

James Mitchell's Anaesthetics Notes

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About these notes

These notes are my study notes from preparing to sit the ANZCA Primary exam in 1997 and the ANZCA Fellowship exam in 2000. A few people wanted a copy of my notes in early 1998, so I made some photocopies. I have been asked if I mind them being copied or distributed; I don't mind as long as they aren't modified and are correctly attributed as my work. Of course they're not exclusively my own work, they have been prepared from the standard texts and from notes from people I have studied with. All the graphs and diagrams I have redrawn myself.

The quality is pretty variable and some topics are not covered in the detail required for the exams. This is because I find the process of *making* notes far more useful than *having* them. Early on I started writing prose paragraphs, but most of the material is in outline format.

There's probably not much point in trying to give advice about studying for these exams; depending on how your assessments at school were performed, the Primary exam is between the 15th and 30th set of exams you will sit so you probably have a fair idea of how to study. The significant difference is that for many registrars it is the first time they will fail an exam.

So how did I study? I started reading the parts of the texts I found interesting about 18 months before I sat the Primary. I was working as a psychiatric resident so I had plenty of time. I prepared notes on a few of the less important topics to get warmed up before tackling the major physiology topics (respiratory and cardiovascular) in detail. I was part of a study group of five from about eight months before the exam. We met once a week for four or five hours. We started by choosing major topics from the red book, splitting up the objectives on that topic between us and each preparing notes to present and share at the weekly session. Later we started going through an old written paper, sharing out the questions between us and each preparing a marking scheme or "model answer" to our questions so that if we did the other questions as timed exam practice we got a marking scheme to assess our answers with. The last couple of sessions we did previous exams strictly to time.

Study for the Fellowship was similar except that we had to go through the MCQ bank as well. We went through it twice, the second time focussing on the new questions from the previous exam and also the marker questions. The syllabus wasn't as clearly defined as for the Primary, so the notes are correspondingly somewhat haphazard in their coverage.

Can you have the notes in electronic format? The answer is yes and no. They are all ClarisWorks/AppleWorks files on my Mac but they don't export well as Word or HTML (or anything else except EPS) without a *lot* of tweaking. If I get around to making them into PDFs then I'll let you have a copy.

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Texts used

Primary

Pharmacology

Wood & Wood

Stoelting: Pharmacology and Physiology in Anaesthetic Practice

Katzung: Pharmacology

Rang, Dale & Ritter: Pharmacology

Cass: Pharmacology for Anaesthetists

Statistics

Miller: Anaesthesia

Physiology

Guyton: Textbook of Medical Physiology

Ganong: Physiology

Despopoulos: Color Atlas of Physiology

Berne & Levy: Cardiovascular Physiology

Vander: Renal Physiology

West: Respiratory Physiology

Nunn: Applied Respiratory Physiology

Brandis: The Physiology Viva

Physics & Measurement

Davis, Parbrook & Kenny: Basic Physics and Measurement in Anaesthesia

Miller: Anaesthesia

Fellowship

Practice of anaesthesia

Miller: Anaesthesia

Clinical Anaesthesia Procedures of the Mass. General

Brown: Regional Anaesthesia

Cousins & Bridenbaugh: Neural Blockade

Shnider & Levinson: Anaesthesia for Obstetrics

Lippincott-Raven Interactive Anaesthesia Library on CD-ROM

ATLS Handbook

ANZCA Policy Documents

Australian Anaesthesia Biennial

Anatomy

Black & Chambers: Essential Anatomy for Anaesthesia

Equipment

Rosewarne: Anaesthetic Equipment

Russell: Equipment for Anaesthesia and Intensive Care

Supplemental (used for occasional reference)

Oh: Intensive Care Manual

Stryer: Biochemistry

Harrison's Principles of Internal Medicine

Souhami & Moxham: Medicine

Gray's Anatomy

RCPA Manual of Pathology Tests

MIMS Annual

NHMRC and AHA websites

The main anaesthetic journals

Lots of other books left over from undergraduate medicine

A. Cellular Physiology

a. Describe the cell membrane and its properties.

b. Describe the functions of mitochondria, endoplasmic reticulum and other organelles.

