Hwee Ming Cheng · Felicita Jusof

Defining Physiology: Principles, Themes, Concepts

Cardiovascular, Respiratory and Renal Physiology

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Definitions are physiology's best touchstone…

To
Betty,
who defined faith in her life

To
Tsung Pai & Shaohannah,
who continue on their journey of faith…

To
the Refiner,
who defines their transient separate paths,
the author and finisher of their faith,
who has placed eternity in their hearts.

Foreword

In physiology, accurate, concise, and reliable definitions of terms are our best friends. They are our rock! We return to those definitions when we feel uncertain or confused and there they are—comfortable as old shoes and ready to stabilize us! How critical is accuracy and precision in those definitions? Well, it is everything. Difficult concepts and subtle differences all can be clarified by precise definitions. Sometimes, a term's definition is easy—it is in the name. End-diastolic volume? Well, that is the *volume in the ventricle at the end of diastole*! Trust it and move on. But other times, the term's name may get us in the door but a more thorough and precise definition is essential. Contractility? Yes, something to do with contraction, but it is not the same thing as contraction or contractile force. Contractility is precisely defined as *the intrinsic ability of myocardial cells to develop force at a given muscle length*. Now that is a mouthful definition that we may need to return to a few times. A definition we will need to practice on graphs and with examples until it becomes second nature and we own its subtleties. Then, there are other times, when the term's name alone does not do much for us. Renal clearance? Sure, vaguely, something is "cleared." But we need the precise definition of clearance to get anywhere in renal physiology. Renal clearance is the *volume of plasma completely cleared of a substance by the kidneys per unit time*. That is a definition we did not see coming! In this case, the definition also tells us what the units of renal clearance will be: volume/time. That is a definition we will need to practice in calculations, practice, and digest until we own it.

Definitions are physiology's best touchstone. Use them well!

Virginia, USA

Linda S. Costanzo, Ph.D.
Professor of Physiology and Biophysics
VCU School of Medicine

Preface

A word fitly spoken is like apples of gold in pictures of silver

KJV, Proverbs 25:11

Keywords and their definitions are like precious peanuts. These can be digested and enjoyed as presented here. In a nutshell, these essential dePHYnitions do not just provide the reader with the specific terminology within each physiological system. These keywords are the major integrating points from which the expanded physiology can be elaborated. Understanding the main principles, themes, and concepts (PTC) also invariably includes a clear grasp of these definitive words. Definitions are, like physiology in a nutshell, ready and available to be broken or cracked open by the physiology educator. These precious peanuts (phynuts) can be tasted, chewed on, and enjoyed by both the student and the teacher.

Perhaps this focus on defining physiology should be included as a core objective among the variety of self-directed learning approaches. I call this PhyNut-based Learning (PhyBL)!

Physiology in a Nutshell

Inaccurate definitions can lead to misconceptions. My thanks go to Prof. Linda Costanzo, who also believes in a definitive approach to physiology and has written a brief, personal precise word here.

Our appreciation to Thijs van Vlijmen of Springer who saw the benefit of extracting the essential physiology asked at the inter-medical school physiology quiz (IMSPQ). These selected, core and conceptual physiology were published in the Springer title Physiology Question-based Learning. This present title on

"Definitions in Physiology" continues the impact of IMSPQ on physiology education.

Kuala Lumpur, Malaysia

Hwee Ming Cheng
Felicita Jusof

Ming's Definition or Decalogue of a Student Enjoying and Learning Physiology

1. Will be seated on time before the class commences and could have already read some of the topics covered in class.
2. Post-class chewing and digesting and then asking questions on undigested and unassimilated nutrients dished out during class.
3. Thinking outside the PowerPoint boxes.
4. Taking initiative to read about the heritage and historical development of foundational Physiological knowledge.
5. Fascinated by the apparent coincidences within physiology, e.g., metabolic CO_2 as vasodilator, functional location of arterial baroreceptors.
6. Engages enthusiastically with the faithful in vivo *homeostasis.*
7. Able to do intra-physiology-based learning (PhyBL), integrating multi-organ tasking.
8. Wonders at the mysteries and paradoxes of physiology, e.g., timing of parturition, puberty, and exercise hyperventilation.
9. Able to talk, explain, and discuss physiology with classmates.
10. Likes to walk into physiology departments to chitchat with teachers.

Contents

Part III Renal Physiology

Part I
Cardiovascular System

Defining Milestones in the Cardiovascular Blood Traffic Flow

Physiology is a *moving* medical discipline. Blood enriched with oxygen and energy substrates, like glucose, amino, and fatty acids, must flow for it to be "bloody" useful (used as an adjective, not an expletive!).

Along the cardiovascular circuit, it is useful for a student of physiology to take note of certain sites in relation to their structure and function. The overall systemic and pulmonary circulations are arranged in series with each other in a closed vascular loop. This confined vascular space defines the need for blood flow to be equal and continuous at any point in the arterial to venous channels.

The intrinsic myocardial Starling's mechanism ensures that the cardiac outputs from the two ventricular pumps in series are equalized over time. Problems with this balance or matching during one sided cardiac failure will result in either peripheral or pulmonary edema.

The heart is a rhythmic pump in this closed system. The requirement for diastolic filling during a cardiac cycle also defines the diastolic blood pressure that ensures uninterrupted blood perfusion to the tissues, in particular the brain and the heart muscle. The diastolic blood pressure is served by the elastic recoil of the aorta. With a rhythmic cardiac pump, the blood pressure (arterial or pulmonary) is both the driving pressure and also the afterload for the left and right cardiac work, respectively. A feedback sensor reflex control mechanism that includes arterial and intrarenal baroreceptors maintains the arterial blood pressure.

The left cardiac output is redistributed to the regional circulations while the lungs receive all the right cardiac output. The arterioles are the vascular resistance gateways to adjust the regional flow in changing physiological scenarios. The regional vasculatures are arranged in parallel to each other so that local control of blood flow can occur independently, without interfering with perfusion in other organs. Examples of this effect are skeletal muscle vasodilation during physical activity or cutaneous vasoconstriction as a response to cold. The radiuses of the arterioles that alter the vascular resistances are changed by several stimuli, including autonomic neural, hormonal, and local vasoactive chemicals and by stretch myogenic autoregulatory mechanisms. The dominant stimulus is defined by the function of the organ involved.

The capillary network is the essential site for the exchange dialogue and conversations between the blood and the cells and tissue fluid. The total blood flow remains the same, but the velocity of flow is much reduced for the physiologic exchange to take place effectively and sufficiently. At most capillaries, there is also the local capillary loop dynamics of filtration and reabsorption at the arteriolar and venular end, respectively. The lymphatic channels link the capillary/tissue fluid flow to the systemic blood flow and functions to prevent edema and to maintain an optimal diffusion distance between the blood and the cells.

The veins are wide open vascular spaces due to their less elastic and more compliant vascular wall. The high capacitance of the veins represents a non-stagnant blood reservoir and venous flow can be increased by reducing this venous capacitance. During exercise, both sympathetic venoconstriction and mechanical compression by the skeletal muscles increase the venous return.

A heartfelt homecoming is welcomed by a rap! The right atrial pressure (RAP) or central venous pressure is close to zero mmHg and needs to be kept low in order for the venous return to match the cardiac output.

Chapter 1
Heart as an Electrical Organ

1 Pacemaker Potential

i. Definition: The pre-potential where a (gradual) spontaneous depolarization of the sinoatrial nodal cells leads to the generation of action potential that determines the heart rate.

ii. Points-To-Consider (PTC):
The heart has inherent autorhythmicity and this (thankfully) makes the transplantation of a denervated donor's heart a possibility. The number of spontaneous action potentials triggered per minute sets the heart rate.
The period of auto-depolarization before the activation of the full action potential is also called the pacemaker potential. The quicker the pacemaker potential (pacept) reaches the firing threshold, the higher the number of action potentials per minute (and heart rate) will be. This also corresponds to a steeper slope of the prepotentials.
Three cations involved in the pacept are sodium, calcium and potassium. There are transmembrane gradients for all three cations and their natural movement or flux follows their respective concentration gradients at the sinoatrial (SA) nodal cells. Both extracellular sodium and calcium diffuse into the SA cells and depolarize the membrane. Efflux of intracellular potassium cations is also reduced during the pacept and this contributes to the decreased negativity of the changing membrane potential of the SA node. The cations set the rate of pacemaker potential/min.
Unlike most other excitable tissues, the fast depolarization phase of the SA action potential is not due to a sudden sodium influx. Instead, it is the opening of voltage-gated calcium channels which allows acute calcium flux during the rapid depolarization of a cardiac SA action potential. The membrane potential reverses its polarity to a positive value.
The intrinsic rate of pacept is modulated by the autonomic nerves. Sympathetic stimulation increases the slope of the pacept or decreases the

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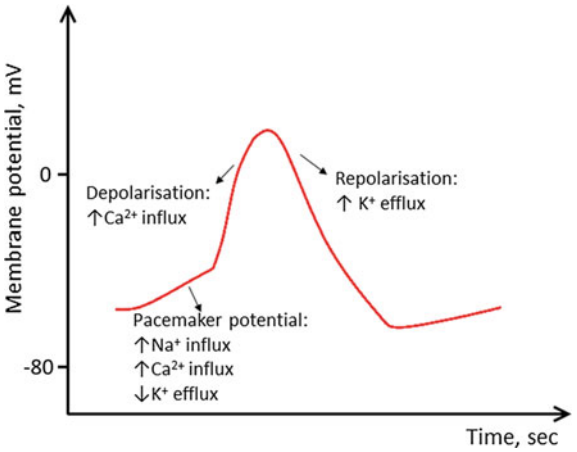


Fig. 1 Action potential seen in cardiac nodal cells, comprising of pacemaker potential, depolarization and repolarization. Ionic fluxes at each phases also are outlined

duration of the pacept. Conversely, vagal parasympathetic input lengthens the pacept time and reduces the slope of the pacept. In normal persons, the vagal is dominant over the sympathetic and this is termed the cardiac 'vagal tone'. Thus, denervation of the heart will lead to an increased heart rate. The sympathetic neurotransmitter is noradrenaline, which binds to beta receptors on the SA cell membranes. Acetylcholine released from vagal fibers binds to muscarinic membrane receptors in the SA pacemaker cells.

iii. Question:
How does adrenaline affect the cardiac pacemaker potential?
Answer: Adrenaline and noradrenaline bind to the same membrane adrenergic receptors. Adrenaline, a catecholamine secreted by adrenal medulla, activates the beta receptors of the SA cells and increases the heart rate during exercise. The slope of the pacept is increased, with a concomitant shortening of the pacept phase.

2 Prolonged Depolarization

i. Definition: The extended period of depolarization before rapid repolarization occurs in cardiac muscle cells. This is visualised as a plateau phase in the ventricular membrane potential curve.

ii. PTC:
The classical action potential in excitable tissues, like skeletal muscles and neurons, shows a rapid depolarization rising phase in the membrane potential profile plotted against time. When a peak positive membrane potential is reached, this is followed by a rapid repolarization, which immediately decreases the membrane potential to the negative resting level milivolt.

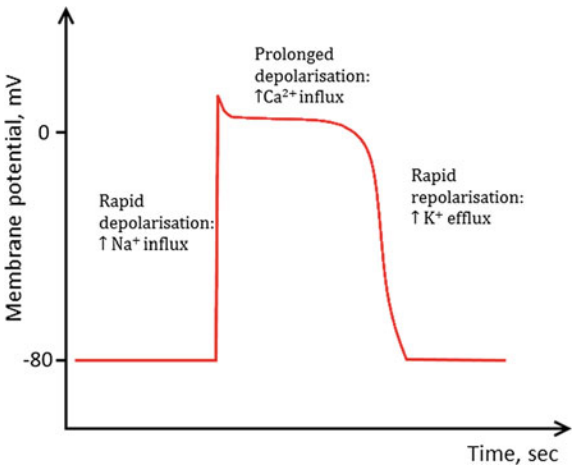


Fig. 2 Action potential seen in cardiac ventricular cells, comprising of rapid and prolonged depolarization (plateau phase) as well as rapid repolarization phases. Ionic fluxes at each phases also are outlined

In the cardiac muscle, particularly in ventricle muscles, the rapid depolarization and subsequent repolarization are characteristically seen. The rapid membrane potential changes have the same ionic basis, where they are based on sudden sodium influx and potassium efflux. However, there is a plateau phase separating the depolarized state of the muscle and the repolarization phase. This can be described either as prolonged depolarization of the ventricular muscle or as delayed repolarization.

This causes a prolonged or extended action potential. The refractory period of the cardiac muscle is thus also longer and another successive stimulus can generate the next action potential only after the muscle becomes excitable again as the voltage-gated sodium channels become responsive after their inactivation phase.

When plotted on the same time scale, the mechanical contraction/relaxation period of the ventricles overlap to a large extent with the duration of the prolonged action potential (extended refractory period).

This serves as a protective mechanism against the development of cardiac muscle spasm or tetany. In skeletal muscles, tetany is a physiological way to produce increased muscle tension. However, in the heart, rhythmic contraction is necessary to allow for ventricular filling. Cardiac tetany will dangerously disrupt the diastolic filling phase of the ventricle.

The ionic basis for the prolonged depolarization is the opening of membrane voltage-gated calcium channels in the ventricular muscle fibers. The influx of calcium cations counteracts the effect of the usual efflux of potassium cations in the repolarization of the cardiac muscles.

iii. Question:

Why can successive mechanical contractions be additive, where this is not the case for action potentials?

Answer: Action potentials are an all-or-nothing event, where the amplitude of each action potential is the same. On the other hand, the tension of mechanical contractions can be graded. In skeletal muscles, recruitment of more motor units and tetany (continuous contraction) increase the muscle tension developed. However, tetany is not observed in the heart as it is prevented by the unique electrical properties of the ventricular muscles. Instead, increased myocardial tension is effected inotropically by sympathetic nerve/adrenaline actions. Intrinsic muscle length/tension mechanisms (Frank-Starling Law) also can pump out a greater stroke volume.

3 Ca^{++}rdiovascular Physiology

i. Definition: The creative word above reflects the key roles of the cation calcium in various aspects of cardiac and vascular functions.

ii. PTC:

The calcium cation plays multiple roles in the normal heart and in blood vessels. Calcium ions contribute to the origin of the heart beat or specifically the pacemaker activity that autorhythmically generates the action potentials that produce the atrial/ventricular contractions. The spontaneous depolarization of the sinoatrial (SA) nodal cells is accounted for by changes in three cationic fluxes, the influx of sodium, the decreased efflux of potassium and the influx of calcium.

The rapid depolarization of the SA node when the firing threshold is reached is due to a sudden opening of voltage-gated calcium channels, an exception to the usual acute sodium influx for excitable tissues. Depolarization of the myocardium involves what is named 'trigger calcium' from the extracellular matrix. The influx of calcium accounts for the prolonged depolarization, which is particularly noticeable in ventricular muscles. The trigger Ca^{++} from the extracellular matrix activates a movement of calcium from the sarcoplasmic reticulum into the cytosol. The rise in cytosolic calcium initiates cardiac muscle contraction. Cardiac sympathetic action in increasing myocardial contractility or in increasing the ejection fraction has the final effect of increasing the cytosolic calcium concentration.

During diastole, cardiac muscle relaxation requires the lowering of cytosolic calcium to its pre-contraction level. The calcium ATPase at the sarcoplasmic membrane actively sequestrates the calcium. At the cell membrane of the cardiomyocytes, a calcium/sodium exchanger also helps to extrude the calcium to produce muscle relaxation.

The smooth muscles of the arteriole have stretch-gated calcium channels. These contribute to the vasomotor tone. The common myogenic mechanism that auto regulates blood flow in the cerebral, coronary and renal circulations is through the pressure- or mechanically-gated calcium channels. Increased

arterial pressure stretches and opens the vascular calcium channels. The influx of calcium contracts the arterioles to increase the resistance to blood flow.

iii. Question:
Does the Starling mechanism of the heart involve calcium ions?
Answer: The Frank-Starling mechanism manifests through length-tension interactions where higher end-diastolic volume leads to greater stretch of the ventricular muscle which results in stronger contraction of the ventricles. The length-tension interactions occurs in the myocardial sarcomeres, thereby hinting at the involvement of calcium sensitivity in the Starling cardiac mechanism of contraction.

4 ECG Isoelectric Line

i. Definition: The horizontal segments of the electrocardiogram which reflect temporal cardiac events when no electrical currents are present and recorded from the external of the cardiac muscle.

ii. PTC:
The ECG is an amplified measurement of the changes in electrical currents that are generated as different portions of the cardiac muscles are sequentially depolarized and repolarized. The external surface of the myocardium becomes negatively charged in an area where depolarization has occurred, while the unstimulated, resting muscle has a positively charged external surface of the membrane. Thus, a difference in the external charges sets up a current within the thoracic compartment. The recorded ECG from the surface of the body reflects the changing electrical activity at the cardiac surface.
Students should note that the ECG are not the same electrical phenomenon as cardiac action potentials. The size of the ECG deflections are much smaller

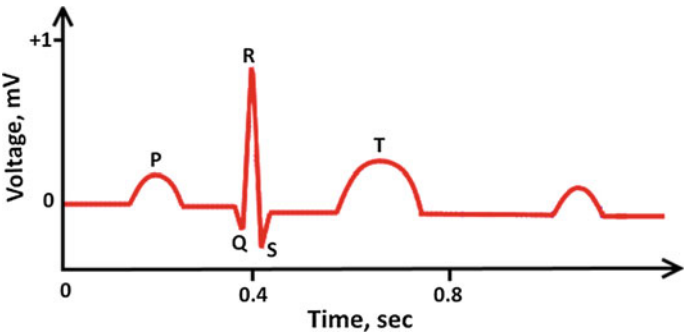


Fig. 3 Electrocardiogram recording of a healthy heart. The P wave represents atrial depolarization, QRS complex, atrial repolarization and ventricular depolarization and the T wave, ventricular repolarisation

than the amplitudes of the action potentials (around 1 mV for the QRS complex compared with about 100 mV for the action potential). The amplitudes of the QRS and P waves depend on the differences in mass between the cardiac ventricles and atria, while the all-or-nothing size of an action potential is determined by the transmembrane sodium concentration gradient.

There are two isoelectric segments in an ECG. One is the T-P segment, from the end of the T wave (ventricular repolarization) to the beginning of the P wave (atrial depolarization). The other isoelectric line is the S-T segment from the end of the QRS complex to the beginning of the T wave. These two isoelectric segments of the body surface ECG are not resting membrane potentials that are measured at the cardiac muscle.

The T-P segment represents the cardiac muscle when all the muscles are in the resting state and there is no difference in charges on the surface of the heart. The S-T segment reflects the ventricles that are fully depolarized in the prolonged state due to the extended duration of the ventricular action potential. The fully depolarized ventricle muscles all have a reversal of the membrane potential (a negative charge on the surface). Thus, no current flow is detected. The duration of the prolonged ventricular action potential (plateau phase) thus overlaps with the S-T segment.

iii. Question:
Is the duration of the S-T segment equal to the systolic phase of a cardiac cycle?
Answer: Electrophysiologically, no. The S-T segment ends before the T wave. The 2nd heart sound however is heard after the T wave. Systole is the period between the first and the 2nd heart sounds. The T-P segment is also shorter than the diastolic period. Diastole is from the T wave (2nd heart sound) to the 1st heart sound at S of the QRS complex.

5 Cardiac Glycoside Inotrope

i. Definition: A prescribed agent that improves myocardial contractility by inhibiting the cardiac muscle Na/K ATPase.

ii. PTC:
Taking a controlled amount of this group of drugs increases the muscle tension that the cardiac muscle can develop. The effect of cardiac glycosides is to increase the intracellular concentration of calcium that is available for the next myocardial contraction.

Cardiac glycosides reduce the amount of calcium extruded from the myocardial fibers during diastole.

How is calcium in the cytoplasm decreased to bring about ventricular relaxation? There are two routes. Firstly, the sarcoplasmic reticulum has membrane calcium ATPase that pumps calcium back into the organelle during muscle relaxation.

Secondly, the plasma membrane of the cardiomyoctes has a transporter, the calcium/sodium exchanger, which removes calcium from the fibers to the interstitial fluid. This calcium/sodium counter transport is powered by their membrane neighbor, the sodium/potassium ATPase. This is an example of a secondary active transport of calcium, where the efflux is coupled to the sodium electro-chemical gradient.

The transmembrane sodium gradient is generated and maintained by the Na/K ATPase. The glycosides inhibit this Na/K ATPase, leading to a reduction in the transmembrane sodium gradient. The potential energy of the sodium gradient that drives the calcium efflux is decreased. More calcium accumulates in the myocardial cytoplasm.

As a result of this, the cardiac contractility is increased. This is an improvement of the cardiac ejection fraction or a positive inotropic effect.

iii. Question:
How would you expect the action of cardiac glycoside to theoretically affect the action potential generation in the cardiac muscle?
Answer: Cardiac action potential is normally generated at the sinoatrial node and transmitted through the atrial and ventricular muscles. Depolarization of the myocardium occurs when sodium cations acutely influx into the muscle fibers, down its concentration gradient. The amplitude of the action potential is determined by the sodium transmembrane gradient. Cardiac glycosides reduce this sodium gradient.
Theoretically, the sodium influx depolarization will be decreased. However, the actual number of sodium ions involved in a single action potential is minute relative to the sodium concentration in the extracellular medium, i.e. the intracellular and extracellular medium sodium levels do not equalize, as the voltage-gated sodium channels are rapidly inactivated. There should then not be any immediate, significant effect on cardiac action potential. In the patients, the benefits of the cardiac glycoside- induced increase in contractility still prevail.

6 Cardiac Cycle

i. Definition: The sequence of cardiac muscle contraction and relaxation that is due to the rhythmic generation of action potential initiated at the right atrium and spreads progressively through both the atria and the ventricles.

ii. PTC:
Electrical activity precedes mechanical events in skeletal and cardiac muscles. The cardiac cycle is mechanically divided into the two phases of ventricular contraction (systole) and relaxation (diastole). The flow through the cardiac chambers is unidirectional, which is ensured by the atrio-ventricular valves and the aortic/pulmonary valves.

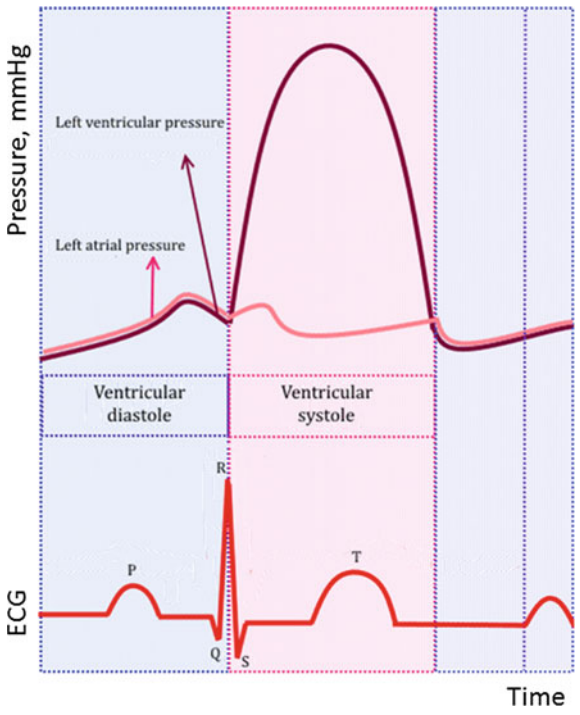


Fig. 4 A simplified graph of events in cardiac cycle outlining changes in left atrial and ventricular pressure, corresponding to the electrical activity seen in the heart (ECG)

Atrial contraction requires atrial depolarization as action potentials spread via gap junctions from their genesis at the sinoatrial (SA) node. The atrial syncytium is also depolarized by impulses along the intermodal fibers from SA to atrioventricular (AV) node.

The only electrical transmission point between the atrial syncytium and the ventricular syncytium is the AV node. The relative AV delay in impulse transmission ensures that the atria will contract before the ventricular systolic contraction. The atrial contraction actively tops up the ventricles during the tail end of diastolic ventricle filling.

Thus, in a cardiac cycle, there will be a sequence of atrial depolarization/repolarization and ventricular depolarization/repolarization. This is reflected in the electrical potential changes that are transmitted to the surface of the chest and which are measured in the ECG.

The heart sounds do not indicate the sound of ventricular contractions. The first heart sound actually occurs before or at the beginning of the heart contraction 'beat'. As ventricular pressure builds up soon after ventricles are filled with blood, the atrio-ventricular valves shut and the first heart sound is generated. This is when the systole phase starts. The brief period of rapid pressure buildup in the left ventricles before the aortic valve opens is called the isovolumetric contraction phase of systole. On the same time scale, the 1st heart sound is seen just after the ventricular depolarization represented by the ECG 'QRS complex'.

The 2nd heart sound is generated by the closure of the aortic/pulmonary valves and this 2nd heart 'beat' is the beginning of diastolic ventricular relaxation. Thus, the 2nd heart sound appears just after the ECG 'T' wave, which represents the electrical activity that occurs during ventricular repolarization. One cardiac cycle is the time duration between two 1st sounds or two 2nd sounds. On the ECG, a cardiac cycle proceeds from one R to the next R point.

The intraventricular pressure/volume changes are more dramatic on the left side of the heart and these are illustrated in standard physiology texts. The aortic pressure profile during a cardiac cycle that has the systolic/diastolic pressure at 120/80 mm Hg is also drawn in on the same graph.

1. Question:
   During which part of the cardiac cycle would you expect to see the greatest decrease in left intraventricular pressure?
   Answer: As the aortic valve shuts, the diastole period begins. The ventricular pressure drops rapidly to almost zero mmHg. The left atrial pressure then exceeds the ventricular pressure and the mitral valve opens to begin the diastolic ventricular filling. The initial brief period when the ventricular pressure sharply decreases is named the isovolumetric relaxation phase.

7 Heart Sounds

i. Definition: The two major heart sounds are produced during the sequential closure of the atrioventricular valves and then the aortic/pulmonary valves.

ii. PTC:
   Heart sounds are not synonymous with heart beats if beats are what occur when a drum is hit. In other words, heart sounds are not heard during the duration of the ventricular contraction. In fact, the 1st heart sound occurs just before or at the start of the ventricular contraction or systole. When the intra-ventricular pressure exceeds the atrial pressure, both the left mitral and right tricuspid valves are shut simultaneously, generating the 1st heart sound. The pressure then builds up rapidly in the ventricles (isovolumetric contraction phase).

   The 2nd heart sound signals the beginning of the ventricle diastolic relaxation phase ('wait a *second*, I am resting' said the ventricle'). As the ventricles are already repolarized, the ventricle muscles relax and the intra-ventricular pressure declines rapidly after the 2nd heart sound. This is the isovolumetric relaxation phase at the beginning of diastole.

   Thus, the 1st and 2nd heart sounds are produced respectively at the beginning of systole and diastole. The time between the 1st and the 2nd heart sound is the systolic period and the duration of diastole is defined by the time between the 2nd and the 1st heart sounds.

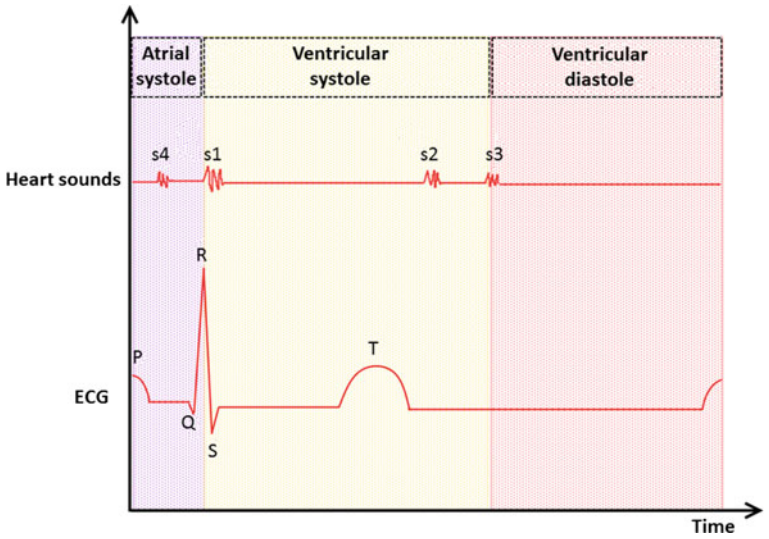


Fig. 5 Occurrence of major heart sounds, s1 and s2, corresponding to the electrical activity seen in the heart (ECG)

The pressure/mechanical closure of the valves occurs after the associated electrical event, meaning that the 1st heart sound occurs just after the depolarization of the ventricles (QRS complex). The 2nd heart sound will be seen just after the repolarization of the ventricles (T wave).

Valves do not produce sound when they open, as in the ejection (atrio-ventricular valves) or filling phase (pulmonary/aortic valves). Just think of the silent opening and noisy closing of doors.

Students should not mix Korotkoff sounds with the heart sounds above. Korotkoff sounds are heard during the measurement of systolic and diastolic blood pressure. The beginning of Korotkoff sounds that represent the maximal aortic pressure or systolic blood pressure is heard during the ejection phase of the cardiac cycle.

iii. Question:

In relation to the timing of two major heart sounds, where would the atrial contraction be located?

Answer: Atrial contraction occurs towards the end of diastole and provides an additional active filling of the ventricles after the larger, passive ventricular filling. The atrial systole would occur between the 2nd and the 1st heart sound.

8 Heart Block

i. Definition: More accurately named as atrioventricular block, it is the abnormal delay or interruption of action potential transmissions from the atria to the ventricles.

ii. PTC:

The heart is functionally a two-muscle syncytium, the atrial muscle and the ventricular muscle. Both atria and ventricles are depolarized rapidly, with impulses spreading via conducting fibers and aided by gap junctions between the atrial muscle fibers and between the ventricular fibers.

The only pathway for transmission of the cardiac impulse from the atria to the ventricles is via the atrioventricular (AV) node and the AV bundle of His (a physiologist's name, not gender biased!). In the normal heart, AV transmission is slightly delayed, which serves an essential purpose in ensuring that the atrial systolic contraction of the depolarized atria is completed before the ventricles are depolarized for their contraction to pump out the stroke volume. The P-R interval, normal about 0.15 s, reflects the time of AV transmission and a normal AV 'delay' should not be more than 0.20 s. The atrial systole is part of the ventricular diastole phase of the cardiac cycle when active filling tops up what has entered the ventricles by passive infilling to give the end-diastolic volume (EDV).

Transmission of action potentials at the AV can be abnormally slowed. This will be represented as a prolonged P-R interval in the ECG. Clinically, this is categorized as a first degree AV block (the slowness of our students to understand our active efforts in explaining CVS physiology can be humorously described as a first degree block! the prolonged Physiology-Response interval).

If the P-R interval becomes more prolonged (0.30–0.45 s), not every action potential generated at the sino atrial node will be transmitted to the ventricles. The atrial P waves are still present but some of the P deflections are not followed by the expected QRS-T ventricular depolarizing/repolarizing waves. The heart is said to have a missed or dropped ventricular beat. This is the category of a 2nd degree AV block (back to the humor, when our students only absorb part of the CVS knowledge we actively teach them, they have 2nd degree block!).

When the AV transmission or conduction is completely absent, a 3rd degree AV block has occurred. The ventricles are now depolarized by a pacemaker activity arising from the AV node/His bundle. The slower rhythmic electrical activity of the ventricles becomes dissociated and independent from the atrial events. The atria might beat at 80 times/min and the ventricular beats, following the natural inherent pacemaker of the AV tissues, would be about 40 times/min.

iii. Question:
How will cardiac vagal, parasympathetic nerve affect the P-R interval?
Answer: The parasympathetic nerve will produce a bradycardia. The P-R interval will be longer but still within the normal limit of 0.20 s, beyond which a 1st degree AV block is defined.

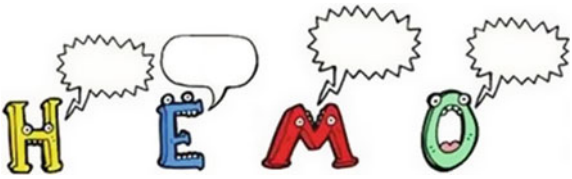
9 Hemo-words

i. Definition: The prefix hemo- or haemo- (British), from the original Greek (*haima*), refers to all things that are related to the blood.
ii. PTC:
Several terms in blood physiology are explained below:

(a) Hematocrit: the percentage volume of red blood cells to total blood volume. (≈45% in men; ≈40% in women)
(b) Hemorrhage: In vivo bleeding either externally or internally. The laboratory bleeding time does not have the same meaning. Laboratory bleeding time is performed in vitro on a small capillary and is used to determine platelet function. Abnormal platelet function will fail to form a platelet plug to seal the capillary leak and the bleeding time will be prolonged. Deficiencies of clotting factors do not affect the laboratory bleeding time. Platelet function can be deficient either due to thrombocytopenia or to some failure of the thrombocyte response to exposed collagen in the damaged tissue.
(c) Hemostasis: Hemostasis is the process towards the cessation of bleeding during an injury. It is not the same as blood clotting or coagulation. Activation of the coagulation cascade is part of the events that are aimed at reducing blood loss. The initial reflex responses to tissue injury include vasoconstriction and platelet activation. Several of the clotting steps require membrane phospholipids on the platelets and take place on the thrombocyte surface.
(d) Agglutination or hemo-agglutination (hemagglutination): When a transfusion with an incompatible blood group is performed, autoantibodies to blood group antigens bind to the erythrocytes of the donor. Hemolysis of the donated erythrocytes is a consequence. Agglutination is not synonymous to clotting of blood. In the latter, the final fibrin meshwork traps the red cells and platelets in the blood clot.

iii. Question:
What would the word ‘hemo-concentration’ refer to?
Answer: Hemoconcentration refers to the loss or greater loss of the plasma compartment of blood. The red cell concentration is increased. This occurs during dehydration, sweating or during a loss of fluid in burns. In dengue

hemorrhagic infection, hypovolemia and hemoconcentration are caused by the excessive shift of plasma fluids into the interstitial space, which is caused by the loss of capillary endothelial permeability function.



10 Cardio-arrows Defined

i. Definition: This is to instruct students to carefully use arrows when they explain physiology specifically and quantitatively.
ii. PTC:
It is common to use an up arrow for increase and a down arrow for decrease. Care should be exercised during the liberal use of arrows so that the specific physiology process is clearly indicated. To give an example; 'Increased cardiac sympathetic action will increase the ventricular muscle tension generated and this produces a larger ejection fraction'.
In arrow language, the student could write ↑ Sym, ↑ Contractility, ↑ Ejection fraction.
While summarizing the physiology involved, the students should not lose sight of the three different parameters that are increased here, namely, the frequency of action potentials in the cardiac sympathetics, the increased cytosolic calcium that enables the greater tension developed during ventricular contraction and the higher fractional stroke volume to EDV ejected from the heart.
Another comment to the student archer on the use of arrows is to define whether an upward arrow means an increase above normal or a compensatory increase back to normal. To illustrate, during hypovolemia, there will always be a reflex tachycardia as the arterial baroreceptors sense the vascular hypotension. An ↑heart rate is accurate.
However, the concurrent effect of the sympathetic fibers on ventricle muscle may not necessarily increase the stroke volume to above normal. The hypovolemia has the initial effect in reducing the stroke volume (SV). In this case the ↑ SV more correctly should represent a compensatory normalization of SV.

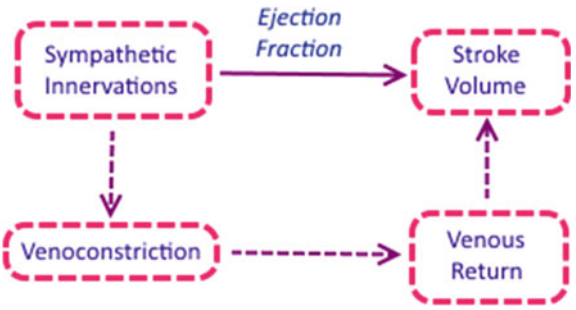


Fig. 6 Bold arrow shows the direct action of sympathetic nerve on stroke volume whilst broken arrows show the indirect sympathetic effect on stroke volume through venous return

Use of horizontal arrows to indicate a sequence of events may result in the loss of mechanistic details. For this stamen, 'Increased cardiac parasympathetic stimulation will increase the duration of the pacemaker potential', the student might write Increased parasym → Increased pacemaker duration. If needed, the ionic basis of the autonomic cardiac vagal tone should be elaborated as a decreased influx of both sodium and calcium cations and a slower closure of the potassium channels (a reduction in K^+ efflux, which has a depolarizing effect, is slowed).

iii. Question:
How would you use arrows to explain depolarization and repolarization?
Answer: The resting membrane potential of cardiac muscle is around −80 mV. Depolarization moves the resting membrane potential to a less negative value, moving it towards a reversal and towards a positive mV value. Hyperpolarization makes the resting membrane potential more negative. If this increase in membrane potential negativity is written as ↑ RMP, this should be made clear to the reader.

Chapter 2
Heart as a Rhythmic Pump

1 Heart Beat, Rate, Contractility

i. Definition: Heart rate is the number of cardiac cycles per minute or the number of cycle beats per minute. Contractility is the strength of the ventricular contraction or ventricle 'beat' at a given muscle cell length, when energized by sympathetic nerve or circulating adrenaline.

ii. PTC:
Some words are employed loosely in physiology and can overlap with common usage. The cardiac 'beat' is a good example. Most would associate the heart beat with the pulse that is palpable or the sound that can be heard with a stethoscope.
Contraction mechanism of the cardiac muscle themselves do not generate the heart sounds. Rather, the pressure differences across the two functional sets of valves, which result from ventricle contraction or relaxation, shuts the specific valves and generates the heart sounds.
Heart rate is the number of heart beats per minute. There are two heart sounds within a cardiac cycle, which we won't normally express as two heart beats per cardiac cycle. We perhaps picture each heart beat with the mechanical ejection of blood from the ventricles. This is the ventricle pump or ventricle 'beat'. The atria also contracts during the atria systole to provide the end filling of the ventricles during ventricular diastole.
During a cardiac cycle, the number of atrial 'beats' would be equal to the number of ventricle 'beats'. The same number of action potentials are sequentially transmitted from the pacemaker sinoatrial node to the atria and then to the ventricles.
The strength of each ventricle contraction or 'beat' can be increased in two ways. One is the greater tension generated by an increase in ventricle filling (EDV) by the venous return (Starling's intrinsic myocardial mechanism).

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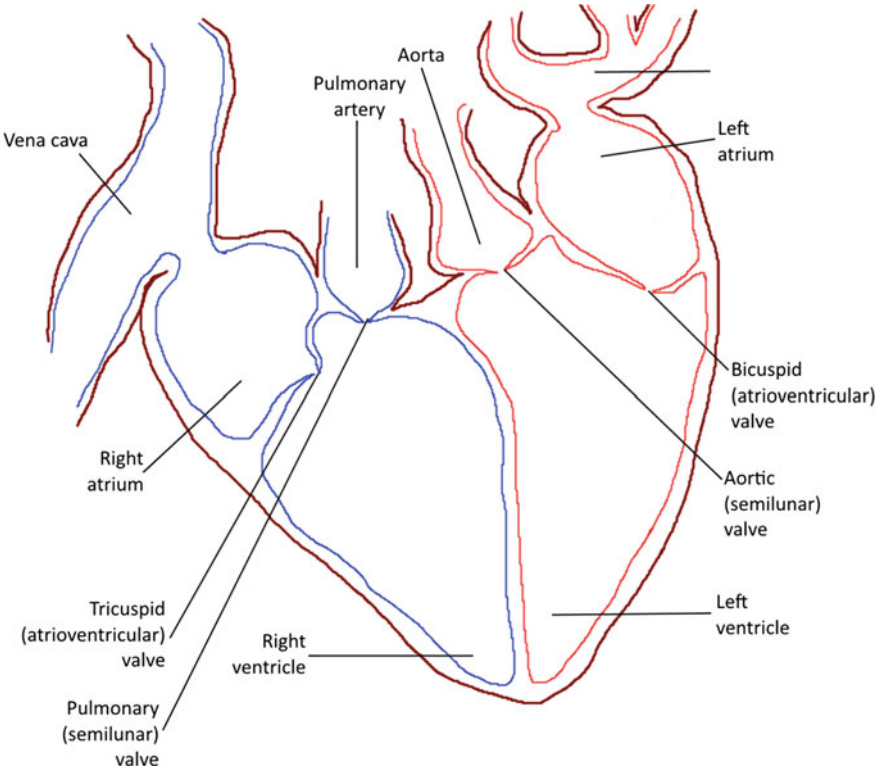

Fig. 1 Structure of the heart

The ventricle 'beat' can also be increased through extrinsic stimuli, these include the action of the sympathetic nervous system or the catecholamine adrenaline. This is specifically termed as increased 'contractility'.

The heart rate (number of beats/min) can indirectly affect the contractility (strength of each ventricle beat). Contractility is increased via a final elevation in intracellular calcium in the cardiomyoctes. With tachycardia, the number of action potentials arriving at the ventricular muscle fibers is increased. With each action potential, there is a calcium influx from the extracellular fluid (ECF) into the ventricular muscle. Thus, tachycardia can lead to a greater, calcium-mediated ventricular contractility.

However, the student should remember that in a state of tachycardia, any such benefit is counteracted by the reduced diastolic filling time. During tachycardia, the cardiac cycle duration is decreased, through a shortening of the diastole phase. So the cardiac output does not continue to be proportionately higher with an increase in heart rate. Each ventricular 'beat' pumps a fraction (stroke volume) of the available blood volume.

iii. Question:
Is pulse rate the same as heart rate?
Answer: The arterial pulse is felt during systole. Heart rate is the number of cardiac cycles per minute. Loosely defined, the pulse rate is the same as heart rate.

2 End-Diastolic Volume

i. Definition: The volume in either ventricle at the end of the diastolic filling phase, when the ventricles are relaxed.
ii. PTC:
The heart is a rhythmic pump. Functionally, there are two cardiac rhythmic pumps, the left and the right ventricle and the two pumps are arranged in series. The ventricles need to be topped up before each new contraction beat of the heart (incidentally, the heart sounds do not synchronize or match with the ventricular contraction, but with the closure of the valves).
Each cardiac cycle has a systolic contraction and a diastolic relaxation phase. The ventricles do not completely empty after each contraction. The ventricular volume that remains at the end of systole is simply named the end-systolic volume (ESV). Similarly, at the end of diastolic filling, the ventricular volume before the next contraction beat is termed the end-diastolic volume (EDV).
The pre-contraction EDV determines the volume of blood ejected by each ventricle. There are two concurrent right and left ventricular EDVs. The blood flow into each ventricle is called the venous return. There is a proportionate relationship between the venous return and the ejected stroke volume in the next contraction beat. In other words, a greater ventricular filling/EDV will result in a bigger stroke volume. This EDV-dependent effect on stroke volume is attributed and credited to Ernest Starling and named Starling's law/mechanism of the heart.
Starling's law is an intrinsic property of cardiac ventricular muscle.
The pulmonary venous drainage into the left ventricle provides the EDV that contributes to the stroke volume. The venous return of deoxygenated blood into the right ventricle also has the Starling's mechanistic action of EDV on right ventricular stroke volume pumped into the pulmonary artery.
Venous return into the right ventricle is improved through sympathetic venoconstriction. The venoconstriction contributes only a little to the total peripheral resistance. The major hemodynamic effect of venoconstriction is a decreased venous capacitance, giving an increased venous return into the right ventricle. Sympathetic constriction of pulmonary veins is not a significant event.

iii. Question:
How are the end-diastolic volume and the end-systolic volume related?
Answer: The end-diastolic volume minus the stroke volume pumped out with each ventricular contraction is equal to the end-systolic volume.

3 Ejection Fraction

i. Definition: The ratio of the stroke volume to the end-diastolic volume, which serves as an index of myocardial contractility.
ii. PTC:
How does one state the strength of cardiac ventricular contraction? The ventricular muscle tension will increase if the ventricle is filled and stretched with more blood volume. This is Starling's mechanism of the heart, an intrinsic cardiac muscle property that is independent of the extrinsic sympathetic innervation and any circulating adrenaline.
The ventricles can also contract with greater tension for a given end-diastolic volume (EDV). This increased myocardial contraction, stimulated by sympathetic stimulation/adrenaline, is termed contractility. From the same EDV, the ejected blood volume is greater. The end-systolic volume is reduced, which means that the fractional ratio of the stroke volume to the EDV is higher. The ejection fraction has increased.
The increased myocardial contractility is also called a positive inotropic effect on the ventricular contraction. The effects of cardiac sympathetic stimulation/adrenaline can thus be described in various synonymous ways:

- Increased ejection fraction
- Increased myocardial contractility
- Positive inotropism.

Students should note that both Starling's mechanism, acting via an increase of the end-diastolic volume, and a sympathetic action (acting through a reduction of the end-Systolic volume), are not separate temporal events during normal physiology. During physical activity, the venous return and cardiac output are greater, through Starling's effect on stroke volume. Starling's cardiac mechanism does not alter the ejection fraction.

(a)

$$\text{Ejection Fraction} = \frac{\text{Stroke Volume}}{\text{End-Diastolic Volume}}$$

(b)

$$\text{Contractility} \neq \text{Force of Contraction}$$

Fig. 2 **a** Equation to calculate ejection fraction. **b** It is important to note that contractility is not the same as force of contraction as contractility refers specifically to the increase in ventricular contraction strength for a given end-diastolic volume in response to sympathetic stimulation

Sympathetic activity is activated during exercise and there will be also be an increased ejection fraction or contractility from a larger EDV.

iii. Question:
In cardiac muscle failure, how do the Starling's intrinsic muscle mechanism and the ejection fraction change?
Answer: The normal curve showing Starling's law of the heart (EDV versus stroke volume) is shifted to the right. The weak pump action of the ventricle reduces the ejection fraction. There will be both intra-cardiac and veno-vascular congestion.

4 Ventricular Volume-Pressure Loop

i. Definition: The changes in intra-ventricular pressure (y-axis) and volume (x-axis) during a cardiac cycle.

ii. PTC:
During a cardiac cycle, the volume and pressure changes, especially in the left ventricle, are quite dramatic. These volume-pressure changes can be traced out graphically as a loop. There is an arrow along the loop going anticlockwise to show the progression of the events during a cardiac cycle.
The lower horizontal line of the loop represents the two ventricular volumes at each end of the line, before and after filling, namely end-systolic volume (ESV) and end-diastolic volume (EDV) respectively. The arrow points rightward from ESV to EDV, the length of the line is the stroke volume.
The two vertical lines indicate a period of sharp changes in intraventricular pressure. The right line with an upward arrow is the rapid increase in intra-ventricular pressure during the isovolumetric contraction phase. The downward arrow on the left vertical is the sharp decline in ventricular pressure during the isovolumetric relaxation phase of diastole.
The ejection phase would begin at the top north east corner of the loop, when the aortic valve opens. The volume is quickly reduced from EDV to ESV, indicated by the leftward arrow. The loop shows a slight elevation of ventricular pressure during the ejection phase.
Passive filling of the ventricle from ESV to EDV begins when the mitral valve opens (the lower south–west corner of the loop).
The effect of cardiac sympathetic action on the myocardium can be represented in the ventricular loop. The EDV point remains unchanged since the sympathetic does not directly alter the EDV (ignoring sympathetic venoconstriction). The ejection fraction is increased when increased myocardial tension is generated. The ESV is reduced with the greater contractility and the left vertical is shifted more to the left.

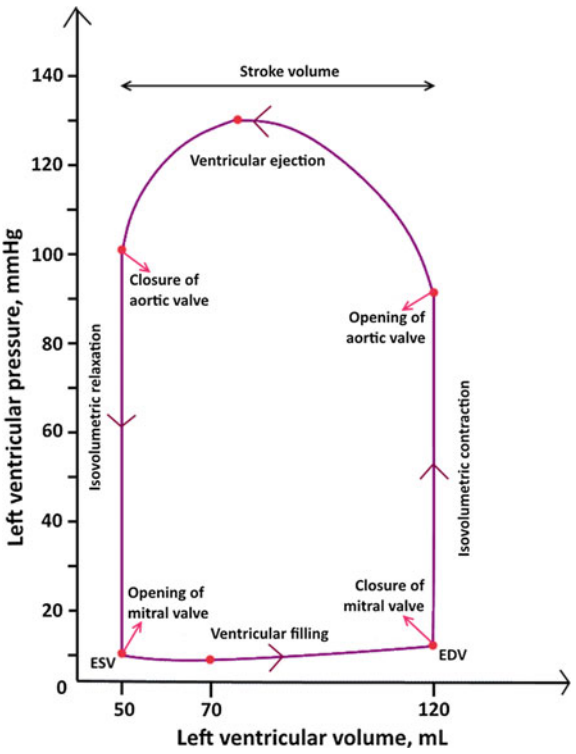

Fig. 3 The ventricular pressure-volume loop and the cardiac events represented within

iii. Question:
How would the intrinsic Starling's mechanism to increase ventricular muscle tension be drawn as a loop in the volume-pressure graph?
Answer: A bigger EDV will stretch the ventricle to give a larger stroke volume with unchanged ESV. The right vertical of the ventricular loop is shifted more to the right.

5 'Sympathetic Starling' and the Heart

i. Definition: The concurrent effect of cardiac sympathetic nerve stimulation and the intrinsic myocardial length-tension response to eject a larger stroke volume during physical activity.
ii. PTC:
The stroke volume can be increased through an increase of the ventricular filling (the heart is a generous organ, the more it receives, the more it gives!) This relationship between end-diastolic volume (EDV) and stroke volume is named after Ernest Starling.

For a given EDV, the ejected stroke volume can also be increased when the myocardium develops a greater tension following stimulation by sympathetic nerve or adrenaline. This is a positive cardiac contractility response.

The student should note that the two events for a greater stroke volume occur concurrently in vivo during physical activity. Venous return is increased during exercise and therefore, EDV is larger. The increased cardiac sympathetic nerve stimulation results in a greater ejection fraction (stroke volume/EDV), starting from the bigger EDV.

'Sympathetic Starling' has been coined for this book to remind readers of this functional merging between the two stroke-volume enhancing factors. Graphically, this is illustrated by a shift of the intrinsic Starling's curve relating EDV (x-axis) and the stroke volume (y-axis). With cardiac sympathetic input, the Starling's curve is shifted to the left. This indicates that for any given EDV, the stroke volume is increased beyond the expected volume based on Starling's mechanism.

The venoconstriction by increased sympathetic activity also indirectly increases the EDV by reducing the venous capacitance, giving a greater venous return. In other words, sympathetic venous action indirectly promotes Starling's cardiac action.

iii. Question:
Besides the two effects of sympathetic action on increasing cardiac output, what is a third positive action of sympathetic activity during exercise?
Answer: Cardiac sympathetic action on the sinoatrial node produces tachycardia. More stroke volumes are pumped out per minute.

6 The Heart Pumps a Fixed Blood Volume

1. The heart is a rhythmic pump.
2. The heart rhythmically pumps around a **fixed volume** of blood.
3. The cardiac rhythmic pump is diastolically filled with blood before each systolic contraction.
4. The portion of the end-diastolic volume (EDV) pumped or ejected out per contraction/heart beat is called the **stroke volume**.
5. This stroke volume can be increased if needed by a greater ventricular contraction.
6. A greater ventricular contractility can be achieved by the stimulation of circulating hormones, e.g. adrenaline, or by the autonomic cardiac sympathetic nerve.
7. The unejected, remaining ventricular volume (end-systolic volume, ESV) is reduced when adrenaline and sympathetic nerve is active on the heart muscles.
8. The cardiac muscle also can achieve a bigger stroke volume independent of the extrinsic effect of adrenaline or sympathetic stimulation through an *intrinsic* myocardial mechanism.

9. This intrinsic mechanism operates via the length-tension relationships of ventricular muscle, described by Starling's as a characteristic 'law of the heart'.
10. This intrinsic increase in stroke volume is proportionate to the ventricular filling, i.e. the greater the EDV, the more contraction tension will be generated by a greater-stretched ventricular muscle length.
11. The **fixed volume** of blood that is circulated or repumped through the body is revitalized, refreshed or rejuvenated in terms of its

    – oxygenation and CO_2 status (lungs),
    – pH and metabolic byproducts (lungs, kidneys).
    – energy substrate (glucose, amino acids, ffa, metabolic hormones; GI, liver, muscle).
    – turnover of aged erythrocytes, every 120 days.

The **fixed, regulated volume** of blood is monitored by **vascular volume sensors** (volume receptors, baroreceptors and intrarenal baroreceptors) and the normal blood volume, a component of the extracellular fluid (ECF), is determined by the total body sodium content, sodium being the major osmoactive electrolyte in the ECF. Blood volume affects venous return, EDV, stroke volume and hence the cardiac output ejected from the heart.

7 Perfusion Pressure

i. Definition: The driving pressure that is responsible for the blood flow, either the systemic cardiac output or the regional blood flow to individual organs.
ii. PTC:
    In the systemic circulation, the cardiac output is supplied by the rhythmic stroke volumes that are ejected during every cycle. The pressure difference between the left and right side of the heart is the actual perfusion pressure. Since the mean right atrial/central venous pressure is near to zero mmHg, the perfusion pressure that sustains the cardiac output in the systemic circuit is basically the mean aortic pressure (mAoP) pressure.
    The mAoP is $\sim$100 mmHg, fluctuating from a peak systolic pressure at 120 mmHg to a minimum pressure during diastole of 80 mmHg. This mAoP is simply the arterial blood pressure or just blood pressure.
    For a regional blood flow, the driving pressure is specifically the difference between the arterial and the venous pressure. The local venous pressure is often ignored due to its low value, e.g. the renal arterial pressure is also referred to as the renal perfusion pressure.
    In a person who is standing up, gravity affects both the arterial and the venous hydrostatic pressure in the same measure, with an increase below the cardiac level. At any level then, since both the hydrostatic pressures are increased/decreased below/above the heart line, respectively, the driving perfusion

pressure that determines the blood flow does not change with the effect of gravity.

Thus, in the upright lungs, the decrease in the pulmonary perfusion from the base to the apex is not due to a reduction in perfusion pressure. The driving pressure at various levels of the upright lungs is uniquely affected by the difference between the arterial pressure and the alveolar air pressure that exerts a mechanical compression on the pulmonary capillaries.

iii. Question:
What is the driving perfusion pressure for the blood flow from the right to the left side of the heart?
Answer: The cardiac output from the right ventricle is the pulmonary blood flow. The perfusion pressure here is the mean pulmonary arterial pressure minus the left atrial pressure.

8 Hyperemia

i. Definition: The increase in tissue blood flow that occurs via local control mechanisms in response to metabolic demands.
ii. PTC:
The blood flow to regional organs are adjusted to match its metabolic needs. This self-regulatory, local adjustment does not require intact autonomic nerve innervations. Increased cell metabolism in active tissues release metabolites and in providential design, all the vasoactive metabolites are vasodilators. The local decrease in PO_2, increased PCO_2 and lactic acid also cause vasodilatation and lower the vascular resistance to blood flow.
This metabolic-triggered increase in tissue perfusion is also called hyperemia. Hyperemia can be active or reactive. Active hyperemia describes the increase in blood flow in response to tissue metabolism. Reactive hyperemia is the rebound increase in blood flow following a period of transient tissue ischemia. In normal persons, during a sustained isometric contraction exercise, there is vascular compression. When the muscles are relaxed, the accumulated metabolite vasodilators and local hypoxia during the mechanical vascular occlusion produce a compensatory sharp increase in tissue perfusion.
As a general term, hyperemia can be mediated by changes in autonomic nerve activity to the arterioles. In most tissues, the arterioles are supplied by sympathetic vasoconstrictor fibers. These fibers release noradrenaline. Vasodilation is effected by a reduction in the sympathetic vascular input.
There is evidence in mammals for cholinergic sympathetic fibers e.g. to arterioles in skeletal muscles. In some tissues, cholinergic parasympathetic

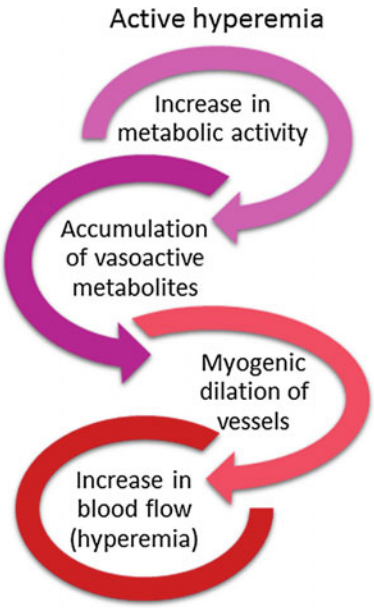

Fig. 4 Flowchart outlining events which lead to hyperemia as the body's response to increased metabolic activity

fibers produce vasodilation. There are also peptidergic parasympathetic vasodilator nerves e.g.in the gastrointestinal physiology.
Sexual function in males involves a unique nitric oxide-releasing parasympathetic fibers that cause an acute inflow of blood during penile erection.

iii. Question:
Is neural, hormonal or local metabolite action more dominant towards increasing blood flow to skeletal muscles during physical activity?
Answer: At rest, the dominant control of skeletal muscle perfusion is the vasoconstrictor sympathetic nerve. During muscle activity, metabolite vasodilators, together with local PO_2 and PCO_2 changes sustain the increased perfusion. Adrenaline, released by sympathetic stimulation of the adrenal medulla, also acts on vascular beta receptors to enhance the blood flow.

9 Coronary Hyperemia

i. Definition: The increase in coronary blood flow with increased cardiac work.
ii. PTC:
It is physio-logic that the heart muscle will be supplied with greater blood flow when it is more active. The cardiac sympathetic nerve action is stimulated during exercise and this provides a higher cardiac output. Both the heart rate and the strength of cardiac contraction are increased.

The coronary arterioles are innervated by sympathetic fibers. However, the increased coronary perfusion during physical activity is not due directly to a neural action. The increased coronary blood flow is enabled and maintained by metabolite vasodilators, a major one is adenosine from the increased cardiac metabolism. Local myocardial hypoxia also results in dilation of the coronary vessels.

Tachycardia and increased myocardial contractility are both actions of cardiac sympathetic nerves. The cardiac work is increased and the myocardial metabolism is higher. The effect of local cardiac tissue hypoxia and metabolite vasodilators matches the coronary blood flow with the increased metabolic demands of the active heart.

Thus, the cardiac sympathetic nerve heightens the coronary perfusion indirectly, via the increased needed cardiac work, in proportion to the increased cardiac output. This phenomenon is strictly defined and it is not synonymous with coronary autoregulation.

The coronary arterioles autoregulate to maintain a normal flow rate at rest, when there are fluctuations in the coronary arterial perfusion pressure. It is an intrinsic mechanism, independent of any direct or indirect neural action.

Coronary hyperemia occurs during physical activity that demands a bigger cardiac output.

iii. Question:

Thinking integratively, will there be any neurally mediated coronary hyperemia when there is a decrease in arterial pressure?

Answer: Hyperemia refers to a blood flow rate above the normal value. When the coronary perfusion pressure is decreased due to the lower arterial head pressure, autoregulation will intrinsically aim to maintain the coronary blood flow. The cardiac sympathetic nerve can be activated via the baroreflex in response to the hypotension. This sympathetic compensatory action can indirectly increase the coronary perfusion above the initial drop in coronary perfusion.

10 Fick's Principle

i. Definition: The principle, based on the 'conservation of mass' is used in the determination of cardiac output.

ii. PTC:

The student should not mix up Fick's Principle with Fick's law of Diffusion. Fick's Principle is based on the conservation of mass. For example, the amount of solute that enters an organ will be equal to the mass that exits the organ plus the amount that has been extracted or used by the organ.

Using this relationship, Fick's Principle is used to determine regional blood flow. The pulmonary blood flow is the right ventricular cardiac output. Fick's

Principle can then be used to derive resting cardiac output, since in a closed cardiovascular circuit, the left and right ventricular cardiac outputs are equalized.

The mass of solute or parameter used in measuring pulmonary blood flow by Fick's Principle is the oxygen content. The rate of delivery of oxygen in mixed venous blood to the lungs will then be equal to the rate of oxygen delivery in the oxygenated, arterial blood that exits the lungs minus the rate of oxygenation in the lungs.

These values are now well established. The oxygen content in arterial and mixed venous blood are around 20 ml O_2% and 15 ml O_2%, respectively. At rest, the rate of oxygenation is about 250 ml/min in a 70 kg male adult. The rate of oxygen delivery in arterial blood is the CO $\times$ CaO_2 (where CO is the cardiac output and CaO_2 is the arterial blood oxygen content).

The oxygen content in arterial and venous blood is fairly constant in all healthy persons. The difference is the rate of oxygen consumption by the tissues that will vary with the body tissue mass. At rest, the rate of cellular use of oxygen will be equal to the replenishment rate by lung oxygenation.

Using Fick's Principle, (CO $\times$ CaO_2) - (CO $\times$ CvO_2) will be equal to the lung oxygenation rate.

iii. Question:
What is the equation for calculating cardiac output based on Fick's Principle?
Answer: Rearranging the relationship for the 'conservation of oxygen' above, the cardiac output will be equal to the *Rate of Lung Oxygenation/CaO_2–CvO_2*.

SUMMARY–Hemodynamics of a Rhythmic Cardiac Pump

Let me elaborate what is often observed as students (and perhaps educators) try to think about 'cause and effect' associations between cardiac output and blood pressure.

1. The basic hemodynamic equation states that blood flow (F) is equal to the perfusion pressure (P) divided by the vascular resistance. This basic formula, when applied to the whole systemic circulation converts to mean arterial pressure (MAP) = Cardiac Output (CO) multiplied by the total peripheral resistance (TPR).
2. When students ponder the relationship between MAP = CO $\times$ TPR, I am commonly asked: 'Does blood pressure determine the cardiac output?' or 'Is Cardiac output a determinant of blood pressure?' as implied by the equation.
3. When control of blood pressure is taught and baro-reflex mechanisms elaborated, changes in blood pressure are compensated by corresponding responses in CO and TPR, demonstrating that cardiac output affects blood pressure.
4. Normally, a few discerning students will follow with the query 'But isn't systemic blood flow determined by the perfusion pressure between the left and right side of the heart (i.e. the mean arterial pressure, MAP)?'

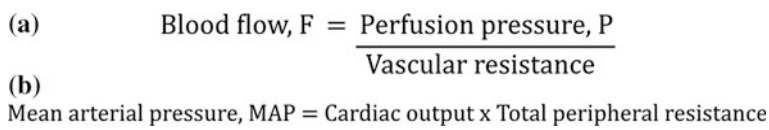

Fig. 5 **a** The basic haemodynamic equation indicating the relationship between blood flow, perfusion pressure and vascular resistance. **b** The two determinants of MAP are cardiac output and total peripheral resistance

5. So we have here the same mental picture of two apparently conflicting statements mentioned in Roberts's 1945 essay in the Lancet [1] on the relationship between cardiac output, venous pressure and venous return, as pointed out by Dr. Beard [2]. We have two events in an apparent contradiction, namely 'Cardiac output is a determinant of blood pressure' and 'Blood pressure determines cardiac output and the peripheral blood perfusion'.
6. In addition, we tell our students that because the ventricles are rhythmic pumps, ventricle contraction involves cardiac work against the MAP, called the 'afterload'. So, in chronic hypertension, the burden of the increased cardiac work against an elevated MAP can eventually lead to a compromised cardiac output.
7. This means that the statement that 'blood pressure determines flow', which applies to a rigid conduit, is no longer simply applicable to the hemodynamics of the pulsative cardiac pump that sustains the systemic blood flow. The maintenance of continual cardiac output to the periphery during ventricular relaxation is the elastic recoil of the arteries that provide the diastolic blood pressure.

The above highlights some of the explanatory problems in describing the mechanistic pressure/flow events unique to a closed circulatory system. These areas are seldom given attention in standard physiology texts and are perhaps avoided in discussion during tutorials. We should rather encourage students to think through physiology [3] and this also for ourselves will serve to engender a better scientific basis for any investigation into the clinico-physiological 'cause and effect' of cardiovascular diseases.

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Chapter 3
Heart as a Pressure Producer

1 Systolic Blood Pressure

i. Definition: The maximum aortic blood pressure that is due to the pressure exerted on the vascular wall by the ejected stroke volume.
ii. PTC:
Since the left cardiac ventricular pump is not a continuous pump, the pressure in the aorta fluctuates during a cardiac cycle. The maximum pressure exerted on the aortic wall during systolic contraction is called the systolic blood pressure.
The systolic blood pressure (SBP) is determined by two major factors. One is the size or volume amount of the stroke volume. The bigger the ejected volume, the greater the pressure applied to the vascular wall will be.
The second factor is arterial compliance. Arterial compliance is the change in pressure per change in volume of the aorta. For a given stroke volume and normal arterial distensibility or elasticity, the measured SBP has a value of 120 mmHg in most adult males. If there is an reduction in arterial compliance due to histological changes with age or atherosclerosis, the aorta will be stiff and less stretchable. The same ejected stroke volume will then exert a higher pressure (SBP) on the vascular wall.
In a graphical portrayal of the cardiac cycle, the ejection phase occurs when the aortic/pulmonary valves are opened at the end of the rapid buildup of ventricular pressure during the systolic, iso-volumetric contraction phase. As blood is pumped out during early ejection, the aortic pressure rises to reach the SBP.
Note that the elastic recoil in a stiffer, less compliant aorta will also be decreased. The arterial elastic recoil is what provides the driving pressure for peripheral perfusion during ventricular relaxation (diastolic blood pressure, DBP, discussed in the next section). In atherosclerosis then, the pulse pressure (which is the difference between SBP and DBP) will be larger.

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iii. Question:
In hyperthyroidism, would you expect a change in the pulse pressure?
Answer: The cardiac output is increased when the thyroid hormone secretion is increased. The increased myocardial contractility pumps out a bigger stroke volume, resulting in a higher SBP. The higher metabolic rate in hyperthyroidism will activate temperature regulatory mechanisms which include cutaneous vasodilatation. This will lower the DBP. The result of both of these effects is that the pulse pressure will be larger.

2 Diastolic Blood Pressure

i. Definition: The aortic pressure during ventricular relaxation that continues to provide the driving pressure for continuous blood flow to the peripheral tissues as the ventricles are refilled with blood for the next contraction.
ii. PTC:
The heart is a rhythmic pump. It might as such be expected that the perfusion pressure would be much reduced and inadequate to ensure continuous delivery of blood to the tissues during the relaxation phase of the cardiac cycle. This scenario would indeed be true if the blood vessels were rigid conduits, similar to the water piping system in our homes. If the water pressure were to be intermittent, the water flow from our taps would also be non-continuous.
However, the aorta and arteries are elastic vessels and they are stretchable. During ventricular contraction, the ejected stroke volume per heart beat is pumped into the periphery. En route, the aorta and large arteries are also distended by the stroke volume.
During diastole, the ventricles relax and the intra-ventricular pressure drops to close to zero mmHg to allow filling of blood via the atria. The aortic pressure decreases during diastole but the drop is limited when the aortic valve closes. In addition, the aorta and arteries, which have been stretched during systole, begin to recoil during diastole. This elastic vascular recoil is what provides the driving pressure for uninterrupted perfusion to the periphery.
The diastolic blood pressure (DBP) is normally cited as 80 mmHg and the systolic (SBP) at 120 mmHg in a 70 kg male adult. It can be imagined that

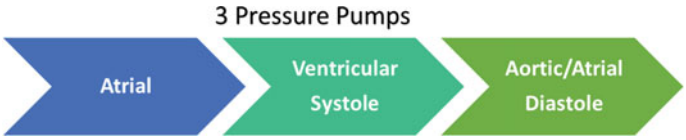

Fig. 1 The continuous, uninterrupted circulation of blood by the cardiac rhythmic muscle activity is provided during diastole by the elastic recoil aortic pump. At the same diastolic time, the atrial systolic pump fills the ventricle for the next systole in the cardiac cycle

the diastolic blood pressure is like the expulsion pressure in an inflated balloon as the opening of the elastic balloon is released. The resistance of the balloon outlet is analogous to the total peripheral resistance (TPR) in the systemic circulation.

As such, a major factor that influences the value of the DBP is the TPR. This explains why the rise in DBP during exercise is not as significant as the increase in SBP. Vasodilation in both the skeletal muscles and in the skin lowers the TPR during exercise. A greater stroke volume during physical activity increases the SBP exerted on the aorta. A bigger stretch will mean a larger elastic recoil, which in turn determines the DBP.

iii. Question:
Is the mean arterial blood pressure an average of the systolic and diastolic blood pressures?
Answer: The mean arterial blood pressure is not actually 100 mmHg. The value is nearer the DBP, since the diastolic time is longer than the systole period. For a person with 120/80 mmHg SBP/DBP reading, the mean blood pressure is 93 mmHg, calculated from the equation, DBP + 1/3 (pulse pressure).

3 Central Venous Pressure

i. Definition: The blood pressure at the level of the heart on the right side of the overall systemic circulation, and related to the right atrial pressure.

ii. PTC:
Overall, the driving pressure from the left side to the right end of the systemic circulation would be the mean arterial pressure minus the central venous pressure (CVP). The CVP is closely related to the right atrial pressure (RAP), the point of entry of the large veins, superior and inferior vena cava. The value of the CVP/RAP is near to zero mmHg.
The CVP has an effect on the venous return. Venous return is determined by the difference between the mean systemic (circulatory) filling pressure [MSFP] and the CVP/RAP ratio. The normal value of MSFP is about 8 mmHg.

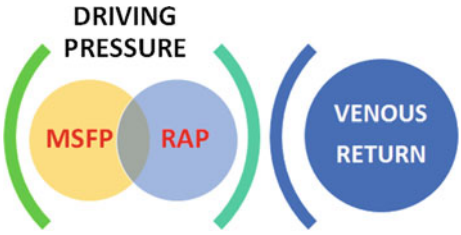

Fig. 2 Venous blood flow or venous return is determined by the driving pressure which is the difference between the mean systemic filling pressure (MSFP) and the right atrial pressure (RAP)

Thus, small changes in the CVP can influence the venous return. The venous vascular resistance is a minor contribution to the venous blood flow, since the veins are capacitance vessels. For example, in right ventricular failure, the CVP is elevated and venous vascular congestion develops. The venous pressure is increased and the capillary hydrostatic pressure upstream is also raised, which is a predisposition to edema.

The CVP/RAP fluctuates slightly during a respiratory cycle. During inspiration, when the intra-thoracic pressure is decreased, the CVP is decreased and lower than during expiration. During a forced expiration, the CVP is markedly raised and this reduces the venous return.

The CVP/RAP also shows changes during a cardiac cycle. The right atrial pressure is increased to different degrees by three events during a cardiac cycle:

(1) The inflow of the venous return before the atrioventricular valve opens
(2) The atrial systolic contraction
(3) The pressure extension of the right ventricular chamber into the right atrium during iso-volumetric contraction

iii. Question:
When a person lies down, do you expect that the central venous pressure will change?
Answer: The central venous pressure, measured at the level of the heart, is independent of gravity.

4 Baroreceptors

i. Definition: The mechanoreceptors that monitor blood volume/pressure. These stretch receptors are found on both the arterial and the venous side of the cardiovascular system.
ii. PTC:
The baroreceptors detect changes in blood pressure. The arterial baroreceptors are those located in the carotid sinus and the aortic sinus. Their location at and above the level of the heart is designed to serve their function. In humans, postural changes are subject to effects of gravity on the hydrostatic pressure of blood, particularly in the standing position. The baroreceptors are positioned to sense a decrease in the blood pressure above the cardiac line in a standing person.

The blood volume and blood pressure are naturally related. Contraction of the extracellular fluid (ECF) or hypovolemia leads to hypotension. The vascular volume sensors that monitor at the low-pressure side of the circulation are named volume receptors. These ‘baro’ receptors are present in the large veins/atrial wall and in the pulmonary vasculature.

Both the carotid/aortic baroreceptors and the volume receptors are linked by sensory fibers to various locations in the brain that are involved in ECF volume and blood pressure regulation. The cardiovascular control neurons in the brainstem receive these afferent signals from the volume/pressure sensors. The afferent impulses from both baroreceptors and volume receptors also provide the signals that influence vasopressin secretion and the thirst sensation during the regulation of water balance.

The kidneys are part of the cardio-renal mechanisms for ECF volume/pressure control. The pressure sensors in the kidneys are called 'intra-renal' baroreceptors. These renal volume/pressure sensors are part of the wall of the pre-glomerular afferent arteriole. The secretion of the sodium-conserving renin from the juxtaglomerular cells at the afferent arteriole is linked to the mechanical stretch of the intrarenal baroreceptors. Hypovolemia reduces the distention of these renal vascular sensors and renin secretion is increased. The renal baroreceptors are not innervated as part of a reflex loop. This is direct sensing whereas for the carotid baroreceptors, there is a reflex sympathetic loop.

iii. Question:
How would the innervated baroreceptors function if they were located in the abdominal cavity instead of their designated positions?
Answer: The blood pressure reduction above the heart when a person stands from lying down would not be detected. Compensatory reflexes that maintain an adequate arterial perfusion pressure to the head (above the heart obviously!) would not be activated. A decrease in cerebral blood flow would result. The person would faint (a physiologic response, as the cerebral perfusion is restored in the supine position!).

5 Total Peripheral Resistance

i. Definition: The overall vascular resistance in the systemic circulation to blood flow from the left side to the right side of the heart, not including the pulmonary vascular resistance.

ii. PTC:
The term 'total peripheral resistance' (TPR) is a determinant of the arterial blood pressure from the relationship: Blood Pressure = Cardiac Output $\times$ TPR. This formula is derived from the basic hemodynamic principle of: Blood Flow = Driving Pressure/Resistance. The systemic blood flow is the cardiac output, the resistance then is the TPR and the driving pressure is the mean arterial pressure, since the right atrial pressure is close to zero mmHg. The 'total' in TPR does not comprise all arteriolar resistances. When the TPR is adjusted in a compensatory reflex to blood pressure changes, selective vasoconstriction (or vasodilation) occurs in regional arterioles. The arterioles

of the cerebral and coronary circulation are spared and must be spared. For instance, if there is hypotension, the cerebral perfusion is threatened, if the TPR would include cerebral vasoconstriction, the hypoperfusion to the brain would worsen, exacerbating the problem.

The selective vasoconstriction will involve non-essential organs, like the kidneys, the skin and the gastro-intestinal tissues. Renal arteriolar constriction helps elevate the TPR. The following temporal decrease in renal blood flow is also a beneficial response in terms of conserving sodium and fluid (reduced urinary excretion) to normalize the blood pressure.

In persons who are exercising, increased blood flow to skeletal muscles is possible through regional vasodilation in response to metabolite vasodilators. This local arteriolar response in the muscles overrides any increased sympathetic vasoconstriction, since activation of the autonomic sympathetic system is a major feature during exercise. The extent of muscle vasodilation, which will decrease the TPR, depends on the intensity of the exercise and associated metabolic needs.

During exercise the lower TPR determinant tends to decrease the blood pressure. However, the cardiac output (CO) determinant is elevated by an increased cardiac sympathetic activity that produces tachycardia and a higher myocardial contractility (further enhanced by the action of adrenaline, secreted when the adrenal medulla is stimulated by its sympathetic nerve supply). A higher blood pressure is still sustained ($BP = CO \times TPR$) during the physical activity to provide the required greater cardiac output.

iii. Question:
Does the change in TPR always occur in response to a fluctuation in blood pressure?
Answer: In the control of arterial blood pressure, yes, the TPR changes as part of the reflex pathway to normalize the BP. In some other situations, a primary change in the TPR can be the initiating cause of a change of the BP. Strong emotions, like anger, can elevate the BP. Subjective, unpleasant sights or sensations can cause an acute drop in TPR and hence in the BP. This causes the person to faint. In certain infections, e.g. dengue fever, a pathophysiologic vasodilation can be induced during the body's immune response to the microorganism.

6 Parallel Vascular Resistance Arrangement

i. Definition: The vascular resistances in every regional organ are arranged in parallel to each other. This allows for local specific control of blood flow.

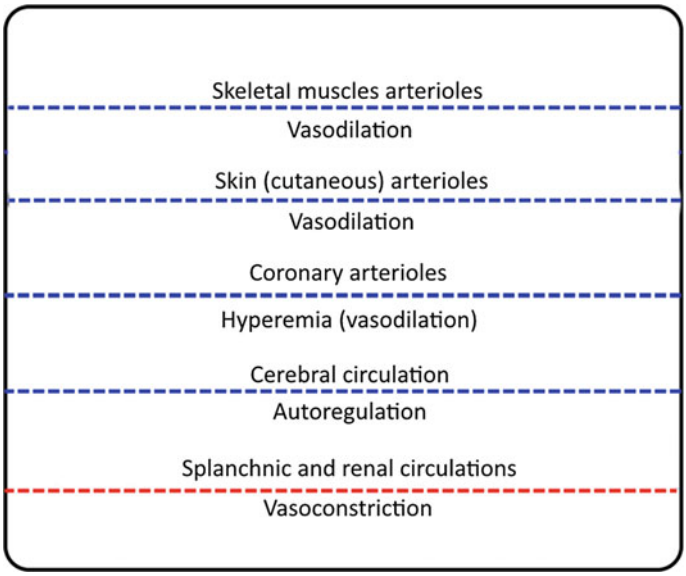

Fig. 3 Parallel resistances enable local increases in perfusion without interfering with blood to other organs during exercise

ii. PTC:
The cardiac output from the left ventricle is distributed unequally to the major organs in the body. The lungs are the only tissues that receive all the cardiac output (CO) from the right ventricle.
The fractional distribution, at rest, of the left ventricular CO to the various organs is determined by the local vascular resistance, mainly at the arterioles. The various arteriolar resistances are arranged in parallel to each other. This is essential to ensure that a local increase or decrease in vascular resistance will not affect the blood flow to other organs.
To illustrate, take the scenario of exercise. The arterioles to the skeletal muscles are vasodilated and a larger proportion of the CO is supplied to the active muscles. During exercise, there is a general increase in sympathetic activity. As such, during physical activity, the sympathetic nerve vasoconstricts the arterioles in organs that are not involved during the muscle activity, including the splanchnic and the renal circulations.
The other tissue where selective vasodilation occurs during exercise is the cutaneous blood supply. This is due to a reduction in the sympathetic vasomotor tone. The vascular response is tied to temperature regulation, in order to lose excess metabolic heat.
The cerebral circulation is autoregulated and maintained at normal values, even though there is an increase in arterial blood pressure during exercise. There is coronary hyperemia, as the cardiac work is increased and the local

cardiac tissue O_2/CO_2 changes and vasodilator metabolites ensure the increased demand for coronary perfusion.
Thus, the differential status of the arteriolar resistances in different organs is possible because of the parallel design of the systemic vasculature.

iii. Question:
The visceral anatomy shows two major organs whose resistances are in series with each other? Which are the two organs?
Answer: The portal venous blood from the gastrointestinal tissues flows towards the liver. It is still true that on the arterial side, the cardiac output is distributed in parallel to all the different organs.

7 Reflex

i. Definition: A physiologic response to changes or fluctuations in a controlled parameter.

ii. PTC:
In common usage, we associate the word 'reflex' with a physical muscular response to an external stimulus. In general terms, there is a whole spectrum of physiological reflexes that are not restricted to skeletal muscle or even to neural responses. The speed of the reflexes also ranges from seconds to minutes.
Some examples of reflexes in cardiovascular physiology are:

(a) The classical long loop baroreflex from arterial carotid and aortic sinus baroreceptors.
(b) The similar neural reflex initiated at the volume receptors that produce the same sympathetic effector actions on the heart, arterioles, veins and adrenal medulla that are seen in the baroreflex.
(c) The afferent impulses from the volume receptors affect the secretion of the hypothalamic hormone vasopressin that is secreted from the pituitary gland. Hypovolemia increases plasma vasopressin levels. This neuro endocrine reflex also occurs with the secretion of adrenal catecholamines by sympathetic stimulation.
(d) The smooth muscle myogenic response or reflex contributes to the phenomenon of cerebral and coronary autoregulation.
(e) The cardiac volume receptors are also linked to a reflex based increase/decrease in the secretion of atrial natriuretic peptide. This local, stretch-endocrine response is part of the homeostatic regulation of ECF/blood volume.
(f) The intrarenal baroreceptors at the renal afferent arterioles also have a stretch-endocrine response that is linked to the secretion of the sodium-conserving renin.

(g) The proportionate muscular tension response as the ventricle muscle are stretched is a 'Starling's reflex' that maintains the equilibrium between the left and right cardiac outputs.
(h) The multiple actions of sympathetic response in the kidneys, produced by both volume receptors and the baroreflex, which lead to a reduction in urinary sodium excretion.

iii. Question:
Is increased skeletal blood flow during exercise considered as a reflex response?
Answer: If reflex is defined as a compensatory response to maintain a normal resting value, then another word should be used. The hyperemia in skeletal muscle is an automatic, appropriate response to increased muscle metabolism. The metabolite vasodilators and local tissue changes (e.g. low O_2, high CO_2, low pH) have a dominant role in sustaining an increased perfusion to active muscles.

8 Venoconstriction

i. Definition: The reduction in the venous capacitance by sympathetic nerve stimulation, adrenaline and skeletal muscle activity, which enhance venous return.
ii. PTC:
Vascular constriction at the arterioles, which is produced by sympathetic nerve and vasoactive agents like angiotensin II, increases the total peripheral resistance. The contribution of the veins to the total peripheral resistance is small. The major hemodynamic effect of venoconstriction is a reduction in the venous capacitance. At any one time, more than 60% of the total blood volume is in the venous 'reservoir' (this is not a static pool; veins are also called capacitance vessels, while arterioles are the major resistance vessels in the circulation).
Venoconstriction as induced by increased sympathetic activity or by adrenaline will supply more of the total blood volume into the closed vascular system to circulate. The venous return is greater, which then increases the stroke volume and the cardiac output.
The muscle contraction during physical activity also mechanically compresses or constricts the veins. In conjunction with the unidirectional valves in the veins, this also promotes venous blood flow returning to the right ventricle. This positive action on venous return is termed the 'skeletal muscle pump'.
Because the two ventricular pumps are arranged in series, the right and left cardiac outputs are equalized over time. The intrinsic Starlings' mechanism of the cardiac muscle ensures this balance of cardiac outputs. This balance prevents vascular congestion if unequal right/left cardiac outputs persist. An

initial increase in right ventricular output will be conveyed 'Starlingly' to increase the venous drainage into the left ventricle. A larger left stroke volume will then 'rightly' result.

iii. Question:
Is the venous return increased above normal value by venoconstriction during hypovolemia?
Answer: Not necessarily. Venoconstriction improves the venous return by reducing the venous capacitance. When the total blood volume is decreased, the venous return will also decrease. The baroreflex triggered will include a venoconstriction response by sympathetic action/adrenaline. If the hypovolemia is significant, the drop in the venous return below normal will be lessened but not increased above normal value.

9 Central, Local Control of Circulation

i. Definition: In cardiovascular integrated functions, the central mechanisms maintain the arterial blood pressure and the local, vascular mechanisms regulate the regional flow.

ii. PTC:
The driving head pressure at the aorta is maintained by compensatory reflexes in response to blood pressure or volume changes. The baroreflex and volume receptor reflex, as main components of the compensations that involve the brainstem, produce selective vasoconstriction to raise the TPR.
At the same time, local vasodilation is needed at the cerebral and coronary blood vessels. The cardiac pump activity is stimulated by increased sympathetic action when the baroreceptors sense hypotension or hypovolemia. There is cardiac hyperemia, served by metabolite vasodilators that are produced by the increased cardiac metabolism.
The cerebral blood flow is maintained by autoregulation in response to a decrease in the arterial perfusion pressure.
During exercise, central mechanisms uphold a higher arterial blood pressure, which is concurrent with vasodilation in the skeletal muscle tissues. Interestingly, there is no reflex bradycardia from the exercise hypertension that is sustained by the greater cardiac pump activity.
It has been suggested that the baroreceptor sensitivity is also reset during physical activity, so no opposing, reflex bradycardia will counteract the cardiac sympathetic effects on the heart.

iii. Question:
Although logically not practiced, why does eating while exercising present a greater work load on the heart?
Answer: During a meal, there is also vasodilation of the splanchnic vasculature. The peripheral reduction in TPR will be more pronounced. To

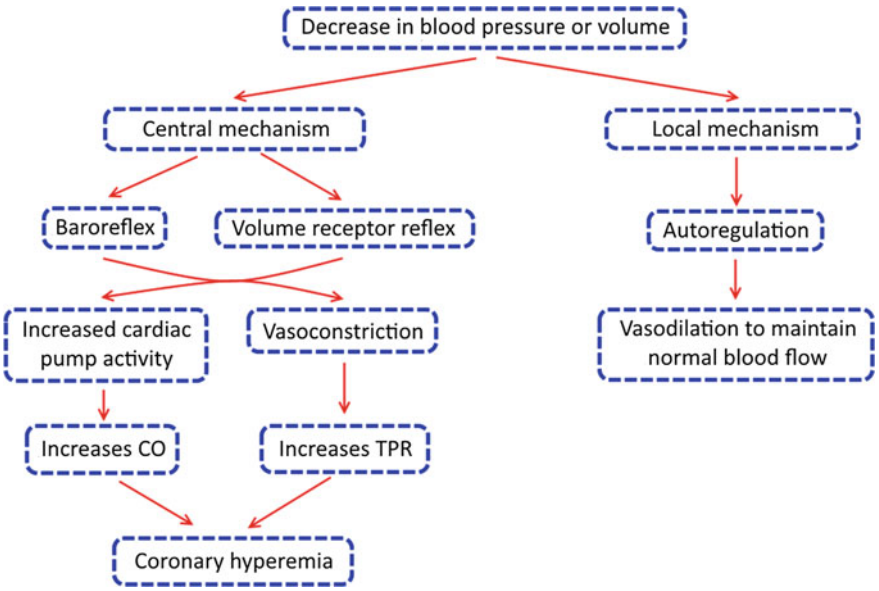

Fig. 4 Central vascular control supplements the local arteriolar (auto)regulation to ensure adequate coronary perfusion

continue providing a driving arterial pressure for a greater cardiac output to supply both the active skeletal and gastrointestinal tissues, the myocardial metabolic work is increased with tachycardia and an increased ejection fraction.

In addition, the need to offset the production of metabolic heat in order to maintain body temperature necessitates vasodilation of the cutaneous vessels to facilitate heat loss from the body's surface. The reduction in the TPR, through vasodilatation of arterioles increases the venous return. This also helps to power the greater cardiac output.

10 Cushing's Reflex

i. Definition: The central ischemic response that elevates the arterial blood pressure to sustain a cerebral perfusion for survival.

ii. PTC:

One primary aim of arterial blood pressure control is to ensure adequate blood flow to the brain for neuronal metabolism. At most times, the human brain is above the cardiac pump and the hydrostatic pressure of the blood fluid is affected by gravity. The hydrostatic pressure drops progressively with distance above the cardiac line.

Think of the giraffe and the dinosaurs … their baroreflex functions need to be even more effective to meet the metabolic needs of their more elevated brains from their respective hearts!

In situations when there is a serious threat of cerebral ischemia due to poor perfusion to the brain, an intense reflex is triggered that raises the blood pressure. The central hypoxia activates a strong sympathetic response to the arterioles and the TPR is increased greatly. The blood pressure rises to improve the cerebral blood flow.

This central ischemic response is also called 'Cushing's reflex'. The elevated blood pressure then stimulates the baroreceptors and a bradycardia is seen in this Cushing's reflex.

In the usual cardiovascular sequence of event, tachycardia contributes towards an increase in blood pressure. In Cushing's reflex, the initiating cerebral ischemia stimulus causes the brain stem to heighten the sympathetic vasoconstrictor activity. The TPR and then blood pressure are raised which then produces the reflex slowing of heart rate.

One condition that depresses cerebral blood flow is a raised intracranial pressure. Since the contents of the brain is a fixed volume within the rigid skull, changes in pressure in one compartment will alter the status of the other spaces in the brain. Elevated intra-cranial pressure mechanically compresses the arterial blood vessels that supply the brain.

A thrombotic stroke that reduces cerebral perfusion can also trigger the Cushing's reflex.

iii. Question:

What is the nature or type of the sensory receptors involved in the Cushing's reflex?

Answer: The cerebral ischemia soon results in local hypoxia in the neuronal tissues. Activated (central) chemoreceptors produce the Cushing reflex, triggered from the brain stem cardiovascular control neurons. This is a special case of the integrated link of chemoreceptors in cardiovascular physiology. Even in normal persons, there is now evidence for significant influence of peripheral chemoreceptor afferent impulses in modulating arterial blood pressure.

Chapter 4
Pathways from the Heart

1 Flow Rate, Velocity

i. Definition: Blood flow rate has the unit volume per time while the unit for velocity of blood flow is distance per time.
ii. PTC:
It is common to talk loosely of 'blood flow faster' when what is meant is not the velocity but the rate of blood flow in volume/min. An increase in cardiac output above 5 L/min in a 70 kg, male adult is an increase in flow rate not the velocity. The blood flow along every sector of the cardiovascular arterial tree to the capillaries is the same. Similarly, the venous return has the same value as the cardiac output. There is no vascular volume congestion along the blood traffic from the arterial to the venous side and into the right heart.
The velocity of blood flow however changes markedly along its bloody journey. The flow velocity is inversely related to the total cross-sectional area (CSA) at every segment of the circulation. In vivo, the flow velocity changes not from one large artery into one smaller artery and then into a single capillary. If that is the case, then the velocity of blood flow will actually increase from the large artery to the capillary. We all know from washing cars or watering our garden that narrowing of the single hose will speed up the jet of water exiting from the hose.
The CSA increases from the aorta to the capillary network. The slowest flow rate is naturally at the tissue capillaries where the combined CSA is greatest. The slow capillary transit time allows for optimal exchange of respiratory gases, energy nutrients and metabolic products.
The basis of the Korotkoff sounds used in measuring arterial blood pressure is turbulent blood flow that is generated by high velocity flow. The pressure cuff that occludes the blood flow is gradually deflated. The first squirt of blood that exits when the external applied cuff pressure is just under the maximal systolic

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pressure is very high velocity and the propelled flow is turbulent. The first turbulence-induced sound coincides with the systolic blood pressure.

iii. Question:
How does the pulmonary arterial blood flow compare with the venous return?
Answer: If the venous return is the pulmonary venous flow into the left atria, the value is the same. If the venous return is the flow into the right side of the heart, the value is and must also be the same in the closed cardiovascular circulatory loop in which the systemic and the pulmonary conduits for blood flow are arranged in series.

2 Effective Circulatory Volume

i. Definition: The blood flow that effectively perfuses the peripheral tissues. This is a conceptual volume and has no unit.

ii. PTC:
The effective circulating volume (EfCV) is not measurable. It is not defined anatomically but physiologically. Berne's Physiology text states that the EfCV is the portion of the extracellular fluid volume that is contained within the vascular compartment and which is effectively perfusing the tissues. This indicates that the EfCV is not related to the vascular volume. Instead it is associated with the pressure generated by a normal cardiac output.
In a normal person, the sodium balance determines the ECF volume/blood volume, the cardiac output/arterial blood pressure and thus the EfCV. An increase in ECF increases the blood volume. The cardiac output, arterial blood pressure and hence the EfCV increase proportionately.
However, if the heart fails to pump normally, the EfCV that supplies the peripheral tissues will decrease. Even though the blood volume is normal, the oxygenated blood flow is sluggish and a stagnant hypoxia results. The kidneys adjust their excretion of sodium chloride in response to changes in EfCV. During cardiac pump failure, the intra-baroreceptors in the kidneys sense the drop in EfCV. A sequence of events will be activated to reduce the urinary NaCl excretion. Since there was no hypovolemia to begin with that triggered

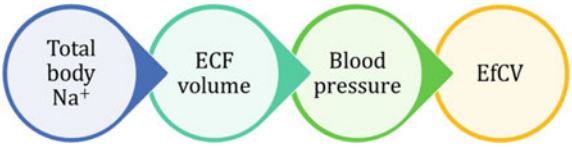

Fig. 1 Increase in total body sodium increases the ECF volume which leads to a proportionate increase in blood pressure, thus increasing the effective circulatory volume. The converse applies as well

the renal NaCl conservation, but due instead to a poor arterial driving pressure, sodium and fluid will be retained with over expansion of the ECF.
The increased ECF volume however will not correct the EfCV to supply adequate peripheral perfusion as the cardiac problem is the underlying cause.

iii. Question:
In a normal person, what is the response of the body to an increased EfCV?
Answer: The normal physiologic response will be an increased in sodium and water excretion (natriuresis). This adaptive response serves to restore the EfCV to its normal perfusing ability. The natriuresis is effected partly via the inhibition of the renin-angiotensin-aldosterone cascade reactions.

3 Capillary Dynamics

i. Definition: The balance of vascular and interstitial forces that determine the direction of fluid flow at the capillary network in the tissues.

ii. PTC:
The classical textbook account of fluid exchanges at the capillaries describes a representative situation in the skeletal muscles. There is filtration at the arteriolar end and reabsorption of fluid at the venular end of the capillary.
The direction of fluid flow is dependent on the net filtration or net reabsorption force at different points along the capillary. There are two hydrostatic forces, one associated with the capillary blood pressure and the other being the interstitial fluid hydrostatic pressure.
The other two forces are due to proteins that are non-penetrating and osmoactive at the capillary (sodium ions are freely diffusing and exert no osmotic pressure at the capillary), namely the plasma oncotic pressure and interstitial fluid oncotic pressure. The plasma oncotic pressure value is due to the plasma protein concentration and is around 25 mmHg.
The hydrostatic pressure along the standard capillary starts at 30+ mmHg at postarteriole and decreases along the capillary to about 15 mmHg at the prevenular end. The interstitial hydrostatic pressure is close to zero mmHg (can be negative in some tissues) and the interstitial oncotic is about 10 mmHg.
Considering the values of these four Starling's capillary forces, there will be a net filtration force at the beginning of the capillary. Filtration of fluid containing substrates needed for cell metabolism takes place. Dissolved oxygen is also in the filtrate. Rapid oxygen diffusion also occurs from the capillary to the cells down its partial pressure gradient.
At the venular end, the plasma oncotic pressure at 25 mmHg is now higher than the 15 mmHg capillary hydrostatic pressure. There will be a net reabsorptive force and fluid moves into the blood vessel from the interstitium. On average, around 90% of the capillary filtrate is recovered by the reabsorption.

Fig. 2 Prolonged standing, results in pooling of blood in the legs. This increases venous pressure, leading to increased capillary hydrostatic pressure which could result in edema

The balance filtrate is prevented from accumulating in the interstitium by lymphatic drainage.

The student should take note that in other capillary networks, either filtration or reabsorption is the dominant event appropriate to the organ function. At the intestines, reabsorption is the essential key activity of the capillaries.

In the kidneys, the glomerular capillary only filters plasma water. In contrast, the renal peritubular capillary only reabsorbs and accounts for 99% of the glomerular filtrate returned to the circulation.

iii. Question:
If there is a reduction in plasma protein concentration, how will the capillary dynamics change?
Answer: A decrease in plasma oncotic pressure will lead to development of edema. There will be increased filtration at the arteriolar end and a decreased reabsorption at the venular end of the capillary. The excess interstitial fluid exceeds the capacity of the lymphatic drainage and edema is presented.

4 Transcapillary Fluid Shift

i. Definition: The shift of fluid from the interstitial fluid space into the vascular compartment as a compensation for hypovolemia.
ii. PTC:
The interstitial fluid (ISF) volume is three times larger than the intravascular plasma volume. This fact providentially supplies fluid from the ISF to restore plasma volume during hypovolemia. This phenomenon is termed' transcapillary fluid shift' (tcfs). This compensation is sometimes described as an intermediate stage adjustment between the rapid baroreflex and the long-term renal responses to normalize sodium and water balance.

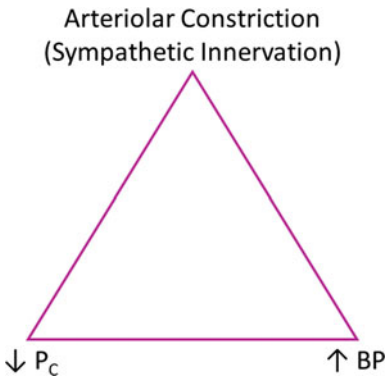

Fig. 3 Dual benefits of arteriolar constriction during hypovolemia. Upstream blood pressure is elevated and downstream capillary pressure is decreased to favour fluid shift into vascular space. P_c is capillary hydrostatic pressure whereas BP is blood pressure

The tcfs takes place due to changes in the balance of Starling's forces at the capillaries. Hypovolemia and the consequent hypotension will reduce the capillary hydrostatic pressure. This will result in less net filtration and more net reabsorption force at the arteriolar and venular end of the capillary respectively.

The baroreflex that activates the sympathetic effector discharge will also vasoconstrict the arterioles. The downstream effect of this arteriolar constriction which raises the TPR is to lower further the capillary hydrostatic pressure (P_C). A trans-capillary fluid shift occurs if the P_C drops considerably. Note that after a blood donation, this tcfs is also a potential event. The fluid shift will produce a hemodilution with a decrease in the hematocrit. The tcfs will also lower plasma protein concentration and the dependent oncotic pressure. The latter will counteract and limit the tcfs.

Students should distinguish this tcfs from the trans-cell membrane compensatory fluid shift from the intracellular fluid (ICF) to the ECF. The ICF volume is twice the ECF space and in dehydration, e.g. after sweating when the ECF is hypertonic, the ECF/blood volume is preserved by this ICF > ECF water flux. Edema is the excess tcfs from the capillary into the ISF.

iii. Question:
Does venoconstriction affect the transcapillary fluid shift in any way?
Answer: The sympathetic arteriolar vasoconstriction decreases the 'downstream' capillary hydrostatic pressure. This leads towards net Starling's forces that favor fluid entering from ISF into the blood vessels. Venoconstriction has a primary effect on improving the venous return. The 'upstream' effect on increasing the capillary hydrostatic pressure is minor.

5 Edema of Vascular Congestion

i. Definition: The accumulation of excess fluid in the interstitial space due to increased capillary hydrostatic pressure that builds up consequent of elevated venous pressure.

ii. PTC:
Filtration occurs at most capillary network to supply the tissues with the energy substrates like glucose, amino acid that are freely filterable between the endothelial cells. The respiratory gases exchange by diffusion between the capillary blood and the tissues.
Most of the capillary filtrate (≈90%) is reabsorbed back towards the venular end of the capillaries. Fluid does not accumulate in the interstitial compartment because the lymphatic vessels drain and return the rest of the filtrate to the systemic circulation.
The capillary dynamics can be disturbed if the capillary pressure is raised due to 'back-up' of pressure as a result of elevated venous pressure. The venular vascular resistance, in contrast to that of the arteriole is low and increased venous pressure is easily transmitted 'upstream' to elevate the capillary hydrostatic pressure.
At the capillary, this will increase the net filtration at the arteriolar end and reduce the net reabsorption of fluid at the venular end. Normally, the net filtration for the whole capillary length will be equal to the lymphatic fluid flow and no net fluid collects in the interstitial space. With increased venous pressure, the net capillary filtration exceeds the capacity of the lymphatic drainage. Edema develops.
The site of edema development is associated with the location of the increased venous pressure. If the left ventricle function is depressed, the pulmonary venous pressure will increase. Pulmonary edema is a consequence. The edema in the lung interstitial space increases the diffusion distance for oxygen and carbon dioxide at the alveolar-capillary membrane. The diffusion capacity is reduced and hypoxic hypoxia with decreased arterial PO_2 occurs. Hypercapnia is also a potential problem if the edema is extensive.
In right heart failure, peripheral edema develops as the central venous pressure and peripheral venous pressure are raised.

iii. Question:
At what capillary hydrostatic pressure would the normal fluid reabsorption at the venular end cease?
Answer: The capillary reabsorption is driven by the major capillary oncotic pressure, which has a value at 25 mm Hg. At the venular end, the hydrostatic pressure is ∼15 mm Hg (30+ mm Hg at the arteriolar end). Should the capillary pressure here becomes 25 mmHg, there will be no net reabsorptive Starling's force.

6 Determinants of CVS

i. Definition: The parameters that contribute to the regulation of cardiac output and the control of arterial blood pressure.

ii. PTC:

Learning physiology well requires distinguishing knowing parameters that are directly determinants of a homeostatic value from other factors that do influence the normal value.

This can be illustrated from the cardiovascular physiology of cardiac output and arterial blood pressure.

Cardiac output (CO) is determined by the heart rate and stroke volume. The frequency of cardiac contraction and the strength of the ventricular ejection provides the volume of blood pumped out by each ventricle per time. The heart rate can be increased slightly during deep inspiration, an example of other influencing factors but this is not defined as a determinant. Similarly, posture affects the cardiac output but again, this change in physical position is not a regulatory determinant.

With arterial blood pressure, the two determinants are CO and the total peripheral resistance (TPR). The mean arterial pressure can vary due to gender, age and there are also observable diurnal pattern in blood pressure. However, the direct effects of CO and TPR are the homeostatic determinants of blood pressure.

In both the cardiac output and arterial blood pressure equations, the explanations for the physiology should be described in a *right to left* direction. In other words, when talking about CO, changes in heart rate or stroke volume determine the CO. It would not make any physiologic sense to state that when CO changes, the heart rate or stroke volume will also change. This illogical cause and effect statement would be like putting the cart before the horse.

In blood pressure control, the CO and TPR determinants are part of reflex responses that maintain a normal blood pressure. Again, it is inaccurate to think that increase in blood pressure will also give a higher CO (a left to right relationship). In reality, chronic hypertension presents an increased 'afterload' and ventricular cardiac work. The heart can weaken with a resultant decreased CO.

In both cardiovascular equations, the two determinants are not independent, meaning that there is hardly ever an in vivo situation when only one determinant changes while the other determinant stay unchanged.

$$\underset{\text{MAP}}{\text{Mean Arterial Pressure}} = \underset{\text{CO}}{\text{Cardiac Output}} \times \underset{\text{TPR}}{\text{Total Peripheral Resistance}}$$

Fig. 4 This CVS equation must be explained physio-directionally, from the right determinants to the left

iii. Question:
During exercise, how do the determinants for cardiac output change?
Answer: In exercise, there is both tachycardia and increased stroke volume. The increased sympathetic activity produces these changes to the determinants of CO. Increased circulating adrenaline, secreted in response to sympathetic stimulation of the adrenal medulla, augments the chronotropic and inotropic effects.

7 Autoregulation of Tissue Perfusion

i. Definition: The intrinsic property of certain regional arterioles to maintain a constant blood flow within a certain range of perfusion pressure fluctuations.
ii. PTC:
Autoregulation is the maintenance of a constant flow within a regulatory range of blood pressure fluctuations. Autoregulation is not the control of perfusion pressure. The classical portrayal of autoregulation is a graph plotted with the variable, blood pressure on the x-axis. The y-axis is the regulated flow and over the range ~60–150 mmHg, the regional blood flow is kept relatively unchanged as shown by a plateau phase of the graph. If autoregulation is not operative, the graph will show a linear relationship between blood pressure and flow.
Three organs demonstrate distinct intrinsic autoregulation, the two essential organs, brain, and heart as well as the kidneys. For the cerebral and coronary vasculature, the two modes of autoregulation are the myogenic and metabolic mechanisms. In the renal circulation, autoregulation proceeds via the myogenic and the macula densa mechanisms.

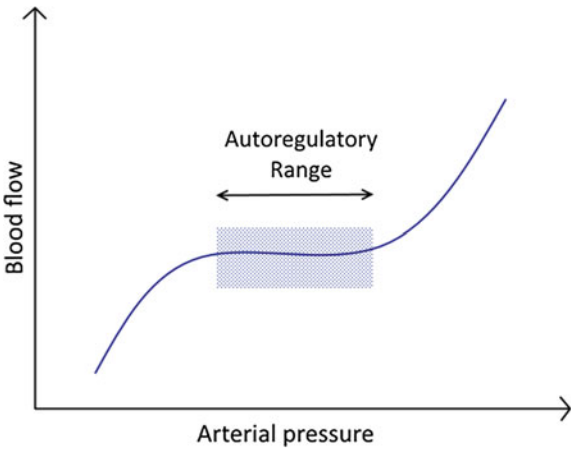

Fig. 5 Within a particular range, blood flow to the brain, heart and kidneys are maintained at a constant despite changes in arterial pressure through autoregulation

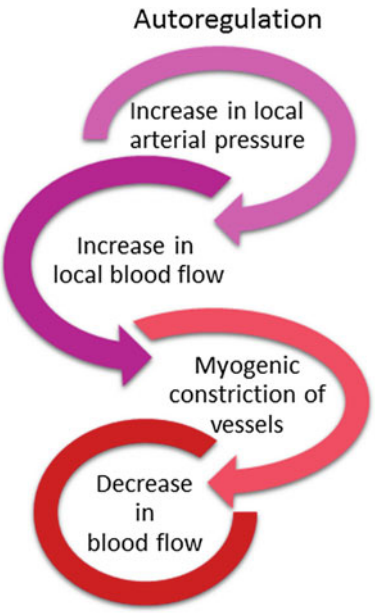

Fig. 6 Flowchart outlining events in autoregulation to maintain normal blood flow to the tissues

Fig. 7 The three organs that demonstrate distinct intrinsic autoregulation are brain, heart and kidneys

Autoregulation has a primary essential role in cerebral and coronary perfusions to maintain normal cellular metabolism. In the kidneys, the renal blood flow is autoregulated mainly to maintain the glomerular filtration rate.

When the coronary blood flow increases intrinsically in proportion to cardiac work, this is active hyperemia (refer to Chap. 2). Strictly defined this is not what is meant by flow autoregulation i.e. the heart is able to automatically increase its own blood supply when its pump activity is increased.

iii. Question:
When a person stands up quickly from lying down, how will vascular autoregulation serve its function in the brain?
Answer: In the standing posture, the hydrostatic blood pressure above the cardiac level is decreased due to the effects of gravity. The venous pooling also decreases the stroke volume. There will be an initial reduction in the arterial pressure that drives the cerebral perfusion. Locally, arterioles in the brain vasodilate in response to maintain the cerebral blood flow. Baroreflex also will be rapidly activated to normalize the arterial pressure. The compensation includes a raised total peripheral resistance produced by systemic sympathetic vasoconstriction.

Chapter 5
Physiological Adaptations of the Cardiovascular System

1 Hematocrit

i. Definition: The percentage of the red cell volume to the total blood volume.
ii. PTC:
The blood cellular volume are largely those of erythrocytes. The gender-dependent normal range is on average 40–45%. Normal erythropoiesis will give a normal hematocrit value.
Since hematocrit is a ratio dependent on the red cell and plasma volumes, its value can change if there is any change in the plasma component.
During dehydration, when ECF/plasma volume is lost, there is hemoconcentration leading to higher hematocrit. Soon after blood loss either from hemorrhage or a blood donation, the hematocrit is unchanged although the total blood volume is decreased as plasma and erythrocytes are lost in equal proportions. However, a few hours after whole blood loss, there is a decrease in the measured hematocrit. This occurs due to hemodilution resulting from the compensatory shift of fluid from the interstitial to the vascular compartment.
In a normal person ascending to a high altitude, the kidneys respond to the hypoxemia and releases the hormone erythropoietin. There will be stimulation of red cell formation at the bone marrow and a secondary polycythemia develops to ensure adequate oxygenation and delivery of oxygen to the tissues. The hematocrit is increased with residency in the mountains!
Polycythemia is thus not always synonymous with increased hematocrit. After sweating, the dehydration increases the hematocrit with normocythemia. During pregnancy, there is increased erythropoiesis. However, the plasma or total blood volume also increases, proportionately more than the red cell volume. The hematocrit value is reduced in this pregnancy-associated 'anemia'.
Hematocrit is the main contributing component in blood viscosity. The blood viscosity offers a resistance to blood flow. This opposing factor limits the benefit of compensatory polycythemia to oxygen delivery to the cells.

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iii. Question:
How will the hematocrit change in vomiting?
Answer: Loss of fluid in the vomitus will reduce the ECF and blood volume. There will be hemoconcentration with resulting increased hematocrit.

2 Perfusion-Limited

i. Definition: The term refers classically to the rate of lung oxygenation (ml O_2/min) that can be increased significantly with increase in cardiac output.
ii. PTC:
The concept of cardio-respiratory function is essential to appreciate the homeostatic end or purpose in all physiology process. The cellular need for oxygen and energy substrates are met by the regional blood flow distributed from an adequate cardiac output. The reoxyygenation of deoxygenated venous blood is achieved by the pulmonary blood flow which is also the cardiac output from the right ventricle.
Oxygenation at the alveolar-capillary membrane boundary is limited by the available partial pressure gradient for oxygen and CO_2. For oxygen, the equilibrium of PO_2 between the alveolar air and the pulmonary capillary blood is reached very rapidly, less than half the alveolar capillary transit time. Further transfer of oxygen from air to blood per unit time is still possible if more deoxygenated blood is pumped from the right ventricle or simply an increased in pulmonary perfusion. Thus, the rate of oxygen exchange diffusion is described as 'perfusion -limited'.
We can take this concept also to the tissue level in the situation when the cells are metabolically more active. Part of the increase in tissue oxygen extraction is determined by the PO_2 gradient between the capillary blood and the tissue fluid. The tissue fluid PO_2 can decrease with higher metabolism and the PO_2 gradient will be greater for more O_2 diffusion.

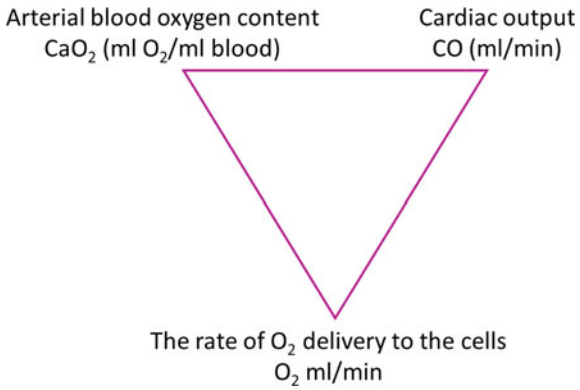


Fig. 1 The rate of oxygen delivery to the cells is dependent on the product of the arterial blood O_2 content (ml O_2/ml blood) and the cardiac output (ml/min). In short, oxygenated blood must flow for it to be useful to the tissues

In addition, if more oxygenated blood/min perfuses the tissues (as will occur with vasodilation and a larger cardiac output), the O_2 uptake by the cells can be increased beyond the limit set just by the PO_2 gradient. This is also an example of perfusion-limited phenomenon in cardio-respiratory physiology. Stagnant hypoxia is the case of a 'perfusion-limited hypoxia'.
The pulmonary vessels in the lungs also indirectly contribute to blood pressure maintenance, to drive a normal cardiac output. The pulmonary vascular endothelial generates angiotensin II. This circulating vasoactive peptide affects the total peripheral resistance and through aldosterone, the blood volume/cardiac output determinants of arterial blood pressure.

iii. Question:
During exercise, how is lung oxygenation increased?
Answer: With more usage of oxygen at the tissues, the PO_2 in mixed venous blood can decrease below the usual 40 mmHg. The PO_2 diffusion gradient for oxygen at the alveolar-capillary membrane will be steeper. In addition, the greater cardiac output/pulmonary blood flow will increase the rate of blood reoxygenation since at rest, the diffusion capacity of oxygen at the lungs is perfusion-limited.

3 Afterload

i. Definition: The mean aortic or arterial blood pressure that constitutes a 'load' on the rhythmic pump.

ii. PTC:
The heart is not a continuous pump. After ventricular filling during diastole, the ventricles contract and blood is ejected when the aortic and pulmonary valves open. There is an existing pressure in the aorta and pulmonary artery against which the left and right ventricles respectively have to pump to generate an adequate pressure for the stroke volume to be ejected.
This pressure to be exceeded in the aorta and pulmonary artery is termed afterload of the left and right side of the heart respectively. Cardiac work of the ventricles is needed to generate the pressure for blood to be pumped out of the rhythmic heart after diastole when the intraventricular pressure drops to ≈zero mmHg.
The presence of the afterload means that cardiac output is not proportionate to the arterial blood pressure. The Mean Arterial Pressure, MAP = Cardiac Output, CO × Total Peripheral Resistance, TPR relationship cannot be simply narrated from a left to right direction. In reality during hypertension, when the afterload is elevated, the left ventricle has a greater cardiac work. With the constant pressure load or burden, the left ventricle can weaken as a pump. Hypertrophy of the left myocardium occur as a compensation.

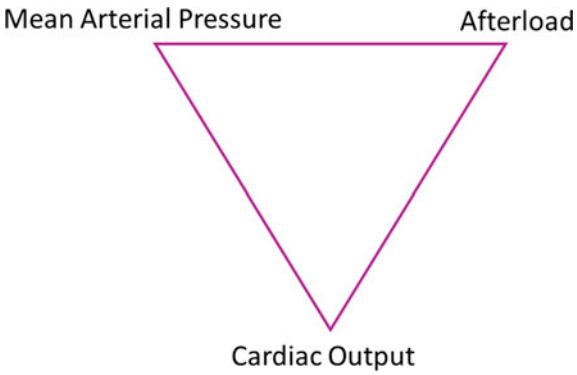


Fig. 2 In the rhythmic cardiac pump, the mean arterial pressure, MAP that drives the systemic perfusion is also the afterload. Thus, in hypertension, the constant increased afterload can weaken the rhythmic pump and the cardiac output is reduced consequently in the failing heart. In the cardiovascular equation, cardiac output, CO is a determinant of MAP when expressed as MAP = CO × TPR

In pulmonary hypertension, the afterload on the right ventricle is raised. The right ventricle can fail after the compensatory ventricle hypertrophy can no longer sustain the pulmonary blood flow.
The use of calcium channel blockers (ccb) is also to lower the cardiac work in heart disease. The TPR is decreased. This reduces the arterial blood pressure or afterload.

iii. Question:
How does the afterload on the left ventricle change during exercise?
Answer: There is quite extensive peripheral vasodilation during physical activity. The skeletal muscle flow is markedly increased for the increased cell metabolism. The need to control body temperature produce the cutaneous vasodilation. There will be a reduction in the TPR. However, the greater cardiac function during exercise sustains an increased arterial blood pressure. The afterload on the normal, active heart is higher.

4 Arteriole Resistance Vessels

i. Definition: The major resistance vessels in the circulatory system where the vascular resistance is also adjustable to respond to changes in arterial blood pressure.
ii. PTC:
In the graphical profile of the systemic blood pressure from the left to the right side of the heart, there is a progressive decrease in blood pressure from a mean pressure in the aorta of ≈ 100 mmHg to almost zero mmHg in the right

atrium. The left to right decrease in blood pressure is not linear and shows a steep decline at the arteriole segment of the cardiovascular circuit. The basic hemodynamic equation (flow = pressure gradient/resistance) explains the location of this sharp decrease in pressure at the arterioles.

Since blood flow rate (ml/min) through every portion of the systemic vascular will be the same, the site of the greatest resistance will be the place where the pressure difference between the pre- and the post resistance point will be the most. Students should note the effects on the 'upstream' and the 'downstream' pressure in relation from an increased resistance point along the 'bloody river' of the circulation. The downstream pressure (post-arteriole will be the capillary hydrostatic pressure) will be reduced. The upstream pressure will be raised and this is the way adaptive resistance changes at the arterioles contribute to arterial blood pressure regulation. Similarly, arteriolar vasodilation will tend to lower the arterial blood pressure but increase the capillary hydrostatic pressure.

The arterioles are the major resistance vessels due to two factors. One is the smooth muscular stretch contraction properties of these vascular structures. In addition to this, the arteriolar smooth muscles are also innervated by vasoconstrictor sympathetic fibers (mostly monosympathetic control with no parasympathetic vasodilator fibers except in a few places e.g. penile arteriolar vasodilation is parasympathetic-mediated).

Local tissue changes during increased cell metabolism produce metabolites that also change the arteriolar resistance. Physio-logically, these metabolites are vasodilators which ensure that the blood perfusion is increased in proportion to the tissue metabolic demands.

In special circulations that supply the brain and the heart, the local metabolic and an intrinsic myogenic arteriolar reflex response autoregulate the blood flow to these essential organs. The renal afferent arteriole also exhibits autoregulation but the reason is not primarily metabolic but to maintain glomerular filtration.

iii. Question

How would you expect the arterioles in the splanchnic circulation to respond during a meal?

Answer: During digestion and absorption, there is increased blood flow to the gastrointestinal structures. The arterioles would be dilated. Effects of local metabolite vasodilators from increased GI motility can contribute to this. The parasympathetic nervous activity is dominant during feeding and there are non-cholinergic, peptidergic fibers that can vasodilate arterioles. A decrease in sympathetic outflow to the splanchnic blood vessels during a meal can also be involved.

5 Multitask Systemic Arterioles

i. Definition: The whole body role of systemic arterioles beyond the control of local regional resistance and total peripheral resistance.
ii. PTC:
Systemic arterioles are the predominant resistance vessels in the vascular circuit. These smooth muscle-rich vessels have vasomotor tone that are, in addition, innervated by mono, autonomic sympathetic vasoconstrictor fibers. Arteriolar vasoconstriction with increased sympathetic action and vasodilation with reduced sympathetic activity are adjusted in response to the homeostatic needs of the whole body.
In blood pressure regulation, the arterioles in selective organs (sparing the cerebral and the coronary arterioles) are central modifiers of the total peripheral resistance (TPR). These adjustable, resistive arterioles include the splanchnic, cutaneous and the renal vessels.
In hypovolemic situations, the raised TPR serves to maintain an adequate arterial perfusion pressure. The selective vasoconstricton can be viewed as a priority vascular response to maintain blood perfusion to the essential tissues of the brain and the heart.
In addition, the reduction in capillary hydrostatic pressure 'downstream' from the increased arteriolar constriction during hypovolemia leads to a compensatory transcapillary fluid shift into the vascular space.
During physical activity, there is instead vasodilation in the skeletal muscles. The local metabolite vasodilators in the active skeletal muscles have a greater potency over the general increased sympathetic activity that presumably be expected to constrict (but would be a contrary, non-physiologic action) the skeletal arterioles.
In the bigger cardiovascular picture, the peripheral vasodilation increases the venous blood flow or venous return. The increased ventricular filling also drives the need for a greater cardiac output besides the cardiac sympathetic action on myocardial contractility.

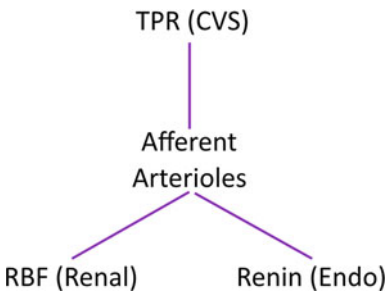


Fig. 3 The multitasking pre-glomerular arterioles link the cardiovascular, renal and endocrine functions

iii. Question:
What two pressures are changed in opposite directions during arteriolar vasodilation?
Answer: The same scenario of differential pressure changes takes place with vasoconstriction. With vasodilation, the effect on the 'upstream', arterial blood pressure is to reduce it. 'Downstream', the capillary pressure will be increased with the lower arteriolar resistance.

6 Chemoreceptor and Cardiac Output

i. Definition: The chemoreceptors associated with respiratory functions are also recruited in monitoring cardiac output.
ii. PTC:
Cardiac output is dependent on the blood volume. The arterial blood pressure in turn is affected by the cardiac output ejected from the two cardiac rhythmic pumps arranged in series. How is an adequate cardiac output monitored? Students thinking only intra-systematically will suppose that the arterial baroreceptors (carotid/aortic sinus) and the volume receptors in the pulmonary vasculature will sense cardiac output via the resultant blood pressure changes. This explanation is not incorrect. However, in addition to this, both the kidneys and the respiratory-related sensory functions also participate in sensing cardiac output. Decreased effective circulatory volume (ECV) is sensed by the intrarenal baroreceptors at the afferent arteriole. In cardiac pump failure, the blood volume is normal but the weak cardiac pump does not supply optimal peripheral blood flow to the tissues. The kidneys detect this reduction in cardiac output.
The peripheral chemoreceptors (carotid/aortic bodies) can also provide information especially when the cardiac output is quite critically reduced. In stagnant hypoxia, the peripheral chemoreceptors are also stimulated when they do not receive sufficient oxygen although the partial pressure of oxygen is normal. The compensated hyperventilation is aimed at preserving adequate oxygen supply to the brain.
Thus, besides the baro- and volume receptors, pressure sensors in the kidneys and the arterial chemoreceptors also serve to monitor cardiac output (CO). This is what I call the physiologic "Reno-Respi CO Sandwich".
During exercise, recent evidence implicate positive afferent inputs from skeletal muscle chemoreceptors in sustaining the hyperventilation of physical activity when the pH and partial pressures of both O_2 and CO_2 are unchanged. Reflexes from these muscle chemoreceptors might also enhance cardiovascular functions during exercise.

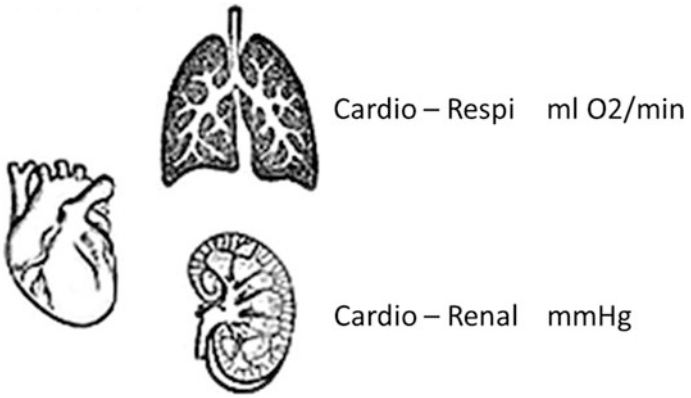


Fig. 4 The Reno-Respi Cardiac Output Sandwich highlighting the different sensors from the cardiovascular (baroreceptors), respiratory (volume receptors) and renal system (intrarenal baroreceptors) which work together to monitor cardiac output

iii. Question:
How is the brain stem involved in respiratory and cardiovascular physiology?
Answer: The respiratory pacemaker neurons are located in the medulla of the brainstem. Cardiovascular control neurons in the brainstem modify the activity of the right atrial cardiac pacemaker cells. The respiratory neurons receive afferent inputs from peripheral and central chemoreceptors, descending signals from higher centers and a spectrum of other sensory inputs. The brain stem via the sympathetic actions on arterioles, veins and myocardial contractility ensure a normal arterial blood pressure and cardiac output.

7 Synergistic, Permissive Effects

i. Definition: A supplementary, enhancing action by a separate input is described as synergistic. A need for the presence of an input before the primary stimulus can be effective is termed a permissive effect.
ii. PTC:
Synergism in cardiovascular physiology can be illustrated from both actions on the cardiac muscle and on the vascular smooth muscles. In cardiac function, the tension generated by the ventricular myocardium is both increased by two synergistic inputs. One is the greater mechanical stretch of the ventricular muscle with more diastolic filling (Frank-Starling Law).
The 2nd input seen during exercise is by cardiac sympathetic nerve (also itself synergized by adrenaline). Sympathetic stimulation pumps out a larger ejection fraction from an already bigger end-diastolic volume, the latter by an increased venous return.

The synergism of circulating adrenaline and sympathetic fibers operate at both the sinoatrial (SA) node and the cardiac muscles. The sympathetic neurotransmitter noradrenaline binds to the same beta adrenergic receptors on the SA node and the myocardial fibers.

A synergistic effect of thyroid hormones on cardiac sympathetic action is encountered in hyperthyroidism. Thyroid hormones can upregulate the beta receptors and this excessive enhancement can precipitate what is called a 'thyroid storm' (hyperthyroidism crisis). Use of beta receptor blocker is prescribed to alleviate the symptoms of this endocrine condition.

In normal conditions, the need for vasodilation in the active skeletal muscles are met by the synergistic actions of metabolite vasodilators and circulating adrenaline acting on the vascular arterioles.

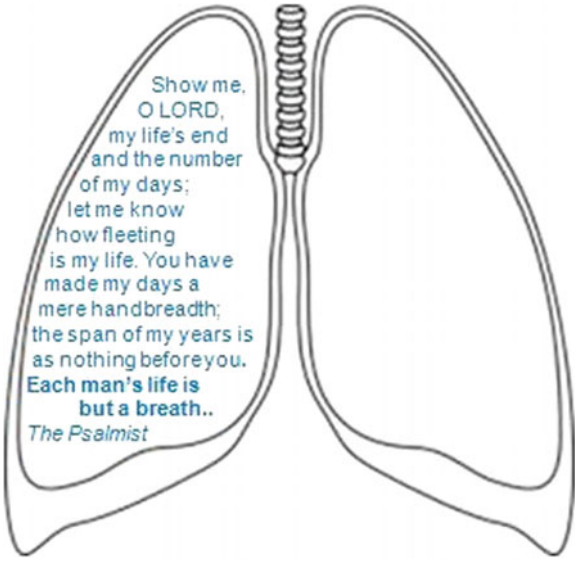
At rest, the normal vascular responsiveness of arterioles to vasoactive molecules like angiotensin II, noradrenaline requires the presence of the steroid hormone cortisol. This is a permissive vascular effect. This priming action of cortisol accounts partly for the hypertension in Cushing's syndrome and for the hypotension in primary adrenal insufficiency.

iii. Question:

Are the concurrent actions of sympathetic nerve on the two determinants of blood pressure a synergistic action?

Answer: Yes. Strictly defined, a synergistic effect describes the actions of two separate stimuli on increasing or decreasing the same parameter (e.g. arteriolar vasoconstriction or vasodilation). The sympathetic action elevates two parameters to increase the blood pressure, namely the increased TPR and the increased myocardial contractility for a bigger cardiac output.

Part II
Respiratory Physiology



Defining Airflow Along the Respiratory Tree and the O_2/CO_2 Journey in the Blood Highways

Respiratory physiology considers how the respiratory gases, oxygen and carbon dioxide, follow the inspired and expired air. Oxygenated blood needs to be delivered to the cells for biochemical cellular respiration. And excess metabolic CO_2 is conveyed in the venous blood to the lungs, to be removed by alveolar ventilation.

Airflow is defined by the available air pressure gradient. Atmospheric air enters the lungs as a tidal volume when the alveolar air pressure becomes subatmospheric

during active inspiration. Passive chest wall/lungs recoil produces the expired tidal volume. The contraction of inspiratory muscles generates the transpulmonary pressure that distends the alveoli.

Aerodynamics follows the same principle as for hemodynamics. Airway radius is the major determinant of airflow. This airflow resistance factor is modified by the branching respiratory tree which increases the total cross-sectional area for airflow as is the case for blood flow in the tiny capillary network.

Unlike the pacemaker in the cardiac right atrium, the pacemaker neurons for the tidal volume and frequency of breathing are in the medulla of the brain stem. Normal breathing is unconscious and the work of breathing overcomes easily the elastic recoil and the alveolar surface tension recoil of the lungs as well as the chest wall recoil. Alveolar ventilation maintains the partial pressure of CO_2 and O_2 in alveolar air so that adequate gradients are present for respiratory gas exchange at the alveolar-capillary membrane.

It will surprise students to note that oxygenated blood actually has a higher CO_2 content (52 ml CO_2 %) than oxygen content (20 ml O_2 %). This indicates that CO_2 has physiologic roles beyond its tag as a metabolic product. CO_2 is the primary regulator of respiration and acts via the central medullary and peripheral arterial chemoreceptors. CO_2 is also a vasodilator and unloader of O_2 from hemoglobin (Bohr).

The red blood cells contain the multi-tasker hemoglobin. Hemoglobin (Hb) binds oxygen, forms carbamino Hb with CO_2, and buffers protons from carbonic acid. Hb also carries nitric oxide, a vasodilator. Both CO_2 and O_2 journey together on the Hb in both arterial and venous blood. This fascinating triad relationship, as defined by Bohr and Haldane, describes the cooperative, give and take interactions, and changing affinity of Hb for CO_2 and O_2.

Deoxygenated venous blood still contains three quarters of the total O_2 content in arterial blood. The partial pressure for O_2 changes significantly from the arterial (97 mmHg) to the venous blood (40 mmHg) highways. This contrasts with the less dramatic "guest" passenger CO_2 from arterial 40 to venous 46 mmHg.

Back at the alveolar airport during the pulmonary transit time, CO_2 and O_2 travel in different directions. CO_2 flies off into the atmosphere in expired air while O_2 touches down in inspired air, which takes the red Hb limousine to arrive at her cellular home.

Chapter 6
Mechanics of Respiration

1 Tidal Volume

i. Definition: Tidal volume is the volume of air breathed in (inspired) or breathed out (expired) during a respiratory cycle. Note that for cardiac stroke volume, it is only the ejected ventricular volume that is indicated, not the inflow of blood volume into the ventricles.

ii. PTC:
The amplitude of the tidal volume as measured in a spirogram reflects the depth of breathing. At rest, in a 70 kg, male adult, the tidal volume is around half a liter. The normal tidal volume is set by the respiratory control neurons in the brain stem. There are pacemaker-like neurons that emit action potentials rhythmically to the inspiratory muscles. The number of action potentials/min from the respiratory center produced is the frequency of breathing.
A bigger tidal volume should be due to a greater contraction of the inspiratory muscles (or perhaps contributed also by a longer duration of active phase of the respiratory neurons?). A greater muscle tension in the inspiratory muscles can physiologically be achieved by either recruitment of more motor units or by increasing the frequency of nerve impulses in the innervating motor nerves. A larger tidal volume can be due to either a voluntary effort (breathing in deeply) or chemoreceptor stimulation as a compensation to improve alveolar ventilation. The student should however note that voluntary effort in breathing is initiated not in the brain stem but in the cerebral cortex and the cortical impulses bypass the involuntary signals that originate from the brain stem.
It might be noted that an increased frequency of action potentials from the brain stem medullary respiratory center does not necessarily translate into an

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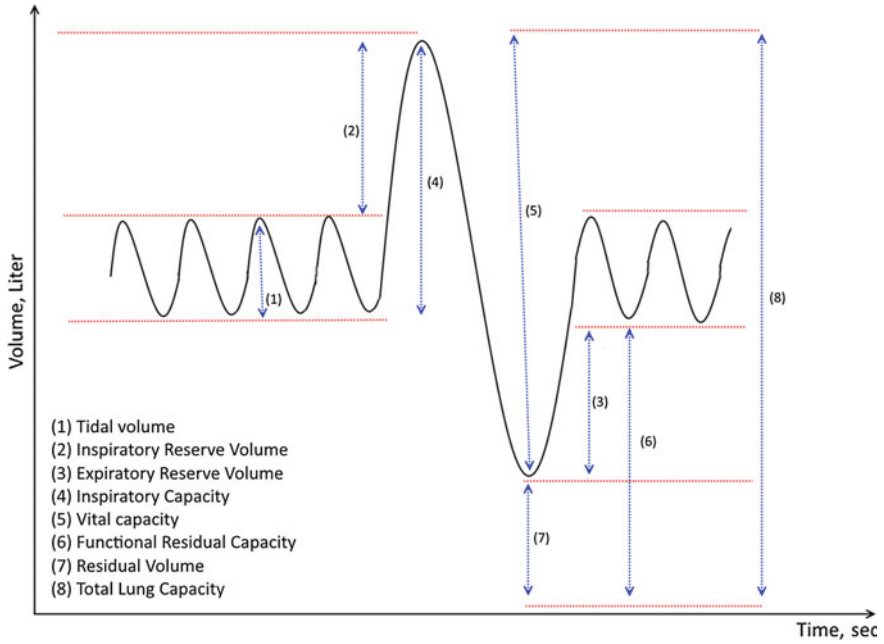

Fig. 1 Graph representing lung volumes and capacities as acquired through spirometry

increase in both the tidal volume and frequency of breathing. Clinically, patients present with either a slow, deep breathing (in obstructive pulmonary problems) or a shallow, rapid breathing pattern (in restrictive lung disease).

iii. Question:
At rest, is the tidal volume due to an active or a passive process?
Answer: The tidal volume is either the volume of air inspired or expired. Inspiration is an active process that involves contraction of the diaphragm and the external intercostal muscles. Resting expiration is initiated with the rhythmic cessation of action potentials from the respiratory control pacemaker neurons. The expanded lung and chest wall recoil passively during the outflow of air in the expired tidal volume. Therefore, the tidal volume can be due to an active or passive process depending on whether it is referring to inspired or expired air.

2 Intrapleural Pressure

i. Definition: Sometimes referred also as intrathoracic pressure, this is the negative pressure in the pleural cavity, a tiny space between the chest wall and the lungs.

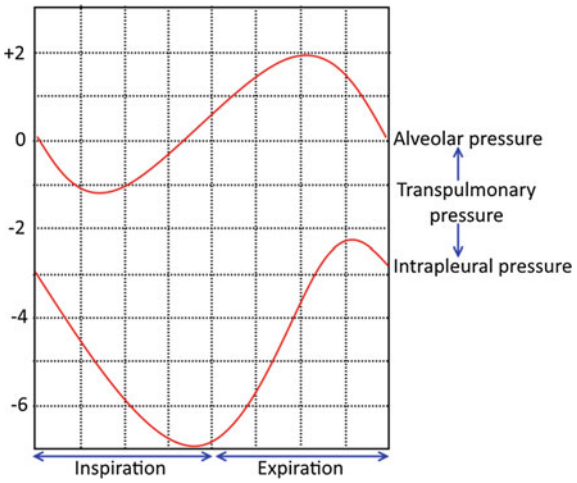

Fig. 2 Changes in alveolar pressure, P_{alv} and intrapleural pressure, P_{IP}, and hence the transpulmonary, P_{TP} pressure during a respiratory cycle

ii. PTC:

The Intrapleural space is subatmospheric at rest. The values of intrapleural pressure (P_{IP}) from the apex to the base of the lungs in the upright person is different. The base of the lungs has a less negative P_{IP} than the apex.

During normal breathing, the P_{IP} remains negative throughout. During inspiration, the average Pip becomes more negative when the inspiratory muscle contract as the muscle action upon the pleural cavity tend to stretch apart the pleural space. The alveolar air at the end of a normal expiration is at atmospheric pressure since there is no airflow.

When the P_{IP} is made more negative, the difference between the alveolar air pressure (0 mmHg, with reference to atmospheric pressure at 0 mmHg) and the P_{IP} is increased. This is an increase in the transpulmonary pressure (P_{TP}) across the alveolar wall. The P_{TP} is a distending pressure and the alveoli expand.

Boyle's law predicts that the expanded alveoli will then have a negative mmHg. Air will flow, similarly to fluid or blood flow, when there is a pressure gradient. A tidal volume of air will enter the lungs as the atmospheric pressure is now higher than the subatmospheric alveolar air.

Normal breathing/inspiration is thus described as 'negative' pressure breathing. The 'negative' term refers to the subatmospheric alveolar air. In intensive care when patients no longer has use of their respiratory muscles, the P_{IP} is not reduced to produce the subatmospheric pressure. A 'positive' external air pressure is now applied to force movement of air into the 0 mmHg alveolar space. This artificial aided breathing is called 'positive' pressure breathing.

iii. Question:
Does the intrapleural pressure becomes positive in a normal person?
Answer: Yes, the P_{IP} can be made positive during a forced expiration. This can be reflexly generated when we sneeze or cough. This can also be musically associated as when we blow the trumpet making a prolonged sound. Straining at stools in a constipated person or doing a Valsalva-like effort during labour to aid delivery of baby also make the P_{IP} positive.

3 Transmural Pressure

i. Definition: The transmural pressure is the pressure difference across the wall (mural) of a physiological structure (e.g. airways or blood vessels). Mathematically, it is represented by the pressure inside the wall minus the pressure outside the wall.
ii. PTC:
The transmural pressure is calculated by the difference between the pressure on the inside lumen of the structure and the pressure on the outside wall of the structure. This will be a distending pressure if the value is positive. The transmural pressure stretches the non-rigid wall of the airways or the vasculature.
In Physiology textbooks, the term transmural pressure is more often used in respiratory system. Students should note that the transmural pressure across the compliant veins in the systemic circulation is what accounts for the venous 'pooling'.
The external pressure that the external wall of the airways are exposed to is the intrapleural pressure. A more negative intrapleural pressure will increase the airway transmural pressure and distends the airways. The airway resistance is decreased as a result.
The resistance of the pulmonary blood vessels also changes with the transmural pressure during a respiratory cycle. The variations in the transmural pressure is different in the alveolar and extra-alveolar vessels. The extra-alveolar vessels are subject to the external intrapleural or intrathoracic pressure. The external pressure on the alveolar vessels is instead the alveolar air pressure that increases during inspiration and decreases during expiration. The transpulmonary pressure is simply the transmural pressure at the alveolar wall. The transpulmonary pressure is increased during active contraction of the inspiratory muscles and the alveoli expand as a result.
iii. Question:
How does increase in lung volume affect the airway resistance?
Answer: Increase in lung volume e.g. a deeper inspiration will be associated with a more negative intrapleural pressure. The airway transmural pressure will be greater and this will stretch and lower the airway resistance. This makes physio-logic sense during an effort to take a deep breath.

4 Anatomical Dead Space

i. Definition: The conducting airways of the respiratory tree where no gas exchange takes place.

ii. PTC:
Alveolar ventilation is calculated, taking into consideration that just over two-third of a tidal inspired volume reaches the alveolar exchange zone. The anatomical dead space (ads) is 'deadly' fixed at a volume equivalent to the body weight in lbs.
In patients with critically low tidal volume and risk of severe hypoventilation, a tracheostomy is done to improve the alveolar ventilation. The concept of the anatomical 'dead' space (gas exchange is not alive) also applies to the hobby of snorkeling to enjoy underwater exotic life. The length of the snorkeling tube adds a further plastic 'dead' space to the ads. Therefore the maximum length of the underwater breathing tube to increase the depth below water that the snorkeler can descend to is limited.
Each tidal volume of the expired air is a mixture of alveolar air and the anatomical dead space air. The partial pressure of the oxygen, O_2 and carbon dioxide, CO_2 in the ads air is similar to humidified inspired air since no gas exchange has altered the gas composition. The PO_2 and PCO_2 will be about 150 mmHg and 0 mmHg respectively. The alveolar air PO_2 and PCO_2 is at 103 mmHg and 40 mmHg respectively.
The expired oxygen and CO_2, which is a combination of alveolar air and ads air, will then have a value between the two contributing lung spaces. Thus expired air will have more oxygen than alveolar air and expired air will have less CO_2 than alveolar air.
In the lungs, an 'alveolar dead space' can result from problems in blood perfusion. Just as in ads, there is normal ventilation and airflow. However in alveolar dead space, the extreme situation of a complete block in blood supply to a bunch of alveoli will mean that the disrupted local region will not participate in gas exchange. With time, the air in those blood-deprived alveoli will have a CO_2 and oxygen partial pressure approaching that of inspired air.

iii. Question:
What would the value of the ventilation/perfusion ratio at an alveolar dead space?
Answer: The blood perfusion is nil to the alveoli. The V/Q ratio will be infinity. An easier way to help students remember is to think of the vast 'outer (dead) space' and the word 'infinity' comes into match the outer 'space'!

$$\text{Anatomical Dead Space} \approx \text{Body weight (pounds)}$$

Fig. 3 The anatomical dead space of a person is approximately their body weight in pounds

5 Alveolar Ventilation

i. Definition: Alveolar ventilation refers to the rate of entry of newly inspired air to the respiratory gas exchange alveolar regions.

ii. PTC:
Alveolar ventilation has a value less than pulmonary ventilation (minute ventilation). The latter is simply the rate of entry/exit of inspired/expired air from the lungs. The respiratory tree is functionally divided into two zones, the conducting zone and the respiratory zone. The conducting zone has functions besides just being conduits for atmospheric air inflow/outflow into the lungs. Since the respiratory system is in direct exposure to the environment, tissue defence mechanisms are present in the epithelial layer of the airways including the conducting zone. The conducting zone does not participate in gas exchange and is not 'alive' in that sense. It is also termed (not the best description!) as anatomical 'dead' space (ads).
The alveolar ventilation is thus calculated by considering only the portion of the inspired tidal volume that refreshes the alveolar region. In a 70 kg, male adult, averaging around 150 lbs, the ads is about one-third of the tidal volume, at 150 ml. Thus the alveolar ventilation is obtained from the equation above. This is approximately (500–150) $\times$ 10 breaths/min giving 3.5 l/min.

iii. Question:
How is shallow, rapid breathing in a patient understood from considering the role of alveolar ventilation?
Answer: If the tidal volume is reduced in shallow breathing, then less fresh inspired air will rejuvenate the alveoli with each breath. In order for the total alveolar ventilation to be adequate, the body responds by increasing the frequency of breaths taken per min. Note that ads is a fixed volume. Therefore, there is a limit to the minimum tidal volume (TV) for alveolar ventilation to continue. If the TV approaches the ads, the situation becomes critical as close to zero volume of new air in each breath enters the alveolar gas exchange region.

$$\underset{\text{mL/min}}{\text{Alveolar Ventilation}} = (\underset{\text{mL/breath}}{\text{Tidal Volume}} - \underset{\text{mL/breath}}{\text{Anatomical Dead Space}}) \times \underset{\text{breaths/min}}{\text{Respiratory Rate}}$$

Fig. 4 The rate of entry of newly inspired air to the alveolar regions can be calculated by multiplying the anatomical dead space-substracted tidal volume with the respiratory rate

6 Airway Resistance

i. Definition: In aerodynamics, the airways present some frictional resistance to the airflow.

ii. PTC:
The physical principles of flow applies to both airflow and blood flow. In both cases, the major determinant of resistance to air or blood flow is the radius of the airways or the blood vessels respectively. Changes in airway resistance occurs in the non-cartilaginous airways where the smooth muscles can respond to bronchodilators or bronchoconstrictors. The autonomic innervation of parasympathetic nerve produce a bronchoconstriction. The effect of sympathetic bronchodilation is a more indirect mechanism by the stimulated release of adrenal catecholamines, especially via circulating adrenaline acting on beta receptors on the bronchial muscles.
In the respiratory tree, extensive branching of the airways mean that the airway resistance is not directly related reciprocally to the radius of the airway in each generation of the respiratory branches. The branching effect of airways are also seen in the blood capillarisation of tissues lowers the total resistance with the increase in the total cross sectional area for airflow or blood flow.
Increase in blood flow velocity can generate turbulent flow and this increases the resistance compared to laminar blood flow. Similar phenomenon occur with increase in airflow velocity. Interestingly, this is reflected in the pattern of breathing in patients with abnormal elevated airway resistance in obstructive pulmonary disease. These patients tend to breathe slowly and deeply to sustain their alveolar ventilation so that the airway resistance will not be worsen.
In the laboratory, airway resistance is assessed by doing a forced vital capacity (FVC) measurement. Specifically, the expiratory phase of the vital capacity is analysed by asking the patient to breathe out, after a maximal inspiration, as fast and as strongly as possible. The forced expiratory volume in one second is obtained. This $FEV_{1.0}$ in normal airway resistance should be at least 70% of the forced VC. A reduced percentage reflects some resistive obstruction to airflow.

iii. Question:
Is the vital capacity value the same as the force vital capacity in a normal person?
Answer: Yes, the two values should be the same. A vital capacity is done with a maximal inspiratory effort to total lung capacity (TLC) followed by a maximal expiratory effort to deplete the lung volume to reserve volume (RV). This can be done at the patient's comfortable pace. For the forced VC, the patient is just required to evacuate her lungs from TLC, as fast and as hard as possible.

$$\text{Airflow} \propto (\text{Airway radius})^4$$

Fig. 5 Airflow is directly proportional to the airway radius

7 Alveolar Surface Tension

i. Definition: The surface tension at the alveoli is due to the air-water interface on the inside of the respiratory exchange unit and this surface tension inward force tends to collapse the alveoli.

ii. PTC:

The recoil of the lungs is due to two forces that opposes the expansion of the alveoli. One is the elastic recoil of the lungs. The second force that resist the work of breathing is the surface tension force that is present due to the thin layer of fluid that covers the alveolar surface.

A potential problem with surface tension force is due to the interconnecting network of numerous alveoli that are not of the same size at the end of a normal expiration (FRC).

Laplace's law states that the distending force required to keep a certain sized alveolus open is determined by the surface tension force/alveolar radius. Thus, there is a higher pressure in the smaller alveolus that is linked to a bigger alveolus in a theoretical consideration. This consideration from Laplace's law indicates that the smaller alveolus has a tendency to collapse when connected to larger alveolar neighbours as air moves from the smaller alveolus to the larger ones.

This potential alveolar instability problem is solved with pulmonary surfactant. This substance, secreted by a type-specific epithelial cells in the alveolar wall reduces the surface tension force. A greater effect of the surfactant is exerted in the smaller alveoli due to a higher effective concentration of

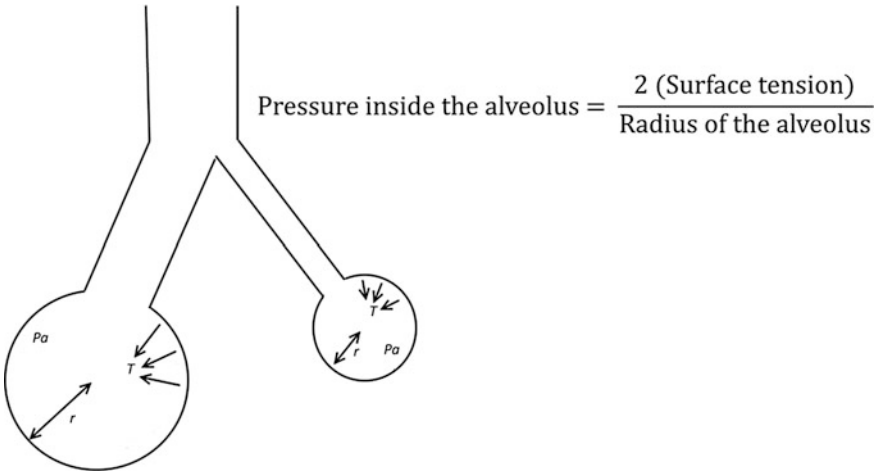

Fig. 6 The Laplace Law states that the force required to distend an alveoli is dependent on the surface tension of the alveoli divided by its radius. The pressure in smaller alveoli in greater than that in larger alveoli. Therefore, smaller alveoli linked to larger ones have a tendency to collapse as air moves from smaller alveoli (higher pressure) to larger alveoli (lower pressure)

surfactant over a smaller area. At the end of a normal breath, the different sized alveoli can co-exist due to the alteration of surface tension which equalizes the pressure in these alveoli.

The effect of surface tension also explains the differential compliance profile of the lungs during inspiration and expiration. The lung compliance at any lung volume point is different not the same during inspiration and expiration. Inspiration is an active process, the work of breathing is needed to expand against both elastic recoil of the lungs and the surface tension. Lung compliance is lower during inspiration compared to normal, passive expiration at any given lung volume. This lung compliance difference during a respiratory cycle is significantly obliterated when the same compliance measurement is done in a saline-filled lungs. The latter removes the contribution of the surface tension operating force.

iii. Question:
How is the labored breathing in a premature new born explained by surface tension effects?
Answer: The mature fetal lungs at full gestation has optimal production of pulmonary surfactant. In pre-term babies, insufficient surfactant is synthesized. Consequently, there is a tendency for the small alveoli to collapse. When the baby takes her next breath, the work of breathing is much greater to expand the collapsed alveoli.

8 Lung Recoil

i. Definition: The tendency for the lungs to recoil and collapse to its natural deflated position is due to its elasticity and its alveolar surface tension.

ii. PTC:
New born babies announce to the world they have arrived from their aqueous world to the gaseous earth by their cries! The lungs are expanded at birth to inspire oxygen to power their growth, development and physical activities.

The lungs are elastic structures and prevented from collapsing since they are held, opposed to the chest wall. The viscera pleura of the lung and the parietal pleura of the chest wall are very thinly separated by the pleural space. The tendency for the lungs to recoil inwards is opposed by the outward chest wall recoil and at rest, the intra-pleural pressure (Pip) is subatmospheric. Should air enters the pleural space due to injury, the Pip becomes atmospheric and the affected lung will collapse.

At the end of a normal expiration, the lung volume is named functional residual capacity (FRC). At this point in the respiratory cycle before the next inspired tidal volume, the lung inward recoil is balanced by the chest wall outward recoil.

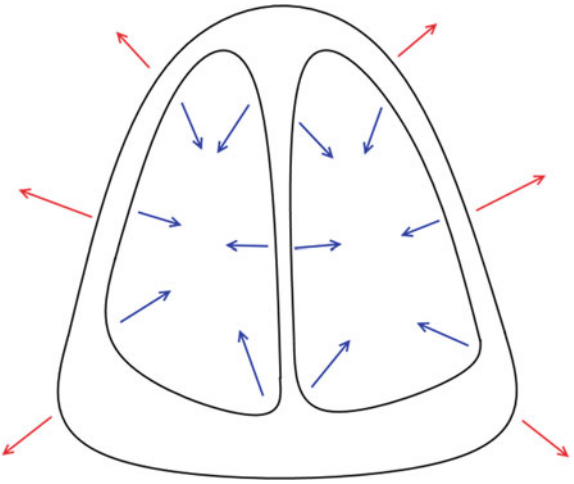

Fig. 7 There are two opposing recoil forces that work together to prevent the lungs from collapsing; the tendency for the lung to recoil inwards is opposed to the tendency of the chest wall to recoil outwards

The lung recoil has two components. One is the elastic recoil of its tissues. The other recoil force is the alveolar surface tension. This pulmonary surface tension (ST) at air/water interface of the very thin fluid layer-lined 'wet' alveoli is directed inwards. In the absence of preventive physiologic mechanism (deficiency of pulmonary surfactant), the ST will deflate the alveoli, especially the smaller-sized respiratory exchange units. The work of breathing required to re-inflate the collapsed alveoli is markedly increased, with labored breaths.

Normal expiration during a respiratory cycle is a passive process that is driven by the elastic recoil of the chest wall and the lungs.

iii. Question:
How will the functional residual capacity change if the elastic tissues of the lungs are damaged?
Answer: In the lung disease, emphysema, there is progressive tissue destruction that includes the elastic elements. The loss of the normal lung elastic recoil will affect the FRC. The balance of the outward chest wall recoil and reduced inward lung recoil will be shifted to a larger FRC. Since smoking is a strong negative factor in emphysema, the enlarged FRC is 'smoked out'!

9 Lung Compliance

i. Definition: The compliance of the lungs is its distensibility or stretchability and is given by the ratio of the change in lung volume/change in distending pressure (dV/dP).

ii. PTC:
The distending pressure of the alveoli is the transpulmonary pressure. If lung compliance is measured experimentally when there is no airflow (alveolar pressure is 0 mmHg), then the distending, transpulmonary pressure is the intrapleural pressure (P_{IP}).
Lung compliance curve can then be graphically drawn at various intrapleural pressure (x-axis) with lung volume on the y-axis. The graph is characteristically sigmoid shaped, with a steep portion of the curve bordered by a slow rise at the beginning where P_{IP} is low and a slow increase at the higher P_{IP}. This indicates that the lung compliance is not static but changes with lung volume. The compliance is greatest at the mid portion of the graph.
The analogy to the 'compliance' of a blown balloon is helpful. It is harder to blow up a balloon at the initial smaller volume and also harder towards the limit of the balloon expansion. Less effort is needed to increase the volume of the balloon in the middle part of the blowing.
The lung is an elastic structure. Physiologically, any elastic tissue will have an elastic recoil and this is the resistance that is opposed to the stretch or distending force. In other words, elasticity is not defined as in everyday language to mean easier to accommodate an increase in volume. Compliance of the lungs is reciprocally related to its elasticity.

iii. Question:
In pulmonary fibrosis, how does the change in the lung recoil affect lung volumes?
Answer: In lung fibrosis, the stiffer tissues present a higher resistance to stretch. The recoil is greater and the lungs have a reduced compliance. The volume of air in the lungs at the end of a normal expiration (FRC) is the balance of two opposing forces; between the lung inward recoil and the outward recoil of the chest wall. Thus in pulmonary fibrosis, the FRC is shifted to a smaller volume.

10 Work of Breathing

i. Definition: Energy is used during normal breathing to expand the lungs against the recoil forces as well as the airway and tissue resistances.

ii. PTC:
Normal breathing is obviously unconscious and taken for granted. Inspiration requires energy for contraction of respiratory muscles. The lungs expand against both the lung recoil forces as well as the chest wall recoil. The lung-chest wall is a functional unit. In addition, airflow encounters the normal resistance of the airways. As the lungs increase in size, there is also some tissue resistance.
The chest wall is a rigid structure and its recoil is dependent on the lung volume. At the end of normal breathing (functional residual capacity), the chest wall recoil is outwards and balanced by the inner recoil of the lungs

(the lungs, given a chance will always recoil inwards to its natural collapse state in the fetus).

At the end of a forced expiratory effort however (at residual volume), the chest wall recoil is outwards. At the end of a normal inspiration and at larger lung volumes towards total lung capacity, the chest wall recoil inwards, contributing to the passive recoil of the lung-chest wall during expiration.

When the patient experience breathing difficulty, her work of breathing has increased and enters consciousness. The succinct slogan from the American Lung Association is spot on. '*If you can't breathe, nothing else matters*'. Increased airway resistance in obstructive pulmonary problems raises the work of breathing. In restrictive lung disease, decreased alveolar ventilation is due to a reduction in tidal volume. The compensatory increase in frequency of breathing increases the work of breathing, with each breath requiring energy to expand against the opposing recoil and resistive forces. Note that although there is compensatory tachypnea (rapid breathing), the alveolar ventilation (tidal volume $\times$ freq. of breaths) can still be depressed.

Besides pulmonary surfactant, alveolar stability is also provided by interdependence, the physical interactions among the meshwork of alveoli helping to keep alveoli patent as neighbouring alveoli 'hang on' to any alveolus that has a tendency to collapse.

iii. Question:

In emphysema, how is the work of breathing increased?

Answer: Emphysema is a complex, destructive pulmonary disease with strong association with smoking. The loss of lung elastic tissues does reduce the lung recoil. Although there is a resultant, abnormal increased lung compliance, the phenomenon of 'air-trapping' leads to an enlarged FRC which will interfere with alveolar ventilation. The airway supporting tissue is also affected and the airways have a greater tendency to collapse, elevating the airway resistance. The 'air-trapping' is due to the regular airway collapse during each expiration. There is likely also, loss of the alveolar interdependence in emphysema. The work of breathing, therefore, is markedly increased in emphysema.

11 Expiratory Volumes

i. Definition: The volume of air breathed out either passively or actively depending on the starting lung volumes and any effort made.

ii. PTC:

The resting volume of air that enters or leaves the lungs with each breath in a respiratory cycle is called the tidal volume. Resting expiration is a passive process with the expulsion of a tidal volume in contrast with the active inspiration of a tidal volume. If intentional effort is made to expel more air after the end of passive expiration, the forced expiration is an energy expending event.

The extra volume of air actively expired is called the expiratory reserve volume. The lungs does not empty and collapse with a forced expiration. The remaining volume of air, untouched by the maximum forced expiration is named the residual volume.

The expiratory reserve volume is then the difference between the lung volume at the end of passive expiration (functional residual capacity, FRC) and the residual volume (RV).

$$\mathrm{ERV} = \mathrm{FRC} - \mathrm{RV}$$

The FRC is determined by the opposite forces of inward lung recoil and the outward chest wall recoil. If a person breathes in deeply and maximally, she achieves the total lung capacity (TLC). If the person lets go passively from TLC, passive lung/chest wall recoil as a unit. Again, the expiration from TLC to FRC is passive.

When a forced expulsion is done from TLC to RV, the person is performing a forced vital capacity. This spirometer test is used to estimate the airway resistance. Vital capacity or forced vital capacity should have the same values as both comprise the ERV, the tidal volume and the inspiratory capacity (IC) (only the speed or rate of air expulsion is different).

During normal expiration, the intrapleural pressure (or intrathoracic pressure) becomes less negative. The intrapleural pressure can be positivized by forced expiration (it is only negative throughout during a normal breathing cycle).

iii. Question:
Why is the airway resistance slightly higher during expiration of a normal respiratory cycle?
Answer: The airway transmural pressure will affect the radius and so the resistance of the airways. The airway transmural pressure will change with changes in the intrapleural pressure (P_{IP}) which the airways are exposed to. The transmural pressure progressively decreases with decreasing lung volume. With a forced expiration, the P_{IP} will be elevated to a positive supra-atmospheric value. The airway resistance is significantly increased with the reduction in airway radius in the non-cartilaginous segment of the respiratory tree.

12 Pneumothorax

i. Definition: The entry of air into the negative intra-pleural space and the affected lung collapses.
ii. PTC:
The intrapleural space is a very thin fluid-filled space between the visceral pleura of the lungs and the parietal pleura of the chest wall. Because it is fluid, it is neither compressible nor expandable. The lung and chest wall are bound

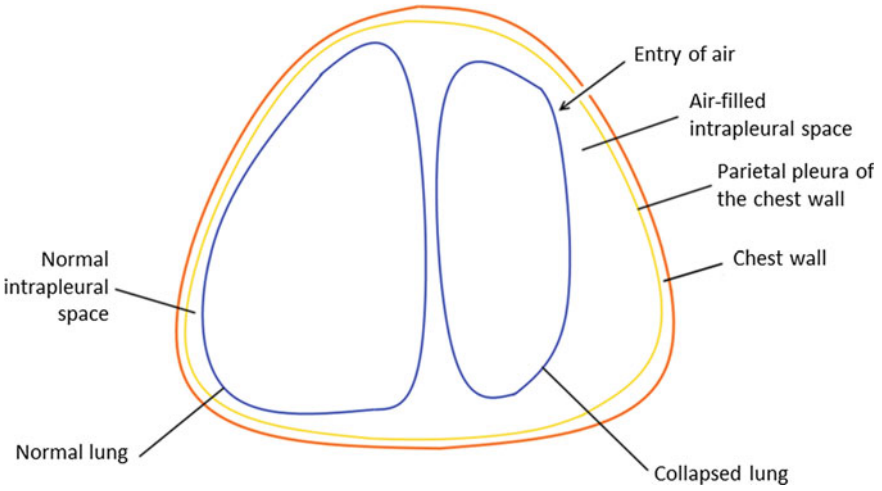

Fig. 8 The collapse of a lung as a result of entry of air into the negative intrapleural space

together as a functional unit. The work of breathing expands the alveoli against the serial resistances of the lung and chest wall.

The inward lung recoil is opposed by the outward chest wall recoil at the end of a normal expiration (functional residual capacity) and this generates the normal negative (relative to atmospheric, reference 0 mmHg) pressure. At the end of normal inspiration and especially with bigger inspired tidal volume, the chest wall and lungs both recoil passively inwards.

When air enters the intrapleural space (pneumathorax), the lungs in the affected side will collapse partially. Pneumothoraces can occur spontaneously or by a traumatic injury to the chest wall. Air can enter the intrapleural space either from the atmosphere or from the alveoli air e.g. a tumour or infection cause a breakdown of the tissues.

Spontaneous pneumothoraces are more common in males, especially tall males (short stature has its benefits!). Spontaneous pneumothoraces are thought to be due to congenital abnormalities that produce thin-walled, air-filled bullae that spontaneously rupture. These bullae do not interfere with normal ventilation.

The event of a pneumothorax is self-limiting. As the lung collapses, the hole of the ruptured bulla is sealed and no further entry of air into the intrapleural space occur. The pneumothorax also spontaneously resolves as the air in the intrapleural space is gradually absorbed into the blood. Resolution takes a few weeks depending on the size of the pneumothorax.

Pneumothorax can be treated using a chest drain. The chest drain is designed with an underwater one-way valve so that the air in the intrapleural space can be removed without allowing more air to enter. As the patient coughs or

expires forcefully, the positive pressure in her intrapleural space will be further drained of the trapped air.

In the rare incidence of a tension pneumothorax, the intrapleural pressure does not only become atmospheric but rises positively above 0 mmHg. The positive intrapleural pressure pushes the mediastinum away from the affected side. A tension pneumothorax is a medical emergency as the heart and major blood vessels are compressed, reducing the cardiac output.

iii. Question:
How does a spontaneous pneumothorax look like in an X–ray?
Answer: The air-filled space between the lung margin and the chest wall will appear darker. The trachea may appear shifted to the affected side where the lungs are partially collapsed. The chest wall or ribcage will also be expanded as it is no longer balanced by the inward recoil of the lungs. On auscultation, breath sounds at the pneumothorax are diminished due to the trapped air reducing the sound transmission. The affected side of the chest wall will also be hyperresonant on percussion because of the air in the pneumothorax. The patient can be breathless as the collapsed lung is less compliant and poorly ventilated.

13 Cystic Fibrosis

i. Definition: A disease caused by a channelopathy, specifically of the CFTR (Cystic Fibrosis Transmembrane Regulator) which is a chloride channel found in the epithelial cells of the lungs, pancreas and sweat glands.

ii. PTC:
Cystic fibrosis is associated with recurring respiratory infections. The mucus at the airways are unusually thick and dehydrated. This increases the airway resistance to airflow. The thickened mucus also provides a platform for bacterial infections.

The normal transport of chloride anions into the airway lumen is accompanied by sodium cations. This generates an osmotic gradient for movement of water. Water efflux through the epithelial cells via aquaporins and also paracellularly from the ECF. The secretion of this saline solution dilutes and thins the mucus. In cystic fibrosis, the CFTR at the apical membrane of the airway epithelial cells is defective. The absence of chloride and thus fluid secretion accounts for the abnormal obstructive mucus lining.

Patients with cystic fibrosis also have elevated NaCl concentration in their sweat. Over a century ago, midwives apparently would lick the newborn's forehead. A salty taste would be an ominous sign that the child could die from a disease that would interfere with the baby's breathing. At the sweat glands, the CFTR allows chloride in the sweat to enter the epithelial cells followed by sodium. The epithelium is quite impermeable to water and thus, normal sweat

is hypotonic. In the absence of CFTR channel activity, the NaCl remains in the lumen and the salt concentration can be four times that in normal sweat.

In cystic fibrosis patients, the pancreatic ducts are also blocked by mucus that is part of pancreatic ductal secretion. Consequently, pancreatic enzymes are prevented from entering the duodenum for digestion of gastric chyme. This results in weight loss and patients will need to take oral enzymes together with their meals to counter this.

The pancreas secretes an alkaline sodium bicarbonate fluid. The bicarbonate is exchanged for chloride at the apical membrane. The source of the chloride is ECF where the anion enters via basolateral Na/K/2Cl cotransporter. Then the chloride exits into the lumen via luminal membrane CFTR channels and reenters the epithelial cells again via the HCO_3/Cl antiporter.

As at the airways epithelia cells, the movement of electrolytes, sodium and HCO_3 osmotically draws fluid into the lumen. In cystic fibrosis, the CFTR is not available to produce this sodium bicarbonate secretion and the pancreatic ducts are occluded by the thickened mucus.

iii. Question:

CFTR is a gated channel. What specific type of gating mechanism is involved for CFTR?

Answer: Voltage-gated channels are opened (or closed) by changes in membrane potential. Mechanically-gated channels respond to pressure or stretch as in the calcium channels of smooth muscle. CFTR is a ligand or chemically-gated chloride channel and the stimulus is an intracellular increase in a nucleotide.

Chapter 7
Alveolar-Capillary Exchange

1 Partial Pressure

i. Definition: The fractional pressure contributed by a gas to the total pressure exerted by a mixture of gases.
ii. PTC:
The partial pressure, P_X is simply calculated by multiplying the fractional concentration of the gas, N_X in the mixture with the total pressure exerted by the gas mixture, P_{Total}. In atmospheric air, the gases of concern are nitrogen, oxygen and carbon dioxide. The atmospheric air partial pressure of oxygen at its fractional concentration of 21% is 0.21 × 760 mmHg, giving 160 mmHg. The partial pressure of a gas dissolved in solution or in the plasma of interest that is in contact with the specific gas is determined by the partial pressure of the gas the fluid is exposed to. Thus, at equilibrium, the PO_2 of the pulmonary capillary blood will achieve the value of the PO_2 in the alveolar air of 103 mmHg when fully oxygenated.
Respiratory gases diffuse down their partial pressure gradients. Note the difference between ventilation and oxygenation. During pulmonary ventilation, air move down a pressure gradient, described as negative pressure breathing. During lung oxygenation, oxygen move down its PO_2 gradient across the alveolar-capillary membrane.
The operating partial pressure gradients for oxygen and CO_2 are quite different. For oxygen the PO_2 ranges from 100 mmHg in the arterial blood to 40 mmHg in the venous blood. The range for PCO_2 is much narrower at 40 and 46 mmHg in arterial and venous blood respectively. Changes partial pressures for oxygen and CO_2 in blood are monitored by peripheral arterial chemoreceptors localized in the carotid and aortic bodies (carO_2tid).

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https://doi.org/10.1007/978-981-13-0499-6_7

$$P_X = N_X \,.\, P_{Total}$$

Fig. 1 The partial pressure of a gas is the mole fraction of the gas in a mixture multiplied by the total pressure exerted by a mixture of gases

iii. Question:
Why does a person at high altitude experience symptoms from a lack of oxygen in his blood?
Answer: The fractional concentration of the gases in thinner air at high altitude does not change. For oxygen it is still 21%. However, the barometric atmospheric pressure has dropped. Thus, if the external air pressure is 500 mmHg, the oxygen partial pressure will be reduced to 0.21 × 500, giving 105 mmHg in the inspired dry air. By the time the fresh mountain air reaches the alveoli, the PO_2 in alveolar air will no longer be the normal 103 mmHg at sea level but significantly lower. Consequently, the arterial blood PO_2 will also be depressed. Sensing by the peripheral chemoreceptors will trigger a compensatory hyperventilatory response, mediated by the control respiratory neurons in the brain stem.

2 Diffusion Capacity of Oxygen

i. Definition: The factors that affect the rate of lung oxygenation as combined in a formula that includes the thickness of the membrane, the partial pressure gradient for oxygen and the total available surface area for diffusion.
ii. PTC:
Oxygen diffuses at the alveolar air/capillary blood interface in the lungs and also at the tissue capillary blood/tissue fluid level. The diffusion capacity of O_2 in the lungs (D_LO_2) is determined by several aspects of the passive oxygenation at the alveolar capillary membrane.
The Fick's law of diffusion applies here.

(a)
$$J_X = D_X\,(X_1 - X_2)$$

(b)
$$D_L O_2 = \frac{VO_2}{(P1 - P2)} \quad \begin{matrix}(ml/min)\\(mmHg)\end{matrix}$$

Fig. 2 **a** A simplified Fick's Law prescribes that Jx, the flow of solute X is proportional to the diffusion capacity of X, Dx and the concentration or pressure gradient of X across. Dx factors in thickness of membrane, surface area for diffusion, solubility and molecular weight of X. **b** The diffusing capacity of oxygen is the volume of O_2 , VO_2, transferred per unit time for every unit mmHg of the partial pressure gradient of O_2

In a formula, D_LO_2 is equal to the oxygen transfer in ml O_2 per time (VO_2) per unit mmHg of the partial pressure gradient across the alveolar capillary membrane.

The VO_2 is affected by the total surface area for oxygen diffusion. The PO_2 gradient is the difference between the alveolar air PO_2 and the *mean* pulmonary capillary PO_2.

The parameter is a *mean* or *average* mmHg because the alveolar capillary blood is rapidly oxygenated and the PO_2 rises quickly along the alveolar capillary from the beginning, entry point of deoxygenated venous blood value at 40 mmHg to the fully oxygenated value at 103 mmHg (Fig. 2b).

The student should note that the D_LO_2 equation is a physiologic relationship and is not meant to be used simply as a equation in mathematics. For example when the PO_2 gradient increases, the overall diffusion capacity of oxygen at the lungs increases because the PO_2 gradient affects the VO_2. Since the PO_2 gradient is placed at the denominator of the equation, a bigger gradient would incorrectly be calculated to produce a reduced D_LO_2 if the concurrent increase in VO_2 is not taken into account.

In lungs of normal persons, the thickness of the diffusive membrane is the least variable when the D_LO_2 increases. During exercise, both the surface area at the alveolar and the capillary side increase. Pulmonary alveolar blood vessels are recruited and distended. The mixed venous blood of a person exercising that enters the alveolar exchange area is more deoxygenated at less than 40 mmHg.

In certain lung pathophysiology, thickening of the alveolar-capillary membrane can occur. This histological change will increase the diffusive distance and if severe, equilibration of the capillary blood to match the alveolar air PO_2 of 103 mmHg may not be achieved during the pulmonary blood transit time at the alveoli.

iii. Question:
How does pulmonary edema affect the diffusion capacity of oxygen in the lungs?
Answer: Pulmonary edema will reduce lung oxygenation. The collection of excess fluid in the interstitial space between the alveolar epithelium and the endothelium of the alveolar capillary will increase the diffusion distance. Lung compliance is also decreased in pulmonary edema as the alveoli expand against the edematous tissues. The available alveolar surface area for oxygen diffusion is then reduced.

3 Gravity and Ventilation

i. Definition: Gravity affects the intrapleural pressure significantly in the upright lungs and this leads to uneven ventilation of the alveoli from the base to the apex of the lungs.

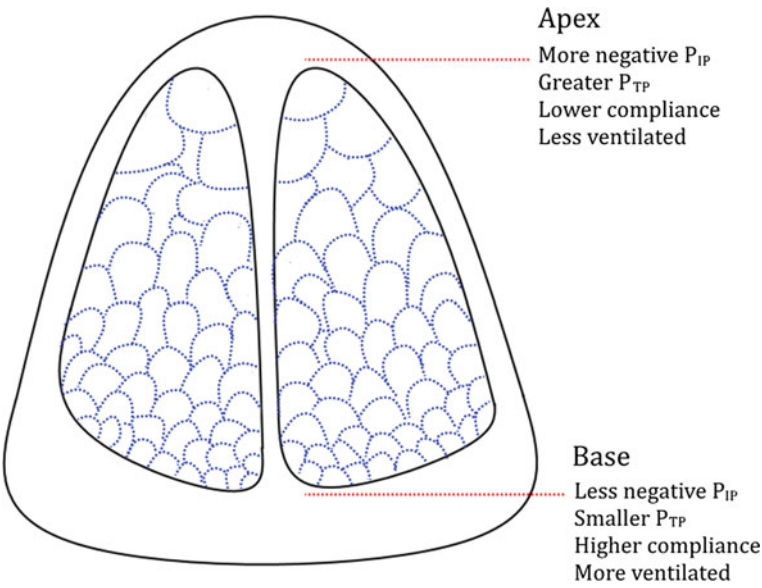

Fig. 3 The intrapleural pressure, P_{IP} in an upright person is significantly affected by gravity with the base of the lung having less negative P_{IP} than the apex

ii. PTC:
In the person at rest, lying down, pulmonary ventilation is quite even over the whole lungs. This means that a single tidal volume is distributed uniformly to all regions of the lungs. When the person assumes a standing posture, gravity affects the distribution of a tidal volume to alveoli at different levels of the upright lungs.
More of a tidal volume is distributed to the base of the lungs compared to the apex. This is found to be due to the higher compliance of the basal alveoli than the apical alveoli in the upright lungs? How does gravity cause this vertical differential in lung compliance?
The explanation is related to the changes in lung (alveolar) compliance with changes in lung (alveolar) volume.
This implies that at the end of a normal expiration (FRC), before the next breath (tidal volume) is inspired, the alveolar size at the base of the lungs is associated with a higher compliance than the size of the apical alveoli at FRC. At FRC, the apical alveoli are actually larger than the basal alveoli.
This puts the apical alveoli at the plateau end of the lung compliance, sigmoid-shaped curve. The relatively smaller basal alveoli at FRC will then be associated with the steep portion of the lung compliance curve. The basal alveoli at FRC have relatively higher compliance and is more distensible.

The question then follows 'how does gravity accounts for the different sized alveoli in the upright lungs'? The transpulmonary pressure that distends alveoli should be greater at the apical compared to the basal alveoli.

The difference in transpulmonary pressure is due to the difference in the negativity of the intrapleural pressure from the base to the apex of the lungs. Under the effect of gravity on the lung tissue mass, the basal intrapleural pressure is less negative than the apical portions.

Thus, one might say that a tidal volume 'gravitates' towards the basal, dependent areas of the lungs. The basal alveoli are thus more well-ventilated with fresh inspired air than the apical alveoli.

iii. Question:

In the upright lungs, would you expect the alveolar partial pressure of oxygen in the apex to be higher than in the base?

Answer: Yes. It might surprise the students to read that the apical PO_2 is higher than the basal PO_2! This is a natural mental response since the alveolar ventilation as discussed is better at the base. This highlights the fact that the value of the alveolar air PO_2 (and also PCO_2) is not merely due to alveolar ventilation alone.

Correctly, the ventilation/perfusion matching at every alveolus is the deciding factor that establishes the PO_2 and PCO_2 values in the alveolar air.

A related observation is that aerobic, tuberculotic bacteria tend to cause pathology of the apex of the lungs. In nursing practice, lying the respiratory patient on the right side will improve alveolar ventilation in the right lung.

4 Ventilation-Perfusion Matching

i. Definition: The interface between the air and blood in respiratory physiology. Specifically, the interactions between alveolar ventilation and pulmonary blood flow or perfusion.

ii. PTC:

The ventilation-perfusion matching is a good example of the integrated cardio-respiratory physiology. If blood is well oxygenated but does not flow, the oxygen-rich blood is wasted since the perfusion is poorly distributed to the tissue that has a metabolic need for oxygen. Similarly, the respiratory alveoli can be well perfused by pulmonary blood but if the alveoli have interrupted ventilation, the blood will not be refreshed through CO_2 removal and O_2 replenishment to be redistributed to the cells.

The ventilation in each alveolus must be matched or balanced by an optimal capillary blood supply. In the overall lungs, the total blood flow in a healthy, 70 kg, male adult is 5 L/min. The total pulmonary ventilation for a 500 ml tidal volume and 10 breaths per minute is 5 L air/min. At the respiratory exchange 'living' zone (taking into consideration the anatomical 'dead' space' air conduits), the alveolar ventilation will be 4 L/min if the 'dead' space is 100 ml.

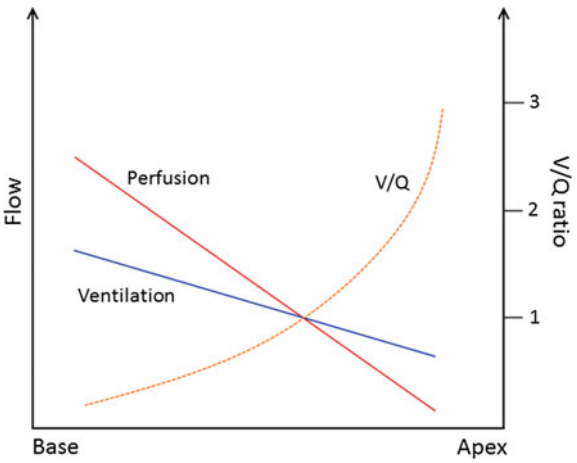

Fig. 4 Due to the effects of gravity, both perfusion and ventilation is higher at the base than the apex. However, the ventilation at the base is lower than its perfusion, whereas the ventilation at the apex is higher than its perfusion. Despite this normal, uneven V/Q ratio in an upright lung, the final V/Q ratio of the whole two lungs is kept optimal at 0.8

The ventilation—perfusion of the whole two lungs is then 4/5 or 0.8. In a person standing, the rather long upright lungs are subjected to the effect of gravity. Both the ventilation and the pulmonary blood flow in the upright lungs differ at different horizontal levels.

Both the ventilation and the pulmonary perfusion decreases from the base to the apex of the lungs ('things are not always better at the top!).

The progressive decrease in the pulmonary blood flow under the effect of gravity is more than the reduction in ventilation (which is only indirectly influenced by gravity). Thus the normal V/Q in the upright lungs tend to increase from the base and be the highest at the apex of the lungs.

This normal, uneven V/Q values in the upright lungs does not cause any significant alterations in the final partial pressure of oxygen or CO_2 in the arterial blood. The word 'final' is used to indicate that at each different V/Q level, the blood that immediately exits the alveoli will contain different PO_2 and PCO_2 values. Blood from each level will mix to give the final PO_2 and PCO_2 in the arterial blood.

iii. Question:

What would be the V/Q values at the two extreme ends of the V/Q spectrum?

Answer:

If a region of the lungs are unventilated due to blockage or a major airway branch, the V/Q will be zero. On the other hand if there is a pulmonary embolus in a major vessel, the region of the lungs deprived of blood supply will have a V/Q of infinity. The V/Q spectrum is from zero to infinity. This is parallel functionally from an alveolar shunt region to an alveolar dead space region (just remember 'outer space' and infinity!).

5 Hypoxic Pulmonary Vasoconstriction

i. Definition: The unique vascular response of the pulmonary blood vessels to hypoxia, which is directed not for metabolic reasons but towards matching alveolar ventilation and perfusion.

ii. PTC:
The smooth muscles of all systemic arterioles respond to local hypoxia by vasodilating. This is the expected physio-logical response in order to compensate and ensure adequate blood supply. The vascular vasodilation to hypoxia is to fulfill a metabolic cellular mission.
The lungs, being the source of inspired, oxygen-rich air would not be expected to need this hypoxia-vasodilate local, vascular reflex. Indeed, pulmonary vessels vasoconstrict when exposed to surrounding hypoxia.
This hypoxic pulmonary vasoconstriction (hpv) serves a different purpose. The hpv is aimed at matching ventilation and the pulmonary perfusion at the alveolar-capillary interface. To give a scenario, if a certain part of the lungs are underventilated, the alveolar air PO_2 will drop. The pulmonary vessels exposed to the regional low PO_2 or hypoxia will vasoconstrict.
This increased vascular resistance will redirect the blood flow to alveoli that are better ventilated. Thus, the blood flow to the under-ventilated alveoli are not wasted or superfluous. The underventilated alveoli are now 'matched' with a reduced perfusion.
This 'matchmaking' hpv response can result in a rise in pulmonary arterial pressure if there is general vasoconstriction throughout the lungs. This is the situation for residents at high altitude where the inspired and thus, the alveolar air PO_2 is low. All the alveoli in these mountain residents have decreased PO_2. Pulmonary hypertension is an occurrence and with time, the right ventricle hypertrophies to compensate, for the needed additional cardiac work against the elevated afterload on the right ventricle.
The ionic mechanism for hpv appears to involve a depolarization effect of the hypoxia on pulmonary vascular smooth muscles. Voltage-gated calcium channels are then opened, leading to the vasoconstriction. The hypoxia is described as a modulator of specific potassium channels. Hypoxia decreases the efflux of potassium cations and the pulmonary vessels depolarize.

iii. Question:
Is there a role of carbon dioxide in ventilation-perfusion matching?
Answer: The action of CO_2 in V/Q balance is said to affect the smooth muscle of the airways. The example usually given is the case of a region of overventilated alveoli. Apical alveoli are underperfused with the V/Q being higher than normal. The relatively overventilated alveoli will have decreased alveolar air PCO_2. The local hypocapnia causes bronchoconstriction. This increased airway resistance serves to redirect the excess airflow to better-perfused alveoli.

6 Pulmonary Vascular Recruitment and Distention

i. Definition: The mechanical way in which the resistance of pulmonary vasculature is decreased during increased pulmonary blood flow from the right ventricles.

ii. PTC:
In almost all tissues except the lungs, the greater need for metabolism in the active tissues will be accompanied by a vasodilation of the blood vessels that supply the tissues. The lungs are obviously the input source of oxygen to the body and the lack of such an oxygen demand-associated vasodilation makes physiologic sense.
In fact, a hypoxic pulmonary vasoconstriction uniquely occur in the lungs for the non-metabolic purpose of ventilation-perfusion matching. The other exceptions are cutaneous vasodilation for thermoregulation rather than to supply the oxygen needs of the skin and renal vasodilation for a higher glomerular filtration in sodium/fluid balance.
The rate of oxygenation in the lungs is increased during physical activity. Both the left and right ventricular pump a greater cardiac output. The right cardiac output increases the rate of oxygen transfer at the alveoli-capillary membrane since normal oxygenation is 'perfusion-limited'.
The increased pulmonary blood flow is not associated with a great increase in pulmonary arterial pressure. This is explained by the concurrent decrease in pulmonary vascular resistance (PVR) when the pulmonary arterial pressure rises. The PVR is reduced by the increased pulmonary blood flow mechanically.
The pulmonary vessels are more compliant compared to the systemic arterial blood vessels. Increased pulmonary blood pressure during stronger right ventricular muscle contraction will stretch and dilate the pulmonary vessels. Distension as well as recruitment of pulmonary vessels occur.

iii. Question:
How does the determinants of the systemic blood pressure equation compare with the pulmonary hemodynamics?
Answer: In the hemodynamics of systemic circulation, the cardiac output and the TPR are determinants of arterial blood pressure. The BP = CO $\times$ TPR is related mostly in a right-to-left direction. As detailed above, in the pulmonary circulation, (Pulm BP = CO $\times$ PVR), a left to right physiology is observed whereby when the pulmonary arterial pressure is elevated, a mechanical decrease in the PVR follows through vascular distention and recruitment.

7 Pulmonary Vascular Resistance

i. Definition: The low-resistance conduits for blood flow through the pulmonary vasculature.
ii. PTC:
The pulmonary vascular resistance (PVR) is a component of the basic hemodynamics of pulmonary blood flow. Pulmonary blood flow is the difference between pulmonary arterial pressure and left atrial pressure divided by PVR. The pulmonary blood flow can be rewritten as cardiac output (right ventricle).
The pressure profiles in the less muscular right ventricle is much lower than that in the left ventricle. In the left ventricle, maximum pressure during systole is 120 mmHg and it is near zero mmHg during diastolic filling. The highest right ventricle pressure is $\sim$30 mmHg and during venous return, it is close to zero mmHg.
The much lower pressure from the right ventricle or pulmonary arterial pressure (about 25 mmHg) that also drives a similar cardiac output (5 L/min in a 70 kg male, adult) implies that the pulmonary vascular resistance is also much less than the total peripheral resistance (TPR) in the systemic circulation.
There are other unique features of the PVR. The TPR is regulated by autonomic sympathetic vasoconstrictor fibers. The autonomic nerves have minor role in determining PVR. However in the more compliant pulmonary vessels, increases in pulmonary arterial pressure will decrease the PVR through mechanical pressure distention and recruitment of the vasculature.
The PVR also fluctuates during a respiratory cycle. This is due to the location of the blood vessels, categorized as alveolar and extra-alveolar vessels. The alveolar vessels are directly compressed by the alveolar air pressure. The extra-alveolar vessels on the other hand are instead subjected to changes in the intrathoracic pressure during a respiratory cycle.
During inspiration, the alveolar vessels are compressed by the expanded alveoli while the extra-alveolar vessels are exposed to a more negative intrathoracic pressure. In other words, during inspiration, the vascular resistance of the alveolar and the extra-alveolar vessels is increased and decreased respectively. The PVR at any time point in the respiratory cycle is then, the arithmetic sum of the two extra-alveolar/alveolar vascular resistances that are in series. The lowest PVR resistance is during FRC, at the end of a normal expiration.

$$\text{Pulmonary Blood Flow} = \frac{\text{Pulmonary arterial pressure - Right arterial pressure}}{\text{PVR}}$$

Fig. 5 The equation of pulmonary blood flow. PVR, Pulmonary vascular resistance

iii. Question:
Which part of the entire spectrum of lung volume changes is the PVR the greatest?
Answer: When the sum of the extra-alveolar and alveolar vascular resistances are taken together, the high ends of PVR is at the total lung capacity, TLC (peak of maximal inspiration) and at residual volume, RV (end of a forced expiration), the latter point being the highest.
The lung volume/PVR graph shows a U-shaped like curve.

8 Pulmonary Transit Time

i. Definition: The time of exposure of pulmonary capillary blood to the alveolar air for the diffusive exchange of both oxygen and CO_2.
ii. PTC:
The pulmonary blood vessels at the lung tissues are functionally classified under extra-alveolar and alveolar capillaries. The dense meshwork of alveolar capillaries supplying each alveolus is like a film of blood surrounding the alveolar air pocket.
Deoxygenated venous blood enters the alveolar-capillary exchange area and reoxygenated blood (sometime described as 'arterialized' blood) exits the alveoli area.
The estimated time spent by the continuously moving blood at the alveoli is very brief, less than one sec. This is also called the 'pulmonary transit time'. We could call the exchange area the *Alveolar Airport Lounge*, and the oxygen and CO_2 molecules are then, the pulmonary passengers!
The passive diffusion of both oxygen and CO_2 at the alveoli is very rapid. Less than half the transit time is sufficient for complete equilibration of the partial pressures of oxygen and CO_2 across the alveolar-capillary membrane.
The PO_2 rises from the mixed venous PO_2 at 40 mmHg to reach the PO_2 of alveolar air at 103 mmHg. The CO_2 equilibrates equally rapidly and the PCO_2 decreases from 46 mm Hg in the deoxygenated blood to 40 mmHg in the arterialized blood that enters the pulmonary veins.
Diffusion and exchange of the respiratory gases at the alveolar capillaries is along or down the respective partial pressure gradients. No energy is required. The maintenance of a normal alveolar PO_2 and PCO_2 is of course an active process since contraction of the respiratory muscles take place during inspiration. Conceptually, pulmonary blood flow itself is also 'passive', down pressure gradients. The maintenance of the driving blood pressure gradient is however, actively provided by the right ventricular pump.

iii. Question:
Which part of the pulmonary transit time is there no net transfer of oxygen and CO_2?
Answer: Oxygen equilibrates in half the transit time at the alveolar capillary membrane. If the transit time is 0.8 s, then during the remaining 0.4+ s, there is no further net oxygenation from the alveolar air into the capillary blood. For CO_2, for at least the same transit time, there will also be no further release of CO_2 from the capillary into the alveoli. The rate of oxygenation can be further increased if the pulmonary blood flow is increased ('perfusion-limited' oxygenation). Although not usually applied to CO_2 removal at the lungs, it is also true to say that the rate of CO_2 exhalation is also perfusion-restricted.

9 Perfusion-Limited Oxygenation

i. Definition: This adjective term of oxygenation means that the total rate of oxygen uptake per time at the pulmonary alveolar exchange units are blood flow-dependent.

ii. PTC:
At rest, with a normal cardiac output/pulmonary blood flow, the maximal rate of oxygenation is not yet reached. This is due to the rapid equilibration of oxygen partial pressure between the alveolar air and the alveolar capillary blood. Equilibrium is achieved within less than half the capillary transit time. The PO_2 of mixed venous blood at 40 mmHg is quickly increased to 100 mmHg. Further net diffusion of oxygen into the pulmonary capillary doses not take place and is thus said to be limited by the absence of a PO_2 gradient further along the alveolar capillary.
If the pulmonary blood flow is increased, the equilibrium point is shifted further 'downstream' along the alveolar capillary. Another way of viewing the new gas exchange scenario is that more deoxygenated blood/time is now delivered to the alveoli to be oxygenated when the cardiac output is increased. There is also a contribution from a greater surface area for diffusion when the cardiac output is greater. The phenomenon of pulmonary blood vessel recruitment and distention increases the available diffusive surface for oxygen transfer.

iii. Question:
Is perfusion-limited phenomenon also observed at the tissue exchange area?
Answer: This is seldom or hardly ever mentioned in standard physiology texts. Reasoning logically, we can expect a similar limitation to the diffusion of oxygen from the capillary blood to the cells. The partial pressure gradient for O_2 diffusion is similar at about 100 mmHg in arteriolar end capillary blood and 40 mmHg in the tissue fluid. Unloading of O_2 will take place as long as there is a PO_2 gradient between blood and tissues. We can imagine a similar

rapid PO_2 equilibration at the tissues as seen at the alveolar-capillary membrane. Further unloading of O_2 to the tissues may also be limited once the venular end capillary blood PO_2 becomes 40 mmHg. Further delivery of O_2 to the cells could then be possible if the tissue perfusion is increased as more oxygenated blood enters the tissue area.
Again, an increase in capillary exchange area in the tissues is also achieved by arteriolar vasodilation.

10 Respiratory Pump

i. Definition: The respiratory 'pump' refers to the effect of deep inspiration on increasing the pulmonary blood flow.
ii. PTC:
The cardiac 'pump' is functionally two pumps arranged in series, with the right ventricular pump ejecting blood into the pulmonary circulation. The pulmonary blood flow is the right ventricular cardiac output. The pulmonary circulation is in series with the systemic circulation and the left and right cardiac outputs are equal over time, intrinsically maintained by the Starling's mechanism of the heart.
In the closed vascular circuitry, the venous return into each ventricle is equal to the cardiac output from the respective ventricle. The venous return into the right atrium/ventricle is propelled by the driving pressure between the systemic mean filling pressure (MSFP) and the central venous pressure/right atrial pressure.
The heart is situated within the thorax and the cardiac chambers are therefore exposed to the intrathoracic pressure. In particular, the central venous pressure (CVP) changes during a respiratory cycle, with the CVP slightly less during the inspiratory phase. When the breathing is deeper, the larger inspiration reduces the CVP more. This decreased CVP has the effect of a respiratory suction pump and increases the venous return. The pulmonary blood flow is also increased and this respiratory pump contributes to the greater right ventricular cardiac output during exercise.
The heart rate is also higher during a deep inspiration. This is due to the proximity of the cardiovascular regulatory neurons to the respiratory control neurons in the brainstem. Thus breathing besides having a respiratory pump effect also indirectly enhances the cardiac pump function.
iii. Question:
What is the effect on pulmonary blood flow if you make a forced expiratory effort?
Answer: The intrapleural/intrathoracic pressure increases during a forced expiration (if against a closed glottis as in Valsalva, the increase in is even

greater. The central venous or right atrial pressure is elevated. This reduced the driving pressure (MSFP minus CVP) for venous return. Pulmonary blood flow is decreased.

Since the left atrial pressure is also raised, the venous return into the left ventricle is also less. During a Valsalva manoeuvre, the arterial blood pressure drops due to the sudden reduction in venous return.

11 Shunts in Respiratory Physiology

i. Definition: Generally, a shunt is an area or a situation where the ventilation that provides oxygenation does not take place.

ii. PTC

A shunt is commonly described in the textbooks as anatomical or physiological. This can be confusing for the students for several reasons.

A *physiologic shunt* in all normal persons refer to the slight mixing of some deoxygenated blood (from certain vascular branches of coronary, bronchial vessels) with the main bulk of oxygenated blood in the pulmonary veins. This leads to a minor drop in the PO_2 comparing alveolar capillary PO_2 at 103 mmHg and arterial PO_2 97 mmHg. This normal PO_2 difference in the physiologic shunt should be less than 15 mmHg and as described, is due to normal vascular anatomical connections.

Traditionally, an *anatomical shunt* indicates a major dilution of oxygenated blood with a significant portion of deoxygenated blood. An example is a septal defect in the heart, and considerable venous blood is shunted from the right to left side of the heart.

Within the lungs, an *alveolar shunt* represents an area where the airflow is blocked. The alveolar ventilation is nil and the pulmonary capillary blood flows pass a shunt. To avoid confusion, students might wonder at the anatomical dead 'space' where oxygenation also do not occur. From the definition given above, the conducting zone of the 'dead' space has ventilation, but there is no gas exchange.

iii. Question

Does the physiological shunt also affects the CO_2 partial pressure in the arterial blood?

Answer: Logically, we might expect a similar difference in the PCO_2 between alveolar capillary blood and arterial blood, with a higher PCO_2 in arterial blood due to the mixing of deoxygenated blood with reoxygenated blood. However, the normal PCO_2 range in the systemic circulation is much lower (40/46 mmHg) compared to that for oxygen (100/40 mmHg). Thus there is no observable or measurable significant increase in arterial PCO_2 above 40 mmHg in arterial blood.

12 Obstructive Lung Disease

i. Definition: Obstructive pulmonary diseases have the common feature of an increased airway resistance to air flow.

ii. PTC:

The two major clinical categories of functional lung diseases are restrictive and obstructive. Obstructive lung conditions refer specifically to abnormal increased airway resistance. The word 'obstructive' and restrictive' can be easily confused (as they are synonyms!) since increased airway resistance should also 'restrict' airflow.

Defined accordingly, restrictive lung problems indicate any conditions that decrease lung compliance.

Patients with asthma have a common obstructive airway resistance due to hyperresponsive airways. The assessment and monitoring of airway resistance in asthmatics in done by spirometry, using the forced expiratory volume in one sec measurement.

The pattern of breathing in persons with obstructive lung disease is quite characteristic. Lung compliance is unaffected and the patient tends to breathe in deeply and slowly. Since velocity of airflow does contribute to airflow resistance, the slow expiration helps in the breathing.

In the complex lung disease emphysema, the supporting tissues that help to hold open the small airways are also destroyed by the disease process. There is a tendency then for these airways to collapse especially during expiration when the intrapleural pressure is less negative (reduced, distending trans-mural pressure).

Emphysema also destroys the elastic tissues of the lungs. The reduction in lung elastic recoil results in an abnormal high compliance. The phenomenon of 'air-trapping' due to collapsed airways plus the increased lung compliance accounts for the expanded FRC in emphysema.

The enlarged FRC is also due to the balance of opposing recoil forces of the chest wall and the lungs. The unaffected chest wall outward recoil is less opposed by a lower lung inward elastic recoil. The abnormal FRC presents a

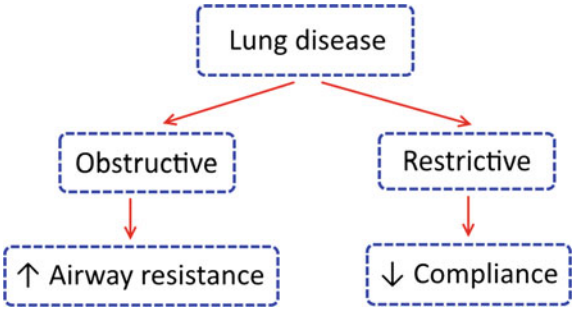

Fig. 6 Obstructive lung disease is characterized by an increased airway resistance to airflow whereas restrictive lung disease is characterized by decreased compliance. The latter is only mentioned briefly in the text

greater 'buffer' air zone between new tidal volume air and the alveolar air. This also interferes with the maintenance of an optimal alveolar PCO_2 and PO_2.

iii. Question:
In normal individuals, how do the autonomic nerves affect airway resistance?
Answer: Parasympathetic stimulation causes bronchoconstriction. If excess mucus is secreted by the neural action, it also increases airway resistance. Sympathetic activity produces bronchodilation although the major sympathetic action seems to be via the release of adrenal catecholamines. Inhalers contain bronchodilator agents that bind to beta adrenergic receptors on the smooth muscle of the airways.

Chapter 8
Oxygen Transport

1 Oxygen Content

i. Definition: The total amount of oxygen carried in the blood expressed as volume of oxygen in unit volume of blood.
ii. PTC:
It is usual to value the total blood content of oxygen as ml O_2 per deciliters of blood. The arterial blood O_2 content is around 20 ml O_2/100 ml blood or 20 ml O_2 %. The deoxygenated venous blood is not completely deoxygenated as the venous O_2 content is still about 15 ml O_2 %. There is at rest, a tissue consumption of a quarter of the total oxygen content in arterial blood.
If we consider the normal cardiac output in a 70 kg, male adult as 5 L/min, the rate of total oxygen delivery to the tissues is (5000 ml/min/100) $\times$ 20 ml O_2. This gives a delivery rate of oxygen at 1000 ml O_2 per minute to the cells. In the venous blood that drains back to the right heart, the O_2 delivery rate will then be 750 ml O_2 per minute. Blood must flow for it to be 'bloody' useful. Sluggish blood flow leads to a stagnant hypoxia and ischemia of the tissues.
In both arterial and venous blood, the oxygen content is determined by the partial pressure O_2 in the blood. The amount of dissolved oxygen gives the partial pressure of O_2 in the blood as described by the physical Henry's gas law.
Hemoglobin is the sole carrier of oxygen in blood, with around 99% of the content associated with oxyhemoglobin. The oxygen bound reversibly to hemoglobin is no longer in solution and does not contribute to the partial pressure of O_2, (PO_2).
However, the saturation of hemoglobin with oxygen is determined by the PO_2. There is a reversible equilibrium between dissolved O_2 and hemoglobin-bound O_2. At the tissues, as oxygen diffuses from the capillary blood to the cells, this initially lowers the blood PO_2. Consequently, oxygen will unload from the hemoglobin to the plasma and then to the interstitial fluid enroute for the cells.

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Similarly as the venous O_2-depleted blood reaches the pulmonary alveoli, oxygen diffuses from the alveolar air where the PO_2 is 103 mmHg. The venous blood PO_2 is 40 mmHg before any oxygenation takes place. As the blood PO_2 rises with more oxygen in solution, very rapidly, more uploading of dissolved O_2 in the plasma/cytosol to the hemoglobin occurs.

iii. Question:
What is the percentage difference between hemoglobin saturation with O_2 in the arterial and venous blood?
Answer: Since the Hb–O_2 saturation represents most of the total oxygen content, the percentage decrease in blood oxygen content should affect the Hb–O_2 saturation to the same degree. Indeed, the blood content decreases by around 25% and the Hb–O_2 saturation is reduced from 97% in arterial blood to 75% in venous blood after the tissue oxygen extraction.
Note however that the relationship between PO_2 and Hb–O_2 is not linear. So the reduction of PO_2 is more pronounced from 97 mmHg in arterial blood to less than half at 40 mmHg in venous blood.

2 Oxygenation

i. Definition: The rate of uptake of oxygen from alveoli air into the pulmonary alveolar blood.

ii. PTC:
Oxygenation is not synonymous with ventilation. Ventilation, either pulmonary or alveolar is the volume of air per minute that is moved into (inspired) or moved out (expired) of the lungs. Oxygenation as the name indicates is the volume of oxygen per minute added to the pulmonary blood at the alveolar-capillary membrane.
The rate of lung oxygenation should be equal to the rate of tissue oxygen consumption. At rest, the cellular usage of oxygen is 250 ml O_2/min. This tissue extraction is accompanied by a reduction of the partial pressure of O_2 from 97 mmHg in arterial blood to 40 mmHg in the venous blood.
In the lungs, oxygenation restores the PO_2 to arterial level. This demonstrates that the lung oxygenation rate ('downloading') matches the rate of cellular O_2 uptake or unloading.
When the tissue metabolism increases, the cellular extraction of O_2 is greater and the venous blood PO_2 will decrease to less than the usual 40 mmHg. Subsequently at the lungs, the diffusion capacity of oxygen is heightened by the larger PO_2 gradient between the more deoxygenated mixed venous blood and the alveolar air.
Increased lung oxygenation during physical activity is NOT primarily provided by hyperventilation. The hyperventilation has the more directed function in preventing hypercapnia. Lung oxygenation in ml O_2/min is increased

primarily by the increased right cardiac output or the pulmonary blood flow. This major flow factor in increased oxygenation is explained by the normal 'perfusion-limited' oxygenation at the alveolar-capillary membrane.

iii. Question:
Why is increased alveolar ventilation not the primary factor towards a greater rate of oxygenation at the alveoli?
Answer: At sea level, the alveolar air PO_2 is 103 mmHg and at this PO_2, the hemoglobin-O_2 is almost fully saturated (97%). Since hemoglobin-bound O_2 already represents around 99% of total oxygen content, hyperventilation will not markedly increase the rate of lung oxygenation. The greater delivery of oxygen (ml O_2/min) in blood to the tissues starts with an increased alveolar oxygenation that is pulmonary blood flow-dependent.

3 Hemoglobin-O_2 Affinity

i. Definition: The affinity index of hemoglobin, Hb for oxygen. The 50 (in P_{50}) refers to the 50% saturation of Hb–O_2. P_{50} is defined as the minimum partial pressure of O_2 that is needed to achieve a 50% Hb–O_2 saturation. Thus, the lower the P_{50} value, less PO_2 is required to obtain a Hb–O_2 saturation. This means that a lower P_{50} indicates a higher Hb–O_2 Affinity. *As an illustration, if you need less persuasion pressure to bring two persons together, this means the natural attraction between the two persons is higher!.*

ii. PTC:
If the oxyhemoglobin curve shifts the P_{50} value will also change. If the curve shifts to the right, a 50% Hb-oxygen saturation will be achieved at a higher partial pressure of oxygen. This indicates that a right shift of the curve is

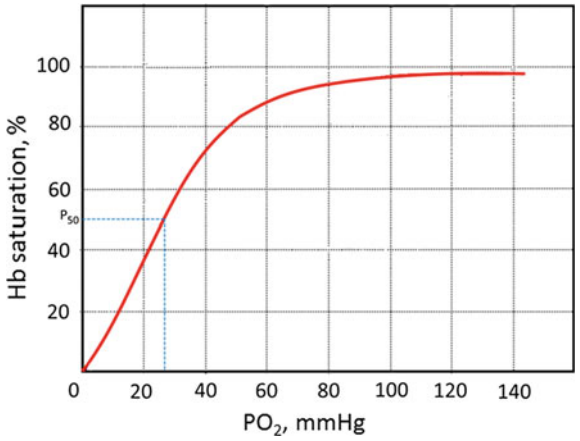

Fig. 1 The oxygen-hemoglobin dissociation curve. The low P_{50} (less than 30 mmHg) indicates a high hemoglobin-oxygen affinity

associated with the decrease in the Hb–O_2 affinity. Oxygen physiology is cell-centered (self-centered!). As long as the cells are receiving more oxygen, it is always a beneficial effect. A decrease in Hb–O_2 affinity means that more oxygen is available to be 'unloaded' to the tissues. To summarize, a right shift of the Hb–O_2 curve increases the P_{50}, decreases the Hb–O_2 affinity and unloads more oxygen to the cells.

iii. Question:
How would you expect the oxyhemoglobin dissociation curve to shift during exercise?'
Answer: The tissues are metabolically more active and demand for oxygen is greater. More unloading of oxygen from the capillary blood to the cells would be physio-logical. Changes in the local muscle tissues indeed lead to a reduction in the Hb–O_2 affinity. The P_{50} is increased as the curve shifts rightward (*AlRight! say the oxygen-hungry cells*).

4 Bohr's Effect

i. Definition: The blood oxygen content is influenced by the amount of dissolved carbon dioxide. In other words, the oxygen carrying capacity of blood is affected by the partial pressure of CO_2.

ii. PTC:
In arterial blood, the partial pressure of CO_2 is 40 mmHg and in venous blood, the PCO_2 is higher at 46 mmHg. The download of O_2 to the cells is dependent on two factors. One is the passive diffusion from O_2 from the capillary blood to the tissues. At the entry point into the capillary, the arterial blood has an oxygenation status of PO_2 around 97 mmHg. Given a resting tissue PO_2 of about 40 mmHg, there is a steep gradient for O_2 diffusion.
In addition, the metabolic status of the cells also appropriately favors extraction of blood O_2. In active tissues, the local environment is acidic, has higher PCO_2 and metabolic heat is also produced. Providentially, all these three local changes in pH, PCO_2 and temperature promote more unloading of oxygen from hemoglobin.
To put this in Hb–O_2 affinity language, a lower pH, higher PCO_2 above 40 mmHg, and a warmer temperature above 37 °C all decrease the Hb–O_2 affinity or increased the P_{50} affinity index.
Mr Bohr and his effects refer to the shift of the Hb–O_2 dissociation curve to the right by PCO_2 and pH.
The mechanism of Bohr's effect sounds similar to the effect described by Haldane for CO_2 transport. Both oxygen and carbon dioxide content in blood is influenced by the PCO_2 and the PO_2 respectively. There is thus, a triad or 'triangle affinity (love!)' relationship between hemoglobin, oxygen and CO_2.

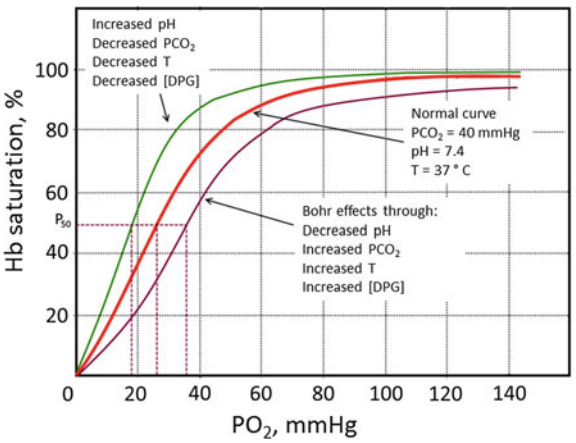

Fig. 2 The oxygen-hemoglobin dissociation curve can be shifted to the right by several factors. The increased P_{50} in these cases indicate a lower hemoglobin-oxygen affinity

Note that at any time, hemoglobin contains both oxygen and CO_2 since even in venous blood, the Hb–O_2 is still 75% saturated.

The dynamics of hemoglobin interactions with O_2 and CO_2 in time is a fascinating physiologic dance of the three inspired, respiratory players.

iii. Question:

Do you observe Bohr's effect in the pulmonary capillary blood in the lungs?

Answer: Indeed, Bohr's effect is operative at both the cellular and pulmonary alveolar sites. In the lungs, removal of CO_2 in the expired air lowers the capillary blood from 46 mmHg to reach the alveolar PCO_2 of 40 mmHg. At the tissues with metabolic production of CO_2, the Hb–O_2 shifts to the right and this favours more O_2 unloading. Now, in the lungs, the return of PCO_2 to normal 40 mmHg reverses the rightward shift back to the arterial blood Hb–O_2 profile. The affinity of de-CO_2 hemoglobin for oxygen uptake in the lungs is higher than the carbonated, deoxygenated hemoglobin present in venous blood.

5 Tissue Oxygen Extraction

i. Definition: At rest, the amount of tissue oxygen uptake or download from the capillary blood is equal to the arterial-venous (a-v) blood oxygen content. The rate of oxygen utilized or consumption will be equal to the amount extracted per 100 ml of blood multiplied by the rate of blood flow.

ii. PTC:

At the resting cardiac output of 5000 ml/L in a 70 kg male adult, the oxygen extracted is 5 ml per 100 ml of capillary blood. This gives a resting oxygen tissue usage of 250 ml O_2/min (from 5000/100 $\times$ 5). The Hb–O_2 relationship is called a dissociation curve and the word 'dissociation' focused on the

cell-centered O_2 need -perspective of oxygen transport and delivery in the cardio-respiratory functions. Venous deoxygenated blood is still 75% saturated with O_2. There is reversible equilibrium between the dissolved oxygen (PO_2) and the Hb-associated O_2. As the oxygen diffuses to the cells from the plasma, more oxygen is unbound from the hemoglobin into the cytoplasm and plasma.

iii. Question:
Is the tissue of extraction in anemic blood any different from that in normal blood?
Answer: Each unit volume of anemic blood will have less oxygen content (either due to less hemoglobin concentration or lower/altered affinity hemoglobin). At the same metabolic rate, more oxygen could be extracted per unit of anemic blood since normally, only a quarter of the total oxygen content in arterial blood is downloaded.
A reduced Hb–O_2 saturation (less than 75%) in the venous blood of the anemic patient will be associated with a decreased PO_2 (less than 40 mmHg). Presumably then, the equilibrium PO_2 in the interstitial fluid of the anemic patient would be lower than normal.

6 Cardio-Respiratory Functions

i. Definition: The cardiovascular and respiratory physiology are integrated in health and is adjusted accordingly in pathophysiology.

ii. PTC:
The cells are the final targets or consumers of oxygen and energy substrates delivered by the pumping of the heart. From the perspective of the cells, the cardio-respiratory physiology is directed towards oxygen delivery and excess CO_2 removal from tissues. There are several areas where we can observe beneficial effects of one system on the other.

(a) The oxygenation at the alveolar-capillary membrane is 'perfusion-limited'. During exercise, the larger pulmonary blood flow from a greater right ventricular cardiac output increases pulmonary oxygenation.
(b) During exercise, a greater venous return also supplies the increased pulmonary blood flow. The deeper inspiration during physical activity also produces a 'respiratory pump' effect in enhancing venous return by lowering the intrathoracic pressure.
(c) The pulmonary endothelial cells are the major sites of generation of angiotensin II in the renin-angiotensin cascade involved in blood volume and pressure regulation.
(d) The systemic and pulmonary circulation are in series with each other in the closed cardio-pulmonary circuit. The intrinsic property of the

myocardium ensures that the left ventricular cardiac output is matched with that of the pulmonary flow from the right ventricle (a la Starling). If this contractile balance is upsetted, e.g.in left heart failure, there will be pulmonary vascular congestion and pulmonary edema. The lung compliance will be reduced and oxygenation across a larger diffusion distance will be diminished.

(e) If blood flow is sluggish (stagnant hypoxia,) the tissue ischemia will produce lactic acidosis. The lungs will compensate for the metabolic acidosis by an increased ventilation stimulated via the peripheral chemoreceptors.

(f) In respiratory causes of pH imbalance, the blood flow to the kidneys with increased or decreased PCO_2 will lead either more or less hydrogen ion secretion respectively. The secretion of protons in the renal tubules is linked to the reabsorption and synthesis of the bicarbonate base.

(g) At high altitudes, the hypoxic hypoxia that develops at the low atmospheric PO_2 will result in a compensatory increased hematocrit (secondary polycythemia). Renal erythropoietin is released by the hypoxia. The oxygen-carrying capacity/unit blood volume is higher.

iii. Question:
When you do a Valsalva manoeuvre, what changes occur in the cardiovascular system?
Answer: A forced expiration against a closed glottis will raise the intrathoracic pressure. The returning venous flow will be reduced. Cardiac output and the arterial blood pressure will decrease during the Valsalva effort. A baroreflex tachycardia will occur in response to the induced hypotension.

7 Stagnant Hypoxia

i. Definition: Cells experience lack of oxygen due to poor blood supply. There is no problem with oxygenation of blood by the lungs.

ii. PTC:
The cells are provided ceaselessly with adequate oxygen in proportion to their metabolic needs. The heart must pump sufficiently to deliver oxygenated arterial blood. Blood must flow if the reoxygenated blood are to be of any use. The normal rate of delivery of oxygen to the cells is given by the product of the arterial blood content and the cardiac output.
In the event of a reduced regional blood supply, either due to a depressed cardiac pump function or a local blockage of tissue perfusion, the cells become ischemic due to the stagnant blood flow. The cellular hypoxia is termed stagnant hypoxia. Obviously, the blood oxygenation status, the PO_2 and the O_2 content are normal. The hypoxia results from the inadequate rate of oxygen

delivery to the cells, consequent from the decreased blood perfusion, to meet their metabolic needs.

The cells will attempt to extract more O_2 from a unit volume of capillary blood. The venous PO_2 and the O_2 content will be less than the normal values of 40 mmHg and 15 ml O_2/100 ml respectively.

iii. Question:

How is the compensation in cardiac output, if any, in stagnant or anemic hypoxia explained?

Answer: In anemia, whole body homeostatic response will generally see an increase in cardiac output. Tissue vasodilation due to local hypoxia will increase the venous return due to a decreased total peripheral resistance. The cardiac output is higher as a result. If the anemia is due to a lower hematocrit, the lower blood viscosity also contribute to a greater cardiac output.

If the cause of the sluggish blood flow to the tissues is due to cardiac failure, no increased pump reflex will be possible.

8 Hypoxic Hypoxia

i. Definition: Inadequate oxygen supply to the tissues due to a decrease in the partial pressure of oxygen in arterial blood.

ii. PTC:

Hypoxia is a general umbrella term for deficiency of oxygen experienced by the cells. Hypoxia is 'cell-centered' and defined from the perspective of the cellular 'hypoxic' experience. Not all hypoxia thus defined, is associated with a reduction in the partial pressure of O_2 in arterial blood. This is the case with an oxygen content reduction due to low hemoglobin concentration or abnormal hemoglobin (anemic hypoxia where the arterial PO_2 of the dissolved O_2 component is unchanged).

When the hypoxia is associated with a decrease in the arterial PO_2, the specific tem is 'hypoxic hypoxia'. Any lung pathophysiology or abnormal thoracic anatomy that results in hypoventilation is a cause of hypoxic hypoxia. All these conditions will decrease the alveolar air PO_2. This leads to a reduction of the arterial PO_2.

In the situation of alveolar-capillary 'block', the alveolar air PO_2 is normal but the arterial PO_2 is still below normal PO_2 range. The 'block' refers to the abnormal changes in the alveolar capillary membrane that thickens or increases the diffusion distance for the passive O_2 movement. Equilibration, which is normally rapid, towards an alveolar capillary blood PO_2 of 103 mmHg is not achieved.

In normal persons, hypoxic hypoxia occurs at high altitude. Mountaineers are exposed to the reduced barometric pressure air that has a decreased PO_2. Inspiring air with lower PO_2 will result in the alveolar air PO_2 to drop below the usual 103 mmHg. The hyperventilatory response to high altitude hypoxia is aimed to restore the alveolar air PO_2.

iii. Question:
How does significant ventilation/perfusion mismatch contribute to a hypoxic hypoxia?
Answer: In affected areas of the lung, the regional imbalance between ventilation and perfusion can cause the alveolar PO_2 to be decreased. Blood draining the healthy portions of the lungs will have normal PO_2. However, the blood that combines as the pulmonary venous blood will then be a mixture of well-oxygenated and insufficiently oxygenated blood. The arterial PO_2 will be reduced.

9 Hypoxic Drive

i. Definition: Refers to the stimulation of respiration via the peripheral arterial chemoreceptors.

ii. PTC:
Both carbon dioxide and oxygen are the primary chemical regulators of respiration. This is logical as the main objective of respiration is to maintain a normal partial pressures of oxygen and carbon dioxide in the arterial blood. This directly means the alveolar air partial pressures for O_2 and CO_2 since the arterial blood values are determined by the alveolar air values during respiratory exchange.
The chemoreceptors are sited in two locations. The central chemoreceptors are in the brainstem in the vicinity of the respirator control neurons. These are primarily responsive to changes in PCO_2 in the ECF.
The peripheral chemoreceptors in the carotid and aortic bodies are sensitive to both CO_2 and oxygen. Hypercapnia and a decreased PO_2 will stimulate the peripheral chemoreceptors. The CO_2 is the primary ventilator drive for respiration. Much smaller increase in PCO_2 compared to reductions in PO_2 will trigger afferent impulses from the peripheral chemoreceptors. CO_2 in addition has central chemoreceptor action. Thus, in normal control of respiration, a hypercapnic drive predominates.
A shift to a hypoxic drive occur in conditions if the chemoreceptors become desensitized as the sensory receptors are exposed to a chronic slight hypercapnia that is still compatible to life as in some pulmonary diseases. The patient's breathing during hypoxic drive is then sustained by a constant slightly depressed arterial PO_2.

iii. Question:
What are the potential risk in giving patients with chronic lung disease a high oxygen concentration air to breathe?
Answer: If the patient no longer responds to increases in CO_2, the hypoxic drive is the mechanism that helps to remove the metabolic CO_2. If the only stimulus that maintains adequate breathing is removed by breathing an oxygen-rich air, the alveolar ventilation will be suppressed. CO_2 will begin to build up in the patient and the hypercapnia becomes more severe and can precipitate an acidotic coma.

Chapter 9
Carbon Dioxide Transport

1 Blood CO_2 Content

i. Definition: The total amount of carbon dioxide carried in blood, expressed as volume of CO_2 in volume of blood.
ii. PTC:
The transport capacity of blood for CO_2 is higher than that for oxygen. This is also true in the arterial blood where the CO_2 content is more than twice that of oxygen.
Unlike for oxygen, there is no specific carrier for CO_2 in blood. The total load of CO_2 in blood is carried in three forms of 'baggages'. Carbon dioxide dissolves in the plasma from the alveolar air in line with Henry's law. The dissolved CO_2 gives the partial pressure of CO_2 in blood (PCO_2).
The other two forms of blood CO_2 are protein-bound CO_2 and as bicarbonate anions. There is a reversible equilibrium between the dissolved CO_2 and the protein-CO_2 and bicarbonate. The two major proteins that bind CO_2 are the plasma proteins and red cell hemoglobin. The latter becomes carbamino-hemoglobin. The higher the PCO_2 in blood, the more the formation of carbamino-hemoglobin on the red cell protein molecule and also CO_2 with the plasma proteins.
The primary mode of CO_2 transport is as plasma bicarbonate. Thus, the higher PCO_2 in the venous blood means that there is a higher concentration of bicarbonate in venous blood than in arterial blood. The blood pH is not just due to the bicarbonate base concentration but determined by the ratio of the bicarbonate to the PCO_2.
The production of 'clothed CO_2' as bicarbonate is tailored within the erythrocytes. A red cell enzyme, carbonic anhydrase catalyses the hydration of tissue CO_2 to carbonic acid which then dissociates to bicarbonate and protons. The bicarbonate is transferred to the plasma by a bicarbonate-chloride exchanger in the red cell membrane. Hemoglobin enhances the bicarbonate

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generation from carbonic acid dissociation by buffering the protons that are released. The tissue CO_2 is couriered from the cells to the lungs and also from the lungs to the cells in three CO_2 baggages.

Thus, both the degree of protonation of hemoglobin and the bicarbonation of CO_2 are dependent on the PCO_2. There is less protonated hemoglobin and lower plasma concentration of bicarbonate in arterial blood than venous blood.

iii. Question:

In the CO_2 transport graph, what is the y-axis when x-axis is the PCO_2 in mmHg?

Answer: The y-axis is then the blood CO_2 content in ml CO_2 per 100 ml blood. There is no saturation value for the y-axis as in hemoglobin-oxygen %. The two relevant points on the x-axis is also a narrow distance, only 6 mmHg difference between venous (46) and arterial (40) blood PCO_2.

2 Carbonic Anhydrase

i. Definition: The erythrocyte enzyme that catalyzes the hydration of metabolic CO_2 to generate bicarbonate, the major form of CO_2 carried in venous blood.

ii. PTC:

Carbonic anhydrase is a key enzyme in several cells that generate hydrogen ions. Two of these cells are epithelial cells that secrete the hydrogen ions, namely gastric parietal cells and the renal tubular cells. The red blood cells contain the carbonic anhydrase and the protons produced are buffered by the hemoglobin. Venous blood is only slightly acidic compared to arterial blood.

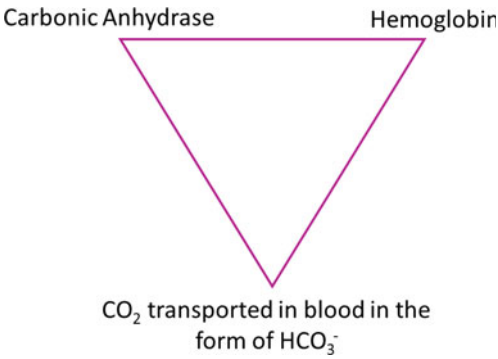

Fig. 1 The blood capacity to carry CO_2 is dependent on two proteins in the red cell. One is the enzyme carbonic anhydrase and the other, hemoglobin. In combination, bicarbonate, the main form CO_2 is transported in the blood, is generated inside the red blood cells. Hemoglobin buffers protons generated from the dissociation of carbonic acid and this enhances the reaction to produce the bicarbonate ion

Bicarbonate is the major species of CO_2 in the total blood CO_2 content. The other two forms are carbamino-hemoglobin and dissolved CO_2. Metabolic CO_2 diffuse from tissues into the red cells down its partial pressure gradient. Rapid hydration of CO_2 into carbonic acid and then dissociation releases bicarbonate and protons.

In gastric parietal cells, the transport of the bicarbonate across the basolateral membrane contributes to the post-prandial 'alkaline tide'. In renal tubular cells, the bicarbonate reabsorbed into the peritubular capillary represents new bicarbonate synthesis or part of the indirect reabsorption of filtered bicarbonate. Intracellular bicarbonate in red cells exchange with plasma chloride via a membrane bicarbonate/chloride antiporter and enters the plasma.

The partial pressure of CO_2 in venous blood is higher at 46 mmHg compared to that in arterial blood at 40 mmHg. Therefore, the bicarbonate concentration in venous blood is higher than that in arterial blood since bicarbonate is the major carbonic anhydrase-transformed component of total blood CO_2 content. Although bicarbonate is a base, the pH of arterial and venous blood is determined rather by the ratio of bicarbonate to carbonic acid concentrations.

iii. Question:
If an excess of an inhibitor of carbonic anhydrase is consumed, how will the venous blood parameter changed?
Answer: The hydration of CO_2 will not proceed within the erythrocytes in the capillary blood that drains the tissues. There is a reversible equilibrium between dissolved CO_2 and the other two forms of CO_2. The tissue PCO_2 will increase and so will the venous blood PCO_2 above 46 mmHg. However, the venous blood CO_2 carrying capacity is reduced since the conversion of metabolic CO_2 to bicarbonate is inhibited.

3 Haldane's Effect

i. Definition: The carbon dioxide carrying capacity of blood is influenced by the amount of dissolved oxygen. To put it in another way, the blood carbon dioxide content is influenced by the partial pressure of oxygen.

ii. PTC:
In arterial blood, the dissolved PO_2 is higher than in venous blood. Simply, the CO_2 content in arterial blood is due to two factors, namely the dissolved carbon dioxide and also the dissolved oxygen. The dissolved PCO_2 will contribute to the amount of CO_2 carried as carbamino-hemoglobin and as bicarbonate besides the dissolved, undissociated carbonic acid. In addition, oxyhemoglobin has a lower affinity for both CO_2 and protons. The latter two decreased affinities for CO_2 and hydrogen ions account for the reduced CO_2 carrying capacity of arterial blood compared to venous blood where the proportion of deoxyhemoglobin is higher.

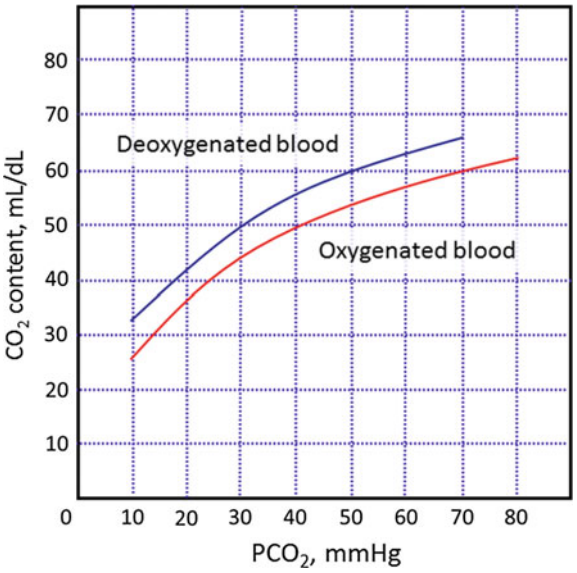

Fig. 2 The carbon dioxide carrying capacity of blood is increased in deoxygenated blood

iii. Question:
At the tissues, how is the uploading of carbon dioxide into the blood promoted?
Answer: The uptake of metabolic CO_2 from the cells into the capillary blood is driven by two mechanisms. One is the passive diffusion of tissue CO_2 into the capillary blood following its partial pressure gradient. In addition, the release of oxygen or tissue extraction of oxygen desaturates the blood hemoglobin-O_2 from about 97 to 75%. The deoxyhemoglobin increased affinities for CO_2 and protons favor the uptake and transport of metabolic CO_2 from the tissues to the lungs.

4 Alveolar Ventilation Equation

i. Definition: The formula that relates alveolar ventilation, the rate of tissue carbon dioxide production and the alveolar air partial pressure of CO_2.
ii. PTC:
One of the primary aims of an optimal, normal alveolar ventilation is to maintain a constant alveolar air PCO_2. The normal alveolar PCO_2 is 40 mmHg and is just 6 mmHg higher than the PCO_2 in mixed venous blood that perfuses the lungs for 'de-carbodioxidenation', besides the oxygenation of pulmonary capillary blood.

The PCO_2 partial pressure gradient across the alveolar-capillary membrane is crucial to ensure that there is a gradient for passive, diffusive removal of CO_2. If e.g. the alveolar PCO_2 is 42 mmHg, the transfer of CO_2 from pulmonary capillary blood to alveolar air would be decreased.

The alveolar ventilation equation brings together three parameters in a relationship; the alveolar ventilation, V_A the alveolar PCO_2 and the rate of cellular CO_2 production, VCO_2. The equation states that the alveolar PCO_2 is determined by the ratio of the VCO_2 to the alveolar ventilation.

To elaborate, at rest, if the student voluntarily hyperventilates, the resting VCO_2 is unchanged (the little contribution from the active breathing ignored) but the alveolar air PCO_2 will be reduced. Hyperventilation is accompanied by a lowering of the alveolar PCO_2 to less than 40 mm Hg. The arterial blood will by hypocapnic and alkalotic (respiratory alkalosis).

In the condition of hyperthyroidism, the cell metabolism is stimulated with higher CO_2 production. Ventilation is also increased in hyperthyroidism (besides the effect of chemoreceptor stimulation by the increased CO_2). The alveolar PCO_2 will thus remain unchanged in a patient with excess thyroid hormone secretion.

In a normal person, during physical activity, the tissues produce more metabolic CO_2. If the alveolar ventilation is unchanged, the alveolar air PCO_2 and the arterial blood PCO_2 will increase. A respiratory acidosis results. However, in reality, alveolar ventilation is ALWAYS increased in parallel with the higher metabolism in active muscles. The alveolar air PCO_2 during exercise is unchanged at 40 mmHg.

In lung pathophysiology, any cause of a depressed alveolar ventilation or hypoventilation will raise the alveolar PCO_2. If the person does some physical activity, the alveolar PCO_2 will be elevated more. Alveolar $PCO_2 \approx VCO_2$/alveolar ventilation.

iii. Question:

In a healthy individual, how does a greater CO_2 release from the active tissues stimulate alveolar ventilation?

Answer: The venous blood PCO_2 is expected to be higher than 46 mmHg during physical activity. At the lungs, the PCO_2 gradient will be higher than usual with alveolar PCO_2 at 40 mmHg. After gas exchange, the pulmonary venous blood from the lungs will have a PCO_2 of 40 mmHg. It may be surprising for students to know that the arterial blood PCO_2 does not rise measurably during moderate exercise.

Fig. 3 The alveolar ventilation equation (left) which relates the alveolar ventilation, V_A, to volume of CO_2 leaving the alveoli per unit time, VCO_2 and partial pressure of alveolar CO_2, $PACO_2$. The balance between V_A and VCO_2 determines the $PACO_2$ (right)

Since the peripheral chemoreceptors (carotid/aortic bodies) are located at the arterial side of the systemic circulation, how are the sensory receptors stimulated if the blood PCO_2 is normal at 40 mm Hg?
The same query of any 'hypoxic stimulation' of the arterial chemoreceptors applies to PO_2, which will be less than 40 mmHg in venous blood during exercise but after equilibrium with alveolar air PO_2 at 100 mmHg, should also be normal in arterial blood. What is certain is that the stimulus for hyperventilation when tissue activity is increased is not PCO_2 or PO_2 (which remain normal). The trigger for the hyperventilation appears to be multifactorial and are elaborated in Chap. 10, topic 5 on exercise hyperventilation.

5 CO_2 Metabolic, Physiologic Functions

i. Definition: Carbon dioxide is a metabolic by-product of cell metabolism. In vivo, carbon dioxide have several physiologic functions that are essential for homeostasis.
ii. PTC:
The coincidental or creative providential design that links the respiratory gases between the flora and humans is taken for granted. Plants use carbon dioxide for their botanical physiology. The oxygen released is 'recycled' and consumed by the animals and humans with metabolic CO_2 generated.
In vivo, in the human body, the extracellular fluid (ECF) is a regulated, aqueous environment that bathes all cells. The constancy of the ECF is essential for cells to continue their metabolism associated with their contributing functions in the specific organs which they are part of e.g. proximal tubular cells in the renal nephrons of kidneys.
During physical activity, the skeletal muscles have an increased metabolic need. The metabolic CO_2 very nicely has two actions that act to sustain the oxygen supply to the more active muscles. Local increased CO_2 relaxes the arterioles and produce vasodilation. In addition, the metabolic CO_2 also enhances the unloading of oxygen from the oxyhemoglobin (Bohr's effect).
This latter action of CO_2 may have a 'selfish' physiologic reason. CO_2 replaces oxygen on the hemoglobin carrier (the ship HM Globe!). This increased capacity to transport CO_2 when the blood oxygen is reduced is known as Haldane's effect.
The vascular effect of CO_2 is also involved in the special circulations that supply the brain and the heart. The cerebral and coronary arterioles are sensitive to CO_2. Autoregulation of cerebral blood flow involve a myogenic mechanism that is operative. Besides a stretch-smooth muscle response, local CO_2 also contributes to the autoregulation of cerebral perfusion.
In the heart, local tissue CO_2 are active during both autoregulation of coronary perfusion and in active hyperemia to the myocardium during increased cardiac work.

CO_2 is a wonderful physiologic 'multitasker'. The major chemical buffer in the ECF is the bicarbonate/carbonic acid system. The kidneys' role is on the bicarbonate determinant of the buffer and the pulmonary ventilation is linked to the carbonic acid that is formed from the hydration of metabolic CO_2.

The primary chemical regulator of breathing is also CO_2, acting on both peripheral arterial and central, brain stem medullary chemoreceptors.

iii. Question:

Does the content of CO_2 and oxygen in arterial blood provide any insight into CO_2 physiologic function?

Answer: If CO_2 was merely a metabolic waste (certainly not a discarded waste for the flora!), we could expect blood CO_2 content in oxygenated arterial blood to be low. Surprisingly, the CO_2 content is more than twice the oxygen content in arterial blood at 48 ml CO_2 % and 20 ml O_2 % respectively.

6 Defining Respiration

The lungs are directly in contact with the precious air that we breathe. The homeostasis of the healthy, functioning body needs the oxygen in inspired air to energize the *in vivo* cellular and integrative mechanisms.

The respiratory system has its own features for airflow and alveolar ventilation and in combination with the circulatory system, the cardio-respiratory physiology serves the metabolic needs of the cells.

There are some key definitions or definitive events in cardio-respiratory physiology that are useful to note.

a. The need for oxygen and thus, any deficiency of oxygen (hypoxia) is defined by the cells. As long as the cells sense a threat to adequate O_2 supply, they sound out the hypoxic cry! For example in stagnant hypoxia, the oxygen content in arterial blood is normal but the delivery rate of O_2 is insufficient.
b. The unique hemodynamics of the pulmonary circulation is defined and determined by the compliant blood vessels. So, we have vascular distention and recruitment when the pulmonary arterial pressure rises during exercise. This pulmonary vascular mechanical vasodilation is essential to sustain the greater right ventricular cardiac output/pulmonary blood flow to match the left ventricular cardiac output in the closed cardiovascular circuit.
c. The unique vascular constriction in response to hypoxia (hypoxic pulmonary vasoconstriction) is defined and designed by the need for ventilation-perfusion matching and not for metabolic requirements. This is the pulmonary hypoxic 'matchmaker'!
d. At the tissues or the lungs, the defining moment for Bohr and Haldane occurs concurrently! The hemoglobin has a triad relationship with O_2 and CO_2. The partial pressure of CO_2 affects the Hb–O_2 saturation/oxygen content (Bohr) while the partial pressure of O_2 influence the blood CO_2 content (Haldane).

e. The physiologic roles of CO_2 are defined as beyond merely a metabolic product from cell biochemical reactions. CO_2 is a vasodilator, an oxygen unloader from hemoglobin (Bohr), an essential component in pH regulation and the primary chemical control of respiration.
f. The factors affecting diffusion of the respiratory gases are defined and described by Fick's law. Partial pressure gradients for both O_2 and CO_2 are the primary determinant for any net diffusion (the water vapor pressure which is temperature-dependent is 47 mmHg at body temperature). The available surface area for diffusion is the other major factor.
g. The objective of alveolar ventilation is defined by the need to maintain a normal alveolar air partial pressure of CO_2 and O_2 for optimal gas exchange at the alveolar-capillary membrane.
h. The main purpose of hyperventilation during exercise is defined not as to increase blood oxygen content but to remove the greater excess of metabolic CO_2 to prevent acidosis. The former is explained by the sigmoid curve relationship of Hb–O_2 and also the normal 'perfusion-limited' lung oxygenation.

These are just a few summary big picture points in defining cardio-respiratory physiology.

7 What Respiration Is not

Making definite negative statements can be useful to define and clarify thinking when learning Physiology.

Below are some of the NOTs to take Note!

a. Tidal volume, TV is NOT the volume of air movement into and out of the lungs during a respiratory cycle (TV is either inspired TV or expired TV).
b. Lung elasticity does NOT mean stretchability. Lung compliance (distensibility) is inversely related to the elasticity. Elastic recoil opposes expansion of the lungs.
c. Expired air PO_2 does NOT mean that it has less than alveolar air PO_2. Expired air is a mixture of alveolar (PO_2 103 mmHg) and unaltered, dead space conducting zonal air ($PO_2 \sim 150$ mmHg).
d. Anatomical 'dead' space air does NOT mean that it is useless; 'dead' means no movement or in this case, no 'exchange' of respiratory gases. In fact, 'dead' air $PO_2 \sim$ inspired air PO_2.
e. Oxygenation is NOT the same as ventilation. Ventilation contributes to alveolar air O_2/CO_2 but oxygenation is the O_2 'top-up' of deoxygenated pulmonary blood.
f. Better oxygenation in the apex of the upright lung (P_A/P_aO_2 higher) does NOT mean a higher rate of O_2 delivered/time from this region. The O_2/min from the basal alveoli is higher due to the greater perfusion.

g. Apical alveoli are relatively overventilated and this is NOT the same as saying the apical alveoli has better alveolar ventilation.
h. Vasodilation in the pulmonary circulation is NOT dependent on nerve or metabolite.
i. Hypoxic pulmonary vasoconstriction implies that this unique vascular response is NOT primarily involve in ensuring blood supply to alveoli. It has a role in V/Q matching.
j. The term 'restrictive' in lung diseases does NOT mean airflow is restricted by increased airway resistance. In 'Restrictive' lung problems, the abnormality is reduced lung compliance that restricts the expansion of the alveoli.
k. The term 'transmural' pressure is NOT only applicable at airway/alveolar. Transmural pressure also exerts effects at blood vessels. It produces the venous pooling in the compliant veins. Transmural pressure is also the dominant factor that distends and recruits more pulmonary vessels ('mechanical vasodilation').
l. Perfusion-limited oxygenation does NOT mean a negative phenomenon but that the rate of O_2/min uptake from the lungs can easily be increased by just increasing the pulmonary blood flow (increased right ventricular CO).
m. Effect of surfactant is NOT only on the small alveoli. The effect is greater in the smaller alveoli in reducing alveolar surface tension recoil, collapsing force.
n. A decreased Hb-O_2 affinity does NOT mean the uptake of O_2 in the lungs is compromised. Physiologically, the beneficial effect is at the cellular level of increased unloading of O_2 from Hb.
o. Pulmonary blood flow is NOT autoregulated, defined classically.
p. Arterial PO_2 is NOT determined by the Hb-bound oxygen.
q. Arterial PO_2 is NOT reduced in exercise.

1. Arterial PCO_2 is NOT increased in exercise [See Alveolar Ventilation; $PCO_2 \sim VCO_2/V_A$].
2. Bohr's effect is NOT only operative at the tissues.
3. Haldane's effect is NOT only applicable at the pulmonary exchange.

Chapter 10
Control of Respiration

1 Peripheral Chemoreceptors

i. Definition: The arterial sensory receptors at the carotid/aortic bodies that detect changes in partial pressures of CO_2, O_2 and the blood pH.

ii. PTC:
The central medullary chemoreceptors in the brain stem responds to arterial PCO_2. The respiratory control neurons also receives afferent inputs from chemoreceptors at the carotid/aortic bodies. After denervation of the carotid chemoreceptors, the response to PO_2 and pH in stimulating ventilation is abolished. However, the response to arterial PCO_2 is reduced only about 35%.
The sensory chemoreceptors are located at the carotid bifurcation on each side. Each carotid/aortic body (glomus) comprises an island of two cell types. The type I cells are associated closely with the sensory fibers that innervate them. These glomus cells contain dense vesicles containing catecholamines, with dopamine as a main constituent.
Hypoxia stimulate the release of dopamine which then binds and activates action potentials in the afferent fibers. Hypoxia appears to affect O_2-sensitive potassium channels, with hypoxia reducing the potassium cation efflux, thus depolarizing the glomus cells.
Each carotid body is only 2 mg and the blood flow/g tissue/time is thus enormous. The metabolic needs of the carotid bodies are sufficiently supplied by the dissolved oxygen or the PO_2. Thus, in anemic hypoxia that does not alter the PO_2 (carbon monoxide toxicity and iron-deficiency anemia), the chemoreceptors are not stimulated even though the oxygen content is reduced.
In stagnant hypoxia, the sluggish blood flow can lead to inadequate O_2 to the chemoreceptors and this will trigger activation of the receptors. Metabolic

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inhibitors, like cyanide that prevents the uptake of O_2 by the chemoreceptors will also stimulate the generation of afferent impulses from the receptors.
One factor that could contribute to the exercise hyperventilation is the rise in plasma potassium. Potassium efflux repolarizes the nerve and skeletal muscle membranes and the frequency of action potentials during exercise is higher. Hyperkalemia is reported to stimulate the peripheral chemoreceptors.

iii. Question:
After a period of voluntary hyperventilation, how will the carotid chemoreceptors respond?
Answer: There will be respiratory alkalosis with increased blood pH and a decreased arterial PCO_2. The arterial PO_2 will also be slightly increased. The PCO_2 reduction especially, will inhibit respiration mainly via the central chemoreceptors. Perhaps, the increased pH and PO_2 may also decrease any tonic, basal afferent impulses from the carotid chemoreceptors to the brain stem.

2 Central Chemoreceptors

i. Definition: In respiration control, the chemoreceptors monitor partial pressure of oxygen, pH and/or partial pressure of carbon dioxide in the ECF/blood.

ii. PTC:
As a general term, chemoreceptors detect the presence or changes in chemicals. Both the oral taste receptors and the olfactory receptors that enrich our lives are chemoreceptors. These chemoreceptors of pleasure however are not involved in homeostasis of the 'internal' ECF environment. Smell and taste are external stimuli.
In respiration, the chemoreceptors are located in the peripheral (carotid and aortic bodies) and centrally at the brain stem medulla in the vicinity of the respiratory neurons. The medullary chemoreceptors respond to changes in the hydrogen ion concentration in the cerebrospinal fluid (CSF) and brain interstitial fluid (ISF). The hydrogen ion concentration in the CSF and brain ISF parallels the changes in the arterial partial pressure of CO_2.
A reduction in arterial pH due to organic acids like lactic or ketoacids does not stimulate the central chemoreceptors due to restriction by the blood brain barrier (BBB). The CO_2 in arterial blood can penetrates the BBB easily, is hydrated in the brain ISF/CSF into carbonic acid. The latter dissociates and produces the rise in hydrogen ions that stimulate directly the medullary chemoreceptors.
The central chemoreceptors do not respond to hypoxia to stimulate ventilation. The peripheral chemoreceptors are the target of hypoxic stimulation. The responsiveness of both the central and the peripheral (carotid/aortic bodies) chemoreceptors to arterial PCO_2 accounts for CO_2 being the primary regulator of respiratory alveolar ventilation.

The operating range for CO_2 is narrow compared with oxygen, from PCO_2 at 40 mm Hg in arterial blood to 46 mmHg in venous blood. A small decrease or increase in PCO_2 from the controlled value at 40 mmHg will inhibit or stimulate the central, medullary and the arterial carotid/aortic chemoreceptors to produce hypoventilation or hyperventilation respectively.

iii. Question:
When you hold your breath underwater, what determines the duration of time before 'breakpoint' when you have to surface?
Answer: The CO_2 accumulates and the O_2 are depleted in blood during breath-holding. At 'breakpoint', it is the hypercapnia rather than the hypoxia that intensely stimulates the central/peripheral chemoreceptors to cause the person to surface to gasp for air.

3 Ondine's Curse

i. Definition: The condition when the voluntary control of breathing is intact but the automatic control of breathing is disrupted.

ii. PTC:
Breathing is a unique physiological process where there are separate mechanisms for voluntary and involuntary control. Sitting in an hour lecture, the students will not be conscious that she has automatically inspire/expire around 600 times (10 breaths per minute). The rhythmic respiratory cycle is controlled by control 'pacemaker' neurons in the brain stem.
We know that we can take a deep breath, hyperventilate before entering to swim underwater in a pool. The pathways for intentional, voluntary control starts in the cortex and the impulses bypasses the brainstem medullary neurons to activate the alpha motor neurons that innervate the respiratory skeletal muscles. A child in tantrum can hold his breath to demand something from his mother! Afferent signals from the cortex in this case can nullify the normal respiratory pacemaker activity. This unique possibility of altering the pattern of breathing voluntarily provides a 'self-directed' learning for the students learning respiratory physiology!
The clinical condition when the voluntary input is still intact but the patient has lost the automatic respiration is called Ondine's curse. This is derived from a German fairy tale about Ondine, a king of the water nymphs who fell in love with her mortal lover. Because of her human lover's unfaithfulness, he was punished by a curse that took away all his autonomic functions! The only way he could stay alive is to remember to breath.
In a patient with Ondine's curse, breathing during sleep is continued and maintained by positive pressure breathing. Ondine's curse is seen in patients who have trauma or compression of the brain stem medulla or in bulbar poliomyelitis.

Other afferents from the 'higher centers' that impinge on respiratory activity include emotional and physical pain. These signals would include descending afferents to the brainstem from the limbic system and the hypothalamus.

iii. Question:
In Ondine's curse, how is the size of the tidal volume differently controlled from automatic breathing?
Answer: With breathing sustained only by conscious effort, the tidal volume or depth of each breath will be variable, depending on the inspiratory effort. The expired tidal volume may also not be the same as the inspired tidal volume. In automatic respiration, the tidal volume (inspired or expired) is set by the pacemaker activity of the rhythmically-discharging medullary neurons in the brain stem.

4 Vagal Reflexes

i. Definition: The afferent sensory inputs involving the tenth cranial mixed vagus nerve that affect respiratory neuron activity in the brainstem.

ii. PTC:
The breathing pattern can be modified by sensory inputs arising from sensory receptors in the lungs. The large vagus nerves run parallel on either side of the trachea. The vagus nerve obviously also receive sensory information from other parts of the body besides the lungs.
The afferent impulses are initiated from three types of pulmonary receptors. These are namely

a. slowly adapting stretch receptors.
b. rapidly adapting (also named 'irritant') receptors.
c. C fibre receptors (juxtapulmonary or J receptors).

The stretch and rapidly adapting receptors are innervated by large and small-diameter myelinated fibres respectively. The C type are slower-conducting non-myelinated fibres.
The classic example of the lung stretch vagal reflex is the Hering-Breur (H-B) inflation reflex. The H-B reflex in humans is still present during sleep and is more pronounced in babies than in adults. The H-B reflex is said to contribute to terminating inspiration and limiting tidal volume. However, rhythmic breathing does not require this vagal stretch reflex as inspiration/expiration continues even when the vagi are cut.
The rapidly adapting receptors (RAR) are mechanoreceptors. Since RAR are also stimulated by irritating stimuli like ammonia and cigarette smoke, they also are called irritant receptors (*'rapidly irritatied'!*). The RAR have a role in the initiation of the first few gasps of breath in the newborns.

The J receptors of the C fibres are close to the pulmonary capillaries and also in the bronchial walls. The J receptors are stimulated by histamine, bradykinin and prostaglandins released during lung tissue damage, and also by edematous tissues. Any physiologic function of the C fibre J receptors in normal breathing is yet to be established.

iii. Question:
What is the meaning of sensory receptor adaptation?
Answer: When a sensory receptor is given a constant applied stimulus, the rate of action potential generation progressively decreases, even though the stimulus is still present. The physiologic stimulus for the slow adapting stretch receptors is lung volume but for the RAR, it is likely the rate of change of lung volume, which is related to the rate of airflow during inspiration or expiration.

5 Exercise Hyperventilation

i. Definition: The increased in alveolar ventilation during physical activity that is paradoxically not driven by any observed changes in the blood PO_2, PCO_2 or pH.

ii. PTC:
By definition, hyperventilation as a cause will lower the alveolar air PCO_2 and increase the PO_2. This occurs in anxiety attacks or during fever. Hyperventilation as a compensatory response is stimulated by arterial hypercapnia or hypoxemia or an acidic blood pH.
Hyperventilation accompanies exercise or physical exertion. The stimulus that sustain the increased ventilation during the physical activity appears to be multifactorial. The arterial PCO_2, pH and PO_2 remain surprisingly normal. Perhaps slight second by second fluctuations in these parameters, not usually measurable could be the stimuli that maintains hyperventilation during the duration of the muscle activity.
Metabolic CO_2 is increased. Alveolar ventilation is increased in parallel, so there is regulation to maintain a normal arterial pH, PCO_2 and PO_2. In heavy exercise or extreme sports, alveolar and arterial PCO_2 decreases and this occurs when the CO_2 removal is greatly increased and outstrips the cellular CO_2 production. In this situation, the lactic metabolic acidosis arising from the greater demand on skeletal muscle metabolism stimulates the ventilation. Other afferent signals can supplement the hyperventilatory input to the respiratory neurons in the brain stem. Proprioceptors in the muscle and joints can provide some of the total stimuli for increased ventilation. Muscle chemoreceptors responding to tissue fluid changes during exercise are also implicated in the hyperventilation.

The hyperkalemia of exercise may also play a role in stimulating arterial chemoreceptors. The hormone adrenaline could also have central actions at the medullary respiratory neurons.

iii. Question:
In anticipation of muscular activity, at the starting block of a 100 m dash, how might respiration be stimulated?
Answer: There must be afferent impulses descending from higher cortical centers that facilitate this effect on the medullary respiratory neurons in the brain stem.

6 High-Altitude Acclimatization

i. Definition: The adjustment at high altitude to provide for an optimal hyperventilation response to compensate for the low atmospheric oxygen.

ii. PTC:
The partial pressure of oxygen decreases with increasing altitude. The fractional concentration of oxygen is unchanged. There is a drop in the barometric atmospheric pressure with altitude. The calculated partial pressure of oxygen (PO_2) in the atmospheric air is then lower.
The inspired air with a decreased PO_2 will lead to a decreased PO_2 in the alveolar air. Lung oxygenation will be limited and the arterial blood PO_2 will only achieve maximally the PO_2 in the alveolar air. The hypoxia is termed a hypoxic hypoxia.
Breathing will be increased in both depth and rate. The hypoxia will stimulate the arterial peripheral chemoreceptors at the carotid/aortic bodies. There will be an increased activity of the medullary respiratory neurons in the brain stem. The expected hyperventilation in both bigger tidal volume and frequency of breathing will soon be opposed by a respiratory alkalosis.
Respiratory alkalosis at high altitude hypoxia results from more carbon dioxide being 'blown out' when the cell metabolism has not increased (alveolar ventilation equation). Carbon dioxide is the more potent chemical stimulus for regulation of respiration. Both the decreased PCO_2 as well as the higher blood pH will suppress respiration, opposing the hypoxic positive stimulus.
Acclimatization in this scenario in order to sustain an adequate hyperventilatory response involves an adjustment to the respiratory alkalosis. The compensation takes a little time and when in operation will lead to the kidneys excreting an alkaline urine. More bicarbonate base is excreted in the urine and this restores the blood pH.
Mountaineers commonly enhance this acclimatization process by promoting urinary bicarbonate excretion. A carbonic anhydrase inhibitor is taken to reduce the reabsorption of filtered bicarbonate at the proximal convoluted tubule. At the proximal tubule, the carbonic anhydrase is present at both the luminal membrane and the cytosol.

iii. Question:
At the alveolar capillary membrane, how is the diffusion of oxygen affected at high altitude?
Answer: Firstly, the gradient for PO_2 will be reduced. The mixed venous PO_2 is unchanged but the alveolar air PO_2 is decreased. The secondary polycythemia at high altitude would help to increase the rate of lung oxygenation (ml/min).

7 Respi-Reno pH Regulation

i. Definition: The integrated functions of the lungs and the kidneys in the maintenance of ECF and blood pH.
ii. PTC:
The cardiovascular system delivers oxygenated blood to the cells and transports deoxygenated venous blood back to the lungs. The cardiovascular circuit is a closed system.
The respiratory system is open to the atmosphere for inspiration of fresh breaths of air and removal of expired air. Besides oxygen and CO_2 carriage, the cardio-respiratory system also has an essential role in the regulation of ECF/blood pH.
Control of ECF pH involves different chemical buffers. The major buffer system in the ECF (plasma and interstitial fluid) is the bicarbonate base/carbonic acid pair. In relation to the pH regulation, this bicarb/carbonic acid buffer is most effective quantitatively as it is an open system. The other chemical buffers e.g. the phosphate ions have a fixed concentration which is depleted when used in buffering.
The bicarb/carbonic acid buffer concentrations can be replenished or 'topped up'. The buffer system is open to both the inputs from respiratory and the renal functions. The carbonic acid denominator in the bicarb/carbonic ratio changes with changes in partial pressure of CO_2.
The renal nephrons contribute to the bicarbonate concentration by both tubular reabsorption of filtered bicarb and tubular synthesis of bicarb.

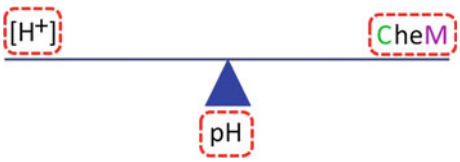

Fig. 1 ECF and blood pH balance is effected against daily net input of acids to the body. The defence is threefold involving extracellular and intracellular CheM buffers that are also linked to the renal and the respiratory functions. The C and M look like the kidney and lungs respectively

Compensation for any non-respiratory (metabolic) causes of pH imbalance is achieved by changes in alveolar ventilation. For example, a metabolic acidosis during diabetic ketoacidosis is associated with stimulated breathing. The ketoacidosis consumes the major bicarb base buffer. To compensate, the arterial PCO_2 is reduced by increased ventilation stimulated via the peripheral chemoreceptors. The acidic pH activates the aortic/carotid chemoreceptors and increased afferent sensory impulses are sent to the respiratory control neurons in the brain stem.

iii. Question:
Besides plasma bicarbonate, what is also a major buffer in blood?
Answer: The hemoglobin in red cells has a significant buffering action in venous blood. The venous blood pH is only slightly acidic during uptake of metabolic CO_2 from the tissues. The hydration of CO_2 inside red cells, catalysed by carbonic anhydrase generates bicarbonate and protons from the carbonic acid. The buffering of hydrogen ions by hemoglobin has the added effect of promoting the dissociation of carbonic acid to bicarbonate, the major species among total CO_2 transported in blood.

Part III
Renal Physiology

Defining Moments in Tubular Fluid and Urine Flow

Renal physiology is not merely about excretion. The kidneys are essential organs that participate in the integrated control of homeostasis of the extracellular fluid. These functions include osmoregulation, sodium, potassium and calcium balance, blood volume/pressure control and pH regulation.

The flow of the glomerular filtrate, modified along the nephrons, to its final exit as urine is linked to these renal homeostatic roles. Clearance is a key concept in renal tubular and urine traffic flow. Since the renal clearance of inulin is used to determine GFR (ml/min), the clearance is also defined not as the amount of solute cleared in urine but instead as the volume of plasma cleared of that solute that is excreted in urine. In normal persons, there is no glucosuria and the glucose clearance is thus, zero ml per min.

In kidneyland, the unidirectional transport of solutes, either reabsorption or secretion, is defined by the polarity of the tubular epithelial cells. The selective location of specific transporters on either the apical or basolateral membrane directs the reabsorption into the peritubular capillary or secretion into the lumen of the nephron. The ubiquitous Na/K ATPase is only localized at the basolateral membrane and the ATPase powers secondary active transport as in the absorption of filtered glucose.

The kidneys have sensors that monitor blood pH and PCO_2. These sensors are then linked to mechanisms that either increases or decreases the secretion of hydrogen ions into the lumen. The major urinary buffers, ammonium and phosphate, are defined not as for ECF buffers to maintain pH. Urinary buffers bind protons and increase the total excretion of acid. The minimum pH of urine can be $\sim$4.0 which represents at least a thousand fold greater concentration of free H^+ than in plasma. The major base, bicarbonate in the ECF, is freely filtered and mostly reabsorbed since on a normal diet, net acid is daily added to the body. The tubular secretion of protons and the tubular reabsorption and synthesis of bicarbonate are not separate events but biochemically linked. The lungs and the kidneys collaborate in pH balance.

The tubular fluid flow contains the two key cations sodium and potassium. For both cations, most of the filtered ions are reabsorbed at the proximal convoluted tubules. Since excess potassium is consumed daily in normal diet, the hormonal, fine control of potassium balance takes place at the collecting ducts via regulated secretion.

By coincidence or design, the same regulatory adrenal steroid hormone, aldosterone acts on the same target principal cells at the collecting ducts to effect potassium and sodium balance. There is no secretion of sodium, and sodium homeostasis is via controlled reabsorption. Sodium balance is not the same as sodium concentration, the latter associated with osmoregulation since sodium concentration (with its *compAnions*, chloride and bicarbonate) are the main determinants of ECF osmolarity. Hypothalamic receptors in the brain function together with the kidneys to maintain water balance or osmolarity control.

Sodium balance is '*sodium*' important for ECF/blood volume and blood pressure control. This is defined as long-term regulation of arterial blood pressure. Urinary sodium flow in our pee is thus essential for our bpee! The neuro-hormonal pathways that maintain sodium balance or homeostasis have the final common pathway in varying the urinary sodium excretion. Hypovolemia will lead to conservation of sodium and a decreased urinary sodium loss.

The cardiorenal integrated pathways include afferent signals from the volume receptors and arterial baroreceptors that in hypovolemia results in a reflex increased renal sympathetic activity as part of general compensatory increase in sympathetic discharge activated from the brainstem. Renal sympathetic action vasoconstricts renal arterioles and decreases GFR and also increases renin secretion. So, the brain directs some of the fluid and sodium flow traffic at the glomerulus and the nephron. The renal blood and fluid traffic flow are monitored, respectively, by intrarenal baroreceptors and the macula densa that together influence renin secretion from the pre-glomerular afferent arteriole.

Chapter 11
Glomerular Filtration and Renal Blood Flow

1 Homeostasis

i. Definition: The regulatory maintenance of the constancy of the extracellular fluid environment of cells by controlled, feedback mechanisms.

ii. PTC:

When asked, 'What are your kidneys for?', the most obvious answer is for excretion by the production of urine. Certainly, that is an essential function of the kidneys where metabolites from both endogenous and exogenous substances are excreted.

A bigger physiologic view of the kidneys is in the essential role of homeostasis. The extracellular fluid, ECF has a variety of parameters that need to be kept relatively constant for normal cell functions. The kidneys are not merely excretory organs. The urine that is produced varies in its composition in the same parameters that are controlled in the ECF.

In other words, homeostatic responses to fluctuations in the parameters in the ECF are reflected in the change in the urine composition as a result of the compensation. For example, in respiratory acidosis, the control of blood pH necessitates the production of a more acidic urine. The ECF pH is regulated at close to pH 7.4, while the urine pH can vary from 4.0 to 8.0.

Another ECF/urine example is the control of sodium balance. A negative sodium balance will soon be rectified by reducing the loss of sodium in the urine. There is much to learn from looking at the urine data. You could call this 'wee-BL' (apologies to problem-based learning enthusiasts!).

In the homeostatic loop, the kidneys in most situations function as one of the effectors of compensatory change in order to normalize the controlled value. This is the case in potassium, and calcium. Osmolarity control is monitored by hypothalamic osmoreceptors. Sodium balance is maintained by different groups of sodium/volume sensors and the kidneys have intrarenal baro- or volume

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sensors. Sensors for pH include the peripheral chemoreceptors as well as sensors at the basolateral membrane of specific cells of the nephron that secrete hydrogen ions and reabsorb/synthesize bicarbonate.

Hypoxic sensing is a key homeostatic activity by certain renal cells that are linked to bone marrow cell formation through the secretion of the renal erythropoietin. In calcium/phosphate regulation, the synthesis of active vitamin D is affected directly by ECF changes in phosphate and calcium.

i. Questions:

Would you consider the kidneys in the glucose homeostasis?

Answer: Although the kidneys reabsorb all the filtered glucose normally, the control of ECF/blood glucose is not a role of the kidneys. The homeostatic regulation of glucose is under pancreatic glucose sensors and pancreatic insulin/glucagon secretion.

2 Bowman's Capsule

i. Definition: The beginning of the nephron where the glomerular filtrate enters from the renal circulation.

ii. PTC:

The glomerular filtrate has basically the same composition as the plasma minus the major plasma proteins (small polypeptides are filterable). The term 'freely-filtered' describes plasma solutes that are not protein bound and are freely-filtered together with the plasma water into the Bowman's capsule.

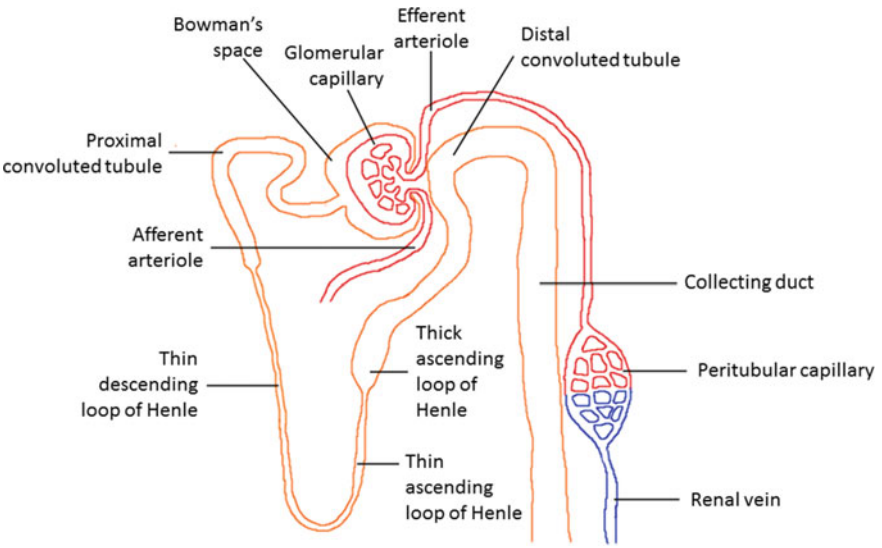

Fig. 1 A simplified version of the structure of a nephron

The concentration of a freely-filtered solute in the filtrate is then equal to the plasma solute concentration.

This means that after filtration, there is no change in the solute concentration in the plasma at the end of the glomerular capillary or in the peritubular capillary. This applies e.g. to both sodium and glucose. For the cation calcium, 40% is plasma protein bound. Calcium is not a freely filtered ion but the filtrate calcium concentration is equal to the free calcium concentration in renal plasma.

The organic solutes are not lipophilic and are carried in blood mostly by plasma proteins. The general formula for calculating the filtration rate of a specific solute is the product of the GFR and the filterable plasma concentration.

The Bowman's capsule containing the plasma-like glomerular filtrate is the starting point of the tubular fluid journey along the nephron. A similar scenario is the gastric chyme that enters the duodenum at the beginning of the intestinal journey. Gastric emptying is a controlled event. The equivalent renal parallel to gastric emptying is the controlled glomerular filtration ('emptying into the Bowman's space). The optimal filtered load of fluid and solute delivered to the rest of the nephron from the proximal convoluted tubule is guarded by renal autoregulation and the glomerulotubular balance.

iii. Question:

What is the concentration of potassium and hydrogen ions in the glomerular filtrate in the Bowman's capsule?

Answer: For freely-filtered potassium, it is the same as in plasma at around 4.5 mmol/L. The glomerular filtrate has the same pH as plasma since the free hydrogen ions in plasma (which determine the plasma pH) enter the Bowman's capsule easily with the filtered plasma.

At the proximal convoluted tubules (PCT), tubular fluid potassium is concentrated by water reabsorption and this enables subsequent passive reabsorption of potassium. For the hydrogen ions, there is no change in the fluid pH since the hydrogen secreted at the PCT is converted to water and carbon dioxide, a reaction catalysed by luminal membrane carbonic anhydrase.

3 Glomerular Filtration Rate

i. Definition: The rate of plasma filtered by all the nephrons in the kidneys.

ii. PTC:

Glomerular filtration rate (GFR) is the rate of filtration at the glomerular capillaries in both kidneys. Unlike some capillary network, there is only filtration at the glomerulus. This is due to the unique balance of Starling's forces at the glomerular capillary. The glomerular hydrostatic pressure does not drop

much along the capillary and this is the main haemodynamic factor that explains why at the glomeruli, only filtration takes place.

GFR has the unit volume/time. The volume is the plasma volume minus the plasma proteins that are too large to be freely filtered. This rate of plasma water filtration in a normal 70 kg, male is around 125 ml/min. In a single day, this value is huge at 180 L of plasma filtered. If the plasma volume in the male above is 3 L, this means that 60 times the total plasma volume is filtered or recycled through the nephrons daily!

The large filtration event depends on a net filtration pressure at the glomerulus. The protein-free filtrate enters the Bowman's capsule. The oncotic pressure in the Bowman's fluid space is thus negligible. The net filtration pressure (netFP) is then the balance between 3 forces, the glomerular hydrostatic/oncotic pressure and the Bowman's capsular hydrostatic pressure. GFR is proportional to the netFP multiplied by the filtration coefficient, Kf.

The coefficient is determined by the total glomerular surface area available for filtration and the *hydraulic* permeability of the filtration membrane. Students should take note that it is not the solute permeability that affects the GFR since GFR is the volume of plasma water filtered/time.

One major parameter that changes the GFR is the renal blood flow (RBF). GFR changes in parallel with GFR. When the RBF decreases, GFR will also decrease. Does the student need to know or is it just 'nice to know' how RBF influences GFR? (an issue for clinical skill competency versus knowledge competency dialogue). Comprehensive physiology texts will emphasize with graphical illustration that changes in RBF alter the mean glomerular oncotic pressure (mGOP) which then changes the netFP.

iii. Question:

In hypovolemia, how would the netFP change?

Answer: In hypovolemia, the renal blood flow will be reduced due to the lower cardiac output. There will be an increase in the mGOP. The net FP will decrease. The expected lower glomerular hydrostatic pressure during hypovolemia also contributes to the reduced netFP. The GFR will be less.

4 Creatinine Clearance

i. Definition: The parameter used clinically to monitor renal function with regards to changes in GFR.

ii. PTC:

Experimentally, GFR is determined by using inulin clearance. Clinically, an endogenous metabolite is used to estimate renal clearance as a measure of GFR. The muscle metabolite, creatinine is the most common in vivo solute used. Although the renal handling of creatinine does not follow exactly that of the unique inulin where filtered inulin load = excreted inulin load, the renal

clearance of creatinine is quite useful to monitor GFR. If GFR drops, the creatinine clearance will also decrease since the excreted creatinine load will be less. Plasma creatinine concentration will be elevated when the GFR is reduced.

In the hospital setting, collection of a 24 h urine to calculate the excreted creatinine rate ($U_X.V$) is not easy for the patients who are often feeling unwell. Thus, the complete renal clearance is often not used but instead, a single plasma creatinine concentration (P_{CR}) is tested. The classic graph shows an inverse relationship between GFR and P_{CR}. The graph does not show a reciprocal, linear line.

Creatinine is released from skeletal muscle at a fairly constant rate. The plasma creatinine is filtered and a little secreted and together excreted in the urine. The P_{CR} is then a balance between the production of muscle creatinine and the removal by the kidneys. When the kidneys do not function well with a decreased GFR, the P_{CR} will be raised.

The initial rise in P_{CR} is gradual with progressive drop in GFR from its normal at 125 ml/min. At GFR about 60 ml/min, the increment in P_{CR} is steep with further lowering of GFR. Thus, the operating range of P_{CR} as a useful indicator of changes in GFR is well observed at the lower GFRs of renal patients.

iii. Question:
How would the clearance of creatinine compare with the actual value of GFR?
Answer: Since there is some tubular secretion of creatinine, the excreted creatinine load used in the clearance formula ($U_X.V/P$) would overestimate the real GFR compared to inulin that is only filtered. Coincidently, the laboratory test for creatinine has some false positives with non-creatinine compounds in plasma. In the clearance formula, this overestimated P_{CR} helps to cancel out some of the overvaluation of GFR.

5 Filtration Fraction

i. Definition: The portion of the renal plasma flow that is glomerularly filtered.
ii. PTC:
The renal blood flow (RBF) is about 20% of the cardiac output at 5 L/min. The plasma portion of RBF would be around 600 ml/min (renal plasma flow, RPF). If we take glomerular filtration rater (GFR) as 120 ml/min, then the filtration fraction will be GFR/RPF at 120/600 or 0.2.

$$FF = \frac{GFR}{RPF}$$

Fig. 2 Filtration fraction, FF is calculated by dividing the glomerular filtration rate, GFR with renal plasma flow, RPF

This significant fraction of filtered protein-free plasma water accounts for the increase in protein plasma concentration along the glomerular capillary. The glomerular oncotic pressure rises along the capillary from 25 mmHg to about 40 mmHg. The greater the filtration fraction, the higher will be the rise in the oncotic pressure. The mean glomerular oncotic pressure is thus used in calculating the net filtration pressure.

The glomerular blood drains into the peritubular capillary network that is in series with the glomerulus, connected by the post-glomerular efferent arteriole. The end glomerular blood will have the same oncotic pressure as the peritubular capillary.

The glomerulus is unique in being sited between two smooth muscle regions of high resistance, the afferent and efferent renal arterioles. Singly, changes in vascular resistance of the pre or the post-glomerular arteriole will affect the filtration fraction differently. Afferent arteriolar constriction will decrease both the GFR and RPF. The filtration fraction remains unchanged.

Vasoconstriction of the downstream post-glomerular, efferent arteriole will tend to decrease the RBF but increase the GFR due to the rise in the glomerular hydrostatic pressure 'upstream'. The filtration fraction is increased. In reality, the renal arterioles vasoconstrict or vasodilate together since both are innervated by renal sympathetic nerves and both arterioles respond to circulating vasoactive agents (e.g. angiotensin II constricts but natriuretic peptides dilate the arterioles).

When both arterioles are constricted concurrently, the reduction in the GFR will be less than the decrease in the RBF. The filtration fraction will be increased.

iii. Question:
How will hypovolemia affect the renal filtration fraction?
Answer: Hypovolemia will be sensed by the arterial baroreceptors. The baroreflex will activate a general increase in sympathetic effector responses. The sympathetic vasoconstriction of both the renal arterioles will reduce the RBF and the GFR. The decrease in the GFR is less than for RBF. Filtration fraction is increased. The end-glomerular and peritubular oncotic pressure are increased. The latter contributes towards the compensatory increase in reabsorption of fluid at the proximal convoluted tubules.

6 Plasma Oncotic Pressure

i. Definition: The osmotic pressure exerted by the non-penetrating plasma proteins at the capillary.

ii. PTC:
The plasma oncotic pressure (POP) or also called colloid osmotic pressure is the osmotic pressure exerted at the capillary network. This POP is due to the

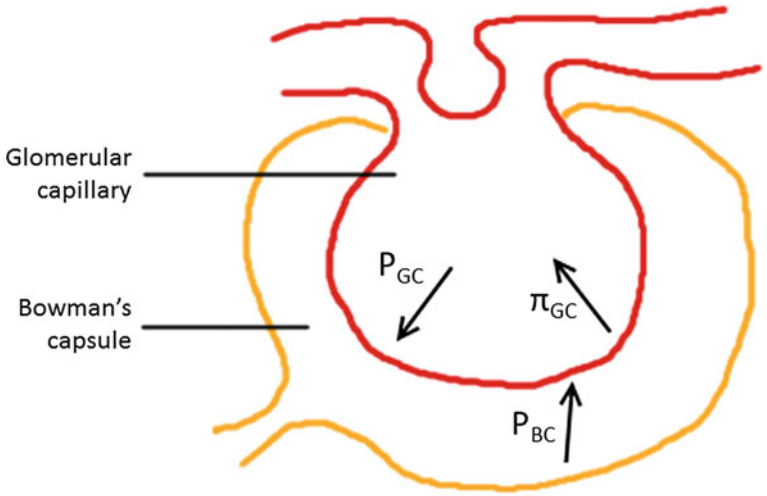

Fig. 3 The glomerular plasma oncotic pressure, π_{GC} and the Bowman's capsular hydrostatic pressure, P_{BC} oppose the filtrative force of the glomerular capillary pressure (P_{GC})

plasma proteins that are not filtered at the capillary like the electrolytes e.g. sodium and chloride. The POP is thus dependent on the plasma protein concentration.

At the cell membrane, the ECF sodium (and its accompanying anions) exerts the major osmotic pressure. At the capillary, the sodium and its associated anions move freely between the plasma and interstitial spaces and therefore, are no longer osmoactive.

The oncotic pressure at the capillary is a very small fraction of the total osmotic pressure operative at the cell membrane. However, it is the essential Starling's force that accounts for the reabsorption of filtered fluid at the venular end of capillaries. The value is 25 mmHg along most capillaries. In the renal glomerular capillary, the POP uniquely increases along the capillary since the filtration fraction is a significant 20% and this concentrates the protein in the glomerulus.

Amino acids, the products of protein digestion do not contribute to the oncotic pressure since amino acids are also freely penetrating at the capillary. This information is noted when we consider how the glomerular filtration rate changes after a protein-rich meal. Proteins are digested and the amino acids are absorbed by the small intestines. The elevated amino acids in postprandial blood does not alter the POP. As such there will not be any increase in the glomerular oncotic pressure with a resulting decrease in net filtration pressure and glomerular filtration rate (GFR).

In reality, an hour after the consumption of a high-protein meal, the GFR actually increases. This is explained by the increased filtered load of amino acids that leads to an activation of the tubuloglomerular feedback. Increased amount of sodium is co-reabsorbed with the amino acids at the proximal

convoluted tubules. The fluid flow downstream at the distal macula densa will now have lower sodium/chloride. The macula densa senses and responds by releasing a paracrine that causes vasodilation (or releases less of a vasoconstrictor paracrine) of the pre-glomerular, afferent arteriole. The renal blood flow increases and so does the GFR after the protein meal.

iii. Question:
How does the observation of an increased GFR with protein meal apply to the care of renal patients?
Answer: Patients with a reduction in functioning nephrons are put on a protein-restricted diet. This is to avoid overloading the remaining healthy nephrons with a high glomerular hydrostatic pressure and net filtration force.

7 Renal Arterioles

i. Definition: The smooth muscle high resistance vascular structures that comprise the afferent, pre-glomerular and the efferent, postglomerular arterioles.

ii. PTC:
The renal circulation is unique is having two arterioles which 'parenthesized' the glomerular capillary. Downstream from post glomerular, efferent arteriole, is the peritubular capillary in series with the glomerulus. The renal arterioles are the major adjustable resistance sites in the renal circulation. Naturally, both the renal arterioles are sensitive to vasoactive agents and both arterioles are also innervated by vasoconstrictor sympathetic fibers.
By their variable resistances, the arterioles contribute to several physiological control events. They function like gatekeepers in renal functions.

a. the **renal blood flow** (RBF) changes with arteriolar resistances. And since the RBF affects glomerular filtration rate (GFR) proportionately, the arterioles control GFR.
b. the **total peripheral resistance** (TPR) component of arterial blood pressure regulation is contributed by the status of renal arteriole. The 'total' here is not inclusive of all regional circulation but is a selective sympathetic vasoconstrictor effect and the renal arterioles is among the targets which include the splanchnic and the cutaneous arterioles.
c. the renal arterioles by their control of GFR are like gatekeepers in also determining the filtered load of solutes. **Filtered solute load** is the product of GFR and the filterable plasma concentration of the solute. Adjusting the filtered sodium load is a compensatory mechanism in sodium homeostasis.
d. Since the peritubular capillary is downstream from the renal arterioles, changes in arteriolar resistances affect the **Starling's peritubular capillary dynamics**. During hypovolemia, increased arteriolar constriction by sympathetic/angiotensin II produce a decrease in the peritubular

hydrostatic pressure. This, in turn, helps to increase the reabsorption of fluid at the proximal convoluted tubules as part of the compensation.

e. Specifically, the afferent, pre-glomerular arteriole are designed to fulfill two roles in renal physiology. One is **autoregulation of RBF** via the myogenic and macula densa mechanisms. The juxtaglomerular cells that secrete renin in response to hypovolemia/hypotension/negative sodium balance are located at the afferent arteriole. Sympathetic fibers stimulate **renin secretion** and paracrines from the macula densa also modulate renin secretion.
So in the **KIDergarten**, when learning the **ALPhyABET** ABC, A should stand for Arterioles.

iii. Question:
How do the arterioles respond in hypervolemia?
Answer: The afferent/efferent arterioles will dilate to lower the TPR. The increase in RBF/GFR will increase the filtered sodium load. The hydrostatic pressure in the peritubular capillary is higher and this decrease the net reabsorption as a compensation for the ECF/blood volume expansion. Renin secretion is suppressed from the afferent arteriole. As usual, the predicted or expected autoregulatory constriction of the afferent arteriole is 'masked' by the physiologic priority for a vasodilation of the renal arterioles to effect the various adjustments during hypervolemia.

8 Renal Clearance

i. Definition: The volume of plasma cleared of a solute per time that has appeared in urine.

ii. PTC:
The term 'clearance' has given some confusion to students as it seems to imply an amount of solute cleared in the urine per time. Perhaps 'renal plasma clearance' might be a more useful terminology as the volume of plasma is highlighted.
Any solute that is found in urine has come from the plasma. The renal clearance is a concept that is interested in the rate of clearance of that solute from plasma. The rate of excretion of a solute X is given by the formula urine concentration of X (U_x) multiplied by urine flow rate (V). The rate of plasma volume cleared of that amount of solute would then be simply $U_x.V$ divided

$$Cx = \frac{Ux \,.\, V}{Px}$$

Fig. 4 Clearance of a substance, C_X is calculated by dividing the mass of the substance excreted through the unit per unit time (given by multiplication of urinary concentration of the substance, U_X to volume of urine per unit time, V), by plasma concentration of the substance, P_X

by the plasma concentration of X (P_x). It can be noted that this volume of plasma is an imagined volume and is not obviously present as a depleted segment of the circulating plasma volume.

The renal clearance is then dependent on the renal handling of the solute. If the filtered solute is neither reabsorbed nor secreted by the renal tubules, then the rate of filtered load (GFR $\times$ P_x) is equal to the rate of excreted load. This is the unique situation with the plant product, inulin. The renal clearance of inulin is thus, used to determine the glomerular filtration rate (GFR), which has a normal value of 125 ml of plasma/min.

If there is net nephron reabsorption of a filtered solute, then the renal clearance of that solute will be less than that for inulin. If there is net tubular secretion, the renal clearance will become greater than for inulin as is the case for secreted organic metabolites.

The unit for renal clearance concept remains as volume of plasma/min. The osmolar clearance is calculated as $U_{Osm} \times V/P_{Osm}$. If the urine osmolarity equals the plasma osmolarity, the osmolar clearance is the value of the urine flow rate. A dilute urine flow is then the sum of the osmolar clearance (C_{Osm}) defined and what is termed the free water clearance (CH_2O).

iii. Question

How does the renal clearance of potassium compare with that for inulin on a normal diet?

Answer: The clearance for potassium is less than for inulin as there is net reabsorption of potassium from the entire nephron. At least 70% of filtered potassium is reabsorbed at the proximal convoluted tubule. Depending on the amount of dietary potassium, there will be varying degrees of active potassium secretion by the collecting ducts under the action of the adrenal mineralocorticoid, aldosterone.

9 Renal Autoregulation

i. Definition: Has the same meaning as for coronary and cerebral circulations where the blood flow is maintained intrinsically by the kidneys over a controlled range of blood pressure changes (60–160 mmHg).

ii. PTC:

Blood perfusion is autoregulated in the cerebral and coronary circulations for metabolic reasons. These essential organs are sensitive to reduction in blood flow that supplies the oxygen and energy substrates. The intrinsic mechanisms include a metabolic vasodilator autoregulatory response.

The kidneys autoregulate its renal blood flow (RBF) not primarily for its metabolic requirements. The nephron functions are relatively resistant to temporary reduction in RBF. In fact, selective sympathetic vasoconstriction of renal arterioles is one of the major vascular contribution to increased total peripheral resistance in reflex compensation during hypovolemia.

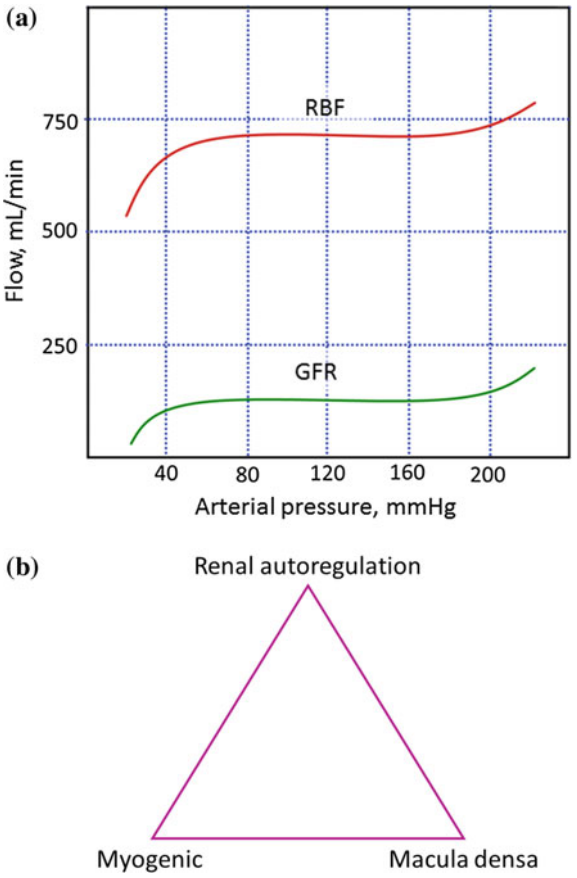

Fig. 5 **a** Within a particular range, renal blood flow, RBF and glomerular filtration rate, GFR are maintained at a constant via autoregulation. **b** Two simultaneous, intrinsic renal mechanisms of renal blood flow comprising of the afferent arteriole (myogenic) and the distal tubule (macula densa)

The renal autoregulation serves a primary role in maintaining a constant GFR and filtered load. By regulating RBF, the GFR is proportionately controlled. This is in the euvolemic situation if there are fluctuations in renal arterial perfusion pressure (variable x- axis in the autoregulation graph). Even when the dominant renal sympathetic constricts the renal arterioles in hypovolemia, the expected vasodilation in autoregulation is 'masked' but still operative. This background vascular tempering can be viewed as a counter response to prevent excessive arteriolar constriction and a potential serious renal ischemia.

The intrinsic nature of renal autoregulation, as first described *in vitro* in the isolated, denervated kidneys indicates that nerve and circulating hormone are not involved in the autoregulation of RBF. Arthur Guyton has a different whole body definition of renal autoregulation and he describes the role of renin, angiotensin II, the efferent arteriole in his autoregulatory scheme.

The two intrinsic autoregulatory pathways are called myogenic and macula densa (MacD) mechanisms. The former involves mechanoreceptor sensing by

the afferent arteriole. The latter includes vaso-active paracrines secreted by MacD to the pre-glomerular afferent arteriole.

iii. Question:
What is the expected renal autoregulatory response in hypervolemia?
Answer: The expanded vascular space will raise the arterial blood pressure. Volume receptor and baroreflexes will diminish the sympathetic effector discharge including the renal sympathetics. The renal arterioles will dilate. The expected, autoregulatory vasoconstrictor response to the hypervolemia is overrided by the priority to normalize the blood pressure.

10 Proteinuria

i. Definition: The presence of proteins in urine detectable by the standard urine dipstick.

ii. PTC:
In normal persons, there is no proteinuria. In the term called microalbuminuria, detectable urinary proteins by more sensitive method than the dipstick is a clinical indicator of perhaps early changes in renal function that is a secondary complication of some cardiovascular diseases e.g. hypertension. Some of the smaller plasma proteins can leak out with the glomerular filtrate. These proteins are endocytosed at the proximal convoluted tubule (PCT). Intracellular digestion releases the component amino acids which are then reabsorbed into the peritubular capillary or reused within the PCT cells.
When proteinuria occurs, the plasma oncotic pressure will decrease. The net filtration pressure will be higher at the arteriolar end of the capillaries in the body. Any net reabsorption at the venular end will be lower. There will then be accumulation of fluid in the interstitial fluid space (edema). The development of edema in proteinuria can worsen if the transcapillary fluid shift into the ISF causes a marked reduction in vascular volume. Hypovolemia will activate the renin-angiotensin-aldosterone system. Retention of sodium and water will then dilute further the plasma protein concentration which determines the oncotic pressure.
Besides proteinuria, a decreased plasma oncotic pressure is also seen in liver disease since the liver is the production site for most of the plasma proteins.

iii. Question:
In nephrotic syndrome where proteinuria occurs, how might a change in dietary sodium help in the edema presentation?
Answer: A low-sodium diet is generally prescribed for such nephrotic patients. A low-sodium diet will tend towards a lower ECF and blood volume. This might maintain an adequate concentration of plasma proteins to exert a sufficient plasma oncotic pressure to prevent edema.

Chapter 12
Tubular Function

1 Renal Handling

i. Definition: The processes that water or any solute undergoes when acted on by the nephrons and these include filtration, reabsorption and/or secretion.

ii. PTC:
The glomerulus together with its associated nephron filters plasma, and the tubules of the nephron either reabsorbs or secretes (or do both) the specific solutes. Only a select few unique solute are untouched (not handled) by the tubules. This is the case with inulin that is just freely filtered and excreted. The unusual renal handling of inulin has allowed the determination of GFR by a relatively easy, non-invasive method using the concept of renal clearance. The knowledge that GFR is such a huge value in normal kidneys led to the understanding that there is no need for the tubular secretion of water to produce the final urine volume. This was previously known as the 'secretion theory of urine formation'.
The renal handling of water is therefore,

$$\text{Excreted Urine/Time} = \text{GFR} - \text{Rate of Reabsorbed Water}$$

Sodium has the same renal handling events as water i.e. sodium is freely filtered and reabsorbed (on average, around 99%). For organic solutes, most are carried as bound to plasma proteins (glucose and amino acids are freely circulating). The free, unbound organic metabolite is filtered and more of the insoluble, protein-bound solute are also passively and actively secreted. There is no problem for bound solute to be secreted as the bound and free forms of the organic solute are in reversible equilibrium. For secreted solutes, the renal handling will be Excreted = Filtered plus Secreted.
There are solutes that are reabsorbed and secreted at different segments of the nephron. Overall, there will be either a Net reabsorption or Net secretion.

H. M. Cheng and F. Jusof, *Defining Physiology: Principles, Themes, Concepts*,
https://doi.org/10.1007/978-981-13-0499-6_12

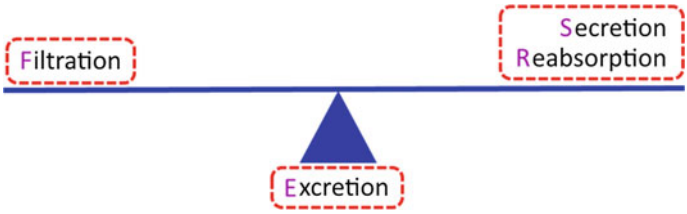

Fig. 1 The renal handling of any solute includes glomerular filtration (F), the tubular reabsorption (R), and/or secretion (S). Excretion (E) is the net urinary balance and is related as E = F − R + S

The renal handling for such solutes will be Excreted = Filtered minus Reabsorbed plus Secreted. Potassium homeostasis involve this profile of renal handling. Urea also has this scenario where the urea recycling between the inner medullary collecting ducts and the loops of the juxtamedullary nephrons include reabsorption and secretion process respectively.

iii. Question:
What do you think is the renal handling of plasma proteins?
Answer: Plasma proteins are mostly large, too big to be freely filtered. The renal handling is no filtration, period. Smaller polypeptides and peptides can be filtered through and some lower molecular weight proteins can leak through occasionally. The amino acids of these solutes are released from their parent molecules by intracellular breakdown after they are endocytosed at the proximal convoluted tubules. The amino acids exit the cells by facilitated transport at the basolateral side of the tubular epithelial cells and enter the peritubular capillary.

2 Downstream Effects

i. Definition: The river flow analogy to describe renal blood flow as well as tubular fluid flow along the nephrons.

ii. PTC:
Viewing the circulation as a river is useful in understanding the effects of vascular resistance. So, if we consider the renal blood flow (RBF) as a 'bloody' river, the effect of changes in the resistance of the afferent or efferent arteriole on RBF is quite easily explained. Vasoconstriction of either afferent or efferent arteriole will reduce the RBF (at whatever point the river flow is obstructed, the downstream flow beyond the point of resistance will be lowered).
The glomerular capillary is sited between the two renal arterioles. The glomerulus is downstream from the pre-glomerular afferent and upstream from the post-glomerular efferent arteriole. As a result, changes in the vascular resistance of each arteriole will have different effects on the glomerular hydrostatic pressure (P_{GC}). Constriction of afferent arteriole will reduce the

downstream P_{GC} but a vasoconstricted efferent arteriole will tend to increase the P_{GC}. When the P_{GC} is altered, the net filtration pressure will change in the same direction.

The tubular fluid flow from the Bowman's capsule to the distal nephron is optimized, so that there are minimal large fluctuations in filtered load. The solute load delivered to the later part of the nephron will then be suited to the capacity of the specific transport handling mechanism. When GFR do fluctuate, the glomerulotubular balance compensates accordingly for this purpose.

If the water and sodium load that reach the collecting ducts are elevated by action of loop diuretics, the downstream effect will be a higher potassium secretion and loss in the urine. The higher sodium concentration in this case, at the collecting ducts will have another downstream effect on the osmotic gradient between the tubular fluid and the hyperosmotic interstitium. The latter interstitial osmolarity is also decreased by action of the loop diuretic on the Na/K/2Cl transporter at the ascending Henle's loop.

iii. Question:

If both the renal arterioles are concurrently vasoconstricted by sympathetic nerve, as they are in vivo, is the change in the glomerular hydrostatic pressure predictable?

Answer: The net effect on the P_{GC} is not easily ascertained. However, the RBF is surely reduced. And the decreased RBF will result in a lower GFR, even if there is no change in the P_{GC}. The RBF affects the GFR via effects on the mean glomerular oncotic pressure (GOP). An increased RBF lowers the mean GOP, thus increasing the GFR and vice versa.

3 Glomerulotubular Balance

i. Definition: The compensatory response of the convoluted proximal tubule to fluctuations in GFR and the filtered load.

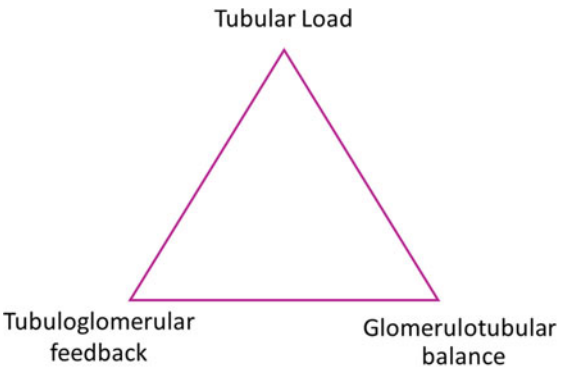

Fig. 2 The glomerulotubular balance is the second line of defence after the tubuloglomerular feedback mechanism for an optimal tubular fluid load

ii. PTC:
The glomerulotubular (g-t) balance sounds similar to the tubuloglomerular (t-g) feedback mechanism. The latter is initiated at the distal tubular macula densa in the renal autoregulation of renal blood flow/GFR. The g-t balance involves instead the proximal tubules.
The g-t balance can be viewed, as insightful proposed by Arthur Vander, as a second line of defence against too much fluctuations in GFR. Renal autoregulation serves to maintain RBF/GFR. But this autoregulatory response to changes in the renal arterial pressure is not perfect and some fluctuations in GFR can still proceed. Changes in GFR will also mean changes in the filtered load as given by GFR $\times$ P_X.
The g-t balance comes into play when there are acute changes in GFR. A sudden increase in filtered load will be accompanied by an increase in proximal tubule reabsorption of sodium and water. The peritubular capillary dynamics accounts for the g-t balance.
Assume that a surge in GFR occurs. Acutely if the renal blood flow is unchanged, there is an increased filtration fraction (FF). The end-glomerular and hence, the peritubular oncotic pressure will be higher. The higher FF will reduce the peritubular hydrostatic pressure. The change in these Starling's forces in the peritubular capillary will thus favour a greater reabsorptive pressure.
The student should bear in mind that the g-t balance operates only in euvolemia as nicely explained in Berne and Levy's Physiology text. In hypovolemia, the reflex responses will predominate and masked the g-t phenomenon. This is the same renal picture for renal autoregulation which is overrided in hypovolemia by the dominant renal sympathetic activity.
In hypovolemia, there will be a compensatory decrease in GFR, to conserve sodium and fluid. In addition, there will be an increase (not decrease as would occur in g-t balance) in sodium and water reabsorption from the proximal convoluted tubule. Both renal sympathetic nerve and circulating angiotensin II action increase the tubular sodium reabsorption. A greater isosmotic reabsorption of water follows.

iii. Question:
In hypervolemia, why is the g-t balance non-operative?
Answer: In volume expansion of the blood space, the GFR will increase. Compensatory decrease in reabsorption of sodium and water will occur at the proximal convoluted tubule. This is to promote more sodium and water excretion in order to normalize the blood volume.

4 Peritubular Capillary Dynamics

i. Definition: The Starling's hydrostatic and oncotic pressures at the network of peritubular capillaries that are arranged in series and downstream from the glomerular capillaries.

ii. PTC:

The renal vasculature is unique in having two sets of capillary in series, the glomerulus and the peritubular capillary that is associated with the nephronic tubules. The peritubular capillary Starling's forces are different from those in the glomerulus that is dedicated to the function of filtration. There is a net filtration pressure along the glomerulus, decreasing towards the post-glomerular efferent end of the capillary.

The peritubular capillary is 'downstream' from the glomerulus and joined by the smooth muscular efferent arteriole. There is a sharp drop in blood pressure at both the pre-glomerular afferent arteriole and the efferent arteriole where both the vascular resistances are highest. The hydrostatic pressure in the peritubular capillary is thus significantly lower than the end glomerular hydrostatic pressure (there is only a slight drop in hydrostatic pressure along the glomerulus due to the efferent arteriolar resistance).

The oncotic pressure along the glomerulus significantly increases due to the filtration fraction at the normal value of 0.2. The peritubular oncotic pressure is then the elevated oncotic pressure in the glomerulus at about 40 mmHg.

Along the length of the peritubular capillary, there is then, an oncotic pressure that is higher than the hydrostatic pressure. There is a net reabsorptive force in the peritubular capillary that is appropriate to its functions in fluid and solute reabsorption. The intrinsic glomerulotubular balance that matches any fluctuations in GFR with the proximal convoluted tubular reabsorption is effected by the corresponding changes in Starling's dynamics at the peritubular capillary.

At the juxtamedullary nephrons, the peritubular capillary is called the vasa recta with long loop of descending and ascending capillary that courses along the long nephrons that penetrate towards the inner renal medulla. The counter current vasa recta blood flow, in conjunction with the countercurrent fluid flow in the juxtamedullary loop of Henle generates a hyperosmotic, stratified interstitium that is essential in water balance regulation.

iii. Question:

How might increased renal arteriolar resistance occur during sympathetic stimulation affect the peritubular Starling's forces?

Answer: In hypovolemia for example, the sympathetic general discharge is increased due to baroreceptor reflex. The downstream peritubular capillary will have a further decrease in hydrostatic pressure. Renal sympathetic vasoconstriction also tend to increase the filtration fraction (less reduction in GFR compared to the decrease in RBF). This will elevate further the plasma oncotic pressure in both the glomerulus and the peritubular capillary. The net reabsorptive force becomes greater in the peritubular capillary and this helps to compensate for the hypovolemia.

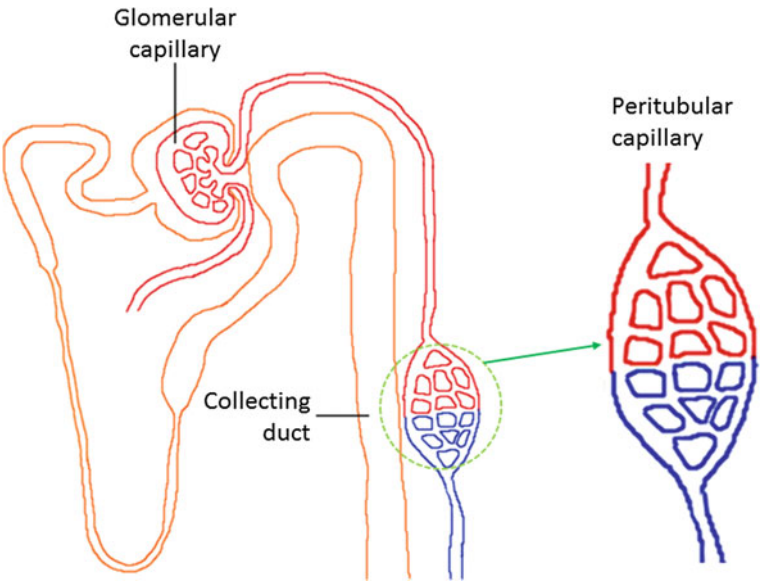

Fig. 3 A simplified representation of the peritubular capillary network, arranged in series with the glomerulus is the site of tubular reabsorption and secretion

5 Clearance of PAH

i. Definition: The clearance of para-amino hippuric acid (PAH) derived from using Fick's principle is used to determine the effective renal plasma flow.
ii. PTC:
Renal blood flow is about 20% of normal cardiac output. The renal blood flow can be determined from a measure of the renal plasma flow and the known hematocrit of the volunteer. Specifically, the effective renal plasma flow (ERPF) can be quite accurately estimated by calculating for the renal clearance of PAH. Effective here refers to the predominant plasma flow that is filtered since a small fraction of renal plasma flow is not supplied to the nephrons.

$$ERPF = \frac{U_{PAH} \cdot V}{P_{PAH}}$$

Fig. 4 Para-aminohippuric acid, PAH is completely filtered and secreted in one renal blood circuit flow. Therefore, effective renal plasma flow, ERPF can be determined by calculating the clearance of PAH, C_{PAH} where urinary concentration of PAH, U_{PAH} is multiplied by volume of urine per unit time, V divided by plasma concentration of PAH, P_{PAH}

Fick's principle is used to determine any regional blood flow using different parameters or markers. Applying the law of conservation of mass, the total delivery rate of a solute to a tissue in the arterial blood is equal to the rate of venous exit of the solute plus the rate of extraction or usage by the tissues. Fick's principle is used to determine cardiac output/pulmonary blood flow by using oxygen as the marker. In the kidneys, the rate of removal of the solute PAH by the kidneys will be the excreted load of PAH, i.e. $U_{PAH} \times V$. The rate of supply of PAH is given by the ERPF $\times$ P_{PAH} where P_{PAH} is the arterial blood concentration of PAH given. When PAH is used at a certain low concentration, all the PAH is removed by filtration and secretion in one renal blood circuit flow. The renal venous PAH concentration will be zero and thus the equation for Fick's principle is simplified.

The ERPF $\times$ P_{PAH} is then equal to $U_{PAH} \times V$.

The ERPF will be $U_{PAH} \times V/P_{PAH}$. This is the renal clearance (Ux.V/Px) of PAH.

iii. Question:

How are the renal clearances of two different solutes used to provide a value of the filtration fraction?

Answer: Filtration fraction (FF) is the glomerular filtration rate as a fraction of the effective renal plasma flow to all the nephrons. Thus, FF is equal to the Clearance of inulin/Clearance of PAH.

6 Tubular Secretion

i. Definition: The transfer or transport of solutes from the peritubular capillary blood to the tubular fluid

ii. PTC:

The tubular secretion can be active or passive. The active secretion is transepithelial and the passive secretion is generally para-cellular. The renal handling of organic solutes are by filtration and secretion. Most organic solutes are either weak acids or bases and the source is either from endogenous metabolism or exogenous in the diet. Since a lot of organic solutes are hydrophobic, they are transported bound to plasma proteins.

The unbound free form of the organic solutes is filtered. The free form is in equilibrium with the protein-bound. As the free form is secreted, more of the bound form will be released.

The secretion of organic anions or cations is achieved by a complex system of membrane transporters at both the basolateral and apical/luminal membranes. Tertiary and even quaternary active transport mechanisms are involved in the tubular secretion of these organic substances. The membrane transporters are polyspecific to receive and bind a wide range of either organic cations or anions for secretion. This makes physio-economic sense. The membrane transporters

exhibit the usual characteristic of saturability and binding competition (the latter applied in the use of hippurate to prolong the half-life of penicillin before the antibiotic is secreted, a pharmacologic innovation for drug scarcity during earlier wars).

Each organic solute can be both actively and passive secreted. For the passive pathway, two major factors influence the rate of secretion. The flow rate of the tubular fluid affects the rate of passive secretion. Increased flow rate keep the local tubular concentration low and the gradient for passive secretion is enhanced. For all solutes that are passively secreted, this flow rate positive effect is observed e.g. potassium secretion at the collecting ducts. For passive solute reabsorption, a negative effect of flow rate is seen e.g. urea at the proximal convoluted tubule.

A second factor that alters the passive secretion of organic solutes is the pH of the tubular fluid. Alkalization of the tubular fluid promotes secretion and excretion of organic acids (applied in bicarbonate administration for salicylic overdose). The mechanism of the pH effect is via 'diffusion trapping' within the tubular fluid, of the charged species of salicylate.

Secretion does not always lead to the excretion of the solute. The best example is hydrogen ions, where the secreted protons at the proximal convoluted tubule is converted to water and CO_2 instead of being excreted.

iii. Question:
What two factors favor excretion of creatinine?
Answer: Creatinine is an organic cation. It is filtered and also secreted by the organic cation transporter complex. For the passive secretion of creatinine, an increased flow rate and acidic urine will both enhance its secretion and excretion.

7 Proximal Urea Transport

i. Definition: The passive reabsorption of filtered urea at the proximal convoluted tubules in normal persons.

ii. PTC:
Generally, organic metabolites are filtered and secreted by the nephrons and excreted into the urine. The solute urea, a product of protein metabolism, is unusual in that about 50% of filtered urea is normally also reabsorbed at the proximal convoluted tubules (PCT). The reabsorption is passive and is mediated by facilitated urea transporters (UT) at the luminal surface of the PCT.

$$C_{Urea} = \frac{U_{Urea}}{P_{Urea}}$$

Fig. 5 The clearance for urea (ml plasma/min), C_{Urea} would be the excreted urea (mg/min), U_{Urea} divided by plasma concentration of urea (mg/ml), P_{Urea}

The passive movement of urea requires a concentration gradient. The urea concentration is increased in the later PCT segment by prior isosmotic water reabsorption.

There is little renal handling of the urea in the tubular fluid as it travels along the loop of Henle and descends again into the collecting ducts. If the body is well hydrated, the excretion rate of urea is more. This is because the collecting ducts remain impermeable to urea in normal water balance.

However, in negative water balance, the action of vasopressin not only increases the water permeability of the collecting ducts, it also increases the urea permeability at the inner medullary collecting ducts (imCD). Urea is then reabsorbed at the imCD and secreted again into the Henle's loop from the renal interstitium. This initiates what is known as urea recycling and this 'merry-go-round of urea' adds to the hyperosmolarity of the renal interstitium that reaches a maximum of 1200 mOsm/L.

In dehydration, the urine urea concentration is increased when the excreted urine is smaller in volume.

When GFR is reduced in renal dysfunction, the PCT reabsorptive function may still be normal for a time. This means that a greater fraction of the reduced glomerular filtrate flow is reabsorbed. This concentrates the tubular fluid urea more than usual and a larger urea chemical gradient is generated. Therefore, in renal GFR failure, there is an abnormal increase in urea reabsorption at the PCT. This contributes to the uremia in the renal disease.

iii. Question:
Why do you think it is important that vasopressin increases the permeability of the collecting ducts to both urea and water simultaneously?
Answer: If urea remains in the tubular fluid, it will be 'non-penetrating' and 'osmoactive' at the collecting ducts. The urea in the lumen of the collecting ducts will osmotically oppose the reabsorption of water facilitated by vasopressin.

8 Flow-Dependent Tubular Transport

i. Definition: The influence of the rate of tubular fluid flow on the passive processes of tubular reabsorption and secretion.
ii. PTC:
Physiology is all about flows. Blood must flow or the oxygenated blood is useless. Pulmonary ventilation sustains airflow. There is also the perfusion-limited phenomenon at the air/blood interface during oxygenation. In the kidneys, nephron functions include the renal handling events of filtration, reabsorption and secretion. There is renal blood flow that is tied to GFR. As the filtrate flows along the nephron, reabsorption and/or secretion of solutes take place.

The fluid flow diminishes from the huge GFR of 180 L per day to the urine output of around 1.5 L per day, less than 1% of GFR. Water is only reabsorbed and never secreted by the tubules (the secretion theory of urine volume is an obsolete 19th century hypothesis).

For solutes that are passively reabsorbed or secreted, the tubular fluid flow affects the process. The flow affects the concentration gradient for the passive secretion or reabsorption.

Urea excretion rate (the $U_{Urea}.V$) is increased when the urine output is higher. Conversely, when the GFR is reduced in renal problems and the urine output decreased, the urea excreted load is less. Uremia is a consequence. When the GFR and the tubular fluid flow is decreased at the PCT, the urea reabsorption is actually enhanced.

For passive secretion of organic solutes, a greater fluid flow promotes secretion into the lumen. A greater flow maintains a low solute concentration in the lumen and thus, a steeper gradient for the passive solute diffusion.

Potassium secretion at the collecting ducts is influenced by the tubular fluid flow. This effect is on the passive, luminal second step of transtubular potassium secretion. This accounts for the secondary hyperkaliuria during increased tubular fluid/urine production induced by loop diuretics.

A parallel flow-dependency is noted in the intestinal handling of the luminal contents. An abnormal faster transit time will reduce the intestinal absorption of solutes and water. A hypermotility diarrhoea results.

iii. Question:

In the peritubular capillary of the vasa recta, how is flow-dependency important?

Answer: Besides its countercurrent structure and permeability to NaCl, urea and water in the medullary interstitium, the relatively slow vasa recta blood flow rate serves its essential function as a countercurrent passive exchange. This role preserves the osmotic stratification in the renal medulla that is important during compensation for negative water balance.

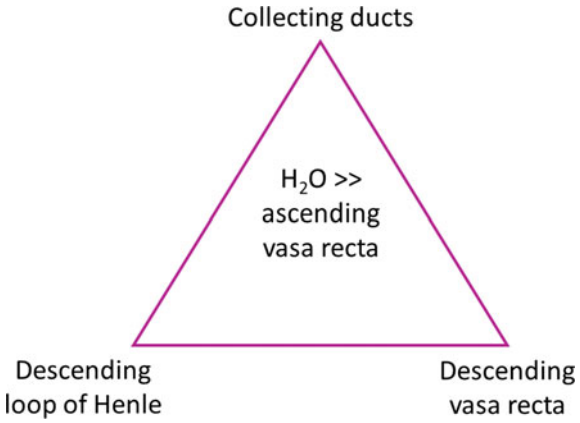

Fig. 6 Water reabsorbed from the three nephronic sites enter the peritubular ascending vasa recta

9 Renal Plasma Threshold

i. Definition: The plasma concentration of a solute above which, the tubular transporter mechanism for its reabsorption is saturated.

ii. PTC:

This threshold term is most familiar in the renal handling of glucose. The reabsorption of filtered glucose is complete at the proximal convoluted tubule. There is no glucosuria in a normal person. The transport mechanism of glucose is identical to the reabsorption of glucose from the lumen of the intestines, using a secondary active transport pathway. The first step of the trans-epithelial reabsorption of filtered glucose across the luminal membrane of the tubular cell is achieved by a sodium-glucose symporter.

At the normal range of plasma glucose, the rate of filtered glucose (also called filtered 'load') is below the maximal tubular rate of glucose reabsorption by the secondary active mechanism. The activity of the basolateral Na/K ATPase uses energy to maintain a potential energy electrochemical sodium gradient for the operation of the Na/glucose co-transporter at the luminal membrane.

Even if the diet is rich in carbohydrates, the rapid insulin response to the postprandial hyperglycemia keeps the filtered glucose load under the upper limit of tubular reabsorption.

In diabetes mellitus, when the insulin action is deficient, the plasma glucose concentration rises much higher than normal. An upper plasma concentration limit is soon reached where the increased filtered glucose saturate all the glucose/sodium symporter.

Any further increase in the plasma concentration will mean that some filtered glucose will remain in the tubular fluid and be excreted in urine. The plasma glucose concentration, above which glucosuria occurs is named the 'renal plasma threshold for glucose'.

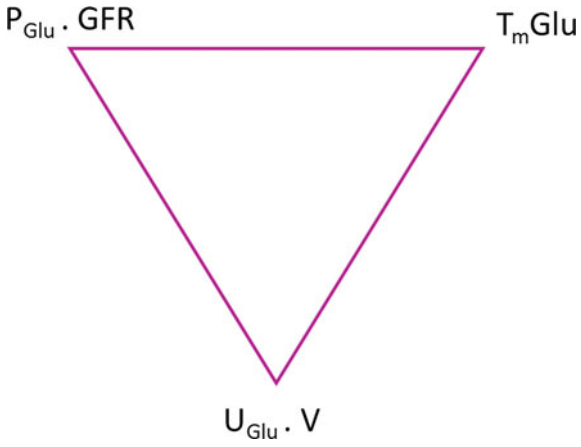

Fig. 7 The threshold for the occurrence of glucosuria is the plasma concentration of glucose, P_{Glu} when the filtered load of glucose exceeds the maximal tubular reabsorption of glucose, TmGlu. GFR, Glomerular filtration rate; U_{Glu}, Urinary glucose concentration; V, Urine flow rate

More specifically, the matching point is between the rate of filtered glucose and the maximal rate of tubular glucose reabsorption (called transport maximum for glucose T_mGlu). Since the filtered rate or filtered 'load' is given by glomerular filtration rate, GFR multiply by the plasma glucose concentration, the relationship is $GFR \times P_{Glu} = T_mGlu$ when P_{Glu} is the renal plasma threshold for glucose.
Theoretically, the concept of a renal plasma threshold can be applied to other filtered solutes that are also reabsorbed by a saturable tubular transporter mechanism. It should also apply to saturable, transporter-mediated secretion process by the tubules. However, the term is best understood in the common clinical problems of diabetes mellitus where glucosuria is a distinguishing parameter when the plasma threshold is exceeded. (Hypercalciuria in primary hyperparathyroidism is another less common example where the plasma calcium overshoots above its renal plasma concentration threshold).

iii. Question:
If glucosuria is not present in a chronic diabetic although the usual plasma threshold is exceeded, what could this indicate?
Answer: Renal complications are common in diabetes when the hyperglycemia is poorly controlled. The GFR becomes abnormal. The tubular transport functions (T_mGlu) can be unaffected before the reduction in GFR. As a result, the renal plasma threshold for glucose, P_{Glu} is elevated. The relationship is still $GFR \times P_{Glu} = T_mGlu$.

10 Transepithelial Potential

i. Definition: The electrical negativity or positivity that is also a driving force for the ionic flux or transport at the renal tubular epithelial cells.

ii. PTC:
Transport at the renal tubules of the nephron can occur through the epithelial cells or between them. This is described as transcellular/transepithelial and paracellular respectively. The passive diffusion or flux of electrolytes via the paracellular route is also influenced by the electrical potential across the epithelial cells.
At the proximal convoluted tubule (PCT), a large portion of filtered sodium cations is reabsorbed. Most of the sodium enter the cell by symporters and also antiporters. Some of the cotransporters are neutral, e.g. for sodium/phosphate. The sodium/glucose cotransporter however is electrogenic, meaning that a small negativity is produced in the luminal surface when the sodium cation enters with the neutral monosaccharide. This lumen negative potential helps to drive the paracellular diffusion of chloride anions at the late segment of the PCT. At the ascending loop of Henle, a positive lumen potential drives the paracellular reabsorption of calcium cations. This positivity is generated by the activity of the

neutral transport Na/K/2Cl and subsequent back diffusion of potassium cations into the lumen.

This electrical phenomenon is also encountered at the principal cells at the collecting ducts where both sodium and potassium are handled. The principal cells tend to secrete more potassium when there is an increased sodium load in the tubular fluid arriving at the cell. An increased reabsorption of sodium cations, via sodium channels leave behind lumen negativity. Intracellular efflux of potassium cations into the lumen is thus enhanced.

iii. Question:
Is the sodium/chloride symporter at the distal tubule an electrogenic transporter?
Answer: Since one sodium cation enters together with one chloride anion, no change in luminal potential is generated.

11 ATPase and Nephronic Sodium Transport

i. Definition: The different transepithelial reabsorption of sodium along the nephron shares or uses the common sodium/potassium ATPase at the baso-lateral membrane.

ii. PTC:
The filtered sodium is reabsorbed along the nephron. The is no transepithelial secretion of sodium from the peritubular capillary into the lumen. The mode of entry of tubular fluid sodium across the luminal membrane varies along the nephron.

At the proximal convoluted tubule, sodium enters the tubular cell coupled to other filtered solutes. The solutes include glucose, galactose, amino acids, phosphate which transverse the luminal surface with sodium symporters. The antiporter for sodium/hydrogen also brings sodium into the cell.

At the descending loop of Henle, there are no membrane transporters for sodium and sodium is concentrated in the tubular fluid as water alone is reabsorbed. At the ascending loop of Henle, the thick segment has a triple co-transporter for Na/K/Cl on the luminal membrane. Upstream, the thin portion of Henle's loop also passively reabsorbs sodium from the tubular fluid.

At the distal tubule, a cotransporter for sodium and its 'comp-anion', chloride enters the cell together. The principal cell at the collecting ducts have sodium ion channels at the apical/luminal membrane for influx diffusion of sodium.

The sodium/potassium ATPase is crucial for the transepithelial reabsorption of sodium from the tubular fluid into the peritubular capillary blood. The entry of sodium at the luminal side employs various membrane transporters/channels.

Once within the tubular cell, the second step of sodium exiting at the basolateral membrane is driven by the same Na/K ATPase at All parts of the nephron.

The interstitial sodium concentration is about ten times higher than the intracellular sodium. Energy is needed and the Na/K ATPase powers this efflux of sodium at the basolateral membrane. In the KIDergarten, A is for ATPase!
Glomerular filtration is a passive process. However the reabsorption of sodium is active and oxygen consumption is proportionate to this tubular transport. Except for the entry via sodium channels at the principal cell, the other modes of sodium trans-epithelial reabsorption are examples of secondary active, sodium-linked transport.

iii. Question:
Is the luminal step for sodium entry from the fluid into the tubular cell active or passive?
Answer: In all secondary active transport in epithelial cells (renal, intestinal etc.), the luminal first step by facilitated carriers/ion channel is passive. In sodium-coupled entry, the electrochemical sodium gradient is generated with active pumping by the basolateral Na/K ATPase.

Chapter 13
Sodium and Potassium Balance

1 Sodium Balance

i. Definition: The total body sodium in particular that in the extracellular fluid.
ii. PTC:
Sodium balance can also be termed sodium homeostasis. This is different from the control of sodium concentration. The concentration of sodium is related instead to water balance and osmoregulation.
Sodium is the major cation in the extracellular fluid (ECF) at around 140 mmol/L. The intracellular fluid (ICF) sodium is ten times less at 14 mmol/L. Most of the total body sodium is in the ECF. For a male adult of 70 kg, the ECF is 14 L and the ICF is 28 L. The amount of ECF sodium is then 1960 mmoles and the ICF sodium will be 392 mmoles.
The ECF sodium determines the ECF volume since sodium is the main determinant of ECF osmolarity. What this means is that if there is a change in diet to a high sodium food, the ECF volume will be the new equilibrium. Although there will be an initial increase in ECF osmolarity, the osmoregulation is rapid and normal osmolarity is achieved at the expense of a higher ECF volume.
The students should note that changes in sodium concentration is not a reflection of the sodium balance status. Rather hypernatremia or hyponatremia is often due to changes in water balance (e.g. drinking a large volume of water gives a positive water balance with hyponatremia, i.e. hypotonic expansion of the ECF). Here, the overhydrated person has unchanged total body sodium or sodium balance. A few other examples will emphasize further this essential non-equivalence between sodium concentration and sodium balance.
If a volunteer consumes a large volume of isotonic saline (isotonic expansion of ECF), there is no change in sodium concentration but extra sodium has been added to the body to produce a positive sodium balance. Another situation is blood donation (isotonic contraction of ECF). There is no change in ECF/

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blood sodium concentration in the donor but there is now a reduction in the total sodium in the ECF. A negative sodium balance has occurred.
The ECF can be hypernatremic and yet the status is a negative sodium balance. This is the common situation during dehydration or exercise. In sweating, more water than electrolyte, mainly sodium and chloride is lost in the hypotonic sweat (hypertonic contraction). There is both negative water and negative sodium balance.
In normal persons with intact control mechanisms for water and sodium balance, a hypotonic contraction never occurs. This ECF status is seen in patients with primary deficiency of mineralocorticoids. There is both urinary sodium and water loss.

iii. Question:
If you eat a packet of salty snack and have no access to water, how does your ECF sodium and water status change?
Answer: The ECF becomes hypernatremic/hypertonic and water shifts from the ICF to the ECF until an equilibrium osmolarity (still above normal) between ICF and ECF is reached (initial hypertonic expansion). Osmoregulation will then respond to the hyperosmotic ECF and reabsorb more water at the kidneys. The eventual ECF will be isotonically expanded (positive sodium and positive water balance).

2 Juxtaglomerular Apparatus

i. Definition: The renal functional structure that comprises the pre-glomerular, afferent arteriole and the macula densa of the distal tubule.

ii. PTC:
The word 'juxta' means 'next to or appose to'. The juxtamedullary nephrons refer then to the 15% of nephron population that have their glomeruli just next to the renal medullary zone. The juxtaglomerular (JG) apparatus has the smooth muscle afferent arteriole in proximity to the macula densa area of the distal tubule as the loop of Henle makes a U-turn and a part of the tubule just beyond the ascending loop makes contact with the afferent arteriole.
The granular cells in the afferent arteriole are called JG cells which secrete renin, a hormone that participates in sodium homeostasis and blood volume control.
The JG apparatus has two functions. First, it is involved in the mechanism to maintain renal blood flow, called renal autoregulation. This is an intrinsinc mechanism and does not require intact innervations or action by circulating hormones.
The second role of JG apparatus is in the regulation of sodium balance. Control of this dominant cation in the ECF is part of the homeostatic pathways

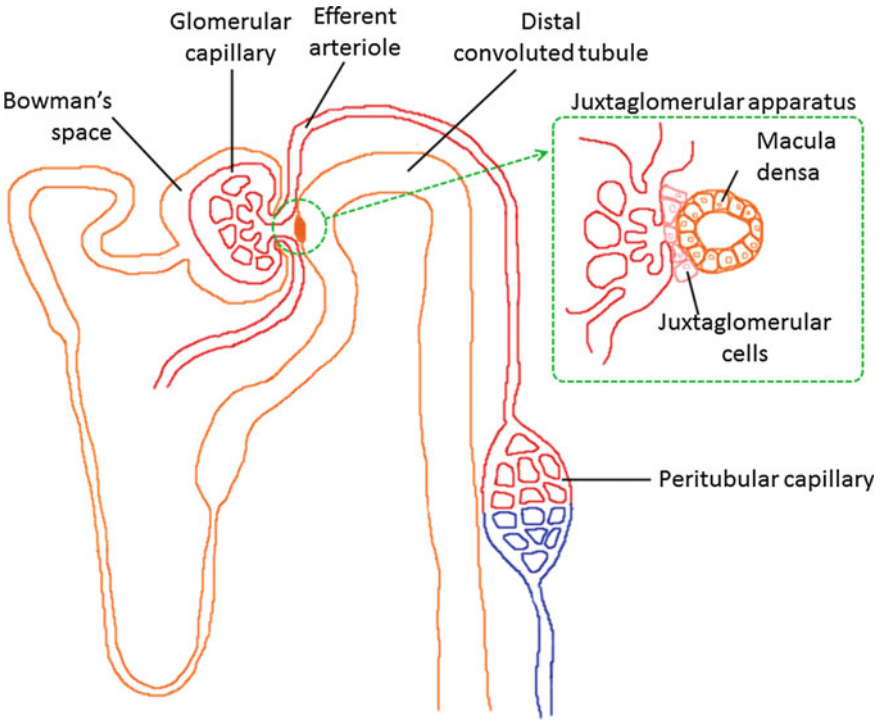

Fig. 1 The juxtaglomerular apparatus is made up of the pre-glomerular, afferent arteriole, juxtaglomerular cells and the macula densa

for maintaining normal ECF/blood volume. Extrinsic renal sympathetic nerve stimulates renin secretion.

In renal autoregulation, the macula densa is the sensor for changes in the distal tubular fluid composition that reflects changes in GFR, 'upstream' at Bowman capsule end of the nephron. The macula densa secretes a paracrine that vasoconstricts the afferent arteriole and increases the vascular resistance to renal blood flow (a paracrine vasodilator could also be a signal from the macula sense). Less of a constrictor or less dilator will produce vasodilation or vasoconstriction respectively.

The separate 2nd signal from the macula densa (McD) is a renin secretion modulator (rsm). The macula densa will send the two signals appropriately in response to any change in blood volume or pressure. In hypervolemia, the McD will release the paracrine vasoconstrictor to help normalize the RBF. At the same time, the Rsm will decrease the renin secretion from the JG cells, since the hypervolemia should be compensated for by an inhibition of the renin-angiotensin-aldosterone reactions that will retain more sodium and water in the body.

iii. Questions:
In hypovolemia, what type of messages does the afferent arteriole receive from her neighbour, Mark Kula (McD)?
Answer: The intrinsic autoregulation of renal blood flow/GFR will tend to inhibit the secretion of the paracrine vasoconstrictor (or more vasodilator or both together) from the McD. The need to restore and achieve euvolemia will mean that the McD will stimulate the JG cells to release renin. Students should note that overall, a systemic, circulating vasoconstrictor, angiotensin II will be increased while the local, renal paracrine constrictor will be inhibited. In vivo, the action of the circulating vasoconstrictor in this scenario will 'override or mask' the paracrine, autoregulatory local vasodilation response.

3 Renal Perfusion Pressure

i. Definition: The renal arterial pressure that is the driving pressure for the perfusion or blood flow in the renal circulation.
ii. PTC:
Occasionally, I encounter students in my office or during writing exams that read 'perfusion' pressure as meaning 'filtration pressure that drives the *perfusion* of fluid from plasma to the Bowman's capsule'. If students remember their respiratory physiology, the same word 'perfusion' is used in the concept of ventilation/perfusion when pulmonary blood flow is meant by the denominator in the ratio.
In renal autoregulation, the x-axis is the renal arterial or perfusion pressure. Autoregulation is thus, defined as the intrinsic capacity of the kidneys to maintain a relatively constant renal blood flow (RBF) when the renal arterial/

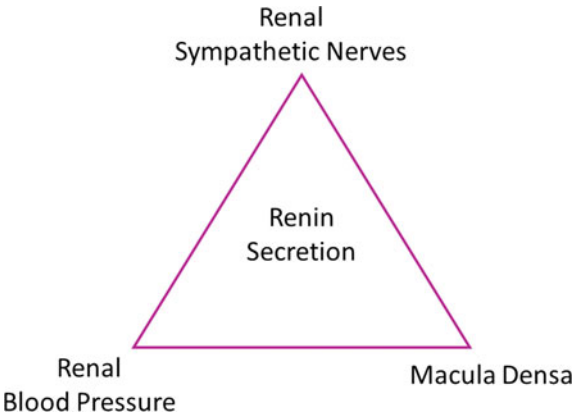

Fig. 2 The renal perfusion or blood pressure directly affects the secretion of renin which is also under sympathetic nerve action

perfusion pressure fluctuates within a certain pressure range (~60–160 mmHg).

In the myogenic mechanism of autoregulation of RBF/GFR, the pre-glomerular afferent arteriole is said to be responsive to the renal perfusion/arterial pressure. Increased renal perfusion pressure (RPP) will stretch the smooth muscular arteriole and trigger a myogenic contraction to produce a compensatory increase in the vascular resistance to RBF.

In the context of sodium balance and ECF volume regulation, intrarenal baroreceptors are volume sensors at the afferent arteriole. These mechanoreceptors may overlap with the receptors in the myogenic mechanism. When the RPP decreases either from a drop in blood volume or a weakened cardiac output, detection by the renal baroreceptors results in an increase in the release of renin from the juxtaglomerular cells.

The renin-angiotensin-aldosterone sequence of hormones is activated to restore the sodium balance/blood volume and hence, the RPP (in the case of cardiac failure, when blood volume is normal, the kidneys still faithfully respond to the reduced RPP in the same manner, and this causes sodium and fluid retention but the RPP remains low due to the cardiac pump failure).

iii. Question:
How does an increase in renal perfusion pressure affect the afferent arteriole in two physiologic ways?
Answer: The pressure sensors at the afferent arteriole will be stimulated by the higher renal arterial pressure. A myogenic contractile response occurs. The raised RPP will directly inhibit the secretion of renin. Note that the intrarenal baroreceptors are not part of any reflex loop that involves an effector sympathetic autonomic response.

4 Long-Term Blood Pressure Control

i. Definition: The regulation of arterial blood pressure via the maintenance of blood volume.

ii. PTC:
Blood pressure control are discussed in standard textbooks as involving mechanisms under ‘short-term’ and ‘long-term’ responses. Short-term and immediate, neurally-mediated reflexes that ensures the continual life of the person. In reversible circulatory shock due to loss of blood volume, mediation by pressure sensors (baroreceptors) detect and activate baroreflexes to produce compensatory changes in the heart rate, stroke volume and peripheral resistance. The person survive the drop in the blood perfusion pressure.

In hypotension due to hypovolemia, the blood volume has to be recovered to restore normal cardiac output and blood pressure. To achieve euvolemia takes time and the hormones involved are all parked under ‘long-term’ pressure

control. The renin-angiotensin-aldosterone system (RAAS) is a major effector in this later sequence in blood pressure maintenance.

The student however should not become too compartmentalized in these two temporal descriptions of blood pressure control. The baroreceptor sensing triggers a general increase in sympathetic discharge which includes the renal sympathetic action to the renal arterioles. The arteriolar vasoconstriction is part of the compensatory increase in total peripheral resistance (TPR) [Blood Pressure = Cardiac Output × TPR]. The renal arteriolar constriction is augmented by the angiotensin II component in the RAAS cascade reactions in plasma.

The immediate renal sympathetic input also leads to subsequent events grouped under 'long-term'. The GFR is reduced with attending decrease in the filtered sodium load. The renin secretion from the juxtaglomerular cells at the afferent arteriole is also stimulated by the sympathetic nerve.

The hormone vasopressin from the posterior pituitary also helps to conserve the water by increasing reabsorption at the collecting ducts. The immediate sensory responses from both the baro- and volume receptors increase afferent impulses that impinge on the secretory mechanism of vasopressin. Circulatory vasopressin, together with aldosterone decrease water and sodium excretion respectively.

iii. Question:

During hypovolemia, is there also transcapillary shift phenomenon in the kidneys to preserve vascular volume as occur in the body?

Answer: In the glomerulus, there is less filtration. However in the peritubular capillary, the sympathetic constriction of the post-glomerular efferent arteriole reduces the hydrostatic pressure, and this favours fluid reabsorption. In addition, the peritubular oncotic pressure is also increased due to a higher filtration fraction caused by the sympathetic action at both renal arterioles (in skeletal muscle capillary, only the capillary hydrostatic pressure drops).

5 Renin-Angiotensin-Aldosterone System (RAAS)

i. Definition: A family of hormones that participates in the overall control of sodium balance, extracellular fluid and blood volume.

ii. PTC:

The renin-angiotensin-aldosterone system (RAAS), when activated has the effect in conserving total body sodium. This ultimate action is effected through the secretion of adrenal aldosterone, the mineralocorticoid that increases tubular sodium reabsorption at the collecting ducts of the kidneys.

The RAAS is linked to the renal sympathetic action. The juxtaglomerular (JG) cells secrete renin in response to sympathetic stimulation. The sympathetic action in the kidneys has the net effect of decreasing the excretion of

sodium. The RAAS when triggered has the purpose of Raising Arterial Sodium (RAS). The use of the word 'arterial' is to remind students of the role of RAAS in arterial blood pressure regulation.

Thus, the action of RAAS contributes to sodium balance and sodium balance is linked to blood volume and blood pressure. This means that any situation that produces negative sodium balance or a reduction in vascular volume will certainly release renin from the JG cells. The vascular volume sensors double up as sodium sensors.

These vascular sodium/volume sensors include the arterial baroreceptors and the volume receptors in the low pressure, large veins and pulmonary vasculature. The afferent arteriole which contains the JG cells also have what is called 'intrarenal baroreceptors', their stretch responses to changing renal arterial pressure linked to the secretion of renin.

The secretion of renin from the JG cells will initiate a cascade of reactions in the circulating plasma with the eventual production of angiotensin II, which is a primary stimulus for aldosterone release from the adrenal cortex. Renin secretion is affected by three inputs; the renal sympathetic nerve, the response of the intrarenal baroreceptors and a paracrine signal from the macula densa in the distal tubular component of the juxtaglomerular apparatus (JGA).

iii. Question:
How does the kidneys function in sodium homeostasis?
Answer: Kidneys release renin, the initiator of the RAAS. The renal sympathetic nerve stimulates renin secretion and the renal nerve also has other actions that together conserve sodium.

6 Anti-Natriuresis

i. Definition: Action or mechanism that reduce sodium and water urinary excretion

ii. PTC:
Natriuresis is a combination of the words 'sodium' and 'diuresis'. It means increased sodium and water excretion by the kidneys. Natriuresis is a response in sodium homeostasis. When the body is in positive sodium balance, natriuresis is a compensatory reaction. There is a family of natriuretic hormones that promote increased excretion of sodium and water by the kidneys. The source of these hormones are the endocrine peptides from cardiac muscles and some are renal paracrines.

In negative sodium balance, anti-natriuresis compensates. Sodium conservation are both hormonally and neurally-mediated. The renin-angiotensin-aldosterone system (RAAS) is activated whenever the total body sodium is below normal. The final goal of RAAS is to stimulate more reabsorption of sodium by the kidneys.

The renal sympathetic nerve is an anti-natriuretic nerve. For a slogan, its the '*so-dium*' *wonderful antinatriuretic*' sympathetic nerve. The renal sympathetic (RSN) have several actions that together reduce natriuresis. Firstly, the RSN vasoconstricts the renal arterioles. The renal blood flow and hence the glomerular filtration rate (GFR) is decreased. This will also lower the filtered sodium load (GFR × plasma sodium concentration).

Secondly, the RSN also innervates the proximal convolute tubules (PCT). RSN activity directly increases the sodium reabsorption at the PCT. One of the three major inputs that increases renin secretion from the juxtaglomerular cells at the afferent arteriole is RSN.

In antinatriuresis, the urine volume will also be lower. Plasma vasopressin will be raised. Conversely, a decreased vasopressin secretion will contribute to the natriuresis.

iii. Question:
How might you expect the natriuretic hormones to affect the secretion and/or action of aldosterone and vasopressin?
Answer: Reasoning physio-logically, natriuretic endocrine peptides would inhibit secretion/action of both aldosterone and vasopressin. Renal natriuretic paracrine however, increases the GFR by vasodilating the renal arterioles. This leads to a greater filtered load. Any effect of these paracrines at the PCT might be expected to inhibit the sodium reabsorption, to promote sodium excretion.

7 Proximal Potassium Reabsorption

i. Definition: The bulk of filtered potassium that is passively returned by reabsorption into the systemic circulation at the proximal convoluted tubules.
ii. PTC:
This entry for potassium is a key aspect of renal handling of essential electrolyte in blood. Plasma potassium is carefully maintained at around 4.5 mmol/L. On a normal diet, excess of potassium is added to the ECF. Thus,

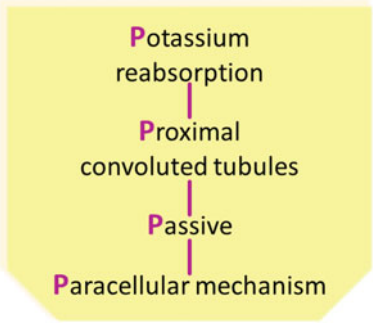

Fig. 3 At the proximal convoluted tubules, potassium is reabsorbed passively via paracellular mechanisms as there are no luminal membrane ATPases

a major control of potassium balance is by renal tubular secretion of potassium that is under the promoting action of aldosterone.

This primary hormonal control of active, potassium secretion often shifts the student's attention of potassium homeostasis towards the final, fine control by the collecting ducts. A greater aspect of renal handling of potassium is the passive potassium reabsorption at the proximal convoluted tubules. At least 70% of freely filtered potassium is reabsorbed here.

Interestingly, the passive potassium movement occurs not transcellularly but paracellularly through the intercellular 'tight' junctions. Reabsorption is not active because there is no active transporters at the luminal membrane to pump filtered potassium into the proximal epithelial cells. The intracellular potassium is around 145 mmol/L and that in the tubular fluid of the lumen, about 4.5 mmol/L, the same as plasma concentration.

A concentration gradient for the paracellular, passive potassium flux is generated at the early proximal segment when the isosmotic reabsorption of water occurs. At the ascending loop of Henle, about another 20% of filtered potassium is also reabsorbed. The luminal membrane carrier here is linked to a secondary active transport mechanism powered by a sodium electrochemical gradient. The neutral symporter transports three passengers besides sodium cation, namely a potassium cation and two chloride anions. The Na/K/2Cl co-transporter has a central role to help generate the hyperosmolarity of the osmotically-stratified renal medullary interstitium.

iii. Question:
How is the filtered load of potassium calculated?
Answer: The formula for any solute that is freely filtered together with the plasma water is GFR $\times$ plasma concentration of the solute. For potassium this will be 180 L/day $\times$ 4.5 mmol/L, giving 810 mmol/day.

8 Factors that Regulate versus Influence

i. Definition: In homeostatic mechanisms, there is regulatory control while other non-homeostatic factors can influence or affect aspects of the physiological process.

ii. PTC:
Words determine our understanding of physiology. In homeostasis, we look at regulation and control system that responds to changes from a set point and brings about the appropriate compensation. There are commonly other factors that input into the system but they do not determine the homeostatic effectiveness of the regulation.

One good example is potassium homeostasis. The direct, rapid response mechanism involve potassium sensors in the adrenal cortex that are linked to

the secretion of aldosterone. This steroid hormone is the dominant key regulator of renal handling of potassium, specifically in the rate of potassium secretion at the collecting ducts. The pancreatic insulin also plays a role especially during postprandial hyperkalemia.

There are factors that affect the tubular secretion of potassium but these are not regulatory mechanisms. Among these are tubular flow rate and sodium load. Blood pH is also implicated. Alkalotic plasma tend to produce a reduction in plasma potassium and vice versa.

This leads to the second example of control or 'companion' factors, in the regulation of arterial blood pH. The homeostatic mechanism is a multi-organ effort; the lungs. The kidneys and some contribution also from bone buffers. pH sensors include the peripheral chemoreceptors and sensors on the tubular epithelial cells that secrete hydrogen and reabsorb/produce bicarbonate. Changes in plasma potassium affect the free hydrogen concentration. Hyperkalemia tends to acidify the plasma and vice versa.

In calcium homeostasis, the triad of regulatory hormones are parathyroid hormone, vitamin D and calcitonin. Calcium is 40% protein-bound in plasma and the unbound, free calcium is the bioactive cation that is under homeostatic control. The blood pH can alter the fraction of bound and free plasma calcium but pH is an influencing but not a regulatory factor in calcium control.

iii. Question:

In the maintenance of normal GFR, is sympathetic nerve part of the renal autoregulation?

Answer: Strictly defined, the intrinsic mechanisms that regulate to ensure a constant GFR do not require sympathetic input, circulating sympathomimetic or vasoactive hormones. The autoregulation is mediated by the myogenic and the macula densa (tubuloglomerular) feedback mechanisms. Renal sympathetic nerve vasoconstricting activity reduces the GFR.

9 Transepithelial Potassium Secretion

i. Definition: The Active secretion of potassium from the peritubular capillary, across the epithelial cells into the lumen at the collecting ducts of the kidneys.

ii. PTC:

On a normal diet, the renal handling of potassium includes both a large reabsorption at the proximal convoluted tubules and controlled tubular secretion at the distal part of the nephron. The principal epithelial cells at the collecting ducts actively secrete potassium. This active secretion is a two-step event. Potassium is actively pumped into the cells at the basolateral membrane by the potassium/sodium ATPase.

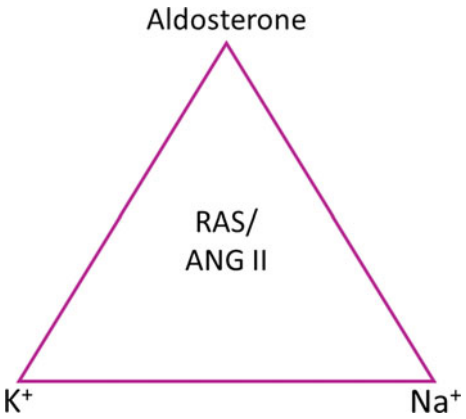

Fig. 4 The transepithelial secretion of potassium and reabsorption of sodium at the principal cells are both under the control of aldosterone. Aldosterone secretion is affected directly by plasma K + and via renin-angiotensin system, RAAS for potassium and sodium homeostasis respectively. Ang II, Angiotensin II

In the second step, the intracellular potassium passively diffuses out of the cell, across the luminal membrane into the lumen. There are potassium ion channels at the luminal/apical side of the principal cells. The overall transepithelial secretion of potassium is energy requiring. The luminal membrane step is dependent on the transmembrane concentration gradient.

Action of aldosterone increases the tubular secretion of potassium. The adrenal steroid hormones increases the activity and also the number of ATPase and potassium channels to effect this transport. Since the luminal step is itself passive and gradient-dependent, the secretion of potassium can be influenced by two factors that secondarily enhance the diffusion of potassium.

One is increased tubular sodium load that arrives at the principal cell. The principal cell is also the cell that reabsorbs sodium and the two step sodium transport shares the same membrane Na/K ATPase activity that is used for the secretion of potassium. Thus increased sodium reabsorption indirectly promotes more potassium secretion and loss in the urine.

The second factor is the rate of tubular fluid flow. A higher flow as in diuresis will favour a steeper gradient for potassium diffusion at the luminal surface. These two factors are present when loop diuretics are used and account for the secondary kaliuria.

iii. Question:
What is the concentration of potassium in the principal epithelial cells at the collecting ducts?
Answer: The intracellular potassium concentration is maintained by the ubiquitous cell membrane K/Na ATPase. The value would be the same as in all cells at around 145 mmol/L.

10 Goldblatt Hypertension

i. Definition: Elevated arterial blood pressure due to renal stenosis, experimental or pathological, which leads to increased release of renin.

ii. PTC:
Goldblatt hypertension was initially observed *in vitro* when the renal arterial blood perfusion was restricted. Clinically, renovascular stenosis results in renal ischemia and a low perfusion pressure. The intrarenal baroreceptors sense the decreased pressure and renin is secreted as a compensation.
The kidneys tend to 'assume' that a low perfusion pressure arises from a low blood volume and its default function is to release renin. Activation of the renin-angiotensin-aldosterone conversions in plasma is aimed at restoring the blood volume by conserving sodium.
If the renal stenosis is unilateral, the juxtaglomerular renin cells at the renal afferent arteriole on the normal side will be inhibited by the ECF volume expansion.
Another situation that triggers renin secretion although the blood volume is normal is during cardiac failure. The inadequate cardiac output decreases the arterial blood pressure and the renal perfusion pressure is low.
In Goldblatt hypertension and in cardiac pump failure, there is development of edema. The capillary hydrostatic pressure is elevated in renovascular hypertension. Left heart failure which is associated with the renin secretion is associated with pulmonary edema (right cardiac failure causes elevation of venous/capillary pressure and a peripheral edema; since the vascular circuit is a closed system, depressed right cardiac output would eventually lead to a decreased left ventricular output also).
If the increased secretion of aldosterone is not stimulated by plasma angiotensin II but due to a primary hypersecretion from the adrenal cortex (Conn's syndrome), the development of edema is seldom encountered. This limit on the effect of aldosterone in ECF volume expansion is called 'aldosterone escape'. The normal cardiac muscle and function account for this 'escapade'. Cardiac natriuretic hormones, released by the increased central venous pressure during intravascular expansion opposes the sodium retention. Intrarenal hemodynamic adjustments may also decrease tubular fluid and sodium reabsorption and promote natriuresis.

iii. Question:
What is the status of renin secretion in Conn's syndrome?
Answer: In Conn's syndrome, the renin secretion from both kidneys are suppressed by the high renal perfusion pressure and reduced, compensatory renal sympathetic input. The patient's blood has high aldosterone and low renin levels.

Chapter 14
Water Balance

1 Tonicity

i. Definition: Tonicity has no quantitative unit. Tonicity is defined by cell behaviour in solution and the solution is either isotonic, hypotonic or hypertonic.

ii. PTC:
The tonicity of a solution is dependent on the osmotic concentration and also the membrane behavior of the solutes. An isotonic solution will contain a minimum of 300 milliOsm/L of solutes that do not penetrate the cell membrane regardless of the osmotic concentration of the non-penetrating solutes. For example a 400 mOsm/L solution containing 150 mOsm/L of sodium chloride and 100 mOsm/L of urea is still isotonic. The NaCl is non-penetrating but urea can move across cell membrane by facilitated urea transporters. The solution is described as hyperosmotic to plasma (300 mOsm/L) but isotonic since there will be no net movement of water across the cell membrane and the cell volume remains unchanged.
The laboratory cell used is red blood cells since they are easily collected and also any hemolysis by a hypotonic solution can be monitored photometrically by measuring the absorbance of hemoglobin.
Changes in the tonicity of the extracellular fluid (ECF) space will be accompanied by fluid shift between the ECF and the cells (intracellular fluid, ICF). The factor that determines the direction of transmembrane water shift is the tonicity change in the ECF. If the ECF becomes hypertonic e.g. in dehydration, compensatory water movement will be osmotically driven out of the cells (efflux). The net water flux will cease when the osmolarity of the ECF and the ICF reaches an equilibrium slightly higher than 300 mOsm/L. There will be some cell shrinkage. Since two-thirds of the total body fluids are found as ICF, this osmotic adaptation can be viewed as a reservoir effect of the ICF to preserve ECF volume.

H. M. Cheng and F. Jusof, *Defining Physiology: Principles, Themes, Concepts*,
https://doi.org/10.1007/978-981-13-0499-6_14

If a person drinks a large volume of water quickly, a hypotonic change in the ECF can be produced. Osmoregulation will soon kick in with the involvement of pituitary vasopressin and kidney excretion of the excess water. Before that is effective, compensatory influx of ECF water into the ICF occur till an equilibrium hypoosmolarity below normal plasma value exists in the ICF and ECF.

iii. Question:
What do you think the tonicity of sweat is?
Answer: Sweat is always hypotonic, containing a hypoosmotic solution of NaCl and other organic solutes. This osmotic perspiration is important as the resultant ECF becomes hypertonic. As discussed above, there will always be an ICF > ECF fluid osmotic response. Should sweat be a hypertonic fluid, the resultant hypotonic ECF will lead to a further reduction in ECF volume when water influx into the cells.

2 Countercurrent Flow

i. Definition: The opposite and parallel flow of tubular fluid or peritubular capillary blood in the U-shaped loop of Henle or the U-shaped vasa recta respectively.

ii. PTC:
The 'countercurrent' in the renal countercurrent mechanisms does not relate the tubular fluid flow and the vasa recta blood flow at the juxtamedullary nephrons. Textbooks' two-dimensional illustration can easily give this misrepresentation. It is still accurate to have a figure showing descending tubular fluid flow and descending vasa recta flow next to each other. This is because in the renal medullary tissue, a cross section will show five circular structures representing the descending/ascending Henle's loop, descending/ascending vasa recta and the collecting ducts.
The interstitial space between the five structures are very small—all five rings are together like a bunch of straws.
The 'countercurrent' refers instead to two countercurrent flows, the tubular fluid in the descending/ascending Henle's loop and the blood flow in the descending/ascending vasa recta peritubular capillaries that course alongside the loops of the juxtamedullary nephrons.
The countercurrent (ccr) fluid flow enables the generation of the hyperosmotic renal medullary interstitium. The vasa recta supplies oxygen and energy substrates to the medullary tissues including the nephrons. The countercurrent vasa recta ensures that the hyperosmotic interstitium is not disrupted by any significant 'wash-out' effect as solutes like NaCl and urea enter the descending vasa recta. These same solutes are returned to the interstitium as the vasa recta ascends.

Thus, the hyperosmotic stratified renal medulla is preserved as a prepared osmoactive region that is ready to reabsorb water from the tubular fluid flowing in the collecting ducts. When the ducts are made permeable by vasopressin during negative water balance, water moves through aquaporins from the lumen transepithelially into the interstitium. From the interstitium, water is returned to the circulation via the ascending vasa recta. Vasopressin action unlikely makes the very tight junction at the collecting ducts permeable to water). Any agent that disrupts the generation of the hyperosmotic interstitium will interfere with the reabsorption of water e.g. a loop diuretic.

iii. Question:
What other feature of the vasa recta flow, besides its countercurrent pattern, serves its role to maintain the hyperosmotic interstitium?
Answer: Vasa recta flow is relatively slow and this allows effective passive exchange of water and solutes between the peritubular capillary and the surrounding interstitium.

3 Differential Permeability of Henle's Loop

i. Definition: The juxtamedullary nephrons have very long loops of Henle that also exhibit different permeability characteristics at the descending and ascending limbs to sodium and water.

ii. PTC:
The renal medullary interstitium is osmotically stratified with increasing osmolarity from 300 mOsm/L at the renal cortex to ~1300 mOsm/L at the inner medulla. The highest interstitial hyperosmolarity determines the maximal concentrating ability of the kidneys i.e. the urine can be concentrated to ~1300 mOsm/L.
This value also sets the minimum obligatory urine volume that is needed to solubilize the osmoles of solute excreted. For example, if the daily excreted load is 1300 milliosmoles, then a minimum of one liter of urine/day is excreted.
The ability to produce a stratified osmotic cortico-medullary/papillary osmotic gradient is due to the permeability characteristic of the long Henle's loops of the juxtamedullary (jm) nephrons. The proximal convoluted tubule in the cortex transports sodium and is permeable to water. Isosmotic reabsorption of water recovers the obligatory water reabsorption here.
The descending limb of these loops are permeable to water but not to sodium. The tubular fluid becomes more and more concentrated and reaches its highest osmolarity at the tip or U-turn of the loop.
The ascending limb of the loops are always impermeable to water. The tight junctions here must be water-tight and the luminal membrane of the tubular cells must be devoid of aquaporins. Here, sodium is passively reabsorbed at the thin segment and by secondary active transport at the thick ascending

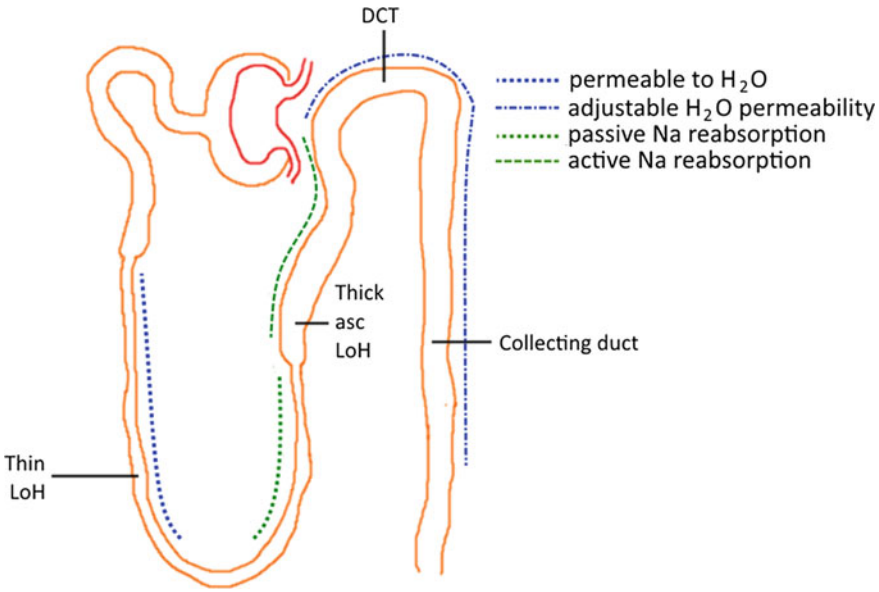

Fig. 1 The different characteristics of permeability in the loop of Henle, LoH is highlighted. The thin descending LoH is permeable to water, H_2O but impermeable to sodium, Na whereas the ascending LoH is permeable to Na but impermeable to H_2O

portion via the Na/K/2Cl symporter. The tubular fluid becomes more and more diluted and the fluid that exits the loop into the distal tubule is always hypotonic. The thick ascending limb that actively transport sodium out of the lumen is described as the 'diluting segment'. Free water is said to be generated in the hypotonic tubular fluid.

The distal tubule and the collecting ducts have adjustable water permeability, depending on the plasma vasopressin concentration. During anti-diuresis, vasopressin action inserts aquaporins into the luminal membrane of the epithelial cells. Water is reabsorbed, driven by the surrounding higher osmolarity. At the renal cortex, the hypotonic tubular fluid is concentrated to 300 mOsm/L. Along the collecting ducts, the fluid becomes progressively more hyperosmotic until 1300 mOsm/L is achieved. The major osmoles in the concentrated urine is NaCl and urea.

iii. Question:

If water could talk to sodium, what would Mr Water say to Ms Sodium at the proximal convoluted tubule (PCT), the descending and ascending limbs of Henle's loop?

Answer: At the PCT, Mr. Water says to Ms Sodium, 'I will follow you'. At the descending limb, 'you can't follow me'. At the ascending limb, 'I can't follow you'.

4 Isosmotic Water Reabsorption

i. Definition: The portion of water that is reabsorbed, following the osmotic gradient generated by solute reabsorption at the proximal convoluted tubule.

ii. PTC:

In many ways there are cross-organ shared mechanisms between the gastrointestinal and the renal tubular epithelial cells. One major common event is the reabsorption of water. In both the intestines and at the nephrons, a major portion of water is reabsorbed isosmotically, following solute transport from the lumen of the intestine or from the nephron.

About 70% of the glomerular filtrate is returned to the circulation at the proximal convoluted tubules. At the normal GFR of 180 L per day, a huge volume of more than 120 L of water is reabsorbed daily by both kidneys. The osmolarity of the glomerular filtrate is the same as plasma osmolarity since sodium, the main determinant of plasma osmolarity is freely filtered.

Most of the solute transported at the proximal convoluted tubules (PCT) are linked to sodium reabsorption using secondary active mechanism. These include glucose/galactose, amino acids, phosphate. The large amount of solutes the leaves the lumen at the PCT initially lowers the osmolarity of the tubular fluid and an osmotic gradient is generated between the lumen and the intracellular fluid as well as the renal interstitial fluid. Water will be driven osmotically and move both transcellularly via aquaporins and paracellularly. This proximal water transport is also termed the 'obligatory water reabsorption' that will follow the solute reabsorption.

The net result of this water reabsorption is that the remaining tubular fluid will not have a change in osmolarity. It can be viewed as the reabsorption of a portion of water that is isosmotic to plasma i.e. $\sim$300 mOsm/L. Hence the term isosmotic reabsorption of water.

The students should note that other parts of the nephron do not absorb water that is dependent or necessarily follows sodium and solute transport. At the juxtamedullary nephrons, the renal medullary interstitium is hyperosmotic and provides the osmotic gradient for water reabsorption at two segments, the descending loop of Henle and at the collecting ducts (when made permeable by vasopressin).

iii. Question:

How will solutes that cannot be reabsorbed at the proximal convoluted tubule affect the water transport?

Answer: If an exogenous solute is administered to a patient and it is filtered but not reabsorbed at the PCT, this solute will interfere and reduce the isosmotic reabsorption of water. Mannitol is given for this purpose to produce an osmotic effect to increase water excretion (osmotic diuresis). Unreabsorbed glucose in diabetes mellitus likewise results in an osmotic diuresis and glucosuria.

5 Water Diuresis

i. Definition: The production of a large volume, hypoosmotic urine resulting from a lack of vasopressin action.
ii. PTC:
Water balance is synonymous with osmoregulation which in turn is linked to extracellular fluid (ECF) sodium concentration. The hypothalamic osmoreceptor/vasopressin response mechanism is sensitive to small changes in ECF osmolarity. In positive water balance, the vasopressin secretion from the posterior pituitary is suppressed. A water diuresis occurs to excrete the excess water.
The juxtamedullary nephrons are functionally dedicated to water homeostasis as these nephrons generate the hyperosmotic medullary interstitium. The tubular fluid that exits the loop of Henle at the juxtamedullary nephrons (cortical nephrons also) is always hypotonic or hypoosmotic in reference to plasma. This is brought about by the 'diluting segment' of the ascending loop of Henle. Here, the loop is uniquely impermeable to water but sodium is reabsorbed.
About 10% of glomerular filtrate enters the collecting ducts (this value is a combined value of all the nephrons, cortical and juxtamedullary). In normal body hydration or water balance, the collecting ducts are quite impermeable to water. Thus, the hyposmotic fluid is excreted in the final urine. In negative water balance, reabsorption of water occurs when the ducts become water permeable by vasopressin action.
In patients with diabetes insipidus (DI), vasopressin action is inadequate. This can be due to dysfunction of the posterior pituitary or vasopressin receptor unresponsiveness at the collecting ducts. In both central and nephrogenic DI, a water diuresis is the consequence. The patient compensates for his water loss by drinking more as his thirst mechanism is stimulated by the dehydration.
iii. Question:
What are the two signals that lead to inhibition of vasopressin secretion?
Answer: The first situation would be a hypoosmotic ECF in positive water balance. The hypothalamic osmoreceptors are not activated to stimulate the posterior pituitary. The other signal comes from peripheral vascular volume sensors. In volume expansion, both the arterial baroreceptors and the low-pressure area, volume receptors detect and send inhibitory afferent impulses to the hypothalamus.

6 Osmoregulation

i. Definition: Osmoregulation maintains the extracellular fluid osmolarity at close to 300 milliOsm/L.

ii. PTC:
The osmolarity of the extracellular fluid (ECF) include that of the plasma volume and the interstitial fluid (ISF) space. The red cell count does not contribute much to the blood osmolarity. The osmotic force in the vascular compartment is due mainly to the sodium concentration in plasma. The sodium concentration in the ISF is basically the same as in plasmas sodium distribute equally across the capillary border between the plasma and ISF.
Thus, a change in ECF osmolarity is also a change in the sodium concentration. In normal persons, changes in ECF sodium concentration is almost always due to changes in the water balance rather than to any change in sodium loss from or sodium gain to the body. Meaning, an excess of water consumption gives a positive water balance with the associated hyponatremia. Conversely, sweating produces a negative water balance with a hypernatremic ECF.
Thus, sensors or receptors that detect changes in ECF osmolarity can also be said to monitor the ECF sodium concentration. Osmoreceptors are functionally ECF sodium concentration detectors. There is then, the triad of three terms that are functionally related or physiologically synonymous namely, water balance, osmoregulation and ECF sodium concentration control.
Osmoregulation needs your brain! No KIDding! While the kidneys are the final effectors of more or less water excretion, the osmoreceptors are localized in the hypothalamus of the brain. Osmoreceptive responses are linked to the secretion of the vasopressin neurohormone from the posterior pituitary. In overhydration, the hypoosmotic ECF is sensed and the hypothalamic osmoreception will inform the pituitary gland to depress its vasopressin secretion. Less hormonal action of vasopressin at the collecting ducts of the nephrons in the kidneys will lead to water diuresis of a large volume of hypoosmotic urine. This will reduce and normalize the ECF osmolarity.

iii. Question:
How does the action or lack of vasopressin produce the change in urine volume excretion?
Answer: The movement of water or reabsorption of water in the kidneys at the collecting ducts is also dependent on a ready osmotic gradient. The vasopressin just increases the water permeability of the ducts. In the normal kidneys, there is a prepared hyperosmotic ISF in the renal medulla, generated and maintained by what is known as the renal counter current mechanism. In negative water balance, the collecting ducts are made permeable by vasopressin and water moves and is reabsorbed by the potential 'ever-ready' osmotic force available.

7 Set Point of Vasopresssin Secretion

i. Definition: The ECF osmolarity concentration above which vasopressin (also known as anti-diuretic hormone, ADH) secretion from the posterior pituitary is stimulated.

ii. PTC:
The homeostatic control point in osmoregulation is the normal ECF osmolarity in the absence of any fluid disturbance. This is around 295 mOsm/L. The osmoreceptors in the hypothalamus are sensitive to changes the ECF/plasma osmolarity. Hyperosmotic ECF will activate the osmoreceptors to then increase the neurohormone vasopressin secretion from the posterior pituitary. Below the control set value, vasopressin secretion is inhibited since there is no longer the need to conserve water when the osmolarity is normal.
There is adaptation of the osmotic set point when there are volume changes concurrent with the hyperosmotic ECF. In hypertonic contraction the ECF volume is reduced. The hypovolemia will shift the osmotic set point to a value below 295 mOsm/L. This means that a larger volume of water can be reabsorbed and recovered before the inhibition of vasopressin occurs. This is an obvious advantageous physiologic adjustment in water balance.
Among the six categories of ECF osmolarity/volume disturbances, hypotonic contraction does not take place in normal person whose water and sodium homeostatic mechanisms are intact. However in certain patients with a deficiency in the hormone aldosterone, the effector hormone is sodium control, hypotonic contraction is seen. With increased urinary sodium loss during aldosterone lack, the ECF/blood volume decreases to a critical value.
In order to ensure that adequate tissue perfusion, especially to the brain, is not compromised, the kidneys continue to reabsorb water as the osmotic set point is lowered. The body copes with a lower osmolarity to meet the more critical need of a reduced vascular volume.
Note that a hypotonic contraction is the result of vasopressin compensatory action to a severe hypovolemia. In describing the other five types of ECF changes, they are osmolarity/volume changes resulting from diverse conditions before vasopressin acts e.g. drinking large volume of water, blood donation, exercise dehydration.

iii. Question:
In diabetes insipidus, would there be a theoretical shift in the osmotic set point?
Answer: Diabetes insipidus is due to lack of vasopressin action, either due to deficiency of secretion or receptor unresponsiveness. The urine excreted will be a large, hypotonic volume. The ECF will be hypertonically contracted. The hypovolemia will lower the osmotic set point to enhance the osmoreceptor response to the hyperosmotic ECF. However, if pituitary secretion is the problem in the diabetes insipidus, no vasopressin will be released. These persons normally will drink more water in response to the thirst mechanisms that input into osmoregulation.

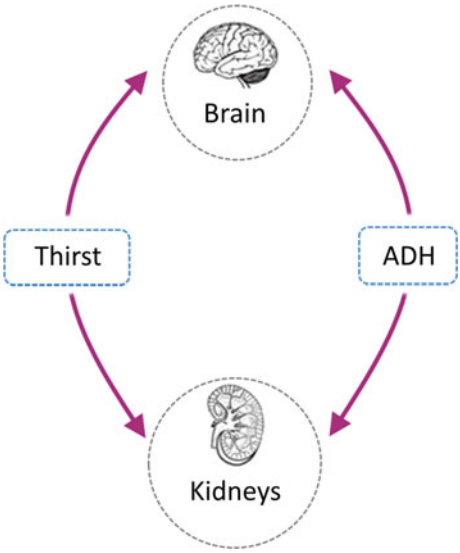

Fig. 2 The brain and kidneys osmo-talk via the thirst sensation and ADH when negative water balance is the pressing physiologic issue

8 Osmotic Diuresis

i. Definition: The production of a high volume urine due to interference with osmotic reabsorption of water by the nephrons.

ii. PTC:

Diuresis or excretion/loss of a high volume urine can be grouped into a water diuresis or osmotic diuresis. Water diuresis is due to lack of vasopressin action at the collecting ducts. Osmotic diuresis occurs independent of vasopressin. The effect of a change in osmotic driving gradient for water reabsorption can occur along the nephron.

At the proximal convoluted tubules (PCT), isosmotic reabsorption of water transport about 70% of the glomerular filtrate. This site is therefore a major location for disruption of water reabsorption if the osmotic gradient is interfered with. When a solute like mannitol which is freely filtered but is not transported by the PCT, the isosmotic reabsorption of water is reduced. Mannitol is given as an osmotic diuretic.

In diabetes mellitus, the glucose remaining in the fluid at the PCT decreases the water flux. Glucosuria is accompanied by an osmotic diuresis.

A secondary effect of giving carbonic anhydrase (C@) inhibitor is a mild diuresis. C@ is given to increase bicarbonate excretion e.g. to aid acclimatizationin mountaineers. The unreabsorbed filtered bicarbonate becomes osmo-active and oppose the water reabsorption.

All diuretics that act by inhibiting sodium reabsorption at the nephron exert an osmotic effect. For loop diuretics, the inhibition of the Na/K/Cl symporter also

lowers the hyperosmolarity of the medullary interstitium. At the descending loop of Henle, the decreased hyperosmotic interstitum will reabsorb less water. At the collecting ducts downstream, the greater amount of sodium remaining in the tubular fluid will reduce the osmotic gradient for water reabsorption even when the ducts become permeable to water.
Other sodium transport-inhibiting diuretics include drugs that inhibit either the sodium/chloride cotransporter at the distal tubule, the sodium channel or aldosterone action. These three types of diuretic all increase the sodium osmolarity of the tubular fluid.

iii. Question:
When a volunteer drink a large volume of isotonic glucose, is her diuresis an osmotic or a water diuresis?
Answer: In normal persons, consumption of glucose-rich foods does not produce a glucosuria as the insulin response is rapid. The glucose in the solution is taken up by the cells and a hypotonic expansion of the ECF results. The osmoreceptor/vasopressin mechanism is not stimulated and this leads to a water diuresis.

9 SIADH

i. Definition: The Syndrome of Inappropriate ADH/Vasopressin secretion is due to a hypersecreting tumour and the ADH secretion proceeds regardless of the positive water balance.

ii. PTC:
In osmoregulation, anti-diuretic hormone (ADH) or vasopressin is released in response to a hyperosmotic or hypovolemic stimuli. In certain lung cancers, the malignant cells secrete ADH continuously. There will be a hypotonic expansion of the extracellular fluid (ECF) compartment. Secretion of ADH from the patient's own pituitary gland will be inhibited as the hypothalamic osmoreceptors are still functioning. The patient's kidneys never cease to reabsorb water under the effect of the extrapituitary ADH and a hyperosmotic, concentrated low urine volume is excreted.
However, the ectopic focus of ADH secretion is not responsive to the hypoosmotic change in the ECF. The secretion of the ADH from the lung tumor cells is said to be Inappropriate as the ECF is already hypoosmotic or hypotonic. SIV would be a shorter acronym for Syndrome of Inappropriate Vasopressin secretion.
SIADH illustrates the importance of maintaining a normal osmolarity in the ECF. Patients with SIADH suffer from neurological related symptoms. The hypotonic ECF is the cause of the neuronal dysfunction. There is general neuronal swelling as fluid enters the hypotonic ECF into the brain cells.

The abnormal enlarged neurons especially at essential control neuronal centers begin to malfunction.

Surgical removal of the ADH-secreting tumour cells is an option. If surgery is not possible, use of drugs that block ADH receptor action can be prescribed.

iii. Question:
How would the hypervolemia in SIADH affect the volume sensors?
Answer: The volume sensors at both the arterial baroreceptors (carotid sinus, aortic sinus) and the volume receptors (large veins/cardiac atria, pulmonary vessels) will stretch and lead to more inhibitory afferent signals to the hypothalamus to reduce the ADH secretion from the patient's posterior pituitary gland. However, the ectopic ADH that is not under homeostatic control continue to produce the pathophysiology of an overexpanded, hypotonic ECF.

10 KIDergarten Cause and Effect

Every year during the Renal Physiology block, one major area that trouble students is the difference between renal control of water and sodium balance. There are several essential concepts that need to be grasped in order for the student to distinguish between the homeostatic regulation of water and sodium balances. These are

a. Changes in water balance is frequently the cause of changes in ECF sodium *Concentration*.
b. Changes in sodium balance (*total body sodium*) is the cause of changes in ECF volume.
c. There is thus no meaningful cause and effect connection between sodium balance and ECF sodium concentration. (e.g. drinking lots of water leads to a hyponatremia but increased ECF volume; sweating results in hypernatremia and a reduced ECF volume during dehydration)
d. Changes in water balance is reflected in ECF osmolarity which is mainly due to sodium and its accompanying anions.
e. Changes in ECF sodium concentration (osmolarity) are detected by hypothalamic osmoreceptors which in fact are detecting sodium Concentration changes.
f. Changes in sodium balance is detected predominantly via changes in the ECF volume by volume sensors.
g. Volume sensors that monitor sodium balance include the high pressure arterial baroreceptors, the low pressure volume receptors and intrarenal baroreceptors that directly sense changes in renal perfusion pressure when the blood volume changes.
h. Thus, changes in ECF sodium concentration are NOT controlled homeostatically by the renin-angiotensin-aldosterone system of hormones. In fact ADH/Vasopressin is the regulator.

i. The distal macula densa detects tubular fluid sodium/chloride concentration but this is purposed in the integrated physiology to control sodium balance, not ECF sodium concentration.
j. When the ECF volume changes, the final compensation are corresponding changes in urinary sodium excretion. Increased ECF volume results in increased sodium excretion and vice versa. The overall renal handling of sodium is Excreted sodium = Filtered sodium—Reabsorbed sodium.

Chapter 15
Acid-Base Balance

1 Net Acid Excretion

i. Definition: The total rate of excretion of non-carbonic acid in the urine.
ii. PTC:
The excreted rate of a solute is given by urine solute concentration (U_X) multiply by the urine flow rate (V). The two major form of excreted acid in urine are urinary phosphate (H_2PO_4) and ammonium (NH_4). Therefore, the net acid excretion will include the addition of (U_X.V) for both the phosphate and the ammonium. Metabolism of foods can generate strong acids e.g. from sulphate-containing substrate.
Urinary phosphate is the main 'titratable acid' (TA) excreted. The TA is a laboratory definition and refers to the amount of an alkali that has to be added to acidic urine to bring the urine pH to 7.4. The urinary acids are excreted as sodium or ammonium salts.
The total rate of tubular hydrogen secretion is actually much more than the total amount of hydrogen excreted as urinary phosphate and ammonium. This is because not all the protons secreted by the tubules are excreted and end up in urine. At the proximal convoluted tubule, the secreted proton is used (like a H^+ook) to bind filtered bicarbonate in an indirect pathway of bicarbonate reabsorption.
On a normal diet, an excess of acid is added to the body. Most of the total daily acid load is carbonic acid and easily removed via respiration. The non-carbonic acid are exclusively excreted by the renal nephrons. Renal dysfunction is commonly accompanied by a metabolic acidosis.
Only a small percentage of the total filtered bicarbonate is excreted normally. The calculated net acid excretion will then be determined by the U_X. V of urinary phosphate (more accurately U_X. V of TA) and ammonium combined minus the minor U_X. V of urinary bicarbonate. Loss of a base in urine is equivalent to the gain in acid to the body.

H. M. Cheng and F. Jusof, *Defining Physiology: Principles, Themes, Concepts*,
https://doi.org/10.1007/978-981-13-0499-6_15

In renal compensation for acidosis, the reabsorption of bicarbonate can be complete with no excretion of the anionic base. In that situation, the renal clearance of bicarbonate is zero ml/min.

i. Question:
How will the net acid excretion change after a bout of voluntary hyperventilation?
Answer: Hyperventilation removes more carbon dioxide and a respiratory alkalosis results. There will be less acid excreted in urine as phosphate and ammonium. The reabsorption of the filtered bicarbonate is reduced and more urinary bicarbonate is present. The net acid excretion is decreased as a renal compensation to the respiratory alkalosis.

2 Urinary Buffer

i. Definition: The molecule or solute that binds to hydrogen ions in the renal tubular fluid in order to excrete the hydrogen ions.
ii. PTC:
A chemical buffer system in the extracellular fluid (ECF) space neutralizes the excess hydrogen ions in pH control. In the tubular fluid, the pH is not 'controlled' but rather, the urine pH can vary as a response to the acid base balance in the ECF. The meaning and function of a urinary buffer thus implies quite different physiology than the ECF buffers. The urine pH can vary from a minimum of 4.0 to around 8.0. This difference of 4 pH units is equivalent to a large concentration difference of $10 \times 10 \times 10 \times 10$ or 10 thousand fold difference.
The two major urinary buffers are urinary phosphate H_2PO_4 and ammonium, NH_4. Hydrogen complexed with urinary buffers do not contribute to the pH of the tubular fluid. Only the free hydrogen ion concentration determines the pH of the fluid. If the urine pH is 4.4, this urine acidity is due to a $(10 \times 10 \times 10)$ or one thousand fold difference in free proton concentration between the tubular fluid and the blood plasma of pH 7.4. Urinary buffers by binding protons increases the total acid secretion and excretion before the $1000\times$ uphill proton concentration gradient limits further active secretion of protons. Active secretion of protons that become bound to phosphate or formed as ammonium is the activity of the H^+ ATPase at the luminal membrane of the epithelial, intercalated cells at the collecting ducts. Protons secreted by the Na/H exchanger at the proximal convoluted tubules are not excreted but embedded into or as water. There is also a hydrogen/potassium ATPase exchanger, which is active when there is a need for potassium reabsorption, during negative potassium balance, by the intercalated cells at the collecting ducts.
An indirect effect of the urinary buffer action is to promote the tubular production of new bicarbonate to 'top up' the anion that has been consumed in

neutralizing acids in the ECF. For every hydrogen ion secreted and buffered in the tubular fluid, one fresh HCO_3 is added to the ECF from the intercalated cells. Hydration of CO_2 into carbonic acid and its dissociation into the proton and HCO_3 are catalysed by intracellular carbonic anhydrase in the intercalated cells.

iii. Question:
Why is the buffering capacity of the urinary phosphate limited?
Answer: The source of the urinary phosphate is the filtered plasma phosphate which is less than 1.5 mmol/L. In contrast, the ammonium buffer can be synthesized and the amount enhanced by the renal tubules in acidotic conditions.

3 Bicarbonate Proximal Reabsorption

i. Definition: The reabsorption of filtered bicarbonate that involves a unique luminal membrane enzymatic reaction by carbonic anhydrase.

ii. PTC:
Bicarbonate is the major anionic base in the ECF. The major chemical buffer system in the ECF is the bicarbonate/carbonic acid buffer system that is isohydrically linked to the other minor chemical buffers. Most of the freely filtered bicarbonate ions are reabsorbed at the proximal convoluted tubules. Any reduction in proximal bicarbonate transport will lead to increased loss of urinary bicarbonate. This is part of the normal response when the pH of the ECF becomes acidic.
Interestingly, filtered bicarbonate does not enter the proximal tubular cells by a symporter with sodium as for other solutes. The filtered HCO_3 enters the cell after its conversion to carbon dioxide. The chemical reaction is catalysed by a luminal membrane carbonic anhydrase (C@) which promotes the reaction between secreted protons and the filtered HCO_3.
Carbonic acid which is formed dissociates into water and CO_2.
The CO_2 enters the cell and undergoes a reverse reaction catalysed by an intracellular C@. Hydration of CO_2 forms carbonic acid which now dissociates into protons and HCO_3. The bicarbonate produced intracellularly in a 'convoluted' pathway then exits the cell by a membrane transporter at the basolateral membrane. The overall event absorbs into the circulation one bicarbonate for one filtered bicarbonate.
The dissociated protons are secreted into the lumen by a luminal membrane sodium/proton countertransporter, to complex further with other filtered HCO_3.
Inhibitors of the luminal membrane C@ can be expected to interfere with this proximal bicarbonate reabsorption. Unreabsorbed bicarbonate in the tubular fluid represents an osmoactive particle and will reduce the isosmotic

reabsorption of water. Action of carbonic anhydrase inhibitors does lead to a mild osmotic diuresis, besides the production of a more alkaline urine.

iii. Question:
What is the destiny of the protons secreted by the proximal convoluted tubule?
Answer: The protons combine with filtered bicarbonate anions and the carbonic acid formed splits into water and CO_2. The hydrogen ion is incorporated into the H_2O. Most of the tubular fluid water is reabsorbed.

4 Bicarbonate/Carbonic Acid Buffer

i. Definition: The major chemical buffer system in the ECF that is also iso-hydrically in equilibrium to the other minor chemical buffers.

ii. PTC:
The main chemical buffer in the extracellular fluid space, which include the plasma and the interstitial fluid compartment is the bicarbonate/carbonic acid buffer system. This buffer system has a pK_a of 6.1 which is quite close to the regulated pH of 7.4. However, the main reason why the bicarbonate/carbonic buffer is the major ECF buffer for acid base balance is that this system is an 'open' system. This 'open' refers to the fact that both the bicarbonate and carbonic acid components are linked to the two major organ function, namely the kidneys and the lungs respectively.

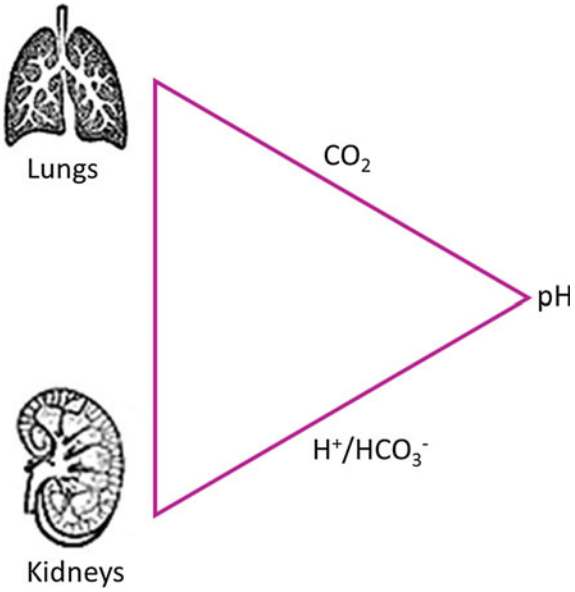

Fig. 1 The bicarbonate/carbonic acid buffer are linked to the function of two major organs, the lungs and kidneys

When ascertaining the acid-base status, the bicarbonate/carbonic acid (bic/carb) ratio only need to be examined since the free hydrogen ion concentration which determines the pH is iso-hydrically in equilibrium with all chemical buffers including the bic/carb.

At the normal pH of 7.4, the bic/carb ratio is 20: 1 with normal bicarbonate at 24 mmol/L and the carbonic acid at 1.2 mmol/L. The carbonic acid concentration is converted from the partial pressure of CO_2 by multiplying with the factor 0.03. Thus normal arterial blood PCO_2 at 40 mmHg gives the 1.2 mmol/L value for carbonic acid.

A bic/carb ratio less than 20 indicates acidosis while a ration above 20 shows an alkalotic ECF. The bic/carb ratio is useful in understanding how compensation will occur in order to maintain an ECF pH compatible with life. Compensation is aimed to restore the bic/carb ratio as close to 20:1. Normalization of the bicarbonate and carbonic acid to 24 and 1.2 mmol/L respectively takes place eventually but the immediate concern for pH regulation is to prevent or minimize the pH change.

iii. Question:

How would the bicarbonate/carbonic acid ratio change if you hold your breath?

Answer: Hypoventilation or cessation of ventilation will lead to an increase in PCO_2 in the arterial blood. The PCO_2 will be higher than 40 mmHg and the carbonic acid rises above 1.2 mmol/L. The bic/carb ratio will be less than 20: 1 and the acid-base imbalance is acidosis, specifically respiratory acidosis.

5 Sensors, Receptors, Detectors

i. Definition: Cell structures that are part of the homeostatic loop to maintain the constancy of the ECF, the internal environment of the cells.

ii. PTC:

Words convey impressions. In physiology, maintenance of normal conditions in the extracellular fluid (*there is the also the overlapping, separate inner world of intracellular homeostasis*) include parameters like pH, electrolyte concentrations, glucose level, osmolarity. Fluctuations in these controlled factors are monitored or detected by sensors or receptors.

ECF osmolarity is carefully regulated at around 295–300 mOsm/L. Changes away from the set osmolarity point are sensed or detected by osmoreceptors in the hypothalamus. The glucose concentration in ECF is also well controlled with a normal range of 4–6 mmol/L.

The pancreas secrete the two major counter-regulatory hormones, insulin and glucagon from the islet cells of Langerhans. These endocrine cells sense the ECF glucose but the mechanism is not mediated by any specific membrane glucose detectors. Rather it is the biochemical pathways activated as glucose

enters the endocrine cells by GLUT facilitated transport that together provide the glucose monitoring.

The kidneys has the important function in maintaining ECF volume. Volume changes in ECF are accompanied by proportionate changes in the blood volume. The body monitors blood volume via volume sensors. These volume detectors are located at several sites and include the arterial baroreceptors, the volume receptors in the large veins/atria and the intra-renal baroreceptors at the pre-glomerular afferent arteriole. The volume sensors are stretch or mechano-sensory receptors.

pH sensors are operative at the renal tubules. The two blood parameters detected in pH control are the free hydrogen ion concentration (pH) and the partial pressure of carbon dioxide. The degree of tubular proton secretion is dependent on the pH and the PCO_2 of the ECF. The mechanisms for PCO_2 sensing likely do not involve membrane structures at the basolateral membrane of the renal epithelial cells. CO_2 enters the cells and produce the appropriate intracellular reactions leading to secretion of protons which can be linked concurrently with production and absorption of a new bicarbonate base anion. There could be membrane sensors for free protons.

The sensors for ECF sodium Concentration are actually the hypothalamic osmoreceptors. ECF sodium concentration changes are reflected in the ECF osmolarity. The sensors for sodium *Balance* are operative via the volume sensors.

Homeostasis of potassium involve potassium sensors present at the aldosterone-secreting cells of the adrenal cortex.

iii. Question:

Where would you expect the sensors for calcium homeostasis be located?

Answer: The kidneys reabsorb filtered calcium, the amount dependent on the calcium balance. Changes in ECF calcium concentration are monitored by sensors found on the membrane of the parathyroid hormone-secreting cells. Normal calcium range at 2.0–2.5 mmol/L is lower than that for potassium at 3.5–5.0 mmol/L. Thus the regulation of both cations requires sensitive, direct detection of their ECF concentrations.

6 Metabolic Acidosis

i. Definition: The reduction in pH of ECF resulting from by any non-respiratory causes.

ii. PTC:

Acid base disturbances are categorized into four types based on the initiating cause. If the pH of blood changes due to lung functions, the pH imbalance is called respiratory acidosis or respiratory alkalosis. Respiratory acidosis is associated with any abnormalities that lead to hypoventilation or a reduced

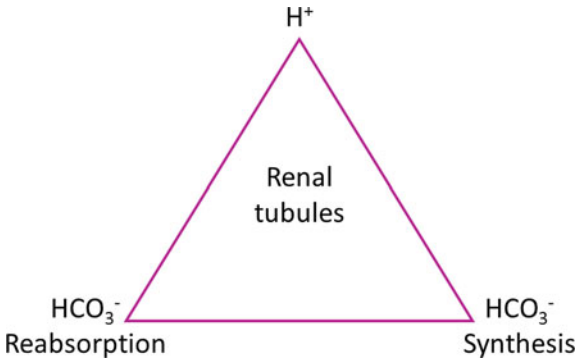

Fig. 2 The hydrogen ion is a double agent! The secreted ('secret') proton in the renal tubules fulfil two roles: the reabsorption of filtered bicarbonate (HCO_3^-) and synthesis of new bicarbonate (HCO_3^-) base to help restore pH

alveolar ventilation. The partial pressure characteristics in respiratory acidosis is a PCO_2 higher than 40 mmHg and a PO_2 less than 97 mmHg. The kidneys will respond to the elevated PCO_2 and increase plasma bicarbonate to compensate and minimize the drop in pH. At the same time as more bicarbonate is reabsorbed and synthesized by the renal tubules, a more acidic urine will be excreted. This is the 'peeH' role of kidneys.

Hyperventilation conversely alkalinizes the blood as a greater rate of CO_2 is expired.

The term 'metabolic' is not the most descriptive of all non-respiratory causes of pH changes. Since the kidneys are obligatory organs for the excretion of non-carbonic acids, renal diseases are often accompanied by a reduction in tubular ability to secrete and excrete the daily acid burden on the nephrons. A metabolic acidosis occurs. Increased loss of bicarbonate in severe diarrhoea also acidify the blood. Incomplete oxidation of lactic acid during prolonged exercise and metabolism of lipids to ketoacids in diabetes mellitus are also pathophysiologic causes.

For metabolic alkalosis, severe vomiting is an example. A primary hypersecretion of aldosterone increases sodium retention and results in an expansion of the ECF. In addition, aldosterone does stimulate tubular acid secretion by stimulating the hydrogen ATPase at the collecting ducts. A metabolic alkalosis besides the positive sodium balance is the clinical picture.

This alkalotic effect of aldosterone accounts for the 'contraction alkalosis' during hypovolemia when the renin secretion is activated. It is also the reason why the metabolic alkalosis of vomiting is resistant to renal compensation and a paradoxical acidic urine is produced. Fluid replacement in the patient is needed to lower the aldosterone and its opposing actions.

iii. Question:

How does the body compensate for metabolic acidosis in severe diarrhoea?

Answer: If the cause of the metabolic acidosis (or alkalosis) is non-renal, then renal as well as respiratory compensations can proceed. In metabolic alkalosis due to an aldosterone-secreting tumour, hypoventilation will raise the PCO_2. The expected renal compensation to decrease tubular acid secretion and bicarbonate recovery is however antagonized by the elevated aldosterone.

7 Reno-Respi pH and BP Regulation

i. Definition: This term is coined to highlight the integrative organ functions of the kidneys and the lungs, including in pH and blood pressure control.

ii. PTC:
In curriculum that have separate lecture blocks for each physiological system, students can miss the crosstalk between organs in whole body regulation and homeostasis. The kidneys and the lungs are physio-partners in the control of blood pH and arterial blood pressure.
In pH regulation, the chemical buffers, both intracell and extracell are the first line of defence against marked changes in pH due to acid or alkali load. The respiratory functions, in association with the hemoglobin buffer operate by handling the carbonic acid component that is used in the major ECF buffer, the bicarbonate/carbonic acid system. In combination with the lung functions, viewed as a second level compensation for pH control, the kidneys take care of all the non-carbonic acid that need to be excreted in the urine.
Respiratory causes of pH problems are then compensated by renal compensation that includes tubular secretion of hydrogen ions, reabsorption and production of bicarbonate. If there are renal cause of pH imbalance, respiratory hyperventilation or hypoventilation responses help to compensate by changing the partial pressure of CO_2 in the arterial blood. If the pH disturbance is due to a non-respiratory, non-renal condition (e.g. in diarrhoea), then reno-respi mechanisms can both help to sustain and normalize the pH.
It might not be obvious that arterial blood pressure has anything to do with lung function. The link between the kidneys and the lungs in blood pressure is the circulating peptide, angiotensin II (Ang II). This vasoconstrictor Ang II is generated as blood courses past the pulmonary vessels, where the endothelial cells have the angiotensin-converting enzyme. The plasma substrate Angiotensin I for the genesis of Ang II is formed as a result of a cascade reaction in plasma triggered by the release of renin from the juxtaglomerular cells at the renal afferent arteriole.
A third reno-respi physiologic collaboration is the essential role of the kidneys in erythropoiesis. The renal hormone erythropoietin is released in response to hypoxia. Red blood cells are bloody 'capsular transporters' of both oxygen and CO_2.

iii. Question:
How does angiotensin II act in its effect on blood pressure regulation?
Answer: The angiotensin II (Ang II), generated at the pulmonary vasculature has several immediate and subsequent actions in the kidneys. The renal arterioles are vasoconstricted by Ang II. This increases the total peripheral resistance. The reduction in the renal blood flow/GFR decreases the filtered sodium load. The peptide Ang II also conserves sodium by its direct action on sodium reabsorption at the proximal convoluted tubules and by its stimulation of aldosterone secretion from the adrenal cortex.

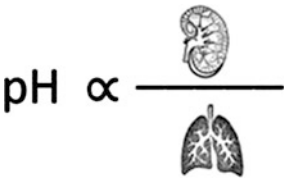

Fig. 3 The control of pH and blood pressure involve cross talk between the renal and respiratory system

8 Wow Wonderful Wee (WWW)

Hopefully, the student reader will have come to the defining moment to appreciate the physiology of urine (*wee, pee*) excretion. Here again, are just a number of essential renal roles in regulating and renewing continuously the extracellular fluid (ECF), the internal milieu of the living cells.

Precious Physiologic Pee (PPP)

a. Wee is part of peeH control
b. Wee is part of bpee control
c. Volume of plasma filtered each day is 180 L! ~90 times the 2 L Peepsi (sorry I mean Pepsi) bottle.
d. Even after unlimited, all you can eat ice cream, there will still be no glucosuria or glucose in your urine!
e. The transepithelial active secretion is able to operate against a hydrogen concentration gradient that is 1000× between the peritubular capillary and the lumen.
f. The kidneys sense hypoxia and increases the red cell formation by secreting erythropoietin that acts in the bone marrow.
g. The kidneys sense decrease in blood volume and restores by adjusting the sodium excretion in pee.
h. Prevents accumulation of potassium (too high hyperkalemia will stop the heart!) by secreting and excreting excess potassium in pee.
i. Pee prevents excess water retention which can lead to hypotonic brain swelling! Wow wee! This is also called water balance or osmoregulation.
j. Pee indirectly maintains normal nerve/muscle excitability by its role in calcium homeostasis.

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