The Australian Short Course on Intensive Care Medicine

1999 Handbook
The Australian
Short Course on
Intensive Care Medicine

1999 Handbook

Editor
L.I.G. Worthley
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FMC = Flinders Medical Centre  
QEH = Queen Elizabeth Hospital  
WCH = Women’s and Children's Hospital  
RAH = Royal Adelaide Hospital  

**DINNER:** Thursday 25th 7 pm: 22 William St, Hawthorn
(registrants at RAH accommodation block will be picked up at 6.45 pm)
### REGISTRANTS

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### FACULTY

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<th>FMC</th>
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<tr>
<td>Dr. L. Worthley (L.W)</td>
<td>Dr. M.O’Fathartaigh (M.O’F)</td>
<td>Dr. J. Myburgh (J.M)</td>
<td>Dr. N. Matthews (NM)</td>
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<td>Dr. A. Vedig (A.V)</td>
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<td>Dr. P. Thomas (P.T)</td>
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<td>Dr. A. Bersten (A.B)</td>
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<td>Dr. E. Everest (E.E)</td>
<td>Dr. M. Finnis (M.F)</td>
<td>Dr. M. Chapman (M.C)</td>
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### GUEST

Dr. B. Venkatesh (B.V) * registrants willing to undergo a 'clinical'
PREFACE

A working knowledge of the basic sciences of, anatomy, physiology and pharmacology is the basis for the understanding and management of the critically ill patient. This year the Australian Short Course on Intensive Care Medicine handbook has included a cursory look at the basic sciences of the cardiovascular system with chapters on cardiac anatomy, physiology of myocardial contractility, cardiac output and oxygen delivery, and the autonomic nervous system. The next and subsequent years handbooks will be devoted to the basic sciences of respiratory, renal, endocrine, neurological and other systems. As with the previous editions, the course registrants presentations (or those that have been submitted on time) have also been included.

The subjects that have been dealt with in the lectures and seminars (along with other reviews), that were included in previous handbooks are now published separately in the journal Critical Care and Resuscitation.

This handbook will still remain the working document of the Australasian Short Course on Intensive Care Medicine and is designed to supplement the course. During the sessions, you may find it useful to mark and note the text to facilitate your recall and review of the course at a later date. Along with the previous editions I trust that you find this edition useful.

Dr. L.I.G. Worthley
Adelaide, March 1999
Chapter 1

CARDIAC ANATOMY

SURFACE ANATOMY
In the adult cadaver about two-thirds of the heart is to the left of the midline. The outline of the heart may be drawn by connecting the points of the, lower border of the second left costal cartilage, 3.5 cm from the midline, to the upper border of the third right costal cartilage, 2.5 cm from the midline, to the sixth right costal cartilage, 2.5 cm from the midline, to the fifth left intercostal space, 9 cm from the midline. The relationship of the cardiac valves are shown in Fig 1.1. In a living erect person, the position of the heart may be 5 cm lower than in a cadaver.\(^1\)

\[\text{Fig. 1.1 Anteroposterior projection of the chest showing the outline of the heart and cardiac valves.}\]

CORONARY ARTERIES (Fig. 1.2)
1. The right coronary artery arises from the sinus of the right aortic cusp, passes forward between the root of the aortic trunk and the right auricle, then down between the right ventricle and the right atrium in the atroventricular groove. At the junction of the right and inferior margin of the heart it gives off an acute marginal branch which travels along the inferior border of the right ventricle. The main artery then turns backward, passing between the atroventricular groove of the inferior portion of the heart until it reaches the posterior interventricular groove, where it anastomoses with the left coronary artery. Near its termination it gives off a posterior interventricular branch and a posterolateral branch. The former runs forwards in the
2. The left coronary artery arises from the sinus of the left aortic cusp and passes forwards between the pulmonary trunk and the left auricle to divide into the left anterior descending and circumflex branches. The left anterior descending branch travels down towards the apex in the interventricular groove, giving off diagonal branches to supply the anterior surface of the left ventricle and septal branches to supply the anterior two-thirds of the intraventricular septum. The circumflex artery passes backwards in the atrioventricular groove, to supply the lateral and posterior portions of the left ventricle, with an obtuse marginal, and left lateral branches, anastomosing finally with the right coronary artery.

In normal individuals, the right coronary artery is dominant (i.e., provides the major blood supply to the heart) in 50%, the left is dominant in 20%, and both left and right coronary arteries supply the heart equally in 30%. The posterior interventricular and the posterolateral branch usually arise from the circumflex artery when there is left coronary dominance.

In 60% of normal individuals, the sinus node is supplied by the right coronary artery, and in 90% of normal individuals, the atrioventricular node is supplied by the right coronary artery. The His bundle is supplied largely by the right coronary artery whereas the right and left bundle branches are usually supplied by penetrating branches of the left anterior descending branch.

CARDIAC VEINS
The great cardiac vein ascends in the anterior interventricular groove and joins the left marginal and posterior veins in the atrioventricular groove to form the coronary sinus. The coronary sinus opens into the right atrium between the orifice of the inferior vena cava and the tricuspid valve and drains virtually all the blood from the left coronary artery. Blood from the right coronary
artery drains into anterior cardiac veins which (apart from the small cardiac vein which drains into the mouth of the coronary sinus) pass directly into the right atrium. The cardiac veins lie superficial to the arteries. Small thebesian veins communicate directly with the cardiac chambers, causing a right-to-left (R-L) shunt when the communication is with the left side of the heart.

CARDIAC VALVES (Fig. 1.3)
The fibrous skeleton of the heart consists of a dense connective tissue structure which forms the four valve rings. To this structure are attached the valve cusps, ventricular muscle and atrial muscle (Fig. 1.4). The thickened area between the tricuspid and mitral valves is known as the central fibrous body and is traversed by the bundle of His.

1. The aortic valve has three semilunar segments, a posterior (or non coronary) and a right and left cusp.
2. The pulmonary valve has three semilunar segments, an anterior and a left and right cusp.
3. The mitral valve has two cusps. An anterior cusp and a posterior cusp. The latter is larger and less mobile and encircles two-thirds of the valve orifice. The orifice has an area of 4-6 cm². Clinical evidence of mitral stenosis occurs when the area is reduced to 1 cm² or less.
4. The Tricuspid valve has three leaflets: anterior (ventral), medial (septal) and posterior (inferior or dorsal).

Fig. 1.3 A diagram showing the fibrous skeleton of the heart joining the four cardiac valve rings, and giving origin to the two arterial trunks and the four cardiac chambers (Modified from Rushmer RF, Functional anatomy of cardiac contraction, In: Cardiovascular Dynamics, 2nd edn, WB Saunders, Philadelphia, 1961:30-52).
The right atrium is 2 mm thick. The superior vena cava joins superiorly and posteriorly and has no valve. The inferior vena cava enters the right atrium inferiorly and posteriorly and has a valve that forms the anterior margin of the junction of the inferior vena cava with the right atrium. The coronary sinus enters the right atrium at the medial end of the valve of the inferior vena cava. The atrioventricular node is anterior and medial to the coronary sinus just above the septal leaflet of the tricuspid valve.

The right ventricle is 4-5 mm thick and separated from the left ventricle by the intraventricular septum which functionally belongs to the left ventricle. The moderator band is a muscle band that contains the right bundle branch and crosses from the lower interventricular septum to the anterior wall of the right ventricle.

There are two major right ventricular papillary muscles, an anterior and inferior as well as septal attachments, which may appear as a third papillary muscle.

The left atrial wall is 3 mm thick and, although there is no true valves at the junction of the pulmonary veins, sleeves of muscle extend from the left atrial wall around the four pulmonary veins for 1-2 cm to act as a sphincter to lessen reflux during contraction.

The left ventricle is cone shaped with muscle thickness of 8-15 mm (i.e. 2-3 times as thick as the right ventricle).

The anterior leaflet of the mitral valve separates the ventricular cavity into inflow and outflow portions. The funnel shaped inflow tract is formed by the mitral valve annulus and by both mitral valve leaflets and chordae. During systole the anterior leaflet forms the posterior portion of the expulsion chamber.
There are two left ventricular papillary muscles, an anterior and a posterior. The anterior arises from the anterolateral aspect of the left ventricular wall, and the posterior arises from the posteromedial aspect of the left ventricular wall. These attach to the adjacent halves of the cusps of the mitral valve by chordae tendineae. The anterior papillary muscle is supplied by the left coronary artery (via the circumflex branch and variable branches of the left anterior descending) and receives fibres from the anterior superior radiation of the left bundle branch, whereas the posterior papillary muscle is supplied largely by the posterior intraventricular branch of the right coronary artery and receives fibres from the posteroinferior radiation of the left bundle branch.

REFERENCES
Normal cardiac function requires the co-ordination of myocardial excitation and contraction, which is achieved by a specialised conducting system and a contracting myocardial syncytium.

The conducting system
The specialised myocardial conducting cells have pacemaker activity (i.e. the ability to spontaneously generate electrical impulses) and conductivity (i.e. the ability to conduct electrical impulses). These cells are arranged to form the cardiac conducting system, which consists of the sinoatrial (SA) node, internodal conducting fibres, atrioventricular (AV) node, His bundle, His bundle branches and Purkinje fibres. In comparison to myocardial contracting cells, the conducting cells have an unstable resting membrane potential, no contractile mechanism, an ability to conduct impulses faster, a different action potential, a larger store of glycogen, and a well-developed anaerobic system with a poorly developed aerobic one, allowing electrical impulses to continue to be conducted (whereas the contractile mechanism is often paralysed) in the presence of severe hypoxia.

The SA node and internodal tracts
The SA node is a crescentic structure 4 mm thick and 2 cm long which lies at the junction of the right atrium and superior vena cava, just beneath the epicardium. The SA node has three conducting tissue pathways to the AV node (Fig. 2.1).

- The anterior internodal tract; this has two branches, Bachmann’s bundle (which provides the electrical connection between the two atria) and a descending branch
- The middle internodal tract (i.e. Wenckebach’s bundle)
- The posterior internodal tract (i.e. Thorel’s bundle).

During sinus rhythm, the anterior pathway is the shortest and probably the preferential pathway for impulse transmission between the SA and AV node. Fibres from all three internodal tracts interdigitate just proximal to the AV node.

Additional strands of cardiac muscle linking the atrium and ventricles are sometimes found in normal human hearts and may become functionally active under abnormal conditions, giving rise to pre-excitation syndromes. The bundle of Kent is the name applied to a strand of muscle that is separate from the AV node and can transmit impulses between the atria and ventricles. Myocardial fibres that bypass the AV node and carry impulses into the upper portion of the bundle of His are known as James fibres. Fibres that arise from the lower end of the AV node and bypass the Bundle of His are known as Mahaim fibres.
The AV node

The AV node is 2 mm thick and 4 mm long and is situated on the right side of the central fibrous body. The posterior margin of the AV node abuts or lies close to the ostium of the coronary sinus. The AV node has a labyrinthine fibrous structure which is responsible for the fragmentation of the activation front and delay in impulse conduction. The delay produced by the node is important for two reasons:

1. It allows the atria time to eject their contents into the ventricles, so that atrial systole contributes to ventricular performance by increasing end ventricular diastolic volume without a major increase in mean atrial pressure.

2. It limits the number of impulses which may be transmitted to the ventricles from the atria.

The node has been functionally divided into an atrionodal (AN) region, which receives impulses from the SA node, a nodal (N) region where the impulse is slowed (spontaneous pacemaker activity is absent in this region) and nodal-His (NH) region where the fibres become straightened to enter the His bundle. The blood supply of the AV node and the bundle of His arises from the right coronary artery in 90% of normal individuals. An AV nodal block is commonly seen in patients who have inferior or posterior myocardial infarction (i.e. myocardial infarction associated with right coronary artery obstruction).

The embryological developments of the SA and AV nodes are such that the right vagus is distributed mainly to the SA node and the left vagus to the AV node. Adrenergic fibres are distributed to the atrial and ventricular myocardium as well as the conducting tissue of the
Physiology of Myocardial Contraction

myocardium, whereas the vagal fibres are distributed only to the nodal tissue and atrial musculature.

**The bundle of His, His bundle branches and Purkinje fibres**
The bundle of His contains an orderly array of parallel fibres. It is approximately 20 mm long and is located inferiorly and posteriorly to the membranous portion of the ventricular septum. The His ‘penetrating’ portion penetrates the central fibrous body between the tricuspid, mitral and aortic valves. The ‘branching’ portion of the bundle gives off a left bundle branch at the top of the ventricular septum and continues as the right bundle branch.

The left bundle branch passes down the left side of the ventricular septum and emerges below the posterior cusp of the aortic valve, dividing into a long and thin superior (anterior) branch, which ends in the medial basal portion of the anterior papillary muscle, and a short thick inferior (posterior) branch which terminates in the medial basal portion of the posterior papillary muscle.

The right bundle branch is a thin structure which passes down the right side of the ventricular septum and along the free edge of the moderator band to the base of the anterior papillary muscle of the tricuspid valve. It gives off very few branches until it reaches the base of the papillary muscle where it branches extensively.

The bundle branches distribute the impulse to the Purkinje system which, in turn, activates the ventricular muscle from the endocardial to the epicardial surface. The thin right bundle branch and the anterior division of the left bundle branch are more susceptible to conduction delays than is the thick fan-shaped posterior division of the left bundle branch.

**ELECTROPHYSIOLOGY OF THE HEART**

**The sarcolemma**
The cardiac cell membrane (sarcolemma) is an ion-impermeable lipid bilayer composed of phospholipid molecules that separate the myocardial extracellular fluid (ECF) and intracellular fluid (ICF) compartments. With the appropriate stimulus, macromolecular proteins that traverse the lipid bilayer (referred to as channels), selectively permit ions to move from one side of the sarcolemma to the other. These channels are selectively permeable to different ionic species (including sodium, potassium and calcium) and are controlled by ‘gates’ which may be voltage sensitive, time sensitive, and receptor operated. Flow through the channel for a particular ion depends upon the driving force (i.e. the difference between the transmembrane potential and the equilibrium potential for that ion) and the ease with which the ion passes through the channel (i.e. the conductance).

The differences in ionic concentrations, or more precisely ionic activities, across the sarcolemma establish the electrochemical gradients. Concentration gradients for \( K^+ \) and \( Ca^{2+} \) cause \( K^+ \) to move from the intracellular to the extracellular compartment, and \( Na^+ \) and \( Ca^{2+} \) from the extracellular to the intracellular compartment. Energy-dependent ionic pumps are required to maintain the differential ionic concentrations across the membrane.

**The sodium-potassium pump**
A specific cell-membrane enzyme, the magnesium- and ATP-dependent, sodium- and potassium-activated adenosine triphosphatase (NaK-ATPase), is responsible for the active transport of \( Na^+ \) out of and \( K^+ \) into the intracellular fluid. This enzyme is a membrane-spanning tetramer consisting of two dimers, each composed of noncovalently interacting alpha and beta subunits (Fig. 2.2). The alpha subunit traverses the cell membrane 10 times and contains an active site for ATP hydrolysis on the intracellular side and a cardiac glycoside binding site on
the extracellular side. Optimal binding of cardiac glycosides to the specific inhibitory site on the alpha subunit requires ATP, \( \text{Na}^+ \) and \( \text{Mg}^{2+} \), and is inhibited by extracellular potassium\(^4\).

![Diagram of NaK-ATPase](image)

**Fig. 2.2** Diagrammatic structure of NaK-ATPase, consisting of two alpha (with an intracellular catalytic site for ATP and an extracellular site to which cardiac glycosides bind) and two beta subunits. (Modified from Sweadner KJ, Goldin SM, Active transport of sodium and potassium ions: mechanism, function, and regulation, N Engl J Med 1980;302:777-83).

During normal NaK-ATPase function, three intracellular \( \text{Na}^+ \) ions bind to the NaK-ATPase, causing the bound ATP to phosphorylate and change the NaK-ATPase conformation so that \( \text{Na}^+ \) ions are moved to the opposite side of the membrane. Two \( \text{K}^+ \) ions move from the ECF to the ICF compartment as the phosphorylated intermediate hydrolyses and the NaK-ATPase returns to the starting conformation. However, while a tetrameric structure of two alpha-beta dimers (Fig 2.2) may exist in the membrane, it appears that the tetrameric structure may not be necessary for the \( \text{Na}^+ - \text{K}^+ \) transport mechanism, as detergent solubilization of the tetrameric structures yield an alpha-beta dimer which retain sodium and potassium-stimulated ATPase activity\(^5\), therefore the transport mechanism as shown in fig 2.3, may not be strictly correct.

As the ratio of \( \text{Na}^+ \) to \( \text{K}^+ \) transported is 3:2 the pump is ‘electrogenic’, i.e. capable of generating an electric current across the cell membrane. The potential so generated, however, probably contributes to less than 10 mV of the resting membrane potential (RMP). The majority of the RMP is due to the cell membrane's permeability to \( \text{K}^+ \).

For the pump to function normally, \( \text{K}^+ \) must be present on the outer side of the membrane and \( \text{Na}^+, \text{Mg}^{2+} \) and ATP must be present on the inner side of the membrane. Cardiac glycosides, only inhibit the pump when they are on the extracellular side of the cell membrane.

Acute stimulation of the pump in skeletal muscle by insulin, \( \beta_2 \)-adrenergic agonists (e.g. catecholamines) and theophylline increases intracellular uptake of potassium and reduces the extracellular potassium concentration. Upregulation of the pump is induced by physical
training, thyroid and glucocorticoid hormones. Downregulation occurs with muscular inactivity, hypokalaemia, hypothyroidism, cardiac failure, myotonic dystrophy and McArdle’s syndrome.\(^6\)

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**Physiology of Myocardial Contraction**

The resting membrane potential

The RMP is the potential difference across the cell membrane during electric diastole. For the myocardial muscle fibre it is - 90 mV (i.e. the ICF has a negative potential when compared with the ECF). The RMP is largely determined by the K\(^+\) gradient across the cell membrane; as K\(^+\) is about 20 times more permeable than Na\(^+\), it tends to move down its concentration gradient leaving the interior of the cell negative. If, at rest, the sarcolemma was more permeable to Na\(^+\) than K\(^+\), then Na\(^+\) would tend to move to the interior of the cell and cause a positive RMP (this movement of sodium is only facilitated during phase 0 of the action potential).

The RMP may be derived from the Nernst equation.

\[ E_K = 61.5 \times \log \left[ \frac{[K^+]_{o}}{[K^+]_{i}} \right] \]

Where  
- \( E_K \) = RMP (equilibrium potential for K\(^+\))  
- \( [K^+]_{o} \) = K\(^+\) concentration outside the cell  
- \( [K^+]_{i} \) = K\(^+\) concentration inside the cell

The extracellular K\(^+\) has a greater effect than intracellular K\(^+\) on RMP. An increase in ECF K\(^+\) reduces the RMP, inactivating the fast response, and reducing the conducting velocity, all of which can cause the electrocardiogram (ECG) changes of, prolongation of the PR interval and QRS wave, which may lead to sinus arrest and broad wave slow ventricular tachycardia, respectively. Hyperkalaemia also accelerates repolarization, producing tall peaked T waves. A decrease in ECF K\(^+\) hyperpolarizes the cell membrane, although as the permeability of the membrane to K\(^+\) reduces with hypokalaemia, the hyperpolarization is smaller than is expected from the Nernst equation\(^7\).

The resting membrane potential is set largely by the inward rectifier K\(^+\) channels (\(I_{K1}\))\(^8\).
**The myocardial cell action potential**

**Phase 0.**
This occurs in all normal cardiac tissue except the SA and AV nodes and represents the initial fast depolarisation phase due to a rapid inward current. The rapid inward current ($i_{Na}$) is initiated by the elevation of the RMP from -90 mV to a threshold value of -60 mV, causing the cell membrane to open the 'm' gate of the Na (fast) channel (i.e. the channel is in the 'open' or 'active' state), increasing the membrane permeability to Na$^+$ (Fig. 2.4). The stimulus also decreases the membrane permeability to K$^+$ (as depolarization deactivates the inward rectifier $i_{K1}$ channels). Both of these changes cause the cell to reverse its polarity, with the interior of the cell changing from -90 to +30 mV.

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**Fig. 2.4** The ECG, intracellular cardiac action potential, myocardial tension and ionic conductances (rapid inward (gNa$^+$), slow inward (gCa$^{2+}$), outward current (gK$^+$)). The absolute refractory period occurs between the first two dashed lines and the relative refractory period occurs between the last two dashed lines. (Modified from Poole-Wilson PA, Potassium and the heart, Clin Endocrinol Metab 1984;13:249-260.)

While the Na channel ‘m’ gate remains open with depolarization, there is a slow closure of the Na channel ‘h’ gate, which terminates the inflow of Na$^+$ ions through the Na channel, causing the initiation Phase 2 (Fig. 2.5). The Na channel system remains inactivated and cannot be reopened immediately, explaining the refractory period which occurs before the system is ‘cocked’ again and able to ‘fire’.
The deactivation of the inward rectifier $I_{K1}$ channels is prolonged being reactivated again during Phase 3, at which stage the slow $\text{Ca}^{2+}$ channels are deactivated. The rapid inward current ($I_{Na}$) is dependent upon the RMP. If the RMP is less negative (i.e. higher) than -90 mV, before the stimulus, the rate of depolarisation is slow and the impulse is conducted slowly. The rapid inward current is blocked by a RMP of less than -60 mV, which may occur with a high external concentration of $K^+$. If the RMP is more negative (i.e. lower) than -90 mV before the stimulus, then the rate of depolarization is rapid and the impulse is conducted rapidly.

Local anaesthetics block the Na channel and inhibit depolarisation by the uncharged lipid soluble local anaesthetic base penetrating the cell membrane, dissociating, and the positively charged cation binding to the anionic components of the Na channel’s internal axoplasmic mouth. The ‘resting’ state of the Na channel exhibits least affinity, and the ‘open’ and ‘inactive’ states of the Na channel exhibit greatest affinity, for local anaesthetic drugs. The Na channel recovers from the block between each action potential and an additional block develops each time the channel opens and inactivates during an action potential, causing a frequency-dependent nature to the block. Quinidine has a higher affinity for the ‘open’ state, amiodarone a higher affinity for the ‘inactive’ state, and lignocaine has equal affinity for both states. Although it acts as primarily as a carrier, the local anaesthetic base contributes to the blockade by causing the membrane to swell, so ‘pinching’ the sodium channel. Tetrodotoxin (unlike local anaesthetic drugs) blocks the external entrance of the sodium channel.

**Phase 1**

Phase 1 represents an initial period of rapid repolarization due to closure of Na$^+$ channels and a transient outward current ($I_{to}$) caused by a rapid activation (i.e. increase in K$^+$ permeability) then inactivation of outward K$^+$ channels.

**Phase 2**

Phase 2 is a plateau period of repolarization which results from an increase in the K$^+$ permeability, due to activation of the delayed rectifier K$^+$ channels ($I_{Kd}$) and a ‘slow’ inward current due to an inflow of Ca$^{2+}$ and Na$^+$ ions through a ‘slow’ channel. This ‘slow’ channel is known as the calcium channel as it is 100 times more selective for Ca$^{2+}$ than Na$^+$, even though...
both Ca\(^{2+}\) and Na\(^{+}\) ions flow through it and Na\(^{+}\) ions may account for nearly one-third of the slow inward current (due to a higher ECF Na\(^{+}\) in comparison to Ca\(^{2+}\))\(^{13,14}\).

During phases 1 and 2 both the ‘m’ and ‘h’ gates of the Na channel are closed (i.e. the Na channel is in the ‘inactive’ state) and there is a gradual return of the intracellular potential toward zero due to an increase in Ca\(^{2+}\) permeability triggered by the inward Na\(^{+}\) current. This slow inward Ca\(^{2+}\) current is also responsible for the coupling of the excitation of the cell membranes to the activation of the contractile proteins and is sensitive to the ECF Ca\(^{2+}\) concentration.

An important feature of many Ca channels is their sensitivity to control by sarcolemmal receptors. Beta-1 agonists in cardiac muscle and alpha-adrenergic agonists in vascular smooth muscle increase Ca\(^{2+}\) influx via the slow inward current. In both cases, the increase in Ca\(^{2+}\) flux appears to be due to the recruiting of an additional number of active Ca channels rather than by increasing the size of the channel or altering the rate at which the gates open or close. However, to explain these differences, the Ca channels have been divided into two broad groups (voltage-sensitive or receptor operated) depending on the stimulus required to achieve the activated state. Channels which are activated in response to an appropriate change in the membrane action potential are known as voltage-sensitive channels. The receptor-operated channel is dependent for its activation on an interaction between cell surface receptors and specific neurotransmitters (e.g. acetycholine, noradrenaline, histamine and adenosine).

Phase 3
This represents a relatively fast period of repolarization with a slow return of the intracellular potential to the RMP of - 90 mV due to a delayed increase in K\(^{-}\) permeability (due to a reactivation of the inward rectifier Ik1 channels and deactivation of the delayed rectifier Ik channels) and decrease in Ca\(^{2+}\) permeability. With repolarization, the sodium channel ‘h’ gate opens while the ‘m’ gate remains closed (i.e., the sodium channel is in the ‘resting’ state).

\(I_{K(\text{ATP})}\) is a K\(^{-}\) current carried through a channel which is opened by intracellular ADP (and other intracellular nucleoside diphosphonates) and blocked by ATP (an effect which is inhibited by adenosine, ADP and other intracellular nucleoside diphosphonates). The channel is not blocked by extracellular ATP. This channel contributes to the shortening of the action potential during myocardial ischaemia and has been associated with the cardioprotective mechanism of ischaemia related preconditioning.\(^{15}\)

Phase 4
The action potential of the myocardial conducting tissue (with the exception of the mid AV nodal region) has an unstable resting membrane potential due to a steady inward current (\(I_{f}\)) carried by Na\(^{+}\) through a relatively nonspecific channel activated by polarization to high membrane potentials in SA and AV nodal cells and His-Perkinje cells.\(^{16}\) This channel is strongly modulated by neurotransmitters and is responsible for the tissues pacemaker activity. Acetylcholine decreases the slow inward current by activating the receptor operated muscarinic K channels (\(K_{\text{ACH}}\)). This channel is also opened by activation of the purinergic (adenosine) receptor. The speed with which the RMP reduces to the threshold potential, determines the rate at which the tissue discharges.

The SA and upper AV node have a diastolic depolarisation phase (Phase 4), a maximum RMP of -70 to - 50 mV, and a threshold potential (with depolarisation) which is - 40 mV, i.e. the slow inward current is activated when the fast inward current is inactivated, implying that an action potential can occur in partially depolarised cells in which the fast Na channels have been inactivated. The action potential of the AV node is due to the slow inward Ca\(^{2+}\) current
alone as it is resistant to Tetrodotoxin (a fast Na channel inhibitor) and is sensitive to verapamil and manganese (slow Ca channel inhibitors).  

The action potential of nodal tissue is slower and the peak of the action potential is rounded with a rounded repolarization curve, with no definite phase 1, 2 or 3 (Fig. 2.6). Mid nodal tissue does not have a diastolic depolarisation phase. The action potential of the bundle of His and Purkinje system is similar to that of ventricular muscle with the addition of a diastolic depolarisation phase.

Fig. 2.6 The action potentials of different regions of the heart.

The action potential gives myocardial tissue one or all of the properties of:

1. Conductivity (i.e. dromotropic effect): this is the ability to conduct an impulse, the speed of which is related to speed of depolarisation (i.e. Phase 0)

2. Automaticity (i.e. chronotropic effect): this is the property of spontaneous impulse formation, and is specific for conducting tissue (i.e. diastolic depolarisation or phase 4)

3. Excitability (i.e. bathmotropic effect): this is the property of all myocardial tissue which relates to an ability to respond to a stimulus. This is influenced by the RMP, threshold potential and speed of diastolic depolarisation.

4. Refractoriness: this describes the period in which there is a reduced ability of the myocardium to respond to a stimulus and is altered by mechanisms that alter phase 1, 2 and 3. Classically the absolute refractory period is defined as the interval in the cardiac cycle during which no stimulus can evoke a propagated response, whereas the relative refractory period is defined as that interval where a strong stimulus can evoke such a response (Fig. 2.4). However, there is no period in the cardiac cycle in which a sufficiently long or strong stimulus will not produce a response. During the supernormal period (i.e. following the end of the relative refractory period), a less than normal stimulus will produce a propagated impulse.

THE NORMAL HEART RATE

Normally, the sinus node initiates the cardiac impulse by depolarising first. The rate is a consequence of the intrinsic rate of the SA node, sympathetic tone, and vagal tone. At rest, the sympathetic tone is quite small as evidenced by the observation that the change in sinus rate, after beta-blockade in resting individuals, is about 10 beats per minute\(^\text{17}\), whereas resting vagal tone is quite high, as evidenced by the observation that vagolysis with atropine results in an increase in resting heart rate by 20-40 beats per minute\(^\text{18}\).
The influence of parasympathetic stimulation is largely limited to the atria and AV node, although some ventricular muscarinic receptors and a vagal influence (particularly of the left bundle branch) have been reported. Vagal stimulation (liberation of acetylcholine), increases nodal tissue permeability to $K^+$ and decreases $Ca^{2+}$ conductance. This increases the RMP and threshold potential, and decreases the diastolic depolarisation and refractory period. These effects act in concert to decrease the rate of reaching the threshold potential and thus the rate of impulse formation by the pacemaker cell.

Sympathetic stimulation, via noradrenaline stimulation of the beta receptors, reverses the above effects due to an increase in membrane permeability to $K^+$ and increase in $Ca^{2+}$ conductance.

The rate of impulse formation (i.e. pacemaker rate) and conduction velocities of different parts of the conducting system vary. The pacemaker rate progressively decreases, with the SA rate varying from 60 to 100/min, AV node rate varying from 40 to 60/min and Purkinje fibre rate varying from 20 to 40/min. The fibres of the Purkinje system and bundle branches conduct at a rate of 2 - 4 m/sec, the atrial pathways conduct at a rate of 1 m/s, ventricular myocardium conducts at a rate of 0.5 - 1 m/s and the AV node conducts at a rate of 0.05 m/s.

The intrinsic heart rate gradually decreases with age. It is approximately 105 /min at the age of 30, compared to 85 /min at the age of 60. The normal sinus rate for adults ranges from 30-100 /min during a 24 hr period, and is slowest during sleep.

**MYOCARDIAL MUSCLE STRUCTURE AND MECHANISM OF CONTRACTION**

Myocardial muscle fibres, like skeletal and smooth muscle fibres, can be excited electrically, chemically or mechanically to generate an electrical impulse (i.e. an action potential) which is transmitted along the cell membrane, into the interior of the cell to activate an intracellular contractile mechanism.

**Myocardial muscle structure**

While the myocardial muscle cell is one-tenth the diameter of the skeletal muscle cell, the myofibrils of cardiac and skeletal muscle are the same morphologically. They are arranged parallel to the axis of the muscle fibre and are contained in repeating units called sarcomeres. The sarcomere is delineated by two successive narrow dark lines known as Z lines. Between the Z lines is a dark centrally located region known as the A band (anisotropic band which rotates polarized light). At either end of the A band are lighter staining sections known as I bands (isotropic band) which are bisected by the Z lines. The central region of the A band has a lighter staining zone known as the H band. In the centre of the H band is a dark line known as the M line (Fig. 2.7). The cross-striated appearance of the myofibrils arises from the arrangement of overlapping thick and thin myofilaments. The thicker myosin filaments form a parallel arrangement that extends throughout the length of the A band and are held by centrally located connections at the M line. The thinner actin filaments attach to and extend from the Z line to interdigitate with the myosin filaments. The interdigitating area of the actin and myosin filaments give rise to the outer dense areas of the A band. The less dense area of the I band is composed only of actin filaments, and the H band contains only myosin filaments. The widths of the H zone and I band are determined by the degree of actin and myosin overlap.

While smooth muscle has a similar contractile mechanism to both cardiac and skeletal muscle, the actin and myosin complexes are arranged at random, and thus smooth muscle is distinguishable from skeletal and cardiac muscle by its lack of visible cross striations.
The sarcolemma
The sarcolemma, or cell membrane, of skeletal and myocardial muscle consists of an inner bilayered structure (plasmalemma) and an outer surface coat (glycocalyx). The latter has an inner ‘surface coat’, which appears as an extension of the plasmalemma, and an outer ‘external lamina’. In cardiac muscle the glycocalyx is believed to be an important site of Ca\(^{2+}\) binding and exchange.

The T-system
The T-system (Fig. 2.7) consists of tubular invaginations of the sarcolemma, entering the cell at right angles to the sarcolemma, with the lumen of the tube being in contact with the extracellular fluid. The invaginations are often in close proximity, but not in direct continuity with the sarcoplasmic reticulum. In cardiac muscle the tubes of the T-system invaginate predominantly at the Z line, whereas in skeletal muscle they invaginate at the junction of the A and I bands of the sarcomere. In both muscle types the tubes penetrate to the centre of the myofibril and occasionally extend longitudinally between adjacent myofibrils to connect adjacent sarcomeres. The tubes of the T-system of cardiac muscle are about five times the diameter of the tubes of the T-system of skeletal muscle, and (unlike the skeletal T-system) the glycocalyx invaginates with the cardiac T-system storing a large amount of Ca\(^{2+}\) bound to the negatively charged mucopolysaccharide of the glycocalyx. The T-system is absent in myocardial conducting fibres.

The function of the T-system is to distribute the surface action potential throughout the internal portion of the muscle cell as well as distributing the cell membrane (sarcolemmal) functions throughout the internal portions of the cell (e.g. maintaining the intracellular milieu of high K\(^+\) and low Na\(^+\), providing a slow current with the plateau phase of the action potential and extruding Ca\(^{2+}\) and Na\(^+\) during diastole).

The sarcoplasmic reticulum
The sarcoplasmic reticulum (SR) is an intracellular system of tubules which are oriented longitudinally within the muscle cell with no direct connection with the extracellular fluid. In skeletal muscle the SR has about four times the volume of the SR in cardiac muscle. The SR of the skeletal muscle have large saccular extensions (cisternae) which abut the T system on both sides. The three structures are known collectively as ‘triads’. In cardiac muscle the SR consists of a tubular network which provides a free lattice over the A band and dilated ends abutting the
Physiology of Myocardial Contraction

T-tubules. The latter structures are known collectively as ‘diads’. The SR functions as an intracellular Ca\(^{2+}\) modulator.

During muscle cell depolarisation, the action potential travels throughout the T-system causing an increase in the Ca\(^{2+}\) permeability of the abutting SR (an effect which may be reduced by lignocaine, procaine or halothane\(^{24}\)), allowing Ca\(^{2+}\) to move passively down its electrochemical gradient, increasing the cytoplasmic Ca\(^{2+}\) concentration around the actin and myosin filaments, thereby initiating contraction. With repolarization Ca\(^{2+}\) is removed from the cytoplasm. As this moves the Ca\(^{2+}\) against its electrochemical gradient, this process requires energy. With sarcolemmal repolarization the SR calcium pump (i.e. Ca\(^{2+}\) and Mg\(^{2+}\)-dependant ATPase), and the sarcolemmal Na/Ca pump removes Ca\(^{2+}\) from the cytoplasm to initiate relaxation. The function of the SR as the primary regulator of myoplasmic Ca\(^{2+}\) during contraction and relaxation is well established for skeletal and smooth muscle.\(^{25}\) However, in cardiac muscle, the SR is not the sole contributor to myoplasmic Ca\(^{2+}\) and an extracellular source of Ca\(^{2+}\) is also required for contraction.

Mechanism of contraction

Regulation of intracellular calcium

Cardiac muscle needs an extracellular source of Ca\(^{2+}\) to contract. This was demonstrated initially by Ringer who showed that the contraction of a frog heart ceased when Ca\(^{2+}\) was removed from the perfusate fluid\(^{26}\). The perfusion of myocardial fibres with a calcium-free solution results in a decrease of contractile tension with a half-time of 1 minute or less, whereas with skeletal muscle the contractile tension decreases with a half-time of about 2 h\(^{27}\). Mines showed that while contraction was inhibited for myocardial fibres, excitation was retained under these conditions, demonstrating the importance of external Ca\(^{2+}\) for cardiac muscle excitation-contraction coupling.\(^{28}\) Excitation-contraction coupling describes the process of activation of muscle contraction by cell membrane excitation.

In skeletal muscle, contraction is modulated by the recruitment of motor units (individually innervated groups of muscle fibres). Cardiac muscle, however, functions as a syncytium, a single stimulus produces a contraction which occurs as an all or none phenomenon. Myocardial contraction is modulated by the degree of activation of individual muscle fibres, and occurs by alterations in the cellular distribution of Ca\(^{2+}\) ions. There are seven mechanisms that control cytoplasmic Ca\(^{2+}\) concentrations.

1. Electrogenic slow inward current (through a voltage-dependent and a receptor-dependent channel). The small but significant, (i.e. 2%-5% of the total Ca\(^{2+}\) required for a contraction) quantity of Ca\(^{2+}\) that enters the myocardial cell from the ECF, does so during the plateau phase (phase 2) of the action potential and is responsible for the inward ‘slow current’. The prolonged action potential also prolongs the refractory period and thus protects the myocardial muscle from initiating a tetanic response. In the mammalian myocardium, this Ca\(^{2+}\) is not immediately available for binding to the contractile proteins; instead, it is first retained in an intracellular store (probably the space immediately beneath the sarcolemma related to the subsarcolemmal cisternae of the SR) and only during subsequent contractions does it become available to augment systolic force. While the ‘slow current’ Ca\(^{2+}\) is of insufficient quantity to fully activate the contractile process, it releases intracellular Ca\(^{2+}\) stores from the inner layer of the sarcolemma, the T-system invaginations and the SR, to fully activate myocardial contraction. Striated muscle has no action potential plateau phase, and thus there is not a Ca\(^{2+}\)-induced Ca\(^{2+}\) release.
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2. A 3Na\(^+\)/Ca\(^{2+}\) exchange across the sarcolemma (extruding Ca\(^{2+}\) from the cell). Digest inhibition of the sarcolemmal NaK-ATPase causes a rise in intracellular Na\(^+\) which in turn inhibits the 3Na\(^+\)/Ca\(^{2+}\) exchange and increases intracellular Ca\(^{2+}\).

3. A Mg\(^{2+}\)-dependent Ca-ATPase which when phosphorylated by cyclic AMP (accounting for rapid relaxation with beta stimulation) sequesters Ca\(^{2+}\) into the lumen of the sarcoplasmic reticulum during relaxation.

4. A sarcolemmal Ca-ATPase which actively extrudes Ca\(^{2+}\) from the cell.

5. Uptake and release of Ca\(^{2+}\) by mitochondria. Mitochondria have a large capacity but low affinity for Ca\(^{2+}\) and can only generate slow changes in intracellular ionised Ca\(^{2+}\) concentrations. Mitochondrial uptake and release is thought to play little if any role in the normal beat-to-beat regulation of the cytosolic Ca\(^{2+}\) concentration, although in disease it may play a role in modifying myocardial contraction.

6. Non-slow channel Ca\(^{2+}\) movement across the sarcolemma.

7. Buffering of Ca\(^{2+}\) by intracellular proteins (e.g. calmodulin, troponin C and myosin-phosphorylase light chains).

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**Contractile proteins**

Five major proteins participate in the contractile process (Fig. 2.8)\(^{32}\) the contractile proteins actin and myosin and the regulatory proteins troponin and tropomyosin and myosin-binding protein C.

1. **Actin** is a globular protein (mol. wt 43,000) that polymerises to form a double helical filament, it also has the property (in the presence of Mg\(^{2+}\)) of activating the extremely low rate at which myosin hydrolyses ATP.

2. **Myosin** is a hexamer (mol. wt 460,000) consisting of a pair of heavy chains (mol. wt 200,000) and two pairs of light chains (mol. wt 20,000). Myosin is an ATPase and may
hydrolyse ATP at an extremely slow rate, however for a rapid and physiological rate it requires actin and Mg$^{2+}$. The ATPase activity resides in the heavy chains which exist in $\alpha$ and $\beta$ isoforms. The $\alpha$ isomer has a higher ATPase activity and in the human predominates in the atria, whereas the $\beta$ isomer predominates in the ventricles. The isoforms are regulated by alteration in genetic expression due to change in activity, innervation and hormonal milieu (e.g. an increase in $\alpha$ isoform occurs in hyperthyroid states).

3. **Tropomyosin** (mol. wt 66,000) is composed of two subunits that coil about each other and lie in the grooves created by the two strands of the actin filament.

4. **Troponin** consists of three subunits, troponin T (mol. wt 36,000), troponin I (mol. wt 24,000) and troponin C (mol. wt 18,000). When Ca$^{2+}$ binds to troponin C, the binding of troponin I to actin is weakened, permitting the tropomyosin to move, thereby exposing the myosin binding site of actin.

5. **Myosin-binding protein C**, binds myosin and (when phosphorylated) modulates contraction.

The affinity of troponin C for Ca$^{2+}$ can be altered. It is reduced (i.e. desensitized) with a reduction in intracellular pH, an increase in intracellular phosphate and anything that increases in intracellular cyclic AMP (e.g. $\beta$ adrenergic receptor stimulation, phosphodiesterase inhibition); and may be increased (i.e. sensitised) by stretch (i.e. Frank-Starling effect), $\alpha$-adrenergic receptor stimulation, caffeine, sulmazole, and pimobendan. While smooth muscle contraction also involves actin, myosin and tropomyosin, troponin is not involved. In smooth muscle, Ca$^{2+}$ combines with an intracellular protein known as calmodulin (phenothiazines may inhibit this combination) when the intracellular fluid Ca$^{2+}$ concentration increases from $10^{-7}$ to $10^{-6}$. The calmodulin-Ca$^{2+}$ complex activates myosin light-chain kinase which phosphorylates one of the light chains of myosin allowing actin and myosin to interact, resulting in contraction.

The action of beta-adrenergic agonists on the myocardial cell differs from that on vascular smooth muscle. In both sites intracellular cAMP increases; however, in the myocardial cell this increases the Ca$^{2+}$ flux through the receptor operated channel and thus increases the intracellular Ca$^{2+}$. In the vascular smooth muscle cell the increase in cAMP inactivates the myosin kinase as well as activating a protein kinase that decreases intracellular Ca$^{2+}$ by stimulating an active Ca$^{2+}$ pump, therefore relaxing smooth muscle.

**Contractile mechanics**

The sliding during muscle contraction is brought about by a breaking and reforming of the cross linkages between actin and myosin. The heads of the myosin molecules link to actin in the presence of Ca$^{2+}$ (Fig. 2.8). Utilising energy supplied by hydrolysis of ATP by the Mg$^{2+}$-dependent actin-myosin ATPase, the head of the myosin cross bridge swivels, moves the actin strand on, disconnects and attaches to the next active actin site. The cyclic attachment and detachment of the globular portion of the myosin molecule to the actin filament, results in the sliding of the filaments past each other, causing muscle contraction. The Ca$^{2+}$ binding to Troponin C is reversible. Relaxation occurs with the onset of repolarization, which closes the calcium gate. The Ca$^{2+}$ which is bound to the troponin is sequestered to the intracellular storage sites and extruded from the cell. Contraction occurs when the intracellular Ca$^{2+}$ concentration increases to $5 \times 10^{-6}$ mol/l, and relaxation occurs when the intracellular Ca$^{2+}$ is reduced to a value of $10^{-7}$ mol/l (i.e. 50 times less than the value in the contracted state). The removal of Ca$^{2+}$ from the contractile process requires ATP and therefore is an energy consuming process. Approximately 15% of total energy output during a cardiac cycle is due to myocardial relaxation, and if there is a myocardial energy deficit relaxation is impaired.
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The rapidly contracting and larger fibre of the skeletal muscle, requires a major intracellular Ca\(^{2+}\) store (i.e. SR) to allow Ca\(^{2+}\) to reach its binding site on troponin C by a short diffusion path. In cardiac muscle, in which the cells are smaller and the onset of contraction is slower, the requirement for an intracellular store of Ca\(^{2+}\) is less, and both intracellular and extracellular Ca\(^{2+}\) stores take part in the contractile process.

Energy metabolism

The mitochondria are more abundant in myocardial muscle than in skeletal muscle, and make up 25-30%, compared to 2-5%, of cell volume respectively.\(^{22,30}\) ATP is generated from oxidative phosphorylation, substrate phosphorylation in glycolysis and the citric acid cycle, and phosphorylation of ADP by creatine phosphokinase. The latter two are ‘back up’ mechanisms, the former accounts for 90% of the total myocardial ATP production. In normal tissue, the rate of oxidative phosphorylation and oxygen consumption is strictly coupled to the rate of ATP utilisation. Substrate (e.g. glucose, free fatty acids, ketones and branched-chain amino acids) limitation is a rare cause of reduction in myocardial output in disease, whereas reduced myocardial oxygen supply in relation to myocardial oxygen demand is often a cause of reduced myocardial performance.\(^{40}\)

Intracellular Ca\(^{2+}\) and cAMP are interrelated. Calcium regulates the rate of cAMP synthesis and breakdown, and cAMP controls Ca\(^{2+}\) ion influx into the cell by regulating the inward calcium current and intracellular uptake and release of stored calcium.\(^{41}\)

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Chapter 3

CARDIAC OUTPUT AND OXYGEN DELIVERY

REGULATION OF CARDIAC OUTPUT
Factors affecting cardiac output can be conveniently divided into disturbances of preload, contractility and afterload (Fig 3.1).  

Guyton suggests that the heart plays a relatively passive role in maintaining output relative to tissue demands, as the cardiovascular system is normally a closed circulatory loop, the blood pumped out must equal the volume of blood returned. Tissues with increased metabolic demands generate a number of vasodilator compounds, increasing their own blood supply. The reduction in peripheral resistance allows a shift of blood from the arterial to the venous side of the cardiovascular system, thereby improving venous return and thus cardiac output. The heart adjusts its output to its input with the input being adjusted by tissue demands. In health, about 75% of blood flow to tissues is controlled by metabolic vasodilating autoregulation. The other 25% of blood flow regulation is controlled by sympathetic control of skin and renal flow, to provide control of body temperature and glomerular filtration, respectively (Fig 3.2).

It is important that the blood pressure not fall when vasodilation occurs, thus cardiac output must be able to increase in response to vasodilation. In cardiogenic shock and congestive cardiac failure there is often generalised vasoconstriction in an attempt to maintain blood pressure and perfusion to the vital organs of heart and brain. Vasodilation in these conditions
may be associated with reduction in blood pressure and a reduction in blood supply to the vital organs, because the heart cannot respond to a decrease in afterload or increase in preload by increasing output.

Cardiac output (CO) is the product of the stroke volume and the heart rate. The stroke volume is altered by factors altering preload, contractility and afterload.

**Fig 3.2.** A circular mechanical model of the circulation in a 70 kg subject with the pulmonary artery systemic arteriolar tone (with regulation in all but cerebral and coronary circulations) and systemic venous tone represented and the systemic venous volume (3.2 l), pulmonary vascular volume (0.7 l) and systemic arterial volume (0.7 l) included.

**Preload**
Preload is defined as the myocardial fibre length before contraction. The Frank-Starling law states that the ‘energy of contraction is directly proportional to the initial length of the cardiac muscle fibre’. This describes a basic property of the normal heart; i.e. within physiological limits, the ventricular stroke work varies directly with the change in ventricular end-diastolic volume. The change in strength of cardiac contraction occurs from beat to beat and enables the heart to adjust rapidly in relation to change in volume. The increase in contraction is due to an increase in the amount of Ca\(^{2+}\) ions delivered to the contractile proteins, as the Ca\(^{2+}\) release during activation is a function of the initial sarcomere length. Since there is usually a direct relationship between the end-diastolic volume and end-diastolic pressure, the latter measurement is often taken as an estimate of preload. Factors which influence preload are listed in Table 3.1.

**Venous pressure**
Venous pressure is influenced by blood volume and venous tone. The major veins contain about 55% of the vascular volume, and as they are able to make rapid adjustments in their size in response to sympathetic stimulus they may be considered as a dynamic modulator of cardiac output.
Table 3.1  Factors which influence preload

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<th>Venous pressure</th>
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<td>Blood volume</td>
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<td>Venous tone</td>
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<th>Cardiac rhythm</th>
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<td>Ventricular rate (i.e. diastolic filling time)</td>
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<td>Atrial beat</td>
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<th>Intrathoracic pressure</th>
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<th>Cardiac disease</th>
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<td>Impedance of myocardium, pericardium, epicardium and endocardium</td>
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<td>Cardiac valve disease</td>
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<td>Atrial or ventricular septal defects</td>
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Cutaneous and splanchnic veins have a large sympathetic supply. Skeletal muscle veins, however, have little or no sympathetic innervation and only a small amount of smooth muscle in their walls. Venous return in these vessels is modulated by skeletal muscle activity (i.e. the skeletal muscle pump).\(^5\)

In the normal resting supine man, ventricular function is at its peak at a left ventricular end-diastolic pressure of approximately 10 mmHg.\(^6,7\) Below this point there is a direct relation between filling pressure and stroke work, while at high filling pressure, a plateau occurs. In patients with left ventricular failure, peak ventricular functions are reported at filling pressures of 18 mmHg, thus a failing left ventricle reaches its peak performance at higher filling pressures.\(^7\) In health, the sinus atrial beat normally contributes 30% of ventricular filling, although the atrial contribution is less effective in augmenting cardiac output when the filling pressure is elevated.\(^7\)

If the pressures are raised then peripheral oedema, due to an elevated right atrial pressure, or pulmonary oedema, due to an elevated left atrial pressure, may occur. Peripheral oedema is of little immediate consequence, whereas pulmonary oedema may be life threatening. In patients with shock, left atrial pressures of up to 16-18 mmHg have been proposed to allow maximum augmentation of the cardiac output with minimum risk of pulmonary oedema.\(^8,9\) However, in patients with increased pulmonary capillary permeability and noncardiogenic pulmonary oedema, left atrial pressures above 10 mmHg may be poorly tolerated.\(^10,11\)

During exercise the pulmonary arterial wedge pressure increases up to 21 mmHg (the mean pulmonary artery pressure increases from 13 mmHg to 37 mmHg) requiring an increased removal of fluid from the interstitial space.\(^12\)

**Impedance of myocardium (i.e. diastolic compliance)**\(^13,14,15\)

Ventricular diastolic function may be divided into active and passive properties of ventricular relaxation. Passive relaxation is influenced by muscle compliance, due to thickness of muscle and non contractile (i.e. fibrous and elastic tissue) elements of muscle. Active relaxation of the myocardium (i.e. lusitropic state) requires energy to shift Ca\(^2+\) from the contractile elements to intracellular stores or the extracellular space. Overt and sometimes severe cardiac failure can occur in patients with normal ejection fractions; this is due to a disorder of left ventricular diastolic compliance, the causes of which are listed in Table 3.2.\(^16\)
Table 3.2 Causes of reduced diastolic compliance

Reduced myocardial energy production
- Acute myocardial infarction
- Angina

Increased left ventricular volume
- Atrioventricular valve regurgitation
- Congestive cardiomyopathy
- Fluid overload

Increased chamber stiffness
- Hypertrophic cardiomyopathy
- Ventricular hypertrophy
- Hypertension
- Aortic stenosis
- Infiltrative myocardial diseases

Contractility

Myocardial contractility may be modified by factors that alter either intrinsic regulation or extrinsic regulation of cardiac muscle. Intrinsic regulation describes contractile properties inherent in cardiac muscle itself; for example, myocardial fibre length before contraction (i.e. preload), forces opposing ventricular fibre shortening during ventricular contraction (i.e. afterload) and heart rate (i.e. Bowditch effect - see later). Extrinsic regulation describes factors imposed from the outside (e.g. neural stimulation, hormones, drugs, disease). In an attempt to standardise intrinsic regulation, contractility has been defined as the contractile status of the heart for a given preload and afterload.17,18

Extrinsic factors that increase myocardial contractility are listed in Table 3.3. Ideally, inotropic agents used to increase myocardial contractility, should improve delivery of oxygenated blood to peripheral tissues in accordance with their metabolic needs, without increasing myocardial oxygen requirement or decreasing myocardial oxygen supply.

Table 3.3 Factors which increase myocardial contractility

Increase in sympathetic tone
Positive inotropic agents
- Sympathomimetic agents
- Cardiac glycosides
- Phosphodiesterase inhibitors

Metabolic disorders
- Hypercalcaemia
- Hypokalaemia
- Hyponatraemia
- Alkalosis

The Frank-Starling curve

This is the curve formed when a measure of cardiac contractility (e.g. cardiac output, cardiac index, left ventricular stroke work) is plotted against a measure of the initial length of the
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muscle fibre (e.g. left ventricular diastolic volume, left ventricular end-diastolic pressure, left atrial pressure, wedge pressure, pulmonary arterial occlusion pressure). The ventricular function or Frank-Starling curve moves up and to the left with agents that increase myocardial contractility, and downward and to the right with agents that decrease myocardial contractility (Fig. 3.3).

![Fig 3.3](image)

**Fig 3.3** A set of Frank-Starling curves with factors that increase myocardial contractility moving the curve up and to the left, and factors decreasing contractility moving the curve down and to the right. (Modified from Braunwald E, Ross J, Sonnenblick EH, Mechanisms of contraction of the normal and failing heart, N Engl J Med 1967;277:910-920).

It was thought that beyond a certain venous pressure, cardiac work decreased (i.e. the Starling curve had a ‘hump’), however this was subsequently shown to be the result of an experimental artifact and that while the Starling curve flattens at high venous pressures it never shows a ‘hump’. Nevertheless, in patients with chronic heart failure there is a diastolic ventricular interaction (i.e. an increase in the volume of one ventricle reduces the volume of the other due to pericardial constraint) such that a reduction in right ventricular end-diastolic volume may cause an increase in left ventricular end-diastolic volume and explain the increase the left ventricular stroke volume which is sometimes observed in patients with chronic heart failure treated with diuretics, vasodilators or venisection.

**Afterload**

Afterload is defined as the forces opposing ventricular fibre shortening during ventricular contraction. It is increased by increasing either vascular resistance or ventricular end-diastolic volume both of which increase isometric contractile activity and decrease the proportion of energy expended in myocardial fibre shortening. Ventricular wall thickness may either increase afterload (by non-contractile tissue increasing resistance to myocardial muscle fibre shortening) or decrease afterload (by ventricular muscle hypertrophy decreasing force per unit of cross-sectional wall area). For cardiac output to be maintained during an increase in afterload, myocardial work has to increase without an increase in stroke volume. Within the constraint of a minimum desirable mean blood pressure which will allow for adequate coronary and cerebral perfusion (i.e. at the lowest level of auto regulation of the coronary and cerebral circulation, which is normally a perfusion pressure of 60 mmHg), one may reduce preload and increase cardiac output without increasing myocardial oxygen demand, by using peripheral vasodilators. These agents reduce afterload by decreasing vascular resistance and ventricular diastolic volume.
Heart Rate
Cardiac rate may vary in the severest of physiological states from 40 to over 200 beats per minute, although such rates are usually not sustained for any length of time. In health, stroke volume changes little during mild or moderate exercise (particularly in the supine position) and the increase in cardiac output is mediated largely by increase in cardiac rate.21 However, in the upright position and at maximum exercise, the stroke volume may double. Increased heart rate also increases myocardial contractility which is known as the Bowditch staircase or treppe effect.

Myocardial oxygen consumption also increases linearly with increase in heart rate.

Myocardial oxygen supply
In health myocardial oxygen extraction is normally 65-70% and increases to 85-90% only under severe stress,22 thus myocardial oxygen supply depends largely upon coronary blood flow. In systole, myocardial tissue pressure is greatest in the subendocardial regions and lowest in the subepicardial regions, whereas during diastole the gradient is reversed (i.e. the pressures in the subendocardial regions are lower than the subepicardial regions24). Coronary blood flow is regulated by changes in coronary vascular resistance, which alters in response to myocardial oxygen requirements.25 Coronary perfusion pressure, within the limits of autoregulation [i.e. mean arterial pressure (MAP) 60-140 mmHg], does not alter coronary blood flow. However, below a MAP of 60 mmHg, or when coronary artery disease is present, increasing the lower limit at which auto regulation occurs, perfusion pressure becomes an important determinant of coronary blood flow, increasing with rise in MAP and decreasing with rise in left ventricular end-diastolic pressure (LVEDP).26 Also, because coronary blood flow occurs largely during diastole, an increase in heart rate can reduce myocardial oxygen supply by reducing the diastolic coronary perfusion period.27 Myocardial oxygen demand, on the other hand, increases with increase in pulse rate, contractility and afterload.28

Myocardial oxygen demand
This depends on the heart rate, afterload, contractility and temperature. While the rate pressure product (i.e. systolic blood pressure x heart rate) has been used an index of myocardial oxygen demand,29 in recent experimental studies it has been shown to have a poor correlation with myocardial oxygen demand.30 The index is seldom used now.

REGULATION OF BLOOD FLOW
Blood flow depends upon vessel diameter, perfusion pressure and blood viscosity. Resistance varies directly with the fourth power of the vessel radius (and therefore is particularly sensitive to the arteriolar diameter), as well as directly with the whole blood viscosity.31

Arteriolar diameter
Blood supply to the organs are influenced largely by the arteriolar diameter, which is regulated by mechanisms that influence the smooth muscle tone both within (intrinsic) and at a distance (extrinsic) from the vessels.

Extrinsic control mechanisms.

Neurogenic. Nerve varicosities in the vessel adventitia from sympathetic (adrernergic) vasoconstrictor fibres are prominent in the skin and mesenteric bed, releasing noradrenaline and ATP with stimulation and causing vasoconstriction usually during exercise, in shock or cardiac failure.32 Sympathetic (cholinergic) vasodilator fibres may cause vasodilation of skeletal muscle
vasculature with exercise (even with the anticipation of exercise) and can be blocked by atropine. Parasympathetic fibres (releasing vasoactive intestinal peptide), and sensory-motor fibres (releasing calcitonin-gene-related-peptide, ATP and substance P) also influence vessel tone.

**Humoral.** Blood-borne excitatory and inhibitory influences acting on the vascular smooth muscle include adrenaline, noradrenaline, prostaglandins and angiotensin.

**Intrinsic control mechanisms.**

**Inherent smooth muscle myogenic activity.** The muscle cells of the metarterioles and precapillary sphincters demonstrate a spontaneous rhythmic activity and a capacity to contract when stretched. This myogenic activity may be enhanced by extrinsic neurogenic or hormonal factors or suppressed by vasodilator metabolites. It is responsible for autoregulation of tissue perfusion within certain limits of the mean arterial pressure, thereby providing a constant blood flow to an organ throughout a wide range of perfusion pressures. Autoregulation of tissue perfusion is influenced:

1. **Phasically** (i.e., over minutes) by endothelium-derived relaxing factor which is thought to be nitric oxide (NO) or a chemically bound form of nitric oxide (e.g., nitrosothiol - which forms when oxidized NO reacts with the highly reactive thiol group on cysteine), which stimulates an intracellular guanylate cyclase and increases cGMP in smooth muscle. The mechanism of cGMP vasodilation is incompletely understood, but it is thought to be secondary to a decrease in \( \text{Ca}^{2+} \) entry into the smooth muscle cell or an increase in \( \text{Ca}^{2+} \) uptake by the sarcoplasmic reticulum. Nitric oxide is released by the vascular endothelium in response to an increased intracellular calcium concentration caused by mechanical shear stress, acetylcholine, bradykinin, substance P, platelet-activating factor, and endogenous substances that can be generated by platelet activation in close proximity to endothelial cells (i.e. thrombin, serotonin and ATP). The increase in endothelial intracellular calcium stimulates the production of nitric oxide from L-arginine by a constitutive endothelial cell nitric oxide synthase (NOS3 or eNOS, which is dependent on calcium and calmodulin), which diffuses into the vascular smooth muscle, altering vascular tone and regulating tissue perfusion.

Inducible nitric oxide synthase (NOS2 or iNOS), on the other hand, is induced in endothelial cells, smooth muscle and macrophages by endotoxin and certain cytokines (e.g. TNF, IL-1 and interferon-gamma), is independent of calcium and additional calmodulin (it binds to calmodulin tightly and therefore does not need additional calmodulin to exert its full biological activity, and is active even at low physiological intracellular calcium concentrations - although it can be made inactive if calcium is chelated), and is responsible for the sustained vasodilation (and may also be responsible for a reduction in myocardial contractility observed in septic shock). As NOS2 is dependent on gene expression and protein synthesis it may take from to 4 to 8 h after cytokine release before large amounts of NO are produced, although it may last for several hours (unlike the short-lived action of constitutive nitric oxide synthase). This induction is inhibited by corticosteroids, platelet-derived growth factor, IL-4, IL-8, IL-10, IL-13 and thrombin. The methylated arginine derivative NG-monomethyl-L-arginine (L-NMMA) is a competitive inhibitor (i.e. its effect can be reversed by L-arginine administration) of both NOS3 and NOS2 and causes vasoconstriction by reducing the formation of NO. Nitric oxide diffuses into vascular smooth
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muscle where it causes relaxation of arterioles, and veins. However, it also inhibits collagen-induced platelet aggregation (although glyceryl trinitrate is almost inactive in platelets), inhibits leucocyte adhesion to endothelial cells, scavenges superoxide, regulates TNF release and phagocytic function (i.e. modulates the inflammatory response), has antimicrobial activity, has smooth muscle antiproliferative effects, in high concentrations is cytotoxic and has a negative inotropic effect (some of which may be due to its effect of attenuating the positive inotropic response to catecholamines).

However, nitric oxide has a bi-phasic dose response on cardiac myocyte contractile function. Low concentrations (as found with sodium nitroprusside or glyceryl trinitrate infusions) have a positive inotropic effect, whereas higher concentrations (as found in patients with septic shock) have a negative inotropic effect.

Haemoglobin readily combines with NO causing it to have a half life of less than 5 seconds. Methylene blue and superoxide anions also inactivate nitric oxide. Other vasodilators may interact with nitric oxide by increasing cAMP and decreasing intracellular Ca²⁺ (i.e. beta-2 agonists, prostacyclin).

2. tonically (i.e. over hours) by endothelin-1 [endothelium-derived contracting factor (EDCF)]. Endothelin-1 is a 21 amino acid peptide which is synthesised de novo by the endothelium, from preproendothelin-1, which undergoes an initial processing to form the 38 amino acid peptide, proendothelin-1, which is in turn cleaved by an endothelin converting enzyme (ECE), forming endothelin-1. Endothelin-1 acts on surface receptors of vascular smooth muscle (endothelin A receptor) activating phospholipase C and producing the secondary messengers inositol 1,4,5-triphosphate (which releases Ca²⁺ from the sarcoplasmic reticulum) and diacylglycerol (which activates protein kinase C), causing contraction of the smooth muscle cell. In addition, endothelin-1 potentiates the effects of other vasoconstrictor hormones (e.g. noradrenaline, serotonin) and stimulates proliferation of smooth muscle cells. It is usually produced in response to hypoxia, ischaemia and shear stress.

The endothelins are a family of three closely related peptides with 21 amino acids, which have short plasma half lives (1-2 minutes) and act as potent, long acting vasoconstrictors. Endothelin-3 is formed in neural tissue, the origin of endothelin-2 is unknown. Two endothelin receptors have been cloned. The ETₐ receptor (which has a higher affinity for endothelin 1 and endothelin-2), and the ETₐ receptor (which has an equal affinity for all endothelins). The ETₐ receptors on the endothelial cells mediate vasodilation via nitric oxide. Selective and nonselective endothelin receptor inhibitors, monoclonal antibodies to endothelin and endothelin converting enzyme inhibitors have been developed as possible therapeutic agents for vasospastic diseases including migraine, Raynaud's disease, Prinzmetal's angina, acute renal failure, heart failure, cyclosporine-induced nephrotoxicity, pulmonary hypertension, and cerebral vasospasm.

Whole blood viscosity
Viscosity is defined as the resistance by a fluid to a change of shape. Factors affecting whole blood viscosity are, plasma viscosity, cellular components (red blood cells, etc.), cell deformity or flexibility and vascular components.

Plasma viscosity
Plasma viscosity is largely determined by its content of protein macromolecules, fibrinogen and globulin fraction.
Cellular components
The relationship between haematocrit and viscosity is exponential. A reduction in packed cell volume (PCV) from 20 to 15% only modestly influences viscosity, although at this level the oxygen carrying capacity is markedly reduced. However, a reduction in the PCV from 50 to 45% leads to a substantial reduction in viscosity, with the small decrease in haemoglobin being outweighed by the decrease in viscosity. This ideal PCV, balancing the reduction in oxygen carrying capacity with an increase in cardiac output due to the reduction in viscosity, is reportedly 30% and in patients who have stenotic arteries and ischaemic leg ulcers, a reduction in PCV has been associated with clinical improvement. However the validity of the conclusion that haemodilution improves tissue oxygenation, has recently been challenged, and a haematocrit of 36% or a haemoglobin (Hb) of 12 gm/dl (1 gm/dl is approx. 3.3% PCV) has been suggested as that which will give ideal conditions for circulatory oxygen transport. In the normal circulation, alterations in blood viscosity which tend to retard blood flow are easily compensated by vasodilation. In the presence of vascular stenosis when vasodilation cannot compensate for an increase in viscosity, then rheological factors may become important determinants of blood flow, and disorders such as intermittent claudication may be improved by reduction in plasma fibrinogen levels or reduction in PCV. However, to date, there are no convincing controlled trials of haemodilution, defibrination agents or drugs affecting blood rheology which have demonstrated improvement in chronic arterial disease of the leg, heart or brain. Indeed, the proponents of haemodilution list coronary insufficiency as a contraindication to haemodilution and state that a perioperative haematocrit of 30% is only acceptable for patients without respiratory or cardiac disease or where there is an increased oxygen demand.

Cell deformity or cell flexibility
This is closely related to cellular ATP, calcium, magnesium, PCO\textsubscript{2} and pH [during red blood cell (RBC) storage there is a progressive reduction in erythrocyte deformability].

Vascular component
The vascular component is related to the diameter of the vessel, state of the vessel, the endothelial surface, interaction between the cellular components and the vessel wall, and vessel wall rigidity.

Clinical features
Clinical features of an increased whole blood viscosity (i.e. the hyperviscosity syndrome) usually occur with macroglobulinaemias, and include, cerebral effects of altered sensorium, headache, dizziness, vertigo, deafness, nystagmus, ataxia, paraesthesias (i.e. Bing-Neel syndrome), visual impairment and oronasal bleeding. In immunoglobulin M (IgM) macroglobulinaemias, retinal circulation times, retinopathy and cerebral dysfunction show a close relationship to viscosity and are reversed by viscosity reduction using plasmapheresis. Plasmapheresis is used to reduce the IgM levels (as IgM distribution is 80% intravascular) to below a symptomatic threshold because some patients are able to tolerate larger quantities of IgM than others.

Function of blood vessels
Arteries
Arteries transport blood under high pressure to the tissues. They also serve as a pressure reservoir due to the elastic properties of their walls: the left ventricle tends to pull the aortic
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valve over the column of blood (as well as pump blood out) leaving the elastic recoil of the stretched arteries to maintain the flow. If the arterial system were completely rigid, very high pressures would develop throughout the system during systole and fall to zero during diastole.

**Arterioles**

Arterioles account for approximately 60% of the total resistance of the vascular system, with a pressure drop from 85-30 mmHg. They control the blood flow to organs.

**Capillaries**

Capillaries allow for an exchange of fluid and nutrients between the blood and the interstitial spaces. As the rate of flow of blood in the capillary is 1 mm/s, each RBC remains in the capillary for approximately 1 s.

Starling first described the basic forces responsible for producing fluid shifts between the circulating blood and the surrounding tissue spaces. While each organ's capillary structure is different, it is useful to consider an idealized capillary, surrounded by a tissue reservoir with a lymphatic system draining the tissues. In this system the volume flow across the capillary walls per unit time ($J_v$) can be described by the formula:

$$J_v = K \left( P_c - P_t \right) - \omega_d \left( \pi_p - \pi_t \right)$$

Where,

- $K$ = filtration coefficient of the capillary wall. This is a product of the hydraulic conductivity of the capillary wall ($k$) and its surface area ($S$).
- $P_c$ = capillary pressure
- $P_t$ = interstitial fluid pressure
- $\pi_p$ = colloid osmotic pressure of plasma
- $\pi_t$ = colloid osmotic pressure of tissue fluids
- $\omega_d$ = osmotic reflection coefficient of all the plasma proteins (i.e. $\omega_d = 1$ if the capillary wall is impermeable to the colloid, and $\omega_d = 0$ if the membrane is freely permeable to the colloid). In health, the pulmonary capillaries have a value of 0.7 while most of the systemic circulation (apart from hepatic capillaries with a value of 0.2) has a value of 0.9.

The bulk flow of water through the interstitium in man has been estimated to be about 20 l each day, although water diffusion is 40 times this rate. Plasma contains 7 g of protein per 100 ml whereas interstitial fluid contains about 1-2 g/100 ml. Because albumin passes through the capillary membrane more readily than globulin, the interstitium has a greater content of albumin (1.3 g/100 ml) compared to globulin (0.5 g/100 ml); the average oncotic pressure of interstitial protein is 4.5 mmHg. The plasma oncotic pressure is normally between 25-28 mmHg, decreasing to 21 mmHg in the recumbent position. This value is 2 mmHg lower in females and 1-2 mmHg lower in the elderly (i.e. over 50 years). A hydrostatic pressure of 19.3 mmHg is equivalent to an osmolar pressure of 1 mosmol.

The intravascular volume is in dynamic equilibrium with the interstitial volume across the capillary wall. If there is a reduction in capillary pressure (e.g. with arteriolar vasoconstriction) then fluid will move from the interstitium to the intravascular space. A reduction in plasma oncotic pressure, however, has not been observed to be consistently associated with a reduction in intravascular volume. Increases in lymphatic flow, vasomotor tone, interstitial pressure and reduced capillary permeability to protein and reduction in interstitial protein concentration by dilution and washout by the lymphatics, have been some of the suggested mechanisms to explain this observation.
Capillary pressures and the osmotic reflection coefficient vary considerably from tissue to tissue. In subcutaneous tissue there is evidence that interstitial fluid pressure is subatmospheric. The magnitude of hydrostatic pressures in a muscle capillary are 37 mmHg at the arteriolar end of capillary and 17 mmHg at the venule end of capillary. The oncotic pressure is 25 mmHg and the interstitial pressure is 1 mmHg. Thus at the arteriolar end there is a net outward pressure of 11 mmHg and at the venule end there is a net inward pressure of 9 mmHg. The venule is three times more permeable than the arteriole. Lymph has the same concentration of protein as the interstitial fluid (i.e. 1.8-2 g/100 ml). However, this varies depending upon the tissue it drains. For example, liver has an interstitial protein content of 6 g/100 ml, thus the thoracic duct in draining most tissues has a flow of 100 ml/h and an average protein value of 3-4 g/100 ml. The total lymph flow is 120 ml/h.

Venules and veins
These function as a reservoir of blood containing approximately two-thirds of the blood volume (Table 3.4).

| Table 3.4 Vascular blood volume (ml) and the amount as a percentage of total blood volume, in a 70 Kg man |
|---|---|---|
| ml | % |
| Veins | 3200 | 58 |
| Lungs | 700 | 13 |
| Heart (each chamber 120 ml) | 500 | 9 |
| Arteries | 700 | 13 |
| Arterioles | 125 | 2 |
| Capillaries | 275 | 5 |
| Total | 5500 | 100 |

TISSUE OXYGENATION

**Global Indicators**

*Mixed venous oxygen tension (PvO₂)*
The driving pressure of oxygen to the tissues is at the level of the mixed venous oxygen tension (PvO₂). Normal PvO₂ levels range between 35-45 mmHg (SvO₂ 70-80%). Levels above 45 mmHg may occur with hyperdynamic circulations (e.g. arteriovenous fistula, beriberi, cirrhosis, peritonitis, excessive catecholamine infusions) and levels between 28-35 mmHg (SvO₂ 50-65%) usually indicate a reduced oxygen delivery. At a PvO₂ below 28 mmHg, anaerobic metabolism normally becomes manifest with increasing blood lactate levels. In patients who have sepsis or acute myocardial infarction, increased lactate levels may occur at higher PvO₂ levels due to changes in regional oxygen delivery and regional tissue metabolism. When the PvO₂ has decreased to 20 mmHg all the possible oxygen extraction from blood has occurred and severe disturbance of tissue metabolism with lactic acidosis is usually evident.

*Oxygen delivery (DO₂)*
Oxygen delivery is defined as the total amount of oxygen delivery to the tissues per unit time and is the product of the cardiac output and the arterial oxygen content. If cardiac output is expressed as an index (i.e. 1.min⁻¹.m⁻²) then oxygen delivery is expressed as an index (i.e.
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The arterial oxygen content \((\text{CaO}_2)\) depends upon, haemoglobin content, haemoglobin oxygen saturation and oxygen dissolved in plasma. In a normal subject who has 15 g Hb/100 ml of blood, the oxygen content of arterial blood is approximately 20 ml/100 ml (i.e. 9 mmol/l), and normal mixed venous blood contains about 15 ml/100 ml (6.8 mmol/l). In normal man at rest with a cardiac output of 5 l/min, approximately 1000 ml of oxygen (45 mmol) is delivered to the tissues each minute. As normal resting oxygen consumption \((\dot{\text{V}} \text{O}_2)\) is 250 ml/min (11 mmol), one-quarter of the total oxygen delivery is utilised. Oxygen delivery, oxygen utilisation and cardiac function variables at rest, exercise and in cardiogenic shock are listed in Table 3.5.

Table 3.5 Oxygen delivery, utilisation and cardiac function, at rest, exercise and in cardiogenic shock in a 70 Kg man

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Shock</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (l/min)</td>
<td>5.4</td>
<td>2.4</td>
<td>25</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72</td>
<td>120</td>
<td>180</td>
</tr>
<tr>
<td>Pulse interval (s)</td>
<td>0.83</td>
<td>0.5</td>
<td>0.33</td>
</tr>
<tr>
<td>Systolic interval (s and %)</td>
<td>0.3 (36%)</td>
<td>0.2 (40%)</td>
<td>0.17 (57%)</td>
</tr>
<tr>
<td>Diastolic interval (s and %)</td>
<td>0.53 (64%)</td>
<td>0.3 (60%)</td>
<td>0.13 (43%)</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>70</td>
<td>20</td>
<td>140</td>
</tr>
<tr>
<td>End-diastolic volume (ml)</td>
<td>145</td>
<td>150</td>
<td>180</td>
</tr>
<tr>
<td>End-systolic volume (ml)</td>
<td>55</td>
<td>110</td>
<td>30</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.62</td>
<td>0.25</td>
<td>0.83</td>
</tr>
<tr>
<td>(\text{O}_2) uptake (ml/min)</td>
<td>250</td>
<td>350</td>
<td>4000</td>
</tr>
<tr>
<td>(\text{CO}_2) output (ml/min)</td>
<td>200</td>
<td>200</td>
<td>8000</td>
</tr>
<tr>
<td>AV (\text{DO}_2) (ml/100 ml of blood)</td>
<td>4.6</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>AV (\text{DCO}_2) (ml/100 ml of blood)</td>
<td>-4</td>
<td>-10</td>
<td>-10</td>
</tr>
<tr>
<td>Arterial (\text{O}_2) Content (ml/100 ml)</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

While \(\text{DO}_2\) provides information concerning global oxygen delivery, it does not indicate whether it is being distributed appropriately, which varies depending on the patients condition (e.g. the regional distribution, ml/min). Values at rest, during exercise and in cardiogenic shock in a 70 kg man are listed in Table 3.6.

The oxygen transport system is critically dependent upon cardiac output. During an acute decrease in cardiac output the oxygen requirement can only be met by increasing oxygen extraction and decreasing \(S\dot{\text{V}}\text{O}_2\). However, a reduction in haemoglobin content or saturation, or an increase in tissue oxygen requirement can be met by an increase in cardiac output and oxygen extraction. In a study of 58 anaesthetised patients after sternotomy but before coronary artery bypass, Shibutani et al, described a critical value for oxygen delivery of 330 ml.min\(^{-1}\).m\(^{-2}\) or 8.2 ml.min\(^{-1}\).kg\(^{-1}\), below which a reduction in oxygen consumption \((\dot{\text{V}} \text{O}_2)\) occurred in proportion to the decrease in oxygen delivery. The \(\text{PVO}_2\) fell to no less than 30 mmHg in any patient, indicating that reduced oxygen delivery in some patients may not be reflected by reduced \(\text{PVO}_2\).
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Table 3.6 Regional distribution (ml/min) at rest, exercise and in cardiogenic shock in a 70 Kg man

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Shock</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary</td>
<td>250</td>
<td>250</td>
<td>1000</td>
</tr>
<tr>
<td>Cerebral</td>
<td>750</td>
<td>500</td>
<td>750</td>
</tr>
<tr>
<td>Skeletal Muscle</td>
<td>850</td>
<td>450</td>
<td>20 000-30 000</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1500</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>Kidney</td>
<td>1250</td>
<td>300</td>
<td>750</td>
</tr>
<tr>
<td>Skin</td>
<td>400</td>
<td>200</td>
<td>800</td>
</tr>
<tr>
<td>Other</td>
<td>400</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Total</td>
<td>5400</td>
<td>2400</td>
<td>25 000-35 000</td>
</tr>
</tbody>
</table>

Oxygen consumption depends on the metabolic needs of the tissues and, as long as a certain minimum level of oxygen reaches the tissues, oxygen consumption is independent of oxygen delivery. In experimental animals, when oxygen delivery is reduced (with either graded anaemia, hypoxia or reduction in cardiac output), oxygen extraction is increased to a critical threshold below which tissue oxygen uptake appears to be delivery-dependent. Anaerobic metabolism is used to provide the shortfall in energy and blood lactate levels rise. In the experimental animal, this threshold oxygen delivery level is increased in sepsis. An elevated blood lactate is due to an increased lactate production caused by a reduced delivery of oxygen to tissues, if it responds to an increase in oxygen delivery. If the lactate level increases or remains the same during therapy it may be caused by a reduced capacity to metabolise lactate, i.e. thiamine deficiency, intoxication (e.g. ethanol, metformin, cyanide, nalidixic acid), liver failure, diabetes mellitus, or leukaemia.

In clinical studies, an increase in cardiac output produced by intravenous fluids was associated with an increase in oxygen uptake, in patients with lactic acidosis. Such an increase was not observed in patients without lactic acidosis, indicating that anaerobic metabolism was more likely to occur when oxygen uptake was delivery dependent.

The increase in oxygen extraction reported with increase in cardiac output in patients with sepsis, acute respiratory distress syndrome (ARDS) and treatment with positive end-expiratory pressure (PEEP), may be due to an increase in perfusion of areas previously underperfused, an increase in cardiac oxygen requirement or an increase in anaerobic threshold. However, in many cases it is more likely due to an arithmetic artefact. As the determination of oxygen consumption in many studies often uses cardiac output in its derivation, the plot of cardiac output against oxygen consumption may result in an error due to mathematical coupling.

While sophisticated mathematical analysis of the data published suggests that the oxygen-utilisation dependence on cardiac output in patients with ARDS and PEEP is a real phenomenon, in experimental studies on dogs with ARDS treated with PEEP, a reduction in oxygen utilisation was only noted with severe reduction in oxygen delivery and was not due to any special effect of PEEP or lung injury. Furthermore, when oxygen uptake has been assessed by metabolic-cart measurements using expired air and compared to the oxygen uptake by the Fick principle, a physiological coupling often occurs in patients when the Fick measurements are used but not when expired gas measurements are used. In a study, where critically ill septic and non septic patients were monitored during withdrawal of life support therapy, Ronco et al, described a threshold value of oxygen delivery almost half that
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described by Shibutani et al., and no different for both groups (e.g. 3.8 ± 1.5 vs. 4.5 ± 1.3 ml.min⁻¹.kg⁻¹ or 153 ± 85 vs. 177 ± 52 ml.min⁻¹.m⁻², septic vs. non-septic). They concluded that sepsis was not associated with an increased critical oxygen delivery or impaired oxygen extraction, and that in critically ill patients interventions to increase oxygen delivery to supranormal levels may be inappropriate, and arterial lactate concentrations may not be a specific marker of tissue hypoxia.⁹⁶

Acute isovolaemic reduction of haemoglobin to 5 g/100 ml does not produce evidence of inadequate systemic oxygen delivery (as assessed by rise in arterial blood lactate and ST segment changes on ECG) in conscious healthy resting humans.⁹⁷ The minimal haemoglobin level required in the absence of disease and at rest is 3 g/100 ml; at this level a maximum extraction of oxygen and maximum increase in cardiac output is required to achieve normal oxygen requirements.⁹⁷ The minimum haemoglobin level recorded in a patient who survived with maximum cardiovascular and respiratory support is 1.4 g/100 ml.³⁸ However, these values will not apply to patient’s who have increased oxygen requirements (e.g. infection, trauma), decreased ability to increase cardiac output (e.g. cardiac disease), hypoxia (e.g. pulmonary disease), or decreased ability to increase organ flow (e.g. arterial stenosis).

Some believe that patients with a haemoglobin of 7 g/100 ml or less should be transfused and that patients with a haemoglobin of > 7 and < 10 g/100 ml should be carefully assessed because they may have an acceptable oxygen delivery and not be subjected to the risks of a transfusion.⁹⁶,¹⁰⁰ In one study of 4470 critically ill patients, anaemia (e.g. haemoglobin < 10 g/100ml) was associated with an increased risk of death in patients with cardiac disease, and that blood transfusions decreased the risk.¹⁰¹ In a multicentre randomised trial (by the same group) of 838 critically ill anaemic patients, a restrictive transfusion approach (i.e. one that kept the haemoglobin between 7.0 - 9.0 g/100ml) was just as effective (and was associated with a lower mortality rate) than when blood transfusions were administered to keep the haemoglobin between 10 - 12 g/100 ml.¹⁰² In a retrospective study of 8787 patients who underwent operative repair of a hip fracture, perioperative transfusion in patients with haemoglobin levels of 8.0 g/100 ml or higher did not alter the 30 or 90 day mortality (although, as a non randomised trial, clinicians may have been astute enough to know when to transfuse the at ‘risk patient’ to achieve similar mortality in both groups).¹⁰²

It is clear that a single threshold for transfusion in all patients is not appropriate.

In general, optimal DO₂ in critically ill patients requires:⁷⁷,¹⁰⁵,¹⁰⁶,¹⁰⁷

1. A haematocrit of 30-35% (e.g. haemoglobin of 10-11.5 g/100 ml) in patients with clinically significant coronary artery disease (post cardiac bypass and patients with angina), chronic obstructive airways disease, cerebrovascular disease and severe trauma as well as older patients.¹⁰⁸ Other critically ill patients can be managed just as effectively with a haemoglobin varying between 7.0 – 9.0 g/100 ml.
2. A SaO₂ of greater than 90% (e.g. PaO₂ > 60 mmHg)
3. A Cardiac index > 2.5 l.min⁻¹.m⁻² (and a MAP > 60 mmHg for adequate tissue perfusion)

which will be associated with a DO₂ of > 330 ml.min⁻¹.m⁻². While some believe that supernormal values (e.g. DO₂ > 600 ml.min⁻¹.m⁻², in association with a cardiac index > 4.5 l.min⁻¹.m⁻² and a VO₂ > 170 ml.min⁻¹.m⁻²) are required to reduce mortality in the critically ill patients,¹⁰⁹,¹¹⁰ recent large prospective randomised, controlled clinical studies have demonstrated improved,¹¹¹ unchanged¹¹² and decreased¹¹³ survivals when intravascular volume expansion and inotropic agents were used in an attempt to achieve these therapeutic goals. In the largest controlled study of critically ill patients, intravascular volume expansion (e.g. blood and colloids), inotropic agents (e.g. dopamine, dobutamine, adrenaline, noradrenaline), and
vasodilator agents (e.g. nitroprusside, nitrates) were used to increase the cardiac index (in one group) to greater than 4.5 l.min\(^{-1}.m^{-2}\), or the mixed venous oxygen saturation to 70% or greater (in another group); both therapeutic interventions were not associated with a reduction in mortality.\(^{112}\)

In clinical practice, if the MAP is < 60 mmHg, intravenous fluids are usually administered to increase the wedge pressure up to 15-18 mmHg; thereafter inotropic agents are used.

The relevance of the position of the oxygen haemoglobin dissociation curve in relation to adequate oxygen delivery for the non anaemic patient is not yet clear.\(^{114}\) Those who argue from the point of view of peripheral tissue oxygenation claim that a rightward shift of the curve is to the patient's advantage. However, when hypoxia is produced by breathing air with low oxygen tensions or by pulmonary diseases characterised by low ventilation/perfusion ratios, then a leftward shift of the curve provides the haemoglobin molecule with an ability to accept more oxygen during its pulmonary capillary transit. In high altitude dwellers a leftward shift adaptation is associated with an improved survival.\(^{115}\)

**Oxygen consumption (\(\dot{V}_O_2\))**

Oxygen consumption (\(\dot{V}_O_2\)) may be determined by the Fick principle, calculating the difference between arterial and mixed venous oxygen contents and multiplying the result by the measured cardiac output. Oxygen uptake can also be measured from inspired and expired respiratory gas measurements using a metabolic gas monitoring system. To estimate oxygen consumption, inspired and expired oxygen concentrations, the expired volume and the temperature at which the expired volume is measured are required. The FIO\(_2\) often has a significant effect on the accuracy of oxygen consumption measurement and errors of greater than 6% often occur when an FIO\(_2\) of greater than 60-80% is used.\(^{116}\) This occurs because the difference between the inspired and expired oxygen concentrations becomes narrow, and small fluctuations in the gas concentrations or drift in the oxygen sensor between measurements of FIO\(_2\) and F\(\dot{E}\)O\(_2\) cause major errors. To reduce the error from separate estimations of FIO\(_2\) and F\(\dot{E}\)O\(_2\), some systems measure the difference between FIO\(_2\) and F\(\dot{E}\)O\(_2\) (using a fast differential paramagnetic oxygen sensor\(^{117}\)), calculate the RQ (using the Haldane transformation which requires gas concentrations only e.g. FIO\(_2\) - F\(\dot{E}\)O\(_2\), FIO\(_2\) and F\(\dot{E}\)CO\(_2\)),\(^{118}\) and then calculate the \(\dot{V}_O_2\) from the RQ and \(\dot{V}_CO_2\).\(^{119,120}\)

In the steady state, the \(\dot{V}_O_2\) measured by the metabolic gas monitoring system is often consistently 8% - 25% larger than the \(\dot{V}_O_2\) measured by the Fick principle.\(^{119,121,122}\)

Intrapulmonary oxygen consumption, (which is approximately 5% of total body \(\dot{V}_O_2\) in health\(^{123}\) and may be up to 15% of total body \(\dot{V}_O_2\) if the lung is infected\(^{124}\)), is not measured by the Fick principle and in experimental animals is responsible for the difference between \(\dot{V}_O_2\) measurements by the two methods\(^{124}\). In clinical practice, however, the difference may not be due to intrapulmonary oxygen consumption alone as it is not related to severity of the lung disease,\(^{125}\) or BAL cellularity.\(^{126}\)

**Regional Indicators**

With the development of shock, regional blood flow changes with a reduction in the splanchnic, skin and renal perfusion occurring to a greater or lesser extent depending on whether the shock is hypovolaemic, cardiogenic, distributive or obstructive. The assessment of regional flow may be performed clinically (e.g. capillary refill, toe-oral temperature gradient,\(^{127}\) urine
Cardiac Output and Oxygen Delivery

output), or by measuring organ venous oxygen saturations, glomerular filtration rate and gastric mucosal pH.

**Organ venous oxygen saturation**

While hepatic venous oxygen saturation has been monitored in critically ill patients and found to be a more sensitive indicator of splanchnic perfusion than mixed venous oxygen measurements, it is not easily measured and currently not widely used. Continuous jugular venous oxygen saturation monitors have been used to assess cerebral perfusion in patients with cerebral trauma.

**Glomerular filtration rate (GFR)**

The kidney is remarkably resistant to hypoxia, although severe ischaemia may cause acute renal failure. Accordingly, glomerular filtration rate (often assessed clinically by measuring urine output hourly) rather than renal venous saturation is a better indicator of adequacy of renal perfusion (and is more easily measured) and is commonly used to monitor renal function during shock.

**Gastrointestinal tonometry**

Using a polyester tube with a Silastic balloon tip and placing the balloon tip in the stomach or colon, filling the balloon with 2.5 ml of saline and allowing the mucosal PCO\(_2\) to equilibrate with the saline (which takes approximately 90 min), tonometric determination of the PCO\(_2\) allows the determination of the intramucosal pH by using the Henderson equation (the gastric intramucosal bicarbonate concentration is assumed to be similar to arterial bicarbonate concentration which is calculated from a simultaneously measured arterial blood sample). The gastric intramucosal pH (as distinct from gastric luminal pH) has been shown to correlate well with changes in splanchnic blood flow if H\(_2\) blockers are used (e.g. 150 mg ranitidine orally 12-hourly). However, as well as gastric mucosal perfusion, there are many other things that influence the gastric intramucosal pH. For example,

a. Arterial HCO\(_3\) may not equilibrate with gastric intramucosal HCO\(_3\) (i.e. during severe gastric hypoxia the gastric mucosal HCO\(_3\) may be less than arterial HCO\(_3\)). Also systemic acid base disturbances (e.g. respiratory and metabolic acidosis and alkalosis) alter the arterial HCO\(_3\), and in such circumstances the calculated gastric intramucosal pH may not reflect gastric mucosal perfusion changes (although a gap between the arterial pH and pHi may suggest a gastric perfusion deficit).

b. Alterations in gastric mucosal PCO\(_2\) may also be caused by,

1. carbon dioxide generating antacids (increasing the PCO\(_2\) and thereby decreasing the gastric intramucosal pH) and should not be used during tonometry (enteral feeding causes a fall in the intramucosal pH which returns to the baseline after 1 hour, indicating that enteral feeding should be withheld for at least one hour before measurement - the effect of sucralfate is not known, so currently tonometry is only performed in its absence).

2. pancreatic bicarbonate secretions (stimulated by gastric acid entering the duodenum) may reflux into the stomach and increase gastric PCO\(_2\) generation (this may be avoided by regular e.g. 2 to 4-hourly gastric aspiration, although continual aspiration using a sump drain may decrease the PCO\(_2\) due to air being continually sucked into the stomach. H\(_2\) blockers will also reduce pancreatic bicarbonate secretion by reducing gastric acid production).

3. Systemic acid base disturbances (e.g. respiratory and metabolic acidosis and alkalosis) which alter arterial PCO\(_2\) (and therefore gastric intramucosal PCO\(_2\)) with the alteration
in the gastric intramucosal pH not reflecting gastrointestinal perfusion changes (although a gap between the arterial pCO₂ and gastric mucosal PCO₂ may suggest a gastric perfusion deficit, and thus maybe more useful)\textsuperscript{134,135}

c. **Technical aspects.**

1. Blood gas analysers calibrated for routine blood gas analysis variably underestimate the PCO₂ in saline, thus each machine will require a specific correction factor to counter the error.\textsuperscript{136} Continuous measurement of gut lumen PCO₂ values has recently been described using a fiberoptic PCO₂ sensor which may be useful in overcoming some of the limitations of gastric tonometry.\textsuperscript{137}

2. While air introduced into the tonometer balloon will also result in artifactually lower PCO₂ measurements with saline tonometry, a technique of air tonometry has been marketed (measuring the PCO₂ using an infra-red method which also measures the end-expired PCO₂ to assess the PCO₂ gap), replacing the measured gas to decrease equilibration time.\textsuperscript{138}

Gastric mucosal pH (pHi) has been used to predict mortality (e.g. a pHi < 7.35 in patients admitted to an ICU and remaining low 12 h later was associated with an 87% mortality rate while the mortality rate was 36% if the pHi value returned to > 7.35 within this period)\textsuperscript{139} This has prompted some to use pHi as an index of resuscitation and to use intravenous fluids and dobutamine or dopexamine (due to their beta-2 effects\textsuperscript{140}) to improve splanchnic circulation if pHi is less than 7.35, even when other circulatory indices (e.g. blood pressure, pulse, cardiac output) may appear to be satisfactory.\textsuperscript{141,142,143} A decrease in gastric mucosal pH (using direct measurement of gastric juice PCO₂) has also been used as an early predictor of unsuccessful weaning in mechanically ventilated patients (e.g. the pHi remained > 7.35 only in those patients who were successfully weaned).\textsuperscript{144}

Nevertheless, while there are some studies that indicate that gastric tonometry may be useful clinically, in a study of elective abdominal aortic aneurysm postoperative surgical patients, therapy to increase low pHi did not show an improved outcome.\textsuperscript{145} Currently, measurement of pHi or tissue to arterial PCO₂ difference (or therapy to improve these values) are not of proven value in the management of critically ill patients.\textsuperscript{144}

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The autonomic nervous system is organised on the basis of the reflex arc. The level of central integration of the reflex arc vary. Simple reflexes (i.e. contraction of the full bladder) are integrated in the spinal cord; reflexes that regulate respiration and blood pressure are integrated in the medulla; and more complex reflexes that involve temperature and chemical milieu are integrated in the hypothalamus.

**Autonomic afferents**
The afferent autonomic nerves are nonmyelinated fibres that are carried via the vagus, pelvic, splanchnic and other autonomic nerves. Other autonomic afferents (e.g. from blood vessels in skeletal muscle), are carried by somatic nerves. The cell bodies of visceral afferent fibres lie in the dorsal root ganglia of spinal nerves and the corresponding sensory ganglia of sensory nerves.

**Autonomic efferents**
The efferent fibres originate in nuclei or cell groups in the mid brain, medulla, pons, cerebellum and spinal cord, as medullated preganglionic neurones. They synapse with nonmedullated postganglionic neurones and are distributed to the visceral effectors. The autonomic outflow is divided into the sympathetic and parasympathetic divisions on anatomic, physiological and pharmacological grounds. The sympathetic system consists of two gangliated trunks, together with their branches, whereas the parasympathetic system utilizes cranial and sacral nerves as its pathways. Physiologically the two systems are almost antagonistic to one another. Pharmacologically, noradrenaline is usually liberated by the post ganglionic sympathetic fibre, and acetylcholine is liberated by the parasympathetic fibre.

**Sympathetic efferents**
The efferent impulse travels via the preganglionic fibre which leaves the spinal cord with the ventral roots of the 1st thoracic to the 3rd or 4th lumbar spinal nerves. They pass via the white rami communicantes to the paravertebral sympathetic ganglion chain, where most of them end on cell bodies of post ganglionic neurones. The axons of the postganglionic neurones pass either to the viscera via sympathetic nerves, or re-enter the spinal nerves via the grey rami communicantes and are distributed to the visceral effectors supplied by these nerves.

**Parasympathetic efferents**
The cranial parasympathetic outflow supplies the visceral structures in the head via the oculomotor, facial, and glossopharyngeal nerves, and structures in the thorax and upper abdomen are supplied via the vagus nerves.

The sacral outflow supplies the pelvic viscera via the pelvic branches of the 2 - 4 sacral spinal nerves. The preganglionic fibres end on short postganglionic neurones located on or near the viscera supplied.
THE AUTONOMIC SYSTEM

The autonomic nervous system may be separated into cholinergic and noradrenergic divisions, in which chemical transmission of an impulse is by acetylcholine and noradrenaline respectively. The activity of transmission is terminated by the enzyme acetylcholinesterase when acetylcholine is the neurotransmitter, and by uptake and diffusion when noradrenaline is the neurotransmitter.

Cholinergic transmission
Cholinergic neurones consist of, preganglionic sympathetic neurones, parasympathetic post ganglionic neurones and sympathetic postganglionic neurones to the sweat glands, and skeletal muscle blood vessels (causing vasodilation). The remaining postganglionic sympathetic neurones are noradrenergic.

Synthesis, storage, release and inactivation of acetylcholine
The cholinergic neurone actively takes up choline from the extracellular fluid (a process which is blocked by hemicholinium) and, along with Acetyl-CoA, is acted on by choline acetyltransferase to produce acetylcholine (ACh). ACh is stored in synaptic vesicles at an estimated 10,000 molecules per vesicle. When an action potential travels down the axon to the nerve terminals, calcium from the ECF enters the cytosol facilitating the fusion of the axonal and vesicular membranes, causing approximately 150-200 synaptic vesicles to disrupt and release ACh into the synaptic cleft. This release of ACh by exocytosis is inhibited by botulinus toxin and hypermagnesaemia. The ACh is hydrolysed by cholinesterases to choline and acetate. True cholinesterase is responsible for the hydrolysis of ACh in the synaptic cleft and is found in the red blood cell and all sites of cholinergic transmission. Pseudocholinesterase is found in plasma, skin and intestine. It hydrolyses succinylcholine and procaine, and its physiological significance is unknown.

Cholinergic receptors
The ACh receptor at the motor end plate protrudes above the cell membrane surface into the ECF. The ion channel within the receptor is funnel shaped with the stem toward the cytoplasm of the ICF. It has a molecular weight of 250,000 and five subunits; two alpha subunits, and a beta, a delta and a gamma subunit. The macromolecule has a half-life of 6-13 days\(^2\). The ACh-binding site on the two alpha subunits in the ECF or synaptic surface of the macromolecule are the sites of competition between cholinergic agonists and antagonists. When both alpha unit sites are occupied by an agonist the central channel undergoes a conformational change to allow the passage of Na\(^+\) and Ca\(^{2+}\) ions in and K\(^+\) ions out. Both alpha units must be occupied simultaneously by an agonist; if only one site is occupied the channel remains closed.

Acetylcholine and drugs which mimic the action of acetylcholine (i.e. cholinergic drugs) act on cholinergic receptors which are classified as either nicotinic or muscarinic and are so named because the response to acetylcholine resembles the administration of either nicotine or muscarine.

Muscarinic receptors
These have been subdivided into three physiological types:

1. M1 receptors, which have a high affinity for pirenzepine and occur mainly in neural tissues,
2. \textit{M2 receptors}, which have a high affinity for gallamine and pancuronium and appear on effector tissues of the heart, neural and smooth muscle; they are also present in postganglionic parasympathetic nerves, themselves functioning as feedback inhibitory receptors. This is a G-protein selective receptor which opens a potassium selective ion channel ($I_{K,ACh}$). In the heart this decreases spontaneous depolarization (pacemaker activity) in the sinus node, and slows the velocity of conduction in the AV node.

3. \textit{M3 receptors}, which occur in the exocrine glands, neural and smooth muscle of central airways

All receptors have the same affinity for atropine whereas, both M2 and M3 receptors have low affinity for pirenzepine.\textsuperscript{3,4,5} The M2 receptors appear to have a lower affinity for glycopyrrolate than atropine as 0.2 mg i.v. of glycopyrrolate has less effect on heart rate than 0.6mg i.v. of atropine

\textbf{Nicotinic receptors}

Nicotinic receptors occur on the postganglionic neurone and adrenal medullary cells. The post synaptic receptors of the neuromuscular junction are also nicotinic receptors, and are sensitive to neuromuscular blocking agents unlike the sympathetic ganglionic receptors which show only mild response to these agents (e.g. D-tubocurarine is a mild ganglion blocker and pancuronium is a mild muscarinic blocker).

\textbf{Drugs which alter cholinergic transmission}

The drugs which alter cholinergic (Ch) transmission\textsuperscript{14} are listed in Table 4.1.

\textbf{Cholinergics.} Slight modifications of the structure of acetylcholine molecule have lead to the development of three choline esters, methacholine, carbachol and bethanechol, which have a reduced rate of degradation by cholinesterases, a reduction in nicotinic activity and act mainly as muscarinic receptor agonists when they combine with the choline receptor. Methacholine has a large cardiac muscarinic effect and has been used for paroxysmal atrial tachycardia. In comparison with methacholine, carbachol and bethanechol have less cardiac effects and more pronounced effects on the urinary bladder and gastrointestinal tract. However, unlike methacholine or bethanechol, carbachol has some nicotinic effects and thus in therapeutic doses may stimulate the autonomic ganglia, adrenal medulla and skeletal muscle. Both carbachol and bethanechol have been used in treatment of postoperative gastrointestinal atony and urinary retention. The naturally occurring cholinergic alkaloid, pilocarpine, is commonly used as a topical application in the management of glaucoma. Subcutaneous doses of 10 mg of pilocarpine have been used to assess sympathetic nerve supply (i.e. sweat test) and small doses have been used for xerostomia, hiccups, and to relieve the itch of obstructive jaundice. Toxicity from any of these agents have the clinical features of anticholinesterase poisoning.

\textbf{Anticholinergics.} Atropine and scopolamine competitively block the muscarinic actions of ACh. Their clinical effects involve many systems including,

1. \textit{Cardiovascular:} both atropine and scopolamine achieve a maximum effect on the pulse rate with an intravenous dose of 2 mg, increasing the resting pulse rate in healthy young adults by 30-50%. In the elderly, the increase in pulse rate is usually less marked. Atropine also causes cutaneous vasodilation, mainly to the face and neck.

2. \textit{Gastrointestinal:} a reduction in volume of saliva occurs with small doses of both atropine and scopolamine (e.g. 0.5 mg). However, large doses are required to inhibit the volume of gastric secretion and reduction in total gastric acid content (e.g. 3 mg). A reduction in tone and

\begin{table}
\caption{Drugs which alter cholinergic transmission}
\begin{tabular}{|l|l|}
\hline
\textbf{Cholinergics} & \textbf{Anticholinergics} \\
\hline
Methacholine & Atropine \\
Carbachol & Scopolamine \\
Bethanechol & \\
\hline
\end{tabular}
\end{table}
motility of the gastrointestinal tract with increased tone of gastrointestinal sphincters occurs with both atropine and scopolamine, and may cause constipation.

Table 4.1 Action of drugs at the autonomic synapse

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>System</th>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthesis of neurotransmitter</td>
<td>Ch</td>
<td>Hemicholinium</td>
<td>ACh Depletion</td>
</tr>
<tr>
<td>Synthesis of neurotransmitter</td>
<td>Ad</td>
<td>Alpha-Methyl</td>
<td>NA Depletion</td>
</tr>
<tr>
<td>Tyrosine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neural membrane reuptake</td>
<td>Ad</td>
<td>Cocaine</td>
<td>Accumulation of</td>
</tr>
<tr>
<td>Storage granule uptake</td>
<td>Ad</td>
<td>Tricyclics</td>
<td>NA at receptors</td>
</tr>
<tr>
<td>Release of neurotransmitter</td>
<td>Ch</td>
<td>Botulinus</td>
<td>Anticholinergic</td>
</tr>
<tr>
<td>Postsynaptic receptor (agonists)</td>
<td>Ad</td>
<td>Bretylium</td>
<td>Antiadrenergic</td>
</tr>
<tr>
<td>Postsynaptic receptor (antagonists)</td>
<td>Ch(M)</td>
<td>Atropine</td>
<td>Anticholinergic</td>
</tr>
<tr>
<td>Postsynaptic receptor (antagonists)</td>
<td>Ch(N)</td>
<td>d-Tubocurarine</td>
<td>Neuromuscular blockade</td>
</tr>
<tr>
<td>Enzymatic breakdown of neurotransmitter</td>
<td>Ad</td>
<td>Prazosin</td>
<td>Antiadrenergic</td>
</tr>
<tr>
<td>Enzymatic breakdown of neurotransmitter</td>
<td>Ad(A1)</td>
<td>Yohimbine</td>
<td>Sympathomimetic</td>
</tr>
<tr>
<td>Enzymatic breakdown of neurotransmitter</td>
<td>Ad(A2)</td>
<td>Metoprolol</td>
<td>Antiadrenergic</td>
</tr>
<tr>
<td>Enzymatic breakdown of neurotransmitter</td>
<td>Ad(B1)</td>
<td>Butoxamine</td>
<td>Antiadrenergic</td>
</tr>
<tr>
<td>Enzymatic breakdown of neurotransmitter</td>
<td>Ad(B2)</td>
<td>Neostigmine</td>
<td>Cholinergic</td>
</tr>
<tr>
<td>Enzymatic breakdown of neurotransmitter</td>
<td>Ad</td>
<td>MAOI</td>
<td>Enhance action of indirect-acting sympathomimetics</td>
</tr>
<tr>
<td>2. Displacement of Neurotransmitter from axon terminal</td>
<td>Ch</td>
<td>Carbachol</td>
<td>Cholinergic</td>
</tr>
<tr>
<td>2. Displacement of Neurotransmitter from axon terminal</td>
<td>Ad</td>
<td>Tyramine (rapid)</td>
<td>Sympathomimetic</td>
</tr>
<tr>
<td>2. Displacement of Neurotransmitter from axon terminal</td>
<td>Ad</td>
<td>Guanethidine (slow)</td>
<td>NA depletion</td>
</tr>
<tr>
<td>3. Mimic Neurotransmitter (agonists)</td>
<td>Ch(M)</td>
<td>Methacholine</td>
<td>Cholinergic</td>
</tr>
<tr>
<td>3. Mimic Neurotransmitter (agonists)</td>
<td>Ch(N)</td>
<td>Nicotine</td>
<td>Cholinergic</td>
</tr>
<tr>
<td>3. Mimic Neurotransmitter (agonists)</td>
<td>Ad(A2)</td>
<td>Clonidine</td>
<td>Antiadrenergic</td>
</tr>
<tr>
<td>3. Mimic Neurotransmitter (agonists)</td>
<td>Ad(B1)</td>
<td>Dobutamine</td>
<td>Sympathomimetic</td>
</tr>
<tr>
<td>3. Mimic Neurotransmitter (agonists)</td>
<td>Ad(B2)</td>
<td>Salbutamol</td>
<td>Sympathomimetic</td>
</tr>
</tbody>
</table>

Although the table gives the impression that the various agents have a single action, one may safely say that no drug has a single effect. Furthermore, agents that combine with a receptor may both excite (by occupying the receptor site) and block the receptor by preventing normal neurotransmitter action. Ch = cholinergic, Ad = adrenergic, NA = Noradrenaline, M = muscarinic, N = nicotinic, ACh = acetylcholine, MAOI = monoamine oxidase inhibitor

3. Respiratory: atropine and scopolamine cause bronchodilation of large airways and a reduction in submucosal secretion.

4. Central nervous system: atropine is a central nervous system (CNS) stimulant at doses greater than 5 mg, and can cause restlessness, irritability, hallucinations, agitation, delirium,
and seizures. Scopolamine, in therapeutic doses (e.g. 0.6 mg) produces drowsiness, amnesia and antiemesis, although with large doses central nervous system excitatory effects are also observed.

5. **Eye**: atropine and scopolamine cause mydriasis which will last several days if they are administered directly onto the eye.

6. **Skin**: both atropine and scopolamine reduce sweating, and may cause hyperpyrexia.

7. **Genitourinary**: both atropine and scopolamine cause urinary retention, particularly in patients who have prostatomegaly.

Intravenous atropine has a half life of 4 h. Other agents which have anticholinergic effects include glycopyrrolate, propantheline, benztropine, ipratropium, phenothiazines, antihistamines, tricyclics, quinidine, and disopyramide.

Anticholinergic agents have been used to treat, bradycardia, asthma, Parkinsonism, motion sickness, iritis, peptic ulceration, renal colic, biliary colic, intestinal spasm, diarrhoea, anticholinesterase poisoning, and as a premedication to dry oral secretions and reduce vagal reflexes with induction of anaesthesia, and to facilitate clinical examination of the fundus. In psychiatric practice, up to 400 mg of atropine three times a week has been used, with clinical recovery occurring in 6-8 h. Anticholinergic agents are contraindicated in narrow angle glaucoma, prostatomegaly and chronic constipation.

Physostigmine 1-4 mg hourly and benzodiazepines may be useful to treat the CNS disturbances due to anticholinergic overdosage.

**Anticholinesterases.** Acetylcholinesterase is a macromolecule that has a number of active centres where the hydrolysis of ACh takes place. These active centres have two areas that interact with ACh; an anionic site and an esteratic site. The anionic site contains a negatively charged amino acid that binds to the positively charged quaternary amine group of ACh. The esteratic site of the molecule contains a serine molecule which is responsible for breaking the ester linkage of the ACh, forming choline and acetylated acetylcholinesterase. The latter is rapidly hydrolysed regenerating the free enzyme.

Anticholinesterases inhibit acetylcholinesterase and prolong the effects of ACh. They can be classified as quaternary amines (e.g. edrophonium), carbamates (e.g. neostigmine, physostigmine, pyridostigmine and carbaryl), and organophosphates. The quaternary amines attach to the anionic site by an electrostatic attachment, competing with ACh for this site (i.e. they form a competitive block). The carbamates attach to the esteratic site as well as the anionic site of the enzyme. This attachment results in a chemical bonding and enzyme block, as hydrolysis of the carbamylated enzyme is about 1 h for neostigmine, physostigmine and pyridostigmine, and 6-12 h for carbaryl. The organophosphates almost irreversibly phosphorylate the esteratic site of the enzyme; therefore unless dephosphorylation is enhanced (e.g. by pralidoxime, which needs to be administered within a few hours of the organophosphate ingestion because of an ‘ageing’ of the phosphorylated enzyme), new enzyme has to be synthesised (which takes 1-3 weeks) before normal synaptic activity occurs. Physostigmine and most organophosphates pass the blood brain barrier and enter the CNS, whereas neostigmine and pyridostigmine (and pralidoxime) do not.

1. **Neostigmine** is poorly absorbed by the gastrointestinal tract and excreted unchanged via the kidneys. The effects of an oral dose of 15 mg are similar to the effects of 1-2 mg of an intravenous dose. The biological half-life of 2.5-5.0 mg of neostigmine is approximately 1-4 h, this increases in patients with renal failure to 3-8 h.

2. **Pyridostigmine** is poorly absorbed by the gastrointestinal tract. The effects of an oral dose of 60 mg are similar to the effects of 2 mg of an intravenous dose. Approximately 75% is
excreted unchanged via the kidneys. The biological half-life of 2-5 mg of an intravenous dose of pyridostigmine is approximately 3-8 h, which increases in patients with renal failure to 12-24 h.

3. **Physostigmine** is readily absorbed by the gastrointestinal tract and is destroyed by cholinesterases. Renal excretion plays only a minor role in terminating its action, thus an intravenous dose of 1 mg has a half-life of 1 h irrespective of renal function.

4. **Edrophonium** has a half life of only 2-5 min if small doses (e.g. 10 mg) are used; doses of 35-70 mg last from 3 to 8 h, and this may be longer in patients with renal failure because 75% of the agent is excreted via the kidney.

The clinical features of anticholinesterase toxicity are listed in Table 4.2.

<table>
<thead>
<tr>
<th>Table 4.2 Clinical features of anticholinesterase toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central nervous system</strong></td>
</tr>
<tr>
<td>Tremor, anxiety, confusion, seizures, coma</td>
</tr>
<tr>
<td>Miosis</td>
</tr>
<tr>
<td>Increase lacrimal secretion</td>
</tr>
<tr>
<td><strong>Skeletal muscle</strong></td>
</tr>
<tr>
<td>Fasciculations, weakness, and paralysis (depolarising block)</td>
</tr>
<tr>
<td><strong>Cardiovascular system</strong></td>
</tr>
<tr>
<td>Bradycardia</td>
</tr>
<tr>
<td>decreases rate of SA node impulse formation</td>
</tr>
<tr>
<td>increases AV block</td>
</tr>
<tr>
<td>Peripheral vasodilation</td>
</tr>
<tr>
<td><strong>Respiratory system</strong></td>
</tr>
<tr>
<td>Bronchoconstriction</td>
</tr>
<tr>
<td>Bronchorrhoea</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>Abdominal cramps, vomiting, diarrhoea</td>
</tr>
<tr>
<td>increase tone, motility and secretion</td>
</tr>
<tr>
<td>decrease tone of sphincters</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
</tr>
<tr>
<td>Diaphoresis</td>
</tr>
</tbody>
</table>

**Adrenergic transmission**

*Synthesis, storage, release, uptake and inactivation of noradrenaline*

*Synthesis and storage* (Table 4.3). Tyrosine is an amino acid which is actively transported from the ECF into the axon and converted to dihydroxyphenylalanine (DOPA) by the substrate specific cytoplasmic enzyme tyrosine hydroxylase. As this enzyme is 100-1000 times less active than the other enzymes involved in noradrenaline synthesis, it is the rate limiting step in this process. It is inhibited by noradrenaline [explaining the reduction in production of noradrenaline in chronic congestive cardiac failure (CCF) or when monoamine oxidase inhibitors are used], and alpha-methyl-*para*-tyrosine. The latter is a substrate competitive inhibitor which has been used in patients with a phaeochromocytoma.
Table 4.3  Synthesis of noradrenaline

TYROSINE  
(tyrosine hydroxylase)  
DIHYDROXYPHENYLALANINE (DOPA)  
(DOPA decarboxylase)  
DOPAMINE  
(dopamine beta-oxidase)  
NORADRENALINE

The cytoplasmic enzyme DOPA decarboxylase uses pyridoxal phosphate as a cofactor and converts DOPA to dopamine. The former is a nonspecific enzyme and may be involved in the conversion of other aromatic amino acids, e.g. tyrosine, 5-hydroxytryptophan, histidine and alpha-methyldopa, to tyramine, serotonin, histamine and alpha-methyldopamine.

Dopamine is transported into vesicles where dopamine beta oxidase uses ascorbic acid as a cofactor, and converts dopamine to noradrenaline. The noradrenaline is stored together with ATP and proteins called chromogranins, in the vesicles. The transport system requires ATP and Mg\(^{2+}\) and is inhibited by reserpine. When reserpine is present, the unstored noradrenaline is metabolised by monoamine oxidase, thus vesicle storage of noradrenaline protects it from enzymatic breakdown by monoamine oxidase. In the adrenal medulla (but not in the adrenergic nerve terminal) the enzyme phenylethanolamine-N-methyl transferase converts noradrenaline to adrenaline. The synthesis of this enzyme is enhanced by glucocorticoids.

While adrenaline, which is produced from the adrenal medulla acts as a circulating hormone, noradrenaline also acts as a circulating hormone, although it is produced largely from a sympathetic-nerve synapse overflow.

**Release.** When an action potential arrives at the nerve terminal, the storage vesicle membrane fuses with the cell membrane and releases stored noradrenaline into the synaptic cleft. This response is sensitive to ECF calcium but resistant to calcium-blocking drugs.\(^6\) The release of noradrenaline by indirectly acting amines such as tyramine, ephedrine and amphetamine, is not blocked by tetrodotoxin and is not dependent upon ECF calcium, although the effect is blocked by the inhibitors of neuronal uptake of sympathomimetic agents, including cocaine, tricyclics, guanethidine and bretylium.\(^22\) Thus, the indirectly acting sympathomimetics and guanethidine and bretylium require neuronal uptake to effect noradrenaline release.

Guanethidine and bretylium are taken up by the adrenergic nerve and initially release noradrenaline; they then block noradrenaline release from the vesicles and they finally block noradrenaline uptake by the nerve terminals. The blocking effect of noradrenaline release is thought to be the reason for the antiarrhythmic effect of bretylium.\(^7\)
Inactivation of noradrenaline. Once released into the synaptic cleft the action of noradrenaline is terminated by, neuronal uptake, extraneuronal uptake and diffusion.

1. **Neuronal uptake** is the main mechanism terminating the action of noradrenaline. Noradrenaline is taken up by the adrenergic nerve terminal (using a process which is inhibited by cocaine and tricyclic antidepressants) and either broken down by mitochondrial monoamine oxidase (MAO). Guanethidine, bethanidine and the indirect acting sympathomimetic agents are also taken up by the adrenergic nerve terminal by this transport process (which can be inhibited by cocaine and tricyclics), displacing noradrenaline from intraneuronal stores and providing an initial sympathomimetic effect. Guanethidine is stored in the vesicle and slowly displaces noradrenaline which is then metabolised by MAO.

2. **Extraneural uptake** is the mechanism in which some of the synaptic noradrenaline is taken up by extraneuronal tissues (e.g. smooth muscle cell) and inactivated by catechol-O-methyl transferase. Adrenaline is the preferred substrate for extraneuronal uptake and is metabolised by the cytosolic catechol-O-methyl transferase (COMT) to metanephrine (normetanephrine is the degradation product of noradrenaline) which is then acted on by MAO to produce 3-methoxy-4-hydroxymandelic acid which is generally (but incorrectly) known as vanillylmandelic acid (‘VMA’). This is the major urinary metabolite (Table 4.4). The normal 24 h urinary excretion of catecholamines and metabolites are, 2-4 mg of 3-methoxy-4-hydroxymandelic acid, 100-300 µg of normetanephrine, 100-200 µg of metanephrine, 25-50 µg of noradrenaline and 2-5 µg of adrenaline.

3. **Dilution and diffusion** out of the synaptic cleft. Once released into the circulation catecholamines undergo O-methylation by COMT in liver and kidneys or are taken up by other tissues.

### Table 4.4 Degradation of adrenaline and noradrenaline.

<table>
<thead>
<tr>
<th>Noradrenaline</th>
<th>MAO</th>
<th>COMT</th>
<th>MAO</th>
<th>COMT</th>
<th>MAO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>→</td>
<td>↓</td>
<td>→</td>
<td>↓</td>
<td>→</td>
</tr>
<tr>
<td>3,4-Dihydroxymandelic acid</td>
<td></td>
<td></td>
<td>3-Methoxy-4-hydroxy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metanephrine</td>
<td>(‘VMA’)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: COMT = catechol-o-methyl transferase, ‘VMA’ = vanillylmandelic acid, MAO = monoamine oxidase.

**Adrenergic receptors**

Adrenergic receptors belong to a family of related membrane proteins that include the muscarinic acetylcholine receptors, opioid receptors and the visual protein rhodopsin. They act via guanine-nucleotide binding proteins (G proteins, which function as on-off switches) to alter an effector protein (e.g. adenyl cyclase) to produce an intracellular effect. The receptor protein is characteristically a single polypeptide which spans the plasma membrane seven times; it contains a hydrophobic extracellular amino terminus, three extracellular connecting loops, a hydrophilic intracellular carboxy terminus and three cytoplasmic connecting loops. In general, the ligand-binding domain is comprised of the amino terminal segment and/or portions of the membrane-spanning domains, while the G protein interaction domains involve intracellular loops and the carboxy terminus.
### Table 4.5 Receptor actions of adrenergic agents

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Site</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-1</td>
<td>Myocardial contractile tissue</td>
<td>Increases contractility</td>
</tr>
<tr>
<td></td>
<td>Myocardial conducting tissue (SA node, AV junction)</td>
<td>Increases automaticity, conduction</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>Increases renin release</td>
</tr>
<tr>
<td></td>
<td>Glycogenolysis</td>
<td>Increased (myocardium)</td>
</tr>
<tr>
<td></td>
<td>Intestinal muscle</td>
<td>Relaxation</td>
</tr>
<tr>
<td></td>
<td>Coronary arteries</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Beta-2</td>
<td>Arterioles and Veins</td>
<td>Vasodilation</td>
</tr>
<tr>
<td></td>
<td>Bronchial smooth muscle</td>
<td>Bronchodilation</td>
</tr>
<tr>
<td></td>
<td>GIT smooth muscle tone</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>Uterine smooth muscle tone</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>Skeletal muscle</td>
<td>Force and duration of contraction white fibres increased; red fibres decreased</td>
</tr>
<tr>
<td></td>
<td>Glycogenolysis</td>
<td>Increased (Liver, Skeletal muscle)</td>
</tr>
<tr>
<td></td>
<td>Gluconeogenesis</td>
<td>Increased (Liver)</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>Increase insulin and glucagon release</td>
</tr>
<tr>
<td></td>
<td>Noradrenaline release</td>
<td>Presynaptic facilitation</td>
</tr>
<tr>
<td>Beta-3</td>
<td>Adipose tissue</td>
<td>Lipolysis</td>
</tr>
<tr>
<td>Alpha-1</td>
<td>Arterioles and Veins</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>GIT smooth muscle tone</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>Glycogenolysis</td>
<td>Increased (Liver)</td>
</tr>
<tr>
<td>Alpha-2</td>
<td>Noradrenaline release</td>
<td>Presynaptic inhibition</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Aggregation promoted</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>Inhibits insulin secretion</td>
</tr>
<tr>
<td></td>
<td>Bronchial smooth muscle</td>
<td>Constriction</td>
</tr>
<tr>
<td></td>
<td>Adipose tissue</td>
<td>Inhibition of lipolysis</td>
</tr>
</tbody>
</table>

Abbreviations: AV = atrioventricular, GIT = gastrointestinal tract, SA = sinoatrial

The transmission of the signal from the extracellular to the intracellular compartment occurs in stages. The first step involves binding of the ligand (e.g. sympathomimetic agent) with the receptor. The activated receptor stimulates the exchange of guanosine triphosphate (GTP) for
guanosine diphosphate (GDP) on a specific G protein. The G proteins are localised to the inner surface of the plasma membrane, and consists of an alpha subunit that binds guanine nucleotides with a high affinity and specificity, and beta and gamma subunits that form a tightly linked dimer. The activated G protein (GTP bound) regulates adenyl cyclase (e.g. activates adenyl cyclase if beta-1,beta-2 or beta-3 receptors are activated, or inhibits adenyl cyclase if alpha-2 receptors are stimulated).

Receptors have two main characteristics, affinity for a specific molecule, and activity initiated by the molecule. The response is either activation (produced by an agonist) or block of activation (produced by an antagonist). Adrenergic receptors are classified as alpha-1, alpha-2, beta-1, beta-2 or beta-3 receptors (Table 4.5). However, recent cloning of the adrenergic receptors have revealed subtypes of the alpha-1 receptor (i.e. alpha-1A, alpha-1B and alpha-1D) and alpha-2 receptor (i.e. alpha-2A, alpha-2B and alpha-2C). The beta-3 receptor is 10 times more sensitive to noradrenaline and isoprenaline than to adrenaline and is the principle receptor mediating catecholamine-stimulated thermogenesis in brown adipose tissue. It is also important in mediating the stimulation of lipoysis by catecholamines in white adipose tissue, inhibition of contractile activity of ileum and colon, peripheral vasodilation in skin and fat, relaxation of airway smooth muscle, and inhibition of cardiac contractility (i.e. negative inotropic effect). Individuals with low beta-3 adrenergic receptor activity are prone to obesity and non insulin dependent diabetes mellitus.

Drugs that alter adrenergic transmission
Drugs which alter adrenergic transmission, and their action, are listed in Table 4.1.

Adrenergic receptor agonists. Sympathomimetic amines are agents that act directly on adrenergic receptors or act indirectly by releasing noradrenaline from the nerve terminal, to produce effects that resemble the responses to stimulation of sympathetic nerves on adrenergic receptors.

Catecholamines are sympathomimetic amines that are characterised by having a short biological half-life of approximately 2 minutes, degradation by the synaptic enzyme COMT and exert the majority of their effects by direct action on the receptor. Noncatechol sympathomimetic amines, have a biologic half-life of 1-4 h, can not be degraded by COMT, and exert at least some of their effects by releasing noradrenaline from the adrenergic nerve terminal (Table 4.6).

In experimental preparations, continued exposure to catecholamines is accompanied by a reduced responsiveness (i.e. desensitization) to agonist stimulation. Three processes are responsible for desensitization: 1) an increase in the rate of uncoupling of the receptor from effector units, due to phosphorylation of the receptor which promotes binding of proteins ('arrestins') to the receptor to block G protein-receptor coupling, 2) a sequestration of the receptor away from the cell surface, and 3) a decrease in the number of receptors, because of decreased production of the messenger RNA for the receptor (i.e. ‘down-regulation’).

The reduction in effect of continued exposure to catecholamines has been reported clinically in asthma patients on long-term sympathomimetic therapy. An increased sensitivity to catecholamines (i.e. ‘up-regulation’) has been observed in patients on beta-blockers, producing an increased sensitivity to sympathomimetic amines when beta-blockers are withdrawn. Regulation of receptor numbers is also affected by thyroid hormones, glucocorticoids, oestrogens, progesterones, ischaemia, denervation, hypertension, CCF, alcohol withdrawal and psychotropic drugs.

1. Alpha agonists: Alpha-1-adrenergic receptor stimulation is usually coupled to processes that regulate cellular Ca2+ ion fluxes. Stimulation of the alpha-1-adrenergic receptor (through
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A G protein intermediate) causes hydrolysis of a class of lipids referred to as polyphosphoinositides (PIs), yielding diacylglycerol (DAG) and inositol 1,4,5-triphosphatase (IP$_3$). The former increases the affinity of protein kinase C for calcium and the latter mobilizes calcium from nonmitochondrial intracellular calcium stores (e.g. sarcoplasmic reticulum). The increased intracellular calcium, activates the primed protein kinase C as well as calcium/calmodulin dependent protein kinases. This catalyses the phosphorylation of myosin light chains which leads to vascular contractility.  

Table 4.6 Adrenergic agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>IV. dosage (µg/min)</th>
<th>Direct effect</th>
<th>noradrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>β$_1$</td>
<td>β$_2$</td>
</tr>
<tr>
<td>Catecholamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>2-4</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>4-8</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Dopamine</td>
<td>100-800</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>2-6</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>150-750</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Rimiterol</td>
<td>5-15</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Dopexamine</td>
<td>40-400</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

Non Catecholamine

<table>
<thead>
<tr>
<th>Drug</th>
<th>IV dosage</th>
<th>Direct effect</th>
<th>noradrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(µg/dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NS (µg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metaraminol</td>
<td>2-10 mg</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>2-10 mg</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>1-5 mg</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>10-20 mg</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

MDI (µg/dose) NS (µg/ml) 4-6 hourly

<table>
<thead>
<tr>
<th>Drug</th>
<th>MDI (µg/dose)</th>
<th>NS (µg/ml)</th>
<th>Direct effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MDI (µg/dose)</td>
<td>NS (µg/ml)</td>
<td></td>
</tr>
<tr>
<td>Orciprenaline</td>
<td>750</td>
<td>20000</td>
<td>+</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>250</td>
<td>10000</td>
<td>+</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>100</td>
<td>5000</td>
<td>+</td>
</tr>
<tr>
<td>(IV Salbutamol 200µg stat and 50-20 µg/min)</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>200</td>
<td>1000</td>
<td>+</td>
</tr>
</tbody>
</table>

+ = minor activity, ++ = moderate activity, +++ = strong activity. Common nebulizing devices and a metered dose inhaler (MDI) often give 1/10 the IV dose of the drug due to deposition of drug in the nebulizer and inhaler respectively. The nebulizer solution (NS) is often recommended as 0.25 - 1 ml in 2 ml of saline or sterile water to nebulize for 8-10 minutes, to be administered 2-4 hourly. The infusion doses of the catecholamines are guided by clinical response, therefore the lower dosage is usually administered first and if the desired effect is not achieved then it may be raised (to levels which may even be greater than that shown). The indirect effect of dopamine is only observed in the myocardial tissue.

Alpha-2 adrenergic receptor stimulation is associated with a decrease in cAMP and in some tissues to the regulation of potassium and calcium channels.

2. Beta agonists: beta-1, beta-2 and beta-3 agonists combine with G-protein-coupled receptors on the external surface of the cell membrane and activate the membrane bound enzyme, adenylyl cyclase to increase the intracellular concentrations of a 'second messenger'.
cyclic 3',5'-adenosine monophosphate (cAMP), which modifies the activities of intracellular enzymes. Enzymatic hydrolysis of cAMP by phosphodiesterase terminates the action of cAMP, thus phosphodiesterase inhibitors produce a beta sympathomimetic effect by allowing intracellular cAMP to accumulate. Other hormones that use cAMP as a ‘second messenger’ include, adrenocorticotropic hormone, calcitonin, chorionic gonadotropin, dopamine, follicle-stimulating hormone, glucagon, histamine, luteinizing hormone, melanocyte-stimulating hormone, thyroid-stimulating hormone, parathyroid hormone and vasopressin.

Table 4.7  Alpha adrenergic blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>IV mg</th>
<th>Oral mg/24 h</th>
<th>Biological half life</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective alpha-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin</td>
<td>2-30</td>
<td>3-4 h</td>
<td>90% Hepatic</td>
<td></td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>10-100</td>
<td>10-60</td>
<td>24 h</td>
<td>90% Hepatic</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>2.5-10</td>
<td>50-100</td>
<td>1-2 h</td>
<td>90% Hepatic</td>
</tr>
<tr>
<td>Nonselective alpha-1, alpha-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentolamine</td>
<td>5-10</td>
<td>200-900</td>
<td>10-30 min</td>
<td>90% Hepatic</td>
</tr>
</tbody>
</table>

Adrenergic receptor antagonists. These include alpha and beta antagonists.

1. Alpha antagonists are listed in table 4.7.
   a. Phenoxybenzamine: a selective non-competitive alpha-1 blocker which is 100 times more potent on alpha-1 than alpha-2 receptors. Full alpha-blockade will be achieved when 100 mg of phenoxybenzamine is administered intravenously. This dose may be given over 1 h, with the blockade being complete 15-30 minutes after the completion of the intravenous dose, as metabolic transformation of phenoxybenzamine to an active metabolite is required first.
   b. Phentolamine: this is a non selective competitive alpha-blocker, having equal affinity for both alpha-1 and alpha-2 receptors, which explains the tachycardia which may occur following the initial dose, due to the early alpha-2-blockade. For a continuous effect, phentolamine may be infused at 0.5-2 mg/min.
   c. Chlorpromazine: this may also be used as a selective alpha-1-blocker, and an intravenous dose of 2.5-10 mg will produce hypotension for 1-2 h in patients with an increased sympathetic tone. Greater amounts than this seem to have no added effect.
   d. Prazosin and doxazosin: these are selective alpha-1-blockers.
   e. Yohimbine: this is predominantly an alpha-2 antagonist, being 50-100 times more active at the presynaptic than the postsynaptic receptor.
   f. Indications: alpha-antagonists are used to treat hypertension, cardiac failure, phaeochromocytoma, Raynaud's phenomenon, and peripheral vascular disease. Yohimbine has also been used for erectile failure associated with autonomic neuropathy.
   g. Side effects: the side effects of most of these agents include postural hypotension, nasal stuffiness, fluid retention, headache and drowsiness. Selective alpha-1 blockers (e.g. chlorpromazine, prazosin) may also cause priapism (rarely) which may resolve with epidural analgesia.
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2. **Beta antagonists** (beta blockers): these are competitive inhibitors of the beta-adrenergic receptor, and have some or all of the characteristics of,
   a. **Cardioselectivity**: beta-blockers are classified as either non cardioselective (i.e. block both beta-1 and beta-2 receptors) or cardioselective (i.e. block the beta-1 receptor only). Most beta adrenergic antagonists (including propranolol) do not block beta-3 receptor responses.
      i. Cardioselective drugs are selective in blocking the effects of cardiac stimulation, renin release and lipolysis (i.e. free fatty acid release) caused by adrenergic stimulation. By leaving the beta-2 receptors unblocked, cardioselective beta-blockers are considered to be safer to use in patients who have, acute or chronic obstructive pulmonary disease, intermittent claudication, chronic fatigue, symptomatic ‘cold hands and feet’, or diabetes mellitus requiring insulin. Severe hypoglycaemia stimulates adrenaline release, causing hepatic gluconeogenesis and glycolysis, tachycardia, and tremor due to beta-2-receptor stimulation. Non selective beta-blockade suppresses the increase in blood glucose and block the clinical effects of hypoglycaemia, although it does not cause, or exacerbate, diabetes mellitus. The cardioselective drugs often exhibit selectivity at low dosage, with beta-2-receptor blockade occurring at a higher dose. Of the existing agents, the most selective agent appears to be atenolol, followed by metoprolol and then acebutolol.
      ii. Noncardioselective drugs are theoretically desirable in the management of patients with hypertension, to block the presynaptic beta-2-receptor stimulation of noradrenaline release. Beta-2-receptor blockade is also thought to be important in the treatment of glaucoma, and the nonselective antagonist (e.g. timolol) is used to achieve this.
   b. **Intrinsic sympathomimetic activity (ISA)**: pindolol, alprenolol and oxprenolol exert a partial agonist effect (i.e. ISA) as well as a beta-receptor blocking effect. These agents tend to have less effect on resting heart rate and cardiac output than agents without this property. There is some evidence that agents with ISA are less likely to exacerbate Raynaud’s phenomenon and symptomatic ‘cold hands and feet’ than the cardioselective agents, and it appears that ISA is more important in promoting skin blood flow than unblocked beta-2 activity.
   c. **Membrane stabilising activity (MSA)**: the MSA (i.e. local anaesthetic activity) of propranolol requires concentrations two to three orders of magnitude higher than those which provide beta-blockade; therefore, unless massive intoxication is present, the MSA is unlikely to be an important clinical effect of any beta-blocking drug. Nevertheless, in patients with glaucoma, a beta-antagonist without MSA (e.g. timolol) is used to reduce any likelihood of decreasing the corneal reflex that can lead to corneal damage.
   d. **Lipid solubility**: propranolol, alprenolol, oxprenolol, and metoprolol are the most lipid soluble of the beta-blockers, whereas sotalol, esmolol and atenolol are the least lipid soluble. Pindolol occupies an intermediary position. The more lipid soluble the drug is, the greater are its gastrointestinal absorption, ‘first pass’ effect (i.e. hepatic and gastrointestinal metabolism) and blood brain barrier permeability. Water-soluble beta-blockers tend to be eliminated more by the kidney and tend to have longer half-lives.
   e. **Other effects**: as well as a beta-blocking effect, labetalol has an alpha-blocking effect, and sotalol has the ability to prolong the cardiac action potential and the QT
The effect of sotalol on cardiac repolarization occurs independently of its beta-blocking actions, because its dextro isomer (which has one-fiftieth the beta-blocking action of the levo compound), is equipotent with the levo isomer in prolonging the cardiac action potential. When adrenergic stimulation occurs in patients treated with beta-blockers, unopposed alpha-stimulation may increase afterload, reduce cardiac output and exacerbate cardiac failure.

**Indications:** beta-adrenergic blockers may be used to treat, hypertension, angina, post myocardial infarction, cardiac arrhythmias, migraine, obstructive cardiomyopathy, hyperthyroidism, glaucoma, anxiety, and autonomic overactivity associated with tetanus, porphyria, alcohol withdrawal and opiate withdrawal, and have been used to achieve hypotensive anaesthesia. Generally the beta-blocker chosen should be, cardioselective (i.e., beta-1-selective) and hydrophilic. Beta-adrenergic blockers are contraindicated in patients who have complete heart block, severe bradycardia, cardiogenic shock, hypotension, congestive cardiac failure, acute and chronic obstructive pulmonary disease, severe depression, and Prinzmetal's angina. The latter may theoretically be exacerbated by unopposed alpha adrenergic receptor stimulation, thus calcium blockers should be used initially for this condition.

dosage: the common oral and intravenous dose ranges, are shown in table 4.8. Propranolol, oxprenolol, metoprolol and alprenolol all undergo a first-pass effect resulting in a 30-50% availability of the drug in comparison to an intravenous dose. Atenolol and sotalol do not undergo the ‘first pass’ effect, and while 100% of oral sotalol is absorbed only 50% of oral atenolol is absorbed. The intravenous dose of propranolol, metoprolol and atenolol usually exerts eight to 10 times the effect of an oral dose and is given at a rate of 1 mg/min up to 10 mg or until the desired effect is achieved. Full beta-blockade should be achieved with an intravenous dose of 10-20 mg (i.e. 0.2 mg/kg) of propranolol.

Esmolol is a beta-blocking agent which is ultra short acting because it is rapidly metabolized by red blood cell esterases. It is cardioselective with an elimination half-life of 9.2 min and a duration of action of 10-30 min. Due to its short acting nature, it has certain therapeutic attractions relating to safety and control in the management of supraventricular tachycardias and hypotension. It is available in 10 ml glass ampoules containing 2.5 g. Two ampoules are diluted in 500 ml of 5% dextrose producing a concentration of 10 mg/ml. A loading dose of 500 μg/kg is infused over 1 min (35 mg/70 kg), followed by a progressively increasing rate at 4-minute intervals, beginning at 25 μg.kg⁻¹.min⁻¹ (1.75 mg/70 kg/min), increasing by increments of 50 μg. kg⁻¹.min⁻¹ (3.5 mg/70 kg/min) until the desired response is achieved. Dosages greater than 200 μg. kg⁻¹.min⁻¹ (14 mg/70 kg/min) are usually not needed, although doses of up to 300 μg. kg⁻¹.min⁻¹ (21 mg/70 kg/min) have been given safely.

**Side-effects:** the side-effects of the beta-adrenergic blockers include fatigue, depression, gastrointestinal disturbances, pulmonary oedema, hypotension, heart block and rebound hypertension. Angina or myocardial infarction may occur in up to 5% of patients 12-48 h after acute withdrawal. Sleep disturbances (e.g. nightmares) are associated with the lipid-soluble beta-blockers (e.g. propranolol, alprenolol, oxprenolol, pindolol, metoprolol) that penetrate the blood-brain barrier and may be reduced by treating with the water-soluble beta-blockers (e.g. atenolol or sotalol).
Table 4.8  Beta adrenergic blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>potency</th>
<th>IV mg/5 min</th>
<th>Oral mg/24h</th>
<th>Plasma half-life</th>
<th>ISA</th>
<th>MSA</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonselective (β-1, β-2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>1</td>
<td>1-10</td>
<td>80-480</td>
<td>2-6 h</td>
<td>++</td>
<td>95% Hepatic</td>
<td></td>
</tr>
<tr>
<td>Alprenolol</td>
<td>0.5</td>
<td>5-20</td>
<td>200-800</td>
<td>1-3 h</td>
<td>++</td>
<td>95% Hepatic</td>
<td></td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>1</td>
<td>1-10</td>
<td>80-640</td>
<td>1-2 h</td>
<td>++</td>
<td>95% Hepatic</td>
<td></td>
</tr>
<tr>
<td>Pindolol</td>
<td>6</td>
<td>0.2-1</td>
<td>10-30</td>
<td>4-5 h</td>
<td>+++</td>
<td>60% Hepatic</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>0.3</td>
<td>10-20</td>
<td>80-480</td>
<td>15-17 h</td>
<td></td>
<td>90% Renal</td>
<td></td>
</tr>
<tr>
<td>Cardioselective (β-1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>1</td>
<td>1-10</td>
<td>50-200</td>
<td>6-9 h</td>
<td></td>
<td>90% Renal</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1</td>
<td>1-10</td>
<td>50-400</td>
<td>3-6 h</td>
<td>+</td>
<td>95% Hepatic</td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>0.07</td>
<td>50-300 (µg/kg/min)</td>
<td>9 min</td>
<td></td>
<td></td>
<td>95% Hepatic</td>
<td></td>
</tr>
<tr>
<td>Mixed (β-1, β-2, α-1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>0.5</td>
<td>50-150</td>
<td>200-2400</td>
<td>3-4 h</td>
<td>+</td>
<td>95% Hepatic</td>
<td></td>
</tr>
</tbody>
</table>

ISA = Intrinsic sympathetic activity. Labetalol has a greater beta- than alpha-blocking effect (beta:alpha ratio of 3:1 with oral and 7:1 with IV dosage). The biological half-life of the beta-blockers exceeds the plasma half-life considerably, so that with all agents (apart from sotalol which is taken once daily), 12-hourly dosage will suffice in most instances. MSA = membrane stabilizing activity.

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TRAINEE PRESENTATIONS

Each registrant has prepared a five minute talk and summary on the topics listed below. The summaries that were received in time for publication have been included (unedited).

1. Discuss the clinical presentation and management of a patient with acute basilar artery thrombosis. Dr. P. Glover. page 69
2. Discuss the indications and complications associated with inhaled NO. Describe how you would use it in a mechanically ventilated patient. Dr. D. Cooper. 72
3. What are the determinants of mean arterial pressure? What range should it be kept in the critically ill patient and why? Dr. K. H. A. Leung. 77
4. Discuss the aetiology, clinical presentation and management differences between papillary muscle rupture and VSD. Dr. N. Ramakrishnan. 80
5. Discuss the clinical presentation and management of a 5 month old child with pneumococcal meningitis. Dr. M. Clifford. 82
6. Discuss the management of a patient with digoxin poisoning. Dr. C. McCalman. 89
7. Discuss the aetiology, clinical presentation and management of a patient with the serotonin syndrome. Dr. M. Chinthamuneedi. 91
8. Discuss the indications for corticosteroids in ARDS. Dr. A. McKee. 93
9. Discuss the causes and describe how you would management a mechanically ventilated patient who suddenly cannot be ventilated. Dr. P. Kruger. 95
10. Discuss the indications and complications of intrathecal medications. Dr. P. Harrigan. 97
11. Discuss the acute haemodynamic effect of intravenous hydrocortisone Dr. V. Yeo.
12. Describe the features and discuss the treatment of acute paraquat poisoning. Dr. R. Holland.
13. List the actions, indications, dose and complications of the angiotensin II receptor antagonists, losartan and ibesartan. Dr. N. Widdicombe. 100
14. Discuss the aetiology and management of a patient with hypokalaemia (1.4 mmol/l) who has rhabdomyolysis, acute renal failure and episodes of torsade des pointes. Dr. M. Hayden.
15. Describe the aetiology, clinical features and management of a patient with hypomagnesaemia. Dr. B. McFadyen. 102
16. Describe the clinical features of myxoedema coma. Discuss how you would manage it. Dr. J. Yeo. 105
17. Discuss the actions, indications and doses of the antithrombotic agents. Dr. K. Quan.
18. Discuss the indications and complications of intravenous albumin. Dr. P. Seal.
19. Discuss the ECG features and treatment of hyperkalaemia. Dr. J. Foy.

20. List the indications and complications associated with measurement of end-tidal CO$_2$. Dr. D. Gattas. 107

21. Discuss the management of paraquat poisoning Dr. T. Leong.

22. Discuss the clinical features and treatment of a thyrotoxic crisis. Dr. C. Simpson. 110

23. Discuss the clinical presentation and describe how you would manage a patient with spontaneous rupture of the oesophagus (Boerhaave’s syndrome). Dr. G. Howard. 114

24. Discuss the indications and complications of muscle relaxants, sedative and analgesic agents used to settle a mechanically ventilated patient. Dr. T. W. Lim.

25. Discuss the clinical presentation and describe how you would manage a 3 day postoperative patient with acute pulmonary embolism and shock. Dr. D. Connor. 117

26. Discuss the management of fulminant asthma in a patient who has become unconscious. Dr. R. Fitzgerald.

27. Discuss current medical therapy of heart failure. Dr. P. Meuer. 118

28. List the clinical features, and management of a patient with spontaneous pneumothorax. Dr. P. Jowitt. 121

29. Describe the procedure and list the indications and complications of plasmapheresis. Dr. A. Harvey. 122

30. List the clinical features and management of a patient with unstable angina. Dr. M. Kluger. 126

31. Discuss the management of a cocaine ‘body packer’ (i.e. patient who has ingested latex balloons filled with cocaine) who develops symptoms of cocaine toxicity due to rupture of the packages. Dr. D. Sidebotham.

32. Discuss the clinical presentation and management of patient with a dissecting aortic aneurysm. Dr. H. Tan.

33. Discuss the management of a patient who has delirium tremens. Dr. C. Lee. 128

34. Discuss the indications, complications and dose of intravenous human immunoglobulin. Dr. A. Love

35. Discuss and compare the management of cardiac arrest caused by asystole with that caused by VF. Dr. B. King.

36. Define and list the causes of a nosocomial pneumonia. Dr. G. Auzinger. 130
DISCUSS THE CLINICAL PRESENTATION AND MANAGEMENT OF A PATIENT WITH ACUTE BASILAR ARTERY THROMBOSIS.

Dr. P. Glover, Department of Critical Care Medicine, Flinders Medical Centre, SA

Vertebrobasilar infarction accounts for 25% of all cerebral infarcts. The single basilar artery supplies the pons and midbrain. It’s branches include paramedian branches, which supply corticospinal and corticobulbar tracts, pontine nuclei, pontocerebellar fibres and VI nerve fibres; short circumferential branches supply the lateral 2/3 of the pons including some pontine nuclei, lateral corticospinal tract, median lemniscus, middle cerebellar peduncle and V and VII nuclei. The long circumferential branches, (superior cerebellar and anterior inferior cerebellar), supply the lateral spinthalamic tract, spinal nucleus, tract of V, cochlear and facial nuclei and superior cerebellar peduncles. Thus, a diversity of clinical syndromes may emerge depending on the site of occlusion. insufficiency.

The caudal 2/3 of the basilar artery is most frequently occluded by thrombus. It may be difficult to distinguish clinically between branch occlusion and main artery occlusion. Bilateral long tract signs, cranial nerve and cerebellar dysfunction suggest complete basilar occlusion. Thrombosis usually occurs on a background of atherosclerosis, with male sex (2:1), older age, diabetes mellitus and hypertension, major risk factors. Concurrent coronary artery disease is less of a feature than with carotid disease. More than 60% of patients will have prodromal symptoms (Table 1), with onset occurring within 2 weeks of a stroke in over 50% of cases. Less than 10% of basilar occlusions are embolic in origin. Onset of thrombosis is usually sudden. Commonly, there is a remission in symptoms which is usually temporary. The frequency of symptoms and signs on admission are shown in Table 2.

Table 1. Prodromal symptoms in patients with basilar artery occlusion.¹

<table>
<thead>
<tr>
<th>Symptom</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>vertigo, nausea</td>
<td>49</td>
</tr>
<tr>
<td>headache, neckache</td>
<td>34</td>
</tr>
<tr>
<td>hemiparesis</td>
<td>17</td>
</tr>
<tr>
<td>double vision</td>
<td>17</td>
</tr>
<tr>
<td>dysarthria</td>
<td>17</td>
</tr>
<tr>
<td>hemianopia</td>
<td>9</td>
</tr>
<tr>
<td>hemihypaesthesia</td>
<td>9</td>
</tr>
<tr>
<td>tinnitus, hearing loss</td>
<td>9</td>
</tr>
<tr>
<td>drop attack</td>
<td>7</td>
</tr>
<tr>
<td>confusion</td>
<td>6</td>
</tr>
<tr>
<td>other</td>
<td>11</td>
</tr>
</tbody>
</table>

The diagnostic gold standard is angiography. CT has poor sensitivity for posterior fossa lesions, does not demonstrate blood flow and may fail to show infarction for several days. MRI assessment of changes in basilar artery blood flow are not reliably diagnostic, but MRA has a 97% sensitivity and 98.9% specificity for the diagnosis of occlusion and stenoses in the posterior circulation compared with angiography while Doppler TCD has a similar specificity but only 76.4% sensitivity.²
### Table 2. Symptoms and Signs on Admission.\(^1\)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>%</th>
<th>Symptom</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>vertigo, nausea</td>
<td>46</td>
<td>Long tract signs</td>
<td></td>
</tr>
<tr>
<td>occipital lobe signs</td>
<td>13</td>
<td>hemiplegia</td>
<td>25</td>
</tr>
<tr>
<td>headache, neckache</td>
<td>26</td>
<td>tetraparesis</td>
<td>36</td>
</tr>
<tr>
<td>dysarthria</td>
<td>27</td>
<td>tetraplegia</td>
<td>18</td>
</tr>
<tr>
<td>ataxia, dysdiadochokinesia</td>
<td>32</td>
<td>locked-in syndrome</td>
<td>11</td>
</tr>
<tr>
<td>respiration</td>
<td>11</td>
<td>hemihypaesthesia</td>
<td>13</td>
</tr>
<tr>
<td>Horner’s syndrome</td>
<td>5</td>
<td><strong>Supranuclear oculomotor disturbances</strong></td>
<td></td>
</tr>
<tr>
<td>seizures</td>
<td>5</td>
<td>horizontal gaze paresis</td>
<td>26</td>
</tr>
<tr>
<td>sweating</td>
<td>6</td>
<td>gaze-induced nystagmus</td>
<td>18</td>
</tr>
<tr>
<td>myoclonias</td>
<td>7</td>
<td>oculocephalic reflex lost</td>
<td>7</td>
</tr>
<tr>
<td><strong>Cranial nerve palsy</strong></td>
<td></td>
<td>vestibular nystagmus</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>15</td>
<td>vertical gaze palsy</td>
<td>5</td>
</tr>
<tr>
<td>IV, VI, VII</td>
<td>35</td>
<td>downbeat nystagmus</td>
<td>5</td>
</tr>
<tr>
<td>VIII</td>
<td>6</td>
<td>ocular bobbing</td>
<td>4</td>
</tr>
<tr>
<td>IX – XII</td>
<td>28</td>
<td>1½ syndrome</td>
<td>2</td>
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<tr>
<td><strong>Consciousness</strong></td>
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<td>internuclear ophthalmoplegia</td>
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<tr>
<td>awake</td>
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<td>other</td>
<td>19</td>
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<tr>
<td>psychosis</td>
<td>6</td>
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<td></td>
</tr>
<tr>
<td>disturbed memory</td>
<td>24</td>
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<tr>
<td>somnolence</td>
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<td>sopor</td>
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<td></td>
</tr>
<tr>
<td>coma</td>
<td>31</td>
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</tbody>
</table>

Untreated basilar artery thrombosis has a mortality of up to 92%. General measures include maintaining cerebral perfusion pressure, assessment of adequacy of gag, cough and ability to clear secretions, nutrition, maintenance of normoglycaemia, and control of pyrexia. No randomised prospective data exists for the use of systemic anticoagulation and low molecular weight heparin offers no benefit in patients with acute vertebrobasilar infarction.\(^3\)

The use of thrombolytics in the management of acute basilar artery occlusion was first reported in 1983. Numerous small uncontrolled studies have shown some benefit from a variety of thrombolytics (rTPa, urokinase, streptokinase). Although no randomised trials comparing local intra-arterial delivery and systemic thrombolysis have been performed, there has been a trend to treat patients with local intra-arterial fibrinolytics. A lower rate of symptomatic haemorrhage has been documented with this route.\(^4\) The success of thrombolysis is dependent on recanalisation of the artery,\(^5\) which if successful, can reduce the mortality to 50%. Recanalisation following intra-arterial thrombolysis is not affected by site of thrombus, time period between symptom onset and lysis, or the state of collaterals, but was adversely affected by increasing patient age, atherothrombotic occlusion, and CT signs of subcortical arteriosclerotic encephalopathy.\(^6\) Reduced survival was associated with increasing age, tetraplegia or coma on admission, and poor collaterals.

Unlike anterior circulation thrombosis, the time to therapy is not as crucial to outcome, benefit having been demonstrated up to 48 hours after the onset of symptoms.\(^7\) The various lytic agents have not been compared in a randomized prospective fashion.
Reocclusion occurs in up to 30% of cases and is almost universally fatal. Aspirin or ticlopidine may be used to prevent reocclusion. Angioplasty may be used post-thrombolysis to treat any significant underlying stenosis. The prognosis for patients who require mechanical ventilation is extremely poor, with the locked-in syndrome being the best outcome in one study of 25 ventilated patients. Despite further advances in therapeutic modalities, many survivors will be left with significant residual deficits that limit functional recovery.

References
DISCUSS THE INDICATIONS AND COMPLICATIONS ASSOCIATED WITH INHALED NITRIC OXIDE. DESCRIBE HOW WOULD USE IT IN A MECHANICALLY VENTILATED PATIENT.

Dr. D. Cooper. Intensive Care Unit, John Hunter Hospital, New South Wales

Introduction:
Nitric oxide (NO) is a gaseous free radical that has been present in the Earth's atmosphere since the cooling of the primitive planet, and has been identified as a biological mediator in some of the earliest animal species, indicating that the L-arginine:nitric oxide pathway may be amongst the oldest regulatory systems in physiology. The biosynthesis of NO is from the semi-essential amino acid L-arginine via a stereospecific process catalyzed by a family of large and complex haemoproteins, the nitric oxide synthases (two constitutive isoforms; eNOS from endothelium and nNOS from neurones, and one inducible isoform from macrophages, mNOS), which require multiple co-factors for their activity (Fig. 1).

Being a free radical NO combines readily with other radicals and reacts with a variety of chemical species. Some might stabilize NO or act as carrier molecules (e.g. glutathione), whilst others (e.g. superoxide $O_2^-$) may lead to the rapid destruction of NO with loss of biological activity or the formation of other radicals.

Multiple physiologic roles for endogenous NO described throughout all systems of the body. Because of this ubiquitous nature and its potential contribution (either in deficiency or in excess) to a wide variety of disease states attempts to modulate patient physiology through NO are ongoing in many fields of medicine.

Indications:
Of particular interest to Intensive Care are the ability of NO to cause vascular smooth muscle relaxation (by stimulation of intracellular guanosine monophosphate formation) and the high degree of pulmonary selectivity of inhaled NO (due to rapid - within seconds - inactivation of systemically absorbed NO by binding to haemoglobin) which limits potential systemic toxicity. Current clinical applications of inhaled nitric oxide (iNO) are diverse, but revolve around the dual benefits of altering ventilation/perfusion (V/Q) relationships in the lung and reducing pulmonary blood pressure:

![Fig. 1. L-arginine:nitric oxide pathway and some factors affecting the synthesis and mechanism of action of nitric oxide. NOS = Nitric oxide synthase enzyme, L-NMMA—N-monomethyl-L-arginine, NO-X = intermediate compound (e.g. nitrosothiol), HaemGC = guanylate cyclase enzyme, MB = merhylene blue, + ve = positive feedback, - ve = negative feedback.](image-url)
1. **Primary pulmonary hypertension** was the original model in which selective pulmonary vasodilatation by iNO was first observed.\(^4\) Although even low doses (2-3ppm) may occasionally be effective, the efficacy of iNO is limited by a loss of pulmonary vasoreactivity as the disease progresses.

2. **Acute respiratory distress syndrome (ARDS).** Although beneficial cardiorespiratory effects were first described in 1993,\(^5\) reduction in mortality has yet to be demonstrated (despite the improvement in clinical parameters). Improvement in oxygenation by selectively vasodilating the pulmonary vessels around ventilated alveoli is felt to be the major achievement of iNO in ARDS, with a reduction in pulmonary artery pressure (PAP) and hence right ventricular (RV) afterload as a potential secondary benefit.

3. **Cardiopulmonary bypass (CPB) and congenital heart disease (CHD).** The endothelial injury in lung vessels secondary to CPB can exacerbate pre-existing pulmonary hypertension. This may be ameliorated to some extent by iNO in patients undergoing heart surgery, and has been found to be especially effective at lowering PAP and increasing PaO\(_2\) in children undergoing surgery for CHD.

4. **Persistent pulmonary hypertension of the newborn and respiratory failure in infants.** Endogenous NO contributes to pulmonary vasodilatation after normal birth but is deficient in premature infants. This finding has lead to the successful use of iNO to improve oxygenation (for up to three months duration) in infants with persistent pulmonary hypertension of the newborn refractory to maximal conventional therapy, and may sometimes provide an alternative to extra-corporeal oxygenation. The use of iNO in pulmonary hypoplasia secondary to congenital diaphragmatic hernia remains controversial.

5. **Other potential clinical benefits (reported in humans):**
   - as a bridge to lung transplantation
   - after lung transplantation iNO decreases PAP and pulmonary vascular resistance (PVR) and improves gas exchange
   - as treatment of paraquat intoxication
   - to reverse right-to-left shunting through a patent foramen ovale in cases of pulmonary embolism
   - as a diagnostic tool to screen the reactivity of pulmonary vessels

6. **Effects seen in animals (but of unconfirmed/minimal benefit in humans):**
   - bronchodilation (reason unclear)
   - prevention of hypoxaemia-induced remodelling of pulmonary vessels and RV myocardium
   - reduction of oedema formation after lung injury
   - inhibition of ischaemia-induced microvascular dysfunction
   - attenuation of endotoxaemia-induced pulmonary hypertension

**Complications:**

1. **Methaemoglobinaemia.** NO has an affinity for haemoglobin (Hb) that is several hundred times greater than that of carbon monoxide, and the reaction of NO with reduced Hb occurs 5 to 20 times faster than with oxygen. It is this avid binding that provides iNO with its unique pulmonary selectivity. Approximately 80-90% of administered iNO is absorbed into the bloodstream and reacts with Hb within erythrocytes to form nitrosylhaemoglobin and methaemoglobin from which nitrates are generated by oxidation. There have been no problems reported due to methaemoglobinemia with longterm iNO administration maintained below 40 parts per million (ppm), and levels below 128 ppm have seldom been reported to cause a methaemoglobin level plateauing above 5% - a clinically insignificant reduction in oxygen carrying capacity under most circumstances.\(^6\)
2. Metabolites.

(i) The higher oxides of nitrogen are produced in proportion to the concentration of NO used, the partial pressure of oxygen (PaO₂), and the duration of contact between the two gases prior to inhalation. Nitrogen dioxide (NO₂) at doses as low as 2 ppm has been associated with terminal bronchial epithelial hypertrophy and alveolar cell hyperplasia in animals, but histologic changes have not been seen in human lungs at concentrations below 25 ppm. The Centres for Disease Control have set the upper limits for occupational safety and health at 5 ppm. Fifty to sixty percent of NO₂ is retained within the lung where it reacts with water over prolonged periods to form nitrous and nitric acids, which are thought to be responsible for the lung toxicity.

(ii) Under hypoxic conditions iNO may react with other free radicals: peroxynitrite (ONOO⁻) is a powerful oxidant and cytotoxic agent produced from reaction of iNO with the superoxide anion (O₂⁻); the nitrosium cation (NO⁺) forms metalonitrosyl compounds implicated in systemic vasodilatation and carcinogenesis; and the nitrosyl anion (NO⁻) whose role is unknown.

3. Dosage. Optimal dosage of iNO that will maximize pulmonary vascular relaxation without incurring toxic side effects, systemic hypotension, or deleterious effects on venous admixture is unclear. Maximal pulmonary vasodilator response to iNO may occur at higher doses (10 – 100 ppm) than those which produce optimal V/Q matching (< 1 – 10 ppm) and thus improvements in oxygenation may be lost at higher doses as “spillover” of iNO into poorly ventilated lung segments causes loss of preferential delivery to, and vasodilatation of, better ventilated areas.

4. Cessation. Rebound pulmonary hypertension or respiratory collapse have been reported upon abrupt cessation of prolonged iNO delivery. This represents an additional hazard, and an appropriate alarm and back-up supply of iNO must be in place.

Delivery:

An ideal delivery system uses medical grade gas manufactured to approved standards, minimises duration of gas in the delivery circuit, can deliver a wide range of precise iNO doses with uniform mixing despite variable flow rates, has on-line analysis of NO/NO₂/O₂, incorporates stringent controls for prevention of environmental pollution by exhaled gases, and has alarms to protect against excessive dosing or inadvertent discontinuation together with an appropriate back-up system. No such system is currently available.

Stable iNO concentrations can be achieved by titrating NO directly from the source tank (usually having a concentration of 100 – 10,000 ppm NO in nitrogen) into the inspiratory side of continuous gas flow ventilators (e.g. neonatal systems, high frequency ventilators, and CPAP circuits) (Fig.2). These systems use substantial amounts of gas, and may be complicated by scavenging systems that interfere with the exhalation valve of the ventilator. Dilution of oxygen and reduction in FiO₂ will vary with NO concentration in the source tank. Low flow meters are required to obtain a wide range of NO doses (1 – 100 ppm).

Adults and older children requiring peak inspiratory flow rates in excess of 12 - 15 litres per minute are generally ventilated with circuits that do not use continuous flow and require a different approach. Large variations in NO concentration will be seen during different portions of a single breath if NO is titrated at a set flow rate into the inspiratory limb of these ventilators. Because the early and late portions of a tidal breath may be distributed to different portions of lung the distribution of NO throughout the lung may be uneven for this reason alone.
The titration method is shown. Nitric oxide (NO) is titrated into the inspiratory limb of a continuous-flow ventilator upstream from the humidifier. A flow meter allows precise NO dosing. Oxygen, NO, and nitric dioxide (NO$_2$) are analyzed after NO is added to the circuit and just proximal to patient. Exhaled gases are scavenged using a central vacuum system.

This unevenness can be overcome by use of a “double-blender” technique (adaptable, but somewhat complicated and bulky) where the final NO/N$_2$/O$_2$ mixture is the sole source of gas flow to the ventilator (Fig.3). Spillage out of the bellows with potential environmental pollution (if gas flow does not match each patient’s minute ventilation), and longer residence times of NO with oxygen leading to development of higher NO$_2$ concentrations are the major problems with this system.

Various other systems have been described for the delivery of iNO, but are in less common usage. These include everything from a Douglas bag through to the use of a ventilator nebulizer to deliver NO during inspiration only. Monitoring devices to guide the clinical use of iNO and guard against the likelihood of NO$_2$ toxicity are regarded as essential for the safe use of this highly potent agent. However all commonly used devices, whether chemiluminescent or electrochemical analysers, infrared or mass spectrometers were originally designed for industrial or scientific use and have limitations when used in the clinical arena (sampling range, large aspirating volumes, long warm-up times, cost, bulk, fragility, frequency of recalibration requirements in the presence of humidification, positive pressure ventilation and changing FiO$_2$). The details of these are beyond the scope of this presentation.
Fig. 3 The double blender method of nitric oxide (NO) delivery is shown. A mixture of NO and nitrogen are mixed and fed into a second blender and mixed with oxygen. The gas flow distal to the second blender is controlled by a flow meter and fed into the high pressure inlet of a volume-cycled ventilator. NO and oxygen concentrations can be altered independently without changing the gas flow.

References

WHAT ARE THE DETERMINANTS OF MEAN ARTERIAL BLOOD PRESSURE? WHAT RANGE SHOULD IT BE KEPT IN THE CRITICALLY ILL? AND WHY?

Dr. K. H. A. Leung. Intensive Care Unit, Queen Elizabeth Hospital, Hong Kong

What are the determinants of mean arterial blood pressure?

**Definition:** It is the pressure in the arteries, averaged over time

**Measurement:**
1. From the arterial pressure tracing by measuring the area under the curve and divided by the time interval involved

   ![Arterial Pressure Diagram]

   \[ Pa = \frac{\int_{t_1}^{t_2} Pa \, dt}{t_2 - t_1} \]

   \( Pa \) (mean arterial blood pressure), \( Ps \) (systolic blood pressure), \( Pd \) (diastolic blood pressure)

2. By means of the formula:
   \[ Pa = Pd + \frac{1}{3}(Ps - Pd) \]

**Determinants:**
1. Physiological factors: - Cardiac output (= Heart rate x Stroke volume)
   - Peripheral vascular resistance
2. Physical factors - Arterial blood volume
   - Arterial compliance

The arterial volume in turn depend on the rate of inflow (i.e. the cardiac output) and the rate of outflow (i.e. peripheral runoff)

The mean arterial pressure varies directly with the cardiac output and total peripheral vascular resistance. In other words, the mean BP will be increased with either the increase in cardiac output or increase in peripheral resistance.

**What range should it be kept in the critically ill? and why?**

Most of the vital organs in the body have the blood flow being autoregulated within a certain range of blood pressure. In the event of overt hypotension that fall beyond this range, blood flow will be jeopardised and may lead to organ dysfunction. Therefore, blood pressure has been used as one of the conventional goals of resuscitation. However, the ultimate aim of resuscitation is to ensure adequate tissue perfusion rather than targeting at one single value.

Hence the mean blood pressure range should be tailored to the need of individual patient base on different clinical scenarios. The following discussion mainly limit to the cardiovascular management of shock.
**Definition of shock:**
It is defined as inadequate perfusion of tissues resulting in cell dysfunction and cell death. It often presents as reduced mean blood pressure.

**Classification:**
Common: Septic, hypovolemic and cardiogenic shock
Less common: Anaphylactic, neurogenic and obstructive shock

**Underlying disease mechanism:**
Septic shock: It is defined as sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include but not limited to, lactic acidosis, oliguria or acute alteration in mental status.
*Clinically:* low blood pressure with warm extremities and good nailbed return, fever and leucocytosis
*Haemodynamically:* low BP with low systemic resistance and high cardiac output. It is also characterised by oxygen extraction defect in tissue level

Cardiogenic shock: It can be caused by direct myocardial damage (e.g. myocardial infarction) or inhibition of the contraction mechanism (e.g. drug toxicity)
*Clinically:* Signaled by small pulse pressure and cool extremities with poor nailbed return
*Haemodynamically:* Usually associated with low cardiac index of < 2.2 L/min/M² and high pulmonary artery occlusion pressure > 18 mmHg

Hypovolemic shock: It is caused by decreasing circulating volume with normal pump function. It is commonly caused by blood loss or intravascular fluid through renal, gastrointestinal (e.g. pancreatitis) or skin loss (e.g. burn)

**General recommendation for cardiovascular management of shock:**
Increasing blood pressure by itself is insufficient since the goal of cardiovascular resuscitation is to attain an adequate cardiac output and oxygen delivery to correct organ system hypoperfusion. Oxygen delivery is the product of cardiac output, oxygen-carrying capacity of the blood, and arterial oxygen saturation. Therefore, cardiovascular resuscitation is closely tied to correcting haemoglobin concentration and oxygen saturation. In general, optimal DO₂ in critically ill patients requires:
1) A haematocrit of 30-35% (e.g. Hb 10.0 - 11.5 g/100 ml)
2) A SaO₂ of greater than 90% (eg PaO₂ > 60 mmHg)
3) A Mean blood pressure of > 70 mmHg

**Physiological bases for the recommendation:**
Blood flow to the brain and the heart is preferentially preserved in hypotension. Usually, blood flow through the heart and brain is maintained at normal level as long as the arterial pressure does not fall below about 70 mmHg. Below this lower limit of autoregulation, perfusion pressure becomes an important determinant of coronary blood flow, increasing with rise in MAP and decreasing with rise in left ventricular end-diastolic pressure.
Pros and cons of using this range of MBP as goal of resuscitation

Pros:
1) easily measured
2) At pressure below an autoregulatory limit, normal flow distribution mechanism is lost so that significant organ system hypoperfusion persists despite increased in cardiac output

Cons:
1) Modest hypotension not always associate with shock
2) Shock may develop despite normal BP. Eg Young fit adult can loss up to 30% of the blood volume before there is a drop in BP
3) Normal MBP in a septic patient may still be inappropriate to their need and patient may show continued evidence of tissue perfusion. On the other hand, vigorous resuscitation with vasoactive drugs to achieve normal BP may result in worsened distribution of CO and increased the myocardial work.
4) Using the MBP as a guide of oxygen delivery to tissue is not adequate in resuscitation. In fact, there is a trend moving towards measuring the utilization of oxygen at tissue level like the pH$_r$.
5) In treatment of vasospasm after clipping of cerebral aneurysm, the MAP should raised to 15 to 20% above baseline rather than an arbitrary value. The MAP should increased progressively until the neurologic deficit is resolved or the risk of systemic toxicity becomes unacceptable high.

References
2. Guyton: Circulatory shock and physiology of its treatment in Textbook of Medical Physiology (8th edition)
DISCUSS THE ETIOLOGY, CLINICAL PRESENTATION AND MANAGEMENT DIFFERENCES BETWEEN PAPILLARY MUSCLE RUPTURE AND VSD

Dr. N. Ramakrishnan. Intensive Care Unit, St Vincent’s Hospital, Victoria

Introduction
With the introduction of thrombolysis and coronary care units, the mortality in AMI are now most often due to mechanical complications & pump failure. The recognition and prompt management of these complications are essential for improved survival. These complications, still account for around 5% of peri-infarction mortality. Unfortunately they, often develop in first time infarctions, and in patients with single vessel disease albeit with poorly developed collaterals.

Clinical clues common to both are a sudden deterioration of clinical state with accompanying shock. Apart from routine clinical exam the next most useful investigation is Echocardiography. The table below explains the pertinent similarities & differences.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Papillary Muscle Rupture</th>
<th>VSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Pulmonary Edema</td>
<td>Common</td>
<td>Rare, usually comfortable @ rest</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td>Murmur</td>
<td>Usually absent due to equalization of pressures</td>
<td>Loud Pansystolic in the LSE</td>
</tr>
<tr>
<td>Thrill</td>
<td>Generally hyperactive precordium</td>
<td>With palpable thrill</td>
</tr>
<tr>
<td>Complicates</td>
<td>5% of AMIs</td>
<td>2% of AMIs</td>
</tr>
<tr>
<td>Timing</td>
<td>2-7th day post infarct</td>
<td></td>
</tr>
<tr>
<td>ECG location of MI</td>
<td>Inferior AMI</td>
<td>Equal frequency of Anteriors &amp; non anteriors</td>
</tr>
<tr>
<td>?Q or Non Q wave infarcts</td>
<td>Both</td>
<td>usually Q wave MI</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Hyperdynamic LV</td>
<td>Hyperdynamic LV</td>
</tr>
<tr>
<td>Colour Flow</td>
<td>Flail segment of Mitral valve</td>
<td>L-R shunt</td>
</tr>
<tr>
<td></td>
<td>Severed postero-medial head</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regurgitant jet</td>
<td></td>
</tr>
<tr>
<td>Pressure tracing</td>
<td>Management</td>
<td>Surgery</td>
</tr>
<tr>
<td>------------------</td>
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</tr>
<tr>
<td>CVP</td>
<td>IABP</td>
<td>Mitral valve repair or replacement +/- CABG(Emergency)</td>
</tr>
<tr>
<td>PCWP</td>
<td>Iontropes</td>
<td></td>
</tr>
<tr>
<td>Oximetry</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raised</td>
<td>Giant V waves</td>
</tr>
<tr>
<td></td>
<td>Large Regurgitant V waves</td>
<td>Step up in RV O₂ sats</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>IABP ionotropes</td>
</tr>
</tbody>
</table>

### References

DISCUSS THE CLINICAL PRESENTATION AND MANAGEMENT OF A 5 MONTH CHILD WITH PNEUMOCOCCAL MENINGITIS

Dr. M. Clifford. Intensive Care Unit, Royal Children’s Hospital, Victoria

Clinical Presentation
NB at 5 months symptoms are non-specific
pneumococcal meningitis correlated with cerebritis and vasculitis
penicillin and cephalosporin resistant strains emerging

Clinical manifestations
At 5 months symptoms are nonspecific - systemic response to infection + encephalopathy

Systemic
acute onset febrile illness pallor ‘sick looking’ +/- antecedant URTI
poor feeding with a weak suck and vomiting (+/- diarrhoea)
temperature instability - hyper or hypothermia
tachycardia (>170) and tachypnoea (>60)
circulatory insufficiency - shock in up to 20%
abnormal peripheral circulation, oliguria, acidosis

CNS
altered conscious state -, irritability alternating with lethargy
high pitched cry especially when moved
meningeal signs uncommon but bulging frontanelle
coma, pupillary changes, cranial nerve dysfunction, altered respiratory pattern
occasionally - apnoea
Brudzinski and Kernigs sign may be positive
10% cranial nerve palsies\textsuperscript{3,4,6,7} or focal neurology

seizures in 20% at presentation
early <72 hours less important than late >72 hours (often focal)
focal seizures more common in pneumococcal disease\textsuperscript{1,2,10}

Management

General

Optimise physiologic status (Resuscitate the patient)

ABCD
as with any life threatening paediatric illness assess and maintain adequacy of airway, breathing and circulation
Intubation and ventilation

who? airway protection obtunded/comatose
seizures
hypoventilation secondary to drugs
treatment for raised ICP
shock/acidosis
Children ventilated for meningitis poor prognostic indicators include PRISM on admission and
tachycardia + hypotension in first 24 hours
IV access +/- central line crystalloid boluses 20ml/kg, inotropes, vasopressors

(NB) signs of shock in 20%
- abnormal peripheral circulation/altered mental state/oliguria
- inadequately treated shock worsens cerebral outcome

Early aggressive resuscitation will minimise the potential for secondary cerebral injury -
hypoxaemia (ischaemia), hypercarbia (increased cerebral blood volume), hypotension
(decreased cerebral perfusion pressure)

**Electrolyte and Fluid Therapy aims to**
- maintain adequate intravascular volume
- remain mindful of SIADH and restrict fluids to at least 60% maintenance

*This remains controversial* A recent trial documenting significantly lower ADH levels with
replacement of estimated losses and 100% maintenance vs restriction and 2 studies finding
opposing mortality trends from restriction vs maintenance have resulted in proposals for
randomised controlled trials.

- monitor for HYPOGLYCAEMIA and treat aggressively
- initial fluids at 50% maintenance and monitor serum Na+
  - if <135 mmol/l reduce the fluid intake
  - if >145 mmol/l increase the fluid intake

FEVER persisting (>7 days) necessitates search for coexistent focus (arthritis, pneumonia,
pericarditis -UNCOMMON), subdural effusion (COMMON and usually sterile), or recurrent
disease

*Re-examine patient for adequacy of resuscitative efforts*
- enlarging head circumference (check daily)
- evolving neurologic deterioration

**Make the Diagnosis (if safe to do so)**

**Lumbar puncture and laboratory evaluation**

**Who to lumbar puncture**
Patients with suspected meningitis should have their CSF examined within 30 mins, and if
results consistent with acute bacterial meningitis, antimicrobial therapy should be initiated
based on results of Gram stain or antigen testing. However, if no causative agent can be
identified or if lumbar puncture cannot be done within 30 mins, empirical therapy should be
initiated….Tunkel.
**Who not to lumbar puncture**

Specific contraindications to LP include:

- Papilloedema or focal neurological signs
- Coma (GCS <8), recent fit (<30 mins), prolonged fit (>30 mins)
- Hypertension with bradycardia
- Irregular or slow respiration
- Abnormal pupils or decorticate/decerebrate posturing
- Septic shock (or cardiovascular instability) esp <12 months
- Skin infection at LP site
- Coagulopathy

At RCH of 445 children with meningitis 5% cerebral herniation of those 75% died
50% within 3 hours (and 75% within 12) of LP
33% of these had a normal CT at the time of LP.

**As a general rule - if they are sick enough for intensive care involvement they will probably be too sick to LP…**

If obtained, specimens should be sent for:
- Urgent microscopy (normal 6-18 WBC/hpf) and gram stain
- Latex-antigen ID
- Culture and sensitivities (PCR for HSV if suspected)
- Protein (normal 0.2-0.4 g/l) and glucose (2.8-4.0 mmol/l) or < 2/3 serum

NB 30% of LP’s result in a bloody tap (and or inadequate volumes for testing)
assume 1 WBC for each 500 RBC but beware if leukopaenia (COMMON)

**Other investigations**

- FBE - WCC high or low (immature to total neutrophil count ie left shift)
- EUC - hyponatraemia of SIADH, BSL, CRP
- Blood culture - may be positive in up to 85%
- ABG and serum lactate
- Coagulation profile

**Radiology**

- CT Brain early primary role is to exclude other pathology
  oedema, hypertension or normal (**not** how safe to LP)
  late infarction, hydrocephalus, subdural effusions.

**Specific**

**Antimicrobial therapy**

Initially broad spectrum bacteriocidal antibiotics with good CSF penetration are used and initial therapy should include *Aciclovir* if any doubt about the diagnosis
Assuming lancet shaped Gram positive diplococci or Latex antigen+ve for pneumococcus

**Cefotaxime (or Ceftriaxone) 50mg/kg Q6H**  (pen A - vancomycin)
covers all 3 likely pathogens
covers penicillin tolerant/resistant pneumococci
cefotaxime resistant pneumococci less an issue (?)

Factors predisposing to penicillin resistant pneumococci.²
- age <10
- day care (or prolonged hospitalisation)
- frequent or prophylactic antibiotics
- immunosuppressed (*)
- recent travel to Spain/USA
- serotypes 14,23

**Vancomycin** recommended as an adjunct to cefotaxime for highly resistant pneumococcus

**Penicillin 60 mg/kg Q6H is drug of first choice for penicillin sensitive strains.⁹**

**CNS specific therapies**

NB
- loss of autoregulation of cerebral blood flow (more sensitive to hypotension)
- ICP elevated and higher pressures correlate with mortality
- open anterior frontanelle NOT protective of herniation syndrome
- seizures in 33% early/generalised less significant than late/focal
- SIADH causing hyponatraemia and worsening cerebral oedema

**Treat raised ICP**
- hyperventilation to normal C02 may improve autoregulation (adults)
- osmotherapy for herniation syndromes
- consider monitoring ICP if coma/features of impending herniation
- ?SjVo2 in future

**Treat seizures**
- prompt and aggressive treatment (? role for continuous EEG)
- phenobarbitone 30mg/kg load and 10 mg/kg aliquot’s to max of 100mg/kg/24
- diazepam/midazolam/phenytoin also useful

**Minimise inflammatory effects**
- **Dexamethasone 0.6mg/kg/day Q6H 4 days** (RCCT - NEJM 1992)
- logical to give BEFORE antibiotics (?10-20 mins)
- no effect if delayed 12 hours
- neurologic sequelae NOT mortality reduced
- 3.3% vs 15.5% mod-severe hearing loss (esp Haem influ 3)

NB caveats with regards rate of CSF sterilisation and decreased Vancomycin penetration (both) may be more significant in pneumococcal disease.⁷,⁸
Supportive

**Infant**
- analgesia (meningitis probably hurts) paracetamol 20 mg/kg Q4H (to 100mg/kg/day)
- temperature control
- glucose (normoglycaemia)
- hyperthermia causes heat stress and may cause (?>40°C) secondary cerebral injury
- hypothermia causes cold stress and develops rapidly if uncovered
- serum Na+ for SIADH
- need for Paediatric Intensive Care and Transport

- currently all children less than 2 years of age
- all children with compromised ABC
- all children with features of raised ICP.¹⁰

**Family**

**Follow Up - short term**
- Serial Head Circumference - plotted on a centile chart
- (if increasing c/w hydrocephalus Cerebral Usound used if ant frontanelle wide enough)
- role for repeat lumbar puncture
- investigation for recurrent fevers
- CT scanning late for complications of the meningitis - infarction, hydrocephalus, subdural effusions, developmental anomalies of cochlear in recurrent meningitis
- Somatosensory evoked responses for prognostication in the more severely affected
REVIEW

DISCUSS THE CLINICAL PRESENTATION AND MANAGEMENT OF A 5 MONTH CHILD WITH PNEUMOCOCCAL MENINGITIS

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circulatory insufficiency - shock in up to 20%, abnormal peripheral circulation, oliguria, acidosis

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meningeal signs uncommon but bulging frontanelle
coma, pupillary changes, cranial nerve dysfunction 10% palsies or focal neurol
seizures in 20% at presentation
   early <72 hours less important than late >72 hours (often focal)
focal seizures more common in pneumococcal disease

Management

Intubation and ventilation airway protection - comatose/seizures/drugs
treatment for raised ICP
shock/acidosis
IV access +/- central line crystalloid boluses 20ml/kg, inotropes, vasopressors

Early aggressive resuscitation will minimise the potential for secondary cerebral injury - hypoxaemia (ischaemia), hypercarbia (increased cerebral blood volume), hypotension(decreased cerebral perfusion pressure)
   remain mindful of SIADH and restrict fluids to at least 50% maintenance (Na 135-145 mmol/l)
   monitor for HYPOGLYCAEMIA and treat aggressively

Specific contraindications to LP include
   papilloedema , focal neurological signs, coma (GCS<8), CVS instability

Antimicrobial therapy (lancet shaped Gram positive diplococci or Latex antigen+ve for pneumococcus)
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neurologic sequelae NOT mortality reduced
3.3% vs 15.5% mod-severe hearing loss 3)

References
DISCUSS THE MANAGEMENT OF A PATIENT WITH DIGOXIN POISONING

Dr. C. McCalman. Intensive Care Unit, Waikato Hospital, New Zealand

1. Background.
   Digoxin is a cardiac glycoside widely used in patients with congestive cardiac failure and atrial fibrillation. Chronic poisoning and unrecognized progressive toxicity in medicated patients is much more common than acute ingestion.
   Relevant pharmacokinetics - 80% oral bioavailability, 60 - 70% renal excretion, half life 42 hours, large volume of distribution.
   Relevant pharmacodynamics - mechanism of action via Na/K ATPase inhibition. Toxicity an extension of this.

2. Toxicity.
   Cardiac - almost any arrhythmia, especially with associated AV block.
   Gastrointestinal.
   Neurological.

   Risk increased with;
   renal dysfunction
   hypo K,Mg
   hyper Ca
   heart disease
   hypothyroid
   advanced lung disease
   pharmacokinetic and dynamic interactions, e.g. new macrolides causing elevated levels.

3. Management.
   A. Obtain a history and examination while instituting basic supportive cares.
      ABC's, oxygen, and intravenous access.
      Baseline investigations of ECG, bloods with emphasis on electrolytes and digoxin level.
      Some authors in 1970's felt serum K was best marker of severe toxicity.
   
   B. Gastric lavage indicated if recent large ingestion. Charcoal will decrease both absorption and enterohepatic circulation.
   
   C. Arrhythmias - atropine and pacing for slow rates. Electrolyte correction, lignocaine and phenytoin for tachycardias. Phenytoin drug of choice as increases both AV conduction and VF threshold. Risk of asystole requires use of low energy for DC shocks.
   
   D. Digoxin specific antibodies.(DIGIBIND)
      Produced by papain digestion of sheep anti digoxin IgG.
      Binds and inactivates both intravascular and ATPase bound digoxin.
      Complex is subsequently renally excreted. Measured digoxin levels will increase.
Indications.
    rapidly progressive or life threatening symptoms.
    hyperkalaemia - 5.5 +
    significant underlying heart disease.
    high serum levels. Range in published articles goes from 5 to 10 ng/ml.
    adults >10mg, children > 0.3 mg/kg.

Dose. 40 mg vial binds 0.6 mg digoxin.
    First calculate body load in mg.
    Either dose ingested x 0.8 , or serum [ ] (in ng/ml) x volume of distribution (5.6 l/kg)
    x weight, then divide by 1000.
    The number of vials to be administered is the body load in mg divided by 0.6.
    In a cardiac arrest situation this can be mixed in saline and given as a push. Otherwise
    run in over 30-60 minutes.
    For unknown ingestion dose or level give 5 - 10 vials at a time.

E. Summary.
    The successful management of digoxin poisoning requires a healthy index of suspicion in
    order to recognise its often varied presentation. Along with basic supportive cares the early
    administration of digoxin antibodies can be lifesaving. Recurrent toxicity can be seen with
    significant renal failure or inadequate digibind dosing.

References
5. Goodman & Gilman et al. eds. The pharmacological basis of therapeutics. 8th ed. 1990.
THE SEROTONIN SYNDROME: AETIOLOGY, CLINICAL FEATURES, DIAGNOSIS AND MANAGEMENT

Dr. M. Chinthamunneedi. Intensive Care Unit, Womens & Children’s Hospital, SA

Serotonin syndrome. A potentially life threatening complication of treatment with psychotropic drugs characterised by alterations in cognition (disorientation, confusion) behaviour (agitation, restlessness), and function of the autonomic nervous system (fever, shivering, diaphoresis, diarrhoea), and neuromuscular system (ataxia, hyperreflexia)\(^8\)

Aetiology. It is a pharmacodynamic adverse effect caused by concurrent use of psychotropic drugs the likely hood of which is increased by the pharmacokinetic interaction of these agents effecting the the cytochrome p450 (CPY) isoenzymes,\(^8\) 75% cases occur in 24 hours of addition of precipitating drug.\(^7\)

Pathophysiology. Excessive stimulation of postsynaptic serotonin receptors (mainly 5HT\(_{1A}\)) located at lower brainstem and spinal cord. Theories about the pathogenesis extend to include endogenous (inherited or acquired) as well as iatrogenic deficits in peripheral 5-HT metabolism, activation of several 5-HT receptor subtypes and stimulus for release of 5-HT.\(^1\)

Drugs implicated\(^4,5\)
1. Serotonergic drugs include agents which increase 5-HT synthesis e.g, L-tryptopan
   - tricyclic antidepressants, SSRIs, sertraline, pethidine and cocaine which inhibit 5-HT uptake
   - 3,4-methylenedioxymethamphetamine or ‘ecstacy’, cocaine, dextromethorphan, pethidine, pentazocinetfenfluramine which increase 5-HT release
2. Serotonin receptor agonists
   - Lysergic acid diethylamaide, L-dopa, psilocin, mescaline, lithium and buspirone
3. MAOIs
   - tranylcypromine, phenelzine, moclobamide, which decrease 5-HT metabolism, while selective MAO-B inhibitor selegiline is likely to cause SS in toxic doses

Clinical features and Diagnosis
Diagnosis is clinical based on Sternbach’s clinical criteria, lab tests like drug levels are non specific, tests like CPK, leukocytosis and other organ function test are used mainly to evaluate ongoing complications eg: rhabdomyolysis.

Sternbach's Diagnostic criteria\(^1,3\)
A. Coincidental with the addition of or increse in known serotonergic agent to an established medication regimen, at least three of the following clinical features present
   - Agitation, diaphoresis, diarrhoea, fever, hyperreflexia, incoordination, mental status changes (confusion, hypomania), myoclonus, shivering, tremor
B. Other aetiologies (e.g., infection, metabolic, substance abuse, or withdrawal) have been ruled out

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C. A neuroleptic agent had not been started or increased in dosage prior to the onset of signs and symptoms listed above

Complications include death, hyperthermia, seizures, respiratory arrest, DIC, ventricular arrhythmia and rhabdomyolysis.

Management majority of cases respond in 24 hours with simple withdrawal of the precipitating agent and with the supporting medications e.g., lorazepam, propranolol

Moderate to severe forms require resuscitation involving active control of temperature by aggressive cooling, institution of NMJ blockers, acid base, fluid and electrolyte balance, haemodynamic and ventilatory support, and treatment of coagulation disturbances.

Other drugs used in the treatment are specific 5-HT\textsubscript{1A} antagonists, propranolol 1-2mg/5min up to 0.1 mg/Kg, non specific 5-HT antagonist methisergide (2mg 12-hourly) cyproheptadine 4 mg fourth hourly up to 20 mg/day

Seizures associated with SS should be treated with benzodiazepines and if necessary a barbiturate.

A number of other agents including dantroline, bromocriptine chlorpromazine have been used with inconsistent results

References
DISCUSS THE INDICATIONS FOR CORTICOSTEROIDS IN ARDS

Dr. A. McKee, Intensive Care Unit, Green Lane Hospital, New Zealand

ARDS Criteria  Acute onset
- PaO$_2$/FiO$_2$ 200mmHg regardless of PEEP
- Bilateral infiltrates on frontal CXR
- PAWP 18 when measured or no clinical evidence of raised LAP

Physiology
Acute Lung Injury (ALI) leads to lung repair and remodelling with high levels of growth factors and markers of collagen synthesis. Attempts to pharmacologically reduce the early inflammatory response thought to contribute to alveolar capillary membrane damage have used corticosteroids, antioxidants, cyclo-oxygenase inhibitors and prostaglandins. None have been shown to be safe and effective.

Evidence
Randomized trials of early high dose corticosteroids in ARDS have shown no benefits.$^{1,2}$ Two recent meta-analyses of randomized trials of short course (< 48hrs) of high dose methyl prednisolone in early sepsis and ARDS found no evidence of benefit$^{3,4}$ There have been some reports of prolonged steroid courses leading to benefit$^{5,6}$

A recent randomized, double blind, placebo controlled trial$^7$ of high dose, prolonged course (32 days) methyl prednisolone showed:
- improved Lung Injury Score
- improved PaO$_2$/FiO$_2$
- improved MOD score
- reduced mortality

They used methyl prednisolone 2mg/kg bolus starting on day 7 then daily for 14 days, reducing to 1 mg/kg/day for 7 days then tailing off to day 32. If there was no improvement after 10 days of treatment then the patients crossed over to the other group, but these patients didn't do well, suggesting a “window period” where corticosteroids are effective. They suggest that previous trials may not have given enough corticosteroids for long enough. The study had some limitations (mainly size related) but was well conducted.

Supporting this study is in vitro and clinical evidence of cytokine mediated glucocorticoid resistance in sepsis$^8$ and evidence that premature discontinuation may cause rebound changes in cytokine levels.$^9$

Indications
Unclear. Recent trials suggestive of benefits. Therefore if little signs of improvement after 7 days of treatment then consideration should be given to a course of methylprednisolone.

Further larger trials are still needed to confirm benefits, timing, dosage and duration of treatment.
References


DISCUSS THE CAUSES AND DESCRIBE HOW YOU WOULD MANAGE A MECHANICALLY VENTILATED PATIENT WHO SUDDENLY CANNOT BE VENTILATED.

Dr. P. Kruger, Intensive Care Unit, Princess Alexandra Hospital, Queensland

The situation of a mechanically ventilated patient who suddenly cannot be ventilated is a crisis situation and as such requires a planned systematic approach to its evaluation and management. Doctors are encouraged through their training and careers to think and problem solve from first principles.\cite{1,2,3} It is well appreciated in other fields such as aviation and increasingly so in medicine\cite{1,2,3} that such an approach is ineffective in a crisis situation. A better approach would be to have a core algorithm, such as COVER ABCD that has been described for anaesthesia crisis management.\cite{3} This will aid in early identification of possible causes and appropriate therapy.

For the mechanically ventilated patient that cannot be ventilated one approach would be:

1. **Assess and ensure adequate oxygenation.** Get an overview of what the problem is. Look at the patient’s color and perfusion, verify oxygen saturation and end tidal carbon dioxide if available. Look at the ventilator and what it is delivering or what alarms and pressures are displayed. Put on 100 % oxygen. Check the circulation, note the pulse rate and blood pressure.

2. **Eliminate the equipment.** Simultaneously with your rapid assessment of the patient use a completely new “checked” T piece circuit (or equivalent) with a different oxygen source and connect to the endotracheal tube directly. Ventilate the patient by hand. If this provides adequate ventilation the problem has been isolated as ventilation equipment. Further investigation of the exact cause can continue with the patient no longer in danger. Hand ventilation also allows some assessment of pulmonary compliance and may decrease peak airway pressures and improve ventilation.

3. **Call for assistance.** Notify those around of your concerns so the necessary staff and equipment can be gathered.

4. **Eliminate the Endotracheal Tube (or tracheostomy).** Pass a suction catheter, this will clear secretions and confirm patency. Deflate the cuff (in case of cuff herniation). Consider replacing the tube or consider fibroptic bronchoscopy to help confirm position (excludes endobronchial, oesophageal or submucosal placement or inadvertent extubation with upper airway obstruction).

5. **Examine the Patient.** This time in more detail than the initial assessment. Reevaluate the vital signs. Look at the chest move, look at the jugular venous pressure. Feel the trachea is midline, feel for subcutaneous emphysema, check the percussion note. Auscultate the chest, listen for equal breath sounds, wheeze or crackles. Look beyond the thorax, think about increased intraabdominal pressure, muscular rigidity and changes in position of the patient.
6. **Particular patient Causes.** It is worth considering and reevaluating some specific causes that need excluding.
   - Kinked tube, Blocked tube with mucous, blood, foreign body.
   - Pneumothorax (is there any evidence to warrant needle thoracocentesis)
   - Anaphylaxis, Asthma and Aspiration
   - Pulmonary Oedema
   - Muscular rigidity (from narcotics in high dose or malignant hyperthermia), biting on the endotracheal tube, poor coordination with the ventilator. Would a dose of muscle relaxant help?

   Specific patient causes found or suspected should be treated as would usually be appropriate.

7. **A Second Opinion.** A fresh look at the situation is invaluable. A significant problem in unresolving crisis situations is the “coning of attention” or clinging to an early “strong but wrong” diagnosis despite mounting evidence demanding a new hypothesis and a second opinion is often helpful.

**References**

## INDICATIONS AND COMPLICATIONS OF INTRATECAL MEDICATIONS

**Dr. P. Harrigan.** Intensive Care Unit, Royal Perth Hospital, **Western Australia**

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**ALL SUFFER THE COMPLICATIONS OF DURAL PUNCTURE**

The use of intrathecal antibiotics for the treatment of CSF shunt infections without removing the devices has been successful in some series, however most series do not support this and more common practice would be shunt removal and systemic antibiotics.

Intrathecal methotrexate is well described for use in the treatment of and prophylaxis against CNS spread of haematological malignancies as well as post-operative adjuvant therapy for some CNS malignancies. Abnormalities of CSF flow may predispose to CNS complications.
of this treatment, although many patients have also undergone CNS irradiation which has similar complications. There is debate in the literature about which is the underlying cause, although there are series describing these complications in patients receiving only one or other modality of treatment.

Neostigmine given at the time of local anaesthetic administration for spinal anaesthesia has received much attention in the last 2 years or so, the analgesia provided is clinically useful although the incidence of complications, particularly nausea and vomiting is high in some groups (post-caesarean section) and at higher doses. Post-operative opioid consumption is often not ablated, but is reduced.

The use of clonidine as an adjuvant to all manner of regional and general anaesthesia and analgesia techniques is widely documented. In Australia its use for neuraxial blocks still requires specific TGA approval, although is becoming more common.

Ketamine has been used in only a few series recently for analgesia and anaesthesia. As a sole anaesthetic agent it was unsatisfactory because of inadequate block, short action and the usual emergence phenomena. Autopsy studies in cancer patients with chronic pain suggest a possible myelopathy associated with the use of ketamine intrathecally.

Midazolam has been studied for its analgesic properties although concerns are raised about neurotoxicity.

Local anaesthetics are in common use for spinal anaesthesia and analgesia. Much of the recent debate has focussed on the neurotoxicity of hyperbaric 5% lignocaine. Because of these problems the FDA has withdrawn approval for the use of intrathecal catheters. The use of these drugs is well described in the usual texts.

Opioids are becoming more widely used intrathecally for acute and chronic pain because of the good analgesia and reduced systemic effects. The more lipid soluble agents such as fentanyl and sufentanyl can provide regional analgesia with low risk of late respiratory depression, but provide only relatively short duration of effect. Morphine will provide analgesia for up to 24 hours over a wide spread of dermatomes but has the risk of rostral carriage and late respiratory depression.

Baclofen is a good agent for the relief of spasticity when used intrathecally, but care must be taken to avoid omission of doses because of the severe withdrawal phenomenon which mimic malignant hyperthermia and have a significant mortality.

References
Angiotensin II receptor antagonists are a new class of drug that provide a site-specific blockade of the effects of angiotensin II; and maybe suitable for first-line management of hypertension and congestive cardiac failure.

**Indications:**
- Treatment mild/moderate hypertension.
- Management of congestive cardiac failure
- Prevention/treatment of left ventricular hypertrophy
- Prevention of ventricular remodelling post myocardial infarction

**Actions:**
- Selective competitive angiotensin II subtype I receptor antagonists. Preventing the binding of angiotensin II to AT\(_{1}\) receptors; have virtually no effect on other angiotensin-receptor subtypes.
- AT\(_{1}\) receptors are located adrenal cortex, arterial vascular smooth muscle, SNS nerves, brain and myocardium.

**Antihypertensive actions:** Effect dependent on activity of the renin/angiotensin/aldosterone system. Reduces SVR maintains cardiac output and heart rate. Mechanism of antihypertensive action include;
1. inhibition direct vasoconstrictive effect of AT II,
2. decreased activity of SNS,
3. decreased AT II mediated renal tubular Na\(^+\) reabsorption,
4. decreased AT II mediated aldosterone release,
5. decreased brain renin/angiotensin thereby altering baroreceptor sensitivity,
6. stimulation of vasodilator prostaglandins,
7. decrease hyperplasia/hypertrophy of vascular and cardiac muscle.

**Cardiac actions**
Reduce left ventricular hypertrophy: a direct AT II antagonist action rather than due to reduction in afterload.
Similar effect to ACE-I in preventing post MI ventricular remodelling.
Clinical efficacy in the treatment of CCF with improved cardiac index, reduced PAOP, and experimental evidence of reduced LVEDV/P

**Antiatheromatous action:** In-vitro evidence that AT II blockade inhibits proliferation of vascular smooth muscle.

**Humoral actions:**
Inhibition of AT II negative feedback on renin release by the juxtaglomerular cells mediated by AT \(_{1}\) receptors leads to increased plasma renin and angiotensin levels.
Aldosterone generally decreased.
Noradrenaline secretion by SNS decreased; resulting in attenuation of cardioacceleratory reflexes to reduced blood pressure.
**Renal actions** Elevated creatinine in susceptible patients.
Uricosuric specific action of losartan, not AT II blockade mediated.
Reduced renal $K^+$ loss.

**Dosage**
- Losartan total daily range 25mg – 100mg
- Irbesartan total daily range 150mg-300mg

**Complications:**
In clinical trails dizziness 1-2% was the only reported adverse effect with a frequency $>$ placebo
Post marketing surveillance reports include;
- Hypersensitivity; angioedema face/lips/tongue some pts same features with ACE-Is.
- Gastrointestinal; hepatitis, altered LFTs, diarrhoea.
- Musculoskeletal; myalgia
- Renal impairment risk groups renovascular disease, elderly, DM, hyporeninaemic hypoaldosteronism
- Neural; migraine
- Drug interactions; hyper$K^+$ with potassium sparing diuretics or potassium supplements. No interactions of clinical significance identified with warfarin, digoxin, B blockers, calcium antagonists, phenobarbitone or ketoconazole

**References**
DESCRIBE THE AETIOLOGY, CLINICAL FEATURES, AND MANAGEMENT OF A PATIENT WITH HYPOMAGNESEAEMIA

Dr. B. McFadyen, Intensive Care Unit, John Hunter Hospital, New South Wales

MAGNESIUM HOMEOSTASIS: - Magnesium is the fourth most abundant cation in the body total stores being approximately 15 mmol/kg. Intracellular stores account for 99% of total body magnesium - tissue distribution comprising: bone 53%, muscle 27%, soft tissue 19% and erythrocytes 0.5%. The remaining 1% of total magnesium is extracellular with 33% protein bound, 12% complexed with anions, and 55% in free ionised form. It is this free extracellular component which is routinely measured in clinical practice.

Absorption of largest magnesium occurs along the entire length of the small bowel in inverse proportion to the load presented. The main site of regulation of body magnesium is the renal tubule. The diffusible fraction is filtered at the glomerulus and reabsorbed along the length of the tubule, predominantly at the thick ascending limb of the loop of Henle. The precise mechanisms of tubular magnesium regulation are not well understood. Aldosterone enhances magnesium excretion. Parathyroid hormone reduces magnesium excretion and enhances absorption from the gut. A circadian rhythm for renal excretion exists, with enhanced loss at night.

DEFINITION: - Serum magnesium is routinely measured by atomic-absorption spectrophotometry with normal values being 0.7-1.05 mmol/l. Hypomagnesaemia exists when serum magnesium is less than 0.7 mmol/l. However, there is very poor correlation between serum and total body magnesium. Significant magnesium depletion may exist despite normal or even elevated serum levels. Deficiency can be detected by measuring intracellular magnesium (eg. muscle biopsy), or by performing a magnesium load test (20 mmol of magnesium is administered IV over several hours. If less than 70% of the magnesium load is excreted in the urine over the following 24 hours then magnesium depletion exists). Both of these approaches have significant practical limitations.

AETIOLOGY: -
Reduced Intake
(i) dietary deficiency
   - magnesium poor diet
   - prolonged fasting
(ii) reduced absorption
   - malabsorption syndromes
   - short bowel syndrome
   - ileal bypass
   - entere fistulas
   - chronic diarrhoea
   - pancreatitis/pancreatic insufficiency
   - prolonged nasogastric suction
   - inherited primary malabsorption
Redistribution
- alkalosis
- chelation by citrate (eg. blood transfusion)
- insulin/dextrose infusion
- catecholamines

Increased Loss
(i) tubular dysfunction
- Interstitial nephritis
- polyuric phase of ATN + post-obstructive diuresis
- renal tubular acidosis
- Bartter’s syndrome
- inherited renal Mg/K wasting
(ii) drug-induced tubular loss
- aminoglycosides
- ticarcillin
- amphotericin
- loop/thiazide/osmotic diuretics including glucose
- cisplatinum
- cyclosporin
- ethanol
- pentamidine
(iii) extrarenal factors
- hyperaldosteronism
- hypercalcaemia
- hypokalaemia
- hypophosphataemia
- excessive sweating

Magnesium depletion is particularly associated with alcohol abuse, poorly controlled diabetes, and as a drug side-effect. There is a high incidence (up to 50%) of hypomagnesaemia in critically ill patients usually because of a combination of the above factors. Some studies have reported increased mortality in this hypomagnesaemic group which may represent an association rather than causation.

CLINICAL FEATURES:
Magnesium is an essential cofactor in many biological systems particularly those involving the generation and utilisation of ATP. The major manifestations of hypomagnesaemia are thought to be due to altered Na-K ATPase function with modified intracellular electrolyte balances and membrane excitability. The combination of hypomagnesaemia, hypocalcaemia, and hypokalaemia is usually present when manifestations occur.

CARDIOVASCULAR
Electrocardiographic - prolongation of PR & QT interval
- T wave flattening
- ventricular dysrhythmias including Torsade de pointes
- atrial fibrillation
- digoxin-mediated dysrhythmias
Clinical - hypertension
- coronary artery spasm

NEUROMUSCULAR HYPEREXCITABILITY
- muscle weakness (incl respiratory muscles)
- tremor/myoclonus/choreoathetosis
- carpopedalspasm/tetany
- Chvostek's & Trousseau’s signs
- Laryngospasm and stridor

NEUROPSYCHIATRIC
- apathy/agitation/delirium/coma
- depression
- Wernicke's encephalopathy
- seizures

ELECTROLYTE DISTURBANCES
- hypokalaemia
- hypocalcaemia

MANAGEMENT :-

(1) Resuscitation of ABC
(2) Magnesium replacement
   The rate and duration of replacement is empiric. Parenteral administration is usually most appropriate in the ICU setting. In established deficiency the whole body deficit will be 0.5 - 1.0 mmol/kg. Given that about 50% of a dose is retained, 1 - 2 mmol/kg is required.
   A common regime is - 10 mmol bolus over 5 minutes
   0.5 mmol/kg/day x 24hrs
   0.25 mmol/kg/day x 3 - 5 days
   Frequent clinical and laboratory monitoring to prevent toxicity is required although this is most uncommon in the absence of renal failure. Calcium chloride or gluconate should be immediately available. Renal failure requires approx. 50% dose reduction + close monitoring. More rapid administration (e.g. 15 mmol slow IV push) can be used for emergency situations such as ventricular arrhythmias. Oral replacement may be satisfactory on a longer term basis – magnesium containing antacids and magnesium aspartate can be used.
(3) Remove the cause as possible.

References
Myxoedema coma

- a state of severe decompensated hypothyroidism
- triad of (1) altered mental state (2) hypothermia (3) clinical features of hypothyroidism (dry, coarse skin, scaly elbows and knees, yellowing of skin without scleral icterus, coarse hair, thinning of lateral aspect of eyebrow, macroglossia)

**Clinical Features**

**CNS**
- Coma
- Symmetrical tendon reflexes with slow relaxation phase
- Seizures, preceding coma in 25%
- Myopathy

**Temperature**
- Hypothermia, may be profound

**Respiratory**
- Hypoxemia, hypercarbia
- Decreased ventilatory responsiveness to hypoxia and hypercarbia

**Cardiovascular**
- Hypotension with inappropriate sinus bradycardia
- Pericardial effusion rarely cardiac tamponade
- ECG findings
  - slow rate, AF
  - low voltage
  - prolonged QT interval
  - T wave flattening
  - J wave

**Electrolyte, Acid-Base derangement**
- Acidosis, both metabolic & respiratory
- Hypoglycaemia
- Hyponatraemia
- Hyperkalaemia
- Hypophosphataemia
- Azotaemia

**GI tract & bladder dysfunction**
- Paralytic ileus
- Megacolon
- Urinary retention
Management

Careful assessment
- Search for precipitating causes, instituting therapy as appropriate
- Infection, sepsis, cardiac failure, cerebrovascular accident, drugs

Supportive measures

ABC
- Adequacy, control & protection of airway
- Maintain adequate ventilation, oxygenation
- Circulatory support with volume repletion, inotropic support as necessary
- Exclude mechanical cause (pericardial effusion) if refractory hypotension despite optimization of parameters

Treat hypothermia
- According to severity of hypothermia
- If mild, measures to prevent heat loss adequate
- Moderate to severe need active treatment
- Need monitoring of temperature gradient, and watch for shock 2° to peripheral vasodilatation

Correct metabolic derangement
- Hyponatraemia
  - usually respond to fluid restriction
  - may require hypertonic saline if severe and complicated with seizures
- Hypoglycaemia
- Replace phosphate

Hormonal replacement

Thyroid hormones
- Principal of therapy is to replenish extrathyroid hormone
- Choice of T4 or T3 depends
  - Those without intercurrent disease T4 adequate
  - In the severely ill, T3 better choice
- Route of administration depends
  - Oral suffice
  - If complicated with paralytic ileus, i/v route more reliable
- Recommended doses
  - 500 mcg T4 loading, then T4 50-100 mcg daily or 25 mcg T3 6 hourly till clinical improvement

Corticosteroids
- 5-10% associated with hypoadrenalism
- Hydrocortisone 50mg 6 hourly
THE MANAGEMENT OF PARAQUAT POISONING

Dr. D. Gattas. Intensive Care Unit, Royal Prince Alfred Hospital, New South Wales

Physicochemical

Paraquat has been marketed since the 1960s as a broad spectrum nonselective contact herbicide and desiccant. In Australia, it is most commonly formulated as a 10-20% w/v liquid (100-200 mg/mL) concentrate. ICI formulations include a stenching agent, an emetic and a blue dye. A dose greater than 40mg/kg is almost always fatal; this means 10-15mL of undiluted formulation is enough to cause death.

Kinetics and Mechanism of Toxicity

Low (5-10%) but rapid absorption occurs from the gastrointestinal tract; peak plasma concentrations occur in less than 2 hours following ingestion. Redistribution occurs, first to the kidneys and lungs and then slowly into muscle. It does not undergo any significant metabolism and is excreted unchanged in the urine. Until renal failure supervenes, renal clearance is very rapid; it is actively secreted by tubular cells. Most of the dose has been excreted in urine by 24 hours although it is detectable in urine for weeks due to slow efflux from muscle and renal failure.

In severe poisonings, death occurs early (hours) due to multiorgan failure with cerebral oedema, haemorrhagic pulmonary oedema, and necrosis of liver, kidney, and muscle (including myocardium). In moderately severe cases, the lung is the primary target organ for toxicity. Alveolar cells take up and accumulate paraquat; reduction-oxidation of paraquat produces superoxide free radicals which cause peroxidation of membrane lipids. A severe alveolitis results with extensive parenchymal destruction (phase I) followed days later by a proliferative phase involving severe fibrosis (phase II).

Clinical Severity and Prognosis

Mild poisoning usually occurs when <20mg/kg is ingested. There may be no symptoms, or some gastrointestinal upset which resolves.

Moderate poisoning occurs following ingestion of 20-40mg/kg. There is severe upper gastrointestinal upset with inflammation and ulceration. Pulmonary fibrosis will occur; renal and hepatic failure may occur after 24 hours. Severe upper gastrointestinal ulceration and renal failure are both associated with a poor prognosis.

Severe poisoning occurs following ingestion of >40mg/kg. Death almost always occurs in hours to days.

Management

1. Washing of the skin
   Any contaminated skin should be washed immediately with large volumes of water. The eyes, if splashed, should be irrigated thoroughly.

2. Gastrointestinal adsorption
   a) Gastric lavage is controversial. Although paraquat is corrosive, lavage is recommended in cases where presentation is less than 2 hours following ingestion.
   b) Fuller’s earth is supplied to Australian hospitals by ICI as a 15% aqueous solution. The adult dose is one litre; the paediatric dose is 1-2g/kg. This dose is repeated every 2-4 hours until it is passed in the stools. Fuller’s earth treatment may be complicated by hypercalcaemia and by ileus; mechanical obstruction and perforation has been reported.
For this reason, a cathartic such as 200mL 20% mannitol should be administered concurrently.

c) Activated charcoal is nearly as effective as fuller’s earth at adsorbing paraquat and should be substituted if the former is unavailable.

3. Investigations
Concentrations of paraquat in plasma and urine are of use prognostically; a nomogram exists for estimating probability of survival from the plasma level and the hours since ingestion. Accurate urine and plasma concentrations are able to be determined by chromatographic and radioimmunoassay methods. Simple qualitative urinary measurement is possible using a colorimetric method for the production of the blue cation dithionate in an alkaline solution; it is possible to distinguish mild, moderate and severe poisoning with this method.

4. Avoid supplemental oxygen
Oxygen may potentiate superoxide formation and pulmonary toxicity. Supplemental therapy should therefore be avoided. When established fibrosis and respiratory failure occur however, this becomes unreasonable.

5. Supportive therapy
Intravenous fluids are required. Opioid analgesia may be required for painful ulceration; local measures such as mouthwashes etc. may be of value. Agitation and seizures may require treatment.

6. Extracorporeal elimination
Haemodialysis, haemoperfusion and haemofiltration are of no proven clinical efficacy in paraquat poisoning. Their use has been very controversial. Most of the dose has been excreted by the kidneys in less than 24 hours, and peak lung concentrations are reached at around 15 hours. Haemoperfusion, in particular, is effective in lowering plasma concentrations of paraquat but is only of theoretical benefit if started less than 12 hours after ingestion; some papers have suggested even 2 hours. This is very difficult to achieve in practice, even at a tertiary referral institution. Plasma levels increase again after haemoperfusion due to redistribution from tissues.

7. Anti-inflammatory/Immunosuppressive Therapy
An important paper and an accompanying editorial appeared in Thorax in 1996. 5,6 87 cases of paraquat poisoning were seen at a Taiwan hospital over 6 years, a very large number for a single centre. A historical control group of moderately severe poisonings (by urine testing) was compared to a similar group who received two 1g doses of cyclophosphamide daily and three 1g doses of methylprednisolone daily. This was done to try to inhibit the fibrotic stage of pulmonary toxicity. 12 out 16 in the treatment group survived, compared to only 5 out of 17 with standard therapy. Given the devastating nature of paraquat poisoning and the absence of demonstrated complications from the therapy, it provided potentially exciting results.

8. Other pharmacological measures
A variety of antioxidants and potential antidotes have been tried without success including vitamins C and E, superoxide dismutase, and desferrioxamine.
REVIEW

THE MANAGEMENT OF PARAQUAT POISONING

Paraquat is a highly poisonous commercial herbicide. As little as 10mL of undiluted formulation is likely to kill an adult.

Kinetics and Toxicity
- 5-10% of the ingested dose is absorbed rapidly. Renal excretion is also rapid until renal failure supervenes.
- The lung is the main target organ for damage by free radical formation in alveolar cells by redox of paraquat.
  - Phase I: intense alveolitis and necrosis.
  - Phase II: proliferation of fibroblasts and fibrosis leading to irreversible respiratory failure and death.

Clinical Severity
- Mild: <20mg/kg - self limiting GI upset
- Moderate: 20-40mg/kg - GI ulceration, hepatic and renal failure, progressive respiratory failure
- Severe: >40mg/kg - fatal

Management
There is no antidote.

1. Wash the skin, eyes
2. Gastrointestinal adsorption: Fuller’s earth
3. Investigations: urine and plasma paraquat levels; nomogram
4. Avoid supplemental O2: potentiation of pulmonary toxicity
5. Supportive therapy: fluids, analgesia
6. Extracorporeal elimination: does not improve outcome
7. Anti-inflammation/Immunosuppression: cyclophosphamide and methylprednisolone may have a role

References
CLINICAL FEATURES AND TREATMENT OF THYROTOXIC CRISIS

Dr. C. Simpson, Intensive Care Unit, Waikato Hospital, New Zealand

Thyrotoxic Crisis (also known as ‘Thyroid Storm’) is a rare but life threatening condition, and is the most severe form of hyperthyroidism. Accounts for 1-2% of hospital admissions for thyrotoxicosis. Untreated thyroid storm is fatal, mortality with treatment est. 20-30%.

Known precipitants include:

- Infection
- Trauma
- diabetic ketoacidosis
- radio-iodine therapy
- withdrawal of antithyroid therapy
- pulmonary embolism
- severe emotional stress

- surgery
- parturition
- hypoglycaemia
- iodinated contrast dyes
- vigorous palpation of thyroid gland
- cerebrovascular accident
- congestive cardiac failure

Laboratory tests have findings consistent with thyrotoxicosis, but there are no specific criteria for thyroid storm.

Diagnosis: is clinical, and is based on multi-organ decompensation in a thyrotoxic patient.

Diverse clinical presentations have precluded the development of a clear set of diagnostic criteria, however the most common findings are fever, CNS signs, tachycardia and GI symptoms.

All factors need not be present to establish the diagnosis. A diagnostic point scale has been proposed to help distinguish uncomplicated hyperthyroidism from impending or present thyrotoxic crisis, but clinical impression is the key to early diagnosis and treatment.

Clinical Features:

1. Fever (usually greater than 38.5°C)
2. Central Nervous System
   Mild: agitation, confusion, apathy
   Moderate: delirium, psychosis, extreme lethargy
   Severe: seizure, coma
3. Cardiovascular
   Tachycardia (out of proportion to the fever)
   Congestive cardiac failure (mild to severe)
   Atrial fibrillation, other tachyarrhythmias
4. Gastrointestinal-Hepatic
   Nausea, vomiting, diarrhoea
   Abdominal pain
   Unexplained jaundice

Management:

1. Treat hyperthyroidism
   aim: block synthesis of new hormone
   a) propylthiouracil (dose: Load 600-1000mg followed by 200-250mg q4h po/ng) or methimazole
b) lithium carbonate*

aim: block release of preformed hormone (after blocking synthesis of new hormone)
   a) iodine: potassium iodide po/ng (SSKI or Lugol’s solution) intravenous sodium iodide** radiographic contrast dye (ipodate or iopanoate)*** (dose: of iodine content: 0.5 - 2.0 gm/day in divided doses)
   b) lithium carbonate*

aim: inhibit peripheral actions of thyroid hormone
a) inhibition of conversion T4 to T3
   a) propylthiouracil plus ipodate
   b) propranolol
   c) corticosteroids (dexamethasone 2mg q6h IV, or hydrocortisone 100mg q8h IV)

b) β Blockade
   a) propranolol (dose: 2-4mg q4h IV, 20-40mg up to 60-120mg q6h po/ng)
   b) if unable to take β Blockers consider reserpine ** or guanethidine

aim: remove excess circulating hormone
   plasmapheresis, plasma exchange, dialysis, exchange transfusions, charcoal plasma perfusion

aim: definitive treatment (once crisis resolved)
   a) radioactive iodine (may need to be delayed because uptake will be limited after high dose iodine therapy)
   b) surgery (partial or complete thyroidectomy)

*use lithium if known allergy to iodine, or toxic reaction to thioureas ** if available (reserpine not currently being manufactured, IV sodium iodide not widely stocked) *** it is unclear if other iodinated contrast media have same inhibition of peripheral conversion T4 to T3, but they can be given as source of iodine

2. Treat decompensation of homeostatic mechanisms

aim: treatment of hyperthermia
   paracetamol, active cooling measures

aim: treatment of dehydration and electrolyte imbalances
   IV fluids and electrolytes, glucose, multivitamins

aim: supportive therapy
   oxygen
   pressors
   treatment of congestive heart failure
   treatment of arrhythmias +/- anticoagulation if AF
   corticosteroids

3. Treat precipitating event
Thyrotoxic Crisis: a rare but life threatening condition, the most severe form of hyperthyroidism.

Clinical Features:
1. Fever
   Usually greater than 38.5°C
2. Central Nervous System
   From agitation and confusion, through to seizures and/or coma
3. Cardiovascular
   Tachycardia (out of proportion to the fever)
   Congestive cardiac failure (mild to severe), Atrial fibrillation
4. Gastrointestinal-Hepatic
   Nausea, vomiting, diarrhoea, Abdominal pain, Unexplained jaundice

Management:
1. Treat hyperthyroidism
   aim: block synthesis of new hormone
   propylthiouracil or lithium carbonate*
   aim: block release of preformed hormone (after blocking synthesis of new hormone)
   Iodine: as potassium iodide solution, IV preparation, ipodate, or iopanoate or lithium carbonate*
   * use lithium if known allergy to iodine, or toxic reaction to thioureas
   aim: inhibit periphera/ actions of thyroid hormone
   a) inhibition of conversion T4 to T3
      propylthiouracil plus ipodate
      propranolol, corticosteroids
   b) β Blockade
      propranolol
   aim: remove excess circulating hormone
   plasmapheresis, plasma exchange, dialysis, exchange transfusions, charcoal plasma perfusion
   aim: definitive treatment (once crisis resolved)
   radioactive iodine, surgery
2. Treat decompensation of homeostatic mechanisms
   aim: treatment of hyperthermia
   paracetamol, active cooling measures
   aim: treatment of dehydration and electrolyte imbalances
   IV fluids and electrolytes, glucose, multivitamins
   aim: supportive therapy
   oxygen, pressers, treatment of congestive heart failure treatment of arrhythmias +/- anticoagulation if AF corticosteroids
3. Treat precipitating event
References
THE CLINICAL PRESENTATION AND MANAGEMENT OF SPONTANEOUS OESOPHAGEAL RUPTURE – BOERHAAVE’S SYNDROME

Dr. G. Howard. Intensive Care Unit, Christchurch Hospital, New Zealand

Presentation:

*History and examination:* Diagnostic error > 50%, clinical exam useful < 1/3 of cases.

- **a) Classic:**
  - Alcoholism
  - Dietary excess
  - Meckler's Triad:
    - Vomiting (71%)
    - Lower left chest pain (85%)
    - Subcutaneous emphysema (22 - 66%)

- **b) Described:**
  - Pain: abdo. > chest ~ shoulder
  - Vomiting after pain (30%)
  - Alcohol ingestion < 1:3 patients.

Common misdiagnoses!
- Myocardial infarction
- Perforated peptic ulcer
- Acute pancreatitis
- Thoracic aneurysm
- Pneumothorax

*Predisposing factors:* <10% known upper Gl disease, commonly reflux disease.

Investigations:

- **a) CXR:** Sensitivity >90%. Pleural effusion (Left predominant) 90%. Pneumothorax (with effusion) 80%. Mediastinal air, subcutaneous emphysema 27 - 66%.
- **b) Contrast studies:** Sensitivity 75 - 95% (Gastrograffin > barium). Right lat. decubitus.
- **c) CT:** Poor localisation of rupture site after free mediastinal leak.
- **d) Thoracocentesis:** Macroscopic: “Foul smelling”, dirty, bloody. pH < 7.0, saliva squames, high amylase content.
- **e) Oesophagoscopy:** Not useful.

Management:

*Non-operative:* - Small perforations
- Contained leak (mediastinum only)
- Diagnosis > 24 hrs following onset of symptoms (Contentious).

*Operative:* - Closure individualised: primary, primary reinforced, (exclusion diversion, intra-luminal stent and thoracoscopic repair less established )
- Pleural/mediastinal debridement and drainage.
- Exclude distal obstruction: gastric and oesophageal sump drainage.
- Nutrition (?TPN Vs enterostomy), antibiotic cover, supportive care

*Prognosis:* - Mortality 33% (8-55%). Surgical mortality after diagnostic delay >24hrs may not be increased in true Boerhaave’s.
- Morbidity related to diagnostic delay
- Complication rate 15 - 40%, Commonly suture line leak.
- High incidence long term dysmotility. Pre-morbid disposition?
The Clinical Presentation and Management of spontaneous Oesophageal Rupture: Boerhaaves Syndrome!

Historical Perspective and clinical presentation:
The first case of spontaneous oesophageal rupture was somewhat ominously reported by Hermann Boerhaave as a post-mortem finding in 1724. The patient had died after 18 hours of self-induced vomiting to facilitate gluttony. The clue at post-mortem came from the smell of duck flesh and olive oil upon opening the left pleural cavity.\(^1\) Meckler subsequently coined a triad of left chest pain, vomiting and subcutaneous emphysema classically said to occur in the setting of alcoholism and dietary excess.

Despite being a well documented condition its varied presentation, and a low index of suspicion by the attending practitioner, has led to a “tradition” of misdiagnosis in over half of all cases.\(^2\) A review of 34 cases found an absence of significant food ingestion in almost half, and only a minority had ingested any alcohol. Rapid onset of pain or vomiting (or both) was the most common symptom. Pain following vomiting has been used as a useful indicator of spontaneous rupture, however up to a quarter of the patients had pain preceding vomiting or did not vomit at all. Abdominal pain proved to be more common than chest pain in this series.\(^2\) Clinical examination has proven as disappointing in clarifying the diagnosis.\(^1\) Subcutaneous emphysema, a useful sign when present, may not be present in patients presenting less than 1 hour after onset of symptoms. In the above review the initial diagnosis was correct in only 14 of 34 patients with common misdiagnosed including perforated peptic ulcer, acute pancreatitis, thoracic aneurysm and spontaneous pneumothorax.

Investigation:
Chest radiographs are abnormal in 80-90% of patients with oesophageal rupture. Chest X-ray abnormalities depend on the time interval from perforation; the site of perforation and the integrity of the mediastinal pleura.\(^3\) Pleural effusion and pneumothorax (or both) are the commonest findings and are left sided in over two thirds of cases. Free mediastinal or subcutaneous air occurs in up to 66% of patients.\(^1\) Contrast studies will confirm the diagnosis in 90% of patients. Sensitivity is said to be highest in the right lateral decubitus position using a water soluble contrast.\(^3\) Computerised Tomography (CT) scanning has proven disappointing in localising the point of injury but is a useful adjunct for localising mediastinal (unruptured) collections, and in post-operative follow-up. Thoracocentesis may be diagnostic if containing food particles. An aspirate with a pH < 6.0 in the presence of salivary squames or high amylase content is similar strong evidence.\(^1,2\) Oesophagoscopy is not considered useful and may even be harmful.\(^4\)

Management:
Patient management must be individualised. Traditionally diagnosis delayed beyond 24 hours has been considered an indication for conservative therapy on the basis of surgical mortality approximating that of non-operative management.\(^1\) These figures were derived from patients with oesophageal rupture from all causes. Pate \textit{et al}, however in their 30 year experience with spontaneous rupture of the oesophagus had similar mortality in patients undergoing surgery both less than and more than 24 hours after onset of symptoms.\(^2\)

Non-operative management has been used in patients with contained perforations demonstrated to drain freely back into the oesophagus. Patients managed in this way should have minimal symptoms and no evidence of clinical sepsis.\(^2\) Under these conditions it may be reasonable to treat with a nil by mouth regime, hyperalimentation, antibiotics and a gastric acid reducing agent. Oral intake is resumed in 7-14 days.\(^3\)
Operative treatment relies on wide debridement of the oesophagus and mediastinum, adequate oesophageal closure and good pleural toilet. Reinforced primary closure using a pleural or other flap is preferred. Alternative techniques have been described including oesophageal resection, exclusion and diversion, intra-luminal stenting and thoracoscopic repair. Most spontaneous ruptures occur in the distal oesophagus on the left side making left thoracotomy in the 7th or 8th space the most common incision. Prolonged gastric drainage by gastrostomy or nasogastric tube is usually practiced, often with additional oesophageal sump drainage. Supportive care includes broad spectrum antibiotic cover and feeding by parenteral or distal enteral routes. Overall mortality remains high (30-50%) despite advances in care of the critically ill. In those who survive, morbidity increases with diagnostic delay. The most common post operative complication is that of leakage at the repair line (17% of patients). Long term follow-up has shown survivors to have significant oesophageal dysmotility. It has been suggested this may have preceded the episode of spontaneous rupture.

Analysis of survival by decade from 1958 to 1989 showed no improvement despite rapid advances in critical care medicine. Awareness of this condition in patients with a compatible presentation would appear to be the key to effective management of this rare but catastrophic condition.

References
DISCUSS THE CLINICAL PRESENTATION AND DESCRIBE HOW YOU WOULD
MANAGE A PATIENT WITH ACUTE PULMONARY EMBOLISM AND SHOCK

Dr. D. Connor, Intensive Care Unit, Manning Base Hospital. New South Wales

Complication of thrombosis somewhere ‘downstream’ in the venous circulation.
Diagnosis should be entertained for every patient admitted to ICU with sudden, unexplained change in clinical condition.

Has pulmonary embolism already occurred?
Does PE explain the patient’s deterioration?
Can the patient stand one more significant insult?

* Note 8% of autopsies of patients receiving CPR at death demonstrate major PE

Presentation
Sudden onset of dyspnoea, tachypnoea, tachycardia, low grade fever, oppressive chest discomfort, apprehension and fatigue are all common.

Hypoxia, hypercapnia, hypotension and shock all indicate massive pulmonary embolism.
Massive PE due to a large embolus causing amputation of a segment of the pulmonary vascular bed. This causes both a large increase in dead space (hypercapnia) and a large amount of blood flow diverted to the unaffected lung, hence causing a low V/Q ratio, and therefore hypoxaemia. The sudden increase in pulmonary vascular pressures cannot be compensated for by an increase in RV stroke volume as this is preload dependent. Instead the RV dilates as the ejection fraction falls, and we see hypotension and shock.

Diagnosis
In extremis, diagnosis is clinical
ABG’s, CXR, ECG may be helpful
V/Q scan may confirm with a high probability result, or pulmonary angiogram is definitive.

Management
Early intervention is essential. If the patient is alive after 30 minutes, they will probably survive.
Hypoxaemia and hypercapnia: intubate and ventilate
Hypotension: optimise preload
PA catheter allows accurate optimisation with intravenous fluid loading to a RAP 15 – 20 mmHg
decrease RV afterload
thrombolysis with streptokinase 1 million units over 30 minutes, followed by heparin infusion
increase RV contractility
inotropes, particularly adrenaline, which will increase contractility of the RV and cause vasoconstriction and increase preload for the RV
Surgery: embolectomy, IVC filter
CURRENT MEDICAL TREATMENT OF HEART FAILURE

Dr. P. Meuer, Intensive Care Unit, North Shore Hospital, New Zealand

Congestive heart failure (CHF) is a syndrome resulting from impaired left ventricular pump function characterized by an impediment to left ventricular emptying and/or left ventricular filling. Long term goals include reducing mortality and reversing or slowing the progressive structural abnormality of the left ventricle termed “remodeling”. Improvement in symptoms does not necessarily correlate with correction of left ventricular dysfunction. Drug therapy that improves symptoms may not improve mortality.

Pharmacological therapy

Diuretics act directly on the kidney to inhibit tubular sodium, potassium and water reabsorption, decreasing cardiac preload and wall tension. Thiazides are used initially followed by loop diuretics with incremented extracellular fluid accumulation. Potassium-sparing diuretics (e.g. aldosterone) may be a useful adjunct to prevent hypokalaemia. This class of diuretic is to be used with caution, however, where patients concurrently receive angiotensin-converting enzyme (ACE) inhibitors, which in combination may produce hyperkalaemia.

ACE inhibitors are a major advance in the management of CHF. They may reverse systemic vasoconstriction by inhibition of angiotensin II and thereby relieve symptoms and improve exercise tolerance. Studies have shown reduction of heart remodeling and associated reduction in long-term mortality. ACE inhibitors may afford limited protection against sudden cardiac death, usually attributed to arrhythmia.

Therapeutic combination of isosorbide dinitrate and hydralazine presently represents the most potent and effective vasodilator regimen for heart failure. Hydralazine has a direct dilating effect on the arterioles and recent studies have identified hydralazine as blocking nitrate tolerance by virtue of an antioxidant effect preventing generation of superoxides which inactivate nitric oxide (NO). The Veterans Administration Cooperative Vasodilator-Heart Failure Trial I (V-HeFT I) trial showed a 34% reduction in 2 year mortality rates in patients receiving hydralazine and isosorbide dinitrate compared with placebo. There is, however, poor patient compliance due to side-effects.

Digoxin can prevent clinical deterioration, decrease symptoms, and improve functional capacity in patients with heart failure due to impaired systolic function. The recently completed Digitalis Investigation Group study confirmed these findings and reported a significant reduction in hospitalization due to CHF in patients receiving digoxin, diuretics, and ACE inhibitors compared to patients treated with diuretics and ACE inhibitors alone. However, digoxin did not have a significant effect on mortality in this study. Digoxin does not alter remodeling.

Amiodarone has anti-arrhythmic, anti-ischaemic and neuromodulating effects. Amiodarone is the only antiarrhythmic not shown to increase mortality in CHF patients. Amiodarone appears to reduce the incidence of sudden death, although this reduction may not be solely attributable to its anti-arrhythmic property.

Oral inotropic agents have not been shown effective.

Phosphodiesterase inhibitor studies with enoximone and milrinone have shown higher death rates in those treated with these drugs despite (in the case of milrinone) improved exercise tolerance and reduction in heart failure symptoms.

Studies with ibopamine, a dopaminergic agonist, demonstrate improved biochemical neurohormonal profile. However, the PRIME II study comparing idopamine with placebo was
halted prematurely because of a significantly higher death rate in the patients treated with ibopamine.² It is clear ibopamine does not affect remodeling.

Non-pharmacologic therapy

Patients with heart failure should be encouraged to reduce dietary sodium (to less than 2-3 grams/day), undertake regular exercise, reduce excessive alcohol intake and avoid unnecessary fluid intake.

Continuous positive airway pressure (CPAP) systems used in emergency departments has averted endotracheal intubations in about 90% of patients presenting with acute pulmonary oedema.

Present trials are attempting to determine if an implantable cardioverter-defibrillator (ICD) can reduce the incidence of sudden cardiac death. Some trials suggest that mortality can be reduced if a high risk group can be selected. The greatest benefit in preventing sudden cardiac death by prophylactic ICD occurs in patients with left ventricular dysfunction featuring mild to moderate symptoms.⁵

Surgical alternatives are generally considered on a prognostic basis (angioplasty, coronary artery bypass grafts, valvular repair).

Reversing the remodeling process

Numerous factors appear to contribute to the remodeling process of the ventricle, including aldosterone, angiotensin, endothelin, and noradrenaline. The relationship between these neurohumoral factors is unclear, but it is evident that chronic activation of the sympathetic nervous system is associated with myocardial damage and left ventricular hypertrophy and remodeling.¹

ACE inhibitors and beta blocking agents appear to alter the remodeling process. In the first Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS I), there was a 36% mortality rate at 1 year with enalapril compared with a 52% mortality rate with placebo in patients with severe heart failure. Enalapril was shown to significantly decrease mortality compared with placebo in patients with ejection fractions <35% and it had a more favourable effect on survival at 2 years than the vasodilator combination of hydralazine-isosorbide dinitrate in patients with decreased exercise capacity and ejection fractions <45%.¹

Recently, patients treated with carvedilol, a second generation beta blocker with vasodilating and antioxidant properties had a 65% risk reduction in mortality and a 38% reduction in cardiovascular hospitalizations. The treated group also exhibited a marked reduction in left ventricular remodeling.¹

Management of advanced heart failure in the intensive care unit

Patients with advanced heart failure achieve their best cardiac output with near normal ventricular filling pressures.³ The pulmonary artery occlusion pressure should be lowered to <15mm Hg with a right atrial pressure reduced to <7mmHg or a mean arterial blood pressure of <80 mm Hg. Systemic vascular resistance should be reduced to 1200 dynes/sec/cm⁻⁵ using diuretics, intravenous vasodilators and inotropic agents such as dobutamine and milrinone.

Failure of maximal pharmacologic therapy is an indication for mechanical assistance and/or transplant surgery.

Despite the use of currently available therapeutic modalities, heart failure remains associated with high mortality rate (approximately 40% at four years).¹
References
1. Cohn JN. Overview of Treatment of Heart Failure. Am J Cardiol 1997;80:2L-6L
LIST THE CLINICAL FEATURES AND MANAGEMENT OF SPONTANEOUS PNEUMOTHORAX.

**Dr. P Jowitt.** Intensive Care Unit, Mildura Base Hospital, Victoria

**Clinical Features**
Clinical features progress with a) increasing volumes/pressures of pleural gas, and b) increasing severity of underlying parenchymal disease

Small primary pneumothorax  
*Asymptomatic*  
↓  
* pain affected side*  
↓  
* anxiety, ease of fatigue*  
↓  
* cyanosis*  
↓  
* dyspnoea tachypnoea*  
↓  
* hyper-resonance, diminished movements & breath sounds*  
↓  
* tachycardia*  
↓  
* hypotension*  
↓  
* jugular distension*  
↓  
* clouding consciousness*  
↓

Increasing volumes/pressures

Pleural gas  
↓  

Increasing severity of underlying lung disease  
↓  

Large pneumothorax  
(+/- tension) secondary to serious parenchymal lung disease  
* respiratory failure*

**Management** – options determined by severity and persistence of clinical features

Small asymptomatic 1° pneumothorax  
* expectant*  
Prophylaxis advice (1)

Symptomatic 1° pneumothorax  
* simple aspiration* (2)

Recurrent 1° pneumothorax  
2° pneumothorax  
* intercostal underwater drain*  
+/- continuous negative pressure

Persistently recurring pneumothorax  
* pleural instillation of*  
Sclerosing agent (4)

Failure of preceding measures  
* thoracoscopy or thoracotomy*  
And pleurectomy (5)

Respiratory failure associated with tension pneumothorax  
* large bore intercostal catheter*  
for immediate pressure release  
+/- IPPV (followed by step 3)

**Reference**
Describe the procedure and list the indications and complications of plasmapheresis

Dr. A. Harvey, Intensive Care Unit, Princess Alexandra Hospital, Queensland

Plasmapheresis (or plasma exchange) facilitates the removal of a pathogenic circulating factor in the blood by the removal of plasma with replacement by albumin-electrolyte solutions or plasma proteins.

The Procedure.
The cell separators for plasmapheresis are broadly divided into 2 groups.
1. Machines which use centrifugation for separation and are therefore also suitable for specific separation and blood component removal. (ie. Thrombopheresis and leukapheresis). Blood removal is via continuous or discontinuous flow.
2. Machines which separate by membrane filtration and therefore can only be used for plasma separation.

Once the plasma has been removed from the patients blood the erythrocytes are reinfused into the patient. Fluid volume is maintained by the administration of albumin solution (or other colloid) or FFP. Usually about 50% of patients plasma is removed with each exchange procedure.

This technique can be combined with immunoabsorption techniques where immunoglobulins can be specifically removed.

Indications.
Plasmapheresis has been used to treat a spectrum of diseases. It is most beneficial for immunoproliferative and autoimmune diseases particularly when they are at the acute stage and when autoantibody production is rising rapidly.

1. Immunoproliferative diseases with monoclonal immunoglobulins (ie. Waldenstrom’s macroglobulinaemia, Multiple myeloma)
   a. Hyperviscosity syndrome – Visual disturbance, neurological dysfunction and hypervolaemia can all be rapidly improved.
   b. Cryoglobulinaemia – An acute fulminant presentation with cutaneous vasculitis, renal failure and neurological impairment can be treated with plasmapheresis.
   c. Renal failure in Multiple Myeloma – This is usually multifactorial in origin, but some factors may be reversible by plasmapheresis.
2. Autoimmune diseases due to autoantibodies or immune complexes.
   a. Goodpastures syndrome – Due to circulating antiglomerular basement membrane antibodies.
      Often a fulminent presentation with rapidly progressive renal failure and life threatening pulmonary haemorrhage. Early plasmapheresis can be used to prevent renal damage.
   b. Myasthenia gravis – Caused by acetylcholine receptor autoantibodies. Plasmapheresis plays a major role in the treatment of myasthenic crisis but has also been used in patients resistant to other forms of therapy.
   c. Guillain-Barre Syndrome – Caused by demyelination due to post infectious autoimmunity.
Plasmapheresis is usually indicated in patients with severe or rapidly progressive
disease. If instituted early it can shorten illness time and decrease complications.
Delayed recovery time is often due to the time needed for remyelination.
d. Systemic Lupus Erythematosus – Plasmapheresis can be used in acute, life threatening
relapses with rapid deterioration of renal function, or acute pneumonitis.
e. Thrombotic thrombocytopenic purpura – Thought to be caused by microvascular
endothelial damage secondary to immune complex deposition. Plasma infusion,
plasmapheresis and antiplatelet therapy all have a role.
f. Rapidly progressive glomerulonephritis – This is immune complex induced and can be
associated with Systemic lupus erythematosus, Polyarteritis nodosum and Wegeners
granulomatosis. Plasmapheresis can improve renal function acutely but long term
recovery depends on immunosupression.
g. Coagulation inhibitors – Autoantibodies may be formed against anticoagulation
factors.
Antifactor VIII antibodies are the most common. These can occur spontaneously or
following factor VIII replacement.
h. Autoimmune haemolytic anaemia – ie idiopathic cold agglutinin haemolytic anaemia.
i. Post-transfusion purpura – Caused by antibodies to platelets.
3. Conditions in which replacement of plasma may be beneficial.
a. Disseminated intravascular coagulation.
b. Overwhelming sepsis syndrome.
a) Paraquat poisoning
b) Envenomation.
5. Miscellaneous acute disorders with unclear immune mechanisms.
a. Renal transplant rejection. Hyperacute renal allograft rejection can be initially treated
with plasmapheresis,
b. Multiple Sclerosis – Treatment with plasmapheresis remains controversial.

Complications.
1. Circulatory effects - Intravascular volume changes
   - Vasovagal reactions
   These are exacerbated in patients with pre existing altered blood volume and renal failure.
   Therefore accurate fluid and electrolyte balance is important.
2. Plasma oncotic pressure – Patients who have a predisposition to interstitial fluid
   accumulation may not tolerate even minor fluctuations in plasma oncotic pressure.
3. Infection - Patients are often immunosuppressed.
   - Indwelling lines predispose to infection.
4. Haemostasis – Plasmapheresis can cause bleeding or thrombosis.
5. Reactions to replacement fluids – Anaphlaxis can occur.ie to FFP.
6. Effects of intravascular protiens – Coagulation components, transport and binding
   protiens become depleted. Therefore there is a decrease in drug binding protiens. ie.
   Potentiation of corticosteroids.
7. Hepatitis to plasma exchange
8. Hypothermia
9. Embolisms of air or micoraggregates
10. Anaemia or thrombocytopenia
REVIEW

DESCRIBE THE PROCEDURE AND LIST THE INDICATIONS AND COMPLICATIONS OF PLASMAPHERESIS

Procedure
2 types of cell separators – centrifugal
Membrane filtration
Albumin or FFP to replace fluid volume
Erythrocytes reinfused

Indications
1. Immunoproliferative disease with monoclonal antibodies.
   a) Hyperviscosity syndrome
   b) Cryoglobulinemia
   c) Renal failure in multiple myeloma
2. Autoimmune diseases due to autoantibodies or immune complexes
   a. Goodpastures syndrome
   b. Myasthenia gravis
   c. Guillain Barre syndrome
   d. Systemic lupus erythematosus
   e. Thrombotic thrombocytopenia purpura
   f. Rapidly progressive glomerulonephritis
   g. Coagulation inhibitors
   h. Autoimmune haemolytic anaemia
   i. Post transfusional purpura
   j. Rhesus alloimmunization in pregnancy.
3. Conditions in which replacement of plasma may be beneficial
   a. DIC
   b. Overwhelming sepsis.
4. Removal of protein-bound or large-molecular-weight toxins
   a. Paraquat poisoning
   b. Envenomation
5. Miscellaneous
   a. Renal transplant rejection
   b. Multiple sclerosis
   c. Heparin induced thrombocytopenia.

Complications
1. Circulatory effects
2. Plasma oncotic pressure
3. Infection
4. Haemostasis
5. Reactions to replacement fluid
6. Effects on intravascular proteins
7. Hepatitis to plasma exchange
8. Hypothermia
9. Embolisms
10. Anaemia or thrombocytopenia
References
LIST THE CLINICAL FEATURES AND MANAGEMENT OF A PATIENT WITH UNSTABLE ANGINA.

Dr. M. Kluger, Intensive Care Unit, North Shore Hospital, Auckland, New Zealand

Introduction
Unstable angina; a syndrome not a definitive diagnosis.
A spectrum of diseases (A) stable angina—non-Q wave infarct; (B) no pathology—thrombosis;
(C) normal coronary arteries—severe three vessel disease

Definition
- Symptoms of angina at rest (> 20 minutes)
- New onset exertional angina of at least CHA Class III
- < 2/12 acceleration of angina by at least one CHA Class

Pathophysiology
- Non-occlusive thrombosis on pre-existing plaque. (J; antithrombotic e.g. unfractionated or LMW heparin and antiplatelet e.g. aspirin, ticlodipine, GPIIb/IIIa inhibitors)
- Dynamic obstruction (spasm or vasoconstriction) e.g. Prinzmetal angina, variant angina, non-focal vasoconstriction, micro-circulatory angina. (J coronary dilators e.g. nitrates or calcium channel antagonists)
- Progressive mechanical obstruction. (J catheter or surgery)
- Inflammation and/or infection. Preponderence of lymphocytes; NPLs and monocytes. Markers of infection raised e.g. C. pneumonia titres, C-reactive protein, serum amyloid A. (J; COX II inhibitors; macrolide antibiotics)
- Secondary unstable angina. Imbalance of MDO2 v MVO2. (J; β blockers)

Management

<table>
<thead>
<tr>
<th>Risk evaluation</th>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likelihood of disease</td>
<td>Documented</td>
<td>Suspect</td>
<td>Low</td>
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<tr>
<td>Severity of ischaemia</td>
<td>Prolonged pain, rec angina, CVS deterioration</td>
<td>Rest pain</td>
<td>New-onset, effort angina</td>
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<tr>
<td>Unstable angina score</td>
<td>6,5</td>
<td>4,3</td>
<td>2,1</td>
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<tr>
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DISCUSS THE MANAGEMENT OF A PATIENT WHO HAS DELIRIUM TREMENS

Dr. C. Lee, Intensive Care Unit, Westmead Hospital, New South Wales

DEFINITION; Delirium Tremens, a late manifestation of alcohol withdrawal syndrome, is characterised by delirium and autonomic hyperactivity in alcohol dependent individuals.

PATHOPHYSIOLOGY; Alcohol withdrawal causes a variable and complex effect on inhibitory and excitatory neuro-receptors in the central nervous system. Chronic alcohol use down-regulates both the gamma-aminobutyric acid (GABA) receptor and the N-methyl-D-aspartate (NMDA) glutamate receptor. Abstinence from alcohol reverses this, but causes a relative increase in the action of excitatory neurotransmitters which produces many of the symptoms and signs of Delirium Tremens. Other pathways stimulated during alcohol withdrawal are the noradrenergic pathways, which probably contribute to the sympathetic hyperactivity and dopaminergic transmission, which may be responsible for hallucinations.

INCIDENCE; Occurs in approx 20% of alcohol-dependent individuals who present to inner city hospitals. In a study in the United States, 1 24% of alcohol dependent persons admitted to a city hospital developed Delirium Tremens, of whom 24% died.

CLINICAL: Natural History - The syndrome described with alcohol withdrawal has historically and temporally been divided into three sets of symptoms,
1. Characterized by symptoms of Autonomic hyperactivity 24 - 48hrs
2. Characterized by symptoms of neuronal excitation 12 - 48hrs
3. Delirium Tremens characterised by delirium and autonomic hyperactivity > 2 days.
   Delirium Tremens occurs in very few cases of alcohol withdrawal syndrome. Symptoms fluctuate but peak on day 3 to 4 post-cessation of alcohol. If untreated the condition may lead to death from respiratory and cardiovascular collapse. The mortality rate 10 years ago was quoted at 15% but with recognition of the importance of intensive care this has reduced to 5%.
Risk Factors - One or more concurrent illness. (e.g. infection)
- Abstinence from alcohol for > 2days.
Symptoms and signs - Delirium, agitation, confusion, hallucinations (visual, tactile, auditory).
- Autonomic hyperactivity (sweating, tachycardia, tremor, mydriasis)
Seizures are unusual in Delirium Tremens and alert the physician to a possible alternative diagnosis, although they are part of the alcohol withdrawal syndrome itself.
- Biochemical - Electrolyte disturbance (Decreased Na⁺, K⁺, Mg²⁺).
- Metabolic disturbance (Usually a metabolic acidosis)
Differential diagnosis - Infection (encephalitis, meningitis)
Alcohol induced hypoglycaemia
Drugs (anticholinergic)
Substance abuse (cocaine, amphetamines, phencyclidine)
Endocrine (Thyrotoxicosis)
Fulminant hepatic failure

Management - Investigations include
- FBC, Urea and electrolytes, Liver function tests,
- Thyroid function tests, Creatinine Kinase
- CT Brain
- Sepsis screen including Lumbar puncture

Resuscitation
- Airway
- Breathing
- Circulation

Supportive care and Detoxification
- Benzodiazepines are the current drugs of choice for detoxification of patients with alcohol withdrawal syndrome. Thiamine should be given to avoid Wernicke's encephalopathy. It is currently recommended that at least 100mg TDS is prescribed.

References
DEFINE AND LIST THE CAUSES OF NOSOCOMIAL PNEUMONIAS

Dr. G. Auzinger, Intensive Care Unit, Alfred Hospital, Victoria

Nosocomial pneumonia is acquired in the hospital and is associated with different organisms that are often more resistant to antibiotic therapy compared with the bacteria responsible for community acquired pneumonia. The mortality rate for nosocomial pneumonia is significantly higher (~30%, vs. 3% - 5%).

Most important predisposing factors:
1. ICU admission
2. Intubation/Mechanical ventilation (VAP)
3. Previous antibiotic use
4. Postsurgical state
5. Preexisting lung disease
6. Renal failure
7. Advanced age
8. Ventilator associated pneumonia:
   a. Early onset (48 - 72h)
   b. Late onset (different causative organisms: Resistant Staph.aureus, Pseudomonas, Acinetobacter, Enterobacter species)

Development of VAP requires:
1. Bacterial colonization of aerodigestive tract
2. Aspiration of contaminated secretions into lower airway
3. Less frequently hematogenous spread or transthoracic infection

Predisposing factors for VAP:
- ETT, nasogastric tube
- Lengthy period of ventilation
- Condensate within ventilator tubing
- Frequent circuit disconnections
- Sinusitis
- Poor dentition
- High gastric pH
- Supine position
- Immobilization
- Immune compromise

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