Plasma membrane semipermeable lipid bilayer 7.5 nm thick

phospholipids, cholesterol

proteins

structural

pumps

active ion/molecule transport

channels

receptors

clathrins cluster to endocytose bound ligands

insulin & other peptides, lipoproteins, viruses

enzymes

intercellular connections

tight junctions

desmosomes

belt with bands of filaments containing actin

spot central stratum of filaments

hemi- epithelial cell to connective tissue

gap junctions

connexons allow molecules up to 800 d to pass

rise in Ca^{2+} closes

Cytoplasm

Golgi complex

vesicles → secretory granules

Endoplasmic reticulum (rough and smooth)

RNA → protein transcription in ribosomes

glycosylation of proteins

formation of vesicles and lysosomes

Lipid droplets

Lysosomes

merge with (auto-)phagocytic vacuoles and release

ribonuclease, deoxy~, phosphatase, glycosidases, arylsulfatases,

collagenase, cathepsins

release of enzymes into the cell causes damage in vit A toxicity, ?gout

enzyme defects cause lysosomal storage disorders

Mitochondria

separate DNA (female lineage)

outer and inner membrane with cristae

operate the citric acid cycle “cellular respiration” → ATP

Secretory granules

Centrioles

2 cylinders and right angles near nucleus

made of 9x3 microtubules

form the mitotic spindle in cell division

Microfilaments

long fibres of actin 4-6 nm diameter operate microvilli and attach to belt

desmosomes

Microtubules

25 nm diameter tubules made of α and β tubulin (5 nm thick)

maintain cell shape, constantly form and disassemble

Cilia

contain 9x2 +2 microtubules and basal granule of 9x3 microtubules

Nucleus

Chromosomes

2x22 + sex chromosomes

composed of DNA (2.5×10^9 base pairs), histones

contain genes, promoters, enhancers, junk

Nucleolus

site of RNA synthesis by transcription

Envelope with perinuclear cisterns

very permeable to allow RNA out

c. Explain mechanisms of transport of substances across cell membranes.

Diffusion

rate determined by (Fick's Law)

chemical gradient

electrical gradient

cross-sectional area of boundary

thickness of boundary

Donnan Effect

non-diffusible ions affect diffusion of other ions.

ratio of diffusible cations between compartments equals inverse ratio of diffusible anions.

Solvent drag

unimportant effect. Solvent bulk flow carries solute.

Filtration

rate determined by

pressure gradient

surface area of boundary

permeability of boundary

Osmosis

solvent molecules cross a membrane to a region of higher activity of a non-diffusible solute.

$$P = nRT/V$$

Carrier-mediated transport

facilitated diffusion

transport usually of large, non-ionized molecules down a

concentration/electrical gradient across the cell membrane via membrane

proteins. e.g. glucose uptake

active transport

transport of molecules or ions against of concentration or electrical gradient, usually mediated by ATPase proteins in the cell membrane e.g. Na^+ - K^+ ATPase, Ca^{2+} ATPase, H^+ - K^+

ATPase

transports 3 Na^+ out of and 2 K^+ into cells

inhibited by cardiac glycosides

composed of 2 α (95 kd binds ATP and digoxin) and 2 β (40 kd glycoprotein) subunits.

Na^+ binding is associated with phosphorylation

generates a membrane potential

rate-limited by intracellular Na^+

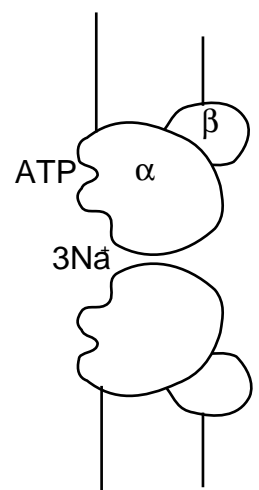
responsible for most of BMR

symport

transport coupled to an electrical or chemical gradient

e.g. Na^+ -glucose exchange in mucosal cells, Ca^{2+} - Na^+ exchange in cardiac muscle

Transport of large molecules



proteins and hormones are commonly transported by exo- or endo-cytosis

d. Explain the Gibbs-Donnan Effect.

e. Outline the role of cellular receptors and the function of secondary messengers within the cell.

f. Outline the sources of energy available to cells through metabolic processes.

Sources of energy

High energy phosphate compounds: ATP, phosphorylcreatine, GTP, CTP, UTP, ITP

Thioesters of Coenzyme-A: acetyl-CoA (\equiv 1 ATP)

Reduced coenzymes: NADH, NADPH (\equiv 3 ATP) via flavoprotein-cytochrome system

H_2 donor, NAD^+ , FAD, Co Q, Cyt B, Cyt c_1 , Cyt c, Cyt a, Cyt a_3 , O_2 .

Carbohydrates

Dietary sugars \rightarrow di- and mono-saccharides in gut \rightarrow circulating glucose, fructose and galactose (\rightarrow glucose) \rightarrow intracellular glucose \leftrightarrow glucose 6- PO_4 (- ATP)

Embden-Meyerhof pathway

glycogen \leftrightarrow n glucose 1- PO_4 \leftrightarrow glucose 6- PO_4 \leftrightarrow fructose 6- PO_4 \leftrightarrow fructose 1,6 di PO_4 (-ATP) \leftrightarrow dihydroxyacetone PO_4 (\leftrightarrow glycerol) + phosphoglyceraldehyde $\rightarrow \rightarrow$ pyruvate (+ 2 ATP, 1 NADH)

Hexose-monophosphate shunt

glucose 6- PO_4 \leftrightarrow 6-phosphogluconic acid \rightarrow pentoses \rightarrow fructose 6- PO_4 or phosphoglyceraldehyde

Tricarboxylic acid cycle

pyruvate + CoA \rightarrow acetyl-CoA (+ 2H + CO_2) ... + oxaloacetic acid \rightarrow citric acid $\rightarrow \rightarrow \rightarrow$ oxaloacetic acid + 8H + 2 CO_2
net yield = 10H \rightarrow 5NADH \rightarrow 15ATP

Aerobic glycolysis proceeds via the Embden-Meyerhof pathway and TCAC for 38 ATP per glucose molecule.

Anaerobic metabolism relies on the Embden-Meyerhof pathway only, yielding 4 ATP per glucose molecule less one for the phosphorylation of fructose 6- PO_4 and one more if glucose 6- PO_4 is generated from circulating glucose. The generation of NAD^+ required is via the conversion of pyruvic acid to lactic acid, generating an "oxygen debt".

Control of glucose metabolism is regulated by

β adrenergic receptors which promote glycolysis via cAMP, protein kinase, phosphorylase kinase and phosphorylase a as well as inhibition of glycogen synthase when it is phosphorylated. This causes a rise in blood glucose and lactate largely arising from glycolysis in liver and muscle respectively.

α adrenergic receptors which activate phosphorylase kinase via intracellular Ca^{2+} .

Glucagon which stimulates phosphorylase in liver only, causing a rise in blood glucose without lactate.

Insulin

g. Explain the ways in which cells use energy for the various cellular processes.

h. Describe the composition of intracellular fluid and its regulation including the role of the sodium-potassium pump.

ECF (20%) \approx estuarine water

Interstitial fluid (15%)

| | | | |
|-----------|-----------|--------------|-----------|
| Na^+ | 143 mEq/l | Cl^- | 117 mEq/l |
| K^+ | 4 | HCO_3^- | 27 |
| Ca^{2+} | 5 | HPO_4^{2-} | 2 |

| | | | |
|--|---|-------------------------------|---|
| Mg ²⁺ | 3 | SO ₄ ²⁻ | 1 |
| | | org acid | 6 |
| | | protein | 2 |
| plus H ₂ CO ₃ and non-electrolytes | | | |

Plasma (5%)

| | | | |
|--|-----------|--------------------------------|-----------|
| Na ⁺ | 152 mEq/l | Cl ⁻ | 113 mEq/l |
| K ⁺ | 5 | HCO ₃ ⁻ | 27 |
| Ca ²⁺ | 5 | HPO ₄ ²⁻ | 2 |
| Mg ²⁺ | 3 | SO ₄ ²⁻ | 1 |
| | | org acid | 6 |
| | | protein | 16 |
| plus H ₂ CO ₃ and non-electrolytes | | | |

Transcellular fluid (small)

CSF, aqueous humor, GIT contents etc.

ICF (40%)

Very rough concentrations:

| | | | |
|--|----------|-------------------------------|-----------|
| Na ⁺ | 14 mEq/l | PO ₄ ²⁻ | 113 mEq/l |
| K ⁺ | 157 | HCO ₃ ⁻ | 10 |
| Mg ²⁺ | 26 | protein | 74 |
| plus H ₂ CO ₃ and non-electrolytes | | | |

i. Describe the role of G-proteins.

j. Describe the general response to injury.

B. 1 Anatomy of the respiratory system.

a. Relate function of the upper airway and larynx to their structure.

The larynx connects the pharynx above with the trachea below and lies opposite C3-6. It is composed of cartilages connected by ligaments and membranes and is lined with mucosa. The walls of the larynx are formed from the thyroid and cricoid cartilages.

The thyroid cartilage is composed of two laminae, joined anteriorly at an angle and ending posteriorly in the superior and inferior cornua. Externally, the laminae are attached to sternothyroid, thyrohyoid and the inferior constrictor of the pharynx. Superiorly they attach to the thyrohyoid membrane and inferiorly to the cricothyroid membrane. The superior cornu attaches to the lateral thyrohyoid ligament and the inferior cornu articulates with the cricoid cartilage. Internally, the laminae attach to the thyroepiglottic ligament medially and more laterally to the vestibular and vocal ligaments and the thyroarytenoid, thyroepiglottic and vocal muscles.

The cricoid cartilage is a continuous ring, much wider posteriorly, which forms the inferior part of the larynx. The posterior lamina attaches to the tendon of the oesophagus in the midline and more laterally the cricoarytenoid. Superolaterally, the lamina articulates with the arytenoid cartilages and inferiorly the cricoid attaches to the trachea.

The arytenoid cartilages are approximately tetrahedral and articulate with the superolateral corner of the cricoid lamina. Posteriorly they attach to the transverse arytenoid which connects them, anteriorly they have a vocal process which attaches to the vocal ligament, posterolaterally the muscular process attaches to posterior and lateral cricoarytenoids. The medial surface forms part of the rima glottidis and the anterolateral part attaches to the vestibular ligament.

The corniculate cartilages sit at the superior tips of the arytenoids, in the aryepiglottic folds. The cuneiform cartilages are in the aryepiglottic folds anterosuperior to the arytenoids. The epiglottis is a fibrocartilage leaf attached inferiorly to the thyroid cartilage, laterally to the aryepiglottic folds and anteriorly to the glossoepiglottic folds which form the vallecula.

The arytenoids can rotate medially and laterally and at the same time slide a small distance medially or laterally to separate or appose the posterior parts of the vocal ligament. The cricoid cartilage can rotate in the sagittal plane to increase or decrease the anteroposterior diameter of the rima glottidis.

The posterior cricoarytenoids rotate and slide the arytenoids laterally, opening the glottis. The lateral cricoarytenoids rotate the arytenoids medially and close the glottis. The transverse arytenoid approximates the arytenoids, bringing the posterior ends of the vocal folds together. The cricothyroids tilt the cricoid, lifting the anterior part and increasing tension on the vocal folds. The thyroarytenoids draw the arytenoids anteriorly, slackening the vocal folds. The oblique arytenoids and aryepiglottici act to close the inlet of the larynx by bringing the aryepiglottic folds together. All of the intrinsic muscles of the larynx are supplied by the recurrent laryngeal nerves except for cricothyroid which is supplied by the external branch of the superior laryngeal nerve.

Below the cricoid cartilage, the trachea extends to the level of T5 where it bifurcates into the right and left main bronchi. These divide further into segmental bronchi:

| | | |
|-------|----------|--|
| Left | upper | apical, posterior, anterior |
| | lingular | superior, inferior |
| | lower | apical, anterior, posterior, (medial), lateral |
| Right | upper | apical, posterior, anterior |
| | middle | lateral, medial |
| | lower | apical, anterior, posterior, medial, lateral |

Also in [head anatomy \(3.G.6\)](#)

b. Explain the structure of the chest wall and diaphragm and relate these to

respiratory mechanics.

In [Respiratory Mechanics \(1.B.3\)](#)

B. 2 Control of Respiration

a. Describe the medullary and pontine respiratory control centres and explain how the ventilatory pattern is generated and controlled.

There are three main groups of neurones involved in control of respiration, each present bilaterally. In the medulla there is a dorsal respiratory group, mostly in the nucleus of the *tractus solitarius*, which receives sensory input from the vagus and glossopharyngeal nerves. In the ventrolateral part of the medulla is the ventral respiratory group in the *nucleus ambiguus* and *nucleus retroambiguus*. In the superior pons lies the pneumotaxic centre in the *nucleus parabrachialis* and in the lower pons, the apneustic centre.

Inspiration is initiated rhythmically by the dorsal respiratory group, generating periodic bursts of action potentials. This results in an “inspiratory ramp” signal of two seconds of increasing signals to the primary inspiratory muscles. This then ceases for three seconds before the cycle repeats. There are two parameters which vary in the inspiratory ramp signal: its rate of increase, controlling the depth of inspiration and its duration, controlling frequency. Output from the pneumotaxic centre limits the duration of the inspiratory ramp.

When rapid and deep respiration is required, output from the dorsal respiratory group recruits neurones in the ventral respiratory group which generate activity in secondary muscle of respiration, allowing for forceful inspiration and expiration.

The apneustic centre in the lower pons acts to prolong the duration of the inspiratory ramp signal. In the absence of the pneumotaxic centre, it results in sustained inspiration.

Regulation of respiration from breath to breath is maintained by projections of the vagus nerve from stretch receptors in the bronchi and bronchioles which result in ending of the inspiratory ramp signal at tidal volumes over 1.5 l, ending inspiration. This results in the Hering-Breuer inflation reflex.

b. Describe the chemical control of breathing via central and peripheral chemoreceptors, and indicate how this is altered in abnormal clinical states.

Respiration is responsive to blood PO_2 and PCO_2 . In normal states, PCO_2 plays the major role as it is far more dependent on ventilation. CO_2 diffuses readily across the blood-brain barrier, altering brain and CSF pH in accordance with the Henderson-Hasselbalch equation:

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 \text{ PCO}_2}$$

In the ventral medulla there is a chemosensitive area of neurones which are highly sensitive to H^+ ion concentration in both the interstitial fluid of the brain and particularly the CSF (which is not well-buffered). Stimulation of the chemosensitive area results in stimulation of the inspiratory (dorsal) group, resulting in increased rate of increase of the inspiratory ramp signal and decreased duration, greatly increasing alveolar ventilation (by a factor of 10 over the range of PCO_2 from 40 to 80 mmHg).

The effect on alveolar ventilation of a change in PCO_2 , is of limited duration. Renal compensation for a respiratory acidosis increases $[\text{HCO}_3^-]$ and normalizes pH over a few days, eliminating most of the effect of a rise in PCO_2 .

PO_2 plays a role in the control of respiration only in unusual circumstances. Chemoreceptors in the carotid and aortic bodies are directly sensitive to PO_2 , producing a strong response as PO_2 falls below 60 mmHg. They are also sensitive to PCO_2 and pH, but this effect is less than that of the central chemoreceptors. The output of the chemoreceptors in the aortic arch is conducted to the medulla via the vagus nerves and that from the carotid bodies via the glossopharyngeal nerves.

Stimulus from the chemoreceptors results in increased alveolar ventilation via action on the dorsal respiratory group. If gas exchange is normal, the increase in ventilation is considerably damped by the effect of a fall in PCO_2 , however if PCO_2 does not fall or pH is

normalized by renal compensation over a few days, the increase in ventilation is sustained.

c. Describe the reflex control of respiration.

The Hering-Breuer reflex is initiated by pulmonary stretch receptors in the airway smooth muscle. The afferent limb is the vagus nerve. The response is via the medulla, inhibiting inspiratory muscle activity. This reflex is not active in adult humans at rest, but may play a role when tidal volume exceeds 1 litre.

Irritant receptors, or rapidly adapting receptors, are present in the airway epithelium and respond to noxious stimuli such as smoke or dust or cold air. They are innervated by the vagus nerve and result in bronchoconstriction and hyperpnoea.

Juxtacapillary ("J") receptors lie in the alveolar walls close to pulmonary capillaries. They respond to chemicals injected into the pulmonary circulation and conduct impulses via non-myelinated fibres in the vagus to the medulla. Stimulation results in rapid shallow breaths or apnoea. They may play a role in the perception of dyspnoea.

The cough reflex is initiated in response to physical or chemical irritation of receptors in the upper airway, particularly the larynx or carina. The afferent limb is the vagus nerve which projects to the medulla. The reflex is a series of responses of the respiratory centres: inspiration to about half VC, closure of the epiglottis and vocal cords, contraction of the muscles assisting expiration (including rectus abdominis and internal intercostals) to raise intrathoracic pressure to about 100 mmHg and sudden opening of the cords and epiglottis to expel air rapidly through airways partly collapsed by the high intrathoracic pressure. This helps to remove any foreign matter in the airways.

The sneeze reflex is similar except that the afferent limb is the trigeminal nerve from the nasal mucosa and during forceful expiration, the uvula is depressed allowing air to leave through the nose, and the eyes are closed.

In regulation of breathing, the same proprioceptive reflexes operate as in other parts of the body: muscle spindles, Golgi tendon organs and joint receptors.

Breathing control is also affected by responses to stimuli outside the respiratory tract. Pain or sudden cold may result in apnoea followed by hyperventilation. Stimulation of the aortic and carotid body baroreceptors by an increase in blood pressure results in hypoventilation.

d. Describe the ventilatory response to exercise.

With exercise, alveolar ventilation can rise from 5 l/min to over 120 l/min and O_2 use from 0.2 l/min to 4 l/min. These changes parallel the rise in metabolism, maintaining pH, PO_2 and PCO_2 at normal values. The increase in alveolar ventilation starts immediately on starting exercise, resulting from central and possible proprioceptive stimuli rather than following a rise in PCO_2 . Thus the initial change in PCO_2 is a fall, followed by a rise back to normal as increased CO_2 production matches the increased alveolar ventilation. The normal ventilatory response to a change in PCO_2 is superimposed on the response to exercise.

The rise in ventilation on starting exercise is partly a learned response.

e. Explain the consequences of altitude on respiratory function.

Barometric pressure falls with altitude from 760 mmHg at sea level to 349 mmHg at 20000 feet. Inspired PO_2 falls proportionally from 159 to 73 mmHg. Alveolar water vapour pressure remains the same at 47 mmHg and P_ACO_2 remains in the same relationship to P_aCO_2 , further reducing P_AO_2 . At 20000 feet, a person not acclimatized to the altitude will hyperventilate on hypoxic drive to a P_aCO_2 of about 24 mmHg, yielding a P_AO_2 of 40 mmHg, not compatible with normal function.

The respiratory rate at altitude rises because of hypoxic drive. The acute rise is limited by inhibition from a fall in P_aCO_2 and rise in CSF pH. As the pH is normalized over a few days, respiratory rate rises further and P_aCO_2 falls, allowing for a higher P_AO_2 and optimal gas exchange. Levels of 2,3-DPG rise with hypoxia, moving the oxygen-haemoglobin

dissociation curve to the right. This opposes the left shift due to alkalaemia and reduced $P_a\text{CO}_2$. Over a longer period, haematocrit rises (up to 200 g/l), blood volume increases, tissue vascularity increases and cellular oxygen useage improves, providing further compensation for hypoxia.

Acute complications of high altitude are: hypoxia with accompanying cerebral dysfunction, acute cerebral oedema due to vasodilatation resulting from hypoxia and acute pulmonary oedema of uncertain mechanism.

Long term complications are termed Chronic Mountain Sickness: a rise in haematocrit and pulmonary vasoconstriction leads to pulmonary hypertension and falling blood flow and oxygen transport as well as shunting through non-alveolar pulmonary vessels. High pulmonary pressure and poor oxygenation results in right heart failure with secondary biventricular failure. Treatment is by oxygen supplementation, generally by moving to a lower altitude.

In an acclimatized person at 20000 feet, PACO_2 falls to 10 mmHg and PAO_2 rises to 53 mmHg, allowing for an oxygen saturation of 85%.

f. Explain the consequences of pregnancy on respiratory control.

in [Maternal Physiology \(1.O\)](#)

g. Describe and explain the effects of anaesthesia on respiratory control.

Anaesthesia affects the CO_2 response curve by flattening the curve and raising the PCO_2 which will be tolerated in apnoea. In an individual patient, ventilation falls as the level of inhalational agent rises, coming to equilibrium at a higher PCO_2 and lower minute volume. Apnoea cannot be sustained on spontaneous ventilation of inhalational agent alone.

Induction and preinduction agents, especially narcotics, flatten the CO_2 response further, surgical stimulus antagonizes it. The inhalational agents all display similar degrees of respiratory depression for a given depth of anaesthesia, but diethyl ether produces less depression up to 2.5 MAC.

The hypoxic ventilatory response is extremely sensitive to inhalational agents, being markedly blunted at 0.1 MAC, and abolished at 1.1 MAC. This is thought to be through action at the carotid body chemoreceptors. This effect necessitates continuous SaO_2 monitoring in anaesthesia and is particularly dangerous for patients reliant on hypoxic drive: those with severe COAD.

The ventilatory response to metabolic acidosis is reduced as much as that to hypoxia.

Breathing reflexes remain intact in spontaneously ventilated anaesthesia. Increased force of inspiration in the face of resistance is a muscle spindle reflex which is unchanged. