative nausea and/or vomiting due to various drugs used in anaesthesia.

Induction agents.
(Atropine premedication, nitrous oxide-oxygen anaesthesia with intermittent i.v. injection of induction agent [4])

Thiopentone	- 17%
Methohexitone	- 26%
Ketamine	- 41%
Etomidate	- 39%

Opiates.
(administered i.m. for premedication [5])

Morphine	- 55-75%
Papaveretum	- 58%

CAUSES OF NAUSEA AND EMESIS

As has already been implied above, there are various possible causes of nausea and emesis. These may be classified as below.

1. Central nervous system causes.

a. Direct mechanical stimulation of the vomiting center by trauma, tumors, etc.
b. Psychic factors such as disgust, fear, anxiety, etc.
c. Hypotension, e.g. due to spinal anaesthesia [4].
d. Rapidly changing motion, e.g. travel sickness.

2. Chemical stimulation of the nervous system.

Drugs such as cytotoxics, digoxin, opiates, anaesthetic induction agents, and nitrous oxide [3], are known to be associated with an elevated incidence of nausea and vomiting.

The percentage frequency of nausea and vomiting associated with various drugs used in anaesthesia are set out in table 11.3.2.

3. Gastrointestinal irritation.

Direct gastrointestinal irritation may stimulate nausea and emesis by causing direct chemical irritation of the stomach, or gastric distension.

a. Direct chemical irritation of the gastrointestinal tract, e.g. copper sulphate.
b. Gaseous gastric distension such as may occur as a result of gas being blown into the stomach during mask ventilation, or due to passive diffusion of nitrous oxide into the stomach during anaesthesia [3].

c. Gastric distension due to excessive ingestion or accumulation of fluids, solids or both.

Table 11.3.3.
Drugs used for treatment and prevention of postoperative nausea and vomiting listed in increasing order of efficacy [4,6,7]. (dosages for i.m. or i.v. administration in adults).

LEAST	Atropine	0.5 mg
EFFECTIVE	Hyoscine	0.4 mg
	Metoclopramide	10 mg
	Domperidone	10 mg
	Promazine	25-50 mg
	Promethazine	25-50 mg
	Trimeprazine	50 mg
	Prochlorperazine	12.5 mg
	Chlorpromazine	25 mg
	Cyclazine	50 mg
	Perphenazine	2.5-5 mg
MOST	Droperidol	2.5-5 mg
EFFECTIVE	Haloperidol	2.5-5 mg

MANAGEMENT OF NAUSEA AND VOMITING

The prevention and management of perioperative nausea and vomiting is adjusted according to the cause, either gastrointestinal irritation, or chemical stimulation.

1. Gastrointestinal irritation.

Nausea and vomiting due to direct gastrointestinal irritation may be prevented by;

a. emptying the stomach with a\nasogastric tube,
b. avoiding manual ventilation of patients under anaesthesia with a face mask,
c. not using nitrous oxide in any anaesthetic gas mixture.

2. Chemical stimulation.

It is obvious that a drug, or combination of drugs, that blocks more than one of the three known receptor types in the vomiting center and chemoreceptor trigger zone, is more likely to be effective than a drug which acts on only one receptor type alone. Such drugs are the phenothiazine derivatives, and the butyrophenones. These block not only dopamine D_2 receptors, but frequently also block histamine-H_1 receptors as well as causing a variable degree of muscarinic blockade. Table 11.3.3 lists various drugs used for treatment of postoperative nausea and vomiting in order of efficacy.

3. Vestibular stimulation.

This is either due to travel sickness, or due to middle ear operations. The most effective groups of drugs for these patients are the anticholinergic drugs such as atropine or hyoscine, or the antihistamine drugs (histamine-H_1 receptor blockers).

4. Intractable vomiting.

Intractable vomiting due to such stimuli as cytostatic drugs responds best to a combination of drugs. The most effective combination reported being nortryptaline and prochlorperazine [1]. Presumably the greater efficacy of combination drug therapy is due to multiple receptor blockade. Antidepressant drugs block the central acetylcholine receptors, while the phenothiazines block the dopamine receptors and often the histamine H_1 receptors too.

REFERENCES

1. Peroutka,S.J., Snyder,S.H.,(1982), Antiemetics: Neurotransmitter receptor binding predicts their therapeutic actions. LANCET, 1, 658-659.
2. Pontopiddan,H., et al.,(1960), Progressive loss of protective reflexes in the airway with the advance of age. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 174, 2209-2213.
3. Lonie,D.S., Harper,N.J.N.,(1986), Nitrous oxide anaesthesia and vomiting. The effect of nitrous oxide anaesthesia on the incidence of vomiting following gynaecological laparoscopy. ANAESTHESIA, 41, 703-707.
4. Clarke,R.S.J.,(1984), Nausea and vomiting. BRITISH JOURNAL OF ANAESTHESIA, 56, 19-27.
5. Norris,W.,(1976), Psychological and drug preparation of patients for anaesthesia. In "General Anaesthesia", 3rd edn., editors Cecil-Gray,T., Nunn,J.F., pub. Butterworths, pages 155-168.
6. Madej,T.H., Simpson,K.H.,(1986), Comparison of the use of domperidone, droperidol and metoclopramide in the prevention of nausea and vomiting following gyaecological surrgery in day cases. BRITISH JOURNAL OF ANAESTHESIA, 58, 879-883.
7. Dundee,J.W., et al.,(1965), Studies of drugs given before anaesthesia. VI: The phenothiazine derivatives. BRITISH JOURNAL OF ANAESTHESIA, 37, 332-350.

Part 12

ELECTROLYTE DISORDERS

Electrolyte disorders are common in the perioperative period. They may be induced by disease, surgery, anaesthesia, and intravenous fluid therapy. These disorders can cause significant clinical problems in their own right, as well as altering the effects of anaesthetic drugs or techniques.

As the management, and indications for management of some of these disorders are often a source of some confusion to many junior physicians, this section is devoted to a detailed clinically oriented discussion of the more common electrolyte disorders.

Chapter 12.1

HYPONATRAEMIA & HYPO-OSMOLALITY

Hyponatraemia and the hypo-osmolar syndrome usually occur simultaneously, as plasma osmolality is mainly determined by the plasma sodium concentration. Hyponatraemia is present when the plasma sodium concentration is lower than 135 mmol/l, (normal range = 135-145 mmol/l).

CAUSES

1. Increased water intake relative to sodium intake.

a. Polydipsia.
b. Iatrogenic causes.
- Excessive intravenous infusion of Glucose 5% solution.
- Transurethral resection of prostate syndrome. This is a syndrome thought to be caused by acute water intoxication due to accidental sudden intravenous infusion of bladder irrigation solutions into open prostatic veins during transurethral resection of the prostate [1].

2. Decreased renal concentrating ability.

This occurs in renal failure, especially if the patient also simultaneously ingests a large amount of water.

3. Fluid losses where relatively more sodium is lost than water.

a. Gastrointestinal fluid losses such as due to vomiting, diarrhoea, or bowel obstruction.
b. Renal sodium losses due to diuretic use.
c. Skin losses due to excessive sweating where the water loss is replaced, but not the sodium loss.
d. Hormonally caused losses, as with hypoaldosteronism or Addison's disease.

4. Increased ADH secretion.

a. Hypovolaemia.
b. Postoperatively, or after any major trauma.
c. Hypothyroidism.
d. "Inappropriate" ADH secretion.

5. Hyperosmolar syndromes.

These are syndromes where hyperosmolar extracellular fluid causes water to be drawn from the cells into the extracellular fluid volume, decreasing the sodium ion concentration. This may occur in situations such as hyperglycaemia, and after mannitol infusion [2].

PROBLEMS

The manifestations of hyponatraemia are dependent on whether it is associated with plasma hyperosmolality or hypo-osmolality. These two forms of hyponatraemia are able to be differentiated on the basis of clinical history, together with measurement of the plasma sodium concentration and the haematocrit.

1. Hyperosmolality & hyponatraemia.

Hypo-osmolality is caused by infusion of hypertonic sodium poor fluid which causes intracellular water to move into the extracellular fluid space, reducing the extracellular plasma sodium concentration. The usual cause of this form of hyponatraemia is a mannitol infusion. Clinical manifestations are those of hyperosmolality, and not of hypo-osmolality [see chapter 12.2].

The effects of infusion of mannitol solutions has been discussed in chapter 9.3 on threatened renal function, and diabetes mellitus has been discussed in chapter 7.1.

2. Hypo-osmolality & hyponatraemia.

Plasma and extracellular fluid osmolality is principally determined by the extracellular fluid sodium concentration as is shown by equation 1 below.

$$O_{ecf} = 1.75x[Na] + 2x[K] + 2x[Ca] + [Gluc] \quad .....(1)$$

O_{ecf} = osmolality of the extracellular fluid in mosm/l.
[Na] = plasma sodium concentration in mmol/l.
[K] = plasma potassium concentration in mmol/l.
[Ca] = plasma total calcium concentration in mmol/l.
[Gluc] = plasma glucose concentration in mmol/l.
(Normal plasma osmolality is 280-300 mosmol/l)

Simultaneous hypo-osmolality and hyponatraemia are due to loss of extracellular sodium relative to water, or of a greater water than sodium intake. Clinical manifestations of hyponatraemia are due to interstitial fluid hypo-osmolality caused by dilution of extracellular sodium.

a. Mortality.

The mortality of acute hyponatraemia due to acute water intoxication in children is about 50% in children whose plasma sodium concentration is below 125 mmol/l, and the morbidity in the survivors is high, consisting mainly of brain damage [7].

b. Cardiovascular manifestations.

Depending on the cause of hyponatraemia, the patient may be either hypervolaemic or hypovolaemic.

c. Neurological manifestations of hypo-osmolar hyponatraemia.

If the extracellular fluid osmolality falls below that of the intracellular fluid, cellular swelling occurs. This has been demonstrated in experimental animals subjected to acute hyponatraemia, where it was demonstrated that intracellular fluid volume of the bodies as a whole increased, with swelling of the brain as well as of other organs [4]. Pathological examination of the brains of patients who have died of acute water intoxication also shows that cerebral oedema is present [7]. Swelling of central nervous system cells causes the neurological manifestations of hyponatraemia. These are variable, ranging from alteration of consciousness to coma., with or without abnormal muscle movements which range in severity from fasciculations to convulsions [6,7, see also table 12.2.1].

In experimental animals, intracellular brain water increases significantly when the plasma osmolality acutely falls by about 45 mosm/kg [5], or when the plasma sodium concentration falls below 125 mmol/l [6], findings which agree well with what is clinically observed in humans [6]. A fall of plasma osmolality of 45 mosm/kg corresponds with a drop of plasma sodium concentration of about 20-30 mmol/l, i.e. plasma sodium drops from the normal value of 135-145 to 115-125 mmol/l.

The severity of the manifestations are related to the rapidity of onset of the hyponatraemia. The more rapid the onset, the more pronounced the clinical disorder for a given plasma sodium concentration [7]. Nerve cell volume tends to return to normal if hypo-osmolar hyponatraemia is maintained longer than 24 hours, and this explains the minimal symptoms of patients with chronic hyponatraemia [4,5].

MANAGEMENT

The requirement for treatment of hyponatraemia depends on whether the hyponatraemia is symptomatic. Asymptomatic hyponatraemia does not require urgent treatment. Symptomatic hyponatraemia is more likely to be acute hyponatraemia, while chronic hyponatraemia is often asymptomatic. These two types of hyponatraemia may be defined by their rapidity of onset.

1. Acute and chronic hyponatraemia.

a. Definition of acute hyponatraemia.

Acute hyponatraemia may be defined as hyponatraemia that occurs within a 24 hour time period. Such rapid onset of hyponatraemia causes cellular swelling. Clinically evident neurological and cardiovascular manifestations occur frequently in these patients, as it takes 24 hours and longer for cell membrane ion pumps to restore cell volume to normal [4,5].

b. Definition of chronic hyponatraemia.

Chronic hyponatraemia may be defined as hyponatraemia which occurs over a period of time longer than 24 hours, or has lasted longer than 24 hours. Because of the slow onset, or chronic nature of hyponatraemia, cerebral intracellular volumes, and other cellular volumes are normal as cell membrane ion pumps restore normal cell volume by 24 hours after acute cellular swelling due to hyponatraemia has occurred [4,5, see above]. Clinical neurological manifestations are usually minimal, being mostly related to the cause of the hyponatraemia.

2. Assessment.

The clinical circumstances under which hyponatraemia has occurred often reveal the cause, whether it is likely to be acute or chronic, and also give information as to whether the patient is either hypervolaemic or hypovolaemic. This may also be determined by measurement of the haematocrit, which is an accurate guide, provided that no significant blood loss has occurred.

3. Types of hyponatraemia.

a. Hypervolaemic hyponatraemia.

The patients have manifestations of circulatory overfilling in addition to hyponatraemia. In such cases, infusion of hypertonic sodium chloride solutions will only aggravate the existing hypervolaemia. The treatment of choice is a powerful rapidly acting diuretic, e.g. frusemide. As more water is lost relative to the sodium loss, both the hypervolaemia and hyponatraemia are effectively treated with this drug. A sodium chloride solution may be administered if the patient is still hyponatraemic after normovolaemia has been restored.

b. Hypovolaemic hyponatraemia.

The hypovolaemic patient does not require reduction of the circulatory volume. Instead the appropriate therapy is to restore both the circulatory and extracellular fluid volumes and sodium concentration with a rapid infusion of hypertonic saline, (NaCl 1.8% or NaCl 2.7%). If the patient is in hypovolaemic shock, the plasma volume should first be increased with a sodium ion containing plasma volume expander, e.g. plasma, a gelatine solution, or dextran in 0.9% sodium chloride solution.

The amount of sodium required to restore the extracellular sodium concentration can be roughly calculated using equation 2 below. This makes the assumption that the normal extracellular fluid volume is about 20% of the body weight, and that sodium is only distributed throughout the extracellular fluid volume.

$$Na_{def} = Na_{dose} = \frac{WEIGHT}{5} \times ([Na]_d - [Na]_m] \quad .....(2)$$

Na_{def} = whole body extracellular sodium ion deficit in mmols.
Na_{dose} = amount of sodium required to replace deficit in mmols.
$WEIGHT$ = body weight in kg.
$[Na]_m$ = measured plasma sodium concentration in mmol/l.
$[Na]_d$ = desired plasma sodium concentration in mmol/l.

During the course of any treatment for hyponatraemia the plasma sodium concentration and the arterial blood gases should be measured regularly.

ANAESTHETIC MANAGEMENT

1. No hyponatraemic patient should be permitted to undergo elective operation until the cause of the hyponatraemia has been investigated and treated.

2. If a patient becomes acutely hyponatraemic during operation, e.g. transurethral resection of the prostate, terminate the operation as speedily as possible, and simultaneously begin treatment.

3. Hyponatraemia has no consequences for anaesthetic management as such. The form and type of anaesthesia required should as usual be dictated by the clinical condition of the patient and the nature of the surgical procedure planned.

REFERENCES

1. Hurlbert,B.J.(1979). Water intoxication after 15 minutes of transurethral resection of the prostate. ANESTHESIOLOGY, 50, 355-356.
2. Berry,A.J., Peterson,M.L.(1981). Hyponatremia after Mannitol Administration in the Presence of Renal Failure. ANESTHESIA AND ANALGESIA, 60, 165-167.
3. Surawicz,B.(1967). Relationship between electrocardiogram and electrolytes. AMERICAN HEART JOURNAL, 73, 814-834.
4. Holliday,M.A., et al.(1968). Factors that limit brain volume changes in response to acute and sustained hyper- and hyponatremia. JOURNAL OF CLINICAL INVESTIGATION, 47, 1916-1928.
5. Stern,W.E., Coxon,R.V.(1964). Osmolality of brain tissue in relation to brain bulk. AMERICAN JOURNAL OF PHYSIOLOGY, 206, 1-7.
6. Arieff,A.I., et al.(1976) Neurological manifestations and morbidity of hyponatremia: Correlation with brain water and electrolytes. MEDICNE, 55, 121-129.
7. Arieff,A.I., Guisado,R.(1976). Effects on the central nervous system of hypernatremic and hyponatremic states. KIDNEY INTERNATIONAL, 10, 104-116.

Chapter 12.2

HYPERNATRAEMIA & HYPEROSMOLALITY

Plasma osmolality is determined to a major degree by the plasma sodium concentration [see equation 1 in chapter 12.1]. Hypernatraemia invariably causes hyperosmolality of the extracellular fluid. A plasma sodium concentration greater 145 mmol/l may be defined as hypernatraemia, the normal range being 135-145 mmol/l.

CAUSES

The cause of hypernatraemia in a patient determines the treatment that is required. Some of the more common causes of hypernatraemia are listed below.

1. Loss of water with a low sodium content.

Many of the body fluids that may be lost contain a lower concentration of sodium than does the extracellular fluid [table 12.2.1]. Loss of excessive volumes of these fluids causes hypernatraemia.

Table 12.2.1.
Normal sodium concentrations of various body secretions and fluids.

Fluid	Normal range of sodium concentrations (mmol/l)
Urine	40-90
Sweat	8-104
Gastric	31-90
Jejunum	72-128
Ileum	91-140
Caecostomy	48-116
Faeces	5-112

a. Pure water loss may occur as a result of tachypnoea causing increased losses of water in expiratory gases, or evaporation of water from extensive surface burns.
b. Polyuria.
c. Vomiting, diarrhoea.
d. Excessive sweating due to high environmental temperatures, fever etc [1].

2. Failure to ingest water.

Failure to ingest water may occur in a variety of conditions such as;

a. reduced level of consciousness,
b. inability to drink due to disease, e.g. severe stricture of the oesophagus, bowel obstruction, etc,
c. or inanition due to disease.

3. Ingestion of salt, or hypertonic sodium containing fluids.

Excessive ingestion of sodium salts may occur for a variety of reasons.

a. Salt ingestion of all kinds, whether as an attempt at self poisoning, or to induce emesis.
b. Seawater ingestion. The sodium concentration of seawater is 450-500 mmol/l, and so is very hypertonic.
c. Infusion of sodium bicarbonate in excessive amounts during cardiopulmonary resuscitation, or correction of acidosis. The sodium concentration in an 8.4% NaHCO3 solution is 1000 mmol/l.
d. Feeding babies with undiluted cow's milk may cause hypernatraemia. Cow's milk has a sodium concentration three times that of human milk. Concentrated powdered cow's milk baby feeds may also cause the same problem.

4. Hormonal.

Several endocrine disorders can cause hypernatraemia, e.g. Cushing's syndrome, and primary hyperaldosteronism.

PROBLEMS

The problems of hypernatraemia are related to the cause of the hypernatraemia, as well as the problems caused by extracellular fluid hyperosmolarity.

1. Mortality.

The mortality of untreated acute hypernatraemia in children is high, varying between 10-70% [5], and even when treated still has a high mortality of about 20% [6].

2. Change of extracellular fluid volume (ECFV).

The ECFV may either increase or decrease, depending on the cause of hypernatraemia. If the change of ECFV is great enough hypervolaemia or hypovolaemia may occur.

3. Altered renal function.

Renal function is altered by most conditions causing hypernatraemia, the change being related to the type of hypernatraemia.

a. Normovolaemic hypernatraemia.

In experimental animals in which normovolaemic hypernatraemia is induced, the urine output increases, but the urinary sodium concentration never rises more than slightly above the plasma sodium concentration. The net result of the increased urinary production is to reduce the ECFV, and make the situation worse by causing hypovolaemia in addition to the existing hypernatraemia [2].

b. Hypervolaemic hypernatraemia.

The situation here is different. Animal investigations show that the urine output increases, and the urinary sodium concentration may be as much as twice that of the plasma sodium concentration. The effect of this is a spontaneous correction of both hypernatraemia and hypervolaemia [2].

c. Hypovolaemic hypernatraemia.

Clinical observation in humans with hypovolaemic hypernatraemia, and animal investigations show that oliguria occurs, with urine of low specific gravity and osmolality being produced [2]. In this situation the normal physiological response does not exacerbate the hypovolaemia, but hypernatraemia is also not spontaneously corrected.

3. Acidosis.

Metabolic acidosis may occur due to reduced renal excretion of hydrogen ion, even in the presence of hypokalaemia [2].

4. Cardiac manifestations.

As the entry of sodium ion into the cell is the cause of membrane depolarization of electrically active cells, it is not surprising that hypernatraemia also has been reported to have some effect on the electrophysiological properties of the heart [3]. Hypernatraemia increases the rate of change of membrane voltage in phase-1 of myocardial cellular depolarization. This has a number of effects on the ECG.

a. In animals whose electrocardiographic QRS complex duration has been increased by quinidine administration, an infusion of hypertonic sodium causes the duration of the QRS complex to decrease [3].
b. The ECG manifestations of hyperkalaemia may also be reversed by a rapid infusion of a hypertonic sodium solution [see chapter 12.4].
c. Electrocardiographic T-wave inversion has been reported in a man with extreme chronic hypernatraemia (plasma sodium concentration 216 mmol/l), and similar T-wave inversion has been induced in dogs and humans by infusion of sodium chloride solutions directly into the coronary arteries [3].

5. Neurological manifestations.

Regardless of whether hypernatraemia is associated with any change of ECFV, elevation of the plasma sodium concentration alters neurological function. This is principally caused by cellular dehydration due to movement of water out of brain cells secondary to increased interstitial fluid osmolality [4,5,7]. An increase of interstitial fluid osmolality relative to intracellular nerve cell osmolality of at least 30-35 mosm/kg is required before any significant change of cell volume occurs [7]. Neurological manifestations are more likely with hypernatraemia of rapid onset, than with chronic sustained hypernatraemia. This is be-

cause nerve cell volume tends to return to normal after about 24 hours of sustained hypernatraemia, due to an increase of intracellular osmolality which occurs by this time [4,7].

The clinical manifestations of hypernatraemia in adults are rather vague, being rather more the manifestations of the cause of the hypernatraemia. In general most patients manifest varying degrees of reduction of consciousness, varying from lethargy to frank coma. Convulsions may occur, but are more common in children [2,5].

The manifestations of acute hypernatraemia in children are directly related to the plasma sodium concentration [5,6, see table 12.2.2].

Acute hypernatraemia may cause such a degree of cellular and brain volume reduction due to cellular dehydration, that intracranial blood vessels are torn, causing a variety of haemorrhagic complications. These range from intracerebral to subdural haematomas with their associated morbidity and mortality [2,5,6].

Table 12.2.2.

Manifestations of acute hyper- and hyponatraemia related to the plasma sodium concentration [5,6,8].

PLASMA [Na] (mmol/l)	CLINICAL MANIFESTATIONS
< 112 mmol/l	- Level of consciousness varies from stupor to coma. - Convulsions occur in most patients.
< 125 mmol/l	- Muscle twitching. - Nausea, emesis. - Altered level of consciousness varying from confusion to coma. - Convulsions may occur in some patients.
< 131 mmol/l	- Muscle cramps. - Impaired taste sensation. - Anorexia.
135-145 mmol/l	- **NORMAL**
145-158 mmol/l	- Level of consciousness decreased. - Marked irritability. - Many patients have increased muscle tone with hyper-reflexia and twitching. - Convulsions may occur in some patients.
> = 158 mmol/l	- As above, plus convulsions occur in most patients.

MANAGEMENT

The requirement for therapy is dictated by the rapidity with which hypernatraemia occurs and the presence of clinical manifestations. Diagnosis of the various syndromes of hypernatraemia is done on the basis of clinical history, as well as haematocrit, together with the plasma sodium concentration.

In general it is acute rather than chronic hypernatraemia that causes symptoms. These two forms of hypernatraemia are defined below.

1. Acute & chronic hypernatraemia.

a. Definition of acute hypernatraemia.

Acute hypernatraemia is defined as hypernatraemia that has occurred within a 24 hour time period. This is too short a time for normal cellular mechanisms to restore the cerebral intracellular volume to normal [4,7]. Neurological manifestations are accordingly more frequent as a result of acute rather than chronic hypernatraemia.

b. Definition of chronic hypernatraemia.

Chronic hypernatraemia may be defined as hypernatraemia that has lasted longer than 24 hours, or which has occurred over a period longer than 24 hours. Because changes of cell volume are reversed by about 24 hours after onset of acute hypernatraemia [4,7], clinical neurological manifestations are not as frequent as during acute hypernatraemia.

2. General measures.

Administer oxygen, maintain a clear airway. Endotracheal intubation with controlled ventilation may be required for some patients. Manage convulsions as they occur with the appropriate anticonvulsive drugs.

3. Rate of correction of hypernatraemia.

The rate of correction of hypernatraemia depends on the duration of the hypernatraemia. If the hypernatraemia is of more than 24 hours duration, the intracellular osmolality has increased, and rapid reduction of the extracellular fluid osmolality causes cellular swelling due to a relative lowering of ECF▼ osmolality. This causes the same manifestations as acute hyponatraemia.

- It is recommended that correction of severe chronic hypernatraemia be carried out over a period of two to three days, otherwise cellular swelling may occur, e.g. in brain [2].
- Hypernatraemia of less than 24 hours duration may be corrected more rapidly.

4. Types of hypernatraemia.

a. Normovolaemic hypernatraemia.

The principle of therapy of any form of hypernatraemia is to dilute the plasma so that the sodium concentration falls. In this case a diuretic drug such as frusemide is administered to increase renal sodium excretion, and simultaneously an infusion of glucose 5% solution is started. During the course of therapy, administration of potassium may be required to correct any dilutional deficiency that may develop.

b. Hypervolaemic hypernatraemia.

Diuretics should be administered to both reduce the blood and ECF volumes. Administration of glucose-5% should be done cautiously so as to avoid further hypervolaemia.

c. Hypovolaemic hypernatraemia.

This is the most common form of hypernatraemia. The primary task of management is first to restore an adequate blood volume, as well as increase sodium excretion. Hypovolaemia may be corrected with plasma, dextrans, or a gelatine solution, etc. If none of these are available, administer 0.9% sodium chloride solution. Once the haemodynamic situation has been restored to normal, an infusion of water, or a hypotonic salt solution may be commenced, although this may not be necessary as restoration of normovolaemia with any of the above solutions tends to correct the hypernatraemia simply by a process of dilution. Administration of other electrolytes may also be required.

5. Monitoring.

The degree of vascular filling should be monitored, e.g. with central venous pressure monitoring. Plasma sodium, potassium and calcium should be regularly measured.

ANAESTHETIC MANAGEMENT

No specific anaesthetic management is required.

REFERENCES

1. Austin,M.G., Barry,J.W.,(1956), Observations on 100 cases of heat stroke. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 161, 1525-1529.
2. Ross,E.J., et al.,(1969), Hypernatremia. MEDICINE, 48,441-473.
3. Surawicz,B.,(1967), Relationship between electrocardiogram and electrolytes. AMERICAN HEART JOURNAL, 73, 814-834.
4. Holliday,M.A., et al.,(1968), Factors that limit brain volume changes in response to acute and sustained hyper- and hypo-natremia. JOURNAL OF CLINICAL INVESTIGATION, 47, 1916-1928.
5. Arieff,A.I., Guisado,R.,(1976), Effects on the central nervous system of hypernatremic and hyponatremic states. KIDNEY INTERNATIONAL, 10, 104-116.
6. Morris-Jones,P.H., et al.,(1967), Prognosis of the neurolog-ical complications of acute hypernatraemia. LANCET, 2, 1385-1389.
7. Stern,W.E., Coxon,R.V.,(1964), Osmolality of brain tissue in relation to brain bulk. AMERICAN JOURNAL OF PHYSIOLOGY, 206, 1-7.
8. Arieff,A.I., et al.(1976) Neurological manifestations and morbidity of hyponatremia: Correlation with brain water and electrolytes. MEDICINE, 55, 121-129.

Chapter 12.3

HYPOKALAEMIA

The normal plasma concentration of potassium is between 3.5-5 mmol/l. Hypokalaemia is defined as a plasma potassium concentration of less than 3.5 mmol/l.

CAUSES OF HYPOKALAEMIA

Hypokalaemia is one of the most common electrolyte disorders encountered in anaesthetic practice, and for this reason some discussion of the possible causes of hypokalaemia relevant to anaesthetic practice is warranted.

1. Polyuria.

Normal urine has an average potassium concentration of about 35-80 mmol/l [1]. The average adult excretes between 500-2000 mls of urine per 24 hours in temperate climates. Normally the potassium lost in the urine is replaced by dietary potassium. But during surgery, or when diet is restricted, dietary potassium replacement is impossible. In such situations even normal potassium losses may eventually cause hypokalaemia, and polyuria can certainly induce hypokalaemia under these circumstances.

Table 12.3.1.
Potassium concentrations of various gastrointestinal secretions/fluids in mmol/l [1,2].

Saliva	14-41
Gastric	6.4-16.6
Pancreas	6-9
Bile	8.4-17.5
Ileostomy	6.8-11.8
Faeces	45-135

2. Use of diuretic drugs.

Many elderly patients coming for surgery regularly ingest diuretic drugs for management of hypertension, peripheral oedema, or heart failure. Use of these drugs commonly causes hypokalaemia.

3. Gastrointestinal losses.

Most gastrointestinal secretions have a higher potassium concentration than plasma [table 12.3.1]. Excessive nasogastric suction, vomiting, diarrhoea, and excessive faecal losses of mucus from large bowel carcinomas can all cause hypokalaemia.

4. Hypocapnia and alkalosis.

Acute hypocapnia causes alkalaemia. The plasma potassium concentration decreases 0.375 mmol/l per 1 kPa decrease of the P_aCO_2, (0.5 mmol/l per 10 mmHg decrease of P_aCO_2) [3].

Acute metabolic alkalaemia causes the plasma potassium concentration to decrease by 0.5-1.3 mmol/l per 0.1 unit increase of pH above 7.4 [3,4]

5. Acute disease, surgery and trauma.

Transient hypokalaemia occurs in patients who are admitted to hospital because of acute illness [5], after major trauma [6], and occurs intra- and postoperatively in patients undergoing surgery.

The cause is thought to be the elevation of plasma catecholamine concentrations due to acute disease and trauma. Canine studies have shown that intravenous bolus injection and infusion of adrenaline to achieve plasma adrenaline concentrations within the ranges occurring in physiological stress, initially causes a transient elevation of the plasma potassium concentration, after which the potassium concentration falls below the baseline level [10]. The potassium causing the initial increase of the plasma potassium concentration originates mainly from the liver [10].

Similar animal [7] and human [8] investigations have shown that catecholamines cause extracellular potassium to move into muscle cells due to a cell membrane ß2-adrenoreceptor mediated stimulation of membrane ion pumps [8]. This effect may be blocked by drugs with ß2-adrenoreceptor blocking activity such as propranolol [8,9].

PROBLEMS

The effects of hypokalaemia are principally due to the effects of hypokalaemia on cell membrane electrical potentials. Cell membrane potential is maintained principally by the potassium concentration difference between the intracellular and the extracellular fluid. Normally the intracellular potassium concentration is about 135-150 mmol/l while the extracellular concentration is about 3.5-5 mmol/l. Rest membrane potential is able to be approximately calculated by equation 1 below, the Goldman-Hodgkin-Katz equation.

$$E_m = \frac{R \times T}{F} \times \ln \frac{[K^+]_e \times P_K/P_{Na} + [Na^+]_e}{[K^+]_i \times P_K/P_{Na} + [Na^+]_i} \quad .....(1)$$

E_m = resting membrane potential in millivolts.
R = the universal gas constant = 8.31434 Joules/°Kelvin/mole.
T = temperature in degrees Kelvin.
F = one Faraday = 96487 Coulombs/mole.
$[K^+]$ = potassium concentration either intracellular or extracellular.
$[Na^+]$ = sodium concentration either intracellular or extracellular.
P_K/P_{Na} = Ratio of membrane potassium ion to sodium ion permeabilities. This is about 100/1 for the resting membrane, and about 1/12 for the fully depolarized membrane.

Using the equation above and the electrolyte concentrations in table 14.1.2, the calculated resting membrane potential in humans is about -86 mV, while cell membrane potential in the depolarized condition is about +46 mV. This corresponds well with the measured human muscle cell resting membrane potential [see below]. If $[Na^+]_i$ and $[Na^+]_e$ are constant, the resting membrane potential is dependent only on the potassium concentrations.

Investigations of hypokalaemic patients with plasma potassium concentrations as low as 2.6 mmol/l has shown that skeletal muscle cell rest membrane potential is more negative during hypokalaemia [11]. Myocardial cell membrane rest potential also becomes more negative during hypokalaemia [12], as does the rest membrane potential of nerve cells.

Hypokalaemia increases the rate of electrical depolarization of cell membranes, but slows the rate of repolarization, and so the duration of the action potential [12]. This latter effect reduces the frequency with which an active cell membrane can depolarize and repolarize per unit time.

1. Skeletal muscle weakness.

Chronic hypokalaemia is associated with depression of deep tendon reflexes when the plasma potassium concentration is less than 3.0 mmol/l, although the degree of hypokalaemia has no relationship to the presence of muscle weakness [14]. This is not the case with acute hypokalaemia [see table 12.3.2], the muscular effects of which are more pronounced. If the plasma potassium concentration is rapidly (minutes to some days) lowered below 2.5 mmol/l in normal persons, clinical muscle weakness develops, principally of the arm, leg and neck muscles [15,16,17,18,19]. Lower plasma concentrations of potassium may be associated with respiratory failure [15,16].

It should always be noted that muscle weakness is not an invariable accompaniment of hypokalaemia. Muscle weakness appears to be related to the relative difference between intracellular and extracellular potassium concentrations, rather than the plasma or interstitial potassium concentration as such. In cases of acute hypokalaemia, (occurring within minutes to hours), where the intracellular potassium concentration has not changed significantly, the difference between intra- and extracellular potassium concentrations is increased, and the plasma potassium concentration correlates well with the manifestations. But this is not so in patients in whom potassium deficiency has developed more slowly, (i.e. days or months), as the intra- and extracellular potassium concentration difference may be normal in these persons.

The mechanism of the muscle weakness is not clear. Human skeletal muscle cell resting membrane potentials are decreased by hypokalaemia ($[K^+]$ = 2.6 mmol/l), to -101.7 mV as opposed to the normal resting membrane potential of -87.2 mV [11]. Extracellular hypokalaemia is also associated with an increase of the stimulation threshold of muscle cell membranes.

2. Rhabdomyolysis.

Potassium is released into the extracellular fluid by skeletal muscle cells during contraction. The amount of potassium released in chronically hypokalaemic persons is reduced in comparison to what is released by normokalaemic persons. Release of potassium from contracting muscle cells plays an important role in inducing muscle hyperaemia during and after exercise. Because the amount of potassium released by chronically hypokalaemic persons is reduced, the degree of exercise hyperaemia, (or vasodilation), is less than normal [11]. This may induce muscle ischaemia with rhabdomyolysis if the degree of hyperaemia or vasodilation is not great enough to elevate the muscle oxygen supply sufficiently during exercise. This is presumed to be the mechanism of the rhabdomyolysis which occurs in hypokalaemic dogs [11] and humans [18].

3. Paralytic ileus.

Severe hypokalaemia may cause a paralytic ileus, which resolves rapidly upon replacement of the potassium deficit [14].

4. Alkalaemia.

An intracellular potassium deficit causes extracellular potassium and hydrogen ions to move intracellularly, so reducing the extracellular potassium and hydrogen ion concentrations. The result of this is hypokalaemia and an extracellular alkalosis in combination with an intracellular acidosis [30]. The effects of alkalosis are discussed further in part 13.

5. Depressed cardiovascular responses.

Acute hypokalaemia increases renovascular, limb and skeletal muscle vascular resistances, and elevates myocardial contractility, all of which elevates the arterial blood pressure [32].

Chronic hypokalaemia has a different effect on cardiovascular physiology, being associated with a reduction of the arterial blood pressure and sodium retention in humans [31]. In-vitro studies show that myocardial contractility is depressed by chronic hypokalaemia [32]. However in-vivo investigations have yielded conflicting results as to the haemodynamic consequences of chronic hypokalaemia [22,32]. These conflicting results may be explained in one study [22], by the significantly elevated plasma volume measured in the experimental animals which was caused by sodium retention, while in another study the blood volume did not significantly change [32]. It is most probable that chronic hypokalaemia causes a reduction of cardiac output and arterial blood pressure in association with an elevation of the systemic vascular resistance.

In addition to the haemodynamic effects above, the pressor response to various vasopressor substances such as angiotensin-II and noradrenaline are reduced in chronically hypokalaemic animals [22,23] as well as humans [21].

Significant effects on cardiovascular physiology, and responses to pressor substances occur when the plasma potassium is reduced below 2.3 mmol/l [see table 12.3.2]. The effect of these changes on cardiovascular function and response, is to reduce the cardiovascular response to surgical stimuli, and the reflex responses to hypovolaemia. Severely hypokalaemic patients are more likely to become hypotensive in response to a given degree of hypovolaemia than is a normokalaemic patient.

Table 12.3.2.
Clinical effects of hypo- and hyperkalaemia related to the plasma potassium concentration. These effects are more pronounced in acute rather than chronic changes of potassium concentration.

PLASMA $[K^+]$ (mmol/l)	CLINICAL MANIFESTATIONS
< 2.0	- Weakness of respiratory, as well as arm and leg muscles [15,16].
< 2.5	- Weakness of arm and leg muscles [15,16,17,18,19]. - Increased chance of spontaneous ventricular tachyarrhythmias [20]. - Decreased myocardial contractility + vasoconstriction + reduced responsiveness to vasopressor substances [21,22,23,32].
< 3.2	- All patients taking digitalis glycosides have cardiac arrhythmias [13].
3.5-5.0	- **NORMAL PLASMA K^+ CONCENTRATION**
6.0	- Lowest myocardial ventricular stimulation threshold [13]. Increased chance of cardiac arrhythmias [13].
> 7.2	- Weakness of arm and leg muscles [24,25,26].
> 8.0	- Paraesthesias of hands and feet [27]. - Ventricular flutter, fibrillation or asystole may occur [28]. - Depression of myocardial contractility, cardiac output, vasodilation and lowered blood pressure [29].
> 9.5	- Weakness of respiratory as well as arm and leg muscles [25,26].
> 10.0	- Usually lethal due to respiratory failure, malignant ventricular arrhythmias, or both [13,25,26].

6. Cardiac arrhythmias.

Hypokalaemia is commonly thought to cause cardiac arrhythmias, But this has recently been the subject of much discussion as no investigators have consistently found a direct association between hypokalaemia and cardiac arrhythmias except under certain defined conditions [20,33]. It is also thought that the development of cardiac arrhythmias due to

hypokalaemia is more likely under conditions of rapid plasma potassium change, than in patients whose plasma potassium while low, does not change at all, or only slowly [13].

Hypokalaemia is associated with well defined changes in the ECG complexes. It should be noted when looking at table 12.3.3 that these changes do not invariably occur at these levels of potassium concentration, but are simply more likely.

Cardiac arrhythmias definitely due to hypokalaemia.

Cardiac arrhythmias unequivocally caused by hypokalaemia occur only under some circumstances.

a. All patients taking digitalis glycosides are observed to have cardiac arrhythmias when their plasma potassium concentration is less than 3.2 mmol/l [13]. For this reason most cardiologists strive to maintain a plasma potassium concentration above 4.0 mmol/l in digitalized patients.
b. Patients who have undergone a recent myocardial infarction are more likely to develop ventricular fibrillation and other arrhythmias if they are hypokalaemic [20,33]. Hypokalaemia in this group of patients may also be related to the stress experienced by these patients, the greater the stress, the greater the degree of hypokalaemia [see causes above].
c. Even persons with no pre-existing heart disease have an increased chance of developing ventricular tachyarrhythmias when the plasma potassium concentration is less than 2.5 mmol/l [20].

Arrhythmias not associated with hypokalaemia.

Chronic mild hypokalaemia, $[K^+]$ = 2.6-3.5 mmol/l, is not associated with an increased chance of developing cardiac arrhythmias, either preoperatively or perioperatively [34]. In fact perioperative arrhythmias appear only to be related to the presence of preoperative arrhythmias [34].

7. Potentiation of neuromuscular blocking drugs.

The in-vitro potency of nondepolarizing neuromuscular junction blocking drugs is inversely proportional to the degree of hypokalaemia [35]. That is the lower the extracellular potassium concentration, the more sensitive the neuromuscular junction is to blockade of transmission by nondepolarizing neuromuscular blocking agents such as pancuronium or tubocurarine. In-vivo animal investigations have not consistently confirmed this relationship for chronic potassium depletion [36,37]. However clinical experience of most anaesthetists is that hypokalaemia does potentiate nondepolarizing muscle relaxants.

Nondepolarizing muscle relaxants should accordingly be administered at lower than usual dosages in patients with known hypokalaemia, and repeat doses only on clinical indication.

INDICATIONS FOR THERAPY OF HYPOKALAEMIA

Correction of a potassium deficiency should only be done on indication. The amount of potassium required to replace any deficit is very dependent on whether the hypokalaemia is acute or chronic.

Table 12.3.3.
Electrocardiographic alterations and occurrence of cardiac arrhythmias related to the plasma potassium concentration [13,20,28].

Plasma $[K^+]$ (mmol/l)	ECG manifestations
< 2.5	- Inversion of T-wave - Lowering of ST segment - Increased chance of developing ventricular tachyarrhythmias.
< 3.0	- Flattening of T-waves - High U-wave
< 3.2	- All patients taking digitalis glycosides have cardiac arrhythmias
3.5-5.0	- **NORMAL**
> 5.5	- Peaking of T-wave
> 6.0	- Lowest ventricular stimulation threshold
> 6.5	- Widening of QRS complex
> 7.0	- Decreased P-wave amplitude
> 8.0	- Increased chance of spontaneous ventricular arrhythmias
> 9.0	- Atrioventricular and intraventricular block occurs - P-wave disappears
> 12-14	- Ventricular fibrillation or asystole very likely

Indications for therapy.

Replacement of any potassium deficit is indicated for any patient satisfying any of the criteria below, regardless of whether the hypokalaemia is acute or chronic.

1. Any patient whose plasma potassium concentration is less than or equal to 2.5 mmol/l.

2. Any patient about to undergo major surgery, especially cardiopulmonary surgery, whose plasma potassium concentration is lower than normal. Significant disorders of cardiac

rhythm may be induced by the surgical procedure, the major fluid and electrolyte shifts occurring in the perioperative period, or any cardio- or vasoactive drugs that may be required. Hypokalaemia in these patients will make any management of any arrhythmias in the perioperative period more difficult.

3. Any patient known to have arrhythmias preoperatively, patients with known cardiac disease, and all patients taking digitalis glycosides. A perioperative plasma potassium concentration between 4-5 mmol/l is desirable in these patients.

4. Replacement of potassium deficit is desirable in all patients with acute hypokalaemia, even if this is only a mild hypokalaemia ($[K^+]$ = 2.6-3.5 mmol/l), as acute hypokalaemia is thought to be more likely to cause cardiac arrhythmias.

5. Replacement of a potassium deficit is also desirable for all patients who have obvious clinical evidence of hypokalaemia.

No indication for potassium replacement therapy.

Replacement of any potassium deficit is not indicated for patients with chronic mild hypokalaemia ($[K^+]$ = 2.6.3.5 mmol/l), who do not have known heart disease, preoperative cardiac arrhythmias, or use digitalis glycosides, or for those patients with no clinical manifestations of hypokalaemia.

MANAGEMENT OF ACUTE HYPOKALAEMIA

Definition of acute hypokalaemia.

Acute hypokalaemia may be defined as hypokalaemia that occurs over a period of minutes to hours. No significant losses of intracellular potassium can occur within this time period, and so the potassium deficiency is confined to the extracellular fluid. The quantity of potassium that is lost is small as the amount of potassium contained in the extracellular fluid volume (ECFV) is not large.

The volume of potassium in the ECFV may be readily calculated. The ECFV is 0.2 l/kg body weight. Take a 70 kg adult. In this person the ECFV is 0.2 x 70 = 14 l. Assume a plasma potassium concentration of 4 mmol/l. This means that the total quantity of potassium in the ECFV is 4 x 14 = 56 mmol. This is equivalent to the quantity of potassium contained in 4.2 grams of potassium chloride (KCl).

Calculation of potassium dosage (acute potassium deficiency).

Calculation of the amount of potassium required to replace an acute potassium deficit may be performed assuming an extracellular fluid volume of 20% of the body weight. The amount of potassium required for replacement of the extracellular fluid potassium deficit is then given by equation 2 below.

$$K_{def} = K_{dose} = \frac{\text{WEIGHT}}{5} \times ([K^+]_d - [K^+]_m) \quad \text{.....(2)}$$

K_{def} = potassium deficiency in mmols.

K_{dose} = total amount of potassium required to replenish the whole body extracellular potassium deficit in mmols.
WEIGHT = weight of patients in kg.
$[K^+]_d$ = desired plasma potassium concentration in mmol/l.
$[K^+]_m$ = measured plasma potassium concentration in mmol/l.

Rate & type of potassium replacement.

Potassium replacement for acute hypokalaemia is best done using an intravenous infusion of potassium.

Because the deficiency is acute and extracellular, the intracellular potassium concentration and content is normal, and so the total potassium deficiency cannot be more than 1-2.5 gms in an adult if the plasma potassium concentration is more than 2 mmol/l. It has been found experimentally that infusion of potassium at a rate of up to 25 mmol/hour in normokalaemic adults does not cause hyperkalaemia [43]. Accordingly, the maximum intravenous potassium infusion rate that is consistent with safety is about 1-2 gms KCl/hour (= 13.4-25 mmol/hour).

MANAGEMENT OF CHRONIC HYPOKALAEMIA

Definition of chronic hypokalaemia.

Chronic hypokalaemia may be defined as hypokalaemia that has occurred over a period of days, or longer. The body contains a large quantity of potassium in the cells, and as the concentrations of potassium in the urine, or other sources of chronic potassium loss is not great, it takes some days for a significant amount of potassium to be lost from the body. Extracellular potassium losses are replaced by intracellular potassium, so that even when a near normal extracellular potassium concentration is measured, this does not always mean that there is not a significant degree of intracellular potassium deficiency.

Calculation of potassium dosage (chronic potassium deficiency).

Studies performed on normal human adults permitted normal water, protein and caloric intake who were subjected to experimental potassium depletion, have revealed a relationship between the plasma potassium concentration and the total body potassium deficit in chronic hypokalaemia in adults [38]. This relationship is expressed in equation 3 below, which may also be used to calculate the amount of potassium required to replace the potassium deficit in chronically hypokalaemic adults.

$$K_{def} = K_{dose} = 370 \times ([K^+]_d - [K^+]_m) \quad \text{.....(3)}$$

K_{def} = whole body potassium deficiency in an average 70 kg adult in mmol.
K_{dose} = amount of potassium required to replace whole body potassium deficit in an average 70 kg adult in mmol.
$[K^+]_d$ = desired plasma potassium concentration in mmol/l.
$[K^+]_m$ = measured plasma potassium concentration in mmol/l.

It is apparent that a considerable quantity of potassium is required to replace the potassium deficiency due to chronic hypokalaemia. It takes about 370 mmol potassium to

increase the plasma potassium concentration by even 1 mmol/l in a chronically hypokalaemic person. Thus a chronically hypokalaemic patient whose plasma potassium is 2.5 mmol/l will need 555 mmol of potassium = 44.4 gm KCl, if the desired plasma potassium concentration is about 4 mmol/l.

Rate & type of potassium replacement.

Potassium replacement in patients with chronic hypokalaemia may be done either with intravenously or orally administered potassium solutions.

The rate at which potassium may be administered intravenously to patients with chronic potassium deficiency depends on the degree of potassium deficiency.

1. Oral potassium solutions for replacement of chronic potassium deficiency.

The use of potassium chloride tablets should be avoided as a means of oral potassium replacement. Gastrointestinal ulceration, perforation and strictures have all been described as a consequence of the ingestion of potassium tablets [39,40]. The cause of these lesions is the local high concentrations of potassium in the gastrointestinal tract which occurs as the tablets break down. Such gastrointestinal lesions have never been described after ingestion of potassium chloride solutions [41], probably because the potassium chloride is more evenly dispersed through the gastrointestinal tract after ingestion.

The peak plasma K^+ concentration after oral administration of a KCl solution occurs by two hours after ingestion. An oral dose of 12.5 gm of an aqueous solution of KCl (containing 167.5 mmol K^+), elevates the plasma potassium concentration 1.9 mmol/l above the resting value [27]. From this it is apparent that potassium deficiency may be rapidly and safely corrected within a day or two using oral administration of an aqueous KCl solution. It is not advisable to administer more than 5 gm of KCl at any one dose in case excessive hyperkalaemia occurs. In addition, it is not advisable to administer oral doses more frequently than at 4-6 hour intervals for the same reason [see table 12.3.4].

Table 12.3.4.
Considerations in oral potassium replacement

DOSAGE INTERVAL = 4-6 hours
1 gram KCL contains 13.4 mmol K^+
2 gram KCL contains 36.8 mmol K^+
5 gram KCl contains 67.0 mmol K^+
10 gram KCl contains 134 mmol K^+
MAXIMUM AMOUNT KCl per dose = 5 gm

2. Intravenous potassium replacement for chronic potassium deficiency.

If oral potassium replacement is impossible or impracticable, then intravenous potassium replacement is required. The amount of potassium contained in an ampule of potassium chloride is usually given in grams. The conversion factor is given below.

1 gram KCl contains 13.4 mmol K^+

Intravenous potassium is always administered as an infusion, never as a bolus injection, as lethal intracardiac potassium concentrations may occur. Infusion of potassium is the same as an intravenous infusion of any drug, the principles of dosage calculation being the same. Potassium ion is distributed between two compartments in the body, the extracellular fluid and intracellular fluid. The rate of transfer of K^+ from the extracellular fluid to the intracellular fluid compartment is associated with a kinetic rate constant and a half life, which is dependent on the relative K^+ concentrations between the two compartments, and is approximated by regression equation 4 [42].

$$T_{1/2t} = 3 + 4.6 \times [K^+] \quad .....(4)$$

(r = 0.41, Standard Error of Estimate = 4.81)
$T_{1/2t}$ = half life for transfer of potassium from the extracellular to the intracellular fluid space in minutes.
$[K^+]$ = plasma potassium concentration in mmol/l.

It is true that with an r = 0.41 that $T_{1/2t}$ is only weakly correlated with $[K^+]$, but it does show a trend, and as can be seen from the standard error of the estimate, the half life that is calculated is accuate to +/- 4.81 minutes in about 68% of patients. In addition to this, a survey of the literature of case reports of potassium replacement rates which may be employed for replacement of chronic severe potassium deficiency reveals that this half life is approximately correct [16,18,19]. Equation 4 may be multiplied by 4 and divided into equation 2 to derive equation 5. This is used to calculate the maximum safe potassium infusion rate for a given degree of hypokalaemia. The assumptions made for practical purposes are that the potassium infused into the extracellular fluid space is fully transferred into the intracellular space by four transfer half lives. Also that the maximum tolerable and safe plasma potassium concentration during infusion is a conservative 4.3 mmol/l. Table 12.3.5 is based on equations 5 and 3.

$$Q_{max} = \frac{3 \times WEIGHT \times (4.3 - [K^+]_p)}{3 + 4.6 \times [K^+]_p} \quad .....(5)$$

Q_{max} = maximum safe potassium infusion rate in mmol/hr
WEIGHT = body weight in kg.
$[K^+]_p$ = pretreatment plasma potassium concentration in mmol/l.

Table 12.3.5.
Initial infusion rates for potassium replacement in persons with CHRONIC POTASSIUM DEFICIENCY using an intravenous potassium chloride infusion. These are calculated using equation 5, assuming a body weight of 70 kg, and a desirable plasma potassium concentration of 4.0 mmol/l. (The infusion rate should be reduced by 1 gm/hour every 3 hours to allow for an increasing transfer half life due to potassium replacement).

Plasma $[K^+]$ (mmol/l)	$T_{1/2t}$ (mins)	K^+ Deficit (mmol)	INITIAL INFUSION RATE (mmol/hr)	(gm/hr)
1.5	9.9	925	60	4.43*
2.0	12.2	740	40	2.95
2.5	14.5	555	26	1.94
3.0	16.8	370	16	1.21
3.5	19.1	185	9	0.65
4.0	21.4	Normal plasma potassium		

* = Maximum potassium infusion rate able to be considered safe on the basis of the accuracy of the calculations and case reports [16,18,19].

The intravenous infusion rates calculated using equation 4 are somewhat conservative due to the choice of four times the transfer half life, and of a lower normal level of acceptable maximum plasma potassium concentration of 4.3 mmol/l. This is done with a view to safety. The maximum potassium infusion rates are in good agreement with those reported to be possible in chronically potassium depleted persons without causing hyperkalaemia in various clinical case reports [16,18,19].

Intravenous potassium replacement therapy should be done using KCl as the source of potassium, mixed with an infusion fluid such as 0.9% NaCl. It should not be mixed with glucose solutions, as the insulin production induced by hyperglycaemia causes hypokalaemia which may actually excaerbate the existing hypokalaemia. If KCl is infused at a rate greater than 2 grams per hour, then it should be administered into a central, rather than a peripheral vein because of the pain and thrombophlebitis caused by highly concentrated KCl solutions. Administration of KCl at a rate greater than 2 gms/hour in an adult should never be done without simultaneous ECG monitoring for cardiac signs of hyperkalaemia, and regular measurement of the plasma potassium concentration.

MANAGEMENT OF ACUTE-ON-CHRONIC HYPOKALAEMIA

Occasionally the problem arises that a patient with an existing chronic hypokalaemia becomes acutely even more hypokalaemic, e.g. due to anaesthesia, trauma, drugs, massive diuresis etc. How should this be managed? The degree of the chronic deficiency is uncertain, and there is also an acute defcicency to add to the uncertainty. In such a situation the

safest and simplest course of action is to treat the hypokalaemia as an acute hypokalaemia, and replace any measured deficit accordingly.

ANAESTHETIC MANAGEMENT

Preoperative.

Hypokalaemic patients for whom there is an indication for potassium replacement should not be permitted to undergo elective anaesthesia and surgery. If these patients require emergency surgery, replace the estimated potassium deficit perioperatively. Otherwise the preoperative management of these patients is the same as for normokalaemic patients about to undergo the same operation.

Anaesthesia.

1. Regularly measure the plasma potassium concentration during the perioperative period, in addition to looking for development of any further ECG signs of hypokalaemia.

2. Do not hyperventilate hypokalaemic patients undergoing general anaesthesia with a controlled ventilation technique, nor administer large volumes of glucose (dextrose), solutions. Hyperventilation causes hypocapnia, and glucose infusions increase the plasma insulin concentration, and both cause the plasma potassium concentration to decrease even further.

3. Severely hypokalaemic patients may have deficient baroreflexes, in addition to reacting inadequately to vasoactive and cardioactive drugs. Careful attention to fluid replacement is required to prevent any hypovolaemia. Avoid excessively high ventilation pressures as this may also cause hypotension in the presence of deficient baroreflexes, [see chapter 8.6 for a detailed discussion of baroreflexes and anaesthesia].

4. Severe hypokalaemia may cause such a degree of skeletal muscle weakness that respiratory failure may be precipitated or exacerbated by anaesthetic drugs or surgery. Patients with existing muscle weakness require a anaesthetic technique with controlled respiration to prevent hypoxaemia due to weakness of respiratory muscles.

5. Any general or regional anaesthetic technique and drugs may be used for hypokalaemic patients. However care must be used when nondepolarizing neuromuscular blocking drugs are administered. The action of these drugs is potentiated by hypokalaemia. In addition to which, because of this potentiation, the effects are more difficult to reverse with neostigmine [36]. It is better to use neuromuscular blocking drugs with a short elimination half life. If the patient is very sensitive to its effects, it will at least be eliminated rapidly from the body. Repeat dosages of these drugs should only be administered according to clinical requirement, (e.g. movements, spasm of abdominal muscles etc), or using a peripheral nerve stimulator to determine the appropriate time for a repeat dose.

6. Avoid the use of glucose solutions, as the hyperinsulinaemia due to these may exacerbate the existing hyperglycaemia in non-diabetic patients. Replace potassium deficiencies with KCL dissolved in 0.9% NaCl as a carrier solution.

Postoperative.

1. Cardiac arrhythmias may occur in hypokalaemic patients due to the combination of postoperative elevation of plasma catecholamines, increased sympathetic nervous activity, and possible hypercarbia or hypoxaemia.

2. Muscle weakness may be so extreme that respiratory failure occurs. Such patients will require mechanical ventilation postoperatively until hypokalaemia has been corrected. This also applies to those patients who have been administered nondepolarizing neuromuscular blocking drugs, who may be resistant to effective reversal of these drugs and so be partially curarized. These patients will also require mechanical ventilation until the neuromuscular blocking drug has been eliminated, the potassium deficiency corrected, or both.

REFERENCES

1. Diem,K., Lentner,C., editors,(1968),"Wissenschaftliche Tabellen", published Ciba-Geigy A.G., Basel, pages 657-661.
2. Hill,G.L., et al.,(1976), Decreased trypsin and bile acids in ileal fistula drainage during the administration of a chemic-ally defined liquid elemental diet. BRITISH JOURNAL OF SURGERY, 63, 133-136.
3. Edwards,R., et al.,(1977), Acute hypocapneic hypokalaemia: An iatrogenic anaesthetic complication. ANESTHESIA AND ANALGESIA, 56, 786-792.
4. Fraley,D.S., Adler,S.,(1977), Correction of hyperkalemia by bicarbonate despite constant blood pH. KIDNEY INTERNATIONAL, 12, 354-360.
5. Morgan,D.B., Young,R.M.,(1982), Acute transient hypokalaemia: New interpretation of a common event. LANCET, 2, 751-752.
6. Shin,B., et al.,(1986), Hypokalemia in trauma patients. ANESTHESIOLOGY, 65, 90.
7. Clausen,T., Flatman,J.A.,(1977), The effect of catecholamines on Na-K transport and membrane potential in rat soleus muscle. JOURNAL OF PHYSIOLOGY (London), 270, 383-414.
8. Vincent,H.H., et al.,(1984), Effects of selective and non-selective ß-agonists on plasma potassium and norepinephrine. JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, 6, 107-114.
9. Lim,M., et al.,(1981), Propranolol, exercise, and arterial plasma potassium. LANCET, 2, 591.
10. Lim,M., et al.,(1982), Continuous intravascular monitoring of epinephrine induced changes in plasma potassium. ANESTHESIOLOGY, 57, 272-278.
11. Bilbrey,G.L., et al.,(1973), Skeletal muscle resting membrane potential in potassium deficiency. JOURNAL OF CLINICAL INVESTIGATION, 52, 3011-3018.
12. Ballantyne,F., et al.,(1975), Cellular basis for reversal of hyperkalaemic electrocardiographic changes by sodium. AMERICAN JOURNAL OF PHYSIOLOGY, 229, 935-940.
13. Surawicz,B.,(1967), Relationship between electrocardiogram and electrolytes. AMERICAN HEART JOURNAL, 73, 814-834.
14. Surawicz,B., et al.,(1957), Clinical manifestations of hypo-potassemia. AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 233, 603-616.
15. Siler,J.N., Discavage,W.J.,(1975), Anesthetic management of hypokalemic periodic paralysis. ANESTHESIOLOGY, 43, 489-490.
16. Pullen,H., et al.,(1967), Intensive intravenous potassium replacement ententententententententtherapy. LANCET, 2, 809-811.
17. Melnick,B., et al.,(1983), Hypokalemic familial periodic paralysis. ANESTHESIOLOGY, 58, 263-265.
18. Campion,D.S., et al.,(1972), Rhabdomyolysis and myoglobinuria. Association with hypokalemia of renal tubular acidosis. JOURNAL OF THE AMAERICAN MEDICAL ASSOCIATION, 220, 967-969.
19. Swales,J.D.,(1964), Hypokalaemia and the electrocardiogram. LANCET, 2, 1365-1367.
20. McGovern,B.,(1985), Hypokalemia and cardiac arrhythmias. ANESTHESIOLOGY, 63, 127-129.
21. Radfar,N., et al.,(1978), Hypokalaemia in Bartter's syndrome and other disorders produces resistance to vasopressors via prostaglandin overproduction. PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 158, 502-507.
22. Galvez,O.G., et al.,(1977), The hemodynamic effects of potassium deficiency in the dog. CIRCULATION RESEARCH, 40, supp. I, 11-16.

23. Adamick,R.A., et al.,(1981), Factors influencing vascular responsiveness to angiotensin-II. CIRCULATION RESEARCH, 49, 932-939.
24. Bell,H., et al.,(1965), Hyperkalaemic paralysis due to adrenal insufficiency. ARCHIVES OF INTERNAL MEDICINE, 115, 618-620.
25.Barker,G.L.,(1980), Hyperkalaemia presenting as ventilatory failure ANAESTHESIA, 35, 885-886.
26. Finch,G.A., et al.,(1946), Clinical syndrome of potassium intoxication. AMERICAN JOURNAL OF MEDICINE, 1, 337-352.
27. Keith,N.M., et al.,(1942), Some effects of potassium salts in man. ANNALS OF INTERNAL MEDICINE, 16, 879-892.
28. Tobey,R.E.,(1970), Paraplegia succinylcholine and cardiac arrest. ANESTHESIOLOGY, 32, 359-364.
29. Surawicz,B., et al.,(1967), Hemodynamic and electrocardiographic effects of hyperpotassemia. Differences in response to slow and rapid increases in concentration of plasma K. AMERICAN HEART JOURNAL, 73, 647-664.
30. Waddell,W.J., Bates,R.G.,(1969), Intracellular pH. PHYSIOLOGICAL REVEIWS, 49, 285-329.
31. Perera,G.A.,(1953), Depressor effects of potassium deficient diets in hypertensive man. JOURNAL OF CLINICAL INVESTIGATION, 2, 633-638.
32. Albrecht,P.H.,(1972), Cardiovascular effects of chronic potassium deficiency in the dog. AMERICAN JOURNAL OF PHYSIOLOGY, 223, 555-560.
33. Harrington,J.T., et al.,(1982), Our national obsession with potassium. AMERICAN JOURNAL OF MEDICINE, 73, 155-159.
34. Vitez,J.S., et al.,(1985), Chronic hypokalaemia and intraoperative dysrhythmias. ANESTHESIOLOGY, 63, 130-133.
35. Waud,B.E., Waud,D.R.,(1980), Interaction of calcium and potassium with neuromuscular blocking agents. BRITISH JOURNAL OF ANAESTHESIA, 52, 863-865.
36. Miller,R.D., Roderick,L.L.,(1978), Diuretic-induced hypokalaemia, pancuronium neuromuscular blockade, and its antagonism by neostigmine. BRITISH JOURNAL OF ANAESTHESIA, 50, 541-544.
37. Hill,G.E., et al.,(1978), Acute and chronic changes in intra-and extracellular potassium and responses to neuromuscular blocking agents. ANESTHESIA AND ANALGESIA, 57, 417-421.
38. Sterns,R.H., et al.,(1981), Internal potassium balance and the control of the plasma potassium concentration. MEDICINE, 60, 339-354.
39. Boley,S.J., et al.,(1965), Potassium-induced lesions of the small bowel: I. Clinical aspects. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 193, 997-1000.
40. Allen,A.C., et al.,(1965), Potassium induced lesions of the small bowel: II. Pathology and pathogenesis. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 193, 1001.
41. Hutcheon,D.E.,(1976), benefit-risk factors associated with supplemental potassium therapy. JOURNAL OF CLINICAL PHARMACOLOGY, 16, 85.
42. Sterns,R.H., et al.,(1979), Disposition of intravenous potassium in anuric man: A kinetic analysis. KIDNEY INTERNATIONAL, 15, 651-660.
43. DeFronzo,R.A., et al.,(1979), Impaired renal tubular potassium secretion in sickle cell disease. ANNALS OF INTERNAL MEDICINE, 90, 310-316.

Chapter 12.4

HYPERKALAEMIA

CAUSES

Some of the causes of hyperkalaemia of relevance to anaesthetic practice are listed below. There are of course many more possible causes, but the reader is referred to an excellent review by DeFronzo et al [1] for a more detailed discussion of these.

1. Excessive potassium intake.

a. Hyperkalaemia may be iatrogenic due to administration of excessive quantities of potassium salts for therapy of hypokalaemia.

b. Some drugs are potassium salts, and may cause hyperkalaemia in patients with renal dysfunction.

2. Excessive potassium release from cells.

a. Massive tissue damage.

Large quantities of potassium may be released from necrotic or damaged cells such as may occur after massive haemolysis, haemolysis secondary to massive transfusion of old blood, massive muscle trauma etc.

b. Exercise, tissue damage and drugs.

Massive tissue damage can certainly cause hyperkalaemia. Physical exercise can also elevate the plasma potassium concentration significantly in normal persons, increases of up to 1.5 mmol/l having been recorded [2]. As the entry of potassium into cells is regulated by a ß2-adrenergic receptor regulated membrane pump [see chapter 12.3], concurrent administration of a ß2-adrenergic blocking drug exacerbates the elevation of plasma potassium caused by exercise and trauma.

c. Hypercapnia and acidosis.

Elevation of the P_aCO_2 above normal causes potassium to move from the cells into the extracellular fluid. The elevation of the plasma potassium concentration is in direct proportion to the degree of hypercapnia, increasing 0.39 mmol/l per 1 kPa increase of the P_aCO_2, (0.52 mmol/l per 10 mmHg increase of P_aCO_2) [3].

The same possibly applies to metabolic acidosis, the plasma potassium concentration increasing in direct proportion to the decrease of the blood pH. However this relationship is not invariably observed in clinical practice, some patients with severe metabolic acidosis, e.g. postictal lactic acidosis, may even be hypokalaemic [4].

d. Suxamethonium.

Suxamethonium administration increases the plasma potassium concentration by up to 0.7 mmol/l in normal patients [5].

Administration of suxamethonium to patients within hours of severe muscle trauma has been reported to cause significant hyperkalaemia (up to 6.2 mmol/l) [6].

Pronounced hyperkalaemia occurs within minutes after administration of suxamethonium to patients 5-15 days after sustaining hemiplegia, hemiparesis, paraplegia, teraplegia, or severe burns. Increased hypersensitivity to the hyperkalaemic effects of suxamethonium persists for 2-3 months in burned patients, and up to 3-6 months in patients who have sustained a significant upper motor neurone lesion [7]. The elevation of plasma potassium under these circumstances may be truly massive, a plasma potassium concentration of 13.5 mmol/l being reported in a paraplegic patient four minutes after administration of only 20 mg of suxamethonium [8]. Similar increases of the plasma potassium concentration have been reported as a result of suxamethonium administration in severely burned patients [8]. It should be noted that not every patient whose plasma potassium suddenly increases above 7 mmol/l as a result of suxamethonium administration develops malignant cardiac arrhythmias [8].

PROBLEMS

As with hypokalaemia, the problems of hyperkalaemia are due to alteration of the membrane potential. This causes changes in voltage regulated ion channel permeability of the K^+, Na^+, and Ca^{++} channels. The result of this is that the stimulation thresholds of cell membranes, the ability to conduct a membrane potential, and Ca^{++} regulated secretory and contractile processes are changed. These changes are more pronounced in acute hyperkalaemia as the membrane potential differs more from normal than during chronic hyperkalaemia, in which the transmembrane K^+ gradient may be near normal. The resting cell membrane potential is principally due to the transmembrane K^+ ion gradient, [see the Goldman-Hodgkin-Katz equation in chapter 12.3].

The clinical problems due to hyperkalaemia which are relevant to anaesthetic practice are shown in tables 12.3.1 and 12.3.2 and are discussed in more detail below.

1. Cardiovascular depression.

a. Effect on cardiac rhythm and the electrocardiogram (ECG).

Acute hyperkalaemia decreases myocardial cell membrane potential by increasing the cell membrane potassium conductance during both rest and depolarization relative to the sodium conductance. The effect of this is to decrease the magnitude of the resting membrane potential, decrease the rate of membrane depolarization, as well as the magnitude of the membrane potential during depolarization, in addition to reducing the action potential duration [9,12]. A reduction of the rate of depolarization slows atrioventricular conduction, inceasing the duration of the QRS complex during hyperkalaemia [12].

A plasma potassium concentration of 6 mmol/l is associated with a minimum threshold for ventricular excitability [10]. The ECG and alterations of cardiac rhythm are a direct result of all these changes and are related to the plasma potassium concentration [see table 12.3.2]. It should always be noted that these effects are not invariable at these concentrations, but are only observed with increasing frequency at or above these concentrations. In addition these changes are more pronounced during acute rather than chronic hyperkalaemia [10,11].

The most commonly occurring arrhythmias during hyperkalaemia are ventricular, ranging from third degree heart block to a wide variety of ventricular arrhythmias, e.g. ventricular extrasystoles, ventricular fibrillation, flutter, asystole [10,12,13]. The level of hyperkalaemia above which malignant ventricular arrhythmias frequently, but not invariably, occur in man is about 10 mmol/l [8,10,13].

b. Effect on systemic haemodynamics.

Acute hyperkalaemia causes a significant reduction of myocardial contractility [11,15], reduces the cardiac output, may elevate the systemic vascular resistance [11,14,15], and if the rate of plasma potassium increase is rapid enough, arterial hypotension may also occur [11]. These effects are thought to be mainly caused by myocardial depression. If the systemic vascular resistance does not increase in proportion to the reduction of cardiac output, the arterial blood pressure also decreases. These changes only begin to become significant during acute hyperkalaemia when the plasma potassium concentration is more than 8 mmol/l [11]. The potassium concentration at which myocardial depression occurs during chronic hyperkalaemia is higher than 8 mmol/l.

2. Skeletal muscle weakness.

Acute hyperkalaemia also reduces skeletal muscle resting membrane potential in man [16]. Experiments in rabbits have shown that the velocity of propagation of depolarization over the muscle cell membrane is slowed by acute hyperkalaemia [17]. Hyperkalaemia also causes the electromyographic response to tetanus at 50 Herz to fade more pronouncedly. This latter is an effect similar to that of the non-depolarizing neuromuscular blocking drugs. But unlike these drugs, the tetanic fade is exacerbated by neostigmine, instead of being antagonized [18]. This is consistent with the known effects of potassium on the mammalian neuromuscular junction. Hyperkalaemia decreases the magnitude of the postsynaptic resting membrane potential, as well as that of the miniature end plate potentials (mepp's) [19], and increases the frequency of the mepp's [19,20]. Mepp's are due to the spontaneous release of vesicles of acetylcholine from the nerve terminal. Further investigations have also shown that acute hyperkalaemia does not reduce skeletal muscle contractile strength [21].

In conclusion it appears that acute hyperkalaemia exerts its effects on skeletal muscle, not by decreasing muscle fiber contractility, but by blocking transmission of nerve impulses across the neuromuscular junction by reducing the responsiveness of the motor end plate, i.e. the muscle cell membrane responsiveness to acetylcholine.

Hyperkalaemia in man causes clinical muscle weakness when the plasma potassium concentration rises acutely above 7.2 mmol/l, and respiratory failure above 9.5 mmol/l [see table 12.3.1 for references]. The mechanism of this is presumably failure of neuromuscular junction transmission. It is therefore not surprising that the leg muscles are first affected, subsequently the arm and shoulder girdle muscles, and last of all the diaphragm. This is the same response as occurs in response to increasing doses of the nondepolarizing neuromuscular blocking drugs [22]. The diaphragm is the last muscle to be blocked as it has the greatest "margin of safety" for neuromuscular transmission.

3. Interaction with neuromuscular blocking drugs.

Despite the fact that acute hyperkalaemia causes muscle weakness, it also decreases the sensitivity of the neuromuscular junction to nondepolarizing neuromuscular blocking drugs, and a greater dosage of such drugs is required to achieve a given degree of blockade

of the neuromuscular junction [23,24]. This is perhaps related to the fact that more acetylcholine is likely to be present in the synaptic cleft, a consequence of the increased resting rate of release of acetylcholine into the neuromuscular junction as is shown by the increased frequency of mepp's measured during acute hyperkalaemia [19,20]. As the clinical significance of these changes is uncertain, all that can be said is that hyperkalaemic patients with clinical muscle weakness should only be administered neuromuscular blocking drugs according to clinical requirements. In addition, no hyperkalaemic patients should be administered a depolarizing neuromuscular blocking drug such as suxamethonium. This may cause a lethal level of hyperkalaemia.

The reversal of nondepolarizing neuromuscular blocking drugs with neostigmine is complicated by the potentiation of the effects of hyperkalaemia on the neuromuscular junction by neostigmine [18]. Neostigmine can itself cause neuromuscular blockade when administered in doses of 2.5-5.0 mg/70 kg body weight [25]. Both neostigmine and hyperkalaemia block the neuromuscular junction by the same mechanism. They cause excessive quantities of acetylcholine to be present within the neuromuscular junction, presumably depressing membrane responsiveness to acetylcholine [27]. It is advisable that the initial dose of neostigmine or other anticholinesterase be smaller than usual, and subsequently more be administered according to the effect achieved.

MANAGEMENT OF HYPERKALAEMIA

All patients whose plasma potassium concentration is greater than 6 mmol/l should be treated for hyperkalaemia. This is the concentration at which cardiac ventricular excitability is maximal [see above]. The rapidity with which therapeutic intervention is required is dictated by the rapidity with which hyperkalaemia has developed and the presence of hyperkalaemic manifestations.

Patients requiring rapid therapy of hyperkalaemia.

The categories of patient requiring urgent therapy of hyperkalaemia are:

- Acute hyperkalaemia with a plasma potassium concentration >6 mmol/l.
- Acute or chronic hyperkalaemia in patients who are receiving digitalis glycosides, especially when the plasma potassium is >6 mmol/l.
- Chronic hyperkalaemia where the plasma potassium concentration is >7 mmol/l.
- Acute or chronic hyperkalaemia at any level which causes clinical or electrocardiographic manifestations which may be due to hyperkalaemia.

Patients not requiring urgent therapy.

Patients with mild, ($[K^+] < 6.5$ mmol/l), chronic hyperkalaemia may be treated at leisure, unless they are symptomatic [26].

1. Chronic management of hyperkalaemia.

a. Dietary potassium restriction.

Dietary potassium restriction is of value only in patients with mild chronic hyperkalaemia.

b. Ion exchange resins.

Oral administration of potassium absorbing cation exchange resins such as sodium polystyrene sulfonate may be required to maintain normokalaemia. The usual oral dose of this resin is about 20 grams ingested 3-4 times a day together with an osmotic laxative to ensure that the potassium absorbed into the resin is effectively removed from the gastrointestinal tract.

Table 12.4.1.
Acute therapy of hyperkalaemia

THERAPIES THAT DO NOT CHANGE PLASMA [K^+]	
Sodium Chloride	- >200 mmol Na^+ infused as hypertonic NaCl solution, e.g. 1.8% or 2.7% NaCl solution. (1 gm NaCl contains 17 mmol Na^+) - Acts within minutes to normalize ECG. - Repeat as indicated.
Calcium	- I.V. injection of 10-30 mls of 10% $CaCl_2$ or of 10% Ca-gluconate. - Acts within minutes to normalize ECG. - Repeat as indicated.
THERAPIES THAT DO DECREASE PLASMA [K^+]	
Sodium bicarbonate	- 80-120 mmol of NaHCO3 as an 8.4% solution of NaHCO3. - Reduces plasma [K^+] within 60 minutes and effect lasts 4-6 hours.
Glucose	- 50 gm glucose infused with or without 4-10 IU insulin. - Reduces plasma [K^+] within 60 minutes and effect lasts several hours.

2. Acute management of hyperkalaemia.

a. Calcium.

Extreme acute hyperkalaemia can cause death. Experimental acute hyperkalaemia induced in hypocalcaemic dogs causes death at a lower plasma potassium concentration

than in normocalcaemic dogs [28]. Another canine investigation has shown that administration of calcium to normocalcaemic dogs subsequently made hyperkalaemic increases the plasma potassium concentration at which death occurs [29].

Calcium ions have a number of effects on electrically active cell membranes, including the cell membranes of myocardial muscle cells. Increasing the extracellular calcium ion concentration causes a concentration related increase of membrane stimulation threshold [30]. This is due to hypercalcaemia causing the resting membrane potassium and sodium conductances to decrease [31], so elevating the resting membrane potential, and myocardial stimulation threshold. Hypercalcaemia also slows the rate of increase of potassium conductance during an action potential [31], which causes a greater degree of membrane depolarization. The end result of these changes is that injection of calcium into hyperkalaemic patients reverses the hyperkalaemia induced changes in the ECG without changing the plasma potassium concentration [10,13]. Patients with ECG evidence of atrioventricular block or malignant arrhythmias due to hyperkalaemia require immediate treatment. Administration of 1 gram of calcium chloride or calcium gluconate will reverse the ECG changes within minutes. This effect is regrettably only temporary, but will maintain a safer cardiac rhythm until more enduring forms of treatment begin to take effect. The dose of calcium salts may be repeated as necessary.

b. Infusion of concentrated sodium solutions.

Elevation of the extracellular sodium ion concentration normalizes the myocardial cell membrane action potential in the presence of hyperkalaemia [9]. This is presumably due to an increased extracellular to intracellular sodium ion concentration gradient, which causes an elevation of the membrane sodium ion conductance relative to potassium conductance during rest and membrane depolarization. This increases the resting membrane potential, the rate of depolarization, and speed of action potential conduction. The result of this is that infusion of hypertonic sodium chloride solutions into patients with ECG manifestations of hyperkalaemia normalizes the ECG [10,13].

This is a rapidly effective treatment for hyperkalaemic patients, especially suitable for those with concurrent hypovolaemia or hyponatraemia. The effect is only temporary and may need to be repeated. Accordingly this is not suitable for hypervolaemic and normovolaemic patients, nor those with heart failure, as hypervolaemia may result from enthusiastic infusion of large volumes of concentrated saline solutions. It does not alter the plasma potassium concentration [13], and so is only suitable for maintenance of life until potentially lethal hyperkalaemia has been treated with other measures.

c. Infusion of sodium bicarbonate.

Intravenous infusion of 80-120 mmol sodium bicarbonate reduces the plasma potassium concentration by 1-2 mmol/l within an hour, an effect which lasts for 4-6 hours [26,32]. This effect is thought to be due to bicarbonate ion alone, as it also occurs without any significant pH change being induced [32,33].

d. Glucose and insulin infusions.

Rapid infusion of 50 grams of glucose increases the plasma insulin concentration and reduces the plasma potassium concentration by 1-2 mmol/l within one hour, an effect which persists for several hours [26]. Diabetic patients may require insulin, as their insulin response to sudden hyperglycaemia is deficient. The usual dose of insulin in such cases is about 4-10 IU of soluble insulin per 50 gms glucose [26].

MANAGEMENT OF ANAESTHESIA

Preoperative.

1. No patient with significant hyperkalaemia should be permitted to undergo elective surgery. The cause of the hyperkalaemia should be investigated, and the hyperkalaemia treated prior to any surgery.

2. Premedication may be administered as deemed necessary by the anaesthetist.

Anaesthesia.

There is no specific form of anaesthesia that is indicated for the hyperkalaemic patient. However there are some factors which should always be considered.

1. Never administer suxamethonium to hyperkalaemic patients. Suxamethonium always increases the plasma potassium concentration, and in hyperkalaemic patients this increase may be all that is necessary to cause a malignant arrhythmia.

Especial caution is necessary with patients with recent burns and major upper motor neurone lesions. Suxamethonium should never be administered to these patients in the time period of 5 days to 9 months after the injury, as pronounced hyperkalaemia may occur.

2. Hyperkalaemia is exacerbated by hypercarbia. If general anaesthesia is required, a technique using controlled ventilation with hyperventilation is advisable. This is especially necessary in the case of patients with hyperkalaemia induced muscle weakness or paralysis.

3. While the effects of the nondepolarizing muscle relaxants in hyperkalaemic patients is somewhat uncertain, they may be potentiated by existing muscle weakness. Repeat dosages of these drugs should only be administered on clinical indication, or using a peripheral nerve stimulator. It is also advisable to use a short acting non-depolarizing neuromuscular blocking drug in these patients. If the effect of the drug is potentiated to an extreme degree, at least the drug will be rapidly eliminated from the body, so terminating its effect.

4. Always have calcium gluconate or calcium chloride available for rapid intravenous injection in case any malignant cardiac arrhythmias occur.

Postoperative.

Patients with hyperkalaemic muscle weakness may require mechanical ventilation until hyperkalaemia has been treated.

REFERENCES

1. DeFronzo,R.A., et al.,(1982), Clinical disorders of hyperkalaemia. ANNUAL REVIEW OF MEDICINE, 33, 521-554.
2. Lim,M., et al.,(1981), Propranolol, exercise, and arterial plasma potassium. LANCET, 2, 591.
3. Hassan,H., et al.,(1979), Hypercapnia and hyperkalaemia. ANAESTHESIA, 34, 897-889.
4. Fulop,M.,(1979), Serum potassium in lactic acidosis and ketoacidosis. NEW ENGLAND JOURNAL OF MEDICINE, 300, 1087-1089.
5. Miller,R.D., et al.,(1972), Succinylcholine-induced hyperkalemia in patients with renal failure? ANESTHESIOLOGY, 36, 138-141.
6. Kopriva,C., et al.,(1971), Serum potassium changes after succinylcholine in patients with acute massive muscle trauma. ANESTHESIOLOGY, 34, 246-249.

7. Gronert,G.A., Theye,R.A.,(1975), Pathophysiology of hyperkalemia induced by succinylcholine. ANESTHESIOLOGY, 43, 89-99.
8. Tobey,R.E., et al.,(1970), Paraplegia, succinylcholine and cardiac arrest. ANESTHESIOLOGY, 32, 359-364.
9. Ballantyne,F., et al.,(1975), Cellular basis for reversal of hyperkalaemic electrocardiographic changes by sodium. AMERICAN JOURNAL OF PHYSIOLOGY, 229, 935-940.
10. Surawicz,B.,(1967), Relationship between electrocardiogram and electrolytes. AMERICAN HEART JOURNAL, 73, 814-834.
11. Surawicz,B., et al.,(1967), Hemodynamic and electrocardiographic effects of hyperpotassemia. Differences in response to slow and rapid increases in concentration of plasma K. AMERICAN HEART JOURNAL, 73, 647-664.
12. Cohen,H.C., et al.,(1971), The nature and type of arrhythmias in acute experimental hyperkalaemia in the intact dog. AMERICAN HEART JOURNAL, 82, 777-785.
13. Finch,C.A., et al.,(1946), Clinical syndrome of potassium intoxication. AMERICAN JOURNAL OF MEDICINE, 1, 337-352.
14. Nugent,M., et al.,(1984), Verapamil worsens rate of development and hemodynamic effects of acute hyperkalemia in halothane anesthetized dogs: Effects of calcium therapy. ANESTHESIOLOGY, 60, 435-439.
15. Leight,L., et al.,(1963), The effect of intravenous potassium on myocardial contractility and cardiac dynamics. AMERICAN JOURNAL OF CARDIOLOGY, 12, 686-691.
16. Bradley,W.G.,(1969), Adymnamia episodica herediteria. Clinical, pathological and electrophysiological studies in an affected family. BRAIN, 92, 345-378.
17. Troni,W., et al.,(1978), Electromyographic study on experimental hyperkalaemia. I. Electrophysiological alterations. ACTA NEUROLOGICA (NAPOLI), 33, 381-389.
18. Troni,W., et al.,(1978), Electromyographic study on experimental hyperkalaemia. II. Effects on neuromuscular transmission. ACTA NEUROLOGICA (NAPOLI), 33, 390-398.
19. Gage,P.W., Quastrel,D.M.J.,(1965),Dual effect of potassium on transmitter release. NATURE, 206, 625-626.
20. Parsons,R.L., et al.,(1965),Presynaptic effects of potassium ion on the mammalian neuromuscular junction. NATURE, 208, 590-591.
21. Troni,W., Luda,E.,(1978), Electromyographic study on experimental hyperkalaemia. III. Motor deficits. ACTA NEUROLOGICA (NAPOLI), 33, 399-407.
22. Foldes,F.F., et al.,(1971), Studies of pancuronium in conscious and anesthetized man. ANESTHESIOLOGY, 35, 496-503.
23. Miller,R.D., Roderick,L.L.,(1978), Diuretic induced hypokalaemia, pancuronium neuromuscular blockade and its antagonism by neostigmine. BRITISH JOURNAL OF ANAESTHESIA, 50, 541-544.
24. Waud,B.E., Waud,D.R.,(1980), Interaction of calcium and potassium with neuromuscular blocking agents. BRITISH JOURNAL OF ANAESTHESIA, 52, 863-865.
25. Payne,J.P., et al.,(1980), Neuromuscular blockade by neostigmine in anaesthetized man. BRITISH JOURNAL OF ANAESTHESIA, 52, 69-75.
26. Levinsky,N.G.,(1966), Management of emergencies. VI. Hyperkalemia. NEW ENGLAND JOURNAL OF MEDICINE, 274, 1076-1077.
27. Dreyer,F.,(1982), Acetylcholine receptor. BRITISH JOURNAL OF ANAESTHESIA, 54, 115-130.
28. Braun,H.A., et al.,(1955), The influence of hypocalcaemia induced by sodium ethylenediamine tetraacetate on the toxicity of potassium. JOURNAL OF LABORATORY AND CLINICAL MEDICINE, 46, 544-548.
29. Winkler,A.W., et al.,(1939), Factors affecting the toxicity of potassium. AMERICAN JOURNAL OF PHYSIOLOGY, 127, 430-436.
30. Frankenhauser,B.,(1957), The effect of calcium on the myelinated nerve fibre. JOURNAL OF PHYSIOLOGY (London), 137, 245-260.
31. Frankenhauser,B., Hodgkin,A.L.,(1957), The action of calcium on the electrical properties of squid axons. JOURNAL OF PHYSIOLOGY (London), 137, 218-244.
32. Fraley,D.S., Adler,S.,(1977), Correction of hyperkalemia by bicarbonate despite constant blood pH. KIDNEY INTERNATIONAL, 12, 354-360.
33. Villamil,M.F., et al.,(1975), Anion effects on cation movements duing correction of potassium depletion. AMERICAN JOURNAL OF PHYSIOLOGY, 229, 161-166.

Chapter 12.5

HYPOCALCAEMIA

The normal plasma calcium concentration is in the range 2.25-2.55 mmol/l (9-10.2 mg/100 mls). Calcium in the blood exists in three forms, bound to plasma proteins, free ionized calcium, and a very small fraction of calcium bound to anions such as citrate etc. It is the free ionized calcium that is physiologically active, being required for such processes as;

- smooth, striated, and heart muscle contraction,
- generation of heart muscle action potentials,
- release of neurotransmitters,
- regulation of many intracellular processes.

The normal plasma ionized calcium concentration is in the range 1.02-1.26 mmol/l [1]. Calcium binds to both albumin and globulins in the plasma, about 83% being bound to the albumin. For the situation of a normal plasma albumin/globulin concentration ratio of 1.89, and a body temperature of 37^{o} Celsius, the "free" almost totally ionized plasma calcium concentration varies with both pH and the plasma total protein concentration in the manner described by equation 1 below [2]. This equation assumes a linear relationship between the pH and the plasma ionized calcium concentration, and because of this is only valid in the pH range of 7.0-9.0 [8].

$$[Ca^{++}] = [Ca] - [Prot] \times (0.006 \times pH - 0.03) \quad ....(1)$$

For the situation where the pH is unchanging and equals 7.4, equation 1 simplifies to;

$$[Ca^{++}] = [Ca] - 0.0144 \times [Prot] \quad .....(2)$$

$[Ca^{++}]$ = plasma ionized calcium concentration in mmol/l.
[Ca] = plasma total calcium concentration in mmol/l.
[Prot] = plasma protein concentration in g/l.
N.B. to convert calcium concentration in mmol/l to mg/100 mls, multiply the concentration in mmol/l by 4.

CAUSES OF HYPOCALCAEMIA

There are a large variety of disorders which may cause hypocalcaemia, such as renal failure, hypoparathyroidism, and pseudohypoparathyroidism [4]. The disorders most relevant to anaesthetic practice are discussed below.

1. Pancreatitis.

Hypocalcaemia in pancreatitis is due to a combination of factors such as a reduction of the plasma albumin concentration, decreased plasma parathyroid hormone concentration, and calcium sequestration in necrotic fat. The level of hypocalcaemia is a reflection of the severity of an episode of pancreatitis, and death is likely when the total plasma calcium concentration is less than 1.75 mmol/l, although hypocalcaemia itself is not necessarily the cause of death [5].

2. Hypoalbuminaemia/hypoproteinaemia.

A reduction of the plasma protein concentration, especially of the albumin concentration, is associated with a reduction of the total plasma calcium concentration [1]. This is because the plasma ionized calcium concentration increases, activating physiological and biochemical process which reduce the total plasma calcium concentration, and restores a normal plasma ionized calcium concentration.

3. Rapid blood transfusion.

Preserved blood is usually anticoagulated with a sodium citrate solution. Examples of such solutions are the commonly used Acid-Citrate-Dextrose (ACD), and the Citrate-Phosphate-Dextrose (CPD) mixtures used to preserve and anticoagulate blood prior to transfusion.

Calcium ion binds to citrate ion, and as a result an intravenous infusion of sodium citrate reduces the plasma ionized calcium concentration in direct proportion to the plasma citrate concentration. It takes approximately 10 minutes for the citrate contained in 500 mls of sodium citrate anticoagulated blood to be metabolized and the plasma ionized calcium concentration to return to normal [6]. Because citrate is rapidly metabolized, the infusion rate of blood must be quite rapid in order to produce a significant degree of hypocalcaemia. In normothermic human adults, ACD or CPD blood must be infused at a rate greater than 50 mls/70 kg body weight/minute for the plasma ionized calcium concentration to be reduced to such a degree that significant cardiovascular depression occurs, i.e. a reduction of systemic vascular resistance, cardiac output, and arterial blood pressure [6,7]. This corresponds well with the rate of metabolism of the citrate contained in preserved blood [see above]. If the patient is hypothermic, or the metabolism of citrate is depressed, hypocalcaemia will occur at a lower infusion rate.

4. Alkalaemia.

Alkalosis reduces the plasma ionized calcium concentration in proportion to the degree of alkalosis [10]. The explanation of this relationship between the pH and the plasma ionized calcium concentration lies in the physical chemical properties of proteins. Most plasma proteins, including the globulins and albumin are Zwitter-ions. That means they may either be positively or negatively changed depending on the pH of their chemical environment. The pH at which they have no charge is called the isoelectric point. For albumin the isoelectric point is a pH = 4.9. If the pH of the plasma is greater than 4.9, albumin is negatively charged, and the negative surface charge per albumin molecule increases with

increasing pH. An increased negative charge on the albumin molecule means that more calcium can bind to it, and the plasma ionized calcium concentration decreases.

5. Hypocapnia.

Acute hypocapnia causes respiratory alkalosis with a concurrent reduction of the plasma ionized calcium concentration [10].

PROBLEMS

The clinical manifestations of hypocalcaemia are related to a reduced concentration of ionized calcium rather than the total calcium concentration. Regrettably the relationship between the plasma ionized calcium concentrations and clinical manifestations has not been studied as extensively as that of the total plasma calcium concentration. The clinical manifestations of hypocalcaemia which are relevant to anaesthetic practice are shown in table 12.5.1.

1. Cardiovascular depression.

Both cardiac output [11,12] and systemic vascular resistance [9] decrease in direct proportion to any reduction of the plasma ionized calcium concentration. A significant reduction of blood pressure and cardiac output occurs in humans when the plasma ionized calcium concentration falls below 0.66 mmol/l [14,15,16].

2. Alteration of the electrocardiogram (ECG) and rhythm.

The duration of the ECG Q-T and S-T intervals increase with decreasing plasma ionized calcium concentration [11,12,13]. The polarity of the T-wave may also change, but this is not a consistent finding [13].

Hypocalcaemia potentiates the arrhythmogenic effects of hyperkalaemia, reducing the potassium concentration at which conduction deficits occur, and the lethal potassium concentration [24]. On the other hand, hypocalcaemia significantly diminishes the arrhythmogenic effects of hypokalaemia [25].

Hypocalcaemia in the absence of other electrolyte disorders does not cause any disturbance of the cardiac rhythm [13,25].

3. Tetany.

There is an increased chance of tetany occurring if the plasma total calcium concentration drops below 2 mmol/l in normoproteinaemic patients [13,22]. Tetany will occur at higher levels of plasma total calcium concentration in hyperproteinaemic or alkalaemic patients [see equation 1]. The threshold of tetanic manifestations appears to be a plasma ionized calcium concentration of 0.86 mmol/l [10].

The cause of tetany is a hypocalcaemia induced elevation of resting and active cell membrane ion conductances of both sodium and potassium channels [27]. This can reduce the stimulation thresholds of both nerve and muscle cells to such a degree that they undergo depolarization, and muscle cells contract at the least small stimulus, or even spontaneously.

4. Increased sensitivity to nondepolarizing muscle relaxants.

Calcium is required for the release of acetylcholine into the neuromuscular junction, and hypocalcaemia is associated with a reduction of acetylcholine release [28]. Because less

acetylcholine is released, the effect of nondepolarizing neuromuscular junction blocking drugs may be expected to be potentiated. Indeed this has been found to occur in-vitro investigations [29].

Table 12.5.1.
Clinical manifestations of hyper- and hypocalcaemia related to the total and ionized plasma calcium concentration. (N.B. 1 mmol/l = 4 mg/100 ml)

TOTAL CALCIUM (mmol/l)	IONIZED CALCIUM (mmol/l)	MANIFESTATIONS
	< 0.1	- Cardiac ventricular arrest [9].
	< 0.66	- Significant reduction of cardiac output and blood pressure [14,15,16].
< 2.0	< 0.86	- Chvostek and Trousseau signs as well as tetany [10,13,22].
< 2.25	< 1.02	- Q-T and S-T intervals increase [11,12,13]. - Cardiac output and systemic vascular resistance decreases [9,11,12].
2.25-2.55	1.02-1.26	**NORMAL**
> 2.55	> 1.26	- Q-T and S-T intervals decrease [11,12,23]. - Cardiac output and systemic vascular resistance increase [9,11,12,17].
> 3.0		- Proximal skeletal muscle weakness [18,19,20,22]. - Polyuria and dehydration [18,19,20,22].
> 4.25		- Neurological manifestations with abnormal motor control and altered level of consciousness [21,23].

MANAGEMENT OF HYPOCALCAEMIA

Treatment is not required for all hypocalcaemic patients, only in those patients with clinical manifestations of hypocalcaemia, or a low plasma ionized plasma calcium concentration. Therapy may be chronic or acute.

1. Chronic therapy.

The only therapy currently available is to treat the cause of the hypocalcaemia if this is possible. Otherwise calcium salts and vitamin-D should be administered to those patients whose hypocalcaemia is due to a cause which is untreatable.

2. Acute therapy.

a. Treatment of the cause of hypocalcaemia.

This consists of treating various correctable causes of hypocalcaemia.

- Correct any alkalaemia.
- Treat hyperventilation if present.
- Reduce the infusion rate of any blood transfusion.

b. Treatment of the manifestations of hypocalcaemia.

The manifestations of hypocalcaemia may be effectively treated by intravenous administration of calcium salts. Any calcium salt may be used, the salts in current clinical use are calcium chloride, calcium gluconate, and calcium gluceptate. Intravenous calcium has no effect on tetany or cardiovascular depression if the plasma ionized calcium concentration is normal or elevated [9]. However in symptomatic patients whose ionized plasma calcium concentration is reduced, intravenous administration of calcium salts elevates the total and ionized plasma calcium concentration [3], effectively raising the arterial blood pressure and the cardiac output [3,17].

The intracellular calcium concentration is only about 0.26 μmol/l [30]. This means that calcium is a predominantly extracellular ion with volume of distribution which is essentially equal to the extracellular fluid volume [3]. Accordingly only a small dose of calcium is required to elevate the plasma ionized calcium to a normal level. The usual dose of calcium chloride for a normal adult is in the region of 0.5-1.0 gm (10-15 mg/kg), or may be calculated using equation 3.

$$Ca_{def} = Ca_{dose} = \frac{WEIGHT}{5} \times ([Ca]_d - [Ca]_m) \quad .....(3)$$

Ca_{dose} = amount of calcium required to replace the extracellular fluid calcium deficit in mmols.
Ca_{def} = extracellular fluid space calcium deficit in mmols.
WEIGHT = body weight in kg.
$[Ca]_d$ = desired total plasma calcium concentration in mmol/l.
$[Ca]_m$ = measured total plasma calcium concentration in mmol/l.

ANAESTHETIC MANAGEMENT

Preoperative.

1. Elective operations in symptomatic hypocalcaemic patients should be delayed until hypocalcaemia has been treated. Hypocalcaemic patients who are asymptomatic with a normal ECG, or who have a normal plasma ionized calcium concentration may be treated the same as any normocalcaemic patient.

2. The symptomatic hypocalcaemic patient should receive no premedication in case the systemic haemodynamic effects of any sedative or opiate drugs are potentiated.

Anaesthesia.

1. The systemic haemodynamic effects of regional anaesthetic techniques such as spinal and epidural anaesthesia may be potentiated by cardiovascular depression due to hypocalcaemia. This may cause a greater degree of hypotension than is normally associated with these techniques. Other regional anaesthetic techniques are not contraindicated.

2. Induction and maintenance of general anaesthesia may be complicated by a greater than normal degree of cardiovascular depression in patients with significant hypocalcaemia, as most general anaesthetic drugs and techniques cause some cardiovascular depression [see chapter 2.1]. The cardiovascular depression may be effectively reversed by intravenous injection of calcium salts.

3. The effects of nondepolarizing muscle relaxant drugs are potentiated. The effects of a given dose will last longer as well as having a more profound effect. Repeat dosages of muscle relaxant drugs should only be administered according to clinical requirements, or using a peripheral nerve stimulator. The enhanced effects of these drugs may be reversed to some degree by intravenous injection of calcium salts. This enhances release of acetylcholine into the neuromuscular junction.

4. Blood transfusion at rates greater than 50 mls/70 kg/min is associated with a reduction of the plasma ionized calcium concentration in normal patients, and will exacerbate hypocalcaemia in those who are already hypocalcaemic. If hypotension occurs during any blood transfusion, 0.5-1.0 gm/70 kg of a calcium salt should be administered to treat possible hypocalcaemia. If the arterial blood pressure subsequently rises, this may be taken as strong evidence for the existence of a low ionized plasma calcium concentration.

Postoperative.

Symptomatic hypocalcaemic patients should be admitted to an intensive care unit postoperatively until hypocalcaemia has been corrected. Tetany and cardiovascular depression will only exacerbate any postoperative haemodynamic instability and hypoxaemia.

REFERENCES

1. Butler,J.G., et al.,(1984), Correlation between serum ionised calcium and serum albumin concentrations in two hospital populations. BRITISH MEDICAL JOURNAL, 289, 948-950.
2. Moore,E.W.,(1970), Ionized calcium in normal serum, ultrafiltrates, and whole blood determined by ion exchange electrodes. JOURNAL OF CLINICAL INVESTIGATION, 49, 318-334.
3. Drop,L.J., Cullen,D.J.,(1980), Comparative effects of calcium chloride and calcium gluceptate. BRITISH JOURNAL OF ANAESTHESIA, 52, 501-505.
4. Bell,N.H.,(1979), Hypercalcaemic and hypocalcaemic disorders: Diagnosis and treatement. NEPHRON, 23, 147-151.
5. McMahon,M.J., et al.,(1978), The nature of hypocalcaemia in acute pancreatitis. BRITISH JOURNAL OF SURGERY, 65, 216-218.
6. Denlinger,J.K., et al.,(1976), Hypocalcaemia during rapid blood transfusion in anaesthetized man. BRITISH JOURNAL OF ANAESTHESIA, 48, 995-999.
7. Cooper,N., et al.,(1973), Myocardial depression following citrated blood transfusion. ARCHIVES OF SURGERY, 107, 756-763.

8. Loken,H.F., et al.,(1960), Ultracentrifugal analysis of protein bound and free calcium in human serum. JOURNAL OF BIOLOGICAL CHEMISTRY, 235, 3654- 3658.
9. Drop,L.J.,(1985), Ionized calcium, the heart, and hemodynamic function. ANESTHESIA AND ANALGESIA, 64, 432-451.
10. Drop,L.J., Miller,E.V.,(1980), Biochemical alterations during tetany. ANESTHESIOLOGY, 52, 82-83.
11. Bristow,M.R., et al.,(1977), Effect of D600, practolol, and alterations in magnesium on ionized calcium concentration - response relationship in the intact dog heart. CIRCULATION RESEARCH, 41, 574-581.
12. Bristow,M.R., et al.,(1977), Ionized calcium and the heart. Elucidation of in vivo concentration-response relationships in the open chest dog. CIRCULATION RESEARCH, 41, 565-574.
13. Bronsky,D., et al.,(1961), Calcium and the elctrocardiogram. I. The electrocardiographic manifestations of hypoparathyroidism. AMERICAN JOURNAL OF CARDIOLOGY, 7, 823-832.
14. Marquez,J., et al.,(1986), Cardiovascular depression secondary to ionic hypocalcaemia during hepatic transplantation in humans. ANESTHESIOLOGY, 65, 457-461.
15. Howland,W.S., et al.,(1977), The cardiovascular effects of low levels of ionized calcium during massive transfusion. SURGERY, GYNECOLOGY & OBSTETRICS, 145, 581-586.
16. Denlinger,J.K., Nehrwold,M.L.,(1976), Cardiac failure associated with hypocalcaemia. ANESTHESIA AND ANALGESIA, 55, 34-36.
17. Denlinger,J.K., et al.,(1975), Cardiovascular responses to calcium administered intravenously to man during halothane anesthesia. ANESTHESIOLOGY, 42, 390-397.
18. Samaan,N.A., et al.,(1976), Hypercalcaemia in patients with known malignant disease. SURGERY, 80, 382-389.
19. Hickey,R.C., et al.,(1981), Hypercalcemia in patients with breast cancer. Osseous metastases, hyperplastic parathyroid tissue, or pseudohyperparathyroidism? SURGERY, 116, 545-552.
20. Patten,B.M., et al.,(1974), Neuromuscular disease in primary hyperparathyroidism. ANNALS OF INTERNAL MEDICINE, 80, 182-193.
21. Henson,R.A.,(1966), The neurological aspects of hypercalcaemia with special reference to primary hyperparathyroidism. JOURNAL OF THE ROYAL COLLEGE OF PHYSICIANS. 1, 41-50.
22. Albright,F., et al.,(1934), Hyperparathyroidism. A common and polymorphic condition as illustrated by seventeen proved cases from one clinic. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 102, 1276-1287.
23. Bronsky,D., et al.,(1961), Calcium and the electrocardiogram. II. The electrocardiographic manifestations of hyperparathyroidism and of marked hypercalcaemia from various other etiologies. AMERICAN JOURNAL OF CARDIOLOGY, 7, 833-839.
24. Braun,H.A., et al.,(1955), The influence of hypocalcaemia induced by sodium ethylendiamine tetraacetate on the toxicity of potassium. An experimental study. JOURNAL OF LABORATORY AND CLINICAL MEDICINE, 46, 544-548.
25. Surawicz,B.,(1967), Relationship between electrocardiogram and electrolytes. AMERICAN HEART JOURNAL, 73, 814-834.
26. Kety,S.S., Schmidt,C.F.,(1946), The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men. JOURNAL OF CLINICAL INVESTIGATION, 25, 107-119.
27. Frankenhauser,B., Hodgkin,A.L.,(1957), The action of calcium on the electrical properties of squid axons. JOURNAL OF PHYSIOLOGY (London), 137, 218-244.
28. Standaert,F.G.,(1982), Release of transmitter at the neuromuscular junction. BRITISH JOURNAL OF ANAESTHESIA, 54, 131-145.
29. Waud,B.E., Waud,D.R.,(1980), Interaction of calcium and potassium with neuromuscular blocking agents. BRITISH JOURNAL OF ANAESTHESIA, 52, 863-865.
30. Marban,E., et al.,(1980), Free calcium in heart muscle at rest and during contraction measured with Ca2+-sensitive microelectrodes. NATURE, 286, 845-850.

Chapter 12.6

HYPERCALCAEMIA

Hypercalcaemia may be defined as a plasma total calcium concentration greater than 2.55 mmol/l, or more realistically as a plasma ionized calcium concentration greater than 1.26 mmol/l.

CAUSES

Hypercalcaemia is not usually a problem which occurs acutely. Most of the causes are disorders are chronic, such as hyperparathyroidism [8], thiazide diuretics [8], hyperthyroidism [8], tuberculosis and sarcoidosis [8], multiple myeloma [8], and cancer, especially when bone metastases are present [9,10].

The main causes of acute hypercalcaemia are vitamin-D intoxication [8], and excessive milk or alkali ingestion [8].

PROBLEMS

Hypercalcaemia does not generally cause symptoms or clinical manifestations until the plasma total calcium concentration exceeds 3 mmol/l [see table 12.5.1]. The clinical syndrome of hypercalcaemia is characterized by muscle weakness, polyuria, dehydration, and neurological disorders.

As with hypocalcaemia, the clinical manifestations are related to the plasma ionized concentration rather than to the total plasma calcium concentration. But the relationship between plasma ionized calcium concentration and the manifestations of hypercalcaemia is not a well researched topic. Table 12.5.1 shows the relationship between plasma total calcium concentration and the clinical manifestations of hypercalcaemia.

The manifestations listed in table 12.5.1 occur at a lower level of hypercalcaemia if the patient is hypoproteinaemic or acidaemic.

1. Cardiovascular.

Cardiac output [1,2,3] and systemic vascular resistance [4] increase in direct proportion to the plasma ionized calcium concentration. Because of this chronic hypercalcaemia is often associated with an elevation of the arterial blood pressure [5].

2. Electrocardiographic changes and cardiac rhythm.

The electrocardiographic Q-T and S-T interval decrease as the plasma ionized calcium concentration increases [1,2,6].

Hypercalcaemia itself, in the absence of other electrolyte disorders does not cause any abnormality of the cardiac rhythm [6], but does potentiate the arrhythmogenic effects of hypokalaemia [7].

3. Polyuria and dehydration.

If the plasma total calcium concentration exceeds 3 mmol/l, polyuria occurs [11,12]. This is due to a calcium induced disturbance of renal water conservation, and produces a syndrome similar to diabetes insipidus. The polyuria is associated with glycosuria, as well as increased losses of sodium and potassium [13]. Excessive water losses, together with inadequate replacement results in dehydration and hypovolaemia, and chronically elevated potassium excretion may cause hypokalaemia too. Chronic hypercalcaemia may eventually cause renal failure, nephrolithiasis, or both [12,13].

4. Neurological disorder.

Extreme hypercalcaemia with a plasma total calcium concentration greater than 4.25 mmol/l may cause manifestations of disordered neurological function. These manifestations vary from lethargy, to abnormal motor control, and alterations of the level of consciousness varying from confusion to coma [6,14]. Reduction of the degree of hypercalcaemia alleviates all these manifestations.

5. Muscle weakness.

A plasma total calcium concentration above 3.0 mmol/l is not only associated with polyuria, but may also cause muscle weakness [9,10,11,12, table 12.5.1]. The weakness mainly occurs in the proximal leg muscles, although it may also affect the proximal arm muscles too [11]. Chronic hypercalcaemia also induces a neurogenic atrophy of type-II muscle fibers, (fast twitch, anaerobic fibers) [11].

The main cause of the abnormal nervous and muscle function is a hypercalcaemia caused reduction of resting and active cell membrane sodium and potassium ion conductance [15]. This increases the stimulation thresholds of both nerve and muscle fibers. If the stimulation threshold of muscle fibers is sufficiently elevated, muscle weakness will occur, despite increased acetylcholine release into the neuromuscular junction due to hypercalcaemia [16], as muscles which are unable to be stimulated to contract are weak.

6. Reduced effects of nondepolarizing muscle relaxants.

Nondepolarizing muscle relaxant drugs are competitive antagonists of acetylcholine at the neuromuscular junction acetylcholine receptors. Hypercalcaemia increases the release of acetylcholine into the neuromuscular junction [16]. It is therefore not surprising that in-vitro experiment has shown that the concentration of a given nondepolarizing muscle relaxant required for a given degree of muscle relaxation is directly proportional to the extracellular calcium concentration [18]. Clinically it has been found that the effect and duration of action of nondepolarizing muscle relaxants is reduced by hypercalcaemia, even when clinical muscle weakness is present [17].

MANAGEMENT

Treatment of hypercalcaemia is indicated for symptomatic patients, those with electrocardiographic evidence of hypercalcaemia, and those with an elevated plasma

ionized calcium concentration. Therapy consists of general resuscitative measures and specific therapy directed at reducing the plasma calcium concentration [13,19].

1. General measures.

a. Correct dehydration.

Dehydration may occur in patients who fail to drink sufficient amounts of water to replace urinary losses. Extreme dehydration may be associated with hypovolaemia. The recommended treatment is infusion of 0.9% NaCl solution, as polyuria is also associated with significant sodium loss. Hypovolaemic patients should initially be administered plasma, or another blood volume expanding fluid, e.g. dextran or gelatine solutions, as the restoration of normal haemodynamic function is the first requisite of any therapy of dehydration. Subsequent to normalization of systemic haemodynamics, dehydration may be further corrected with an appropriate crystalloid solution, e.g. a glucose-saline solution, to replace the whole body water deficit.

Plasma electrolytes should be regularly monitored so that any reduction of plasma potassium and sodium concentrations may be treated before they become too gross.

Correction of dehydration causes significant haemodilution, simultaneously reducing the extracellular calcium concentration too.

b. Correct hypokalaemia.

Hypokalaemia may occur secondary to hypercalcaemic polyuria. Hypercalcaemia potentiates the arrhythmogenic effects of hypokalaemia. Replacement of potassium should be done simultaneously with treatment of dehydration. As hypokalaemia develops over a matter of days it should be treated as for chronic hypokalaemia [see chapter 12.3].

c. Correct hypoproteinaemia.

Hypercalcaemic patients may also be hypoproteinaemic. If this is the case then both hypoproteinaemia and the elevated plasma ionized calcium concentration may be simultaneously corrected with an infusion of concentrated human albumin, or plasma.

2. Acute therapy & Rapid reduction of plasma calcium.

a. Loop diuretics.

"Loop diuretics" such as frusemide and ethacrynic acid reduce the plasma calcium concentration within minutes after intravenous administration. The recommended dose of frusemide is 40-80 mg/70 kg every 2-4 hours. During administration of diuretics, careful attention should be paid to prevention of dehydration and hypokalaemia.

b. Disodium ethylen-diamine-tetra-acetate (EDTA).

This is a compound that chelates with plasma calcium, and so doing immediately reduces the plasma calcium concentration. The calcium salt formed is filtered in the glomeruli, and as it does not undergo any significant tubular resorbtion, calcium is eliminated from the body. One disadvantage of this therapy is that overdosage may cause a sometimes fatal cardiovascular depression due to extreme hypocalcaemia.

The usual dose recommended for adults is 50-100 mg/kg per day to a maximum of 6 gm/day. The total daily dose may be administered by intravenous infusion over 4-6 hours.

c. Peritoneal or haemodialysis.

Peritoneal and haemodialysis rapidly reduce the plasma calcium concentration, albeit only temporarily.

d. Calcitonin.

Intravenous infusion of 2-8 MRC units/kg of calcitonin reduces the plasma calcium concentration by 2-3 hours after administration. Calcium leaves the circulation and is deposited in bone.

3. Slow & Chronic management of hypercalcaemia.

a. Parathyroidectomy.

Parathyroidectomy is indicated in patients with proven hyperparathyroidism.

b. Phosphate administration.

Intravenous infusion of sodium phosphate reduces the plasma calcium concentration by causing calcium phosphate deposition in bone. One disadvantage is that calcium phosphate may also be deposited in other organs too, e.g. the kidneys. This may exacerbate any existing renal dysfunction.

The dose recommended for adults is 1.5 gm/70 kg of sodium phosphate infused intravenously over 6-8 hours. A single dose begins to work within minutes and exerts its peak effect by 24-48 hours. The effect of two doses administered on consecutive days may last as long as 6-15 days.

c. Glucocorticoids.

Chronic administration of glucocorticoids also reduces the plasma calcium concentration.

d. Mithramycin.

A course of the cytostatic drug mithramycin may be used to treat hypercalcaemia.

ANAESTHETIC MANAGEMENT

Preoperative.

1. No patient with symptomatic hypercalcaemia should be permitted to undergo elective surgery. General anaesthesia may exacerbate the neurological disorder in addition to causing profound cardiovascular depression in dehydrated patients. Hypercalcaemia which is severe enough to cause neurological manifestations and muscle weakness should be treated priore to any elective operation.

Asymptomatic hypercalcaemic patients may be managed the same as any normocalcaemic patient for the operation planned.

2. No sedative drugs should be administered preoperatively to patients with neurological manifestations of hypercalcaemia. The already reduced level of consciousness may be further depressed.

3. Dehydration and hypovolaemia should be corrected prior to induction of anaesthesia, and certainly prior to any elective surgical procedure.

Anaesthesia.

1. Strict attention should be paid to fluid balance, so that existing dehydration is not exacerbated, or that dehydration may be prevented. Hypoproteinaemia may occur perioperatively due to loss of plasma into traumatic oedema, ("third space" losses). Hypoproteinaemia elevates the plasma ionized calcium concentration, exacerbating any existing hypercalcaemic manifestations. Plasma, or albumin concentrates should be infused peroperatively during major surgery to prevent this occurring.

2. Regional anaesthetic techniques such as spinal and epidural anaesthesia are contraindicated in the patient who is dehydrated. The hypotension caused by these techniques is more extreme in hypovolaemic patients [see chapter 14.4].

3. When administering general anaesthesia to a symptomatic hypercalcaemic patient there are a number of factors that should be taken into consideration.

a. Use a general anaesthetic technique with controlled ventilation. This will guarantee oxygenation in spite of muscle weakness, in addition to which slight hyperventilation will reduce the plasma ionized calcium concentration.
b. The potency and duration of action of the nondepolarizing muscle relaxant drugs is reduced by hypercalcaemia. This necessitates higher doses and more frequent administration of these drugs than usual. Muscle relaxants should be administered according to clinical requirements, or using a peripheral nerve stimulator as a guide.
c. If the patient is dehydrated, drugs should be selected that cause minimal cardiovascular depression. General anaesthetic drugs will further exacerbate any haemodynamic disorder due to hypovolaemia [see chapters 14.4 and 2.1].

Postoperative.

Symptomatic severely hypercalcaemic patients should be admitted into an intensive care unit postoperatively for further management of hypercalcaemic manifestations as well as postoperative care.

REFERENCES

1. Bristow,M.R., et al.,(1977), Effect of D600, practolol, and alterations in magnesium on ionized calcium concentration - response relationship in the intact dog heart. CIRCULATION RESEARCH, 41, 574-581.
2. Bristow,M.R., et al.,(1977), Ionized calcium and the heart. Elucidation of in vivo concentration-response relationships in the open chest dog. CIRCULATION RESEARCH, 41, 565-574.
3. Denlinger,J.K., et al.,(1975), Cardiovascular responses to calcium administered intravenously to man during halothane anesthesia. ANESTHESIOLOGY, 42, 390-397.
4. Drop,L.J.,(1985), Ionized calcium, the heart, and hemodynamic function. ANESTHESIA AND ANALGESIA, 64, 432-451.
5. Kesteloot,H., Geboers,J.,(1982), Calcium and blood pressure. LANCET, 1, 813-815.
6. Bronsky,D., et al.,(1961), Calcium and the electrocardiogram. II. The electrocardiographic manifestations of hyperparathyroidism and of marked hypercalcaemia from various other etiologies. AMERICAN JOURNAL OF CARDIOLOGY, 7, 833-839.
7. Surawicz,B.,(1967), Relationship between electrocardiogram and electrolytes. AMERICAN HEART JOURNAL, 73, 814-834.
8. Bell,N.H.,(1979), Hypercalcaemic and hypocalcaemic disorders: Diagnosis and treatment. NEPHRON, 23, 147-151.
9. Hickey,R.C., et al.,(1981), Hypercalcemia in patients with breast cancer. Osseous metastases, hyperplastic parathyroid tissue, or pseudohyperparathyroidism? SURGERY, 116, 545-552.

10. Samaan,N.A., et al.,(1976), Hypercalcaemia in patients with known malignant disease. SURGERY, 80, 382-389.
11. Patten,B.M., et al.,(1974), Neuromuscular disease in primary hyperparathyroidism. ANNALS OF INTERNAL MEDICINE, 80, 182-193.
12. Albright,F., et al.,(1934), Hyperparathyroidism. A common and polymorphic condition as illustrated by seventeen proved cases from one clinic. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 102, 1276-1287.
13. D'Orisio,T.M.,(1978), Hypercalcemic crisis. HEART & LUNG, 7, 425-434.
14. Henson,R.A.,(1966), The neurological aspects of hypercalcaemia with special reference to primary hyperparathyroidism. JOURNAL OF THE ROYAL COLLEGE OF PHYSICIANS. 1, 41-50.
15. Frankenhauser,B., Hodgkin,A.L.,(1957), The action of calcium on the electrical properties of squid axons. JOURNAL OF PHYSIOLOGY (London), 137, 218-244.
16. Standaert,F.G.,(1982), Release of transmitter at the neuromuscular junction. BRITISH JOURNAL OF ANAESTHESIA, 54, 131-145.
17. Al-Mohaya,S., et al.,(1986), Abnormal responses to muscle relaxants in a patient with primary hyperparathyroidism. ANESTHESIOLOGY, 65, 554-556.
18. Waud,B.E., Waud,D.R.,(1980), Interaction of calcium and potassium with neuromuscular blocking agents. BRITISH JOURNAL OF ANAESTHESIA, 52, 863-865.
19. Lee,D.B.N., et al.,(1978), The pathophysiology and clinical aspects of hypercalcemic disorders. WESTERN JOURNAL OF MEDICINE, 129, 278-320.

Part 13

DISORDERS OF ACID-BASE BALANCE

Normal physiological processes require the simultaneous functioning of many hundreds of enzyme and non-enzyme catalyzed chemical reactions. The rates of all these reactions are dependent on the pH of the chemical environment in which they occur. Normal physiological function is dependent on these reactions occurring at rates determined by the pH normally present in the regions in which these reactions occur. A change in the intracellular or extracellular pH changes the rates of these reactions relative to each other, so causing organ dysfunction.

This section deals with the practical clinical aspects of the disorders of acid-base balance, and as such does not discuss the biochemistry or pathogenesis of these disorders in any great detail. For the latter, the reader is referred to the many excellent works currently available on this subject. The average clinician has a very pragmatic view on this matter. He wishes to know only a few things.

- What effects do these disorders have, and are they clinically significant?
- At what pH is the level of physiological dysfunction such that treatment is required?
- What is the treatment?

Chapter 13.1

DEFINITIONS & DIAGNOSIS OF ACID-BASE DISORDERS

NORMAL PARAMETERS AND DEFINITIONS

When considering any acid base disorder, one should not only consider extracellular changes, but also the intracellular changes in acid-base balance. Cellular function is affected by extracellular changes in acid-base balance, but as most of the enzymes that regulate cell function are intracellular, intracellular changes of acid-base balance are of even greater importance. Regrettably the only tissue easily amenable to clinical analysis is blood, and here only changes in plasma acid-base status are measured. Normal values of the parameters measured are shown in table 13.1.1, and defined below.

Table 13.1.1.
Normal values of parameters measured for determination of blood acid base status.

Parameter	Arterial	Venous
pH	7.36-7.44	7.34-7.42
PO_2	11.3-13.3kPa (80-100mmHg)	5.5-6kPa (37-42mmHg)
PCO_2	4.8-5.9kPa (36-44mmHg)	5.6-6.7kPa (42-50mmHg)
$[HCO_3^-]$	21-25 mmol/l	21-25 mmol/l
Base excess	+/- 2 mmol/l	+/- 2 mmol/l
O_2 saturation	98%	75%

pH.

This is the negative logarithm to the base 10 of the hydrogen ion (H^+), concentration ($[H^+]$). It should be noted that the usual glass pH electrode does not measure $[H^+]$, but instead measures H^+ activity [2].

$$pH = -\log[H^+] \quad \text{.....(1)}$$

Bicarbonate ion concentration ($[HCO_3^-]$).

The concentration of bicarbonate ion in the plasma, expressed in millimoles per liter, or milliequivalents per liter.

Base excess.

This is a measure of the acidity or alkalinity of the blood. It is defined as the number of millimoles of an acid or base required to bring the pH of one liter of the blood sample under investigation to a pH of 7.40, if that blood sample is kept at a temperature of 38°C at a PCO_2 of 5.33 kPa (40 mmHg). It is expressed as a positive number. If there is an excess of acid, the base excess is expressed as a negative quantity.

Intracellular pH.

The intracellular and extracellular pH are regulated within a narrow range, and this is the range within which the body as a whole functions best. Normal values for intracellular and extracellular pH are shown in table 13.1.2.

Table 13.1.2.
Normal ranges of pH for intracellular and extracellular fluid.

PLASMA & EXTRACELLULAR FLUID	= 7.35-7.45
INTRACELLULAR FLUID (depends on tissue)	= 6.51-7.29 [1]

TYPES OF ACID-BASE DISORDERS

Equations and chemical reactions.

Maintenance of pH within a narrow range in each tissue is achieved by a number of buffer systems which tend to minimize any change of the hydrogen ion concentration. The most important of these buffer systems, for both intracellular and intracellular fluid is the bicarbonate (HCO_3^-) buffer system. The principal reactions occurring are shown below.

$$CO_2 + H_2O \xleftrightarrow[\text{anhydrase}]{\text{carbonic}} H_2CO_3 \xleftrightarrow{\text{spontaneous}} H^+ + HCO_3^-$$

Hydration of carbon dioxide to carbonic acid, and the reversal of this same reaction, does occur spontaneously, but is speeded up by a factor of 5000 times by the enzyme carbonic anhydrase. Carbonic anhydrase is not widely distributed throughout the body, being present only inside erythrocytes, acid secreting cells of the stomach, renal tubular cells, and choroid plexus, but not in other cells, plasma, or interstitial fluid.

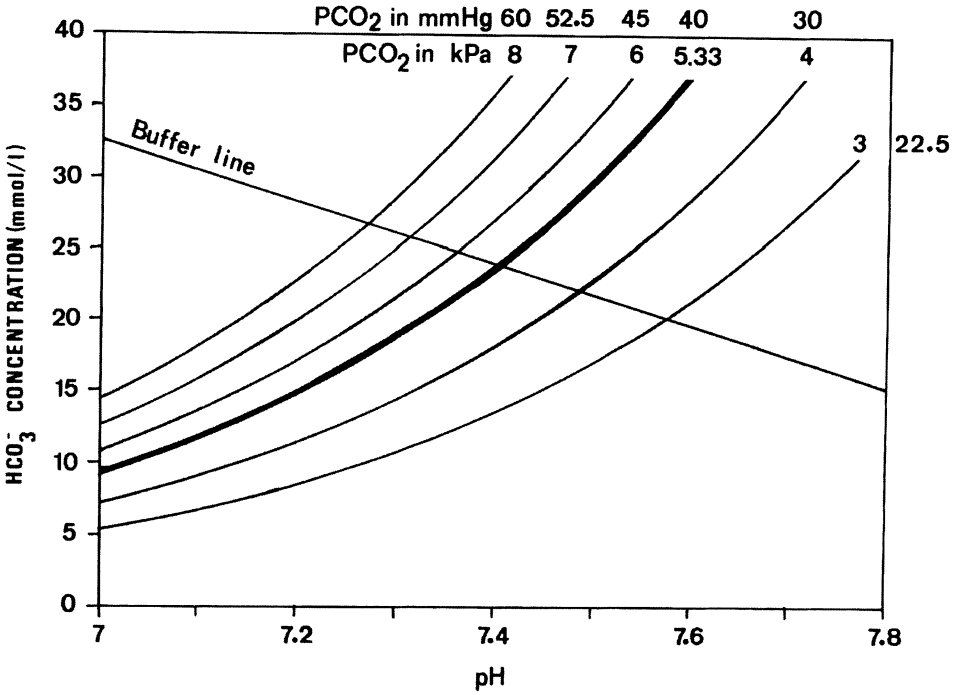

FIGURE 13.1.1. - The relationship between the bicarbonate ion concentration and the pH of plasma is shown for various levels of PCO_2 as calculated by the Henderson-Hasselbach equation. The buffer base line for human whole blood in-vitro is also shown. This is the well known Davenport diagram.

It is the relative concentrations of H^+ and HCO_3^- which determine the pH of the fluid that they buffer, be it intracellular or extracellular. This relationship is usually expressed by the Henderson-Hasselbach equation (equation 2).

$$pH = 6.1 + \log_{10} \frac{[HCO_3^-]}{[H^+]} \quad .....(2)$$

It is more usual to express the Henderson-Hasselbach equation using the partial pressure of carbon dioxide as a measure of the $[H^+]$. This gives rise to the well known form of the Henderson-Hasselbach equation, (equation 3).

$$pH = 6.1 + \log_{10} \frac{[HCO_3^-]}{0.225 \times PCO_2(kPa)} \quad ..... (3)$$

(N.B. for those who wish to express the PCO_2 in mmHg, the constant by which the PCO_2 must be multiplied is 0.03 instead of 0.225).

For any given pH and PCO_2 there is a unique $[HCO_3^-]$, and vice versa for the PCO_2. The equations describing this are derived by rearranging equation 3 above.

$$[HCO_3^-] = 0.225 \times PCO_2 \times 10^{(pH - 6.1)} \quad \ldots\ldots (4)$$

and

$$PCO_2 = \frac{[HCO_3^-]}{0.225 \times 10^{(pH - 6.1)}} \quad \ldots\ldots\ldots\ldots (5)$$

These equations may be represented graphically by the well known Davenport diagram to show the relationship between the pH and $[HCO_3^-]$ for any given PCO_2, [see fig. 13.1.1].

Reaction rate of the blood carbonic anhydrase system.

Carbon dioxide and HCO_3^- diffuse freely across capillary endothelium between the blood and interstitial fluid, as well as across cell membranes. Because of this, rapid exchange and equilibrium of carbon dioxide and HCO_3^- is possible between interstitial fluid and erythrocyte intracellular fluid, in addition to the rapid exchange of carbon dioxide across the pulmonary alveolar endothelium. Both hydrolysis and synthesis of HCO_3^- occur rapidly in erythrocytes because of the high cytoplasmic carbonic anhydrase concentration. In-vitro and in-vivo canine investigations have shown that the rate at which a new pH equilibrium in plasma occurs after acute addition of carbon dioxide to blood has a half life of about 6-7 seconds [8]. Equilibrium in whole blood is slowed by the fact that HCO_3^- is only formed inside the erythrocytes as there is no carbonic anhydrase in the plasma itself, therefore the rate of change of plasma pH is dependent on the rate at which HCO_3^- diffuses into the plasma across the erythrocyte membrane. Because of this, and also because HCO_3^- is exchanged between plasma and interstitial fluid, it is not surprising that it takes 5-10 minutes in humans for a new steady state pH to be achieved in blood after acute induction of respiratory acidosis [3], respiratory alkalosis [4], metabolic acidosis [5], or metabolic alkalosis [6]. The new acid-base status measured after acute induction of an acid-base disorder in humans remains stable for at least an hour [3].

CLASSIFICATION OF ACID-BASE DISORDERS

The usual method of classifying acid-base disorders is to divide them into metabolic or respiratory acidosis and alkalosis.

1. Acute metabolic acidosis.

Metabolic acidosis is either due to administration of non-volatile acids such as HCl, lactate, acetylsalicylic acid etc, or endogenous production of acids such as lactate or ketoacids. This increases H^+ concentration relative to the HCO_3^- concentration, and so pH is reduced [see fig. 13.1.2 for an illustration of the changes occurring].

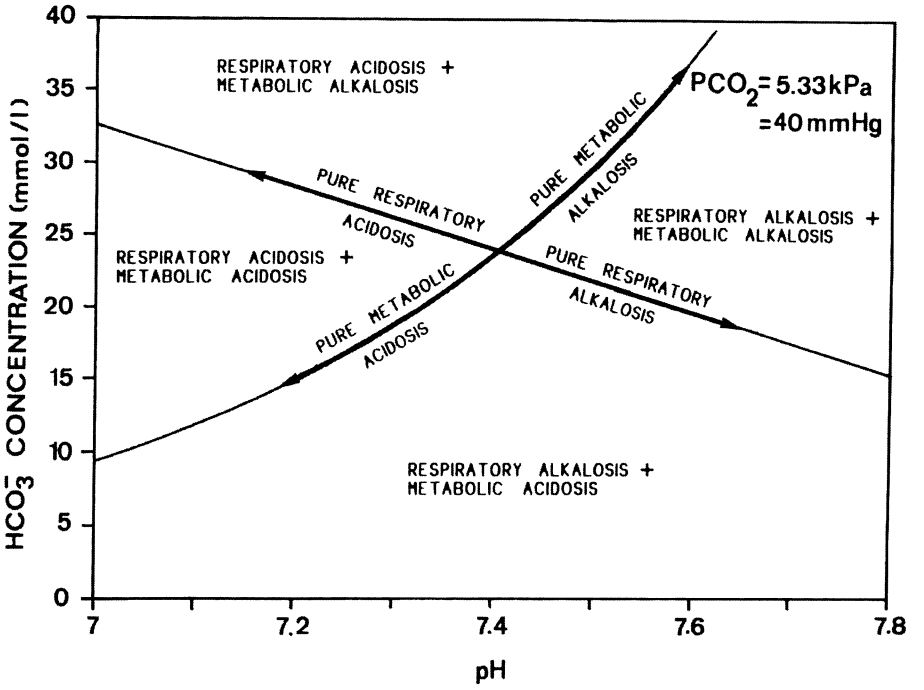

FIGURE 13.1.2. - The relationship between the PCO_2, pH, and bicarbonate ion concentrations are shown for various pure and mixed acid-base disorders.

2. Acute metabolic alkalosis.

Metabolic alkalosis is due to an elevation of the plasma HCO_3^- concentration. This may be caused by infusion of an $NaHCO_3$ solution, or metabolism of sodium lactate, or citrate [see chapter 13.3]. Elevation of $[HCO_3^-]$ relative to the $[H^+]$ increases the pH, [see fig. 13.1.2 for an illustration of the changes occurring].

3. Acute respiratory acidosis.

Carbon dioxide is eliminated from the body through the lungs. A reduction of alveolar ventilation relative to carbon dioxide production elevates the PCO_2 in the body. As the concentration of HCO_3^- does not change as rapidly as that of the PCO_2, the plasma $[H^+]$ is elevated relative to that of $[HCO_3^-]$ and the pH falls, [see fig. 13.1.2].

4. Acute respiratory alkalosis.

Elevation of alveolar ventilation relative to the carbon dioxide production decreases the PCO_2 of the blood and whole body. As the PCO_2 and hence the $[H^+]$ decreases at a faster rate than the $[HCO_3^-]$, the $[HCO_3^-]$ is elevated relative to $[H^+]$ and alkalosis occurs, [see fig. 13.1.2 for an illustration of the changes occurring].

COMPENSATION OF ACID-BASE DISORDERS

If a given change of acid-base status lasts for several hours, further changes of acid-base status occur, mainly as a result of changes in intracellular HCO_3^- concentration. The rate at which this occurs is dependent on the cardiac output, and the activity of the erythrocyte carbonic anhydrase system.

As the only other cells, besides erythrocytes, in which carbonic anhydrase is present are acid producing cells of the stomach, and the cells of the choroid plexus of eye and brain, it is obvious that the erythrocytes are effectively the main source of HCO_3^- that diffuses into the interstitial and intracellular fluid, and the main site of hydrolysis of any HCO_3^- that diffuses out of cells. The rate at which HCO_3^- exchange occurs is dependent on the HCO_3^- concentration gradients existing between the plasma, interstitial fluid, and intracellular fluid, which in turn is dependent on the cardiac output. Cardiac output is the factor determining the rate at which HCO_3^- and CO_2 are transported to and from tissues where exchange takes place.

The total volume of carbon dioxide stored in the average 70 kg adult human body is equivalent to about 123 liters of carbon dioxide gas, of which only 2.4% is present in the lungs and blood. About 70-90% of this carbon dioxide is stored as carbonates in bone and as HCO_3^- [7], which means that there is a total of approximately 3.8-4.9 moles of carbonates and HCO_3^- stored in the whole body. A new blood and interstitial fluid pH equilibrium takes about 5-10 minutes to occur after an acute change of acid-base status [3,4,5,6]. As this volume embraces only about 6% of the total carbon dioxide stores, it is apparent that it takes some hours for a new acid-base equilibrium to occur in all fluid compartments after any change of acid-base status.

This slow change of whole body HCO_3^- and CO_2 content after establishing a new blood acid-base status tends to normalize the blood and intracellular pH, and is called "compensation" of an acid-base disorder. While the process of compensation tends to normalize the pH after establishment of an acid-base disorder, the pH never becomes completely normal. The magnitude of the changes required for any given degree of compensation may be calculated using equations 4 and 5 in this chapter or by reference to figure 13.1.1.

A simple outline of the basic events that occur in the hours and days following an established acid-base disorder is given below. Should the reader wish a more detailed explanation, he is advised to consult one of the various excellent standard works on the pathophysiology of acid-base disorders.

1. Compensation for metabolic acidosis.

During metabolic acidosis the renal tubular cells secrete increased amounts of H^+ in exchange for Na^+, and HCO_3^- is also retained. The effect of this is to increase the body HCO_3^- concentration relative to the H^+ concentration, which increases the pH. Renal tubular HCO_3^- excretion is reduced in spontaneously breathing patients, albeit not significantly, by an acidaemia induced elevation of respiratory minute volume, which while it decreases the PCO_2 and the $[H^+]$, also reduces the $[HCO_3^-]$.

2. Compensation for metabolic alkalosis.

The effect of metabolic alkalosis in spontaneously breathing persons is to reduce the respiratory minute volume. This causes the PCO_2 to rise, which does elevate the H^+ concentration, but also increases the HCO_3^-, which tends to reverse this beneficial effect. In some patients the reduction of respiratory minute volume is so extreme that the P_aCO_2 may rise as high as 8.8 kPa (66 mmHg) [9]. As HCO_3^- is not excreted in the urine until the plas-

ma concentration rises above 28 mmol/l, it is obvious that renal compensation is not an important mechanism of compensation for metabolic alkalosis unless it is quite severe.

Table 13.1.3.
Changes in arterial pH, PCO_2, and $[HCO_3^-]$ relative to one another in various acid-base disorders.

DISORDER	INITIAL CHANGES			AFTER COMPENSATION		
	pH	PCO_2	$[HCO_3^-]$	pH	PCO_2	$[HCO_3^-]$
RESPIRATORY ACIDOSIS	↓	↑	N	0/↓	↑	↑
RESPIRATORY ALKALOSIS	↑	↓	N	0/↑	↓	↓
METABOLIC ACIDOSIS	↓	N	↓	0/↓	↓	↓
METABOLIC ALKALOSIS	↑	N	↑	0/↑	↑	↑

"↑" = increase; "↓" = decrease; "0" = no change;"N" = normal.

3. Compensation for respiratory acidosis.

The elevated H^+ concentration causes increased renal tubular secretion of H^+ and a greater degree of HCO_3^- resorbtion in exchange for chloride ion. In fact the plasma Cl^- concentration falls as the HCO_3^- concentration rises. Elevation of the HCO_3^- concentration relative to the H^+ concentration increases the pH.

4. Compensation for respiratory alkalosis.

During respiratory alkalosis, renal tubular excretion of H^+ is depressed while the excretion of HCO_3^- is increased. As the maximum rate of renal HCO_3^- excretion in adults is about 0.5 moles/day [10], renal compensation of respiratory alkalosis takes some hours to days to be effective. The effect of a reduction of HCO_3^- concentration relative to the H^+ concentration is to reduce the pH.

DIAGNOSIS OF ACID-BASE DISORDERS

The diagnosis of any acid-base disorder must be made on the basis of;

- clinical history,
- measurement of blood acid-base parameters and gases,
- measurement of plasma electrolytes.

1. Clinical history.

This is necessary because measurement of intracellular pH and cytoplasmic composition in living humans is at present technically difficult. An idea of what is occurring in the intracellular compartment of the body can only be inferred from the blood acid-base status, plasma electrolyte concentrations, and the clinical history. The clinical history also enables the primary cause of the disorder to be more definitively established.

2. Analysis of arterial blood gases and acid-base status.

Measurement of the arterial plasma pH, PCO_2, $[HCO_3^-]$, and PO_2 provide further information as to any diagnosis. Reference should be made to table 13.1.1 and figures 13.1.1, and 13.1.3 for a guide as to interpretation of the data.

Most of the disorders encountered clinically are of the mixed type. They have both a metabolic as well as a respiratory component because a degree of compensation has occurred. The clinical history is then of value in determining the primary cause.

Table 13.1.4.
Anions most commonly causing increased anion-gap acidaemia.

Ketoacidosis	- Diabetes mellitus, starvation, alcohol.
Lactic acidosis	- Severe hypoxaemia, shock. - Lactic acidosis secondary to biguanide drug usage.
Renal failure	- Due to failure of excretion of SO_4^{2-}, HPO_4^{2-}, etc.
Intoxications	- Salicylates, methanol, paraldehyde, etc.

3. Plasma electrolyte concentrations.

Measurement of the plasma sodium (Na^+), potassium (K^+), chloride (Cl^-), and HCO_3^- concentrations allows the "anion gap" to be calculated according to equation 6 below [11].

$$\textbf{ANION GAP} = [Na^+] + [K^+] - [HCO_3^-] - [Cl^-] \quad ....(6)$$

(Normal anion gap is between 9-14 mmol/l)

The "anion gap" provides a measure of the concentration of unmeasured anions. It is significantly elevated when it is greater than 14 mmol/l. The clinical history usually gives an idea as to the likely anion to be considered [see table 13.1.4].

REFERENCES

1. Waddell,W.J., Bates,R.G.,(1969), Intracellular pH. PHYSIOLOGICAL REVIEWS, 49, 285-329.
2. Davis,R.P.,(1967), Logland: A Gibbsian view of acid-base balance. AMERICAN JOURNAL OF MEDICINE, 42, 159-162.
3. Brackett,N.C., et al.,(1965), Carbon dioxide titration curve of normal man. Effect of increasing degrees of acute hypercapnia on acid-base equilibrium. NEW ENGLAND JOURNAL OF MEDICINE, 272,6-12.
4. Wollman,H., et al.,(1968), Effects of extremes of respiratory and metabolic alkalosis on cerebral blood flow in man. JOURNAL OF APPLIED PHYSIOLOGY, 24, 60-65.
5. Orringer.C.E., et al.,(1977), Natural history of lactic acidosis after grand-mal seizures. A model for the study of an anion-gap acidosis not associated with hyperkalaemia. NEW ENGLAND JOURNAL OF MEDICINE, 297, 796-799.
6. Mithoefer,J.C., et al.,(1968), Effect of intravenous $NaHCO_3$ on ventilation and gas exchange in normal man. RESPIRATION PHYSIOLOGY, 4, 132-140.
7. Cherniak,N.S., Longobardo,G.S.,(1970), Oxygen and carbon dioxide gas stores of the body. PHYSIOLOGICAL REVIEWS, 50, 196-243.
8. Hill,E.P., et al.,(1977), Rate of pH changes in blood plasma in vitro and in vivo. JOURNAL OF APPLIED PHYSIOLOGY, 42, 928-934.
9. Tuller,M.A., Mehdi,F.,(1971), Compensatory hypoventilation and hypercapnia in primary metabolic alkalosis. AMERICAN JOURNAL OF MEDICINE, 50, 281-290.
10. Berthelson,P., et al.,(1986), Dissociation of renal and respiratory effects of acetazolamide in the critically ill. BRITISH JOURNAL OF ANAESTHESIA, 58, 512-516.
11. Oh,M.S., Carroll,H.J,(1977), The anion gap. NEW ENGLAND JOURNAL OF MEDICINE, 297, 814-817.

Chapter 13.2

FACTORS MODIFYING CLINICAL MANIFESTATIONS OF ACID-BASE DISORDERS

The clinical manifestations of any given acid-base disorder are not only determined by the magnitude of the acid-base disturbance, but are also considerably modified by any coexisting diseases that a patient may have, or drugs that are ingested. Accordingly the physician should never just look at the laboratory measurements of anion-gap and blood gas values, but assess the clinical condition of the patient as a whole.

Some of the most important factors affecting the manifestations of clinical acid-base disorders are discussed in this chapter. It should be noted that this chapter should be read in conjunction with chapter 13.3, as both chapters are complementary.

Table 13.2.1.
Manifestations of of acute hypoxia on cerebral function.

P_aO_2	CLINICAL MANIFESTATIONS
4.6 kPa (35 mmHg)	- Dimming of vision, lightheadedness, nausea and restlessness in acutely hypoxic normal humans [2].
3.3-4 kPa (25-30 mmHg)	- Threshold for loss of consciousness in acutely hypoxic normal humans [3].
2.7-3.3 kPa (20-25 mmHg)	- Threshold for loss of consciousness in acutely hypoxic, chronically hypoxic and hypercarbic humans [3].
2.7 kPa (20 mmHg)	- Threshold for slowing of electro-encephalographic frequencies [4,5].
Circulatory arrest	- Unconsciousness by 7.5 seconds, and cerebral damage after 3 minutes [1].

HYPOXAEMIA

Adequate supplies of oxygen are absolutely vital for the maintenance of normal organ function. Severe hypoxaemia can cause organ dysfunction independently of any acid-base disorder. The heart and the brain are the two organs most sensitive to the effects of hypoxia.

1. Effects of hypoxia on brain.

The human brain is very sensitive to hypoxia. This is well shown by the rapidity with which unconsciousness occurs after cerebral circulatory arrest. Sudden cerebral circulatory arrest in humans causes unconsciousness by 7.5 seconds [1]. Systemic hypoxaemia induces cerebral dysfunction in proportion to the degree of hypoxaemia. Below a P_aO_2 of 2.7 kPa actual cerebral tissue hypoxia occurs as is shown by slowing of the electroencephalogram frequencies. The manifestations of varying levels of acute cerebral hypoxia are shown in table 13.2.1.

2. Heart.

Absolute myocardial hypoxia causes pump failure within seconds, one of the reasons presumably being rapid consumption of the meager adenosine triphosphate (ATP) stores of the heart [6]. Another part explanation for the rapid loss of contractility is that hypoxia also very rapidly induces intracellular acidosis, which inhibits binding of calcium ions to troponin, a process essential for activity of the myocardial contractile proteins [7].

Few human investigations have been performed on the effects of hypoxaemia on the cardiovascular system. In one investigation performed on humans with normal cardiovascular function who were held upright while administered 4.2% oxygen for periods of 3-16 minutes, none of the subjects developed cardiovascular collapse, despite the P_aO_2 dropping as low as 2.45 kPa (18.38 mmHg) in one subject [8]. No cardiovascular collapse occurs in patients with severe respiratory disease who become unconscious due to the P_aO_2 falling below 2.67-3.3 kPa (20-25 mmHg) [3]. In fact the heart appears to be rather resistant to hypoxia. Canine studies have shown that hypoxic cardiac failure only occurs when the coronary sinus oxygen saturation is below 5-7%, which is equal to a PO_2 of about 0.53-0.67 kPa (4-5 mmHg) [9]. Anaerobic glycolysis and hypoxic heart failure begin simultaneously in the myocardium at this critically low level of oxygenation of coronary sinus blood [9].

In conclusion.

These investigations reveal that brain hypoxia and dysfunction will occur if the P_aO_2 is lower than 3 kPa (23 mmHg). The heart is more resistant to the effects of hypoxia than the brain. However these are extreme degrees of hypoxaemia, and the question arises of what happens with lesser degrees of hypoxaemia. This is discussed below.

OXYGEN TRANSPORT

1. Effects of acid-base disorders on oxygen transport.

Oxygen transport, or flux, is the amount of oxygen transported to the body from the heart per unit time. The equation describing this is in chapter 4.5, and is reproduced as equation 1 below. Note that for the sake of simplicity, the small amount of oxygen dissolved in physical solution in the blood is ignored.

$$\text{OXYGEN FLUX} = 0.216 \times S_aO_2 \times CO \times [Hb] \quad .....(1)$$

OXYGEN FLUX = mls of oxygen pumped out of the heart per minute.
S_aO_2 = percentage saturation of the arterial blood.
CO = cardiac output in l/min.
[Hb] = haemoglobin concentration in mmol/l,(1 mmol/l = 0.6205 gm/100 mls).
N.B. See appendix-D and chapter 4.1 for conversion factors to old cgs units. If the assumption is made that tissue hypoxia occurs if the venous PO_2 drops lower than 2.67 kPa (20 mmHg) [see above], then the well known Fick equation may be rearranged to calculate the minimum arterial S_aO_2 required to prevent tissue hypoxia for a given set of circumstances [see chapters 4.2 and 4.3].

$$S_aO_2 = \frac{V_{O2}}{0.216 \times [Hb] \times CO} + S_vO_2 \quad .....(2)$$

V_{O2} = Volume of oxygen consumed by the body per minute (ml/min).
S_vO_2 = venous oxygen saturation (%).
S_aO_2 = arterial oxygen saturation (%).

Haemoglobin oxygen saturation is very dependent on the pH, PCO_2 etc [see chapter 4.2]. For this reason the saturation of haemoglobin with oxygen at a PO_2 of 2.67 kPa varies considerably with pH as is shown in table 13.2.2.

Table 13.2.2.
% Saturation of haemoglobin with oxygen at PO_2 = 2.67 kPa (20 mmHg) for various pH values.

pH	SO_2(%)
7.1	19.77
7.2	23.27
7.3	27.34
7.38	31.0
7.5	37.1
7.6	42.8
7.7	48.8

This has obvious consequences for the minimum arterial SO_2 required to prevent tissue hypoxia occurring at a given level of oxygen consumption. These data and equation 2 have been used to construct figures 13.2.1 and 13.2.2 which show the consequences of both

acidaemia and alkalaemia respectively on the minimum arterial SO_2 required to prevent tissue hypoxia for a given oxygen consumption, cardiac output and haemoglobin concentration, for blood at pH = 7.2 and 7.6 respectively. It is seen from these figures that the product of cardiac output and haemoglobin concentration is a critical parameter in determining whether tissue hypoxia will occur at a given level of arterial oxygen saturation.

2. Effects of acid-base disorders on oxygen consumption.

Alkalosis increases total body oxygen consumption, even in the situation of total paralysis with controlled ventilation. Canine investigations have shown that oxygen consumption is elevated for the whole body, and also for isolated tissues during alkalaemia [10,11]. The elevation of total body oxygen consumption in dogs as a result of alkalaemia is quite considerable, increasing about 9% per 0.1 unit pH increase [11].

3. Effects of acid-base disorders on erythrocyte deoxygenation rate.

The rate of erythrocyte deoxygenation is also influenced by the pH. The rate of deoxygenation of human erythrocytes in-vitro decreases about 5% for each 0.1 unit increase of pH in the range 6.5-7.9 at a temperature of 37° Celsius [16]. Acidosis increases the rate of oxygen transfer into tissues, while alkalosis retards it.

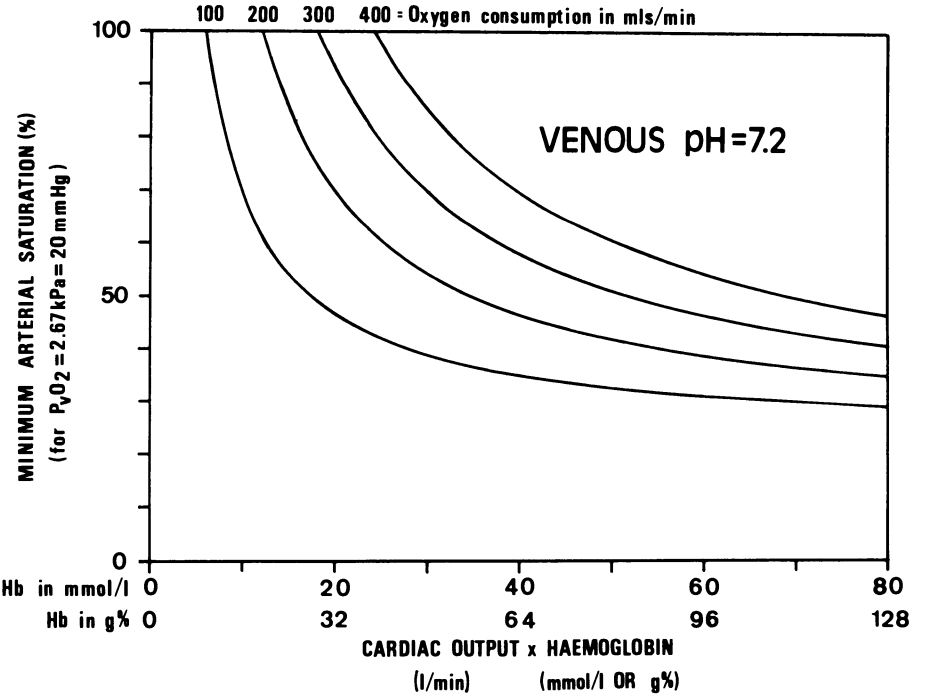

FIGURE 13.2.1. - The minimum S_aO_2 required to prevent cerebral hypoxia is related to the **CO x [Hb]** product for various levels of oxygen consumption. The curves in this figure are for normocarbic acidotic blood with a mixed venous pH = 7.2 and a S_vO_2 = 23.27% (PO_2 = 2.67 kPa). The assumption is made that manifestations of cerebral hypoxia occur when the jugular venous PO_2 is less than 2.67 kPa (20 mmHg). If the measured S_aO_2 is less than that given by the graph for the level of oxygen consumption and the **CO x [Hb]** product, then cerebral hypoxia is likely.

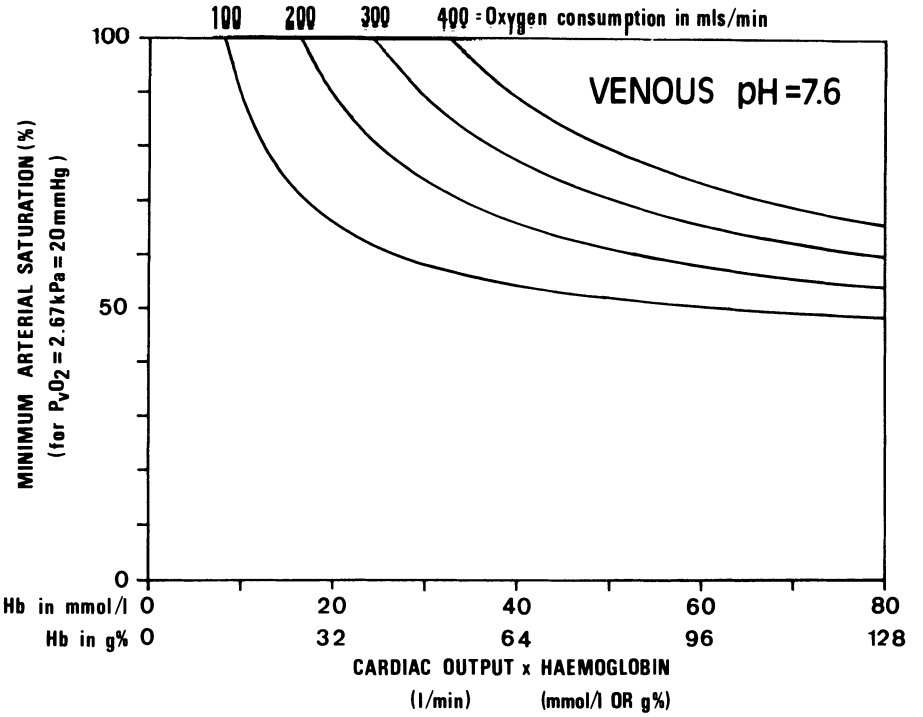

FIGURE 13.2.2. - The same as fig 13.2.1, except that here the mixed venous pH = 7.6, i.e. there is a marked alkalosis present.

A clinical example.

Use equation 2 in this chapter and the relevant equations in chapters 4.1 and 4.3. Take the example of a sick elderly adult patient with a V_{O2} = 300 mls/min, [Hb] = 5 mmol/l = 8.1 gm/100 mls, and a maximum cardiac output = 5 l/min as a result of ingestion of a ß-blocker drug plus heart disease. In this case the CO x [Hb] product is 25. At a blood pH = 7.2, i.e. acidaemia, tissue hypoxia will not occur until the S_aO_2 falls below 78.8%, meaning a P_aO_2 = 6.9 kPa = 52 mmHg. But the situation is quite different if this same patient were to become acutely alkalaemic, pH = 7.6, due to overly enthusiastic administration of sodium bicarbonate. Now the minimum S_aO_2 required to prevent tissue hypoxia is 98.35%, that is a P_aO_2 = 12.55 kPa = 94 mmHg. This level of saturation and P_aO_2 is usually able to be maintained in patients whose respiratory function is normal, but this is certainly not possible in patients with severe cardiopulmonary disease. Even a slight reduction of the P_aO_2 under these circumstances would be sufficient to cause cerebral hypoxia in this theoretical patient.

It is apparent from these fascinating calculations that an alkalaemic patient is less tolerant of hypoxaemia than is an equivalent acidaemic patient. In fact the above calculations are somewhat of a simplification in the case of the alkalaemic patient, as the situation

is in actual fact even worse than depicted up to this point. This is because of the other undesirable effects of alkalaemia.

If the whole body oxygen consumption in humans increases to the same degree as in dogs, the above example patient above would have his oxygen consumption increased by about 20% due to alkalosis. This means his V_{O2} would be about 360 mls/min, and accordingly the minimum S_aO_2 required to prevent tissue and cerebral hypoxia would be 109%, which is impossible except in a hyperbaric tank, and so the patient will develop tissue hypoxia with all the consequences of this. This effect is further exacerbated by the reduced transfer rate of oxygen from erythrocytes into tissues.

In the above patient, a cardiac output of 5 l/min is the maximum that can be achieved, and so cannot be further increased. However this is not so for the haemoglobin concentration. If the V_{O2} were to remain at 360 mls/min, and the haemoglobin concentration was increased to 8 mmol/l = 12.8 gm/100 mls, then the CO x [Hb] product would be 40. In such a situation the minimum tolerable S_aO_2 during alkalaemia with pH = 7.6 would be 84.46%, i.e. a P_aO_2 = 5.45 kPa = 41 mmHg, which is a dramatic reduction. This enables such a level of alkalaemia to be tolerated without tissue hypoxia occurring. Increasing the cardiac output would also have a similar effect, if this were possible in this patient.

4. Clinical correlations.

a. Healthy persons.

The above considerations correlate well with clinical practice. There are reports of patients with normal cardiovascular systems undergoing prolonged apnoeic mass movement oxygenation. None of these patients developed cardiovascular collapse or cerebral hypoxic damage, despite a blood pH which varied between 6.67-6.96, because the S_aO_2 was greater than 75% [12,13]. This means that tissue oxygenation was adequate in these patients. It is obvious from this that moderate acidosis need not be corrected in patients with a more than adequate cardiac output, blood pressure and arterial oxygen saturation.

Healthy young volunteers in whom acute combined respiratory and metabolic alkalosis is induced to a pH of 7.792 do not become unconscious, nor develop any manifestations of depressed cardiovascular function [14]. Nor does cardiovascular collapse, or heart failure develop in persons made acutely hypoxic, hypocarbic, and unconscious by breathing 4.2% oxygen for periods of up to 16 minutes. In one subject the arterial pH was 7.6, S_aO_2 = 40%, and P_aCO_2 = 3.1 kPa (23 mmHg) [8]. The subjects almost certainly did develop a degree of cerebral hypoxia, but the effects were transient because the hypoxia was not total, causing only minimal, if any permanent damage. Or any hypoxic damage that did occur was not easily observable because the subjects were long-term institutionalized catatonic and hebephrenic schizophrenics [8].

The conclusion able to be drawn from these extremes is that the healthy human cardiovascular system appears to tolerate extremes of hypoxia rather better than the brain.

b. Sick patients.

The above is true of persons with a normal cardiovascular system, but is not necessarily applicable to the elderly, to patients ingesting sympathetic nervous system blocking drugs, e.g. ß-blockers, or those with cardiovascular disease such as heart failure, severe coronary vascular disease, etc. Such patients approximate the example patient above, in that their [Hb] x CO product is limited. Restoration of a normal [Hb], elevation of cardiac output with inotropic drugs, and correction of alkalosis are all required in such patients, in addition to maintenance of a high arterial oxygen saturation.

The above finds support in the observation that the mortality of critically ill surgical patients increases in direct proportion to the degree of alkalaemia. Mortality is as high as 80% in patients whose arterial pH is between 7.65-7.7 [15]. These patients often have respiratory dysfunction, are hypoxaemic, are frequently anaemic, and often have some limitation to any elevation of their cardiac output due to hypovolaemia, drugs, or cardiovascular disease.

CARDIAC OUTPUT

Cardiac output is one of the main determinants of oxygen transport. During alkalosis, patients with a limited ability to increase their cardiac output will develop manifestations of tissue hypoxia at a lesser degree of alkalosis than normal persons [see "A clinical example" this chapter]. The patients who are least able to increase their cardiac output in response to hypoxia are the elderly, those using ß-blocking drugs, those with heart failure, or severe coronary vascular disease, and with cardiac valvular disorders.

The direct effect of acidosis on the heart is a cardiovascular depression which increases in direct proportion to any reduction of the pH. This effect is minimized in normal persons by an increase in sympathoadrenal activity induced by acidaemia. Persons whose sympathoadrenal system is blocked by drugs, e.g. ß-blockers, ganglion blockers, general anaesthetic drugs etc, or if the activity is already depressed by disease or old age, are more than usually sensitive to the cardiovascular depression that may be induced by acidosis. Those persons whose baroreflexes are deficient also fall into this category of patient [see chapter 8.6].

HYPOVOLAEMIA

Hypovolaemia reduces the cardiac filling pressures, and accordingly the cardiac output. As has been discussed above, the cardiac output is one of the critical factors in determining the survivability of an acid-base disorder [see chapter 14.4].

ANAEMIA

The haemoglobin concentration is also a critical factor in determining whether tissue, and especially brain hypoxia occurs, [see chapters 4.3 and 5.1].

MECHANICAL or SPONTANEOUS VENTILATION

1. Effects of controlled ventilation.

Controlled ventilation exerts systemic haemodynamic effects which significantly alter the response of the body to acid-base disorders. Cardiac output during intermittent positive pressure ventilation (IPPV), is inversely proportional to the respiratory minute volume and the mean intrathoracic pressure, an effect which is independent of the P_aCO_2 [17]. The cardiac output is further reduced by the application of positive end expiratory pressure (PEEP) [18].

2. Effects of spontaneous ventilation.

Cardiac output increases in humans during spontaneous hyperventilation, even when the P_aCO_2 falls as low as 3.2 kPa (24 mmHg). This is an effect that occurs mainly when hy-

perventilation is commenced, as the cardiac output subsequently subsides to a level only slightly above, or equal to, the resting cardiac output [20]. The increase of cardiac output is presumably due to the increased respiratory work of hyperventilation.

3. Effect of carbon dioxide.

Cardiac output in humans is directly proportional to the P_aCO_2. Hypocarbia reduces cardiac output, while hypercarbia increases it, regardless of whether respiration is spontaneous, or controlled with IPPV [19,21].

SYMPATHETIC NERVOUS SYSTEM FUNCTION

Both acidosis and alkalosis have a marked and physiologically important effect on sympathoadrenal activity and plasma catecholamine concentrations.

1. Acidosis.

Acidosis increases plasma catecholamine concentration by a direct effect on sympathetic nerve terminals [23] and the adrenal medullae [24] by increasing release of catecholamines. In addition to this direct effect, acidosis also causes central nervous stimulation of sympathoadrenal activity [25].

2. Alkalosis.

Alkalosis has the reverse effect to acidosis, decreasing sympatho-adrenal responsiveness, so reducing the elevation of plasma catecholamine catecholamines in response to stimuli such as haemorrhage [26,27].

3. Physiological importance.

This sympatho-adrenal response is of utmost importance in maintaining cardiovascular function during acid-base disorders. The direct effect of acidosis on the ISOLATED heart is to decrease the myocardial contractility and cardiac output. This effect begins at a pH of 7.3, is significant by pH = 7.22, and the depression is so great at pH = 6.96, that the cardiac output is minimal. Alkalosis, even up to pH = 7.7 has no effect on isolated heart performance, cardiac output and contractility being unchanged [22].

But during acidosis in an INTACT living animal or person, the elevation of plasma catecholamine concentrations and elevation of sympathetic nervous activity reverses the direct acidosis-induced myocardial depression to some degree [22], and appears to be vital in maintenance of adequate haemodynamic function in severe degrees of acidosis. Because of this, a lower pH is then required to cause a given degree of myocardial depression.

Sympathetic blockade with ß-adrenergic blocking drugs exacerbates cardiovascular depression due to acidosis [28], as does any condition in which elevation of the cardiac output is limited, or there is baroreflex dysfunction [see chapter 8.6]. For these reasons, patients with deficient sympathoadrenal responses to acidosis in may be expected to develop cardiovascular depression, rather than the cardiovascular stimulation observed in healthy humans.

SEVERITY OF ACID-BASE DISORDER

It is the severity of the acid-base disorder that ultimately determines the effect on the body, and it is the intracellular pH that determines the functioning of the various organs af-

fected by the disorder. The intracellular pH is directly proportional to the extracellular pH in both metabolic as well as respiratory acid-base disorders. Intracellular pH is always somewhat lower than the extracellular pH, normally varying between 6.94-7.28 [29]. In the extracellular pH range of 7.2-7.5, there is little variation of the intracellular pH of mammals, because of effective intracellular buffering in this range [29,30]. This correlates well with the clinical observation that few problems due to acid-base disorders occur in this pH range.

The extremes of extracellular pH compatible with life are listed in table 13.2.3. These extremes have been measured in patients with normal cardiovascular systems. In the case of acidosis, a pH of 6.67 has been recorded in one patient who underwent apnoeic mass movement oxygenation for a period of three hours without developing cardiovascular collapse [13]. Acute combined metabolic and respiratory alkalosis has been induced in healthy human subjects to a pH of 7.79 without significant changes in systemic haemodynamics occurring [14]. In-vitro studies have shown that mitochondrial oxidative phosphorylation ceases when the intracellular pH has fallen to 6.0 [31].

The above are extremes in healthy humans. But systemic haemodynamic disorders manifest at a lesser degree of pH abnormality in most sick patients because of the presence of one or more of the factors discussed in this chapter.

Table 13.2.3.
Normal ranges, and lethal extremes of pH for intracellular and extracellular fluid.

PLASMA	
NORMAL RANGE	7.35-7.45
LETHAL EXTREMES	<6.67 [12,13] and >7.8 [14]
INTRACELLULAR	
NORMAL RANGE (depends on tissue)	6.51-7.29 [29,30]
LETHAL EXTREMES	<6.0 [31] and ?

REFERENCES

1. Rossen,R., et al.,(1943), Acute arrest of cerebral circulation in man. ARCHIVES OF NEUROLOGY AND PSYCHIATRY, 50, 510-528.
2. Cohen,P.J., et al.,(1967), Effects of hypoxia on cerebral blood flow and metabolism in conscious man. JOURNAL OF APPLIED PHYSIOLOGY, 23, 183-189.

3. Refsum,H.E., et al.,(1963), Relationship between state of consciousness and arterial hypoxaemia in patients with pulmonary insufficiency breathing air. CLINICAL SCIENCE, 25, 361-367.
4. Meyer,J.S., et al.,(1965), Effects of anoxia on cerebral metabolism and electrolytes in man. NEUROLOGY, 15, 892-901.
5. Gotoh,F., et al.,(1965), Cerebral effects of hyperventilation in man. ARCHIVES OF NEUROLOGY, 12, 410-423.
6. Hearse,D.J.,(1979), Oxygen deprivation and early myocardial contractile failure: A reassessment of the possible role of adenosine triphosphate. AMERICAN JOURNAL OF CARDIOLOGY, 44, 1115-1121.
7. Katz,A.M.,(1973), Effects of ischemia on the contractile processes of the heart muscle. AMERICAN JOURNAL OF CARDIOLOGY, 32, 456-460.
8. Horvath,S.M., et al.,(1943), Effects on man of severe oxygen lack. AMERICAN JOURNAL OF PHYSIOLOGY, 138, 659-668.
9. Bretschneider,H.J., et al.,(1957), Uber den kritischen Wert und die physiologische Abhangigkeit der Sauerstoff-Sattiging des venoses Coronarblutes. PFLUGERS ARCHIV. GES. PHYSIOL. 264, 399-423.
10. Khambatta,H.J., Sullivan,S.F.,(1973), Effects of respiratory alkalosis on oxygen consumption and oxygenation. ANESTHESIOLOGY, 38, 53-58.
11. Rastegar,H., et al.,(1979), Respiratory alkalosis increases tissue oxygen demand. JOURNAL OF SURGICAL RESEARCH, 26, 687-692.
12. Frumin,M.J., et al.,(1959), Apneic oxygenation in man. ANESTHESIOLOGY, 20, 789-798.
13. Comroe,J.H., Dripps,R.D.,(1946), Artificial respiration. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 130, 381-383.
14. Wollman,H., et al.,(1968), Effects of extremes of respiratory and metabolic alkalosis on carotid blood flow in man. JOURNAL OF APPLIED PHYSIOLOGY, 24, 60-65.
15. Wilson,R.F., et al.,(1972), Severe alkalosis in critically ill surgical patients. ARCHIVES OF SURGERY, 105, 197-203.
16. Lawson,W.H.,(1966), Interrelation of pH, temperature, and oxygen on deoxygenation rate of red cells. JOURNAL OF APPLIED PHYSIOLOGY, 21, 905-914.
17. Morgan,B.C., et al.,(1966), Hemodynamic effects of intermittent positive pressure respiration. ANESTHESIOLOGY, 27, 584-590.
18. Annat,G., et al.,(1983), Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins, ANESTHESIOLOGY, 58, 136-141.
19. Prys-Roberts,C., et al.,(1968), Hemodynamics and alveolar- arterial PO_2 differences at varying P_aO_2 in anaesthetized man. JOURNAL OF APPLIED PHYSIOLOGY, 25, 80-87.
20. Richardson,D.W., et al.,(1972), Systemic circulatory responses to hypocapnia in man. AMERICAN JOURNAL OF PHYSIOLOGY, 223, 1308-1312.
21. Cullen,D.J., Eger,E.I.,(1974), Cardiovascular effects of carbon dioxide in man. ANESTHESIOLOGY, 41, 345-349.
22. Nahas,G.G., Cavert,H.M.,(1957), Cardiac depressant effect of CO_2 and its reversal. AMERICAN JOURNAL OF PHYSIOLOGY, 190, 483-491.
23. Euler, von U.S., Lishajko,F.,(1963), Influence of pH on uptake and release of noradenaline in adrenergic nerve granules. JOURNAL OF NEUROCHEMISTRY, 10, 145-149.
24. Nahas,G.G., et al.,(1967), Acidemia and catecholamine output in the isolated canine adrenal gland. AMERICAN JOURNAL OF PHYSIOLOGY, 213, 1186-1192.
25. Tenney,S.M.,(1956), Sympatho-adrenal stimulation by carbon dioxide and the inhibitory effect of carbonic acid on epinephrine response. AMERICAN JOURNAL OF PHYSIOLOGY, 187, 341-346.
26. Darby,T.D., Watts,D.T.,(1964), Acidosis and blood epinephrine levels in hemorrhagic hypotension. AMERICAN JOURNAL OF PHYSIOLOGY, 206, 1281-1284.
27. Fiorica,V., et al.,(1969), Influence of blood pH on adrenomedullary response to hemorrhage. AMERICAN JOURNAL OF PHYSIOLOGY, 217, 1211-1215.
28. Beierholm,E.A., et al.,(1975), Effects of acid-base changes, hypoxia, and catecholamines on ventricular performance. AMERICAN JOURNAL OF PHYSIOLOGY, 228, 1555-1561.
29. Waddell,W.J., Bates,R.J.,(1969), Intracellular pH. PHYSIOLOGICAL REVIEWS, 49, 285-329.
30. Poole-Wilson,P.A., Cameron,I.R.,(1975), Intracellular pH and K^+ of cardiac and skeletal muscle in acidosis and alkalosis. AMERICAN JOURNAL OF PHYSIOLOGY, 229, 1305-1310.
31. Hillered,L., et al.,(1984), Influence of in-vitro lactic acidosis and hypercapnia on respiratory activity of isolated rat brain mitochondria. JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM, 4, 430-437.

Chapter 13.3

CLINICAL ACID-BASE DISORDERS

This is chapter provides a detailed discussion of the clinical effects of common acid-base disorders encountered by the physician. It contains little discussion on the pathophysiology of these disorders as this is more than adequately covered in other texts. The physiological changes decribed are the unmodified changes produced by these disorders, and as such are not always observed. For this reason, the chapter on factors modifying the manifestations of acid-base disorders has preceded this chapter, and this chapter should be read in conjunction with the preceding chapter [chapter 13.2].

CAUSES OF ACID-BASE DISORDERS

1. Respiratory alkalosis.

This is due to a reduction of the PCO_2 secondary to increased alveolar ventilation relative to the carbon dioxide production of the body. The P_ACO_2 is related to the alveolar ventilation by the formula below (equation 1).

$$P_ACO_2(kPa) = \frac{100 \times VCO_2(l/min)}{V_A(l/min)} \quad .....(1)$$

Causes of alveolar hyperventilation range from;

- hypoxaemia,
- central nervous system damage,
- hypermetabolism, e.g. fever, hyperthyroidism,
- renal or hepatic failure,
- intoxications, e.g. salicylates,
- to hypoventilation during controlled ventilation.

2. Respiratory acidosis.

This is the reverse of respiratory alkalosis and is due to alveolar hypoventilation relative to the rate of carbon dioxide production [see equation 1 above]. The causes of alveolar hypoventilation vary from;

- restriction of respiratory excursion due to pain, e.g. upper abdominal surgery.

- drugs, e.g. muscle relaxants, barbiturates, benzodiazepines, and opiates.
- respiratory diseases, usually chronic obstructive airways disease.
- neuromuscular diseases, e.g. muscular dystrophies, myasthenia gravis, etc,
- severe electrolyte disorders, e.g. hyper- and hypokalaemia, hypercalcaemia,
- hypoventilation during controlled respiration.

3. Metabolic acidosis.

This may be due to excessive ingestion or administration of acids, retention of hydrogen ion (H^+), or loss of bicarbonate ion (HCO_3^-).

a. Excessive H^+ intake or production.

- Severe hypoxia which causes increased lactic acid production.
- Circulatory shock which also causes a lactic acidosis.
- Ketoacidosis.
- Lactic acidosis secondary to biguanide ingestion, e.g. phenformin.
- Intoxications, e.g. salicylates, methanol, paraldehyde.

b. Failure of H^+ excretion.

- Drugs ,e.g. acetazolamide.
- Renal failure or renal tubular acidosis.

c. Excessive HCO_3^- losses.

This usually only occurs as a result of excessive gastrointestinal or urinary losses. These are the two principal routes of loss of HCO_3^- apart from the lungs [see table 13.3.1].

- Gastrointestinal losses, e.g. vomiting, gastric drainage, intestinal fistulae, cholestyramine therapy.
- Renal losses, e.g. due to renal failure and renal tubular acidosis.

4. Metabolic alkalosis.

Metabolic alkalosis is a surprisingly common disorder. In one study of hospitalized patients, metabolic alkalosis occurred in 51.1% of patients with an abnormal acid-base status (N = 743 patients), and in this group about 70% had a pure metabolic alkalosis [3]. There are a relatively large number of causes of this common and troublesome disorder.

a. Excessive H^+ losses.

- Gastric losses, e.g. protracted vomiting, excessive gastric drainage through a gastric tube.
- Hypokalaemia. This increases renal excretion of H^+.

b. Excessive loss of Cl^-.

- Gastric losses, e.g. protracted vomiting or gastric drainage.
- Diuretic drugs. Diuretics which primarily act by blocking the sodium-potassium-chloride (Na-K-2Cl) transport system of the loops of Henle increase Cl^- excretion, to a greater degree than they do the excretion rates of sodium or potassium ions. The deficiency of anions is replaced by HCO_3^-, which causes an alkalosis. The diuretics of this type that are most commonly used are bumetanide, frusemide and ethacrynic acid. Thiazide diuretics may also cause a slight alkalosis by increasing Cl^- excretion too.

Table 13.3.1.
HCO_3^-, pH, Cl^-, and K^+ concentrations in mmol/l of various fluids. [1,2].

Fluid	K^+	pH	Cl^-	HCO_3^-
Gastric	6.4-16.6	1.9-2.6	78-159	0
Pancreatic	4.1-5.5	7.5-8.8	4-129	25-150
Bile	2.6-12	5.6-8	89-118	30
Ileal fistula	9.3	?	?	?
Faeces	3.3-19.3	5.6-8.5	0.5-3.0	<30
Diarrhoea	30	?	0	20-80
Urine	17-40	4.8-7.5	50-100	0

c. Excessive administration of HCO_3^-.

Excessive quantities of HCO_3^- may be administered during cardiopulmonary resuscitation, during correction of an acidaemia, or as an attempt to correct acidosis due to massive blood transfusion.

HCO_3^- is usually administered as an 8.4% solution of the sodium salt ($NaHCO_3$). This contains 1 mmol of NaHCO3 per ml, and as such is a very hypertonic solution with an osmolality of 1000 mosm/l, (normal plasma osmolality is in the range 275-285 mosm/l). Large quantities of 8.4% $NaHCO_3$ solution will cause hypervolaemia in addition to an alkalosis. A further problem is that administration of $NaHCO_3$ increases carbon dioxide production. The mechanism of the latter is simple. The reaction forming carbonic acid is left-shifted by elevation of the HCO_3^- concentration, and more carbon dioxide is formed. This effect is only of short duration, the extra carbon dioxide produced being eliminated through the lungs within 5 minutes after discontinuation of a rapid infusion of a $NaHCO_3$ solution in spontaneously breathing humans [4]. But the extra carbon dioxide produced will not be so rapidly eliminated in patients whose ventilation is controlled, and in such cases may actually exacerbate an existing intracellular acidosis, due to rapid intracellular diffusion of the carbon dioxide produced.

d. Administration of sodium lactate or citrate.

Administration of both sodium lactate or citrate causes an alkalosis. Both citrate and lactate are metabolized faster than the sodium is excreted in the urine. The resulting anion deficiency is made up by HCO_3^-, and an alkalosis occurs. This effect is further exacerbated and prolonged by the sodium retention occurring as a result of trauma, surgery and major disease.

Lactic and citric acids do not cause an alkalosis as they are not salts of a metal, and the two acids are metabolized to water and carbon dioxide only.

Both sodium lactate and citrate are commonly administered during the perioperative period, and for resuscitation of shocked patients. The two most common fluids in which they are found are blood and lactated Ringer's solution (Hartmann's solution.

i. Blood.

2.5 gm (10.6 mmols), of disodium citrate are present in every 500 mls of blood preserved with the common Acid-Citrate-Dextrose (ACD) anticoagulant. An equivalent amount is present in Citrate-Phosphate-Dextrose (CPD) blood.

ii. Ringer's lactate (Hartmann's solution).

29 mmols of sodium lactate are present in every liter of lactated Ringer's solution (Hartmann's solution).

The distribution volume of bicarbonate ion in the body is about 300-333 mls/kg body weight [4]. Taking an "average" 70 kg adult, this means a distribution volume of about 21 liters. From this it may be readily appreciated that 500 mls of ACD anticoagulated blood, or 1000 mls of lactated Ringer's solution is all that is required to elevate the plasma bicarbonate concentration by about 1 mmol/l. Use of larger quantities of these fluids alone or together will have an even greater effect. Indeed, clinical studies of severely ill alkalotic surgical patients have shown that infusion of more than 1-2 liters of these fluids can cause a significant metabolic alkalosis [27]. Metabolic alkalosis also occurs quite commonly after cardiac operations when a lactated Ringer solution + ACD blood is used as a priming solution in the cardiopulmonary bypass pump and oxygenator. Metabolic alkalosis in these patients is exacerbated and prolonged in the postoperative period by the sodium retention and increased potassium excretion occurring in the first few days [5].

PROBLEMS AND MANIFESTATIONS

The clinical effects of acid-base disorders are caused by changes of cellular function induced by changes of intracellular as well as extracellular hydrogen ion concentration. Intracellular pH is directly related to the extracellular pH, but is constant when the extracellular pH is in the range 7.2-7.5, because of a variety of efficient intracellular buffer systems [6,7]. Only when the extracellular fluid or plasma pH is greater than 7.5, or less than 7.2, does the intracellular pH change, and significant alterations of systemic physiology occur.

It is not only the magnitude of an acid-base disturbance that affects the clinical manifestations, but also the rate of onset of the disorder. Some degree of compensation always occurs during the onset of slowly developing acid-base disorders, and this minimizes any clinical manifestations. This is not the case with rapidly developing disturbances of acid-base balance, because not enough time will have elapsed for any significant compensation to have occurred.

The clinical manifestations of acidosis and alkalosis will now be discussed in some detail. Effects of factors which modify these responses have been discussed in chapter 13.2.

1. Metabolism.

Canine [8,9] and human [10,11] investigations have shown that alkalosis increases oxygen consumption for any given level of work performed. The percentage increase of oxygen consumption is quite considerable in dogs, being given by equation 2 below for the pH range 6.9-7.7 [9].

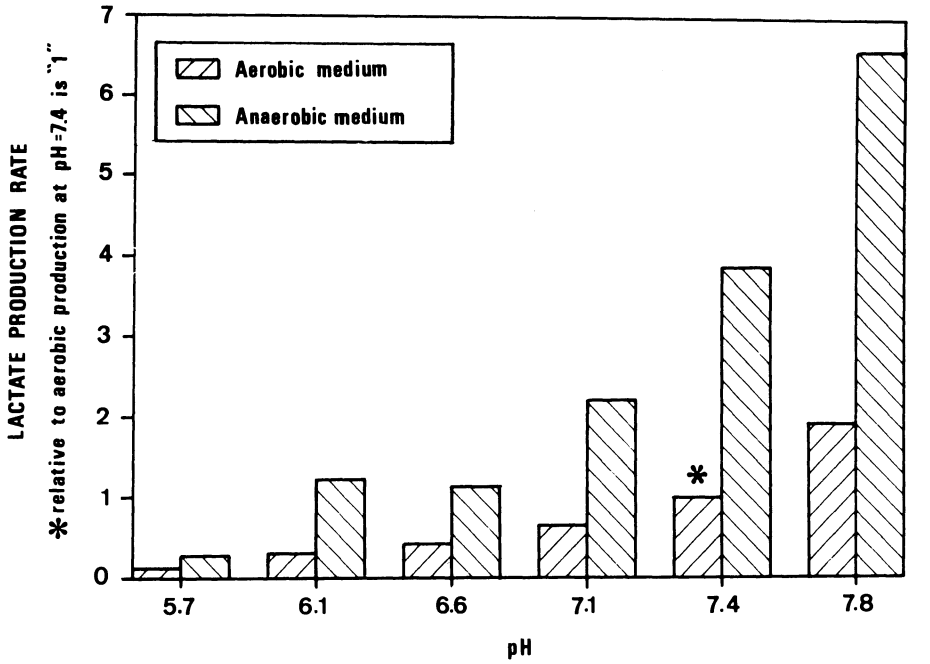

FIGURE 13.3.1. - The relative effects of extracellular pH on the rate of lactate production in rat diaphragm in-vitro under both aerobic and anaerobic conditions. The reference point "*" is the normal rate of lactate synthesis under aerobic conditions at a pH of 7.4, and this is given a rate of 1 [12].

$$V_{O2}(\%) = 90 \times pHa - 551 \quad .....(2)$$

V_{O2} (%) = Oxygen consumption as percentage of the normal oxygen consumption rate (100% = normal rate).
pHa = pH of arterial blood.

This means that total body oxygen consumption in dogs increases by about 9% per 0.1 unit increase of pH above 7.4 and decreases by the same amount per 0.1 unit decrease of pH. Alterations of oxygen consumption due to alterations of acid-base status have not been extensively studied in humans, although it has been found that alkalosis does increase human cerebral oxygen consumption [10,11], but not to the same degree as in dogs. This effect is obviously of great clinical importance in critically ill alkalaemic patients [see chapter 13.2].

Increased oxygen consumption may be caused by the effects of the acid-base disorders on intracellular metabolism. One of the more prominent, and best investigated effects is that on lactate production. Acidosis decreases tissue lactate production and alkalosis increases it, while hypoxia increases lactate production at all levels of pH [12, see fig. 13.3.1].

Increased lactate production due to alkalosis is the result of an increase in the rate of pyruvate synthesis by the glycolytic Embden-Meyerhof pathway, the rate of which is increased in alkalosis and decreased by acidosis [12]. As not all of the pyruvate that is synthesized can enter the citric-acid cycle, the remainder is metabolized by lactate dehydrogenase to lactic acid, and so the lactate production is increased.

The rate of lactate synthesis in humans is also increased by alkalosis [10,11]. But despite the increased rate of glycolysis and other changes in glucose metabolism during alkalosis [12], no hypoglycaemia occurs in humans even at an arterial pH of 7.79 [11].

2. Effects on the central nervous system (CNS).

Acid-base disorders can affect the function of the CNS, the main effects being related to disturbances of consciousness.

Both respiratory [13] and metabolic [14] changes of blood acid-base status cause simultaneous changes in the pH of the cerebral interstitial fluid, but not in the cerebrospinal fluid [14]. This accounts for the rapid changes of alveolar ventilation as a result of acute alterations of blood pH, as the brainstem chemoreceptors are located within the medulla, and are therefore not directly affected by the cerebrospinal fluid [see chapter 4.5].

Respiratory acid-base disorders have a more pronounced effect on both the cerebral circulation and level of consciousness than do the metabolic acid-base disorders, but the effects are essentially similar. The reason for this is that carbon dioxide can diffuse into and out of the brain cells very rapidly, while this is not true of many other acids or bases. Because of this a measure of compensation has usually occurred by the time that a metabolic acid-base disorder has achieved a new steady state. Altered CNS function due to acid base disorders is discussed more fully in chapter 8.1.

3. Effects on the sympatho-adrenal system.

Both acidosis and alkalosis affect the plasma catecholamine concentrations.

a. Acidosis.

Acidosis increases plasma catecholamine concentrations by increasing catecholamine secretion from sympathetic nerve terminals [15] and the adrenal medullae [16] by a direct effect on these. In addition to this effect it also causes a central nervous system mediated elevation of sympatho-adrenal activity [17].

b. Alkalosis.

Alkalosis has the reverse effects of acidosis, decreasing sympatho-adrenal responsiveness, so reducing the elevation of plasma catecholamines in response to stimuli such as haemorrhage [18,19].

Elevation of sympathoadrenal activity is vital in the maintenance of adequate systemic haemodynamic function during hypovolaemia or conditions where the cardiac output is depressed, e.g. anaesthesia, heart failure, severe coronary vascular diseases, valvular disorders, ß-blockers etc. Correction of acidosis under these circumstances may cause severe hypotension due to a lowering of the catecholamine concentrations and sympathetic nervous activity [see cardiovascular responses].

4. Altered neuromuscular function.

Acid-base disorders also have an effect on neuromuscular function, and accordingly also on the action of neuromuscular junction blocking drugs.

a. Alkalosis.

Respiratory alkalosis may induce tetany when the P_aCO_2 falls below 4 kPa (30 mmHg) [47]. While this effect is related to the pH caused reduction of ionized calcium concentration, the hypocalcaemic effect of increased pH alone is usually not sufficient. Tetany and carpopedal spasm are more likely if the person is already hypocalcaemic [48]. In addition to increasing neuromuscular irritability, respiratory alkalosis also increases skeletal muscle twitch tension in response to peripheral nerve stimulation [49].

The effects of metabolic alkalosis have not been as extensively investigated.

b. Acidosis.

Extremes of acidosis may induce skeletal muscle weakness. Certainly, respiratory acidosis does reduce skeletal muscle twitch tension in response to peripheral nerve stimulation [49].

c. Acid-base disorders and muscle relaxants.

The reported effects of acidosis and alkalosis on the effects of nondepolarizing muscle relaxants are minor, and vary from one relaxant to another. Nondepolarizing muscle relaxants are highly ionized drugs, (see appendix-A), and their degree of ionization and protein binding are not significantly affected by pH changes occurring in ranges of pH compatible with life. It is quite likely that the effects of any acid-base disorder on the action of these drugs is negligible, most of any reported effect being due to the effects of acid-base disorders on neuromuscular junction function.

5. Altered responsiveness to catecholamines.

The responsiveness to catecholamines is altered by the acid-base disorders.

a. Acidosis.

The myocardial contractile response to adrenaline [20], but not to isoprenaline [21] is reduced. Peripheral vascular responses to adrenaline [20] and isoprenaline [21] are reduced if the plasma pH is less than 7.2.

b. Alkalosis.

Alkalosis appears to have no effect on the cardiac or peripheral vascular responses to catecholamines such as dopamine, isoprenaline, and adrenaline [22].

6. Alterations of potassium concentration.

Respiratory acidosis elevates [23], and respiratory alkalosis decreases [24] the plasma potassium concentration. The change due to either hyper-or hypocapnia is of the same magnitude, being about 0.375-0.39 mmol/l per 1 kPa change of P_aCO_2 (0.5-0.52 mmol/l per 10 mmHg change of P_aCO_2).

However metabolic acid-base disorders are not necessarily associated with alterations of the plasma potassium concentration. Human metabolic acidosis does not necessarily cause hyperkalaemia as is well demonstrated by the absence of hyperkalaemia during lac-

tic acidosis secondary to epilepsy caused hypoxaemia [25,26], and other causes of lactic acidosis, such as diabetic ketoacidosis [26].

Hypokalaemia in sick surgical patients is unrelated to alkalaemia [27], except in those patients whose alkalosis is due to excessive vomiting or gastric drainage, as gastric fluid has a relatively high potassium concentration.

7. Cardiovascular responses.

a. Cardiac rhythm.

Abnormalities of cardiac rhythm are known to occur during acid-base disorders. The causes vary with the nature of the disorder.

i. Acidosis.

During acidosis the rate of rise of the cardiac cellular membrane action potential is slowed, and as a result the intracardiac conduction velocity of pacemaker activity is also slowed along the intracardiac conduction systems [28]. Slowing of the cardiac rate by this mechanism increases the chance of spontaneous non-pacemaker activity which can initiate cardiac arrhythmias. During acidosis the heart develops a greater degree of bradycardia and longer asystolic periods in response to a given level of vagal stimulation, an effect which is exacerbated by hypoxaemia [29]. These effects of acidosis on the myocardium are exacerbated by other effects of acidosis such as;

- hyperkalaemia due to acidosis,
- increased plasma catecholamine concentrations due to acidosis,
- increased sympathetic nervous stimulation due to acidosis,
- associated myocardial hypoxia due to the cause of the acidosis.

ii. Alkalosis.

Alkalosis may also cause cardiac arrhythmias. The effects of alkalosis on the cardiac action potential are the reverse of those of acidosis, but are much less in degree and are unrelated to the severity of alkalosis [28]. Alkalosis does however reduce the effects of vagal stimulation, the duration of asystole and the level of bradycardia occurring in response to a given level of stimulation being much less than that occurring at a normal pH [29]. Other cardiac arrhythmias that occur during alkalosis are likely due to a combination of factors such as are listed below.

- Hypokalaemia due to alkalosis, especially respiratory.
- Myocardial or cerebral hypoxia secondary to reduced oxygen transport, and increased oxygen requirement resulting from alkalosis.

iii. Ventricular fibrillation threshold.

Ventricular fibrillation is one of the arrhythmias that may occur as a result of acid-base disorders. Canine experimental work has shown that the threshold to electrically induced ventricular fibrillation is decreased by metabolic acidosis, and elevated by metabolic alkalosis. But neither respiratory acidosis nor alkalosis have any effect on the ventricular fibrillation threshold, which remains the same as for dogs with a normal blood pH [30].

b. Cardiac performance.

Cardiac performance may be markedly affected by acid-base disorders, but the effect depends on a number of factors which have already been discussed above, as well as the direct effects of the disorder on the myocardium itself.

i. Direct effects on myocardium.

Acidosis reduces myocardial contractility directly by affecting intracellular calcium ion (Ca^{2+}) activity and concentration. Calcium influx is reduced, decreasing the amount of intracellular Ca^{2+} available for muscle contraction and generation of energy [32]. In addition to this, a reduction of the intracellular pH decreases the binding of Ca^{2+} to troponin, a process that is essential for contraction of myocardial muscle cells [31]. In-vitro investigations on strips of myocardium, as well as on heart lung preparations have shown that acidosis depresses myocardial contractility and cardiac output to a degree that is directly related to the decrease of pH [32,33,34,37]. Acidosis induced depression of the cardiac output of isolated heart preparations begins to be significant when the extracellular pH drops below 7.2 [33].

The direct effect of alkalosis on the myocardium is minimal. The contractility or cardiac output in heart lung preparations, or of isolated myocardial strips is either unchanged or slightly increased from that measured at normal pH, even when the extracellular fluid pH is increased to as much as 7.9 [33,35,36].

ii. Sympathoadrenal response.

The sympatho-adrenal response to acidosis is the most important factor in the maintenance of systemic haemodynamics during acidosis. If this response is blocked [34,38], or does not occur [33], then cardiac output begins to fall significantly at a lesser degree of acidosis than if it were present and effective [33,38].

Because of the sympatho-adrenal response, systemic haemodynamic performance in humans is well maintained during respiratory acidosis [25,39], even at P_aCO_2 levels as high as 33.3 kPa (250 mmHg) and an arterial pH of 6.72 [39]. In fact hypercarbia in healthy non-hypoxic humans is always associated with an elevation of the cardiac output and blood pressure, and reduction of the systemic vascular resistance in direct proportion to the degree of hypercarbia [41].

Respiratory alkalosis is associated with maintenance of normal haemodynamics, even when the P_aCO_2 is as low as 1.34 kPa (10.1 mmHg) and the arterial pH is 7.76 [40]. The same is also true of combined respiratory and metabolic alkalosis to an arterial pH of 7.79 [40].

iii. Other effects of acid-base disorders on the heart.

Other factors also significantly modify cardiovascular responses to acid-base disorders in sick patients. These are listed below and have already been discussed in chapter 13.2.

- The elderly have a lower cardiac output than younger persons.
- Increased sympatho-adrenal activity due to acidosis.
- Hyper- or hypokalaemia.
- Altered extracellular ionized calcium concentration [see chapter 12.5].
- Changes of systemic vascular resistance.
- Normo- or hypovolaemia.
- Normal oxygenation or hypoxia.

- Cardiac disease, e.g. coronary vascular, valvular etc.
- Drugs, e.g. ß-blockers, verapamil, etc.

c. Peripheral vascular responses.

Respiratory acidosis decreases the systemic vascular resistance in direct proportion to the elevation of the P_aCO_2 [41,42]. Respiratory alkalosis has minimal effects on the systemic vascular resistance, the systemic vascular resistance remaining unchanged [42], or decreasing slightly [43].

Metabolic acidosis changes the systemic vascular resistance minimally unless the cardiac output also changes, while metabolic alkalosis reduces the systemic vascular resistance [42].

d. General.

It is obvious from the above discussion that cardiovascular collapse as a result of acid-base disorders only occurs in humans as a result of the combination of the acid-base disorder with one or more other disturbances. This has already been discussed in chapter 13.2. In anaesthetic practice there are several situations in which hypotension or a low cardiac output occur as a result of acid-base disturbances.

i. The blood pressure of an acidotic hypovolaemic patient may be normal because of the acidosis caused potentiation of the normal sympatho-adrenal response to hypovolaemia. Hyperventilation during controlled ventilation, or administration of sodium bicarbonate may cause hypotension because of the reduction of catecholamine release and sympathetic nervous activity that acidosis causes. Accordingly alkalosis is likely to exacerbate the reduction of cardiac output due to hypovolaemia.
ii. All patients taking ß-adrenergic, other sympathetic nervous system blocking drugs, or with deficient baroreflexes, will develop hypotension or a reduction of the cardiac output at a higher pH during acidosis than a healthy person.

8. Respiratory problems.

These have been discussed in chapter 13.2. A summary of these effects is given.

a. Alkalosis.

The effect of severe alkalosis is to impair tissue oxygenation. It does so by a number of mechanisms.

- Depressing respiration in spontaneously breathing patients with metabolic alkalosis. This may cause significant elevation of the P_aCO_2 which may increase as high as 8.8 kPa (66 mmHg) [46].
- Increasing oxygen consumption, especially dangerous in those with impaired oxygenation [see above and chapter 13.2].
- Decreasing the rate of erythrocyte deoxygenation [see chapter 13.2].
- Left-shifting of the oxyhaemoglobin dissociation curve which necessitates a high P_aO_2 in order that tissue oxygenation be maintained [see chapters 4.1, 4.3, 5.1, and 13.2].

b. Acidosis.

This has the reverse effects to those of alkalosis. In general the effect is to increase tissue oxygenation for a given P_aO_2 [see chapter 13.2].

9. Altered drug effects.

Acid-base disorders may affect the action of many drugs used in anaesthesia by a number of mechanisms.

a. Altered pharmacokinetics.

Elevation or reduction of the cardiac output decreases or increases the elimination half lives of drugs respectively [see chapter 15.2].

b. Altered protein binding.

Many drugs are bound to proteins in the plasma and extracellular fluid to varying degrees. Most proteins are negatively charged at all levels of pH above 5.0, and are increasingly more negatively charged as the pH increases above this level.

Acidic drugs are less protein bound during alkalosis, but the reverse may be expected for basic drugs. The only acidic drugs at present used in anaesthetic practice are the barbiturates, all the rest being bases. Indeed, hyperventilation does potentiate the effects of the barbiturates, but whether it is actually due to a reduction of protein binding is uncertain.

Increased protein binding of ionized basic drugs may be expected to occur during acidosis. This reduces the amount of active drug penetrating any target organ.

c. Altered degree of ionization.

Basic drugs are less ionized during alkalosis, and more ionized during acidosis. This affects the penetration of drugs into target organs. Ionized drugs cannot diffuse across biological membranes, only the non-ionized form is able to do so. This has a number of important consequences for anaesthesia. Some examples are given below.

- Local anaesthetic drugs must diffuse through the nerve cell membrane and enter the axon in order to block the sodium channels on the inside of the axon membrane. Only the non-ionized form of the drug can cross the cell membrane. Acidosis, by increasing the proportion of ionized drug, reduces the amount available to diffuse through nerve cell membrane, and so decreases the rate of onset and magnitude of effect of these drugs.
- Opiates are also basic drugs. Respiratory alkalosis increases, and acidosis decreases, the brain concentrations of both morphine [45] and fentanyl [44] relative to plasma. The effects of opiates and other centrally acting basic drugs are likely to be potentiated by alkalosis, and inhibited by acidosis. Hyperventilation during general anaesthesia is likely to potentiate the effects of a given dose of most opiates.
- The effects of muscle relaxants are not likely to be affected by changes of ionization induced by acid-base disorders, as their degree of ionization is so great that changes of pH in the pH ranges compatible with life do not significantly alter their degree of ionization. However their availability may be affected by changes in protein binding due to acid-base disorders.

Table 13.3.2.
Thresholds for initiation of therapy in acid-base disorders.

PARAMETER	ACIDOSIS	ALKALOSIS
pH	<7.2	>7.5
Base excess	<-10	> +10
Venous PO_2	< =2.7 kPa (20 mmHg)	< =2.7 kPa (20 mmHg)
Arterial SO_2(%)	Not critical	<90%
[Hb]	<6 mmol/l (10 gm/100 mls)	<6 mmol/l (10 gm/100 mls)
Hypotension +/- low cardiac output	Treat acid-base disorder	Treat acid-base disorder

INDICATIONS FOR THERAPY OF ACID-BASE DISORDERS

The question in the mind of the clinician on diagnosing an acid-base disorder is the point at which a given disorder is significant enough to require therapy. This has been touched upon in the last two chapters, and will be discussed in more detail below. Table 13.3.2 shows the thresholds for therapy of acid-base disorders.

1. pH.

Intracellular pH is well buffered and does not change when the extracellular pH is between 7.2-7.5 [6,7]. Below and above this range significant physiological changes occur due to altered cellular metabolic function, especially in those whose clinical condition is poor [see above and chapter 13.2].

An acid-base disorder should be corrected if the extracellular pH is above 7.5 or below 7.2.

2. Base excess.

The base excess is a measure of the excess concentration of the anion causing an acid-base disorder [see chapter 13.1 for definition]. An abnormal base excess is an indication of an abnormal extracellular and intracellular chemical environment, regardless of whether the pH is normal or not. This has clinical significance.

For example, a metabolic acidosis may be corrected by hyperventilation, but the base-deficit remains. An example of the importance of this concept is the effect of metabolic acidosis on cardiac ventricular fibrillation threshold. Metabolic acidosis decreases the ventricular fibrillation threshold of the heart, and the fibrillation threshold remains decreased, even if the pH is returned to normal by induction of respiratory alkalosis. Only reduction of the base-excess to normal reverses the decreased ventricular fibrillation threshold [30].

A clinically usable threshold at which to correct an acid-base disorder is if the base excess is lower than -10 or greater than + 10.

3. Mixed venous PO_2 < = 2.67 kPa (20 mmHg).

If the mixed venous PO_2 is < = 2.67 kPa (20 mmHg), then the chance of tissue, and especially cerebral hypoxia is high [see 13.2]. Tissue hypoxia will occur at a venous PO_2 of less than this regardless of what the acid-base status is. Such levels of hypoxaemia are more likely to be survived by an acidaemic, rather than an alkalaemic patient [see chapter 13.2]. The level of oxygenation of the blood should be increased regardless of the acid-base balance, and if the patient is even slightly alkalotic, the alkalosis should be corrected, preferably with induction of a slight acidosis.

4. Arterial haemoglobin oxygen saturation < 90%.

Severely alkalaemic patients, especially those with a relatively low cardiac output, may develop tissue hypoxia even when the arterial haemoglobin oxygen saturation is normal. This is not the case with acidaemic patients [see chapter 13.2].

Alkalosis, but not necessarily acidosis, should be corrected if the arterial haemoglobin oxygen saturation is less than 90%.

5. Haemoglobin < = 6 mmol/l (10 gm/100 mls).

Haemoglobin is essential for oxygen transport, and this is reduced in anaemic patients. Alkalosis further reduces transfer of oxygen to tissues, in addition to increasing oxygen consumption. Because of this, tissue hypoxia may occur in normoxaemic but anaemic alkalaemic patients. Tissue hypoxia is less likely in acidaemic patients [see chapter 13.2].

a. Anaemia & alkalosis.

In patients with a pH > 7.5, plus signs of tissue hypoxia, as well as significant anaemia, i.e. [Hb] < 6 mmol/l, alkalosis should be corrected simultaneously with administration of blood. If blood is not available, treatment of the alkalosis will allieviate tissue hypoxia to some degree.

b. Anaemia & acidosis.

Acidosis maintains tissue oxygenation in the face of a low CO x [Hb] product [see chapter 13.2. First correct anaemia, and only then correct the acidosis if this is required.

6. Hypotension and/or low cardiac output.

Acidosis and alkalosis may both cause hypotension or depress the cardiac output [see above and chapter 13.2]. If either hypotension or a low cardiac output occurs in association with an acid-base disorder, then the acid-base disorder should be treated as well as the specific haemodynamic disorder itself.

MANAGEMENT OF SPECIFIC ACID-BASE DISORDERS

1. Respiratory acidosis.

a. Respiratory acidosis occurring during controlled ventilation.

Treatment is simple, consisting of increasing the respiratory minute volume.

b. Respiratory acidosis occurring during spontaneous respiration.

i. Treat the cause of the respiratory depression. For example, antagonize the effects of opiates, discontinue administration of respiratory depressant drugs, e.g. barbiturates, benzodiazepines, etc. Other causes of respiratory depression should also be treated, e.g. chronic obstructive airways disease.

ii. As a general measure respiratory stimulant drugs may be administered to all patients with respiratory depression regardless of the cause, e.g. doxapram, nikethamide.

iii. Endotracheal intubation and controlled ventilation may be required. Caution should be used when starting controlled ventilation in patients with chronic respiratory acidosis, as the PCO_2 should be reduced slowly. Acidosis elevates sympathoadrenal activity and plasma catecholamine concentrations. Acidosis facilitates transfer of oxygen to tissues from the blood, and the effects on the sympathoadrenal system elevates the cardiac output. Sudden elevation of the pH reverses these changes, decreasing sympathoadrenal activity, plasma catecholamine concentrations, cardiac output, and oxygen transfer to tissues. The effect of this is to cause hypotension. In addition to this, severe neurological disorders such as coma and convulsions have been reported to occur after rapid reduction of the PCO_2 in chronically hypercarbic patients [49,50].

2. Respiratory alkalosis.

The therapy of respiratory alkalosis is to treat the cause. Acute therapy of respiratory alkalosis itself consists of a variety of manoeuvres to reduce the respiratory minute volume, or add some dead space to the tidal volume so as to reduce the alveolar ventilation.

a. Reduce the respiratory minute volume of patients whose ventilation is controlled.
b. Add a piece of "dead-space" tubing to the ventilator tubing of a patient whose ventilation is controlled.
c. Patients with psychogenic hyperventilation can be requested to rebreathe in a paper or plastic bag.

3. Metabolic acidosis.

The goal of therapy is to raise the arterial pH to more than 7.2 and the base excess to more than -10 mmol/l. One complication of a normalization of pH is a reduction of the plasma potassium concentration. This latter is likely to have a greater effect in acidotic patients who are already hypokalaemic. Hypokalaemia may combine with acidosis to cause cardiac arrhythmias.

While metabolic acidosis may be corrected to some degree by induction of respiratory alkalosis in patients whose ventilation is controlled, the principal form of therapy is intravenous administration of sodium bicarbonate. The dosage of sodium bicarbonate required may be calculated by the well known formula below (equation 3). Equation 3 assumes a bicarbonate distribution volume of 300-333 ml/kg body weight.

$$\text{Dose } HCO_3^- = \frac{\text{BE x WEIGHT}}{3} \quad \text{.....(3)}$$

Dose HCO_3^- = total quantity of bicarbonate required to correct a given whole body base deficit in mmol.
BE = base excess in mmol/l.
WEIGHT = body weight in kg.

The usual solution of sodium bicarbonate that is used is an 8.4% solution, which contains HCO_3^- at a concentration of 1 mmol/ml. Some of the disadvantages associated with the use of this solution have been discussed earlier in this chapter.

Only 50-75% of the calculated dose should be administered initially, so that the acidosis is never fully corrected. This is because of all the problems associated with alkalosis which may be induced by too large a dose, and also due to the possibility of hypervolaemia due to excessive volumes of this very hyperosmolar fluid (1000 mosm/l).

4. Metabolic alkalosis.

The aim of therapy when correcting metabolic alkalosis is to slightly overcorrect, or at least reduce the pH to less than 7.45, and the base excess to less than + 10 mmol/l.

a. Hypokalaemia and alkalosis.

Hypokalaemia itself causes alkalosis by increasing renal hydrogen ion excretion, and should always be corrected simultaneously with the correction of alkalosis. Potassium chloride (KCl) is the best potassium salt to use for this purpose [see chapter 12.3 for a discussion of potassium replacement].

b. Hypochloraemic alkalosis.

A sodium chloride solution e.g. 0.9% NaCl, should be infused to replace both the lost chloride ion as well as correct the hypovolaemia often associated with this form of alkalosis, e.g. the alkalosis due to protracted vomiting such as due to pyloric stenosis, or excessive gastric drainage. Potassium replacement may also be required. The effect of treatment is monitored by regular measurement of the arterial blood gas status, as well as of the plasma potassium, sodium and chloride concentrations.

c. Acetazolamide.

Acetazolamide administered intravenously at a dosage of 2.5-5 mg/kg (200-500 mg/70 kg) two to three times per day to adults is effective in preventing alkalosis occurring after major operations [5,54], as well as for treatment of existing metabolic alkalosiss. It corrects and prevents metabolic alkalosis by blocking renal tubular carbonic anhydrase as well as increasing urine production. The effect of acetazolamide at the above dosage in normal post-surgical patients is to cause the renal excretion of bicarbonate ion to increase up to 350 times normal [51,54]. This increases $[H^+]$ relative to $[HCO_3^-]$, correcting any alkalosis. However adequate renal tubular function is essential in order for acetazolamide to be effective in reversing alkalosis.

Infusion of sodium chloride solutions is contraindicated in patients who are oedematous or hypervolaemic, as they will exacerbate interstitial oedema. But

acetazolamide is a diuretic, and so reduces any oedema and hypervolaemia, making it the treatment of choice in these patients.

d. Hydrochloric acid (HCl) infusion.

Should any of the above therapies be contraindicated or unsuccessful, then infusion of an HCl solution is indicated. This is a very effective method of correction of all forms of metabolic alkalosis. But as HCl solutions readily cause tissue damage because HCl is a strong acid. Accordingly HCl should only be infused through a properly situated central venous line. The dose may be calculated using either equation 4 or 5 below [references 52 and 53 respectively].

$$\text{Dose}_{HCl} = \frac{\text{BE x WEIGHT}}{3} \quad \text{.....(4)}$$

$$\text{Dose}_{HCl} = \frac{\text{WEIGHT}}{5} \text{ x } (103 - [Cl^-]) \quad \text{.....(5)}$$

Dose_{HCl} = quantity of HCl required to correct the alkalosis in mmol.
BE = base excess in mmol/l.
WEIGHT = body weight of patient in kg.
$[Cl^-]$ = plasma chloride concentration in mmol/l.

HCl may be administered mixed with a 5% glucose or 0.9% NaCl solution, made up to a concentration that varies from one author to another from 0.1-1.0 mol/l [52,53]. Initially about only one half of the calculated dose should be infused, and subsequently the acid-base status determined. If necessary, more may then be infused. The dose calculated should be infused slowly over a 6-12 hour period to minimize the chance of thrombophlebitis.

ANAESTHETIC MANAGEMENT

Preoperative.

1. If possible, any existing acid-base disorder should be corrected prior to surgery, as this minimizes the chances of any further perioperative exacerbation of existing problems. However this is not always possible, as many patients with a significant acid-base disorder are very ill and surgery cannot be delayed. The only category of patients who do benefit from delay and correction of their acid-base disorder are those with metabolic alkalosis secondary to protracted vomiting, excessive nasogastric suction, or diuretic use. These patients are both alkalotic as well as hypovolaemic, especially those with pyloric stenosis.

2. No preoperative sedative or anticholinergic drugs should be administered unless required, as these patients are by virtue of their disease(s) in an unstable physiological condition which may be exacerbated by any of these drugs.

Anaesthesia.

1. As far as is possible, begin therapy of the acid-base disorder preoperatively so as to minimize any intraoperative and postoperative problems due to acidosis or alkalosis.

2. There is no particular form or type of anaesthesia that is preferable or especially indicated for patients with acid-base disorders. Anaesthesia should be administered in accordance with the clinical condition of the patient and the type of surgery planned. There are really only a few specific anaesthetic considerations.

a. The acidotic patient is likely to be less sensitive, and the alkalotic patient more sensitive to the central nervous system effects of opiate and sedative drugs.
b. The effects of nondepolarizing muscle relaxant drugs may be potentiated by acidosis.
c. Excessive hyperventilation should be avoided in patients whose ventilation is controlled as this will exacerbate any existing alkalosis.
d. Lactated Ringer's solution should not be administered to alkalotic patients as it will further exacerbate any alkalosis. Instead use a 0.9% NaCl for the same indications as lactated Ringer's solution would be used.

Postoperative.

The level of postoperative care required depends on the clinical condition of the patient.

REFERENCES

1. Diem,K., Lentner,C.,(eds.),(1968), "Wissenschaftliche tabellen", 7th edn., pub. CIBA-GEIGY AG, Basel.
2. Hill,G.L., et al.,(1976), Decreased trypsin and bile acids in ileal fistula drainage during the administration of a chemically defined liquid elemental diet. BRITISH JOURNAL OF SURGERY, 63, 133-136.
3. Hodgkin,J.E., et al.,(1980), Incidence of metabolic alkalemia in hospitalized patients. CRITICAL CARE MEDICINE, 8, 725-728.
4. Mithoefer,J.C., et al.,(1968), Effect of intravenous NaHCO3 on ventilation and gas exchange in normal man. RESPIRATION PHYSIOLOGY, 4, 132-140.
5. Grigor,K.C., et al.,(1971), The effect of acetazolamide on postperfusion metabolic alkalosis. BRITISH JOURNAL OF ANAESTHESIA, 43, 352-361.
6. Waddell,W.J., Bates,R.J.,(1969), Intracellular pH. PHYSIOLOGICAL REVIEWS, 49, 285-329.
7. Poole-Wilson,P.A., Cameron,I.R.,(1975), Intracellular pH and K^+ of cardiac and skeletal muscle in acidosis and alkalosis. AMERICAN JOURNAL OF PHYSIOLOGY, 229, 1305-1310.
8. Khambatta,H.J., Sullivan,S.F.,(1973), Effects of respiratory alkalosis on oxygen consumption and oxygenation. ANESTHESIOLOGY, 38, 53-58.
9. Rastegar,H., et al.,(1979), Respiratory alkalosis increases tissue oxygen demand. JOURNAL OF SURGICAL RESEARCH, 26, 687-692.8.
10. Alexander,S.C., et al.,(1965), Cerebral carbohydrate metabolism during hypocarbia in man. Studies during nitrous oxide anesthesia. ANESTHESIOLOGY, 26, 624-632.
11. Alexander,S.C., et al.,(1968), Cerebral carbohydrate metabolism in man during respiratory and metabolic alakalosis. JOURNAL OF APPLIED PHYSIOLOGY, 24, 66-72.
12. Relman,A.S.,(1972), Metabolic consequences of acid-base disorders. KIDNEY INTERNATIONAL, 1, 347-359.
13. Bradley,R.D., Semple,S.J.G.,(1962), A comparison of certain acid-base characteristics of arterial blood, jugular venous blood and cerebrospinal fluid in man, and the effect on them of some acute and chronic acid-base disturbances. JOURNAL OF PHYSIOLOGY (LONDON), 160, 381-391.
14. Davies,D.G., Nolan,W.F.,(1982), Cerebral interstitial fluid acid-base status follows arterial acid-base perturbations. JOURNAL OF APPLIED PHYSIOLOGY, 53, 1551-1555.
15. Euler, von U.S., Lishajko,F.,(1963), Influence of pH on uptake and release of noradenaline in adrenergic nerve granules. JOURNAL OF NEUROCHEMISTRY, 10, 145-149.

16. Nahas,G.G., et al.,(1967), Acidemia and catecholamine output in the isolated canine adrenal gland. AMERICAN JOURNAL OF PHYSIOLOGY, 213, 1186-1192.
17. Tenney,S.M.,(1956), Sympatho-adrenal stimulation by carbon dioxide and the inhibitory effect of carbonic acid on epinephrine response. AMERICAN JOURNAL OF PHYSIOLOGY, 187, 341-346.
18. Darby,T.D., Watts,D.T.,(1964), Acidosis and blood epinephrine levels in hemorrhagic hypotension. AMERICAN JOURNAL OF PHYSIOLOGY, 206, 1281-1284.
19. Fiorica,V., et al.,(1969), Influence of blood pH on adrenomedullary response to hemorrhage. AMERICAN JOURNAL OF PHYSIOLOGY, 217, 1211-1215.
20. Bendixen,H.H., et al.,(1963), Influence of respiratory acidosis on circulatory effect of epinephrine in dogs. CIRCULATION RESEARCH, 13, 64-70.
21. Schroeder,J.S., et al.,(1970), Effects of respiratory acidosis on circulatory response to isoproterenol. AMERICAN JOURNAL OF PHYSIOLOGY, 218, 448-452.
22. Yakaitis,R.W., et al.,(1978), Effects of catecholamines during respiratory alkalosis in dogs. JOURNAL OF APPLIED PHYSIOLOGY, 44, 581-584.
23. Hassan,H., et al.,(1979), Hypercapnia and hyperkalaemia. ANAESTHESIA, 34, 897-889.
24. Edwards,R., et al.,(1977), Acute hypocapneic hypokalemia: An iatrogenic anesthetic complication. ANESTHESIA AND ANALGESIA, 56, 786-792.
25. Orringer,C.E., et al.,(1977), Natural history of lactic acidosis after grand-mal seizures. A model for the srudy of an anion-gap acidosis not associated with hyperkalemia. NEW ENGLAND JOURNAL OF MEDICINE, 297, 796-799.
26. Fulop,M.,(1979), Serum potassium in lactic acidosis and ketoacidosis. NEW ENGLAND JOURNAL OF MEDICINE, 300, 1087-1089.
27. Wilson,R.F., et al.,(1972), Severe alkalosis in critically ill surgical patients. ARCHIVES OF SURGERY, 105, 197-203.
28. Vaughan-Williams,E.M., Whyte,J.M.,(1967), Chemosensitivity of cardiac muscle. JOURNAL OF PHYSIOLOGY (LONDON), 189, 119-137.
29. Campbell,G.S.,(1955), Cardiac arrest: Further studies on the effect of pH changes on vagal inhibition of the heart. SURGERY, 38, 615-634.
30. Gerst,P.H., et al.,(1966), A quantitative evaluation of the effects of acidosis and alkalosis upon the ventricular fibrillation threshold. SURGERY, 59, 1050-1060.
31. Katz,A.M.,(1973), Effects of ischaemia on the contractile processes of heart muscle. AMERICAN JOURNAL OF CARDIOLOGY, 32, 456-460.
32. Poole-Wilson,P.A., Langer,G.A.,(1979), Effects of acidosis on mechan ical function and Ca^{2+} exchange in rabbit myocardium. AMERICAN JOURNAL OF PHYSIOLOGY, 236, H525-H533.
33. Nahas,G.G., Cavert,H.M.,(1957), Cardiac depressant effect of CO_2 and its reversal. AMERICAN JOURNAL OF PHYSIOLOGY, 190, 483-491.
34. Bos, van den,G.C., et al.,(1979), Effect of carbon dioxide on myocardial contractile performance, blood flow and oxygen consumption. JOURNAL OF PHYSIOLOGY (LONDON), 287, 149-161.
35. Clancy,R.L., et al.,(1967), Influence of sodium bicarbonate on myocardial performance. AMERICAN JOURNAL OF PHYSIOLOGY, 212, 917-923.
36. Wead,W.B., Little,R.C.,(1967), Effect of hypocapnia and respiratory alkalosis on cardiac contractility. PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY & MEDICINE, 126, 606-609.
37. Poole-Wilson,P.A.,(1982), Acidosis and contractility of heart muscle. CIBA FOUNDATION SYMPOSIUM, 87, 58-76.
38. Steinhart,C.R., et al.,(1983), ß-adenergic activity and cardiovascular response to severe respiratory acidosis. AMERICAN JOURNAL OF PHYSIOLOGY, 244, H46-H54.
39. Frumin,M.J., et al.,(1959), Apneic oxygenation in man. ANESTHESIOLOGY, 20, 789-798.
40. Wollman,H., et al.,(1968), Effects of extremes of respiratory and metabolic alkalosis on cerebral blood flow in man. JOURNAL OF APPLIED PHYSIOLOGY, 24, 60-65.
41. Cullen,D.J., Eger,E.I.,(1974), Cardiovascular effects of carbon dioxide in man. ANESTHESIOLOGY, 41, 345-349.
42. Kittle,C.F., et al.,(1965), The role of pH and CO_2 in the distribution of blood flow. SURGERY, 57, 139-153.
43. Richardson,D.W., et al.,(1972), Systemic circulatory responses to hypocapnia in man. AMERICAN JOURNAL OF PHYSIOLOGY, 223, 1308-1312.
44. Ainslie,S.G., et al.,(1979), Fentanyl concentrations in brain and serum during respiratory acid-base changes in the dog. ANESTHESIOLOGY, 51, 293-297.
45. Schulman,D.S., et al.,(1984), Blood pH and brain uptake of C14 morphine. ANESTHESIOLOGY, 61, 540-543.

16. Tuller,M.A., Mehdi,F.,(1971), Compensatory hypoventilation and hypercapnia in primary metabolic alkalosis. AMERICAN JOURNAL OF MEDICINE, 50, 281-290.
17. Kety,S.S., Schmidt,C.F.,(1946), The effects of acive and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men. JOURNAL OF CLINICAL INVESTIGATION, 25, 107-119.
18. Edmondson,J.W., et al.,(1976), Tetany: Quantitative interrelationships between calcium and alkalosis. AMERICAN JOURNAL OF PHYSIOLOGY, 228, 1082-1086.
19. Rotheram,E.B., et al.,(1964), CNS disorder during mechanical ventilation in chronic pulmonary disease. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 189, 993-997.
20. Kilburn,K.H.,(1966), Shock, seizures and coma with alkalosis during mechanical ventilation. ANNALS OF INTERNAL MEDICINE, 65, 977-984.
21. Mudge,G.H.,(1966), Influence of plasma composition on sodium excretion and diuretic action. ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 139, 304-311.
22. Williams,D.B., Lyons,J.H.(1980), Treatment of severe metabolic alkalosis with intravenous solution of hydrochloric acid. SURGERY, GYNECOLOGY & OBSTETRICS, 150, 315-321.
23. Harken,A.H., et al.,(1975), Hydrochloric acid in the correction of metabolic alkalosis. ARCHIVES OF SURGERY, 110, 819-821.
24. Berthelson,P., et al.,(1986), Dissociation of renal and respiratory effects of acetazolamide in the critcally ill. BRITISH JOURNAL OF ANAESTHESIA, 58, 512-516.

Part 14

PERIOPERATIVE FLUID & TRANSFUSION THERAPY

Intravenous fluid and transfusion therapy play an important role in modern perioperative patient management. The reasons are simple.

- Maintenance of a normal blood volume and haemoglobin concentration ensures a normal cardiac output and normal peripheral oxygen transport.

- Maintenance of a normal cardiac output and interstitial fluid volumes means that transfer of oxygen from the alveoli to the blood is normal, and that transfer of oxygen from the blood into the cells is also normal.

- Maintenance of normal intracellular and extracellular fluid volumes and compositions means that the chemical environments within which the sum total of all biochemical reactions that are required for physiological function are maintained as near normal as possible.

The purpose of this section is to provide a review of the basic physiology of fluid balance and exchange, and a logical and simple approach to the assessment and practical fluid therapy of perioperative patients. Simple easily applied clinical guidelines are also provided.

Chapter 14.1

NORMAL FLUID AND ELECTROLYTE DISTRIBUTION

Prior to any discussion of fluid and electrolyte balance it is essential to define some physicochemical concepts, and the various fluid compartments together with their volumes and electrolyte compositions. This chapter also discusses the basic physiology of transcapillary fluid exchange.

BASIC PHYSICAL CHEMICAL CONSIDERATIONS

1. Osmole.

The osmotic force able to be exerted by a substance is related to the molecular or atomic particular concentration of that substance. One mole of a molecule or ion has a concentration of one osmole.

2. Osmolarity.

This is defined as the osmolar concentration of a solute per liter of SOLUTION. Its usual units are osmoles/liter.

3. Osmolality.

This is defined as the osmolar concentration of a solute per liter or kilogram of SOLVENT. Its usual units are osmoles/kilogram, or osmoles/ liter.

NOTE.

Because the concentrations of electrolytes and proteins in physiological solutions is low, the terms osmolality and osmolarity may be interchanged without any significant loss of accuracy.

4. Osmotic pressure.

If there is a semipermeable membrane separating two solutions with differing osmolar concentrations, a force is exerted which forces fluid through the membrane into the solution with the highest concentration. This is the osmotic pressure. Its units are also those of pressure. The osmotic pressure exerted by a given osmolar concentration may be calculated approximately using equation 1.

$$\text{OSMOTIC PRESSURE(mmHg)} = 19.3 \times \text{OSMOLALITY(mosm/l)} \quad \ldots(1)$$

Table 14.1.1.
Volumes of the various fluid compartments in humans.

TOTAL BODY WATER

Prepubertal children [4]

AGE	TBW
0 - 1 month	75.7%
1 - 12 months	64.5%
1 - 10 years	61.7%

Adults [3, pages 6-7]

Body Build	LEAN	AVERAGE	OBESE
MALES	60%	55%	50%
FEMALES	55%	50%	45%

EXTRACELLULAR FLUID VOLUME

ADULT MALES = 25% of body weight (kg).
= 250 mls/kg.
ADULT FEMALES = 20% of body weight (kg).
= 200 mls/kg.

INTERSTITIAL FLUID VOLUME [5]

ADULT MALES and FEMALES = 120-200 mls/kg body weight.

PLASMA VOLUME

ADULT MALES = 45 mls/kg body weight.
ADULT FEMALES = 40 mls/kg body weight.

BLOOD VOLUME [3 page 146]

NEONATES = 80-85 mls/kg body weight.
CHILDREN = 75 mls/kg body weight.

ADULTS

BODY BUILD	muscular	normal	thin	obese
MALES	75	70	65	60
FEMALES	70	65	60	55

N.B. Volumes are in mls/kg body weight.

Equation 1 reveals that the plasma osmotic pressure, (Normal plasma osmolality = 280-300 mosmol/l), is about 5400 mmHg, meaning that the plasma proteins which exert an osmotic pressure of about 25 mmHg are osmotically only minimally active. The osmotic pressure exerted by proteins is sometimes called the "colloid osmotic pressure" or the "oncotic pressure".

NORMAL FLUID AND ION PHYSIOLOGY

1. Volumes of various fluid compartments.

More than 50% of the weight of the average human body consists of water. This water is distributed throughout various compartments. Table 14.1.1 shows the volumes of these compartments related to body weight, as mls/kg body weight, or a percentage of the body weight. As the density of the human body is only slightly different from that of water, the mass of water in kilograms may for practical purposes be given as liters, i.e. 1 liter water = 1 kilogram. The most important fluid compartments and their abbreviations are listed below.

a. Total Body Water (**TBW**) = total volume of water in the body.

b. Interstitial Fluid Volume (**ISFV**) = volume of fluid that is situated between the cells of the body, but does not include plasma.

c. Plasma Volume (**PV**) = plasma volume.

d. Extracellular Fluid Volume (**ECFV**) = total volume of fluid that is not situated intracellularly. This fluid volume consists of the PV plus the ISFV.

e. Intracellular Fluid Volume (**ICFV**) = total volume of fluid inside all the cells of the body.

f. Blood Volume (**BV**) = blood volume which includes the plasma volume plus the volume of the erythrocytes within the blood.

The tables giving the volumes of the various fluid compartments are useful for clinical anaesthetic practice and are sufficiently accurate for nearly all purposes. The reader who wishes to use more complicated regression equations is referred to references 1 and 2.

2. Normal electrolyte concentrations.

a. Intracellular and extracellular differences.

The composition of intracellular and extracellular fluids is quite different. These concentration differences are maintained by energy requiring membrane pumps functioning in intact cell membranes. The maintenance of these concentration gradients, especially that of ionic concentration gradients, determines the distribution of intravenously or orally administered electrolyte solutions within the body. Table 14.1.2 shows the average intracellular and extracellular ionic and protein concentrations.

b. Volumes and composition of various body secretions.

The key to understanding the nature of many electrolyte, fluid and acid-base disorders is knowledge of the production rates and composition of the various secretions of the body. These are shown in table 14.1.3. It should always be remembered that this table is

only a guide to the average values. These vary with the secretion rate as well as the stimulus causing secretion.

Table 14.1.2.
Normal ionic and protein concentrations in the extracellular and intracellular compartments.

ION	EXTRACELLULAR (mmol/l)	INTRACELLULAR (mmol/l)
Sodium	146	14
Potassium	4	140
Calcium	2.5	0.001
Magnesium	1.5	31
Chloride	105	4
Bicarbonate	24	10
Hypophosphates	2	11
Proteins (concn. in mosm/l)	1.2	4

Table 14.1.3.
Composition and production rates of various body secretions in adults [6].

FLUID	Volume (ml/day)	Na^+ (mmol/l)	K^+ (mmol/l)	Cl^- (mmol/l)	HCO_3^- (mmol/l)
Saliva	500-1500	14	21	24	7
Gastric	2000-3000	49	12	120	0
Bile	250-1100	149	5	100	30
Pancreas	700-2500	141	5	129	25
Small intestine	1000-3000	110	5	100	30
Faeces	100-200	30	50	40	40
Diarrhea	>500	75	30	0	50
Sweat	200-300	42	8	30	0
Urine	510-2000	85	25	90	0
Lungs (respiration)	300-500	0	0	0	0

3. Normal water requirements.

The basal volume of water required for replacement of losses and excretion of waste products varies with the body weight, age and metabolic rate. The same is also true of electrolyte requirements.

a. Children.

Basal water requirement in children may be calculated using the well known "Liverpool formula" which is set out in table 14.1.4, or the formula below (equation 2) [8].

$$\mathbf{Q = WEIGHT \times (100 - 3 \times AGE) \quad ....(2)}$$

Q = volume of fluid required per 24 hours.
WEIGHT = body weight in kg.
AGE = age in years.

Table 14.1.4.
"Liverpool formula", used for calculating the basal water requirements of children and infants [7].

Weight up to 10 kg	-	100 mls/kg/day.
Weight 10 - 20 kg	-	1000 mls/day + 50 mls/kg/day for each kg above 10 kg.
Weight >20 kg	-	1500 mls/day + 20 mls/kg/day for each kg above 20 kg.

b. Adults.

Adult basal water requirement is usually estimated as 2 mls/kg/hour.

4. Normal vascular molecular permeability.

The distribution of fluids is dependent on whether they have an osmolality that is greater or less than that of the body, the types of ions and macromolecules in solution, and the permeability of vascular endothelium to these molecules.

Arteries, veins and arterioles are virtually impermeable to water and other molecules. But venules and capillaries are freely permeable to molecules with a molecular weight less than about 10,000 Daltons [fig 14.1.1], e.g. glucose, water etc. However capillaries and venules are not uniformly permeable. The permeability of these vessels to water and other small molecules with an MW < 10,000 Daltons is least at the arteriolar ends of capillaries, while the venules are more permeable. The permeability of venules and the venular ends of capillaries to water may be twice that of the arteriolar capillaries [9,10]. In addition to

their greater permeability, the endothelial surface area of the venules and the venular ends of the capillaries is about 2-6 times that of the arteriolar ends of capillaries, a feature which facilitates absorbtion of fluid from the interstitium [9]. The permeability of the capillaries and venules of different organs also differs from one organ to another [11,12,14,15]. This is shown in figure 14.1.1.

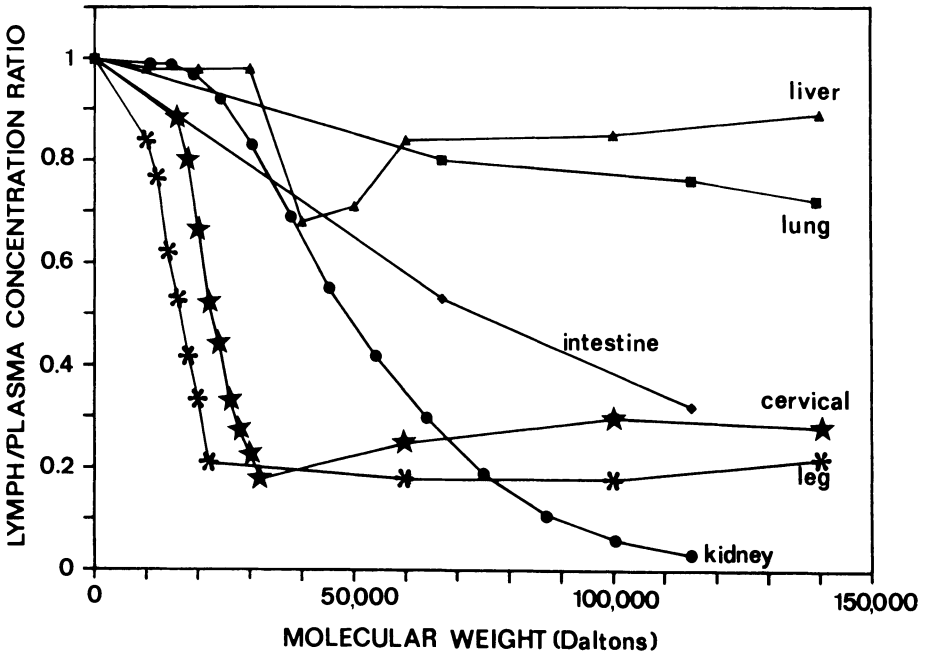

FIGURE 14.1.1. - Lymph/plasma concentration ratio is related to the molecular weight of proteins. In the case of the kidney, the ratio is the ratio of the glomerular filtrate concentration to that in the plasma. The lymph/plasma concentration ratio is a measure of the capillary/venular permeability to molecules. The nearer the ratio is to 1, the greater the permeability. The data used are derived from investigations using various animals, and either proteins or dextrans of various molecular weights [11,12,14,15].

In figure 14.1.1 the lymph/plasma concentration ratio is used as a measure of capillary and venular permeability to molecules of varying molecular weights, (in the case of the kidneys the urine/plasma ratio is used). The nearer this ratio is to "1", the more permeable the capillary endothelium. From this it is obvious that capillaries and venules perfusing predominantly muscle and connective tissue are relatively impermeable to molecules with a molecular weight above 30,000 Daltons [11]. The ability of large molecules to enter the glomerular filtrate decreases markedly as the molecular weight increases from 15,000 to 75,000 Daltons [12]. However for all practical purposes the glomerular capillary en-

dothelium may be considered impermeable to molecules with a molecular weight above 60,000 Daltons, as minimal amounts of albumin appear in normal urine [13]. The situation for the liver [11], lung [14] and intestines [15] is quite different, as the capillaries in these organs are quite permeable to molecules with molecular weights of as high as 100,000 Daltons.

Capillary and venular permeability to macromolecules accounts for the measured rate of loss of 4.7% of the total plasma content of albumin per hour from the circulation in humans, (molecular weight of albumin = 66,241 Daltons) [16]. The albumin and other proteins that leak into the interstitial space are subsequently returned to the circulation via the lymphatics.

Capillary permeability to proteins means that there are significant quantities of albumin and other proteins within the interstitial fluid space. In humans the subcutaneous interstitial fluid albumin concentration is about 62% that in the plasma [17]. This implies that interstitial fluid volume in the average adult contains about 2.5 times more albumin than the plasma does.

While the capillaries are somewhat permeable to these macromolecules, they are not freely permeable. This is clearly demonstrated by the fact that elevation of the capillary blood pressure causes interstitial fluid and lymphatic concentrations of these proteins to decrease [15,18]. It is this limitation of the rate of protein movement out of vessels which are permeable to proteins of larger molecular weights that causes the intravascular to interstitial fluid protein concentration gradient. Because of this plasma colloid osmotic pressure is greater than that of interstitial fluid. This is vital for normal transcapillary fluid exchange, and is of most relevance to albumin, as it is albumin which provides the greatest contribution to the plasma and interstitial colloid osmotic pressure in man [21].

The permeability of capillaries to proteins and fluids is increased by up to 7-9 times normal by inflammation, trauma, and surgery [10]. This has consequences for perioperative fluid management as will be discussed later.

5. Transcapillary fluid exchange.

Because capillaries are freely permeable to molecules whose molecular weight is less than 10,000 Daltons, there is free movement and exchange of water, electrolytes and small molecules between the plasma and interstitial fluid across the capillary and venular endothelium. Water is very rapidly exchanged between the intravascular and interstitial fluid compartments, human studies showing that each minute a volume of water is exchanged between the plasma and interstitial fluid that is equivalent to the plasma volume. The volume of plasma filtered out of the capillaries into the interstitium per unit time is much less, the rate of filtration in human adults being about 20 liters/day, most being resorbed at the venous end of the capillaries and venules, and the remainder being returned to the circulation as lymph [25].

Factors of importance in regulating transcapillary fluid exchange are the intravascular-extravascular pressure and colloid osmotic pressure differences. In humans these parameters have been found to have the approximate values listed below.

a. Capillary pressures.

Capillary blood pressures have been measured in the skin of fingers in humans. Pressure in the arteriolar ends of capillaries varies between 21-48 mmHg (mean = 32 mmHg), and that in the venular end of capillaries between 6-18 mmHg (mean = 12 mmHg). In the middle of the capillaries the mean intravascular pressure is about 20 mmHg [19].

b. Interstitial fluid pressure.

Interstitial fluid pressure in man is less than atmospheric pressure, and varies between -2 to -10 mmHg (mean = -6 mmHg) [20].

c. Colloid osmotic pressure.

Mean colloid osmotic pressure of normal human plasma varies from 21.6 to 29 mmHg in various studies [21,22], while that in human subcutaneous interstitial fluid varies between a mean of 11 mmHg at the ankle and 14.5 in thoracic subcutaneous interstitial fluid [22].

d. Plasma albumin and interstitial oedema.

Interstitial oedema develops in undamaged tissue when the plasma colloid osmotic pressure is lower than 15 mmHg, or the plasma albumin concentration is lower than 20 gms/l [22,28,29,30,31].

A simple modification of the well known Starling equation permits a simple view of the forces driving fluid across capillary and venular endothelium at any given point [9,27]. This relationship is shown in equation 3. Examples of the use of this equation are shown in figures 14.1.2 to 14.1.7 for various situations frequently encountered in clinical practice.

$$P_{tc} = [P_c - P_i] - [COP_p - COP_i] \quad .....(3)$$

P_{tc} = transcapillary pressure driving water across capillary endothelium in mmHg.
P_c = Capillary blood pressure at any given point in mmHg.
P_i = Interstitial fluid pressure in mmHg.
COP_p = Plasma colloid osmotic pressure in mmHg.
COP_i = Interstitial fluid colloid osmotic pressure in mmHg.

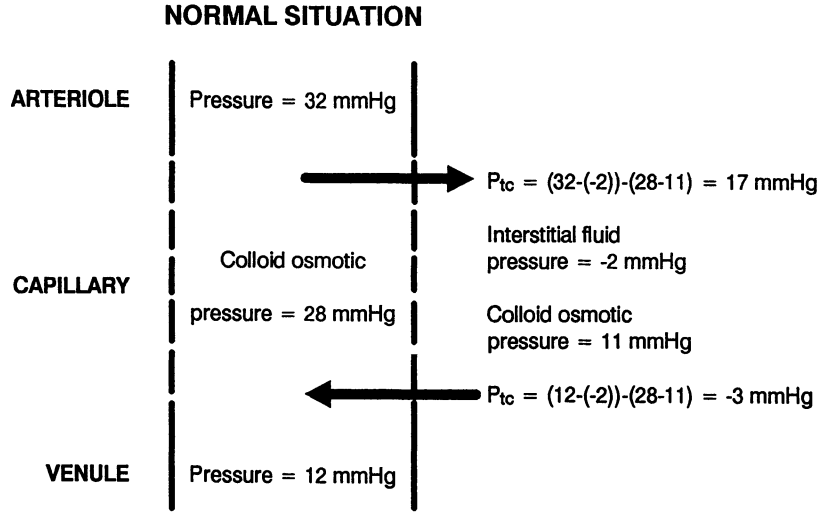

Figure 14.1.2. - The normal situation. Even though the pressure forcing fluid out of the arteriolar capillary is greater than that in the venous capillary, the greater venous capillary surface area ensures that the rate of fluid movement back into the circulation is almost as great as it is out of the arteriolar capillary. Fluid that remains in the interstitium is returned to the circulation via the lymphatic system.

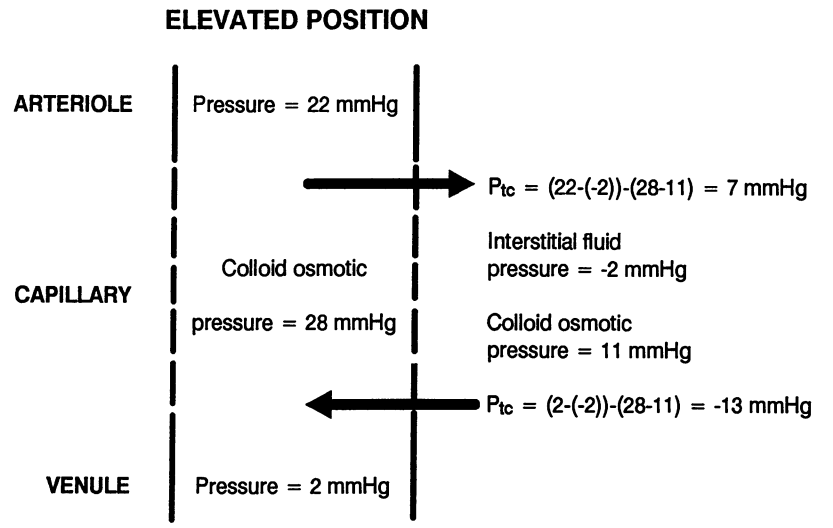

Figure 14.1.3. - Elevation of a traumatized, operated or swollen limb is often employed to prevent or reduce interstitial oedema. Elevation reduces both venous and arterial pressures equally. If these pressures are low enough, the pressures driving fluid out of the capillaries are less than that of the colloid osmotic pressure which draws fluid back into the circulation. This reduces existing oedema, and minimizes its formation.

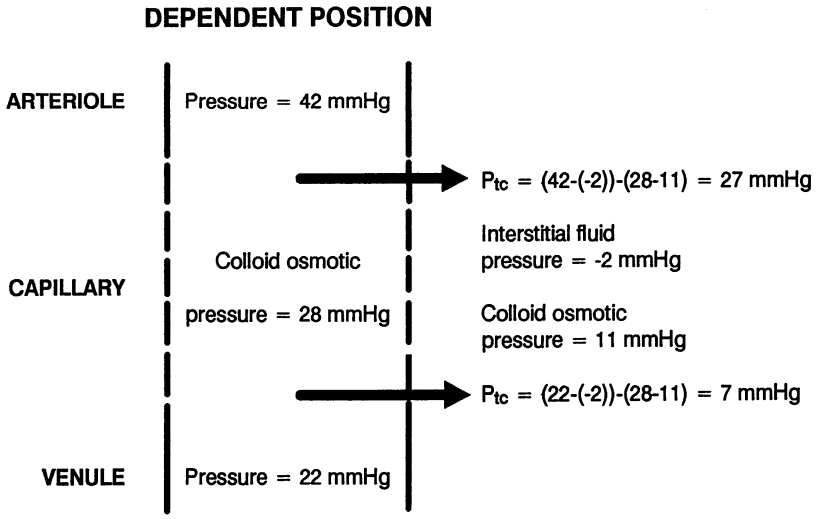

Figure 14.1.4. - Placing a limb or portion of the body in a dependent position elevates both the venous and arterial pressures equally. In the situation depicted, this causes the intravascular fluid pressures to be so high that they are greater than the osmotic pressure drawing fluid back into the circulation. If the rate of capillary fluid loss is greater than the maximum rate at which the lymphatic system can clear it from the interstitium, interstitial oedema occurs.

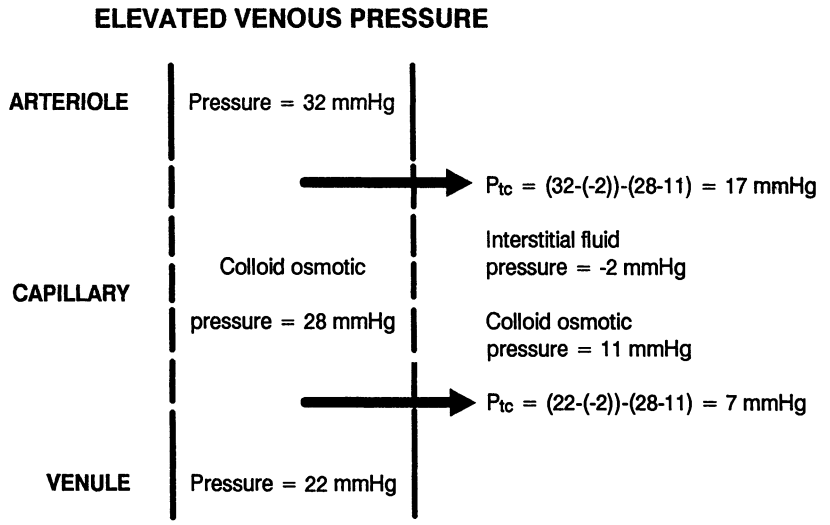

Figure 14.1.5. - Elevated venous pressure as caused by a venous tourniquet, incompetent venous valves etc, also causes interstitial oedema. This figure shows that if the venous pressure is sufficiently elevated it will exceed the colloid osmotic pressure drawing fluid back into the circulation. Interstitial oedema then occurs.

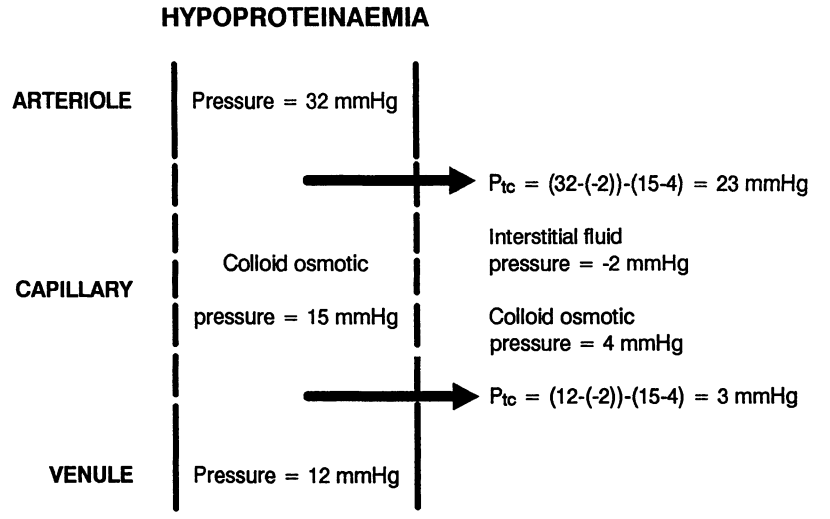

Figure 14.1.6. - Severe hypoproteinaemia significantly reduces the colloid osmotic pressures relative to the intravascular fluid pressures. In such cases interstitial oedema occurs when the rate of fluid loss from the capillaries exceeds the rate at which it can be cleared by the lymphatic system. Interstitial oedema occurs in humans when the plasma colloid osmotic pressure falls below 15 mmHg, or when the plasma albumin concentration falls below 20 gm/l [22,28,29,30].

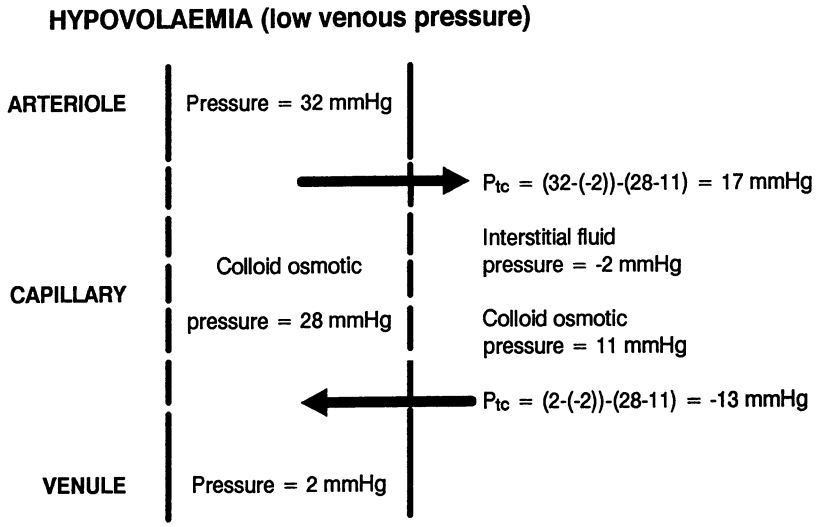

Figure 14.1.7. - Hypovolaemia, negative end-expiratory pressure during controlled ventilation, and slight elevation of a limb reduce the venous pressures without significantly reducing the arterial blood pressures. If the venous pressure is reduced far enough, the rate at which fluid enters the circulation is greater than the rate at which it leaves. This is a phenomenon effectively increasing the circulating blood volume. It is an important means for restoration and maintenance of circulating blood volume in humans and animals after haemorrhage, plasma loss into localized oedema, or from burns, and dehydration.

6. Transcapillary refill.

Transcapillary refill is the name given to the phenomenon whereby the rate at which fluid flows into the circulation from the interstitium is greater than the rate at which it leaves it. This occurs when the intravascular pressures are so low that the intravascular-interstitial colloid osmotic pressure difference is sufficient the draw fluid into the venular ends of capillaries at a faster rate than it leaves the capillaries at the arteriolar ends [see fig. 14.1.7]. The effect is to increase the circulating blood volume. It is a very important mechanism in humans and animals by which a blood volume deficit may be rapidly replaced, and normovolaemia maintained.

There are a variety of common clinical situations in which transcapillary refill occurs. These are listed below.

- Haemorrhage reduces blood volume and intravascular pressures.
- Loss of plasma from burns or into traumatic oedema reduces circulating blood volume and intravascular pressures.
- Dehydration of sufficient degree to cause a reduction of blood volume.
- Negative end-expiratory pressure during controlled ventilation reduces intravenous pressures.
- Administration of vasodilator drugs reduces intravascular pressures.
- Increased sympathetic nervous activity increases both precapillary as well as postcapillary vascular resistance. The effect of this is to reduce capillary and

venular pressures to such a degree that more fluid enters the capillaries in the organs affected than leaves them [26].

7. Rate of transcapillary refill.

Haemorrhage is the most well studied situation in which transcapillary refill occurs. After haemorrhage in humans, without replacement of the lost blood volume, fluid enters the circulation from the interstitium at a rate dependent on the pressure difference between capillary and interstitium. In fact the rate of refill declines exponentially as the process of transcapillary refill continually reduces the interstitium-capillary pressure difference, and so the time to completion of transcapillary refill is able to be described by a half life [23,25]. Human investigations have shown that after loss of 10-19% of the blood volume that transcapillary refill is complete by 12 hours, and about 95% complete after 6 hours, meaning that the process of transcapillary refill after haemorrhage has a completion half life of about 1-2 hours. This means that transcapillary refill will restore 50% of lost blood volume by 1-2 hours after haemorrhage, and indeed there is evidence that this is so [23].

8. Reversal of transcapillary refill.

The direction of transcapillary fluid exchange may be reversed by increasing intravascular pressures above normal. This can occur as a result of a number of events.

- Infusion of blood volume expanding fluids raises intracapillary and venular pressures [25].
- Administration of vasoconstrictor drugs elevates intracapillary and venular pessures. Plasma volume may actually be decreased below normal as a result of adminstration of vasoconstrictor drugs [16].

Table 14.1.5.
Distribution of interstitial fluid [5].

SITE	ISFV as % weight of organ	% of total body ISFV
Skin	40-60	33
Skeletal muscle	8-20	33
Viscera	20-30	20
Other organs	varies	13

9. Principal sources of fluid for transcapillary refill.

The source of the fluid entering the circulation during transcapillary refill is the interstitium. However interstitial fluid is not evenly distributed throughout the body as is shown by table 14.1.5. There is evidence that the skin and muscle are the source of most of

the fluid entering the circulation during transcapillary refill, as skin and muscle contain the largest proportion of the ISFV of the body [5]. But clinical evidence suggests that the visceral interstitium also provides a significant proportion of the volume of fluid entering the capillaries during transcapillary refill, as has been shown experimentally by the virtual non-occurrence of transcapillary refill in eviscerated dogs and rabbits [24]. This latter finding correlates well with the clinical experience of most anaesthetists, which is that patients undergoing major intra-abdominal surgery require a greater infused volume of fluid to maintain normal haemodynamic function than patients undergoing major leg or hip surgery of comparable magnitude. The most plausible explanation of this phenomenon is that the intra-abdominal viscera are concentrated in a relatively small space. Major intra-abdominal surgery affects all the abdominal viscera, increasing the permeability of the visceral capillary and venular endothelium to proteins [10], so decreasing the efficacy of transcapillary colloid osmotic forces. Transcapillary refill then no longer occurs from a region of the body which contains about 20% of the interstitial fluid volume available for this purpose, i.e. the abdominal viscera. Major hip or leg surgery only affects the transcapillary refill from a small percentage volume of tissues which are possible sources of interstitial fluid, i.e. one leg or one hip only. Because of this a larger proportion of the total body ISFV remains available for transcapillary refill during hip or leg surgery than during major abdominal surgery.

REFERENCES

1. Skrabal,F., et al.,(1973), Equations for the prediction of normal values for exchangeable sodium, exchangeable potassium, extracellular fluid volume, and total body water. BRITISH MEDICAL JOURNAL, 2, 37-38.
2. Moore,F.D., et al.,(1963),"The Body Cell Mass and its Supporting Environment. Body Composition in Health and Disease", pub. W.B.Saunders Co., U.S.A..
3. Moore,F.D.,(1959),"Metabolic Care of the Surgical Patient", pub. W.B.Saunders Co., U.S.A..
4. Bradbury,M.W.B.,(1973), Physiology of body fluids and electrolytes. BRITISH JOURNAL OF ANAESTHESIA, 45, 937-944.
5. Aukland,K., Nicolaysen,G.,(1981), Interstitial fluid volume. Local regulatory mechanisms. PHYSIOLOGICAL REVIEWS, 61, 556- 643.
6. Diem,K., Lentner,C.,(1968),"Wissenschaftliche Tabellen", 7th edn., pub. CIBA-GEIGY AG, Basel.
7. Bush,G.H.,(1971), Intravenous fluid therapy in pediatrics. ANNALS OF THE ROYAL COLLEGE OF SURGEONS OF ENGLAND, 49, 92-101.
8. Filston,H.C., et al.,(1982), Estimation of postoperative fluid requireme nts in infants and children. ANNALS OF SURGERY, 196, 76-81.
9. Wiederhelm,C.A.,(1968), Dynamics of transcapillary fluid exchange. JOURNAL OF GENERAL PHYSIOLOGY, 52, part2, 29s-63s.
10. Landis,E.M.,(1964), Heteroporosity of the capillary wall as indicated by cinematographic analysis of the passage of dyes. ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 116, 765-773.
11. Grotte,G.,(1956), Passage of dextran molecules across the blood-lymph barrier. ACTA CHIRUGICA SCANDINAVICA, supplement 211, 5-84.
12. Chang,R.L.S., et al.,(1975), Permselectivity of the glomerular capillary wall: III. Restricted transport of polyanions. KIDNEY INTERNATIONAL, 8, 212-218.
13. Renkin,E.M., Robinson,R.R.,(1974), Glomerular filtration. NEW ENGLAND JOURNAL OF MEDICINE, 290, 785-792.
14. Brigham,K.L., Owen,P.J.,(1975), Mechanism of the serotonin effect on lung transvascular fluid and protein movement in awake sheep. CIRCULATION RESEARCH, 36, 761-770.
15. Granger,D.N., Taylor,A.E.,(1980), Permeability of intestinal capillaries to endogenous macromolecules. AMERICAN JOURNAL OF PHYSIOLOGY, 238, H457-H464.
16. Parving,H.H., et al.,(1974), Increased transcapillary escape rate of albumin, IgG, and IgM during Angiotensin-II-induced hypertension in man. SCANDINAVIAN JOURNAL OF CLINICAL AND LABORATORY INVESTIGATION, 34, 111-118.

17. Poulsen,H.L.,(1974), Interstitial fluid concentrations of albumin and Immunoglobulin G in normal men. SCANDINAVIAN JOURNAL OF CLINICAL AND LABORATORY INVESTIGATION, 34, 119-122.
18. McNamee,J.E., Staub,N.C.,(1979), Pore models of sheep lung microvascular barrier using new data on protein tracers. MICROVASCULAR RESEARCH, 18, 229-244.
19. Landis,E.M.,(1930), Micro-injection studies of capillary blood pressure in human skin. HEART, 15, 209-228.
20. Guyton,A.C., et al.,(1971), Interstitial fluid pressure. PHYSIOLOGICAL REVIEWS, 51, 527-563.
21. Bevan,D.R.,(1980), Colloid osmotic pressure. ANAESTHESIA, 35, 263-270.
22. Noddeland,H.S., et al.,(1980), Interstitial colloid osmotic pressure in patients with hypoproteinemia (abstr.). ACTA PHYSIOLOGICA SCANDINAVICA, 108, 16A.
23. Skillman,J.J., et al.,(1967), Plasma protein kinetics of the early transcapillary refill after hemorrhage in man. SURGERY, GYNECOLOGY & OBSTETRICS, 125, 983-996.
24. Marty,A.T., Zweifach,B.W.,(1971), Splanchnic contribution to transcapillary refill after hemorrhagic shock. ANNALS OF SURGERY, 174, 131-136.
25. Moore,F.D., et al.,(1966), Hemorrhage in normal man. I. Distribution and dispersal of saline infusions following acute blood loss: Clinical kinetics of blood volume support. ANNALS OF SURGERY, 163, 485-504.
26. Diana,J.N., Heesch,C.M.,(1987), Neural modulation of transcapillary exchange of fluid and solutes in whole-organ preparations. CIRCULATION RESEARCH, 61, suppl. II, 12-19.
27. Taylor,A.E.,(1981), Capillary fluid filtration. Starling forces and lymph flow. CIRCULATION RESEARCH, 49, 557-575.
28. Tullis,J.L.,(1977), Albumin 2. Guidelines for clinical use. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 237, 460-463.
29. Schüpbach, et al.,(1978), Perfusate oncotic pressure duing cardiopulmonary bypass. Optimum level as determined by metabolic acidosis, tissue edema, and renal function. VOX. SANG., 35, 332-344.
30. Lundsgaard-Hansen,P., Blauhut,B.,(1988), Die Beziehung von Hypoxie und Ödem in Darmwand und Haut zum kolloidosmotischen Druck. DER ANAESTHESIST, 37, 112-119.
31. Stein,L. et al.,(1975), Pulmonary edema during volume infusion. CIRCULATION, 52, 483-489.

Chapter 14.2

PROPERTIES OF INTRAVENOUS FLUIDS

There are two basic types of intravenous fluids in clinical use, colloids and crystalloids. Crystalloid solutions are solutions of salts or small molecules with a molecular weight of less than 1000-2000 Daltons, while colloidal solutions are solutions of macromolecules such as starches, gelatins, dextrans, and proteins.

CRYSTALLOID SOLUTIONS

These are solutions of salts or molecules with a molecular weight less than 1000 Daltons. Solutions that fit into the latter category are solutions of electrolytes, fructose, sorbitol, glucose (dextrose), amino-acids and lipids.

Their final volume of distribution, and hence long-term effect on systemic haemodynamics, is determined by the nature of the molecules dissolved in them. As these fluids are electrolyte solutions, or solutions of organic molecules with a molecular weight less than 1000, they rapidly diffuse out of the capillaries to distribute throughout the ECFV. Redistribution from the intravascular compartment to the whole of the ECFV is a process which is essentially complete 5 minutes after infusion of a given volume of any of these solutions [1,2,3,50]. The amount of fluid that then subsequently remains in the blood is dependent on the relative volume of the plasma to the total body ECFV. Table 14.1.1 shows that the plasma volume is about 20% of the ECFV. Therefore it is not surprising that clinical investigation also shows that the volume of such crystalloid solutions remaining in the circulation 5 minutes after completion of a very rapid intravenous infusion is indeed about 20% of the infused volume [1,3,4]. Any subsequent changes of plasma and ECFV are dependent on the nature of the solute in the fluid infused, the rate of excretion of water and ions, as well as the rate at which any organic molecules are metabolized.

1. Glucose solutions.

Clinically important properties.

a. 5% glucose is the most common glucose solution in clinical use. It contains 50 gms glucose per liter of solution, which is equivalent to a concentration of 5 gm/100 mls = 275 mmol/l. Rapid infusion may cause hyperglycaemia, especially in diabetic patients.

b. Infusion of a 5% glucose infusion in pregnant patients causes significant foetal hyperglycaemia and hyperinsulinaemia. If more than 350 mls of a 5% glucose solution is administered to the mother during caesarean section prior to delivery, the delivered baby has significant hyperinsulinaemia and hyperglycaemia at birth. After delivery the neonatal plas-

ma glucose concentration then falls rapidly as no new glucose is supplied by the placenta, and because plasma glucose concentration falls faster than the plasma insulin concentration, hypoglycaemia is likely. In fact hypoglycaemia almost invariably occurs by 2 hours after delivery in those infants whose mothers receive an infusion of 1000 mls of 5% glucose immediately prior to delivery [7].

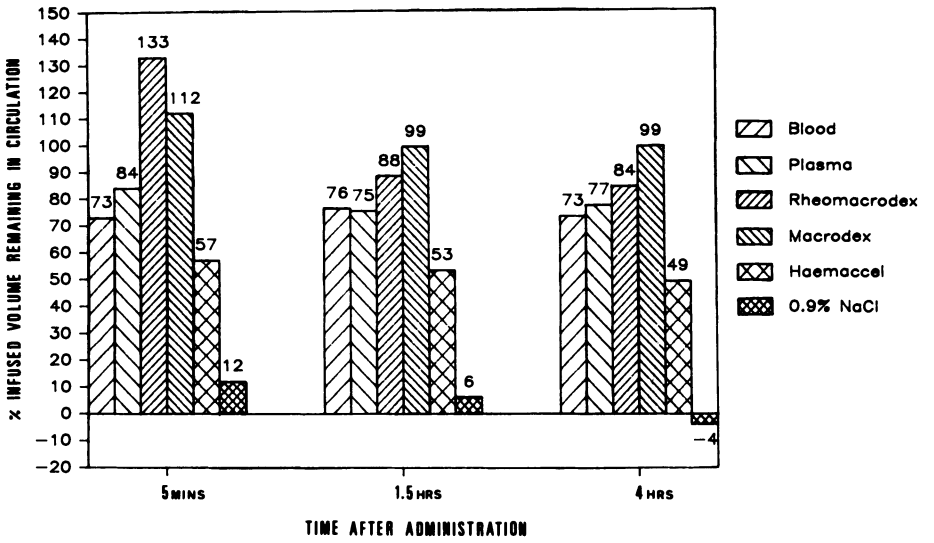

FIGURE 14.2.1. - This figure shows the results of serial blood volume measurements at various time periods in healthy persons after 500 mls of various colloidal solutions, or a 0.9% NaCl solution were infused subsequent to the withdrawal of 400 mls of blood [1]. It is obvious that all the colloidal solutions and blood cause a lasting elevation of blood volume, as 50% and more of the infused volume is still present in the circulation 4 hours after infusion. The 0.9% NaCl solution causes only a minimal and short lasting elevation of the blood volume.

c. Infusion of glucose solutions elevates the plasma insulin concentration. This in turn may cause significant hypokalaemia [8].

d. Infusion of 5% glucose at a rate of 600-800 mls in 40 minutes causes a significant degree of hyponatraemia due to a dilution effect [15]. Prolonged infusion of large volumes of 5% glucose over several days causes hyponatraemia if the urinary, skin, and faecal sodium losses are not replaced.

Distribution.

a. An infusion of 5% glucose initially distributes throughout the ECFV, but does not increase the ECFV above the volume of fluid infused, as the osmolality of the solution is the same as that of plasma. After metabolism of the glucose the osmolality of the extracellular fluid falls, as all that remains after metabolism of glucose is water and carbon dioxide. The

water is subsequently distributed throughout the TBW. As plasma volume is only 8% of the TBW the final effect on blood volume is minimal.

For example, a rapid intravenous infusion of 1,000 mls of a 5% glucose solution will have increased the plasma, and hence blood volume, by only 80 mls after the infusion is stopped. The real level of blood volume expansion is probably even less as the kidneys simultaneously eliminate some of the infused water.

b. If a hypertonic (>5%), solution of glucose is infused, the volume remaining in the circulation after about 5 minutes is still only 20% of the volume infused. But because intracellular movement of glucose takes some time, a situation arises in which the osmolality of the ECFV is temporarily elevated relative to the intracellular fluid. This causes movement of water down the osmotic gradient from inside cells to the ECFV. The result is a temporary increase of blood volume that is greater than that caused by 5% glucose.

Indications.

The main use of 5% glucose is as a source of glucose, or for rehydration after pure water loss. Hypertonic solutions are mainly useful as a source of energy.

2. Sodium chloride (NaCl) solutions.

Clinically important properties.

a. Solutions of NaCl are either isotonic relative to plasma, or hypertonic. Problems associated with their use are associated principally with their expansion of the ECFV. This manifests as a measurable increase of the pulmonary closing volume, and decreased pulmonary compliance after infusion of as little as one liter of 0.9% NaCl solution [9]. Presumably both these phenomena are a result of an increase in the pulmonary interstitial fluid volume. Pulmonary oedema may be caused by the infusion of large volumes of 0.9% NaCl [10] or Ringer's solutions [11], which both significantly elevate the ECFV.

b. Infusion of NaCl solutions, (e.g. Ringer's lactate, dextrose/saline, saline 0.9%), elevates the coagulability of blood both in-vitro and well as in-vivo [12]. In one study, only 7% of the patients who were given no more than a minimal volume of oral fluids postoperatively developed a deep venous thrombosis, while 30% of those patients administered "normal" perioperative volumes of Ringer's lactate and glucose/saline solutions developed a deep venous thrombosis [12].

c. Ringer's lactate solution may cause a variety of problems due to the presence of the sodium lactate.

i. Ringer's lactate solution causes a significant postoperative metabolic alkalosis if more than 1-2 liters of is administered peroperatively [13]. This is due to metabolism of the lactate and retention of the sodium ion [see chapter 13.3].
ii. Perioperative hyperglycaemia is significantly exacerbated by Ringer's lactate in patients with maturity onset diabetes mellitus [14].

Distribution.

a. The composition of the various sodium containing intravenous infusion fluids are shown in table 14.2.1. The volume of distribution for most sodium solutions whose sodium con-

centration is greater than 129 mmol/l is the ECFV. The duration of ECFV expansion is determined by the rate of sodium and water excretion. Further redistribution into cells is minimal as the intracellular sodium concentration is only 10% that of the ECFV.

b. Five minutes after stopping a rapid infusion of a 0.9% NaCl solution, the plasma and blood volume is only increased by a volume equivalent to 12% of the volume of 0.9% NaCl solution that was infused [1, and see fig. 14.2.1]. Little of the solution enters the intracellular compartment as sodium is actively pumped out of cells. Because of distribution throughout the ECFV, a 0.9% NaCl solution is useless for significant expansion of the blood volume, in addition to which the duration of the minimal degree of expansion it does cause is limited to somewhat more than 5 minutes [1]. Infusion of 1 liter only induces a temporary elevation of the blood volume of about 100-120 mls, which is insignificant in proportion to the volume infused.

c. After rapid infusion of lactated Ringer's solution (Hartmann's solution), the plasma or blood volume is elevated by a volume equivalent to only 20% of the volume infused [3,4]. As with 0.9% NaCl solution, the duration of the minimal blood volume expansion that it does induce is also short, being less than one hour [4].

d. A hypertonic (2400 mosm/l) NaCl solution is also distributed only within the ECFV. But because of the high osmolality of the solution, the ECFV becomes hyperosmolar and fluid is drawn into the ECFV from the intracellular fluid volume. This increases the ECFV by a greater volume than the volume infused. The systemic haemodynamic effects of an infusion of a hypertonic NaCl solution (2400 mosm/l) may persist for several hours until renal sodium excretion eliminates some of the infused sodium [5].

Indications.
a. The main use of 0.9% NaCl in anaesthetic practice should be mainly to replace extracellular fluid volume deficits.

b. The principal use of Ringer's solutions should, as with 0.9% NaCl, be mainly for replacement of extracellular fluid volume deficits.

c. The uses of hypertonic saline should be seen at present as offering an interesting alternative to the use of colloid solutions for blood volume replacement, as well as replacement of depleted body sodium stores. However the major disadvantage to their use for blood volume replacement is that the whole of the ECFV increases, not just the plasma volume. This means that clinically significant interstitial oedema may occur after infusion of large quantities of hypertonic saline solutions.

3. Mixed saline and glucose solutions.

The clinical problems associated with the use of glucose/saline solutions are the same as those for both glucose as well as saline solutions.

Distribution.

Various solutions which are a mixture of glucose and saline, or of Ringer's solution and glucose are in common clinical use. After distribution to the whole of the ECFV and

metabolism of the glucose, further distribution is determined by the concentration of sodium ion in these solutions. If the sodium concentration is lower than that in plasma or the extracellular fluid, then water diffuses into the cells until the extracellular osmolality is the same as that inside the cells.

Take the commonly used solution of 4% Glucose/0.18% NaCl as an example. Applying the above simple analysis, one arrives at the conclusion that 20% of an infused volume will distribute only within the ECFV (0.18% NaCl = 1/5th the sodium of 0.9% NaCl), and the remaining 80% will distribute throughout the total body water after metabolism of the glucose.

COLLOID SOLUTIONS

A colloid solution is a solution of macromolecules with a molecular weight greater than 10,000 Daltons. The colloidal solutions used in clinical practice are those of human plasma proteins, blood, dextran, gelatine, and hydroxyethyl starch. After intravenous infusion, the majority of the infused volume of any of these solutions remains in the intravascular compartment, as the mean molecular weights of most of the molecules in these solutions is greater than 30,000 Daltons. Capillary and venular endothelium is relatively less permeable to molecules with molecular weights above this level [see chapter 14.1 and figure 14.1.1]. Figure 14.2.3 shows the differences between various colloidal solutions as regards their blood volume increasing effect.

Table 14.2.3 also shows the pharmacokinetic elimination half lives, the water binding capacities, and other parameters of the various colloidal solutions in common clinical use. It should be noted that the pharmacokinetic elimination half life of the colloidal molecule concerned does not necessarily have any relationship to the duration of the blood volume expanding effect of the solution concerned. But it is of relevance when it comes to deciding how much, and how frequently a given colloidal solution may be administered, as excessive accumulation of some synthetic colloidal molecules should be avoided, e.g. the dextrans..

The main problems associated with the use of colloidal solutions are anaphylactic or anaphylactoid reactions, and bleeding tendencies. The frequencies of occurrence of clinically significant haemorrhagic and allergic reactions are shown in table 14.2.2.

1. Plasma and plasma protein solutions.

Preparations available.

The most commonly used and available human plasma protein preparations in clinical use are listed below.

a. Fresh citrated plasma. This is plasma which has been separated from the erythrocytes within 3 hours after collection. It may be stored at 4°C, but is more usually stored as frozen plasma at a temperature of -20 to -30°C so as to prolong the usable life. Because the plasma is not sterilized, the risk of disease transmission is the same as for blood.

b. Pasteurized plasma protein solution. This is a 4-5% solution of the proteins remaining after the coagulation proteins and blood cells have been removed. About 83% of the protein present is albumin, the rest being α- and ß-globulins. Because it is pasteurized at 60°C for 10 hours the chance of transmission of hepatitis and other diseases is minimal.

Table 14.2.1.
Composition of various commonly used synthetic intravenous fluids.

FLUID	pH	Na^+	K^+	Ca^{++}	Cl^-	Glucose (g/l)	Other ions or substances	Osmolality (mosm/l)
Glucose 5%	4.5					50		276
Glucose 4% + 0.18% NaCl	4.5	31			31	40		286
NaCl 0.9%	5	154			154			304
Ringer's solution	5	147	4	4.5	155.5			311
Ringer/glucose 5%	4.5	147	4	4.5	155.5	50		589
Ringer's lactate (Hartmann's soln.)	7	130	4	2.7	109.7		Lactate 27 mmol/l	273.4
$NaHCO_3$ 8.4%	8	1000					HCO_3^- 1000 mmol/l	2000
Haemaccel	7.3	145	5.1	6.25	145		Gelatin 35 g/l	334
Gelifundol	7.0	154			154		Gelatin 56 g/l	
Plasmagel	5.8	120		13.5	147		Gelatin 30 g/l	
Physiogel	7.2	120	0.4	12	125		Gelatin 42 g/l	
5% Dextran-40 in - Glucose 5% - NaCl 0.9% (e.g. Isodex)		 154			 154	 50 	 Dextran 50 g/l Dextran 50 g/l	 360 388
10% Dextran-40 in - Glucose 5% - NaCl 0.9% (e.g. Rheomacrodex)		 154			 154	 50 	 Dextran 100 g/l Dextran 100 g/l	 445 473
6% Dextran-70 in - Glucose 5% - NaCl 0.9% (e.g. Macrodex)		 154			 154	 50 	 Dextran 60 g/l Dextran 60 g/l	 334 362
Mannitol 20%							Mannitol 200 g/l	1100
Mannitol 10%							Mannitol 100 g/l	550

N.B. Ion concentrations in mmol/l unless otherwise stated.

Table 14.2.2.
Frequencies of clinically significant bleeding and allergic reactions occurring after administration of various colloidal solutions, expressed as percentage reactions per 100 infusions [18,19,20,21].

SOLUTION	All anaphylactic /anaphylactoid reactions	Clinically significant bleeding tendency
Plasma protein and albumin solutions	0.014%	0.001%
Dextran-40	0.013%	about 0.01%
Dextran-70	0.025%	about 0.01%
Gelatins	0.079%	$<<0.01\%$
Hydroxyethyl-starch	0.085%	about 0.01%

c. Purified human albumin. Human albumin is available as either a 5% or 20% solution. Because it is pasteurized, the risk of disease transmission is minimal.

Clinically important properties.
a. The main problem with all the plasma protein solutions is cost. They are considerably more expensive than the synthetic plasma volume replacing solutions.

b. Another major problem is the possibility of disease transmission. However this is more a problem with plasma protein preparations that have not been pasteurized. Pasteurization destroys hepatitis A and B viruses as well as all other organisms, e.g. treponema pallidum, the Acquired Immune Deficiency (AIDS) virus, etc.

c. Anaphylactic and anaphylactoid reactions occur with a frequency of about 14 per 1000 units of plasma protein solutions administered. This is a very low rate, only equalled by dextran-40, but without as high a chance of clinically significant bleeding disorders occurring [see table 14.2.2].

d. Infusion of large quantities of albumin (150 gms albumin), can cause an alteration in blood coagulation, although the clinical significance of this is uncertain as a clinically significant bleeding tendency does not occur when these amounts of albumin are administered intraoperatively [22].

Distribution.
A 4-5% solution of pasteurized plasma protein solution, or a 5% albumin solution have the same blood volume expanding effect as plasma [23]. These solutions all cause a long lasting elevation of plasma volume [fig. 14.2.1 and table 14.2.3].

Indications.
For replacement of plasma and blood volume losses, and for treatment of hypoproteinaemia.

2. Gelatine solutions.

Types of preparation available.
These are listed in table 14.2.1.

Clinically important properties.
a. Gelatine is made by heating collagen until the molecules break down into polypeptide chains with molecular weights in the range 17,000-18,000 Daltons. Aqueous solutions of gelatine gel at room temperature, but this can be prevented by crosslinking the gelatine molecules with urea as in Haemaccel™, or with dialdehyde glyoxal as in Gelifundol™. Or the gelatine molecules may be modified by removing the $-NH_2$ groups from the terminal aminoacids and replacing them with -COOH groups as in Plasmagel™ and Physiogel™. The molecular weights of the resulting molecules range between 17,000-100,000 Daltons, with a mean molecular weight of 30,000-35,000 Daltons [24].

b. Elimination of gelatine molecules from the body is primarily by urinary excretion as the molecular weight of most of the molecules is under 60,000 Daltons. After 2 days about 85% of a given dose is excreted unchanged in the urine, while 10% is excreted unchanged in the faeces, and only 3% is metabolized [25,44]. The pharmacokinetic elimination half life of gelatine molecules in a Haemaccel™ solution is 8.4 hours in patients with normal renal function, and does not increase above this even in patients with renal dysfunction, until the glomerular filtration rate decreases below 30 mls/min (Normal > = 90 ml/min), i.e. the creatinine clearance is less than one third of its normal value [45].

c. Renal function is not adversely affected by infusion of 500-1000 mls of a gelatine solution, even when administered to shocked patients with minimal urinary production [26,27]. Administration of 500 mls of a gelatine solution to patients requiring renal dialysis has not been shown to worsen the remaining renal function [45]. But because the elimination half life of these solutions is increased in patients with severe renal dysfunction (creatinine clearance $< 1/3^{rd}$ normal), the possibility of accumulation does arise during chronic administration.

d. Clinically significant haemostatic defects are seldom, if at all, observed as a result of administration of gelatine solutions, even when they are administered in quantities as large as 10-15 liters per 24 hours [20].

e. While gelatins do cause some degree of erythrocyte aggregation [28], they do not interfere with blood group typing or crossmatching for transfusion [29].

f. The main problem with the gelatine solutions is the relatively high frequency of anaphylactic/anaphylactoid reactions that they cause. This is in the order of 7-8 reactions per 100 infusions administered [see table 14.2.2], which is quite high, and is one of the major impediments to wider use of these solutions.

Distribution.

Most of the solutions in clinical use are solutions of molecules with a mean molecular weight of 30,000-35,000 Daltons, and so half the molecules have a molecular weight less than this. Accordingly it is not surprising in view of the relative permeability of the capillary and venular endothelium to molecules with a molecular weight less than 30,000, that about 10-20% of an administered dose diffuses into the interstitium [25,44]. This accounts for the fact that only 60% of the infused volume remains in the circulation 5 minutes after termination of an infusion of Haemaccel™ [1]. For practical purposes the volume of distribution may be taken as being somewhat less than twice the blood volume.

Indications.

The principle use of gelatine solutions is as a blood and plasma volume replacement fluid.

3. Dextran solutions.

Preparations available.

See table 14.2.1 for examples of some commonly available solutions.

Clinically important properties.

a. Dextran molecules are large branched chain polysaccharide molecules produced by the action of the bacterium Leuconostoc mesenteroides on sucrose. Molecules are produced with a broad spectrum of molecular weights. The dextran solutions in current clinical use contain molecules with a mean molecular weight of 40,000 Daltons (dextran-40), or molecules with a mean molecular weight of 70,000 Daltons (dextran-70). Mean molecular weight means that one half of the molecules in each of these solutions has a molecular weight greater than, and the other half less than, the mean molecular weight. In the case of the dextran-70 solutions the molecules have weights varying from 20,000 to 200,000 Daltons, and for the dextran-40 solutions the molecular weights vary between 10,000 to 100,000 Daltons. This has clinical implications for the excretion of these molecules.

b. After infusion of 500 mls of a 10% solution of dextran-40, about 50% of the dextran is been excreted in the urine by 3 hours, while it takes longer than 24-48 hours before 50% of the dextran contained in 500 mls of a 6% solution of dextran-70 is excreted in the urine [6]. The renal threshold for excretion of dextran molecules is about 50,000-70,000 Daltons [see fig. 14.1.1]. Dextran molecules with molecular weights greater than the renal threshold are unable to be excreted in the urine, and so the molecular weights of the molecules remaining steadily rises as urinary excretion of low molecular weight molecules continues [25]. Dextran remaining in the body is metabolized by enzymes in the liver, spleen and kidneys, the end product of metabolism being carbon dioxide and water. The rate of dextran metabolism is about 70 mg dextran/kg body weight/day [30].

c. Dextran molecules are highly electrically charged molecules and so are attracted to, and coat blood and endothelial cells. This reduces their surface charges, and because of this dextran solutions cause erythrocytes to aggregate and form rouleaux and irregular aggregates [37]. This increases blood viscosity, but is a problem that only occurs with dextran preparations containing dextrans with a mean molecular weight greater than 60,000-80,000 Daltons, and is really only clinically significant for dextrans with a molecular weight greater than 100,000 Daltons [31,33]. Aggregates may actually be so large as to cause microcirculatory infarction, especially in the liver and myocardium [32]. Dextran solutions of molecules with a molecular weights of 40,000 Daltons and less cause no erythrocyte rouleaux or aggregate formation in in-vivo studies [31].

Administration of dextran-40 solutions enhances microcirculatory blood flow by reducing the haematocrit and dilation of small blood vessels [33]. Reduction of the haematocrit reduces blood viscosity, an effect which is most pronounced in vessels with low flow velocities, i.e. venules arterioles, and capillaries [3].

d. Dextrans can cause erythrocyte rouleaux and aggregate formation. This can make crossmatching of blood difficult, as aggregation of red cells is used to indicate incompatibility to the test sera. But this is mainly a problem with the high molecular weight dextrans with a molecular weight > 100,000 Daltons [35]. This correlates well with their known erythrocyte aggregating effect [31,33]. Because dextran-40 only causes a minimal degree of red cell aggregation, and dextran-70 appears to cause only a slightly greater degree of aggregation [28], these solutions cause minimal problems with blood grouping and crossmatching [36].

e. One of the major problems with the dextrans is that their use is not infrequently associated with haemorrhagic problems. Dextran has a number of effects on primary haemostasis. Molecules of dextran coat the platelets as well as the vascular endothelium [37,38]. They reduce the plasma concentrations of fibrinogen, factor VIII and von Willebrand's factor, so producing a situation similar to von Willebrand's disease [40,41]. This functional deficit is in agreement with the reduction of platelet aggregation, metamorphosis and release of platelet factor-3 that dextran solutions also cause [37,39].

The critical dextran concentration above which a measurable reduction of platelet aggregating ability is observed, is a plasma dextran concentration of 30-50 gm/l [37]. This concentration is easily achieved. Consider the "average" 70 kg adult with a plasma volume of 2.8 liters. A plasma dextran concentration of 30 gm/l is achieved after infusion of 1.4 liters of a 6% solution of dextran-70 (e.g. 1.4 liters of Macrodex™). This is equivalent to 1-1.5 gm dextran/kg body weight. This corresponds well with the observation that no significant abnormality of haemostasis is able to be measured when dextran-70 is administered at a dose of less than 20 mls/kg (1.4 l/70 kg) [49]. However it should always be remembered that haemorrhagic problems may still occur in some patients at a dose of 20 mls/kg, as about 46% of adult patients develop a lengthened bleeding time after administration of only 1 liter of a dextran solution [40], and the bleeding time of dogs is significantly lengthened after more than 10% of the blood volume has been replaced with either dextran-40 or dextran-70 [42].

f. Because the elimination half life of dextran-40 is about 9-10 hours, it is usually recommended that no more than 1000 mls of a 10% dextran-40 solution be infused per day if this

Table 14.2.3.
Properties of various intravenous fluids [1,16,17,45].

FLUID	$T_{1/2e}$	Water binding (mls H_2O/ gm colloid)	Volume increase (% vol. infused)	Volume of distribn. (hours)	Duration of effect
Glucose 5%			5%	TBW	< 1 hour
NaCl 0.9%			10-12%	ECFV	< 1 hour
Ringer's lactate			10-12%	ECFV	< 1 hour
Gelatine (MW = 35000)	8.4-17 hrs	39	50-60%	2 x BV	> 4 hours
Dextran-40 (MW = 40000)	9-10 hrs	37	133%	BV	> 4 hours
Dextran-70 (MW = 70000)	24 hrs	29	112%	BV	> 4 hours
Plasma (Albumin MW = 67000)	5-10 days	17.4	84%	BV	> 4 hours
Whole blood			75%	BV	> 4 hours

$T_{1/2e}$ = pharmacokinetic elimination half life of the molecule.
Water binding = volume of water bound per gram of colloid.
Volume increase = percentage of volume of solution infused that remains in the circulation.
Duration of effect = duration of clinically useful blood volume replacement effect.

solution is to be regularly administered. Regular infusion of a greater quantity per day may cause haemorrhagic problems due to accumulation of dextran.

g. The use of dextrans is associated with a relatively high frequency of anaphylactoid/anaphylactic reactions [see table 14.2.2], although this appears to be confined more to dextran-70 than dextran-40. In fact the use of dextran-40 is associated with as low a frequency of allergic reactions as plasma.

h. One problem limiting the use of dextrans is the possibility of renal damage. Infusion of dextran solutions into normovolaemic humans and animals increases the urine production [46,48]. The urinary osmolality increases after dextran-40 infusion [47], but does not increase after infusion of dextran-80 [46], as the higher molecular weight dextran molecules cannot enter the glomerular filtrate. However the elevation of urine output is a consequence of the elevation of the cardiac output due to an increased blood volume, and not due to any osmotic effect of dextran molecules in the urine [47].

Administration of dextran solutions to hypovolaemic humans and animals has several deleterious effects. The urinary viscosity increases enormously, and the urinary output drops in hypovolaemic humans after the administration of dextran 40 at a dose of 1 gm/kg body weight [47]. In addition to this, animal studies show that the kidneys enlarge due to dilation of the tubules with thick viscous fluid [47]. Presumably this thick and viscous tubular fluid limits urinary flow in the tubules. There have been several reports of renal failure due to administration of dextran-40 to patients in established shock with oliguria [43]. Because of this it is advisable not to use dextran-40 for initial resuscitation of hypovolaemic patients, if other colloidal solutions are available, e.g. gelatines, plasma.

Distribution.

Dextran solutions are always hypertonic relative to plasma, because the dextran molecules are always dissolved in either a 5% glucose or a 0.9% NaCl solution. Accordingly it is not surprising that shortly after infusion the measured increase of blood volume is greater than the infused volume, as the now hypertonic plasma draws water into the circulation from both interstitium and the cells. Dextran-40 solutions have a greater blood volume elevating effect than do dextran-70 solutions [1, see also fig. 14.2.1]. This is because solutions of dextran-40 contain a greater number of dextran molecules per unit weight dextran than does dextran-70., and the dextran-40 solutions contain a higher concentration of dextran than do the dextran-70 solutions. The duration of the blood volume elevation induced by dextrans is almost as enduring as that caused by infusion of blood or plasma [1].

Indications.

The principal use of dextran solutions is as a plasma and blood volume replacing fluid.

REFERENCES

1. Ahnefeld, von F.W., et al.,(1965), Unterzuchungen zur Bewertung kolloidaler Volumenerzatzmittel. der ANESTHESIST, 14, 137-143.
2. Mithoefer,J.C., et al.,(1968), Effect of intravenous NaHCO3 on ventilation and gas exchange in normal man. RESPIRATION PHYSIOLOGY, 4, 132-140.
3. Moore,F.D., et al.,(1966), Hemorrhage in normal man. I. Distribution and dispersal of saline infusions following acute blood loss: Clinical kinetics of blood volume support. ANNALS OF SURGERY, 163, 485-504.
4. Hauser,C.J., et al.,(1980), Oxygen transport responses to colloids and crystalloids in critically ill surgical patients. SURGERY, GYNECOLOGY & OBSTETRICS, 150, 811-816.
5. Auler,J.O.C., et al.,(1987), Hemodynamic effects of hypertonic sodium chloride during surgical treatment of aortic aneurysms. SURGERY, 101, 594-601.

6. Arturson,G., et al.,(1964), The renal excretion of low molecular weight dextran. ACTA CHIRURGICA SCANDINAVICA, 127, 543-551.
7. Kenepp,N.B., et al.,(1982), Fetal and neonatal hazards of maternal hydration with 5% dextrose before caesarean section. LANCET, 1, 1150-1152.
8. Levinsky,N.G.,(1966), Management of emergencies. VI. Hyperkalemia. NEW ENGLAND JOURNAL OF MEDICINE, 274, 1076-1077.
9. Collins,J.V., et al.,(1973), Some aspects of pulmonary function after rapid saline infusion in healthy subjects. CLINICAL SCIENCE AND MOLECULAR MEDICINE, 45, 407-410.
10. Rackow,E.C., et al.,(1983), Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutins in patients with hypovolemic and septic shock. CRITICAL CARE MEDICINE, 11, 839-850.
11. Modig.,J.,(1986), Effectiveness of dextran-70 versus Ringer's acetate in traumatic shock and adult respiratory distress syndrome. CRITICAL CARE MEDICINE, 14, 454-457.
12. Janvrin,S.B., et al.,(1980), Postoperative deep vein thrombosis caused by intravenous fluids during surgery. BRITISH JOURNAL OF SURGERY, 67, 690-693.
13. Wilson,R.F., et al.,(1972), Severe alkalosis in critically ill surgical patients. ARCHIVES OF SURGERY, 105, 197-203.
14. Thomas,D.J.B., Alberti,K.G.M.M.,(1978), Hyperglycaemic effects of Hartmann's solution during surgery in patients with maturity onset diabetes. BRITISH JOURNAL OF ANAESTHESIA, 50, 185-187.
15. Dudley,H.F., et al.,(1954), Studies on antidiuresis in surgery: Effects of anesthesia, surgery and posterior pituitary antidiuretic homone on water metabolism in man. ANNALS OF SURGERY, 140, 354-367.
16. Klotz,U., Kroemer,H.,(1987), Clinical pharmacokinetic considerations in the use of plasma expanders. CLINICAL PHARMACOKINETICS, 12, 123-135.
17. Warren,J.V., et al.,(1944), Chemical, clinical and immunological studies on the products of human plasma fractionation. IX. The treatment of shock with concentrated human albumin: A preliminary report. JOURNAL OF CLINICAL INVESTIGATION, 23, 506.
18. Ljungstrom,K.G., et al.,(1983), Adverse reactions to dextran in Sweden 1970-1979. ACTA CHIRURGICA SCANDINAVICA, 149, 253-262.
19. Ring,J., Messmer,K.,(1977), Incidence and severity of anaphylactoid reactions to colloid volume substitutes. LANCET, 1, 466-469.
20. Lundsgaard-Hansen,P., Tschirren,B.,(1981), Clinical experience with 120,000 units of modified fluid gelatin. DEVELOP. BIOL. STANDARD., 48, 251-256.
21. Munoz,E.,(1987), Costs of alternative colloid solutions (dextran, startch, albumin). INTENSIVE CARE WORLD, 4, 12-17.
22. Lucas,C.E., et al.,(1982), Altered coagulation protein content after albumin resuscitation. ANNALS OF SURGERY, 196, 198-202.
23. Bertrand,J.J., et al.,(1959), Clinical investigations with a heat-treated plasma protein fraction - Plasmanate. VOX SANG., 4, 385.
24. Werner,F.M.,(1974), Dextranen of gelatines? NEDERLANDSE TIJDSCHRIFT VOOR DE GENEESKUNDE, 118, 1121-1131.
25. Rudowski,W., Kostrzewska,E.,(1976), Blood substitutes. ANNALS OF THE ROYAL COLLEGE OF SURGEONS OF ENGLAND, 58, 115-125.
26. Howard,J.M., et al.,(1955), The fate of dextran and modified gelatine in battle casualties with renal insufficiency. SURGERY, GYNECOLOGY & OBSTETRICS, 100, 207.
27. Moeller,J., Sykudes,A.,(1962), De Verträglichkeit von Haemaccel unter besonderer Berückzichtigung der Nierfunktion. DEUTSCHE MEDIZINISCHE WOCHENSCHRIFT, 87, 726.
28. Ehrly,A.M.,(1969), The effect of plasma substitutes on erythrocyte aggregation and blood viscosity. BIBLIOGAPHIA HAEMATOLOGIA, 33, 302-310.
29. Koop,C.E., Bullitt,L.,(1945), Gelatin as a plasma substitute; effect of gelatin infusion on subsequent typing and crossmatching of blood with method of eliminating phenomena of pseudoagglutination. AMERICAN JOURNAL OF MEDICAL SCIENCE, 209, 28.
30. Editorial, (1953), Metabolism of the plasma expanders dextran and polyvinypyrrolidine. NUTR. REV., 11, 281.
31. Stalker,A.L.,(1967), The microcirculatory effects of dextran. JOURNAL OF PATHOLOGY AND BACTERIOLOGY, 93, 191-201.
32. Stalker,A.L.,(1967), Histological changes produced by experimental erythrocyte aggregation. JOURNAL OF PATHOLOGY AND BACTERIOLOGY, 93, 203-212.

33. Hint,H.,(1968), The pharmacology of dextran and the physiological background for the clinical use of Rheomacrodex and Macrodex. ACTA ANAESTHESIOLOGICA BELGICA, no. 2, 119-138.
34. Burke,A.M., et al.,(1979), Effects of low molecular weight dextran on blood viscosity after craniotomy for intracranial aneurysms. SURGERY, GYNECOLOGY & OBSTETRICS, 148, 9-15.
35. Marston,N.,(1954), Cross-matching of blood in the presence of dextran. LANCET, 2, 688.
36. Roche,P., et al.,(1952), Effect of dextran on blood typing and crossmatching. BLOOD, 7, 373.
37. Weiss,H.J.,(1967), The effect of clinical dextran on platelet aggregation, adhesion and ADP release in man: In vivo and in vitro studies. JOURNAL OF LABORATORY & CLINICAL MEDICINE, 69, 37-46.
38. Harmer,D.S., et al.,(1962), Coating of vascular surfaces and cells. A new concept in prevention of intravscular thrombosis. CIRCULATION, 26, 690.
39. Berman,H.J.,(1964), Platelet agglutinability as a factor in hemostasis. BIBL. ANAT., 4, 736.
40. Alexander,B., et al.,(1975), Coagulation, hemostasis, and plasma expanders: a quarter century enigma. FEDERATION PROCEEDINGS, 34, 1429-1440.
41. Aberg,M., et al.,(1979), Effect of dextran on factor VIII (antihemophilic factor) and platelet function. ANNALS OF SURGERY, 189, 243-247.
42. Gollub,S., et al.,(1967), The bleeding tendency associated with plasma expanders. SURGERY, GYNECOLOGY & OBSTETRICS, 124, 1203-1211.
43. Feest,T.G.,(1976), Low molecular weight dextran: a continuing cause of acute renal failure. BRITISH MEDICAL JOURNAL, 2, 1300.
44. Köhler,H., et al.,(1982), Die Elimination von Hydroxyäthylstarke 200/0.5, Dextran 40 und Oxyploygelatine. KLINISCHE WOCHENSCHRIFT, 60, 293-301.
45. Köhler,H., et al.,(1978), Elimination of hexamethylene diioscyanate cross-linked polypeptides in patients with normal or impaired renal function. EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, 14, 405-412.
46. Bergström,J., et al.,(1959), The effect of intravenous infusion of large quantities of dextran solution on kidney function in man. SCANDINAVIAN JOURNAL OF CLINICAL & LABORATORY INVESTIGATION, 11, 82-96.
47. Bergentz,S.E., et al.,(1965), Diuresis and urinary viscosity in dehydrated patients: Influence of Dextran-40,000 with and without mannitol. ANNALS OF SURGERY, 161, 502-586.
48. Murphy,G.P.,(1965), The renal effects of acute hemdilution with hydroxyethylstarch, dextran, or saline. SURGERY, GYNECOLOGY & OBSTETRICS, 121, 1325-1333.
49. Halonen,P., et al.,(1987), A study of haemostasis following the use of high doses of hydroxyethyl starch 120 and dextran in major laparotomies. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 31, 320-324.
50. Ginsburg,J.M., Wilde,W.S.,(1954), Distribution kinetics of intravenous radiopotassium. AMERICAN JOURNAL OF PHYSIOLOGY, 179, 63-75.

Chapter 14.3

PRINCIPLES OF FLUID THERAPY

EFFECTS OF TRAUMA AND SURGERY

Trauma and surgery have a profound effect on body metabolism, and renal handling of water and electrolytes. This has consequences for perioperative fluid and electrolyte management.

The effect of surgery and trauma is to cause renal water and sodium retention, an effect which is observable within minutes after surgery is commenced [1,2,3,8]. Renal sodium excretion is halved from the normal average rate for adults of 167 mmol/day, to about 83 mmol/day in adult postoperative patients [3]. The plasma sodium concentration does not fall or change significantly despite the water retention, unless large volumes of sodium poor fluids are administered perioperatively [4,5].

The plasma colloid osmotic pressure falls due to a reduction of the plasma albumin concentration [8].

The duration of the sodium and water retention, as well as the reduction of plasma albumin concentration, depends on the magnitude of the surgery performed, and may last as long as 2-7 days after major surgery [1,2,3,8].

There are a number of possible causes of postoperative or post-traumatic water and sodium retention.

1. Antidiuretic hormone (ADH).

ADH secretion increases perioperatively [4,6]. The magnitude of the ADH response to surgery is independent of the presence of hypovolaemia [4], and appears to be a direct consequence of surgical stress. Postoperatively, ADH secretion remains increased for up to 2-7 days depending on the magnitude of the surgery performed.

2. Adrenocortical hormones.

Plasma concentrations of glucocorticoid and other adrenocortical hormones, e.g. cortisol and aldosterone, are elevated for up to 2-7 days after major surgery [7]. This causes both sodium and water retention in this time period.

3. Sympathetic nervous activity.

Increased sympathetic nervous system activity decreases total renal blood flow and changes the intrarenal distribution of blood flow too. Flow in the vessels supplying the cortical nephrons is reduced to a greater degree than flow in the vessels supplying the juxtamedullary nephrons. As it is the juxtamedullary nephrons which have the long loops of Henle and vasae rectae, it is these nephrons that are most active in concentrating the urine, and so one result of these intrarenal changes in blood flow distribution is that water and

sodium retention occur [7]. The role of the sympathetic nervous system in perioperative sodium and water handling is shown by the effect of epidural anaesthesia sufficient to block the thoracic spinal roots T_6-T_{12}. This blocks the sympathetic nervous innervation of the kidneys, and significantly increases perioperative sodium excretion, but not water excretion, while the nerve blockade lasts [7].

EFFECTS OF SURGERY ON TRANSCAPILLARY EXCHANGE

Prior to reviewing clinical studies of the effects of surgery, and developing a model of perioperative fluid exchange and therapy, it is instructive to first view a simple model of the effect of surgery and trauma on transcapillary fluid exchange. This may be done using a model of which most people have some experience, and which despite its simplicity provides useful didactic insights into the substance of this chapter.

Consider the effects of letting a heavy stone fall on some unfortunate person's foot. The foot swells. This swelling does not occur immediately, but develops over several hours, being maximal after a day. The fluid causing the swelling is obviously brought to the foot by the circulation, fluid flowing out of damaged blood vessels into the traumatized tissues. If the swelling is not due to a massive haematoma, the fluid causing the swelling is either a plasma filtrate or plasma that has flowed into the interstitium. If the foot which has been maltreated in such a way does not become necrotic, this is evidence that capillary circulation is maintained in the swollen traumatized regions. After a day or two the swelling begins to subside due to resorbtion of oedema fluid into the circulation as healing of the damaged vascular endothelium occurs.

This is a very simple model, but it is also a very accurate description of the events occurring in a traumatized or operated region of the body. Surgery, and trauma which occur anywhere in the body have precisely the same effects. The various components of this model will be discussed in detail in this chapter along with their clinical consequences.

1. Traumatic and inflammatory oedema and "third space" losses.

Tissue damage due to surgery, trauma and inflammation may cause actual mechanical disruption of blood vessels in the affected tissues, and so blood leaks into surrounding tissues or into wounds. Lesser degrees of damage in directly, or indirectly traumatized or inflamed vessels may not cause mechanical disruption of capillary endothelium, but does increase capillary and venular endothelial protein permeability by up to 7-9 times normal [9]. In both situations the endothelial barrier to protein movement into the interstitium is no longer effective, with as a result the plasma proteins diffuse readily into the interstitium [10], and the intravascular and extravascular protein concentrations equalize.

Because the colloid osmotic pressure difference between plasma and the interstitium no longer exists, the only factor governing transcapillary fluid exchange are the fluid pressure differences between the interstitium and inside the capillaries and venules. Capillaries and venules are collapsible vessels kept open by the fact that the blood pressure inside these vessels is higher than the tissue pressure, and so plasma always flows out of damaged vessels. The rate at which plasma is lost from damaged vessels is determined by the magnitude of the damage and the intravascular-tissue pressure difference. That this is so is well demonstrated by the clinical observation that not all traumatized and operated tissues become necrotic as they would if the tissue pressures were higher than, or equal to, the capillary blood pressure. If plasma flows into the interstitium at a rate faster than the rate at

which it can be removed by the lymphatic system, interstitial oedema occurs. Interstitial oedema due to trauma or inflammation is called the "Third Space" [see fig. 14.3.1].

There are a number of properties of the third space which are well worth discussing because of their clinical relevance.

a. Type of fluid forming third space.

The fluid that flows through the damaged vascular endothelium into the interstitium to form the third space is plasma. This is well shown by the leakage of albumin into the interstitium of operated regions [10], and the demonstration of a postoperative plasma deficit which is not explained either by blood loss, or loss of plasma into wound exudate [11,13].

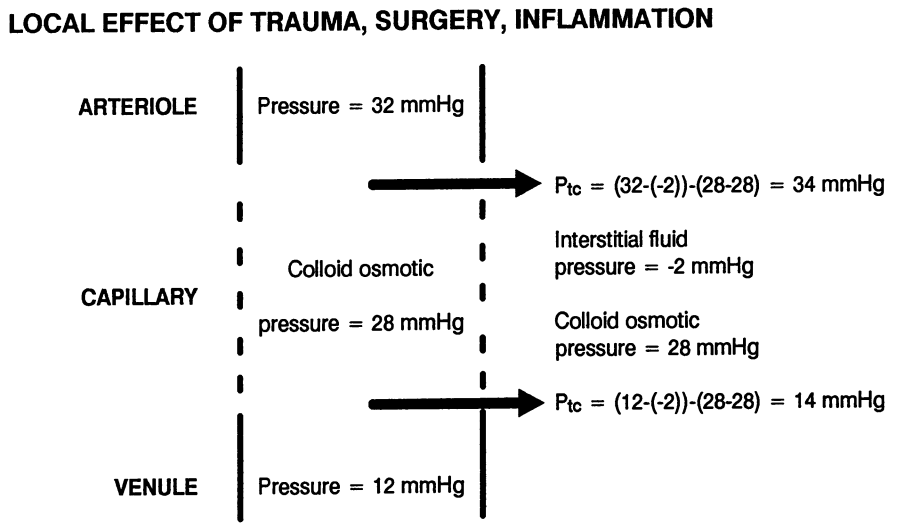

FIGURE 14.3.1. - Trauma, surgery and inflammation greatly increase the capillary and venular endothelial permeability to proteins. This means that plasma can flow into the interstitium of the damaged area. The result is that transcapillary fluid exchange is governed only by the intravascular to interstitial fluid pressure difference, as there is no longer any colloid osmotic pressure difference between the plasma and the interstitial fluid. In practice this means that plasma flows out of the damaged vessels causing interstitial wound oedema, the so-called "third fluid space" of surgical patients.

b. Interstitial oedema, the ECFV, and transcapillary refill.

Traumatic or inflammatory interstitial oedema only forms if the rate of plasma removal by lymphatics is less than the rate at which plasma flows into the interstitium through the damaged vascular endothelium. Because the integrity of the vascular endothelium is lost, no transcapillary refill occurs in an inflamed or traumatized region, as this is a process requiring a transcapillary colloid osmotic pressure difference. Because of this the plasma in traumatic or inflammatory oedema does not form a part of the functional ECFV, and so it may be considered to form a third fluid compartment, i.e. intracellular and extracellular fluid compartments, and a "third-space" due to a volume of non-functional traumatic or inflammatory oedema.

Measurements of the ECFV after major operations yield varying results. If large volumes of crystalloid solutions are administered perioperatively the postoperative ECFV is actually greater than the preoperative ECFV, because of ECFV expansion due to these fluids [12,14]. So it is not surprising that if the volume of fluid that is infused is taken into account, that the postoperative ECFV is the same as that measured preoperatively [12,14]. Some investigators have found a postoperative reduction of the ECFV postoperatively in comparison with the preoperative ECFV [15,16]. Such results may indicate a reduction of functional ECFV, which is a finding consistent with the volume of the ECFV involved in the wound oedema. Or it may be a be a manifestation of an incorrect ECFV measurement technique, as has been proposed by investigators who have failed to find any reduction of the ECFV postoperatively [12].

Table 14.3.1.
Volume of wound oedema related to the type of surgery.

Type of surgery	Plasma volume lost (mls)	% of total plasma volume
Thyroidectomy, parathyroidectomy, simple mastectomy [11].	0	0
Cholecystectomy, vagotomy, gastric resection, gastrojejunostomy, colon resection [11,13,31].	0-850 (mean=300)	0-30% (mean = 10%)
* Aortic reconstruction, cystectomy, pancreatic resection [18,19,20].	1100-2100	35-67%

* Derived from the volumes of albumin required to maintain normal oncotic pressure and haemodynamic function.

c. Duration of third space fluid loss.

Plasma continues to flow into the interstitium until the interstitial fluid pressure equals the intravascular pressures, and until healing and repair of the damaged vascular en-

dothelium has occurred. The situation of equal tissue and intravascular pressures is apparently never achieved clinically, as most wounds heal instead of becoming necrotic. Necrosis would occur if the intravascular and interstitial pressures were to equalize, as then there would be no pressure difference to keep the small collapsible arterioles, capillaries and venules open.

Clinical studies of patients undergoing major abdominal surgery show that the requirement for a fluid input above normal requirements in order to replace third space losses disappears after 24 hours [17,18,19]. It may be assumed from this that significant third space losses may continue as long as 24 hours postoperatively. This has obvious implications for the postoperative care of patients who have undergone major surgery.

d. Magnitude of operation & third space volume.

The volume of the third space losses varies with the operative site. The plasma volume deficit (i.e. third space loss), is minimal to absent after operations such as thyroidectomy, parathyroidectomy or mastectomy, but may be as much as 30% of the preoperative plasma volume as a result of operations such as cholecystectomy, or portocaval shunt [11, see also table 14.3.1].

e. Duration of operation & third space volume.

The volume of the third space loss is directly proportional to the duration of operation [11], as the longer the operation lasts, the greater the volume of tissue damaged.

2. Systemic effects.

Perioperative third space losses have two major consequences.

a. Third space fluid losses (i.e. plasma losses), causes hypovolaemia in patients undergoing major trauma or surgery without administration of intravenous fluids to replace the losses [2].

b. Plasma lost into the interstitium is normally replaced by fluid entering into the circulation by transcapillary refill from undamaged capillary beds. This is fluid which has a lower protein concentration than plasma, and accordingly the plasma protein concentration drops perioperatively [8,19], predisposing to the development of generalized perioperative interstitial oedema [see fig. 14.1.6].

A MODEL OF FLUID EXCHANGE DURING SURGERY & TRAUMA

Effective and safe intravenous fluid therapy of common clinical problems of fluid deficits (e.g. haemorrhage), or problems of redistribution (e.g. third space losses), requires that the clinician have a clinically usable model of these processes, an understanding of the effects of intravenously administered fluids, and of the basic physiology of the clinical disorders treated. All these factors have been discussed above, as well as in the previous chapters. They will now be unified in a simple clinical model able to be used for making therapeutic decisions for most problems of fluid balance arising during inflammatory diseases and in the perioperative period. A flow chart of this model is shown in figure 14.3.2.

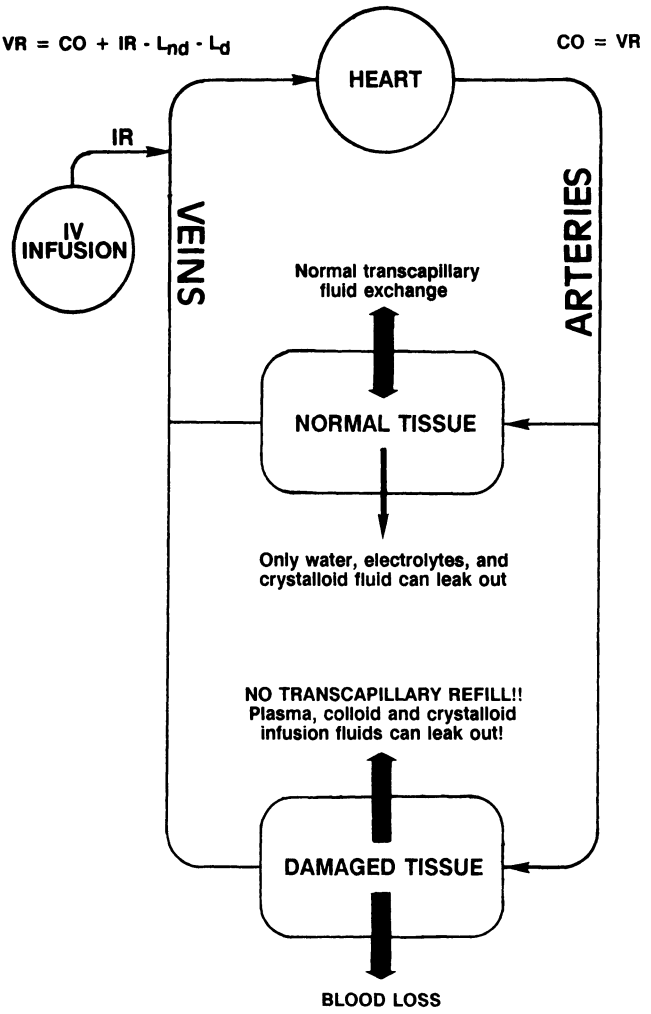

FIGURE 14.3.2. - This is a diagram of the model of transcapillary fluid exchange during trauma, surgery or inflammation. The symbols used in the equations in the upper part of the figure, as well as a full description of the model are to be found in the text.

1. Veins and arteries are impermeable.

The walls of veins and arteries are impermeable to all fluids and all molecules, regardless of molecular weight.

2. Permeability of normal venular and capillary endothelium.

Capillary and venular endothelium of normal undamaged tissue is relatively permeable to molecules with a molecular weight of less than 30,000 Daltons [see chapter 14.1]. Because of this, normal capillary and venular endothelium is totally permeable to crystalloid infusion fluids, is relatively impermeable to plasma and colloidal infusion fluids, and quite impermeable to cells such as erythrocytes etc.

3. Permeability of damaged venular and capillary endothelium.

The permeability of inflamed or traumatized venular and capillary endothelium is so increased that the endothelium of these vessels no longer presents a barrier to protein movement, and in fact is freely permeable to both colloid as well as crystalloid infusion fluids. Actual mechanical disruption of vessels only exacerbates this by permitting extravasation of cells too. Because the vascular endothelium no longer is a barrier to protein movement, the intravascular and interstitial protein concentrations in traumatized and inflamed tissues equalizes.

4. Third space losses.

Plasma is lost into inflamed or traumatized tissue, and this is the cause of traumatic or inflammatory oedema, "third space loss".

5. Transcapillary refill.

No transcapillary refill occurs from an inflamed traumatized region. Any transcapillary refill that occurs takes place in venules and capillaries in undamaged regions of the body.

6. Urinary losses.

If both blood pressure and cardiac output are high enough, the kidneys produce urine [see chapter 9.2]. Polyuria may cause significant loss of water. Urinary losses reduce the TBW [see urine composition table 14.1.3]. As the plasma volume is only about 8% of the TBW [see table 14.1.1], it is apparent that considerable quantities of urine must be lost before a significant reduction of plasma volume occurs.

7. Evaporation, and pure water losses.

a. Physiological losses.

An average adult in a temperate climate loses water from the respiratory tract at a rate of about 200-500 mls/day. Evaporative water loss also occurs from the skin, and this is also about 200-300 mls/day in temperate climates.

The rate of evaporative water loss increases with environmental temperature, and is given by the regression formula below for the environmental temperature range 21-35°C [21]. It is apparent from this formula that physiological evaporative water losses during the perioperative period are only significant at environmental temperatures of about 30°C, being about 2000 mls/day.

$$\text{EVAPORATIVE WATER LOSS(mls/day)} = 217 \times \text{TEMP}(^{\circ}\text{C}) - 4545 \quad .....(1)$$

b. Evaporation from operative wounds.

Pure water may also be lost by evaporation from wound surfaces. Here there is a situation where there is a raw warm wet wound surface exposed to a relatively cool operating

room environment. In situations where the surface so exposed is on the skin surface, e.g. burns, this loss is likely to be significant.

Perioperative evaporative water loss is unlikely to be very significant in adults during most operations, even major ones. Evidence for this contention is provided by the fact that the plasma sodium concentration never increases postoperatively, it always decreases, or at best remains the same. If evaporative water loss was significant, the plasma sodium would increase or remain the same, but it would never fall, as sodium does not evaporate. The effect of a given degree of evaporative water loss on the plasma sodium concentration can be calculated, making the assumption that loss of pure water decreases the TBW, and not the ECFV alone. As the ECFV is about 36.4% of the TBW, and the ECFV is about 20% of the body weight, one then gets equation 2.

$$[Na]_2 = \frac{0.2 \times WEIGHT \times [Na]_1}{0.2 \times WEIGHT - 0.364 \times LOSS_{water}} \quad .....(2)$$

$[Na]_1$ = initial plasma sodium concentration in mmol/l.
$[Na]_2$ = plasma sodium concentration after water loss in mmol/l.
WEIGHT = body weight in kg.
$LOSS_{water}$ = volume of pure water loss in liters.

Assuming an "average" 70 kg adult with an initial preoperative plasma sodium concentration of 140 mmol/l, the effect of a pure water loss of 1000 mls is to elevate the plasma sodium concentration to 144 mmol/l. This change is not great, but no such consistent small elevation of the plasma sodium concentration has ever been reported as a result of surgery. For this reason perioperative evaporative water losses from most wounds is likely to be insignificant in situations where the operating room is relatively cool, and where the surgeons operate within a body cavity.

c. Physiological effect of pure water loss.

Loss of water by evaporation is loss of pure water. This reduces the total body water, and because of this a very large amount of water indeed must evaporate before the plasma and blood volumes decrease to any significant degree in an adult.

The effect of evaporative water loss on blood and plasma volume is readily calculated. Plasma volume is about 8% of the total body water [see table 14.1.1]. Consider an evaporative water loss of 2000 mls. The reduction of plasma volume that such a large evaporative loss causes is 160 mls, hardly a major loss of blood volume in an adult. In practice this means that evaporative water losses of up to 2 liters or more in an adult has a minimal to absent haemodynamic effect. This is however not the case in children, in whom such an evaporative loss causes a proportionally greater percentage reduction of the blood volume.

8. Distribution of intravenously administered fluids.

All of the fluid infused into a central or peripheral vein enters the heart, regardless of the composition of the fluid, as no fluid can pass through the walls of normal veins. This fluid is in its turn pumped out of the left ventricle into the arterial system.

It is true that some of the fluid pumped out of the right heart may enter the interstitium of the lungs, especially if they are traumatized or inflamed. But this volume is minuscule in comparison to the rates of most intravenous infusions. If significant volumes of intravenously infused fluids were to enter the pulmonary interstitium, most patients would develop fulminant lethal pulmonary oedema as a result of intravenous infusions as the maximal human pulmonary lymphatic flow rate is about 200 mls/hour [22], which is much less than the rates of most peroperative intravenous infusions. The fact that this does not occur, means that essentially all the intravenously administered fluids enters the arterial system. Cardiac output and venous return may then be expressed by equations 3 and 4.

$$CO = VR + IR \quad \text{.....(3)}$$

and

$$CO = VR + IR - L_d - L_{nd} \quad \text{.....(4)}$$

CO = cardiac output in liters/min.
VR = venous return in liters/min.
IR = infusion rate in liters/min.
L_d = rate of blood and fluid loss into damaged tissues in liters/min.
L_{nd} = rate of fluid lost into non-damaged tissue in liters/min.

The above equations all look rather forbidding, but all that they say is that if blood volume is lost faster than it is replaced, the cardiac output will fall.

USE OF MODEL, AND HAEMODYNAMIC EFFECTS OF VARIOUS FLUIDS

The model described above is of considerable utility for explaining, as well as predicting, the effects of any fluid therapy administered after trauma, in the perioperative period, or for fluid balance problems caused by regional inflammation e.g. adult respiratory distress syndrome.

The results of fluid therapy with different intravenous infusion fluids vary with the type of solution infused [see figure 14.3.3].

1. Ringer's lactate or 0.9% NaCl.

Consider an intravenous infusion of Ringer's lactate or 0.9% NaCl solutions. When infused intravenously these fluids mix with the venous blood flowing to the heart, increasing the volume of blood returning to the heart per unit time. All of the fluid infused passes through the right heart, as none is able to be absorbed into any tissues from the peripheral or central veins. This increases the cardiac output [see equation 3].

The haemodynamic situation is improved by infusion of these fluids, and they are distributed through the arteries to both damaged and undamaged tissues. Normal capillary and venular endothelium is permeable to these fluids, and the vessels in the damaged regions are certainly permeable. Ringer's lactate or 0.9% NaCl enters the interstitium of both damaged as well as undamaged tissues, and the total ECFV increases [12,14]. Distribution of both of these solutions throughout the ECFV is essentially complete by 5 minutes after termination of a rapid infusion (e.g. 500 mls in 10 minutes) [see chapter 14.2]. Because

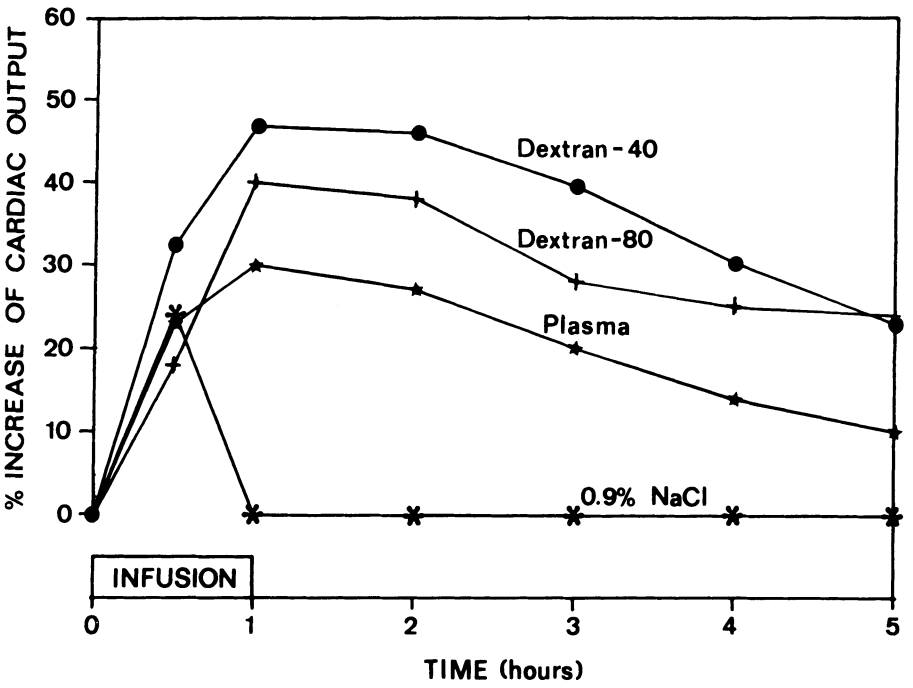

FIGURE 14.3.3. - The differences in both magnitude, and duration of clinical effect after intravenous infusion of 500 mls of various fluids in human patients over a period of one hour for treatment of postoperative hypovolaemic shock is well illustrated in this figure. This figure is a modified composite of those in reference 23.

the plasma volume is only 20% of the ECFV, only about 20% of the infused fluid remains in the circulation, the rest being distributed throughout the interstitium and the third space.

Indeed, clinical investigation has confirmed the above. The elevation of cardiac output due to infusion of 0.9% NaCl in patients with postoperative hypovolaemic shock is initially of the same order of magnitude as that due to plasma or blood etc, but subsides to insignificance within 30 minutes after redistribution has occurred [23,24, and see fig. 14.3.3]. It is apparent that if it is desired to replace a plasma volume deficit with either Ringer's lactate or 0.9% NaCl, that the systemic haemodynamic effects of a given volume of these fluids is only short lived, and that the infusion volume must be about 4-5 times the plasma volume deficit, if the plasma or blood volume deficit is to be replaced. In practice this is actually less, about 2-4 times the plasma volume deficit being required [15,17,18,20].

The use of crystalloid solutions not only means that large volumes must be infused for only a temporary haemodynamic improvement, but also that interstitial swelling occurs when they are used in significant quantities. For example, consider a perioperative infusion of 3 liters of 0.9% NaCl or of Ringer's lactate in an average 70 kg person. At best, only 750 mls remains in the plasma, while the rest of the infused volume is distributed throughout the ISFV. The ISFV in a person of this weight is about 10.5 liters, which means that the addition of an extra 2.25 l increases the ISFV by 21%. This is a considerable elevation of the

ISFV, and is clinically significant. Some of the problems reported after perioperative infusion of 3-5 liters of Ringer's lactate and 0.9% NaCl in adults are listed below.

- Increased Vd/Vt (dead space/tidal volume ratio) [17].
- Increased (A-a)D_{O2} [17,18,20,24].
- Increased chance of pulmonary oedema [18,25].
- Peripheral oedema [18,19].

Table 14.3.2.
Replacement fluids indicated for various types of fluid losses.

Fluid lost	Replacement fluid indicated
WATER	- Glucose 5%, Glucose/Saline solutions.
ECFV	- Ringer's solution, 0.9% NaCl.
PLASMA	- Plasma. - Plasma protein, dextran, and gelatin solutions.
BLOOD	- < = 10-15% blood volume - replace loss with a plasma substitute, e.g. gelatin, dextran solutions. - > 10-15% blood volume - replace loss with blood.

2. 5% glucose solution.

The situation here is much the same as for 0.9% NaCl or Ringer's lactate, except that the final volume of distribution is the TBW. This means that the elevation of plasma volume is even less than that due to an equivalent volume of 0.9% NaCl or Ringer's lactate.

3. Colloid solutions.

The effects of infusion of a colloidal solution into traumatized patients, or those with a regional inflammatory disorder, e.g. adult respiratory distress syndrome, are quite different as is apparent from figures 14.3.2 and 14.3.3. These solutions also mix with the blood returning to the heart and elevate the venous return and cardiac output, (CO = VR + IR). The reason for the different duration of haemodynamic effect is their volume of distribution. Normal undamaged capillary and venular endothelium is relatively impermeable to molecules with a molecular weight greater than 30,000 Daltons [see chapter 14.1]. Accordingly little of the infused colloid solution enters the interstitium of normal tissue. But the vascular endothelium of damaged tissues is very permeable to all molecules regardless of molecular weight, and so some of the infused fluid enters the interstitium of the damaged

region. If the volume of traumatized or inflamed tissue is not large in proportion to the body volume, the majority of the infused volume of a colloid solution remains in the blood. The plasma volume remains elevated, and an enduring elevation of blood volume and cardiac output for a given volume of infused fluid are the result of the infusion of a colloid solution to a hypovolaemic person. In practice the volume of a colloidal solution required to restore a given plasma volume deficit is about equal to the volume of plasma deficit.

As the ISFV of normal undamaged tissue does not increase when colloidal fluids are used to restore plasma volume deficits in perioperative or traumatized patients, the problems associated with an excessive ISFV, i.e. interstitial oedema, do not really arise [17,18,19,20,24,25].

CLINICAL INDICATIONS FOR VARIOUS INTRAVENOUS FLUIDS

The above discussion points to really only one system of efficiently replacing fluid losses. Replace any fluid losses with a similar fluid, or a substitute which is distributed throughout the same volume in the body and can perform the same function [see table 14.3.2].

ADULT RESPIRATORY DISTRESS SYNDROME (ARDS)

Much is spoken and written about ARDS because it is a serious condition with a high mortality which varies between 20-83% [28]. ARDS is the result of traumatic or inflammatory oedema of lung tissue, just as perioperative, traumatic, or inflammatory oedema is oedema of other tissues. Unlike traumatic or inflammatory oedema elsewhere in the body its course is readily followed by serial chest X-rays, arterial blood gases, and the pressures in the vessels entering and leaving the lungs are easily measured. Its location makes it a relatively easily studied form of traumatic or inflammatory oedema.

The same colloid osmotic and fluid pressure forces regulate the flow of fluid into and out of pulmonary interstitium as in all other tissues. Pulmonary interstitial fluid volume begins to increase when the left atrial pressure, (a measure of pulmonary venous pressure), is greater than 23 mmHg in normal lungs, and this critical pressure is reduced by hypoalbuminaemia [26]. Such an increase in interstitial fluid volume only occurs when the rate of fluid flow into the interstitium into the interstitium exceeds the rate of interstitial fluid removal by pulmonary lymphatics. The estimated maximum rate of pulmonary lymphatic flow in normal human lungs is thought to be about 200 mls/hour [22].

Because the capillary and venular endothelium in damaged regions of lung is permeable to proteins regardless of molecular weight, the volume of interstitial fluid in patients with ARDS is independent of the plasma colloid osmotic pressure [27,32]. In other words the ARDS affected lung regions behave in precisely the same way as any other traumatized or damaged tissue. It is apparent that therapy of patients with ARDS with albumin concentrates in the hope of reducing the extravascular lung water in the affected lung regions is ineffective. However it is effective in reducing extravascular lung water in normal regions of the lung, especially in hypoalbuminaemic patients [22].

THE "COLLOID-CRYSTALLOID" NON-CONTROVERSY

No mention has as yet been made of the so-called "colloid-crystalloid controversy". The controversy is about whether to replace inflammatory or traumatic plasma volume

deficits with crystalloid or colloid infusion fluids. In the opinion of this author this is a non-controversy, as has been made evident by the discussion of the relative effects of crystalloid and colloid fluids in the preceding chapters.

The volumes of crystalloid solutions required to replace a given plasma loss is about 2-4 times greater than the volume of plasma lost. Because these solutions are distributed throughout the ECFV, such volumes cause an increase of the whole body ISFV with all the consequences of this. Furthermore, as their distribution throughout the ECFV is essentially complete within 5-15 minutes their haemodynamic and blood volume replacing effects are short lived. In contrast to this, the colloid solutions are distributed only within the blood volume, and the interstitium of the regions of damaged tissue. Because of this the volume required to replace a given volume of plasma or blood is only slightly greater, or equal to the volume lost. The haemodynamic and blood volume increasing effect is also greater in comparison to crystalloids, and is more enduring, lasting some hours. But colloidal solutions are associated with an increased morbidity due to histamine release, anaphylactic and anaphylactoid reactions, bleeding problems etc.

The relative merits of these two forms of therapy reduce to the simple question of which is more effective and associated with the least clinical problems. The conclusions of one researcher in this field, Dr W.C.Shoemaker are particularly relevant. He stated in one paper, "With regard to the cost problem, albumin does cost more than saline solution, but 1 day in the intensive care unit costs the equivalent of 30-50 units of albumin, and if the patient gets well faster and has less complications (especially less adult respiratory distress syndrome), certainly colloids are more cost-effective" [29]. Cost is used as a determining factor because the more care a person requires due to ineffective fluid therapy, the more the management of that person costs. These costs are those of the time of nurses, physicians, complications due to hypovolaemia, a possible requirement for admission to a more expensive higher care unit for postoperative management, and possibly a longer stay in hospital after operation due to complications arising from ineffective management. This conclusion [29] is supported by other studies [17,18,20,24,25], which have also shown that infusion of crystalloid solutions is less effective than infusion of colloidal solutions for replacement of plasma and blood volume deficits.

As to the question of which is the best colloid solution to use, one large study done to compare the cost effectiveness of various colloid solutions came to the conclusion that dextran-40 solutions were the cheapest colloidal solution to use. This cost-efficacy analysis also took account of the cost of the complications associated with the use of various colloidal solutions such as dextrans, albumin, hydroxyethyl starch, and gelatine solutions [30].

In conclusion, the most effective fluid therapy is infusion of a fluid that does no more than replace the deficit for which it is administered.

REFERENCES

1. Mackenzie,A.I., Donald,J.R.,(1969), Urine output and fluid therapy during anaesthesia and surgery. BRITISH MEDICAL JOURNAL, 3, 619-622.
2. Irvin,T.T., et al.,(1972), Plasma-volume deficits and salt and water retention after surgery. LANCET, 2, 1159-1162.
3. Quesne,le L.P., et al.,(1953), Postoperative water and sodium retention. LANCET, 153-158.
4. Sinnatamby,C., et al.,(1974), Antidiuretic hormone response to high and conservative fluid regimes in patients undergoing operation. SURGERY, GYNECOLOGY & OBSTETRICS, 139, 715-719.
5. Singh,C.M., et al.,(1968), Why does the plasma sodium level fall after surgery? BRITISH JOURNAL OF SURGERY, 55,858.

6. Schrier,R.W., et al.,(1979), Osmotic and nonosmotic control of vasopressin release. AMERICAN JOURNAL OF PHYSIOLOGY, 236, F321-F332.
7. Bevan,D.R.,(1973), The sodium story: Effects of anaesthesia and surgery on intrarenal mechanisms concerned with sodium homeostasis. PROCEEDINGS OF THE ROYAL SOCIETY OF MEDICINE, 66, 1215-1220.
8. Moore,P.J., Clark,R.G.,(1982), Colloid osmotic pressure and serum albumin following surgery. BRITISH JOURNAL OF SURGERY, 69, 140-142.
9. Landis,E.M.,(1964), Heteroporosity of the capillary wall as indicated by cinematographic analysis of the passage of dyes. ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 116, 765-773.
10. Mouridsen,H.T., Faber,M.,(1966), Accumulation of serum-albumin at the operative wound site as a cause of postoperative hypoalbuminaemia. LANCET, 2, 723-725.
11. Robarts,W.M.,(1979), Nature of the disturbance in the body fluid compartments during and after surgical operations. BRITISH JOURNAL OF SURGERY, 66, 691-695.
12. Roth,E., et al.,(1969), Ringer's lactate solution and extracellular fluid volume in the surgical patient. ANNALS OF SURGERY, 169, 149-164.
13. Kragelund,E.,(1971), Loss of fluid and blood into the peritoneal cavity during abdominal surgery. SURGERY, 69, 284-287.
14. Shizgal,H.M., et al.,(1977), Body water distribution after operation. SURGERY, GYNECOLOGY & OBSTETRICS, 144, 35-41.
15. Roberts,J.P., et al.,(1985), Extracellular fluid deficit following operation and its correction with Ringer's lactate. ANNALS OF SURGERY, 202, 1-8.
16. Shires,T., et al.,(1961), Acute changes in extracellular fluids associated with major surgical procedures. ANNALS OF SURGERY, 154, 803-810.
17. Zetterstrom,H.,(1981), Albumin treatment following major surgery. II. Effects on postoperative lung function and circulatory adaptation. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 25, 133-141.
18. Virgilio,R.W., et al.,(1979), Colloid vs crystalloid resuscitation: Is one better? SURGERY, 85, 129-139.
19. Zetterstrom,H., Hedstrand,U.,(1981), Albumin treatments following major surgery. I. Effects on plasma oncotic pressure, renal function and periperal oedema. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 25, 125-132.
20. Skillman,J.J., et al.,(1975), Randomized trial of albumin vs. electrolyte solutions during abdominal aortic operations. SURGERY, 78, 291-303.
21. Kambal,A.,(1978), Evaporative water loss in adult surgical patients in the Sudan. BRITISH JOURNAL OF SURGERY, 65, 128-130.
22. Staub,N.C.,(1978), Pulmonary edema due to increased microvascular permeability to fluid and protein. CIRCULATION RESEARCH, 43, 143-151.
23. Carey,J.S., et al.,(1965), Comparison of hemodynamic responses to whole blood and plasma expanders in clinical traumatic shock. SURGERY, GYNECOLOGY & OBSTETRICS, 121, 1059-1065.
24. Hauser,C.J., et al.,(1980), Oxygen transport responses to colloids and crystalloids in critically ill surgical patients. SURGERY, GYNECOLOGY & OBSTETRICS, 150, 811-816.
25. Rackow,E.C. et al.,(1983), Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. CRITICAL CARE MEDICINE, 11, 839-850.
26. Jones,J.G., et al.,(1982), The physiology of leaky lungs. BRITISH JOURNAL OF ANAESTHESIA, 54, 705-721.
27. Feeley,T.W., et al.,(1985), Failure of the colloid oncotic-pulmonary artery wedge pressure gradient to predict changes in extravascular lung water. CRITICAL CARE MEDICINE, 13, 1025-1028.
28. Fein,A.M., et al.,(1982), Adult respiratory distress syndrome. BRITISH JOURNAL OF ANAESTHESIA, 54, 723-735.
29. Shoemaker,W.C., et al.,(1981), Comparison of the relative effectveness of colloids and crystalloids in emergency resuscitation. AMERICAN JOURNAL OF SURGERY, 142, 73-84.
30. Munoz,E.,(1987), Costs of alternative colloid solutions (dextran, startch, albumin). INTENSIVE CARE WORLD, 4, 12-17.
31. Rustad,H., et al.,(1966), Changes in blood volume, plasma volume and red cell volume following gastric resection. ACTA CHIRURGICA SCANDINAVICA, supplement 357, 127-132.
32. Pearl,R.G., et al.,(1988), Pulmonary effects of crystalloid and colloid resuscitation from haemorrhagic shock in the presence of oleic acid induced pulmonary capillary injury in the dog. ANESTHESIOLOGY, 68, 12-20.

Chapter 14.4

HYPOVOLAEMIA

Hypovolaemia may be defined as a volume-capacitance mismatch. That is, the blood volume is less than is required to fill the vascular system to a normal mean circulatory filling pressure. The vascular system is normally filled so that there is an intravascular pressure of about 7 mmHg during circulatory arrest, the "mean circulatory filling pressure", and it is this pressure which is the principal determinant of the rate at which right ventricular filling occurs during diastole, and hence cardiac output [9]. Decreased blood volume or vasodilation may reduce the mean circulatory filling pressure to such a degree that the cardiac output falls because of reduced venous return. From this it is apparent that two types of hypovolaemia may be defined, relative and absolute.

Absolute hypovolaemia.

This is hypovolaemia due to an actual reduction of the blood volume below normal. Baroreflex activity causes vasoconstriction, and increases both heart rate as well as myocardial conctractility. These processes tend to maintain arterial blood pressure and cardiac output unless their capacity to compensate is reduced or exceeded. Some of the causes of absolute hypovolaemia are listed below.

1. Haemorrhage.
2. Excessive plasma losses from burned or traumatized body surfaces, or losses into traumatic/surgical oedema (i.e. third space losses).
3. Excessive water losses, e.g. dehydration as a result of insufficient water intake, bowel obstruction with sequestration of fluid into intestines, excessive evaporative losses.

Relative hypovolaemia.

Vasodilation due to any cause increases the capacitance of the vascular system relative to the blood volume. Baroreflex activity increases both heart rate and myocardial contractility, processes which tend to maintain arterial blood pressure and cardiac output, unless their capacity to compensate for reduced cardiac filling pressures is reduced or exceeded. Once this latter point is exceeded, the cardiac output falls. Various common causes of relative hypovolaemia are listed below.

1. Spinal or epidural blockade cause vasodilation secondary to sympathetic nervous system blockade.
2. Vasodilator drugs increase the volume of the vascular system.
3. Overdosage of sedative and hypnotic drugs causes vasodilation by a direct effect on vascular smooth muscle, as well as a degree of depression of sympathetic nervous activity.

4. Normal induction, and anaesthetic doses of anaesthetic drugs may have a direct vasodilator effect as well as causing sympathetic nervous system depression [see chapter 2.1].

CLINICAL MANIFESTATIONS

The main effect of hypovolaemia is a reduction of the cardiac output as a result of reduced filling pressures. Extreme hypovolaemia causes circulatory shock. Baroreflexes minimize the effects of reduced intravascular pressures, by causing vasoconstriction, as well as increasing myocardial contractility and heart rate, all of which tends maintain the cardiac output and arterial blood pressure [see chapter 8.6]. The typical manifestations of hypovolaemia are;

- Tachycardia.
- Peripheral vasoconstriction.
- Reduced mean and systolic blood pressure together with a reduction of the pulse pressure.
- Reduced urine production.
- Air hunger.

Haemorrhagic hypovolaemia is the best studied form of hypovolaemia, and the clinical manifestations have been found to be related to the percentage blood loss [see table 14.4.1]. The critical percentage blood volume reduction in healthy adult humans before haemodynamic and other changes occur appears to be 10-15% of the blood volume [table 14.4.1]. All the changes are more profound after rapid rather than slow haemorrhage or hypovolaemia [4,5], in persons under general anaesthesia, and in those in whom the efficacy of the baroreflexes are reduced [see chapter 8.6].

PROBLEMS DUE TO HYPOVOLAEMIA

1. Reduced cardiac output and blood pressure.

If the blood volume deficit is greater than 10-15% of the normal blood volume, the cardiac output decreases significantly as a result of decreased filling pressures, despite increased heart rate and myocardial contractility. Simultaneously there is also a baroreceptor mediated elevation of systemic vascular resistance. Should the product of both cardiac output (CO) and systemic vascular resistance (SVR) decrease, the mean arterial blood pressure (MABP) also decreases, reducing the perfusion pressures of all organs. The relationship between these parameters is shown by equation 1.

$$\mathbf{MABP = CO \times SVR} \quad \text{.....(1)}$$

Hypoxic damage occurs if the MABP or cardiac output fall below critical levels for any organs [see chapter 2.7 for these critical values for brain, heart and kidneys].

Table 14.4.1.
Physiological effects of differing degrees of experimental haemorrhagic hypovolaemia in healthy young human volunteers.

% Reduction of blood volume	Clinical effect
< 10-15% [1,2,3]	- Reduced central venous pressure. - No change in pulse rate or systolic blood pressure. - Urine production decreases.
> 10-15% [3,4,5]	- Increased pulse rate. - Decreased cardiac output. - Decreased mean and systolic arterial blood pressures. - Decreased central venous pressures. - Increased systemic vascular resistance. - Decreased oxygen flux. - Decreased urine production.
> 30-40% [6]	- Circulatory shock.

2. Altered effects of drugs.

Hypovolaemia considerably modifies anaesthetic drug pharmacokinetics and pharmacodynamics, slowing the redistribution and elimination of drugs, as well as potentiating their cardiovascular depressant and hypnotic effects [see chapter 15.2]. These factors should always be taken into account whenever administering anaesthesia to hypovolaemic patients.

a. Effect of reduced blood volume.

Many drugs used in anaesthesia are administered intravenously, and are initially only distributed throughout the blood volume. If the blood volume is reduced, the initial concentrations of any intravenously administered drug will be higher than normal for any given drug dose. The initial concentration will in fact be elevated by the same percentage as the percentage blood volume deficit [see equation 2 below]. A consequence of this is that the minimum hypnotic and anaesthetic dosages of intravenous hypnotic agents are reduced by the same percentage [13].

$$\text{CONCENTRATION OF DRUG IN BLOOD} = \frac{\text{DOSE}}{\text{BLOOD VOLUME}} \quad \text{.....(2)}$$

As the initial plasma concentrations of intravenously administered drugs are initially higher than normal for a given dose, the cardiovascular depression induced by many anaesthetic drugs is more profound [see chapter 15.2]. This explains the extreme cardiovascular depression due to thiopentone [14], ketamine [14], and midazolam [15] when administered to hypovolaemic animals and humans.

b. Effect of reduced cardiac output.

A reduction of cardiac output means that any drug injected intravenously remains longer than usual in the so called central blood volume, i.e. blood which perfuses brain, liver, kidney, and heart. As an injected drug remains longer in the central blood volume, more time is available for the drug to diffuse into these tissues from the blood, and both a higher tissue concentration as well as a greater drug effect is achieved in these well perfused tissues. The effect of this is to enhance cardiovascular depressant and hypnotic effects of drugs that have these effects.

Some confirmation for these hypotheses is provided by human studies relating cardiac output to the pharmacokinetics and hypnotic dose of thiopentone. These have shown that the induction dosage of thiopentone is directly proportional to cardiac output [8]. Further confirmation is provided by primate studies using experimentally induced haemorrhagic shock, which demonstrate that lignocaine [7] and midazolam [15] redistribution and clearance are both slowed by hypovolaemia.

3. Modification of effects of anaesthetic techniques.

The cardiovascular depression due to some anaesthetic techniques is exacerbated by hypovolaemia.

a. Controlled ventilation.

During IPPV, the systolic arterial blood pressure rises at the beginning of inspiration due to the pressure of the inspiratory gases compressing the pulmonary vessels, so increasing left atrial return of blood and systemic cardiac output. Compression of the pulmonary vessels also increases the pulmonary vascular resistance, reducing the output of the right ventricle. During the later phase of inspiration, the arterial blood pressure falls due to a reduction of the cardiac output, which is secondary to the combination of decreased systemic venous return because of increased intrathoracic pressure, and increased pulmonary resistance, both of which reduce right ventricular output, and in turn reduce the left ventricular output. These changes are reversed during expiration. The effect of all these changes is to cause an inspiratory-expiratory variation of blood pressure and cardiac output [16].

Pulmonary blood volume and systemic venous return are both reduced by hypovolaemia, and so it is not surprising that the inspiratory-expiratory pressure variation is increased by hypovolaemia. In fact the inspiratory-expiratory systolic arterial pressure variation appears to be a relatively sensitive indicator of hypovolaemia, the magnitude of the variation being directly proportional to the degree of hypovolaemia [17].

Hypotension is particularly likely to occur as a result of the institution of IPPV in hypovolaemic patients. Cardiac output decreases with increasing respiratory minute volume in normovolaemic patients [18], and this effect is only exacerbated by the addition of PEEP [19]. Hypovolaemia exacerbates the reduction of cardiac output by further decreasing venous return and cardiac filling pressures.

b. Epidural and spinal anaesthesia.

Epidural and spinal anaesthesia cause vasodilation due to sympathetic nervous blockade in the regions blocked. High epidural and spinal blockade cause considerable vasodilation, inducing a relative hypovolaemia which of itself can cause a reduction of cardiac output and blood pressure. They can also reduce the cardiac output by blockade of the cardiac sympathetics if the block is high enough, (i.e. higher than T_4). Hypovolaemia, such as that due to haemorrhage, exacerbates the hypotension due to epidural [10] and spinal [11] anaesthesia.

Table 14.4.2.
The relationship of the shock index to the degree of hypovolaemia [6].

$$\text{"SHOCK INDEX"} = \frac{\text{HEART RATE (beats/minute)}}{\text{SYSTOLIC BLOOD PRESSURE (mmHg)}}$$

% Blood volume deficit	SHOCK INDEX
NORMOVOLAEMIA	0.5
< = 20-30%	< 1.0
> = 20-30%	> 1.0

CLINICAL AND LABORATORY ASSESSMENT OF HYPOVOLAEMIA

1. Clinical assessment.

Hypovolaemia is diagnosed by clinical history and physical examination. Many of the manifestations of hypovolaemia are the same regardless of the cause of hypovolaemia, and are shown in table 14.4.1.

a. "Shock index".

The magnitude of hypovolaemia may be assessed clinically by use of the "shock index" [6]. This is derived by dividing the pulse rate by the systolic blood pressure, and is directly related to the magnitude of hypovolaemia [see table 14.4.2]. It should always be remembered that while the shock index is a very useful clinical parameter, pulse rate and blood pressure are also affected by factors other than hypovolaemia alone. Factors such as anxiety, terror, old age, hypoxaemia, hypercarbia, neurological damage, and concurrent ingestion of medication such as ß-blocking drugs, etc, all affect the blood pressure and pulse rate. The

shock index as measured in any particular patient should always be interpreted in the light of these factors.

b. Other measures of the degree of hypovolaemia.

Pulse pressure, (i.e. systolic arterial pressure minus the diastolic arterial pressure), is reduced by hypovolaemia and is a useful clinical indicator of the presence of hypovolaemia.

The central venous and pulmonary artery pressures, as well as cardiac and urine output are also reduced by hypovolaemia.

These measurements all provide useful information as to the degree of hypovolaemia, and are of great use in guiding therapy.

Table 14.4.3.
Laboratory indicators of the type of hypovolaemia [12].

CAUSE OF HYPOVOLAEMIA	Haematocrit	Total protein	Plasma [Na]
Haemorrhage	↓	N	N
Pure plasma loss	↑	N	N
Extracellular fluid loss	↑	↑	N
Pure water loss	↑	↑	↑

"↑" = increase; "↓" = decrease; "N" = normal.
Total protein = total plasma protein concentration.
Plasma [Na] = plasma sodium concentration.

2. Laboratory diagnosis.

Laboratory investigations can only be used in conjunction with a clinical history and physical examination. The tests required are simple consisting only of measurement of the haematocrit, total plasma protein concentration, and plasma sodium concentration [12, see table 14.4.3].

MANAGEMENT OF HYPOVOLAEMIA

Therapy of hypovolaemia is aimed at restoring normal haemodynamics by reversing the volume-capacitance mismatch. In patients with severe hypovolaemia this should be

done as rapidly as possible so as to prevent organ damage. The treatment of severe life-threatening hypovolaemia is the same regardless of its cause, and may be divided into the following sequence of steps.

1. Restore arterial blood pressure & cardiac output.

The first priority is to restore blood pressure and cardiac output so as to restore adequate coronary and cerebral perfusion. Treatment depends on the type of hypovolaemia and its severity.

a. Hypovolaemic hypotension + cerebral or myocardial ischaemia [see chapter 2.2].

If blood pressure is so low that cerebral or myocardial ischaemia occurs, then the arterial blood pressure must be rapidly elevated using a combined vasoconstrictor/inotropic drug. This is especially relevant in patients with existing raised intracranial pressure or coronary vascular disease. Such patients tolerate hypotension poorly.

It must be stressed that this is NOT a definitive form of therapy of hypovolaemic hypotension, but merely a temporary measure to preserve function in these vital organs until definitive therapy can be administered. Such desperate measures may be required in those with clinical manifestations of decreased cerebral perfusion, or myocardial ischaemia, as it may take several minutes to significantly elevate the blood pressure and cardiac output even with a rapid intravenous infusion. But ischaemic cerebral damage can occur within minutes, and may have occurred before acceptable haemodynamics have been restored with an infusion.

b. Loss of blood volume.

Treatment of hypovolaemia due to actual reduction of blood volume consists of rapid infusion of any colloidal solution available, or blood if indicated, so as to rapidly increase the blood volume, and restore near normal, or at least acceptable systemic haemodynamic function. Any ECFV deficit may subsequently be corrected at a more leisurely pace, as the risk of organ damage due to extreme or prolonged hypotension is then no longer present.

c. Hypovolaemia due to drugs or spinal/epidural anaesthesia.

Therapy of relative hypovolaemia due to spinal or epidural anaesthesia, overdosage of drugs etc, consists of treating the cause, which is negative inotropy plus excessive vasodilation. Administration of a vasoconstrictor/inotropic drug is indicated for these patients as relative hypovolaemia is due to a temporary cause such as drugs, spinal, or epidural anaesthesia. It is true that an infusion of intravenous fluids will increase the blood volume and correct the relative hypovolaemia in this situation, but such therapy always carries the risk of causing hypervolaemia and heart failure once the effects of drugs, spinal, or epidural anaesthesia have disappeared.

Patients with spinal cord injury have a non-temporary form of relative hypovolaemia. The blood volume of these patients should be increased, and inotropic drugs administered as indicated.

2. Correct acidosis.

Do not correct acidosis until normovolaemia has been restored, as acidosis enhances peripheral oxygen transfer [see chapter 13.2]. In any case dilution of the blood with infusion fluids will partially correct any acidaemia. Should any significant acidaemia remain after

restoration of a normal haemoglobin concentration and blood volume, then it may be corrected.

On the other hand, severe acidosis with an arterial pH < 7.2 should be treated, especially if there are factors which make it likely that cardiovascular depression is due to acidaemia.

3. Treat cause of hypovolaemia.

Only after restoration of near normal haemodynamics should any consideration be given to correction of the specific disorder causing hypovolaemia. Time is then available to do this as a more leisurely rate.

The exception to this rule is rapid haemorrhage. Treatment of hypovolaemia without simultaneously stopping any bleeding is obviously quite futile.

ANAESTHETIC MANAGEMENT

Preoperative.

1. Anaesthesia should never be administered to any hypovolaemic patient unless there is a good reason why surgery cannot be delayed [see chapter 1.3]. Anaesthesia and surgery under these circumstances will only worsen any existing reduction of cardiac output and blood pressure.

2. Should surgery be unable to be delayed, no sedative, opiate or anticholinergic premedication should be administered preoperatively. Sedative and opiate drugs will further reduce cardiac output and blood pressure, and an anticholinergic is not necessary as the patients often already have a tachycardia. All these drugs are better administered under well controlled conditions in the operating theater as necessary.

Anaesthesia.

1. A large bore intravenous infusion should always be inserted prior to beginning any form of anaesthesia in a hypovolaemic patient. After induction of anaesthesia the blood pressure may fall precipitously, making it very difficult or impossible to insert any intravenous infusion.

2. Adequate monitoring should always be used as clinically indicated. In general a hypovolaemic patient has a reduced blood pressure and cardiac output because the blood volume is reduced. The therapy is simple, increase the blood volume. Administer a vasoconstrictor/inotropic drug if the blood pressure is so low that myocardial or cerebral perfusion are compromized. Obviously no elaborate monitoring is required for this. However, while this is adequate for initial resuscitation at the beginning of any emergency surgical procedure, more extensive monitoring is required in some patients because of continuing blood loss, or to more accurately guide any intravenous infusion therapy in patients with heart failure, septicaemia etc.

3. All forms of regional anaesthesia may be used, with the exception of spinal or epidural anaesthesia, as the latter two forms of regional block will further reduce the cardiac output and blood pressure by inducing a relative hypovolaemia. Saddle block, or hemi-spinal anaesthesia are not contraindicated because they cause minimal to no changes in systemic haemodynamics.

4. Some principles must always be kept in mind when administering general anaesthesia to hypovolaemic patients.

a. Drugs should be selected that cause minimal cardiovascular depression. The tables in chapter 2.1 may be used for this purpose.
b. Induction of anaesthesia is best done with ketamine as this causes least haemodynamic depression [see chapter 2.1]. Otherwise etomidate, or methohexitone may be used.
c. A technique using controlled ventilation should be used as oxygenation of the lungs can then be guaranteed. But hyperventilation causes respiratory alkalosis which should be avoided if at all possible, as alkalosis reduces sympathetic and adrenal secretion of catecholamines. This in turn may cause profound hypotension, or exacerbate existing hypotension. Controlled ventilation may also cause hypotension in hypovolaemic patients by further reducing venous return.
d. The use of anaesthetic vapors should be avoided. They all reduce the cardiac output, an effect which is only exacerbated by hypovolaemia.
e. D-tubocurarine should not be used as it causes significant cardiovascular depression secondary to ganglion blockade and histamine release. If no other non-depolarizing muscle relaxant drugs are available, then an infusion of suxamethonium has much to recommend it. It is a short acting drug causing minimal changes in systemic haemodynamics.
f. The choice of opiate is not critical.

Postoperative.

Postoperative monitoring and therapy depend on the clinical circumstances.

REFERENCES

1. Northfield,T.C., Smith,T.,(1970), Central venous pressure in clinical management of acute gastrointestinal bleeding. LANCET, 2, 584-586.
2. Skillman,J.J., et al.,(1967), Hemorrhage in normal man: Effect on renin, cortisol, aldosterone, and urine composition. ANNALS OF SURGERY, 166, 865-885.
3. Skillman,J.J., et al.,(1971), Cardiorespiratory, metabolic and endocrine changes after hemorrhage in man. ANNALS OF SURGERY, 174, 911-922.
4. Bassin,R., et al.,(1971), Rapid and slow hemorrhage in man. I. Sequential hemodynamic responses. ANNALS OF SURGERY, 173, 325-330.
5. Bassin,R., et al.,(1971), Comparison of hemodynamic responses of two experimental shock models with clinical hemorrhage. SURGERY, 69, 722-729.
6. Allgöwer,M., Burri,C.,(1967), "Schockindex". DEUTSCHE MEDIZINISCHE WOCHENSCHRIFT, 92, 1947-1950.
7. Benowitz,N.L., Meister,W.,(1976), Pharmacokinetics in patients with cardiac failure. CLINICAL PHARMACOKINETICS, 1, 389-405.
8. Christensen,J.H., et al.,(1982), Pharmacokinetics and pharmacodynamics of thiopentone. A comparison between young and elderly patients. ANAESTHESIA, 37, 398-404.
9. Guyton,A.C., "Textbook of Medical Physiology", 6th edn., pub. W.B.Saunders, U.S.A., 1981, pages 214-217.
10. Bonica,J.J., et al.,(1972), Circulatory effects of epidural block: III. Effects of acute blood loss. ANESTHESIOLOGY, 36, 219-227.
11. Kennedy,W.F., et al.,(1968), Cardiovascular and respiratory effects of subarachnoid block in the presence of acute blood loss. ANESTHESIOLOGY, 29, 29-35.
12. Robarts,W.M. et al.,(1979), A simple clinical approach to quantifying losses from the extracellular and plasma compartments. ANNALS OF THE ROYAL COLLEGE OF SURGEONS OF ENGLAND, 61, 142-145.

13. Weiskopf,R.B., Bogetz,M.S.,(1985), Haemorrhage decreases the anaesthetic requirement for ketamine and thiopentone in the pig. BRITISH JOURNAL OF ANAESTHESIA, 57, 1022-1025.
14. Weiskopf,R.B., et al.,(1984), Cardiovascular and metabolic sequelae of inducing anesthesia with ketamine or thiopental in hypovolemic swine. ANESTHESIOLOGY, 60, 214-219.
15. Adams,P., et al.,(1985), Midazolam pharmacodynamics and pharmacokinetics during acute hypovolemia. ANESTHESIOLOGY, 63, 140-146.
16. Jardin,F., et al.,(1983), Cyclic changes in arterial pulse during respiratory support. CIRCULATION, 68, 266-274.
17. Perel,A., et al.,(1987), Systolic blood pressure variation is a sensitive indicator of hypovolaemia in ventilated dogs subjected to graded haemorrhage. ANAESTHESIOLOGY, 67, 498-502.
18. Prys-Roberts,C., et al.,(1968) Haemodynamics and alveolar-arterial PO_2 differences at varying P_aCO_2 in anaesthetized man. JOURNAL OF APPLIED PHYSIOLOGY, 25, 80-87.
19. Kumar,A., et al.,(1970), Continuous positive pressure ventilation in acute respiratory failure. Effects on hemodynamics and lung function. NEW ENGLAND JOURNAL OF MEDICINE, 283, 1430-1436.

Chapter 14.5

HAEMORRHAGE AND BLOOD TRANSFUSION

PROBLEMS DUE TO HAEMORRHAGE

Haemorrhage causes three main groups of problems; hypovolaemia, anaemia and sometimes a haemostatic disorder.

1. Hypovolaemia.

Manifestations of hypovolaemia occur if more than 10-15% of the blood volume has been lost [see chapter 14.4].

2. Anaemia.

Hemorrhage does not immediately reduce the haemoglobin concentration as it takes time for sufficient transcapillary refill to have occurred to significantly dilute the remaining haemoglobin. In fact, after rapid haemorrhage in healthy human subjects it takes about one hour for the haemoglobin concentration to fall significantly as a result of dilution by tanscapillary refill. But if bleeding occurs slowly over an hour or more, the haemoglobin concentration declines simultaneously with the loss of blood [1].

Another common cause of anaemia subsequent to haemorrhage is replacement of the lost blood volume by intravenous infusion of fluids which contain no erythrocytes.

3. Altered haemostasis.

Massive blood loss with subsequent replacement of lost blood volume with equally large volumes of intravenous fluids containing low concentrations of, or no coagulation factors or thrombocytes causes a haemostatic disorder.

ASSESSMENT OF THE VOLUME OF BLOOD LOSS

An estimation of the volume of blood loss may be done by a number of clinical and laboratory methods.

1. From the type of injury.

The volume of blood lost may be estimated from the average volume of blood known to be lost from well defined injuries. This is mainly applicable to fractures and is shown in table 14.5.1.

Table 14.5.1.
Blood loss in milliliters associated with various fractures [2,3].

Radius and ulna	500
Humerus	500-1000
Rib	250+
Pelvis	3000+
Femur	500-3000
Tibia and fibula	500-1000

2. Visual estimation.

Visual estimation of the volume of blood loss. This requires some experience in visual estimation of fluid volumes. There are some aids to facilitate this.

a. The volume of blood represented by a contracted blood clot is about twice the volume of the clot, if a haematocrit of about 40-50% is assumed, and that most of the plasma has been squeezed out of the clot in the process of clot contraction.
b. Relate the volume of visible blood to something whose volume is known. The average adult male hand has a volume of about 400-500 mls.
c. Counting the number of blood soaked swabs during operation. A given size of surgical swab can only hold a certain volume of blood at a given level of saturation.

3. Haemodynamic parameters.

Haemodynamic parameters such as the shock index may be used to derive a rough estimate of the volume of blood loss [see chapter 14.4].

4. Measurement of blood loss.

Measurement of blood loss and blood volume may be made. Various methods are available for this.

a. Perioperative measurement of blood loss.

During any surgical procedure the swabs may be weighed, and the volume of blood in the suction apparatus reservoir is also measured. This usually tends to underestimate the blood loss during most operations by up to 25% because of evaporation and the presence of blood on drapes, gowns, in the wound, and on the floor [5].

b. Perioperative & non-perioperative measurement of blood loss.

Circulating blood volume, and blood loss may be measured, and the result compared with the expected, or previously measured blood volume. These methods usually employ complicated colorimetric or gravimetric techniques together with simultaneous measurement of the blood volume. Because of this they are usually impracticable in the clinical situation, or at best the benefit acquired from the increased accuracy is so marginal as to

make their use unjustifiable. Replacement of a given volume of blood loss does not cease once the exact volume has been replaced, but is only discontinued once acceptable haemodynamics and haemoglobin concentration have been restored.

BLOOD STORAGE & AVAILABLE PREPARATIONS

1. Blood storage.

Blood preparations are always stored in a refrigerator. This is because the more rapid metabolic processes at room temperature will cause the same deleterious changes in stored blood in a few hours, that require several weeks of storage at a low temperature. The usual temperature at which anticoagulated blood is stored is about 4-6°C. Anticoagulated blood stored at this temperature is usable for 3-4 weeks, while blood stored as washed erythrocytes can be stored indefinitely in liquid nitrogen.

2. Anticoagulant solutions in common use.

All stored blood is mixed with an anticoagulant solution. The function of the anticoagulant solution is not only to prevent coagulation, but also to provide a source of energy for the erythrocytes, and to prevent any deleterious changes occurring during storage. There are two solutions in common use.

a. Acid-Citrate-Dextrose (ACD) solution.

i. English version.

A mixture of 2.5 gm disodium citrate + 3 gm dextrose (glucose) is mixed together with 120 mls water. This is added to 420 mls of donor blood making a total volume of 540 mls per unit of blood.

ii. United States of America version.

A mixture of 2.5 gm disodium citrate + 3 gm dextrose is added to 67.5 mls water. This is mixed with 450 mls of donor blood making a total volume of 517.5 mls per unit of blood.

b. Citrate-Phosphate-Dextrose (CPD) solution.

A mixture of 26.3 gms trisodium citrate + 3.27 gm citric acid + 2.22 gm sodium dihydrogen phosphate + 25.5 dextrose is added to 1000 mls of water. About 63 mls of this CPD mixture, (63 mls contains 1.66 gms of trisodium citrate), is added to 450 mls of donor blood, making a volume of 513 mls per unit.

3. Types of blood preparation available.

a. Whole blood.

Whole blood is preserved by cooling and mixing with one of the anticoagulant solutions listed above. It used with increasingly less frequency in many western countries, as the plasma is removed for fractionation into plasma proteins for treatment of coagulation disorders. One of the principal uses is in the form of fresh whole blood for therapy of patients with haemorrhagic hypovolaemia which occurs together with a haemostatic defect, or patients who are massively bleeding. In the latter case blood component therapy is often not practical because of the great rapidity with which blood must be replaced in some patients.

b. Whole blood without buffy coat.

The "buffy coat" of blood is the white colored layer covering the erythrocytes after they have been centrifuged or allowed to settle. It is composed of all the white blood cells, that is, the leukocytes, monocytes, platelets etc. Removal of the buffy coat has a number of advantages.

i. Patients who have a prior history of blood transfusion may develop a reaction to subsequent blood transfusions. This reaction is usually caused by antibodies to leukocyte antigens. Removal of the buffy coat reduces the likelihood of this.
ii. Platelets and leukocytes form aggregates after 5 days of storage in ACD or CPD medium. No microaggregates can form in blood without a buffy coat, and so no filter need be used when this type of blood is administered.

c. Packed cells.

This is a concentrated suspension of erythrocytes from which most of the plasma has been removed, and often the buffy coat too. The main use of this suspension is to replace losses of erythrocytes only.

d. Washed red cells.

The plasma and the white cells are removed, and the remaining erythrocytes are resuspended in saline. The chance of human lymphocyte associated (HLA) antigen transfer to a patient is minimized with this suspension. It may also be used to elevate the haemoglobin concentration of patients with known antigens to blood components, or where it is desired to prevent this occurring.

e. Frozen red blood cells.

Packed cells are washed and resuspended in a glycerol solution, frozen, and then stored in liquid nitrogen. The storage life is many years. This method of preservation is principally useful for autotransfusion of patients for elective operations, and for central stores of blood against large numbers of civilian or military casualties.

PROPERTIES OF STORED BLOOD

The following discussion applies to the problems that may be associated with the storage and transfusion of whole blood only. The reader who wishes to know more about blood transfusion should consult the standard haematology texts, as these give a more than adequate as well as more extensive discussion of this large subject.

1. Increased erythrocyte fragility and haemolysis.

Normal aging of erythrocytes, plus the reduction of membrane function due to storage causes the erythrocytes to swell somewhat during storage. In addition to this, the plasma haemoglobin concentration progressively increases due to haemolysis of erythrocytes as well as leakage of haemoglobin from cells. The percentage of transfused red cells that survive transfusion decreases with increasing storage duration. After 21 days of storage, about 20-25% of the transfused erythrocytes undergo haemolysis within 24 hours after transfusion [18].

Transfusion of old blood is therefore less effective in elevating the haemoglobin concentration, as well as being associated with a considerable degree of haemolysis. This may

not matter so much in normally healthy young patients, but is possibly of relevance in the critically ill who have less physiological reserves.

2. Reduced oxygen transport.

The oxygen-haemoglobin dissociation curve of the stored blood is left-shifted because of a decreased 2,3-diphosphoglycerate (2,3-DPG) concentration inside the erythrocytes [16]. This reduces oxygen transfer to tissues at a given PO_2 [see chapters 4.3 and 5.1]. It takes about 24 hours after blood transfusion before the 2,3-DPG concentration in the transfused erythrocytes increases to a near normal level [16]. However, regardless of these considerations, the haemoglobin does transport and release oxygen, which is better than no haemoglobin at all. This is well demonstrated by the survival of patients who have undergone massive transfusions of old bank blood for equally massive haemorrhage.

A reduced erythrocyte 2,3-DPG concentration is only of practical interest in those patients with minimal cardiac reserve. Such patients have a slightly lower cardiac output when administered blood with a low erythrocyte 2,3-DPG concentration, than when administered blood with a normal 2,3-DPG concentration [17].

3. Leukocytes.

Granulocytes become non-functional within 24 hours of storage, their numbers begin to fall after a week due to breakdown of the cells and formation of microaggregates [see below].

Lymphocyte number and function is well preserved in stored blood for 21 days in ACD medium [9].

4. Platelets.

Platelet function declines measurably by 6 hours of storage, and after 72 hours they are no longer functional [18,19]. By 7 days of storage, platelet concentration is reduced to 20% normal as a result of microaggregate formation [9].

5. Microaggregates and microembolization.

Microaggregates begin to form in stored ACD or CPD blood within 24 hours after donation [9,10]. They are initially formed of clumped platelets, but after a week they are also formed of clumped platelets, granulocytes, and fibrin. If these clumps are large enough they may cause embolization in the microcirculation. A measure of the microaggregate concentration is given by the Screen Filtration Pressure (SFP). The SFP is the pressure required to force blood at a set rate through a screen which blocks the passage of particles greater than 20 microns in size. The SFP is maximal in stored blood by 5-8 days after donation [15].

The total volume of microaggregates in a given volume of stored blood increases progressively during storage at 4-6^{0}C, so that after 21 days a 500 mls volume of stored blood contains a volume of 4 mm^3 of these microaggregates. In the first week of storage the microaggregates are mainly composed of clumped platelets, and after 7 days of storage the platelet count reaches its lowest point. After a week the granulocytes also begin to degenerate and clump together, adding to the volume of the platelet microaggregates. This latter process continues throughout the storage period [9].

About 72% of the microaggregates have a diameter less than 20 microns. However about 82% of the total volume of the microaggregates consists of aggregate particles with a diameter equal to or greater than 20 microns, and 52% of the microaggregate volume con-

sists of particles with a diameter greater than 40 microns [9]. Aggregate particles with a diameter of more than 20-40 microns can cause pulmonary and systemic arteriolar and capillary embolization [10,11]. Such embolization may be one of the factors precipitating the development of adult respiratory distress syndrome after massive transfusion [11,12]. In fact an increased alveolar-arterial oxygen gradient can be measured after administration of as little as 1000-2000 mls of microaggregate containing blood to normal "healthy" surgical patients [13].

Because of the effects of microaggregate embolization on pulmonary function, it is recommended that a 20-40 micron blood filter be used if more than 4 units (2000 mls) of buffy coat containing blood is to be administered. If the blood has been donated less than 5 days prior to use, no filter is required as there has not been enough time for significant microaggregate formation. As the microaggregates are formed from platelets and granulocytes, they can be removed by removing the buffy coat [9]. Accordingly no filter is required for any blood preparation that does not contain the buffy coat.

6. Acid-base balance.

The pH of ACD blood is initially 6.9-7.0, and falls to about 6.4-6.5 after 21 days of storage. The pH of CPD blood is slightly higher than that of ACD blood. Rapid transfusion of blood initially causes a slight acidaemia, and subsequent metabolism of the citrate causes an alkalaemia [20, and see chapter 13.3 on causes of alkalosis]. Acidosis due to blood transfusion should not be corrected unless it is associated with significant cardiovascular dysfunction [see chapter 13.3 for indications for treatment of acid-base disorders]. Acidosis causes right-shifting of the oxyhaemoglobin dissociation curve, tending to correct the effects of the reduced 2,3-DPG concentration of transfused erythrocytes on oxygen binding and release, and so a mild degree of acidosis is actually beneficial [see also chapters 13.2, and 4.3].

7. Potassium concentration.

The potassium concentration in the plasma of stored blood increases in direct proportion to the duration of storage. This is due to leakage of potassium from intact cells, as well as from cells that undergo haemolysis during storage. The plasma potassium concentration may rise to 20-40 mmol/l after 21 days of storage. Rapid infusion of blood can result in a transient hyperkalaemia, but this quickly returns to normal [20]. In fact a severely ill, traumatized patients undergoing major surgery are more likely to be hypokalaemic as a result of the elevated catecholamine concentrations associated with these conditions [see chapter 12.3]. Another factor is that the quantity of potassium contained in the plasma of one unit of blood is not great. For example, a plasma potassium concentration of 40 mmol/l in 500 mls of old blood bank blood. Assuming a haematocrit of 40% this means that the quantity of potassium is only 13 mmols. This is usually rapidly redistributed, especially in hypokalaemic patients [see chapter 12.3]. However acute hyperkalaemia does occasionally occur after rapid administration of old very hyperkalaemic blood.

8. Coagulation disorders.

The concentrations of most of the coagulation factors do not change significantly during storage, except for those of factors V and VIII. After 21 days of storage, both ACD and CPD blood only contain 20-50% of the normal concentrations of these factors [4]. A concentration of more than 30% of either of these factors is required for adequate haemostasis [see table 6.4.3].

A clinically evident bleeding tendency can occur after massive blood transfusion used for replacing equally massive blood losses. The volume of blood replacement at which a bleeding tendency manifests depends on the type of blood preparation transfused.

a. Whole blood transfusion.

Transfusion of more than 15 units (= 7.5 liters) of ACD anticoagulated whole blood stored for more than 8 days, causes a bleeding disorder in healthy young adults. The cause of the bleeding disorder is a thrombocytopenia. Coagulation factor deficiency only becomes significant after about 20 units = 10 liters of blood have been transfused [4].

b. Packed cells plus Ringer's lactate or 0.9% NaCl.

At present, the blood banks of masny western countries usually only provide erythrocyte concentrates. The concentrate is frequently mixed with an equal volume of 0.9% NaCL or Ringer's solution to enable the mixture to flow more readily, and to provide extra volume. Transfusion of a volume of such a mixture which is equivalent to the blood volume of the patient, causes a clinically significant increase in the rate of surgical bleeding due to a combined deficiency of platelets and coagulation factors [21].

9. Plasma cholinesterase.

Plasma cholinesterase activity does not decrease greatly during storage. After 21 days the activity is still 80-90% of normal in both ACD as well as CPD blood [14].

10. Citrate intoxication.

Citrate intoxication and its treatment have been discussed extensively in chapter 12.5, and 13.3. It only occurs during rapid blood transfusions at a rate of more than 50 mls/minute in adults. No calcium need be routinely given during blood transfusion. The only indication for intravenous administration of calcium salts is for therapy of the actual manifestations of citrate intoxication, which is a hypotension which occurs as a result of blood transfusion, or hypovolaemic hypotension which is not reversed by blood transfusion.

11.Hypothermia.

Infusion of large volumes of cold blood at storage temperature, i.e. about 4-6^{o}C, causes hypothermia. This is also true, but to a lesser degree of fluid infused at room temperature, i.e. 16-20^{o}C. If large volumes of cold blood and fluid are to be infused, the use of an intravenous infusion fluid warmer is recommended.

12. Transmission of disease.

Many viral, bacterial, and parasitic diseases may be transmitted in stored blood.

PRACTICAL ASPECTS OF BLOOD TRANSFUSION

1. Check patient data.

Prior to administering any blood transfusion, always check the blood to see if the blood is indeed blood intended for that patient. Administration of incompatible blood can be lethal.

2. Use a blood-warmer during massive transfusions.

Blood which is fresh from the refrigerator has a temperature of about 4-6°C, and when it has been kept outside for some time, it is at room temperature. Transfusion of large volumes of blood at these temperatures can cause hypothermia, and so if transfusion of large quantities of blood is required, warm the blood prior to infusion. This also applies to other intravenous fluids too.

3. Microaggregate filters.

A 20-40 micron microaggregate filter should be used when transfusing more than 4-5 units of blood which is more than 5 days old and still contains the Buffy coat. A filter is not required when transfusing any blood which does not contain the Buffy coat, and when transfusing blood which does contain the Buffy coat, but is less than 5 days old.

4. Blood volume replacement, and haemostatic effect of transfused blood.

Erythrocytes are transfused together with a multitude of suspending fluids. These different fluids are the cause of variation in the blood volume replacing effect of the transfusion, and the effect of the transfusion on haemostatic function.

a. Whole blood.

A volume of whole blood replaces an equal volume of blood loss [see table 14.2.1]. Thrombocytopaenia may occur after transfusion of a volume of old whole blood equivalent to one blood volume. Coagulation defects do not occur until more than two blood volume equivalents have been transfused [4].

Prevention and treatment of a haemostatic disorder consists of measurement of the haemostatic status after a volume of old blood equivalent to one blood volume of the patient has been transfused. If this indicates a significant thrombocytopaenia, a platelet transfusion should be administered.

b. Erythrocyte concentrate plus fresh plasma.

A mixture of equal volumes of fresh plasma and erythrocyte concentrate has the same volume replacing effect as whole blood. As with old whole blood, a dilutional, haemostatically significant thrombocytopaenia may occur after more than one blood volume equivalent of this mixture has been transfused. Coagulation protein deficiencies do not occur as fresh plasma is used. Measure haemostatic status after a volume of blood equivalent to one blood volume of the patient has been administered. A significant thrombocytopaenia requires a transfusion of platelets.

c. Erythrocyte concentrate plus a plasma volume replacing fluid.

A mixture of equal volumes of an erythrocyte concentrate plus a plasma volume replacing fluid, such as pasteurized plasma protein solution, dextran and gelatin solutions, has the same blood volume replacing effect as whole blood. But because no coagulation proteins and platelets are infused, a dilutional coagulopathy and thrombocytopaenia may occur after transfusion of a volume equivalent to one blood volume.

Measure the haemostatic function after transfusion of a volume of blood equivalent to one half to one blood volume of the patient. Coagulation protein deficits should be treated with infusion of fresh frozen plasma, and platelets deficiencies with a platelet transfusion.

d. Erythrocyte concentrate plus a crystalloid solution.

A mixture of an equal volume of an erythrocyte concentrate with an equal volume of Ringer's solution or 0.9% NaCl solution does not have the same blood volume replacing effect as whole blood. The erythrocytes remain in the blood vessels, but the crystalloid solution diffuses out rapidly, and only $1/5^{th}$ of the crystalloid remains in the plasma [see chapter 14.2, 14.3]. A dilutional thrombocytopaenia and coagulopathy may occur after a volume equivalent to one blood volume of this solution has been transfused.

Management of haemostatic effects is the same as in paragraph "c" above.

5. Monitoring of intraoperative haemostatic function.

Regular monitoring of haemostatic function is required during massive blood transfusion. It should be done whenever there is a suspicion of a bleeding disorder, or when a volume of blood equivalent to one blood volume of the patient has been infused. Only a few tests are required, consisting of measurement of [see chapter 6.2 for a description of these tests];

- aPTT/PTT,
- PT,
- and platelet count.

MANAGEMENT OF HAEMORRHAGE & INDICATIONS FOR BLOOD TRANSFUSION

Haemorrhage is managed in the same way as hypovolaemia due to any cause. There are some factors specific to haemorrhage which must be kept in mind, as some patients require blood transfusion.

The indications for a blood transfusion may be summed up as below.

- Reduced oxygen transporting capacity secondary to anaemia.
- Hypovolaemia secondary to whole blood loss.
- Reduced haemostatic function [this has been dealt with above].

1. Reduced oxygen transporting capacity.

Reduced oxygen transporting capacity is the only indication for transfusion of erythrocytes. This has been extensively discussed in the chapter on anaemia [chapter 5.1], and oxygen flux [chapter 4.3]. Acute normovolaemic anaemia increases cardiac output in direct proportion to the reduction of haemoglobin concentration [see fig. 5.1.1]. The increase of cardiac output is due to elevation of the stroke volume rather than heart rate, as anaemia reduces blood viscosity. Heart work does not increase significantly unless hypovolaemia increases the heart rate [6,7].

The minimum acceptable haemoglobin concentration resulting from acute haemorrhagic anaemia is about 6 mmol/l = 9.6 gm/100 mls [see chapter 5.1]. Assuming normal erythrocytes, (haemoglobin concentration = 328 gm/liter erythrocytes), then the relationship of the haemoglobin concentration ([Hb]) to percentage haematocrit (Hct) is given by the equations below, and the minimum acceptable haematocrit is about 30%.

$$[Hb](mmol/l) = Hct/5 \quad .....(1)$$

OR

$$[Hb](gm/100\ mls) = 0.328 \times Hct \quad ...(1)$$

The maximum permissable percentage, or fractional blood loss (**MFBL**) above which blood transfusion is required may be calculated using equations 2 and 3 below and assuming normovolaemic anaemia [see also table 14.5.2].

$$MFBL = 1 - \frac{\text{Minimum acceptable [Hb]}}{\text{Preoperative [Hb]}} \quad .....(2)$$

OR

$$MFBL = 1 - \frac{\text{Minimum acceptable [Hct]}}{\text{Preoperative [Hct]}} \quad .....(3)$$

Table 14.5.2.

Maximum percentage blood loss calculated on the basis of a minimum acceptable haemoglobin concentration of 6 mmol/l = 9.5-10 gm/100 mls), which is equivalent to a haematocrit of 30%. This table assumes that normovolaemia is maintained. Blood transfusion is required if this percentage blood loss is exceeded.

Preoperative [Hb] (mmol/l)	Preoperative [Hb] (gm/100 mls)	Preoperative Hct (%)	Maximum % blood loss
10	16	50	40
9	14.5	45	33
8	13	40	25
7	11.3	35	14
6	10	30	0

2. Hypovolaemia.

Hypovolaemia is another consequence of blood loss. However, no blood is required if the haemoglobin concentration is more than adequate for oxygen transportation [see above, and chapter 5.1]. When considering therapy for blood loss, the interval between haemorrhage and the therapy should be considered as this has therapeutic consequences.

a. Acute blood loss.

This is bleeding which has just occurred, or is still taking place. No transcapillary refill has as yet taken place in this situation, and so the only deficit is in the blood volume. Treatment depends on the magnitude of the blood loss, and the haemoglobin concentration prior

to haemorrhage. Transfusion of erythrocytes should be commenced at a lesser degree of blood loss in patients with pre-existing anaemia, and at a greater percentage of blood loss in patients with polycythaemia [see table 14.5.2].

i. Blood loss < 10% of normal blood volume.

Minor haemorrhage of less than 10% of the normal blood volume usually has no effects on systemic haemodynamics. No therapy is required unless systemic cardiovascular effects due to hypovolaemia are observed.

ii. Blood loss > 10-15% of blood volume.

Blood loss of this magnitude always causes some haemodynamic disorder, and so the volume deficit should be replaced. The first 15% may be replaced with a colloid solution. Blood loss above 15% of the normal blood volume should be replaced volume for volume with whole blood, or equivalent. 15% is only a rough estimate of the tolerable percentage volume of blood loss. The maximum permissable blood loss actually depends on the preoperative haemoglobin concentration [see table 14.5.2].

b. Existing blood loss (haemorrhage > 1 hour before therapy).

Transcapillary refill occurs after haemorrhage, and significant transcapillary refill has occurred by one hour after haemorrhage [1]. In this situation there is not only a blood volume deficit, but also a deficit in the ISFV too. An ISFV deficit is not without consequences, as it is this which determines the functioning of the space between the cells of the body.

In one investigation, the percentage survival of dogs in whom haemorrhagic shock was maintained for a period of 2.5 hours was considerably less when the volume of blood lost was replaced with whole blood only, than when these dogs were administered not only a volume of blood equivalent to the blood loss, but also were administered a volume of Ringer's lactate solution equivalent to 5% of the body weight [8].

In practice, therapy is exactly the same as for acute blood loss, except that there is also an ISFV deficit which should be replaced with 0.9% NaCl or Ringer's lactate. The volume of 0.9% NaCl or Ringer's lactate required is equal to the volume of blood lost, and the volume of blood that is required, is that volume necessary to restore normal haemodynamics.

ANAESTHETIC MANAGEMENT

This is the same as for any hypovolaemic patient.

REFERENCES

1. Skillman,J.J., et al.,(1967), Plasma protein kinetics of the early transcapillary refill afetr hemorrhage in man. SURGERY, GYNECOLOGY & OBSTETRICS, 125, 983-996.
2. Wilson,J.N.,(1967), The role of the orthopaedic surgeon in accident surgery. PROCEEDINGS OF THE ROYAL SOCIETY OF MEDICINE, 60, 951-952.
3. Clarke,R., Fisher,M.R.,(1956), Assessment of blood loss following injury. BRITISH JOURNAL OF CLINICAL PRACTICE, 10, 746-769.
4. Miller,R.D., et al.,(1971), Coagulation defects associated with massive blood transfusions. ANNALS OF SURGERY, 174, 794-801.
5. Caceres,E., Whittembury,G.,(1959), Evaluation of blood losses during surgical operations. Comparison of the gravimetric method with the blood volume determination. SURGERY, 45, 681-687.

6. Gisselsson,L., et al.,(1982), Myocardial blood flow, oxygen uptake and carbon dioxide release of the human heart during hemodilution. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 26, 589-591.
7. Jobes,D.R.,, Gallagher,J.,(1982), Acute normovolemic hemodilution. INTERNATIONAL ANESTHESIOLOGY CLINICS, 20, 77-95.
8. Shires,T., et al.,(1964), Fluid therapy in hemorrhagic shock. ARCHIVES OF SURGERY, 88, 688.
9. Solis,R.T., et al.,(1974), Physical characteristics of microaggregates in stored blood. TRANSFUSION, 14, 538-549.
10. Bisio,J.M., et al.,(1982), The formation and effect of stored platelet concentrate microemboli on pulmonary ultrastructure.SURGERY, GYNECOLOGY & OBSTETRICS, 154, 342-347.
11. Reul,G.J., et al.,(1974), Prottection of the pulmonary microvasculature by fine screen blood filtration. CHEST, 66, 4-8.
12. Reul,G.J.,(1973), Prevention of post-traumatic pulmonary insufficiency. ARCHIVES OF SURGERY, 106, 386-394.
13. Takaori,M., et al.,(1977), Changes of pulmonar function following transfusion of stored blood. TRANSFUSION, 17, 615-620.
14. Epstein,H.M., et al.,(1980), Plasma cholinesterase activity in bank blood. ANESTHESIA AND ANALGESIA, 59, 211-214.
15. McNamara,J.J., et al.,(1970), Screen filtration pressure in combat casualties. ANNALS OF SURGERY, 172, 334-341.
16. Kopriva,C.J., et al.,(1972), Biochemical and hematological changes associated with massive transfusion of ACD-stored blood in severely injured combat casualties. ANNALS OF SURGERY, 176, 585-589.
17. Dennis,R.C., et al.,(1975), Improved myocardial performance following high 2-3 diphosphoglycerate red cell transfusions. SURGERY, 77, 741-747.
18. Machin,S.J.,(1979), The problems of blood transfusion. BRITISH JOURNAL OF HOSPITAL MEDICINE, 19, 294-300.
19. Urbaniak,S.J., Cash,J.D.,(1977), Blood replacement therapy. BRITISH MEDICAL BULLETIN, 33, 273-282.
20. Linko,K., Saxelin,I.,(1986), Electrolyte and acid-base disturbances caused by blood transfusion. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 30, 139-144.
21. Murray,D.J., et al.,(1987), Blood replacement therapy: Decreases in coagulation factors. CANADIAN JOURNAL OF ANAESTHESIA, 34, supplement, pages s122-s127.

Chapter 14.6

PERIOPERATIVE FLUID THERAPY

Basic physiology of fluid balance in the perioperative period has been discussed in the preceding chapters. This chapter is a practically oriented discussion of perioperative intravenous fluid therapy in adults. Perioperative fluid therapy for children will not be discussed as this is beyond the scope of this book. The main aims of perioperative fluid therapy are listed below.

- To initially resuscitate the patient and restore normal haemodynamics prior to any operation.
- To maintain normal haemodynamics and organ function in the intraoperative and postoperative period by replacing actual and functional fluid losses, and supplying basal normal fluid requirements.

The various methods of realizing these aims will be discussed for each part of the perioperative period.

INDICATIONS FOR PERIOPERATIVE INTRAVENOUS FLUID THERAPY

Perioperative administration of intravenous fluids is not required for all patients, and ideally should only be administered on indication as this lessens the number of complications of such therapy, as well as reducing treatment costs.

1. Patients requiring NO perioperative intravenous fluid therapy.

Non-dehydrated healthy patients who come for elective surgery which does not cause significant loss of blood volume, does not cause significant third space plasma losses, and causes no prolonged gastrointestinal inactivity, require no intravenous fluids in the perioperative period.

Significant loss of blood volume means more than 10% of the blood volume. This blood volume loss may consist of blood or third space losses. The volume of 10% is chosen as this is the volume of blood which a blood donor donates without any ill effects, and which has been shown in human investigations to cause minimal to no deleterious effects in healthy persons.

2. Patients requiring perioperative intravenous fluid therapy.

Patients whose operation causes prolonged gastrointestinal dysfunction, or a blood volume loss greater than 10% of the blood volume, do require perioperative intravenous fluid therapy as it reduces perioperative morbidity and mortality if carried out effectively.

PREOPERATIVE CONSIDERATIONS

Emergency operations.

1. Delay any operation until any blood volume deficit has been replaced.

2. The above may not be possible for those patients who fall into the category of patients who require immediate operation [see chapter 1.3]. In such cases, cardiovascular function, and in particular blood pressure, must be maintained with infusion of colloidal solutions or blood, with or without vasoconstrictor and inotropic drugs while the surgeons perform the necessary operation. The anaesthetist must replace any deficits during and after the operation [see chapter 14.4].

Elective operations.

All patients coming for elective operation are fasted for a period of at least 4-6 hours prior to induction of anaesthesia. Many patients are fasted overnight from midnight. Some patients may actually have fasted fo a period of about 12-14 hours.

Consider an "average" adult patient who has fasted overnight. The "normal" basal fluid requirement for an adult is about 2-2.5 liters/day, and so such a patient will in theory have a TBW deficit of 500-1250 mls. However this is not really true, as during sleep the activity level is low, and the urine production and water requirement are correspondingly low too. This is because the metabolic rate decreases during sleep, the plasma concentration of antidiuretic hormone increases, and the respiratory minute volume decreases. These factors account for the well known reduction of urine production during sleep, and also reduce cutaneous insensible water loss, as well as respiratory water loss. The water deficit as a result of overnight fasting is therefore less than would be expected from such a simple calculation as above.

The water deficit due to an overnight fast, or a fast of lesser duration, may be replaced in the average adult with 500 mls of a crystalloid solution. Ideal fluids for this purpose are 4% glucose/0.18% NaCl solution, or a 5% glucose solution as these are effectively infusions of water only.

PEROPERATIVE FLUID MANAGEMENT

Peroperative intravenous fluid therapy in adults has a number of aims.

- To provide normal basal fluid requirements 2 ml/kg/hour.
- To replace lost blood volume [see chapter 14.5].
- To replace third space losses [see chapter 14.3].
- To replace possible evaporative fluid losses in very major and extensive surgery [see chapter 14.3].
- To replace urinary water and electrolyte losses.
- To maintain normal haemodynamic and renal function:
  - Arterial blood pressure at a level normal for that patient, or at a systolic pressure > 100 mmHg.
  - Central venous pressure > 5 cm H_2O.
  - Pulse rate < 100 beats/minute.
  - Urine output > = 0.3 mls/kg/hour.

1. Basal fluid requirements.

The average adult requires about 2-3 mls/kg body weight of water per hour under conditions of normal activity in a temperate climate. This should be continued in the perioperative period and can be provided as 4% glucose/0.18% NaCl solution, or 5% glucose.

2. Replace urinary losses.

Urinary losses decrease the TBW, and for this reason loss of even 1000 mls of urine has little effect on the plasma volume [see chapter 14.3]. Significant volumes of urinary water losses may be replaced with a glucose/saline solution.

Urine does contain a relatively high concentration of potassium, about 20 mmol/l. Acute loss of 1000 mls of urine can cause acute hypokalaemia [see chapter 12.3]. Hypokalaemia should always be suspected in polyuric patients.

3. Replace lost blood volume.

Replacement of blood losses has been discussed in chapter 14.5.

4. Replace third space losses.

Third space fluid loss has been extensively dealt with in chapter 14.3. Table 14.3.1 shows the approximate volumes of plasma loss to be expected for various operations. There are various systems in current use for replacing third space fluid losses. Regrettably, none is entirely satisfactory as they are all based on the incorrect supposition that the loss of fluid for a given operation is the same for all patients. However as regular routine measurement of body fluid compartment volumes is impossible in the clinical setting of an operating theater at this time, clinical practice based on average population values must be used. This provides a guide as to the volumes and types of fluid required, and haemodynamic parameters can be used to further guide fluid therapy. Perioperative fluid regimes in common use are discussed below.

a. Crystalloid regime.

Loss of plasma may be replaced using crystalloid solutions. A commonly used regime is set out below [1].

Intra-abdominal surgery.

7-10 mls Ringer's lactate/kg body weight/hour of operation.

Intrathoracic surgery.

3-5 mls Ringer's lactate/kg body weight/hour of operation.

Major orthopedic surgery.

3-5 mls Ringer's lactate/kg body weight/hour of operation.

These volumes of fluids are also sufficient to provide the normal basal water requirements too. A major disadvantage of such a regime is that significant generalized interstitial, and even pulmonary oedema can occur, especially if these volumes are exceeded, or the patient has poor cardiovascular reserve [2,3,4,6, and see chapter 14.3 for further discussion].

b. Colloid regime.

A volume of a colloidal solution may be infused which is sufficient to replace the estimated third space loss [see table 14.3.1]. This regime has the major advantage that most of the infused fluid remains in the vascular system, only diffusing out into the interstitium of operated or traumatized tissues. No generalized interstitial fluid space expansion with all its attendant problems occurs. However, this regime is as speculative as the above crystalloid regime in that it also uses volumes estimated from clinical experience, and not from measurements made on the individual patient being treated.

c. Mixed colloid and crystalloid regime.

A combined colloid/crystalloid regime may be used [3].

i. Use the crystalloid regime above. However the use of Ringer's lactate should be avoided [see chapter 14.2], and instead 0.9% NaCl solution should be used as this is associated with fewer undesirable effects [see chapter 14.3].
ii. If the volume of crystalloid fluid required to maintain normal haemodynamics exceeds that advised by the crystalloid regime above, infuse a colloidal solution until normal haemodynamics have been restored.
iii. If very large volumes of colloid are required, then the patient is either losing large volumes of blood or plasma, or has developed heart failure.

Advantages of combined regime.

The combined regime is the most satisfactory for a number of reasons.

i. The volume of crystalloid solutions required is reduced. One benefit is that less generalized interstitial oedema occurs. One example of the effect of generalized interstitial oedema is the elevation of the pulmonary alveolar-arterial oxygen gradient often observed as a consequence of a purely crystalloid regime, as opposed to its absence in patients administered a mixed colloid-crystalloid regime [5, and see chapter 14.3].
ii. It reduces the requirement for colloid solutions with their attendant risk of haemorrhagic and allergic complications.
iii. Early use of colloidal solutions tends to maintain a near normal colloid osmotic pressure. If the colloid osmotic pressure falls below 15 mmHg, interstitial oedema with all its problems occurs [chapter 14.1].
iv. It is true that the amount of sodium infused with both colloidal and crystalloid solutions is far in excess of daily requirements, especially when one considers that surgery may reduce the urinary sodium excretion by about a half. But the maintenance of normal extracellular sodium concentration is also important, as acute hyponatraemia is not without consequences [see chapter 12.1]. Excessive hyponatraemia, or reduction of extracellular sodium concentration causes swelling of cells. Interstitial swelling is always present in traumatized regions, and has the effect of increasing the distance that oxygen molecules must diffuse from the capillaries to reach the mitochondria in the cells. Cellular swelling due to acute hyponatraemia further exacerbates this situation. For this reason, no glucose 5% or glucose/saline solutions should be used perioperatively, except to supply basal water requirements.

5. Replace evaporative losses.

Evaporative losses are minimal during most surgical procedures. [see chapter 14.3]. Even evaporative losses or more than 1-2 liters in an adult has only a slight effect on the blood volume, as evaporative water loss is loss of TBW. However in those few situations where it is significant, the volumes of crystalloid infused using the above regimes are more than sufficient to replace this water loss.

6. Monitoring.

All patients should be adequately monitored perioperatively. Haemodynamic parameters and urine output are used as criteria for the adequacy of any intravenous infusion therapy, and should be frequently measured to guide therapy. The level of monitoring should always be appropriate to the type of surgery being performed. The anaesthetist should aim to maintain urine output and haemodynamic parameters at or above the levels listed in the beginning of this chapter.

POSTOPERATIVE MANAGEMENT

1. Minor surgery.

No special therapy is required as the volume of third space loss is minimal. All that is required are basal fluid requirements.

2. Major surgery.

The rate of loss of plasma into a region of traumatic oedema is significant for up to 24 hours after operation, although the rate declines rapidly in the hours after surgery as the interstitial fluid pressure in the operated region rises due to flow of plasma out of the damaged vascular endothelium [see chapter 14.3]. Patients may therefore still lose large quantities of plasma in the first 24 hours after surgery, especially in the first few hours after operation.

Aggressive monitoring and plasma volume replacement therapy is required for all patients who have undergone major surgery. Such patients should be admitted into an intensive care unit, or a recovery area until cardiovascular stability has been achieved. The most commonly used postoperative regime is listed below.

1. Administer the basal fluid requirement as a glucose/saline solution. This reduces the plasma sodium concentration less than does a 5% glucose solution.

2. Patients should be monitored using the same parameters as in the operating room The frequency with which the parameters should be measured depends on the magnitude of the operation and the clinical condition of the patient.

3. Replace any significant blood losses as they occur.

4. Should patients develop manifestations of hypovolaemia, infuse a colloid solution or blood. Hypovolaemia occurring in the immediate postoperative period is always due to plasma or blood loss.

REFERENCES

1. Jenkins,M.T., et al.,(1965), Electrolyte therapy in shock: Management during anesthesia. CLINICAL ANESTHESIA, 2, 40-58.
2. Virgilio,R.W., et al.,(1979), Colloid vs crystalloid resuscitation: Is one better? SURGERY, 85, 129-139.
3. Zetterstrom,H., Hedstrand,U.,(1981), Albumin treatments following major surgery. I. Effects on plasma oncotic pressure, renal function and periperal oedema. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 25, 125-132.
4. Roth,E., et al.,(1969), Ringer's lactate solution and extracellular fluid volume in the surgical patient: A critical analysis. ANNALS OF SURGERY, 169, 149-164.
5. Zetterstrom,H.,(1981), Albumin treatment following major surgery. II. Effects on postoperative lung function and circulatory adaptation. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 25, 133-141.
6. Stein,L., et al.,(1975), Pulmonary edema due to volume infusion. CIRCULATION, 52, 483-489.

Part 15

PHARMACOKINETICS

Much use is made of pharmacokinetic concepts in this book. It is the purpose of this section to explain these more fully, to use these and other factors as a guide to selection of the best drugs for a given patient, and to show how a practical application of pharmacokinetic and pharmacodynamic principles may be used to predict, as well as to provide insights into the observed effects of drugs.

Chapter 15.1

PHARMACOKINETIC PRINCIPLES

Pharmacokinetics is regrettably considered by many physicians to be a difficult subject. This is true when one wishes to study it in great depth. But for practical clinical purposes a more simplified approach provides very useful didactic insights, as well as having utility for daily practice. No mathematical genius is needed for this except for the ability to perform simple multiplication and division. Pharmacokinetics at this level may be called "Volkskinetiek", (people's pharmacokinetics, or "pharmacokinetics for the masses"), after the popular Volkswagen automobile (people's car).

DEFINITIONS.

What is pharmacokinetics? Pharmacokinetics may be defined as the quantitative study of the distribution and elimination of drugs. This is quite distinct from pharmacodynamics which is the study of the effects of drugs in relation to their concentrations in various tissues and fluids.

Pharmacokinetics and compartments.

Anaesthetists usually administer drugs either by intravenous bolus injection or by intravenous infusion, (with the exception of the gaseous anaesthetics). The discussion that follows is oriented towards intravenous bolus and infusion pharmacokinetics.

After a single rapid intravenous injection of a drug, the plasma concentration achieves a peak level within seconds and subsequently falls because of the processes of distribution and elimination. The decline of the plasma concentration with time is well described by an exponential decay equation. Usually the mathematical description is more accurate if more than one exponential term is used. Such multiple exponential equations are derived by making the mathematical assumption that the drug is distributed throughout various compartments within the body, each compartment with its own rate of uptake and elimination of the drug. The various shapes of curves and equations for single, two- and three-compartment models are shown in fig 15.1.1.

The discussion that follows uses the two-compartment model, as this is conceptually the easiest kinetic model to understand. Variation of plasma drug concentrations with time is described by the double exponential equation in figure 15.1.1. However as this equation is difficult to use clinically, and is unnecessarily complex for didactic purposes, it will not be used in the discussion that follows.

The two-compartment model is simple in principle. After administration of a drug it is distributed immediately throughout a volume of tissue, the central compartment volume. Subsequently the circulation further redistributes the drug until it is distributed as exten-

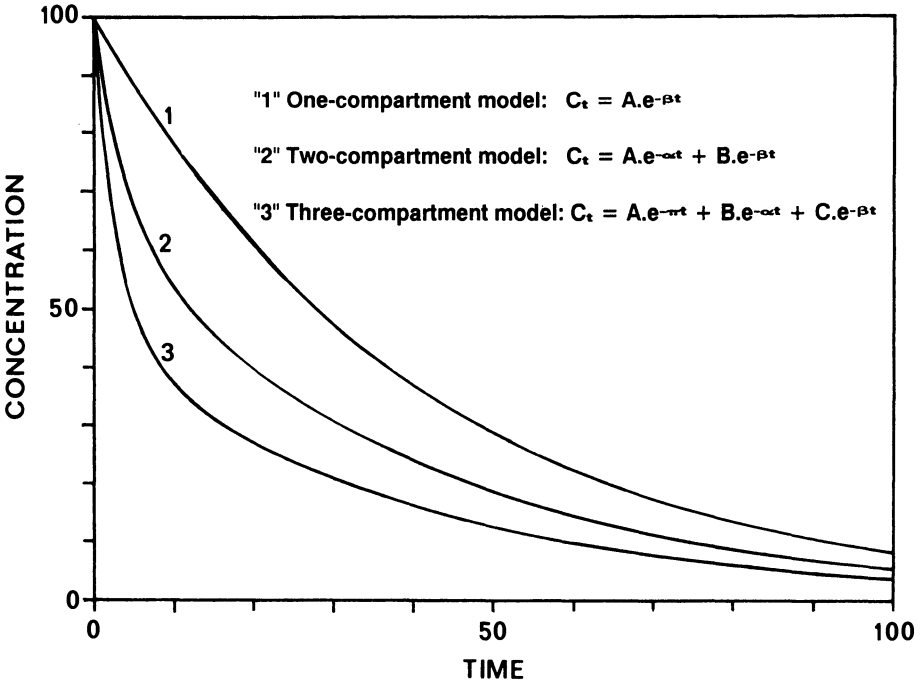

FIGURE 15.1.1. - The change of plasma concentration with time after a single rapid intravenous injection at zero time is shown for the same drug for one-, two- and three-compartment models using the same elimination half life ($T_{1/2\beta}$) and the same initial plasma concentration. The general multi-exponential equations are shown in the figure. The reader should consult any one of the many excellent texts on pharmacokinetics for a description of how to use these equations.

sively as is possible. The maximum volume throughout which a drug is distributed is the distribution volume. But distribution from the central to distribution volume is not instantaneous. The rate of transfer is dependent on the cardiac output as well as diffusion processes, and so it can be described by an exponential equation. This means that the rate of distribution is described by a half life, the distribution half life. Drug is also eliminated from the body, a process whose rate is also determined by diffusion and blood transport, and so may also be described by an exponential equation with its associated half life, the elimination half life. These concepts will be further expanded below.

Central compartment (V_C).

After intravenous injection, a drug mixes with the blood and simultaneously rapidly diffuses into the pericapillary regions of those tissues with a high blood flow. This is a very rapid process as is well demonstrated by the speed with which persons administered a hypnotic dose of thiopentone fall asleep. Such rapid diffusion through the capillary endothelium is not at all surprising in view of the fact that most drugs are compounds with a molecular weight of less than 10,000 Daltons. Molecules of this molecular weight and lower can freely pass through the capillary endothelium of most vascular beds [see chapter 14.1].

This initial volume throughout which the drug is distributed is the central compartment volume, and is given by equation 1 below.

Reference to appendix-A shows that the V_C may be greater than the blood volume. This is only to be expected as drug diffuses out of the blood into perivascular tissues, lowering plasma drug concentrations, and it is the plasma drug concentration data which are used to derive kinetic parameters.

$$V_C = D/C_0 \quad .....(1)$$

D = amount or dose of drug in mg.
C_0 = theoretical plasma concentration of drug at time = 0 seconds.

The tissue drug concentrations are initially highest in those organs with the highest blood flow per unit weight of tissue, i.e. heart, brain, liver kidneys and lungs [see table 15.1.1]. This is of clinical relevance. The higher the tissue concentration of a drug, the greater the magnitude of any desired as well as undesired drug effect. Haemodynamic and central nervous system effects of drugs are of great importance in clinical anaesthesia, and the magnitudes of these effects are certainly related to plasma drug concentrations.

Table 15.1.1.
Distribution of cardiac output.

ORGAN	Percentage cardiac output	Blood flow (mls/100 gm/min)
Lungs	100	1200
Liver	28	60
Kidneys	23	420
Skeletal muscle	16	3
Brain	14	54
Skin	9	13
Heart	5	84
Others	5	

Distribution half life ($T_{1/2d}$, $T_{1/2\alpha}$, $T_{1/2\pi}$).

After initial distribution throughout the central compartment volume, the plasma concentration of an intravenously injected drug rapidly declines as the drug diffuses into tissues with a lower blood flow per unit mass, but a greater tissue volume or capacity to absorb the drug. Once the plasma drug concentrations fall below the drug levels inside the tis-

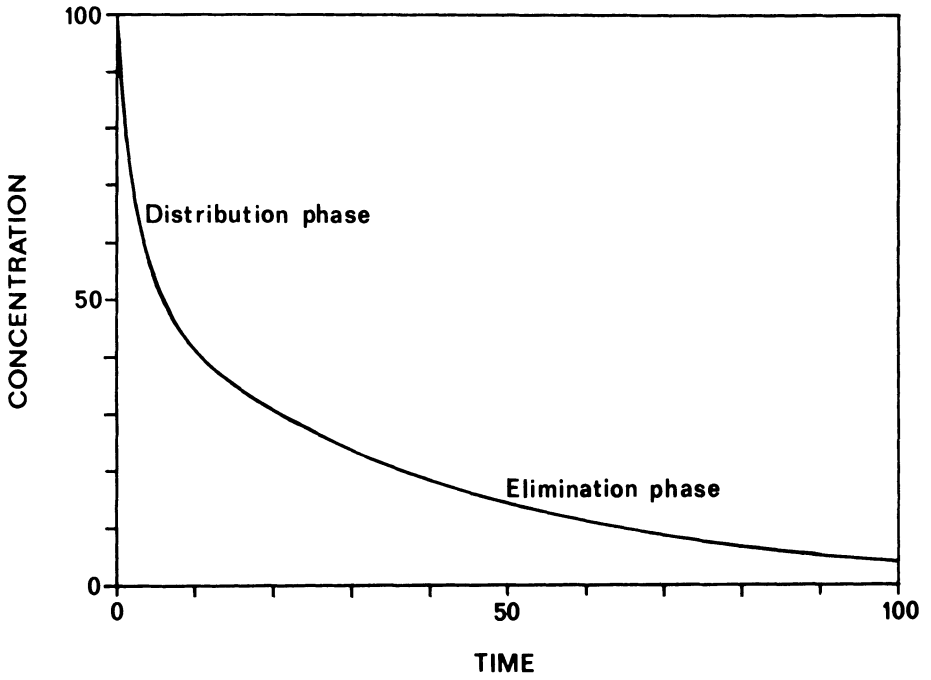

FIGURE 15.1.2. - A typical multicompartmental concentration-time curve showing the distribution and elimination phases of a drug.

sues with a high relative blood flow, drug diffuses out of these tissues into the plasma, so reducing the drug concentration in these high flow tissues, e.g. brain heart, etc. This process is called redistribution, and as its rate is dependent on cardiac output and diffusion processes, the decline of plasma drug concentration with time is able to be described by an exponential equation, and so has a half life, the distribution half life.

Distribution volume (V_d) and Peripheral compartment volume.

After redistribution is complete, the drug is distributed as extensively as is possible for that drug throughout the body. This is the distribution volume.

The volume of distribution may be calculated from the plasma drug concentration data in a number of ways, each method yielding a slightly different volume. These various distribution volumes are the V_{dss}, $V_{d\beta}$ and the $V_{d(area)}$. The V_{dss} assumes conditions that can only be achieved during an intravenous infusion which has achieved "steady state", i.e. that the plasma concentration is constant, and that the amount of drug entering the body is the same as that being eliminated per unit time. This is not accurate for situations where a drug is being administered in intermittent boluses, as the plasma drug concentrations are continually changing under these circumstances. The $V_{d(area)}$ or the $V_{d\beta}$ are more appropriate under these circumstances, as both are calculated on the basis of changing plasma concentrations. $V_{d\beta}$ is actually the same volume as the $V_{d(area)}$, and so these two terms

may be interchanged [1]. Unless otherwise stated, any mention of the distribution volume (V_d) in this book implies the $V_{d\beta}$ or the $V_{d(area)}$.

Another commonly used term is the peripheral compartment. The peripheral compartment volume is the volume remaining after subtracting V_c from V_d.

Elimination half life ($T_{1/2e}$, $T_{1/2\beta}$).

Drugs are either excreted unchanged, or metabolized to a more water soluble form and then excreted by the drug eliminating organs. Because drug must diffuse out of the blood vessels into the eliminating organs, and the amount of blood presented to an organ per unit time is flow dependent, the decline in plasma concentration due to elimination is also described by an exponential equation, and so is also associated with a half life.

Clearance (Cl).

Drug clearance is, as with urinary creatinine or urea clearance, a measure of the rate at which a drug is eliminated per unit volume of drug concentration in the plasma. Only total body clearance is referred to in this book. Total body clearance is related to the V_d (i.e. $V_{d(area)}$ or $V_{d\beta}$) and the $T_{1/2e}$ by equation 2 below.

$$T_{1/2e} = \frac{0.693 \times V_d}{Cl} \quad .....(2)$$

This equation clearly shows the relationship of these three kinetic parameters, and explains some of the effects of alterations of any one of them on the $T_{1/2e}$ in patients with disorders which affect either clearance or distribution volume, e.g. liver or kidney diseases.

Description of the plasma concentration curve after a single intravenous bolus injection.

From the discussion above it is now possible to explain the shape of the plasma concentration curve as measured after a single intravenous injection. The initial rapid decline of plasma drug concentration is due to distribution (distribution phase), and occurs at a rate determined by $T_{1/2d}$, while the later slower decline is due to elimination (elimination phase), and occurs at a rate determined by $T_{1/2e}$. This is shown in fig. 15.1.2.

Relationship of kinetic parameters to body weight.

In the tables of kinetic parameters of anaesthetic drugs that are given in appendix-A, the parameters are related to the body weight. This is a convention that is often used, however the relationship varies from one drug to another. For many drugs there is no relation at all, e.g. thiopentone [2]. However it is perhaps practical to adhere to such a convention when calculating dosages as there is then less chance of an inadvertent overdose being administered.

USE OF KINETIC PARAMETERS and SIMPLE CALCULATIONS

The kinetic parameters in appendix-A may be used in a variety of ways, both didactic and clinical.

- To explain the effects of drugs.
- To calculate drug doses.
- To calculate intravenous infusion rates.

1. Some concepts.

Prior to beginning it is first necessary to list the basic concepts and equations necessary for understanding what is to follow.

a. Half life.

This is a pervasive concept in many fields where a process can be described by an exponential factor. For our purposes it is not necessary to know precisely what the properties of exponential equations are, only to know how to use the concept of a half life. A half life for the purposes of pharmacokinetic calculations is the time taken for the drug concentration, if it is falling, to drop by one half of the value at the beginning of that half life period. If the concentration of a substance is rising to a given level, then it is the time necessary for the drug concentration to rise to one half of the difference between the concentration existing at the beginning of that half life period and the final concentration. This is set out in table 15.1.2.

Table 15.1.2.

** This table shows the change of plasma concentration of a drug with time as a percentage of the initial concentration achieved after a single intravenous bolus, related to multiples of the drug half life.

** The same is also shown for the situation of a constant intravenous infusion, where the change of the plasma drug concentration with time is shown as a percentage of the target concentration related to multiples of the half life of the drug.

NUMBER OF HALF LIVES	Intravenous bolus (begin concn. = 100%)	Intravenous infusion (end concn. = 100%)
0	100	0
1	50	50
2	25	75
3	12.5	87.5
4	6.25	93.75
5	3.125	96.875

b. Concentrations of drugs in various pharmacokinetic volumes.

The concentration of any substance dissolved in a given quantity of solvent is equal to the amount of that substance divided by the volume of solvent. The same is true in pharmacokinetics. In practical terms the clinician is concerned with three volumes when he injects a drug intravenously. The plasma volume, V_c and V_d. Distribution of an injected drug into these volumes results in one of three different concentrations.

$$C_{pv} = D/V_p \text{ .....(3)}$$

$$C_{vc} = D/V_c \text{ .....(4)}$$

$$C_{vd} = D/V_d \text{ .....(5)}$$

D = dose of drug in mg/kg body weight.
$\mathbf{C_{pv}}$ = plasma concentration of drug if it only distributes in the plasma volume (mg/l).
$\mathbf{V_p}$ = plasma volume in l/kg [normal range = 0.04-0.045 l/kg, see chapter 14.1].
$\mathbf{C_{vc}}$ = plasma concentration of drug if it only distributes throughout the V_c (mg/l).
$\mathbf{C_{vd}}$ = plasma concentration of drug if it is distributed throughout the V_d (mg/l).

c. Concentration after a repeat dosage.

The plasma concentration of a drug after a repeat dosage and subsequent distribution throughout the various kinetic compartments is given by the three equations below.

$$C_{pv} = X + D_r/V_p \text{ .....(6)}$$

$$C_{vc} = X + D_r/V_c \text{ .....(7)}$$

$$C_{vd} = X + D_r/V_d \text{ .....(8)}$$

X = plasma concentration of drug at the time of repeat dosage.
$\mathbf{D_r}$ = repeat dosage in mg/kg.

d. Minimum effective concentration (MEC).

The effects of a drug on any given tissue usually only manifest after a minimum tissue drug concentration has been achieved. Drug concentrations in most tissues are difficult to measure, but are directly related to plasma drug concentrations, and indeed it has been found that the effects of many drugs only occur once a minimum plasma concentration has been exceeded. This is the Minimium Effective Concentration or MEC. Values for the MEC of many drugs used in anaesthesia are listed in appendix A and appendix B.

2. Short-lasting effects of drugs with a long $T_{1/2e}$.

There are many drugs in use whose clinical effect is short, in spite of the drug possessing a relatively long $T_{1/2e}$. A good example of this is thiopentone. In appendix-A the elimination half life is given as about 11.6 hours, but when administered at a dose of 3-5 mg/kg to adults, the duration of sleep that it induces is only about 5 minutes.

A simple example calculation shows why thiopentone which has such a long elimination half life can have such a short clinical effect. Consider an average dose of 4 mg/kg. In that case;

- MEC of thiopentone = minimum sleep concentration = 23 mg/l.
- C_{pv} = 4/0.04 = 100 mg/l.
- C_{vc} = 4/0.38 = 10.52 mg/l.
- C_{vd} = 4/3.4 = 1.176 mg/l.

It is apparent from these three calculations that the hypnotic effect of thiopentone occurs before full distribution throughout the V_c has occurred, and is terminated by distribution throughout the V_c, and certainly by redistribution to the V_d ($T_{1/2d}$ = 8.5 mins). The concentration remaining after redistribution to the V_d, even were no elimination to have occurred, is far below that required for hypnosis. Indeed, the duration of the hypnotic effect of such a dose of thiopentone agrees well with this. In the first few seconds after intravenous injection, the drug is mainly in the blood. At this point, the plasma thiopentone concentration in the blood leaving the heart is even higher than is given by the C_{pv}, as mixing

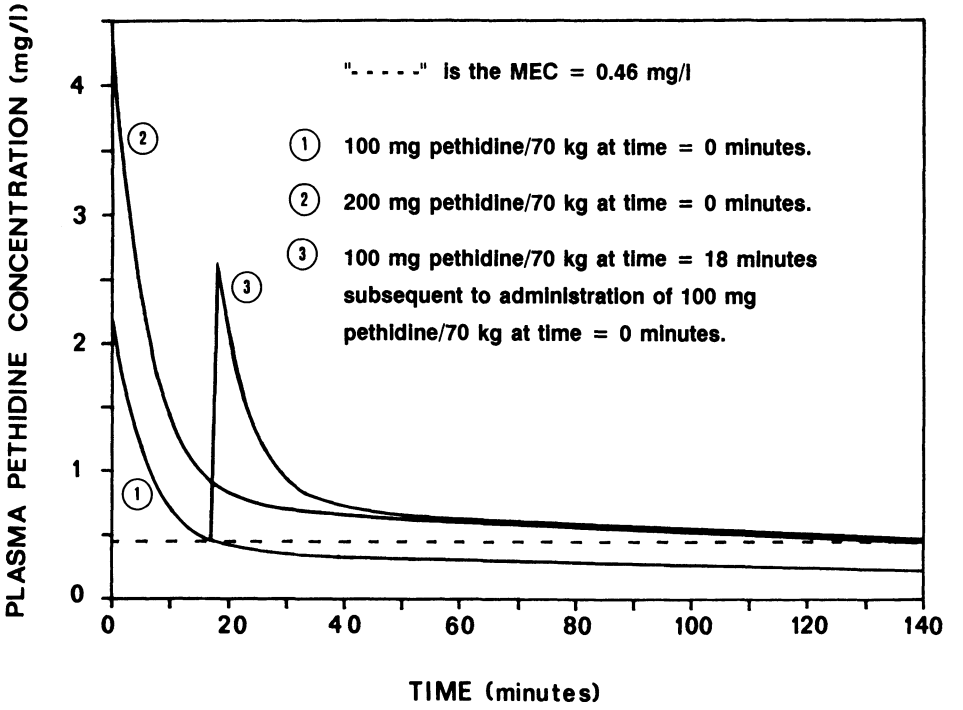

FIGURE 15.1.3. - The concentration-time curve of pethidine injected intravenously at a dose of 100 mg/70 kg initially at point '1', and after 4 times the $T_{1/2d}$ the same dose is repeated at point '3'. This shows that the second dose has a very much more prolonged effect than the initial dose because of drug accumulation. A single dose of 200 mg/70 kg at point '2' has the same duration of effect as the two smaller doses of 100 mg/70 kg, but at the cost of a much higher initial plasma concentration.

with the whole blood volume is not instantaneous. The brain is an organ with a high relative perfusion and receives a large proportion of the cardiac output. Therefore it is not surprising that the induction of sleep is so rapid, and that awakening is also rapid after a single dose. This also explains why a greater dose of thiopentone is required to induce sleep when it is injected slowly. Distribution throughout the V_c occurring during intravenous injection lowers the plasma concentration, so reducing the peak plasma concentration able to be achieved. This same type of analysis is applicable to all drugs.

3. Repeat doses have a more profound and longer effect.

The anaesthetist frequently encounters the phenomenon that a repeat dose of a drug has a more profound and longer lasting effect than the first dose. This observation is frequently made when administering intermittent thiopentone or opiates.

Consider the case of pethidine. The usual clinical dosage both postoperatively and intraoperatively is 1-1.5 mg/kg. Consider a dose of 1.4 mg/kg (100 mg in an average 70 kg adult). The MEC = 0.46 mg/kg. After intravenous injection of this dose C_{vc} = 1.4/0.63 = 2.22 mg/l. This is well above the MEC. After about 4 distribution half lives = 4 x 4.1 = 16.4 minutes, the drug is almost completely distributed throughout the distribution volume [see table 15.1.2], and the plasma concentration is given by C_{vd} = 1.4/3.0 = 0.46 mg/l. This is not an unreasonable result as the $T_{1/2e}$ = 3.2 hours, and so very little of the pethidine will have been eliminated by 16.4 minutes. This concentration is sufficient for analgesia too, but will fall below the MEC in less than one $T_{1/2e}$. More pethidine is then required.

This has been simulated using a two compartment model for pethidine pharmacokinetic data [3], and is shown in figure 15.1.3. From figure 15.1.3. it is seen that the plasma concentration falls under the MEC at about 18-20 minutes after intravenous injection. Administration of another dose of 1.4 mg/kg pethidine (100 mg/70 kg) at this time elevates the plasma concentration above that achieved by the first dose. This is also shown below, using equations 7 and 8.

- Pethidine concentration at the time of repeat injection = 0.46 mg/l.
- C_{vc} = 0.46 + 1.4/0.63 = 2.68 mg/l.
- C_{vd} = 0.46 + 1.4/3.0 = 0.92 mg/l.

Both concentrations are well above the MEC and the concentration should remain above the MEC for about one $T_{1/2e}$ (3.2 hours). This is also confirmed by the simulation in figure 15.1.3. Clinical practice also shows that a repeat dose of pethidine has a longer analgesic effect than the initial dose.

Similar principles apply to a repeat dose which is smaller than the initial dose. Here too the duration of action is also longer than would occur if that same dose had been administered without the preceding initial dose. These are good examples of the effects of drug accumulation.

4. Use of distribution or elimination phase of a drug.

In some situations, such as during anaesthesia, it is desired that the action duration of a drug be either long or short depending on requirements. An example of this is the use of opiates. A given opiate may be required to provide intraoperative analgesia for a short operation, or the same opiate may be used to provide long lasting intraoperative or postoperative analgesia. Both aims are able to be realized with the appropriate dosage, so that the MEC is achieved only in the distribution phase for situations where short action is

desired, and stays above the MEC in the elimination phase if a longer lasting effect is required.

Consider the effects of two different doses of pethidine, one dose of 1.4 mg/kg = 100 mg/70 kg, and a dose of 2.8 mg/kg = 200 mg/kg [see also fig 15.1.3].

- MEC = minimum analgesic dosage = 0.46 mg/l.
- 1.4 mg/kg : C_{vc} = 1.4/0.63 = 2.22 mg/l : C_{vd} = 1.4/3.2 = 0.44 mg/l.
- 2.8 mg/kg : C_{vc} = 2.8/0.63 = 4.44 mg/l : C_{vd} = 2.8/3.2 = 0.875 mg/l.

It is apparent from these calculations that the analgesic effect of the lower dose is unlikely to last longer than the distribution phase of the drug, i.e. about 16-17 minutes, while the effect of the larger dose is such that the plasma concentration remains higher than the MEC for about one elimination half life = 3.2 hours.

5. Single versus divided dosage.

One problem with administration of large doses of a drug is that the initial plasma concentration is very high, with accordingly a greater chance of undesired drug effects. This problem may be minimized by injecting a large drug dose in smaller divided doses.

Consider the case of pethidine again. A problem with use of pethidine, as with any opiates, in spontaneously breathing patients is respiratory depression. Respiratory depression due to pethidine is measurable at the MEC, and the degree of respiratory depression increases in direct proportion to the plasma pethidine concentation above the MEC [12]. One way of avoiding high plasma concentrations of any drug is to inject the total dose in divided doses, e.g. instead of administering a single dose of 2.8 mg/kg, the same dose could be administered as two doses of 1.4 mg/kg at an interval determined by the time that distribution of the drug is likely to have occurred = 4 x $T_{1/2d}$ = 16-17 minutes for pethidine. This is shown in figure 15.1.3, and the calculations have already been demonstrated in the previous examples.

This same method of analysis may of course be applied to any drug.

6. Duration of drug overdose or effect.

Sometimes a drug is inadvertently administered in a dosage that is higher than that intended, or the wrong drug is injected, or an intravenous infusion is discontinued.

The kinetic parameters of the drug determine the duration of its effect after any of these events. In general, it takes 3-4 elimination half lives for the amount of drug in the body to diminish to about 10% of the initial quantity. However this says nothing of the effect, which is determined by whether the plasma concentration is above the MEC or not. This is able to be illustrated by the case of discontinuation of a midazolam infusion which has been administered for sufficient time to have reached steady state. In such a case the midazolam is distributed throughout all kinetic compartments, and any reduction of plasma concentration occurs by elimination. If the initial plasma midazolam concentration was 0.4 mg/l at discontinuation of the infusion, then it will take two elimination half lives, i.e. 2 x 2.73 hours = 5.46 hours, before the patient is likely to awaken, as the MEC or sleep concentration for midazolam is 0.1 mg/l [see appendix-A]. The author's own personal experience with midazolam infusions has shown this simple method of analysis to be roughly correct.

The method of calculation of the duration of drug effect after discontinuation of an intravenous drug infusion that has not reached "steady state", or of a single intravenous drug

bolus are the same, but now the termination of effect is determined by both redistribution and elimination processes.

Table 15.1.3.
The half life of the interval between achieving a given plasma drug concentration after intravenous injection, and the effect associated with that concentration is listed for various drugs ($T_{1/2}K_{eo}$).

DRUG	$T_{1/2}K_{eo}$ (minutes)
Thiopentone [4]	1.2
Etomidate [10]	1.6
Fentanyl [5]	6.4
Alfentanil [5]	1.1
d-Tubocurarine [6]	4.7-7.9
Vecuronium [11]	2.6

RELATIONSHIP OF PLASMA CONCENTRATION TO DRUG EFFECT

The impression may have been created in the preceding discussion that the effect of a drug is directly related to the plasma or blood concentration. This is not entirely true.

Consider the case of an intravenous bolus of a drug. Shortly after injection, the plasma drug concentration is greater than the drug concentration in the tissues on which the drug exerts its clinical effects. The drug is subsequently redistributed and eliminated. During elimination the plasma drug concentration is lower than that in the tissues where the drug exerts its clinical effects. It is apparent from this that the plasma concentration at which the drug effects occur during the distribution phase is higher than that at which the same effect occurs during the elimination phase. This is because it takes time for the drug to diffuse from the blood into the effector tissues, and vice versa. Because the process is one of diffusion, it is also described by an exponential equation, and as such is associated with a half life, the $T_{1/2}K_{eo}$. Table 15.1.3 lists the $T_{1/2}K_{eo}$ for some drugs. It should be noted when looking at these figures that clinical effects can manifest before even one $T_{1/2}K_{eo}$ has elapsed. This is determined by the dose of the drug administered. A high initial plasma drug concentration will cause rapid elevation of the tissue drug concentration.

During an intravenous infusion of a drug, the same arguments apply to the plasma concentrations at which a drug effect occurs after starting and discontinuation of an infusion. However there is a direct relationship between plasma drug concentration and effect when the intravenous infusion has achieved steady state conditions, as the relationship between plasma and tissue drug concentrations is constant at this time. "Steady state" has occurred during an intravenous infusion when the amount of drug infused into the body equals the amount being eliminated.

CALCULATIONS USING KINETIC PARAMETERS

The preceding paragraphs have shown the didactic uses to which these simple pharmacokinetic principles can be put, but it is also possible to perform a number of clinically useful calculations using the kinetic data in appendix-A. Some of these formulae have been discussed in the preceding paragraphs. They may be used to calculate;

- degree of ionization of a drug at a given pH,
- bolus intravenous dosages, and subsequent repeat dosages,
- or intravenous infusion regimes.

1. Drug ionization.

The tables of kinetic data in appendix-A also give the pKa of many of the drugs. The pKa is the pH at which 50% of the drug is ionized in solution. This, plus knowledge of whether a drug is an acid or a base may be used to calculate the degree of ionization at any pH of a drug whose pKa is known.

Most drugs are only active in their non-ionized state. But there are some drugs, e.g. local anaesthetic agents and neuromuscular blocking drugs, which are only active when ionized. Diffusion of drugs across biological membranes is only possible in the non-ionized state. These few aspects of drug transfer make it apparent that the degree of ionization does have practical significance.

Formulae which may be used to calculate the percentage ionization at any pH for acid and basic drugs are presented below.

ACIDS

$$\%\text{IONIZATION} = 100 \times [\text{antilog}(\text{pH}-\text{pKa})]/[1 + \text{antilog}(\text{pH}-\text{pKa})] \quad \text{....(9)}$$

BASES

$$\%\text{IONIZATION} = 100 \times [\text{antilog}(\text{pKa}-\text{pH})]/[1 + \text{antilog}(\text{pKa}-\text{pH})] \quad \text{....(10)}$$

1. Bolus intravenous dosages and subsequent repeat doses.

a. Bolus dose calculation.

The magnitude of an intravenous bolus dose depends on the effect desired. The relevant formulae are listed below.

$$D_{pv} = C_p \times V_p \quad \text{.....(11)}$$

$$D_{vc} = C_p \times V_c \text{ .....(12)}$$

$$D_{vd} = C_p \times V_d \text{ .....(13)}$$

C_p = desired plasma concentration in mg/l.
D_{pv}, D_{vc}, D_{vd} = the minimum dose of a drug in mg required to achieve a given C_p if the drug is only to achieve that concentration if distributed only in the plasma volume, V_c or V_d respectively.

The duration of drug effect is able to be very roughly approximated by using the plasma half lives and the MEC for the drug in question, and the methods already used.

b. Calculation of a repeat dose.

Calculation of the magnitude of a repeat dose may be done by rearranging the equation below.

$$C = X + D/V \text{ .....(14)}$$

Where C is the concentration achieved after administering a dose 'D' of a drug which is distributed throughout a volume 'V', while there was already some drug present in the body with a plasma concentration 'X'.

Equation 11 may be rearranged to give the three formulae below.

$$D_{pv} = V_p \times (C_p - X) \text{ .....(15)}$$

$$D_{vc} = V_c \times (C_p - X) \text{ .....(16)}$$

$$D_{vd} = V_d \times (C_p - X) \text{ .....(17)}$$

The duration of the effect of the repeat dose can be roughly calculated using the MEC and the half lives.

Example.

Consider the use of the drug fentanyl. Assume an average 70 kg patient, to whom 0.2 mg fentanyl is administered at the start of an operation.

- The initial plasma concentration is C_{vc} = 0.2/(70 x 0.77) = 0.0037 mg/l, which is above the MEC of 0.001-0.002 mg/l. The patient initially has sufficient analgesia for a not too painful operation. But the plasma concentration of fentanyl falls to 0.0018 mg/l after one distribution half life = 9 minutes, after which analgesia is just adequate. After 2 distribution half lives = 18 minutes, the plasma concentration is about 0.0009 mg/l which is inadequate for analgesia.
- The operation is expected to last another 4 hours, and the anaesthetist decides that he wishes to administer a single dose of fentanyl to provide analgesia for this

time. Let the C_p at the end of the operation be 0.001 mg/l, a concentration just insufficient to provide intraoperative analgesia. As one elimination half life of fentanyl is about 4.4 hours, the repeat dose should be such that the C_{vd} at the beginning of the 4 hour period is 0.002 mg/l. The existing plasma concentration of fentanyl at the time of the repeat dose is 0.0009 mg/l, therefore using equation 17 of this chapter, the D_{vd} is;

- $D_{vd} = 3.81 \times (0.002 - 0.0009) = 0.0042$ mg/kg = 0.293 mg/70 kg.

The supplemental dose required to provide analgesia for 4 hours is about 0.29 mg for this hypothetical 70 kg patient.

It may be said that this simulation does not actually correspond with reality. But it should always be remembered that during anaesthesia, fentanyl is always administered simultaneously with other drugs which potentiate its analgesic effect, e.g. nitrous oxide, anaesthetic gases, opiates in the premedication, etc..

3. Calculation of an infusion regime.

It is occasionally desired to administer anaesthetic drugs by intravenous infusion. There are a number of factors that must be considered when considering such an infusion.

a. Calculation of infusion rate.

When an intravenous drug infusion has achieved "steady state" conditions, the rate at which a drug is infused is equal to the rate at which it is eliminated from the body. In addition, the plasma concentration of the drug is constant, and the relationship between the plasma and other tissues drug concentrations is also constant. The rate of infusion under steady state conditions is dependent on only one kinetic parameter, the whole body clearance of the drug, and is calculated in the same way regardless of the number of compartments in the kinetic model used for that drug.

$$\mathbf{Q = C_{pss} \times Cl} \quad .....(18)$$

Q = infusion rate, mg/kg/hr.
C_{pss} = steady state plasma concentration in mg/l.
Cl = whole body clearance of drug as l/kg/hr.

b. Calculation of loading dose.

If an intravenous infusion is commenced at a constant infusion rate calculated by equation 18 above, it takes 4 elimination half lives of that drug before the plasma concentration has reached 93.75% of the desired C_{pss}. This is not a problem for drugs such as dobutamine with a very short $T_{1/2e}$, but it means that the infusion has little to no clinical effect for a long time for drugs with a long $T_{1/2e}$. This is because it takes time for the infused drug to distribute within the body. To bypass this problem a "loading dose" of the drug is administered simultaneously with the commencement of an intravenous infusion.

The purpose of a loading dose of a drug is to rapidly provide a plasma concentration of that drug equal to or greater than the C_{pss}, and maintain that concentration greater than this until the infusion can maintain the plasma drug concentration at the C_{pss}. There are a

large number of methods of calculating and administration of a loading dose, each with its own advantages and disadvantages. The interested reader is referred to the papers by Wagner [7], Rigg and Wong [8], and Lauven et al [9].

By far the simplest, and clinically most easily applicable, method of calculating and administering a loading dose is to use the method of Mitenko and Ogilvie [8]. The loading dose is administered as an intravenous bolus at the same time as the infusion is started. Loading dose is calculated on the basis of the loading dose achieving the C_{pss} if it were distributed throughout the V_d.

$$D_L = C_{pss} \times V_d \quad .....(19)$$

D_L = loading dose in mg/kg

Of course, shortly after injection the drug is only distributed within the V_c, and so the plasma concentration is much higher than the C_{pss}. The drug then redistributes throughout the V_d, and simultaneously with this redistribution process, the intravenous infusion is also infusing drug into the body. The result of this is that the plasma concentration never falls below the C_{pss}. One disadvantage of this technique is that the initial plasma concentration of drug may be high enough to cause undesired effects from the drug being infused. However in practice this does not arise too often, and is able to be avoided by dividing the loading dose into smaller doses and administering them at intervals, or as an infusion where the duration of the loading infusion is short in relation to the $T_{1/2e}$ of the drug.

An example of the application of these equations is the calculation of an infusion of midazolam for hypnosis of patients in an intensive care unit [kinetic data and MEC are to be found in appendix-A].

- desired C_{pss} = MEC = 0.1 mg/l = threshold plasma concentration for hypnosis.
- $D_L = C_{pss} \times V_d = 0.1 \times 1.91 = 0.191$ mg/kg = 13.4 mg/70 kg.
- $Q = C_{pss} \times Cl = 0.1 \times 0.48 = 0.048$ mg/kg/hr = 3.4 mg/70 kg/hr.

As can be seen, the calculations are not difficult. Should the infusion be inadequate, the infusion rate can always be increased after administration of another intravenous loading dose, using equation 20 in this chapter to calculate the new loading dose, and equation 18 to calculate the new infusion rate.

$$D_{L(repeat)} = V_d \times (C_{pss} - X) \quad .....(20)$$

X = plasma drug concentration existing at time of repeat loading dose.
$D_{L(repeat)}$ = repeat loading dose.

REFERENCES

1. Greenblatt,D.J., Koch-Weser,J.,(1975), Clinical pharmacokinetics (first of two parts). NEW ENGLAND JOURNAL OF MEDICINE, 293, 702-705.
2. Christensen,J.H., et al.,(1980), Pharmacokinetics of thiopentone in a group of young women and a group of young men. BRITISH JOURNAL OF ANAESTHESIA, 52, 913-917.
3. Mather,L.E., et al.,(1974), Meperidine kinetics in man. Intravenous injection in surgical patients and volunteers. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 17, 21-30.
4. Homer,T.D., Stanski,D.R. (1985), The effect of increasing age on thiopental disposition and anesthetic requirement. ANESTHESIOLOGY, 62, 714-724.
5. Scott,J.C., et al.,(1985), EEG quantification of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. ANESTHESIOLOGY, 62, 234-241.
6. Stanski,D.R., et al.,(1979), Pharmacokinetics and pharmacodynamics of d-tubocurarine during nitrous oxide-narcotic and halothane anesthesia in man. ANESTHESIOLOGY, 51, 235-241.
7. Wagner,J.G.,(1974), A safe method for rapidly achieving plasma concentration plateaus. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 16, 691-700.
8. Rigg,J.R.A., Wong,T.Y.,(1981), A method for achieving rapidly steady-state blood concentrations of i.v. drugs. BRITISH JOURNAL OF ANAESTHESIA, 53, 1247-1257.
9. Lauven,P.M., et al.,(1982), Ein pharmakokinetisch begründetes Infusionsmodell für Midazolam. Eine mikroprozessorgesteuerte Applikationsform zur Erreichung konstanter Plasmaspiegel. DER ANAESTHESIST, 31, 15-20.
10. Arden,J.R., et al.,(1986), Increased sensitivity to etomidate in the elderly: Initial distribution versus altered bain response. ANESTHESIOLOGY, 65, 19-27.
11. Veen,F. vd, Bencini,A.,(1980), Pharmacokinetics and pharmacodynamics of ORG NC45 in man. BRITISH JOURNAL OF ANAESTHESIA, 52, 37S-41S.
12. Rigg,J.R.A., et al.,(1981), Relationship of ventilatory depression to steady-state blood pethidine concentrations. BRITISH JOURNAL OF ANAESTHESIA, 53, 613-619.

Chapter 15.2

FACTORS MODIFYING DRUG KINETICS

Disease and variations of normal physiology can considerably modify drug kinetics, as well as altering the responses of the patients affected to any drugs that are administered. These effects should all be taken into account when selecting and using anaesthetic drugs. This subject has already been touched upon in the chapters dealing with specific diseases, and this chapter will further discuss some of these factors.

RATE & ROUTE OF DRUG ADMINISTRATION

1. Oral administration.

The peak plasma concentration of a drug is usually achieved at a time between 1-3 hours after oral administration. Hepatic clearance of orally administered drugs as they enter the liver via the portal vein after intestinal absorbtion, reduces the amount of drug actually entering the systemic circulation. This is called the "first pass effect".

2. Intramuscular administration.

Drug absorbtion is more rapid after intramuscular injection in the deltoid than in the gluteus muscle, as the deltoid is more vascular than the gluteus muscle. Peak plasma drug concentrations occur about 30 minutes after intramuscular injection of most opiate and sedative drugs. One advantage of intramuscular administration is that the total quantity of the drug actually reaching the circulation is not initially reduced by the "first pass effect".

About one hour after intramuscular administration of opiates, the plasma concentrations, and their rate of decline, are the same as that occurring one hour after intravenous administration of the same opiate at the same dose [21,22]. This has clinical application, as intravenous bolus drug kinetics may then be used to approximately calculate drug concentrations after this time. A clinical application of this is the calculation of dosage schemes for intramuscular administration of opiates for analgesia.

3. Intravenous administration.

Most drugs used during anaesthesia are administered intravenously. There are a number of clinically important consequences of using the intravenous route of drug administration.

a. High plasma concentrations.

As drugs are injected directly into the systemic circulation, no hepatic drug extraction occurs during drug absorbtion as it does after oral drug administration. In addition to this, drug entry into the systemic circulation is more rapid after intravenous than after any other

route of administration. Both of these factors mean that peak plasma drug concentrations are higher after intravenous administration than after oral administration. Any drug related undesired effects due to high plasma drug concentrations are accordingly more likely after intravenous, than after oral administration.

b. Rate of administration.

The more rapidly a drug is administered intravenously, the higher the initial intracardiac, vascular smooth muscle, and cerebral concentrations of that drug. This has a number of important clinical consequences.

i. Some drugs relax vascular smooth muscle, e.g. the barbiturates [1], or depress the myocardium as do etomidate and thiopentone [2]. Many drugs have both effects. Rapid intravenous injection will cause such drugs to induce a more profound degree of cardiovascular depression than would occur with a slower injection rate.
ii. If the drug has a central nervous system effect, e.g. hypnosis, rapid intravenous injection will induce hypnosis more rapidly at a given dose because of the higher brain drug concentrations achieved. Another consequence of this is that a smaller dose of a hypnotic drug is required to induce a given level of hypnosis if it is injected rapidly.

CARDIAC OUTPUT

Cardiac output has a profound effect on drug kinetics, as it is blood flow to the various organs of the body that determines the rates of redistribution and elimination of a drug.

1. Low cardiac output.

There are a number of causes of reduced cardiac output particularly relevant to anaesthetic practice.

- High doses of gaseous anaesthetic drugs.
- High spinal or epidural anaesthesia.
- Hypovolaemia.
- Circulatory shock.
- Heart failure.
- Hypothyroidism.
- Hypothermia.
- Old age.

a. Reduction of the cardiac output causes a lengthening of the $T_{1/2d}$ as drugs are more slowly redistributed from organs with a relatively high flow to organs with a lower relative flow. A good example of this is the slower kinetic intercompartemental transfer rates of thiopentone in persons with a low cardiac output [3].

b. If a drug remains longer in the central circulation, the heart and blood vessels are subjected to high concentrations of drug for a longer time. More drug diffuses into the myocardium and blood vessel walls. The result of this is a more profound cardiovascular depression due to drugs capable of this.

c. Organs with the highest relative blood flows are those with the highest tissue drug concentrations shortly after intravenous drug administration. One consequence of this is that the sleep dose of anaesthetic induction agents is decreased in direct proportion to any reduction of cardiac output, as the relative proportion of the cardiac output going to the brain increases with decreasing cardiac output [see table 2.8.1]. Certainly this has been shown to be the case with thiopentone, where the sleep dosage is directly proportional to the cardiac output [3].

d. A reduced cardiac output means reduced venous and arterial flow rates. It takes longer for an intravenously administered drug to reach its target organs, and the effect lasts longer as the drug is eliminated more slowly.

e. The extraction of a drug by liver or kidney may be so great that liver or kidney blood flow are important determinants of the $T_{1/2e}$. A reduction of cardiac output decreases clearance of such drugs, e.g. lignocaine [4].

2. Elevated cardiac output.

Causes of elevation of cardiac output relevant to anaesthetic practice are listed below.

- Pain.
- Anxiety, terror, fear, etc.
- Fever.
- Inotropic drugs.
- Hyperthyroidism.
- Liver disease.
- Right-to-left intracardiac shunting.
- Arteriovenous shunting, e.g. renal haemodialysis shunts.
- Administration of vasodilator drugs.

The effects of a high cardiac output are the reverse of those occurring with a low cardiac output. Time to onset of action is reduced, action duration is less than usual, and there is less cardiovascular depression from drugs which are capable of doing this. The dosage required for a given effect is larger because redistribution and elimination occur more rapidly. For example, induction of hypnosis in a patient with an elevated cardiac output requires a higher dose of an induction agent, e.g. thiopentone, as elevation of cardiac output significantly shortens the time for distribution from the plasma to the V_c. This is frequently observed in febrile, or very anxious patients and those with severe liver disease. These patients not only require a greater than normal dose of a hypnotic drug to induce sleep, but also wake up from that dose more rapidly than normal patients.

ALTERED KINETIC COMPARTMENTAL VOLUMES

Variations in normal physiology or disease may change the various kinetic compartmental volumes.

1. Reduced blood volume.

The blood is the first volume in which an intravenously injected drug is mixed. A reduction of blood volume increases the initial plasma concentration of a given dose of a drug in direct proportion to the reduction of blood volume [see equation 2, chapter 14.4], with as a result the hypnotic dose of intravenous anaesthetic drugs such as ketamine and thiopentone are decreased by the same percentage as the reduction of blood volume [7]. In addition to the reduction of hypnotic dosage, the higher initial plasma concentration of a given dosage of most drugs causes a more profound cardiovascular depression [8,9].

a. V_c and hypovolaemia.

The V_c is not reduced by hypovolaemia, except for drugs such as non-depolarizing neuromuscular blocking drugs whose V_c is about equal to the plasma volume. Usually the V_c is much greater than the blood volume, so any reduction of the blood volume sufficient to cause significant haemodynamic effects is unlikely to affect the V_c.

Example.

Consider the effect of a 50% reduction of the blood volume on the V_c of midazolam.

- blood volume = 0.07 l/kg.
- V_c of midazolam = 0.58 l/kg.
- New V_c after 50% reduction of the blood volume = 0.58 - 0.07/2 = 0.545 l/kg.

A 50% reduction of blood volume will in theory reduce the V_c to 0.545 l/kg, hardly a large reduction from 0.58 l/kg. Indeed, the absence of any significant effect of haemorrhage of up to 30% of the blood volume on the V_c has been confirmed experimentally for midazolam [8].

b. V_d and hypovolaemia.

Similarly, by consideration of the above example, and reference to appendix-A, it is apparent that the distribution volumes of most drugs will not be significantly altered by degrees of haemorrhage that are compatible with life.

2. Reduced central compartment volume.

The central compartment is not really an anatomical compartment, but is a functional compartment whose volume is determined by the blood volume, the cardiac output and the rate at which a drug can diffuse into perivascular tissues. It is the cardiac output that determines the rapidity with which blood is distributed throughout this compartment.

Reduction of the V_c may be caused by a number of factors.

- Reduced cardiac output.
- Old age, e.g. thiopentone [5] or etomidate [6].

A reduction of the V_c means that the initial plasma concentrations of a drug after injection are higher than normal for a given dose. As a result of this the initial myocardial, vascular smooth muscle, and brain concentrations of the drug are also higher than normal for a given dose of that drug.

a. If a drug causes cardiovascular depression, the higher myocardial and vascular smooth muscle concentrations induce a greater degree of depression than normal at all dosage levels.

b. Higher brain concentrations of drugs for a given dose mean that a lower dosage of hypnotic drugs is required for a given depth of hypnosis, e.g. of thiopentone [5] and etomidate [6].

3. Altered distribution volume.

The distribution of drugs depends on a number of factors, such as the degree of ionization, protein binding, fat solubility and water solubility. The main effect of a change of V_d is to change the $T_{1/2e}$. The relationship between $V_{d\beta}$, Cl and $T_{1/2e}$ is given by equation 1.

$$T_{1/2e} = \frac{0.693 \times V_{d\beta}}{Cl} \quad .....(1)$$

a. Highly ionized and water soluble drugs are distributed almost exclusively throughout the ECFV, e.g. neuromuscular blocking agents and dobutamine. An increase of the ECFV such as occurs in cardiac oedema increases the V_d of such drugs, e.g. dobutamine [10]. A reduction of the ECFV as occurs in old age and dehydration would be expected to decrease the V_d.

b. Highly protein bound drugs tend to a have a smaller volume of distribution than poorly protein bound drugs, as they tend to remain bound to plasma proteins within the circulation. Hypoproteinaemia increases the plasma free drug concentration, and so increases the V_d of such drugs, because more of the drug is able to diffuse out of the circulation. The clinical effect of a given dose of highly protein bound drugs is increased in proportion to the degree of hypoproteinaemia in hypoproteinaemic patients [11].

c. The V_d of highly fat soluble drugs is increased in obesity due to the relative increase in body fat per unit body weight, e.g. midazolam [12]. The effect of an elevation of V_d without any change in whole body clearance is an increase of $T_{1/2e}$.

ALTERATIONS OF WHOLE BODY CLEARANCE

The clearance is what determines the rate of elimination of a drug. It is related to the $V_{d\beta}$ and the $T_{1/2e}$ by equation 1 above. A reduction of clearance increases $T_{1/2e}$, increasing the duration of effect of drugs whose clinical action duration is determined by $T_{1/2e}$. The reverse occurs with increased drug clearance.

Whole body clearance of a drug is dependent on a number of factors.

1. The cardiac output.

The greater the quantity of drug that is presented to a drug metabolizing and excreting organ per unit time, the greater the quantity of drug that is eliminated, and the geater

the clearance. Drugs whose hepatic or renal extraction is low have a clearance which is less dependent on organ flow than those drugs whose extraction is high.

2. Protein binding.

The more highly protein bound a drug, the less free drug there is available for diffusion out of the capillaries into the parenchyma of organs eliminating that drug, and so the less the clearance.

3. Intrinsic organ clearance.

This is the ability of the eliminating organs to eliminate drugs. Patients with liver or renal dysfunction, or both, have a reduced intrinsic clearance of one or both of these organs [see chapters on liver and renal disease].

EFFECTS OF SPECIFIC CONDITIONS ON KINETICS AND DRUG EFFECTS

Variations of normal physiology, and disease may all alter the kinetics and effects of drugs administered during anaesthesia. These will be discussed briefly below.

1. Hypovolaemia.

Both the blood volume and cardiac output are reduced. The effects of these changes have been discussed above [see also chapter 14.4].

2. Cardiac failure and myocardial infarction.

The cardiac output is reduced in cardiac failure, and is reduced after a myocardial infarction in which more than 20-25% of the myocardium has been damaged [see chapter 2.9]. The effects of reduced cardiac output on drug kinetics have already been discussed in this chapter. Oedema due to heart failure may elevate the V_d of some more water soluble drugs.

3. Changes of body temperature.

The cardiac output is elevated in febrile patients [12], and reduced in hypothermia [13]. The effects of these changes have been discussed.

4. Acid-base disorders.

Acid-base disorders affect the degree of drug ionization by altering the pH of the body fluids. The percentage ionization of a drug can be calculated using equations 9 and 10 in chapter 15.1. Because the exact pH in each tissue is never known, all that can be said is that the degree of ionization is changed by an acid-base disorder. Acidic drugs are more ionized in alkalosis, and less ionized in acidosis, while the reverse is the case for basic drugs. The degree of ionization of a drug affects both the ability of the drug to penetrate into the target organs, as well as its activity once there. For example;

a. the ionized form of a drug cannot cross biological membranes,

b. except for muscle relaxant and local anaesthetic drugs, it is the non-ionized form of a drug that is active.

- Consider the case of the local anaesthetic drugs. These are basic drugs which must diffuse into the nerve axon where they are active. Diffusion across biological membranes only occurs when the drug is in a non-ionized form. Once inside the axon, it is the ionized form which blocks the sodium channels. Acidosis, either local or generalized, reduces the effect of these drugs by increasing the percentage of ionized drug in the extracellular space, so decreasing the amount of local anaesthetic that can diffuse into the axon. The reverse occurs with alkalosis.
- The opiates are another important drug group whose distribution is influenced by acid-base status. These are also basic dugs. Alkalosis significantly increases, and acidosis decreases the brain concentration of morphine [14] and fentanyl [15] relative to the plasma concentration. The effect of these changes is that alkalosis increases the potency of opiates, while acidosis reduces opiate potency.

5. Altered plasma protein concentrations.

Hypoproteinaemia increases the free plasma concentration of a drug. This increases the effect of a given dosage of a highly protein bound drug as there is more free drug available to diffuse into tissues where the drug is active.

Another effect of hypoproteinaemia is to increase plasma clearance of highly protein bound drugs as more drug is available to diffuse into the liver and renal glomerular filtrate.

The reverse effects are true for hyperproteinaemia.

6. Renal disease.

See chapter 9.4.

7. Liver disease.

See chapter 10.3.

8. Obesity.

Obesity has considerable effects on drug kinetics [16]. The V_d of lipophilic drugs increases while the clearance is generally not much changed. The result is a lengthening of the elimination half life of these drugs.

Another effect is observed with volatile anaesthetic agents. These are in general a very lipophilic group of drugs. However despite this the recovery from general anaesthesia is not delayed with these drugs relative to the speed of recovery with intravenous agents [17]. But the degree of metabolism of these drugs as a group is probably increased in obese patients. Certainly this is the case for halothane [18].

9. Old age.

The physiological performance and composition of the body varies with age. This has a corresponding effect on drug kinetics and pharmacodynamics [20]. The elderly adult has undergone a number of significant physiological changes relative to the young adult.

- The resting cardiac output in the 70 year old adult is on average about 30% less than that an adult of 20 years of age [19].
- Plasma albumin concentration decreases with age [20].
- The quantity of body fat increases with age in both men and women, eventually becoming double that in young persons [20].
- Renal function declines with age [20].

The implications of all these changes have been discussed in the beginning of this chapter. In general, the elimination half lives of most drugs are increased in the elderly, either due to elevation of the V_d, reduction of the clearance, or both. The changes in physiology due to the aging process causes most drugs used in anaesthesia to induce a greater degree of cardiovascular depression in aged patients than that which occurs in younger persons who are administered the same dose.

REFERENCES

1. Altura,B.T., Altura,B.M.,(1975), Barbiturates and aortic and venous smooth-muscle function. ANESTHESIOLOGY, 43, 432-444.
2. Kissin,I., et al.,(1983), Inotropic and anesthetic potencies of etomidate and thiopental in dogs. ANESTHESIA AND ANALGESIA, 62, 961-965.
3. Christensen,J.H., et al.,(1982), Pharmacokinetics and pharmacodynamics of thiopentone. A comparison between young and elderly patients. ANAESTHESIA, 37, 398-404.
4. Benowitz,N., et al.,(1974), Lidocaine disposition kinetics in monkey and man. II. Effects of hemorrhage and sympathomimetic drug administration. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 16, 99-109.
5. Homer,T.D., Stanski,D.R. (1985), The effect of increasing age on thiopental disposition and anesthetic requirement. ANESTHESIOLOGY, 62, 714-724.
6. Arden,J.R., et al.,(1986), Increased sensitivity to etomidate in the elderly: Initial distribution versus altered brain response. ANESTHESIOLOGY, 65, 19-27.
7. Weiskopf,R.B., Bogetz,M.S.,(1985), Haemorrhage decreases the anaesthetic requirement for ketamine and thiopentone in the pig. BRITISH JOURNAL OF ANAESTHESIA, 57, 1022-1025.
8. Adams,P., et al.,(1985), Midazolam pharmacodynamics and pharmacokinetics during acute hypovolemia. ANESTHESIOLOGY, 63, 140-146.
9. Weiskopf,R.B., et al.,(1984), Cardiovascular and metabolic sequelae of inducing anesthesia with ketamine or thiopental in hypovolemic swine. ANESTHESIOLOGY, 60, 214-219.
10. Kates,R.E., Leier,C.V.,(1978), Dobutamine pharmacokinetics in severe heart failure. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 24, 537-541.
11. Wood,M.,(1986), Plasma drug binding: Implications for anesthesiologists. ANESTHESIA AND ANALGESIA, 65, 786-804.
12. Bull,J.M., et al.,(1979), Whole body hyperthermia: A phase-1 trial of a potential adjuvant to chemotherapy. ANNALS OF INTERNAL MEDICINE, 90, 317-323.
13. Blair,E., et al.,(1956), Posthypothermic circulatory failure. I. Physiologic observations on the circulation. CIRCULATION, 13, 909-915.
14. Schulman,D.S., et al.,(1984), Blood pH and brain uptake of 14C-morphine. ANESTHESIOLOGY, 61, 540-543.
15. Ainslie,S.G., et al.,(1979), Fentanyl concentrations in brain and serum during respiratory acid-base changes in the dog. ANESTHESIOLOGY, 51, 293-297.
16. Abernethy,D.R., Greenblatt,D.J.,(1982), Pharmacokinetics of drugs in obesity. CLINICAL PHARMACOKINETICS, 7, 108-124.
17. Cork,R.C., et al.,(1981), General anestesia for morbidly obese patients - An examination of postoperative outcomes. ANESTHESIOLOGY, 54, 310-313.
18. Bentley,J.B., et al.,(1982), Halothane biotransformation in obese and nonobese patients. ANESTHESIOLOGY, 57, 94-97.
19. Brandfonbrener,M., et al.,(1955), Changes in cardiac output with age. CIRCULATION, 12, 557-566.
20. Crooks,J., et al.,(1976), Pharmacokinetics in the elderly. CLINICAL PHARMACOKINETICS, 1, 280-296.
21. Stanski,D.R., et al.,(1978), Kinetics of intravenous and intramuscular morphine. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 24, 52-59.
22. Bullingham,R.E.S., et al.,(1980), Buprenorphine kinetics. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 28, 667-672.

APPENDIX - A

ANAESTHETIC DRUG KINETIC, DYNAMIC & METABOLIC PARAMETERS

The table in this appendix lists the clinically most relevant properties of many of the drugs commonly used in anaesthesia. Pharmacokinetic parameters are for healthy adult volunteers, or ASA class I-II adults undergoing elective surgical procedures. These parameters are of course somewhat different in other age groups, such as the very young or aged, and are also modified by disease [see chapter 15.2].

This table has as its main purpose the provision of data with which;

- a more informed estimate can be made as to the duration of drug effect in the average patient,
- the dose at which a given effect may be expected,
- data with which to calculate intravenous infusion regimes,
- and as an aid to selection of drugs in those patients with diseases affecting the organs eliminating the drugs used, the protein binding, or acid-base balance.

Data used for the table are derived from a large variety of sources. Kinetic data are as far as possible derived from single intravenous bolus, rather than an intravenous infusion studies. Studies using a two-compartment analysis were given preference over those using a three-compartment analysis as this increases the accuracy of kinetic calculations which use the equations and methods in chapter 15.1 more accurate. Only those kinetic studies where the plasma concentrations were measured for at least three elimination half lives of the drugs were chosen. The units in which the parameters are expressed may deviate somewhat from the standard units given in many articles. However this is done with a view to eliminating conversions from one unit to another when making simple calculations.

Various abbreviations are used in the tables. These are explained below.

- '*' after the drug name means that the kinetic data are derived from a three compartment model. The kinetic data for drugs which do not have an asterisk after the name are derived from a two compartment model.

- $T_{1/2d}$ = distribution half life in minutes.

- $T_{1/2e}$ = elimination half life in hours.

- V_c = central compartment volume in liters/kg.

- **V_d** = the $V_{d\beta}$ or the $V_{d(area)}$ distribution volume calculated on the basis of changing plasma concentrations of the drug as after intermittent intravenous bolus injection, in liters/kg.

- **Cl** = plasma or whole body clearance of the drug in liters/ kg/hour.

- **MEC** = minimum effective plasma drug concentration.

- **SLEEP** = minimum plasma concentration required to induce sleep.

- **ANALGESIA** = minimum plasma concentration required for perioperative analgesia.

- **EC95** = plasma concentration at which a neuromuscular blocking agent causes 95%, (relative to pre-drug control), twitch height depression of peripheral skeletal muscles on testing with a peripheral nerve stimulator. This degree of muscle relaxation is sufficient for intra-abdominal surgery.

- **pKa** = the pH at which a substance is 50% ionized in solution. The 'B' and 'A' after the pKa indicates whether the drug in question is an acid or a base.

- **% IONIZED** (pH = 7.4) = percentage ionization of a drug at pH = 7.4.

- **ELIMINATION** = percentage of drug eliminated by various means per 24 hours.

- **BILE** = percentage of drug dose excreted unchanged in the faeces per 24 hours.

- **URINE** = percentage of drug dose excreted unchanged in the urine per 24 hours.

- **METAB** = Percentage of dose metabolized per day in the body.

N.B. Should any reader wish to perform computer or other mathematical simulations using these data he is advised to refer to the original articles for a more extensive view of the kinetic data for these drugs. Useful algorithms for computer simulation of two-compartment kinetics are to be found in reference 79, and for three compartment model simulation in reference 80.

KINETIC AND DYNAMIC PARAMETERS OF DRUGS USED IN ANAESTHESIA - 1

DRUG	$T_{1/2d}$ (min)	$T_{1/2e}$ (hrs)	V_c (l/kg)	V_d (l/kg)	Cl (l/kg /hr)	MEC (mg/l)	% Protein binding	pKa	% ionized (pH = 7.4)	ELIMINATION (% dose/24 hours) BILE	URINE	METAB	REFERENCES
INDUCTION AGENTS						SLEEP							
Thiopentone*	8.5	11.6	0.38	3.4	0.2	23	85	7.6A	39	?	<1	most	1,2,3,4,10
Methohexitone*	5.6	3.9	0.35	3.7	0.65	3.4	73	7.9A	24	?	<1	most	2,5,6,10
Hexobarbitone	23.4	5.4	0.54	1.6	0.2	10	47	A	?	?	0.3	43	7,10
Pentobarbitone	10	22.3	0.44	1.0	0.03	?	66	8.0A	20	?	<1	some	8,9,10
Etomidate	2.6	1.1	0.3	2.2	1.4	0.3	75	4.24B	0	0	2	90	11,12,13,14
Ketamine	11	2.5	0.86	3.1	1.1	0.9	12	7.5B	56	0	2.3	>20	15,16,17
Profolol	2.5	0.91	0.63	4.7	3.6	1.1	?	B	?	2	<0.3	>95	18,19
OPIATES						ANALGESIA							
Morphine	4.4	1.85	1.1	5.16	2.01	0.015	36	7.93B	77	5-10	9-11	>49	20,21,22,27
Pethidine	4.1	3.2	0.63	3	0.7	0.46	40	8.5B	93	?	7	>13	23,24,25
Methadone	6.1	35	1.1	8.2	0.16	0.06	85	9.26B	98.6	0.6	13	9	26,27,28
Pentazocine	?	3.4	?	5.6	1.2	0.03	?	9.16B	98.3	<2	16	most	29,30,31
Buprenorphine*	2.1	2.33	0.13	2.7	0.8	0.001	96	8.51B	93	68	0	>27	32,33
Phenoperidine	2.2	3.2	0.9	6.8	1.5	0.005	?	B	?	?	2.3	?	34,35,36
Fentanyl	9	4.4	0.77	3.81	0.65	0.002	84	8.4B	91	1.2	6	77	37,38,81
Alfentanil	3.8	1.14	0.17	0.54	0.33	0.2	92	6.5B	11	?	0.4	most	38,39,40,78
Sufentanil*	1.4	2.7	0.16	2.9	0.76	?	93	B	?	?	?	?	41
ANALEPTICS & OPIATE ANTAGONISTS						MEC							
Naloxone	1.8	0.32	0.81	2.4	5.3	?	?	7.82B	72	0	0	54	42,43
Doxapram*	5.5	5.9	0.44	3.2	0.36	2-3	?	B	?	?	<5	most	44,45
Physostigmine	2.3	0.36	?	0.6	1.2	0.004	?	B	?	0	0	all	46

KINETIC AND DYNAMIC PARAMETERS OF DRUGS USED IN ANAESTHESIA - 2

DRUG	$T_{1/2d}$ (min)	$T_{1/2e}$ (hrs)	V_c (l/kg)	V_d (l/kg)	Cl (l/kg /hr)	MEC (mg/l)	% Protein binding	pKa	% ionized (pH = 7.4)	ELIMINATION (% dose/24 hours) BILE	URINE	METAB	REFERENCES
MUSCLE RELAXANTS						EC95							
Suxamethonium	?	?	?	?	?	3.5 mg/min	79	B	?	0	0	all	47,48
Gallamine	6.7	2.4	0.1	0.2	0.065	10	74	>13B	100	<0.1	15-100	0	47,49,50,51
Tubocurarine*	1.7	5.8	0.05	0.47	0.056	1.2	67	8.6B	94	11	45	small	47,50,52
Alcuronium	13.8	3.3	0.13	0.37	0.083	0.9	78	B	?	15	80	0	47,50,53,54
Pancuronium	10.7	1.9	0.12	0.31	0.11	0.43	88	>13B	100	11	40	20	47,50,55,56
Vecuronium*	2.2	1.2	0.05	0.53	0.31	0.2	91	B	?	30-50	15	<3	47,50,57,58
Atracurium	2.1	0.33	0.05	0.16	0.33	1.6	82	B	?	0	0	all	47,59,60
ANTICHOLINERGICS & ANTICHOLINESTERASES						MEC							
Atropine	1.7	3.0	0.09	1.6	0.41	?	18	9.8B	99.6	small	94	3	61,62
Neostigmine	3.4	1.3	0.22	1.02	0.55	?	?	B	?	?	67	?	63,64
Pyridostigmine	6.8	1.87	0.3	1.4	0.52	?	?	B	?	?	?	?	65
Edrophonium	7.2	1.8	0.32	1.52	0.58	?	?	B	?	?	?	?	63
ANTI-EMETICS & NEUROLEPTICS						MEC							
Droperidol*	1.4	1.7	0.17	2.04	0.85	?	?	7.6B	61	11	<1	86	66,67
Haloperidol*	11.4	26.2	?	24.5	0.65	?	92	B	?	?	<1	?	68
Metoclopramide	21	4.6	?	3.43	0.53	?	?	B	?	?	?	?	69
BENZODIAZEPINES						SLEEP							
Diazepam*	18	37.7	0.21	1.23	0.024	1.0	99	3.3B	0	0	0	some	70,71,72
Lorazepam*	2.6	14.1	0.22	1.21	0.06	0.02	93	B	?	?	<0.5	48	71,73,74
Midazolam	18.6	2.73	0.58	1.91	0.48	0.1	96	B	?	?	<0.5	most	75,76,77

REFERENCES

1. Christensen,J.H., et al.,(1982), Pharmacokinetics and pharmacodynamics of thiopentone. A comparison between young and elderly patients. ANAESTHESIA, 37, 398-404.
2. Hudson,R.J., et al.,(1983), Pharmacokinetics of methohexital and thiopental in surgical patients. ANESTHESIOLOGY, 59, 215-219.
3. Pandele,G., et al.,(1983), Thiopental pharmacokinetics in patients with cirrhosis. ANESTHESIOLOGY, 59, 123-126.
4. Becker,K.E.,(1978), Plasma levels of thiopental necessary for anesthesia. ANESTHESIOLOGY, 49, 192-196.
5. Breimer,D.D.,(1976), Pharmacokinetics of Methohexitone following intravenous infusion in humans. BRITISH JOURNAL OF ANAESTHESIA, 48, 643-649.
6. Brand,L., et al.,(1963), Physiologic disposition of methohexital in man. ANESTHESIOLOGY, 24, 331-335.
7. Richter,E.,(1980), Disposition of hexobarbital in intra- and extrahepatic cholestasis in man and the influence of drug metabolism-inducing agents. EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, 17, 197-202.
8. Ehrnebo,M.,(1974), Pharmacokinetics and distribution properties of pentobarbital in humans following oral and intravenous administration. JOURNAL OF PHARMACEUTICAL SCIENCES, 63, 1114-1118.
9. Reidenberg,M.M., et al.,(1976), Pentobarbital elimination in patients with poor renal function. CLINICAL PHARMACOLOGY AND THEAPEUTICS, 20, 67-71.
10. Greene,N.M.,(1968), The metabolism of drugs employed in anesthesia. Part II. ANESTHESIOLOGY, 29, 327-340.
11. Schüttler,J., et al.,(1980), Pharmacokinetische Untersuchungen über Etomidat beim Menschem. DER ANAESTHESIST, 29, 658-661.
12. Fragen,R.J., et al.,(1983), A pharmacokinetically designed etomidate infusion regime for hypnosis. ANESTHESIA AND ANALGESIA, 62, 654-660.
13. Carlos,R., et al.,(1979), Plasma protein binding of Etomidate in patients with renal failure or hepatic cirrhosis. CLINICAL PHARMACOKINETICS, 4,144-148.
14. Hamme,J van, et al.,(1978), Pharmacokinetics of etomidate, a new intravenous anesthetic. ANESTHESIOLOGY,49, 274-277.
15. Wieber,J., et al.,(1975), Pharmacokinetics of ketamine in man. DER ANAESTHESIST, 24, 260-263.
16. Little,B., et al.,(1972), Study of ketamine as an obstetric anesthetic agent. AMERICAN JOURNAL OF OBSTETRICS & GYNECOLOGY, 113, 247-258.
17. Domino,E.F., et al.,(1982), Plasma levels of ketamine and two of its metabolites in surgical patients using a gas chromatographic mass fragmentographic assay. ANESTHESIA AND ANALGESIA, 61, 87-92.
18. Adam,H.K., et al.,(1983), Pharmacokinetic evaluation of ICI- 35868 in man. BRITISH JOURNAL OF ANAESTHESIA, 55, 97-103.
19. Cockshott,I.D.,(1985), Profolol ('Diprivan') pharmacokinetics and metabolism - an overview. POSTGRADUATE MEDICAL JOURNAL, 61, suppl. 3, 45-50.
20. Mazoit,J-X, et al.,(1987), Pharmacokinetics of unchanged morphine in normal and cirrhotic subjects. ANESTHESIA AND ANALGESIA, 66, 293-298.
21. Brunk,S.F., Delle,M.,(1974), Morphine metabolism in man. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 16, 51-57.
22. Brunk,S.F., et al.,(1974), Effect of propranolol on morphine metabolism. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 16, 1039-1044.
23. Mather,L.E., et al.,(1974), Meperidine kinetics in man. Intravenous injection in surgical patients and volunteers. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 17, 21-30.
24. Austin,K.L., et al.,(1980), Relationship between blood meperidine concentrations and analgesic response. ANESTHESIOLOGY, 53, 460-466.
25. Verbeeck,R.K., et al.,(1981), Meperidine disposition in man: Influence of urinary pH and route of administration. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 30, 619-628.
26. Gourlay,G.K., et al.,(1982), Pharmacodynamics and pharmacokinetics of methadone in the perioperative period. ANESTHESIOLOGY, 57, 458-467.
27. Gourlay,G.K., et al.,(1986), A double-blind comparison of the efficiency of methadone and morphine in postoperative pain control. ANESTHESIOLOGY, 64, 322-327.
28. Verebely,K., et al.,(1975), Methadone in man: Pharmacokinetic and excretion studies in acute and chronic treatment. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 18, 180-190.

29. Ehrnebo,M., et al.,(1977), Bioavailability and first-pass metabolism of pentazocine in man. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 22, 888-892.
30. Berkowitz,B.A., et al.,(1969), Relationship of pentazocine plasma levels to pharmacological activity in man. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 10, 320-328.
31. Beckett,A.H., et al.,(1970), The absorbtion, distribution, and excretion of pentazocine in man after oral and intravenous administration. J. PHARM. PHARMAC., 22, 123-128.
32. Bullingham,R.E.S., et al.,(1980), Buprenorphine kinetics. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 28, 667-672.
33. Heel,R.C., et al.,(1979), Buprenorphine: A review of its pharmacological properties and therapeutic efficiency. DRUGS, 17, 81-110.
34. Fischler,M., et al.,(1985), Pharmacokinetics of phenoperidine in anaesthetized patients undergoing general surgery. BRITISH JOURNAL OF ANAESTHESIA, 57, 872-876.
35. Milne,L., et al.,(1980), Plasma concentration and metabolism of phenoperidine in man. BRITISH JOURNAL OF ANAESTHESIA, 52, 537-539.
36. Isherwood,C.N., et al.,(1984), Elimination of phenoperidine in liver disease. BRITISH JOURNAL OF ANAESTHESIA, 56, 843-847.
37. McClain,D., Hug,C.C.,(1980), Intravenous fentanyl kinetics. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 28, 106-114.
38. Bovill,J.G., et al.,(1982), The pharmacokinetics of alfentanil (R39209): A new opioid analgesic. ANESTHESIOLOGY, 57, 439-443.
39. Hull,C.J.,(1983), The pharmacokinetics of alfentanil in man. BRITISH JOURNAL OF ANAESTHESIA, 55, 157s-164s.
40. Schüttler,J., Stoeckel,H.,(1982), Alfentanil (R 39209) ein neues kurzwirkendes opioid. Pharmacokinetiek und erste klinische Erfahrungen. DER ANAESTHESIST, 31, 10-14.
41. Bovill,J.G., et al.,(1984), The pharmacokinetics of sufentanil in surgical patients. ANESTHESIOLOGY, 61, 502-506.
42. Goldfrank,L., et al.,(1986), A dosing nomogram for continuous infusion of intravenous naloxone. ANNALS OF EMERGENCY MEDICINE, 15, 566-570.
43. Fishman,J., et al.,(1973), Disposition of naloxone-7,8-3H in normal and narcotic-dependent men. JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, 187, 575-580.
44. Clements,J.A., et al.,(1979), The disposition of intravenous doxapram in man. EUROPEAN OF CLINICAL PHARMACOLOGY, 16, 411-416.
45. Robson,R.H., Prescott,L.F.,(1978), A pharmacokinetic study of doxapram in patients and volunteers. BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, 7, 81-87.
46. Hartvig,P., et al.,(1986), Pharmacokinetics of physostigmine after intravenous, intramuscular and subcutaneous administration in surgical patients. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 30, 177-182.
47. Foldes,F.F., et al.,(1982), The binding of neuromuscular blocking agents to plasma proteins. ANESTHESIOLOGY, 57, A274.
48. Williams,J.P., Bourke,D.L.,(1985), Effects of succinylcholine on respiratory and non-respiratory muscle strength in humans. ANESTHESIOLOGY, 63, 299-303.
49. Ramzan,M.I., et al.,(1980), Pharmacokinetic studies in man with gallamine triethiodide. I. Single and multiple doses. EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, 17, 135-143.
50. Shanks,C.A.,(1986), Pharmacokinetics of non-depolarizing neuromuscular relaxants applied to calculation of bolus and infusion dosage regimes. ANESTHESIOLOGY, 64, 72-86.
51. Agoston,S., et al.,(1978), A preliminary investigation of the renal and hepatic excretion of gallamine triethiodide in man. BRITISH JOURNAL OF ANAESTHESIA, 50, 345-351.
52. Meijer,D.K.F., et al.,(1979), Comparative pharmacokinetics of d-tubocurarine and metocurine in man. ANESTHESIOLOGY, 51, 402-407.
53. Walker,J., et al.,(1980), Clinical pharmacokinetics of alcuronium chloride in man. EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, 17, 449-457.
54. Raaflaub,J. von, Frey,P.,(1972), Zur Pharmakokinetik von Diallyl-nor-toxiferin beim Menschen. ARZNEIMITTELFORSCHUNG, 22, 73-78.
55. Duvaldestin,P., et al.,(1978), Pancuronium pharmacokinetics in patients with liver cirrhosis. BRITISH JOURNAL OF ANAESTHESIA, 50, 1131-1135.
56. Agoston,S., et al.,(1973), The fate of pancuronium bromide in man. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 17, 267-275.

57. Cronnelly,R., et al.,(1983), Pharmacokinetics and pharmacodynamics of Vecuronium (ORG NC45) and pancuronium in anesthetized humans. ANESTHESIOLOGY, 58, 405-408.
58. Hilgenberg,J.C.,(1983), Comparison of the pharmacology of vecuronium and atracurium with that of other currently available muscle relaxants. ANESTHESIA AND ANALGESIA, 62, 524-531.
59. Ward,S., et al.,(1983), Pharmacokinetics of atracurium besylate in healthy patients (after a single i.v. bolus dose). BRITISH JOURNAL OF ANAESTHESIA, 55, 113-117.
60. Madden,A.P., et al.,(1983), Recovery from neuromuscular blockade after infusion of atracurium. BRITISH JOURNAL OF ANAESTHESIA, 55, 226P.
61. Virtanen,R., et al.,(1982), Pharmacokinetic studies on atropine with special reference to age. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 26, 297-300.
62. Shutt,L.E., Bowes,J.B.,(1979), Atropine and hyoscine. ANAESTHESIA, 34, 476-490.
63. Morris,R.B., et al.,(1981), Pharmacokinetics of edrophonium and neostigmine when antagonizing d-tubocurarine neuromuscular blockade in man. ANESTHESIOLOGY, 54, 399-402.
64. Nowell,P.T., et al.,(1962), Determination of neostigmine and pyridostigmine in the urine of patients with myasthenia gravis. BRITISH JOURNAL OF PHARMACOLOGY, 18, 617-624.
65. Cronnelly,R., et al.,(1980), Pyridostigmine kinetics with and without renal function. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 28, 78-81.
66. Fischler,M., et al.,(1986), The pharmacokinetics of droperidol in anesthetized patients. ANESTHESIOLOGY, 64, 486-489.
67. Cressman,W.A., et al.,(1973), Absorbtion, metabolism and excetion of droperidol by human subjects following intramuscular and intravenous injection. ANESTHESIOLOGY, 38, 363-369.
68. Holley,F.O., et al.,(1983), Haloperidol kinetics after oral and intravenous doses. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 33, 477-484.
69. Ross-lee,L.M., et al.,(1981), Single-dose pharmacokinetics of metoclopramide. EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, 20, 465-471.
70. Ghonheim,M.M., et al.,(1981), Diazepam effects and kinetics in caucasians and orientals. CLINICAL PHARMACOLOGY & THERAPEUTICS, 29, 749-756.
71. Kanto,J., Klotz,U.,(1982), Intravenous benzodiazepines as anaesthetic agents: Pharmacokinetics and clinical consequences. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 26, 554-569.
72. Mahon,W.A., et al.,(1976), Biliary elimination of diazepam in man. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 19, 443-450.
73. Greenblatt,D.J., et al.,(1979), Lorazepam kinetics in the elderly. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 26, 103-113.
74. Greenblatt,D.J., et al.,(1977), Clinical pharmacokinetics of lorazepam. II. Intramuscular injection. CLINICAL PHARMACOLOGY & THERAPEUTICS, 21, 222-230.
75. Greenblatt,D.J., et al.,(1984), Effect of age, gender, and obesity on midazolam kinetics. ANESTHESIOLOGY, 61, 27-35.
76. Allonen,H., et al.,(1981), Midazolam kinetics. CLINICAL PHARMACOLOGY & THERAPEUTICS, 30, 653-661.
77. Crevoisier,Ch., et al.,(1983), Relationship between plasma concentration and effect of midazolam after oral and intravenous administration. BRITISH JOURNAL OF CLINICAL PHARMACOLOLGY, 16, 51S-61S.
78. Stanski,D.R., Hug,C.C.,(1982), Alfentanil- a kinetically predictable narcotic analgesic. ANESTHESIOLOGY, 57, 435-438.
79. Prys-Roberts,C., Hug,C.C. (eds.),"Pharmacokinetics in Anaesthesia", pub. Blackwell, 1984, pages 21-23.
80. Hull,C.J., et al.,(1978), A pharmacodynamic model for pancuronium. BRITISH JOURNAL OF ANAESTHESIA, 50, 1113-1123.
81. Haberer,P., et al.,(1982), Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. BRITISH JOURNAL OF ANAESTHESIA, 54, 1267-1269.

APPENDIX - B

KINETIC PARAMETERS OF CARDIOVASCULAR STIMULANT DRUGS

Regrettably there have been few studies made of the pharmacokinetic properties of the vasoactive drugs, despite the fact that they are in common daily use. Because even fewer studies have been made of vasodilator drugs than of cardiovascular stimulant drugs, only kinetic data of the cardiovascular stimulants is presented. The abbreviations used are the same as those used in appendix-A.

KINETIC & DYNAMIC PARAMETERS OF CARDIOVASCULAR STIMULANT DRUGS

DRUG	$T_{1/2d}$ (min)	$T_{1/2e}$ (min)	V_c (l/kg)	$V_{d\beta}$ (l/kg)	Cl (l/kg /min)	MEC (μg/l)	REFER-ENCES
Adrenaline	3.07	10.9	?	1.89	0.12	0.1	1,2
Calcium	?	?	?	0.2	?	2.8 mmol	3
Digoxin	?	39 hrs	?	6.96	0.0012	>0.8	
Dobutamine	?	2.37	?	0.2	0.06	42	4
Dopamine	0.9	9.2	?	0.89	0.072	70	5
Ephedrine	?	405	?	3.18	0.006	?	6
Isoprenaline	2.5-5	3-7 hrs	?	?	?	?	7
Noradrenaline	2	34	?	1.96	0.04	1.8	8,9

REFERENCES

1. Fitzgerald,G.A., et al.,(1980), Circulating adrenaline and blood pressure: the metabolic effects and kinetics of infused adrenaline in man. EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, 10, 401-406.
2. Clutter,W.E., et al.,(1980), Epinephrine plasma metabolic clearance rates and physiologic thresholds forr metabolic and hemodynamic actions in man. JOURNAL OF CLINICAL INVESTIGATION, 66, 94-101.
3. Denlinger,J.K., et al.,(1975), Cardiovascular responses to calcium administered intravenously to man during halothane anesthesia. ANESTHESIOLOGY, 42, 390-397.

4. Kates,R.E., Leier,C.V.,(1978), Dobutamine pharmacokinetics in severe heart failure. CLINICAL PHARMACOLOGY AND THERAPEUTICS, 24, 537-541.
5. Järnberg,P.O., et al.,(1981), Dopamine infusion in man. Plasma catecholamine levels and pharmacokinetics. ACTA ANAESTHESIOLOGICA SCANDINAVICA, 25, 328-331.
6. Pickup,M.E., et al.,(1976), The pharmacokinetics of ephedrine after oral dosage in asthmatics receiving acute and chronic treatment. BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, 3, 123-134.
7. Kadar,D., et al.,(1974), Isoproteranol metabolism in children after intravenous administration. CLINICAL PHARMACOLOGY & THERAPEUTICS, 16, 789-795.
8. Esler,M., et al.,(1981), Effect of norepinephrine uptake blockers on norepinephrine kinetics. CLINICAL PHARMACOLOGY & THERAPEUTICS, 29, 12-20.
9. Silverberg,A.B., et al.,(1978), Norepinephrine: hormone and neurotransmitter in man. AMERICAN JOURNAL OF PHYSIOLOGY, 234, E252-E256.

APPENDIX - C

ABBREVIATIONS

RESPIRATORY PHYSIOLOGY

VC = vital capacity.
FEV_1 = forced expiratory volume in 1 second.
PEFR = peak expiratory flow rate.
CC = closing capacity.
V_T = tidal volume.
FRC = functional residual capacity.
RV = residual volume.
V_D = dead space volume.
MV = minute volume (expiratory).
MBC = maximum breathing capacity in one minute.
V_A = alveolar ventilation.
(A-a)D_{O2} = alveolar arterial PO2 difference.
IPPV = intermittent positive pressure ventilation.
PEEP = positive end expiratory pressure.
O_2 = oxygen.
V_{O2} = oxygen consumption.
CO_2 = carbon dioxide.
V_{CO2} = carbon dioxide production.
F_IO_2 = fractional inspired oxygen concentration.
P_AO_2 = alveolar partial pressure of oxygen.
P_ACO_2 = alveolar partial pressure of carbon dioxide.
P_aO_2 = arterial partial pressure of oxygen.
P_aCO_2 = arterial partial pressure of carbon dioxide.
SO_2 = percentage saturation of haemoglobin with oxygen.
FSO_2 = fractional saturation of haemoglobin with oxygen.

CARDIOVASCULAR PHYSIOLOGY

HR = heart rate = pulse rate.
SV = stroke volume.
CO = cardiac output.
SVR = systemic vascular resistance.
PVR = pulmonary vascular resistance.
SABP = systolic arterial blood pressure.
MABP = mean arterial blood pressure.

DABP = diastolic arterial blood pressure.
CVP = mean central venous blood pressure.
PCWP = pulmonary capillary wedge pressure.

FLUID PHYSIOLOGY

BV = blood volume.
PV = plasma volume.
TBW = total body water.
ICFV = intracellular fluid volume.
ECFV = extracellular fluid volume.
ISFV = interstitial fluid volume.
[Hb] = haemoglobin concentration.
Hct = haematocrit (%).

PHARMACOKINETICS AND DYNAMICS

i.m. = intramuscular.
i.v. = intravenous.
$T_{1/2d}$ = distribution half life.
$T_{1/2e}$ = elimination half life.
V_c = volume of central drug compartment.
V_d = volume of distribution of a drug.
Cl = whole body clearance of a drug.

APPENDIX - D

CONVERSION FACTORS

PHYSICAL UNITS

Pressure

1 Atmosphere = 760 mmHg = 101.33 kPa = 1 Bar
1 kPa = 7.5 mmHg = 10.2 cm H_2O
1 mmHg = 0.133 kPa = 1.36 cm H_2O
1 cm H_2O = 0.09806 kPa = 0.735 mmHg

Length

1 cm = 0.394 inch
1 inch = 2.54 cm

BIOCHEMICAL & HAEMATOLOGICAL PARAMETERS

Haemoglobin	1 gm/100 mls = 0.6205 mmol/l 1 mmol/l = 1.612 gm/100 mls
Proteins	1 gm/100 mls = 10 gm/l
Bilirubin	1 mg/100 mls = 17.1 mol/l 1 mol/l = 0.0585 mg/100 mls
Glucose	1 mg/100 mls = 0.055 mmol/l 1 mmol/l = 18.18 mg/100 mls
Creatinine	1 mol/l = 88.5 mg/100 mls 1 mg/100 mls = 0.0113 mol/l
Urea	1 mmol/l = 0.167 mg/100 mls 1 mg/100 mls = 5.988 mmol/l
Sodium	1 milliequivalent/l = 1 mmol/l
Potassium	1 milliequivalent/l = 1 mmol/l
Calcium	1 mg/100 mls = 0.25 mmol/l 1 mmol/l = 4 mg/100 mls
Chloride	1 milliequivalent/l = 1 mmol/l
Bicarbonate	1 milliequivalent/l = 1 mmol/l

INDEX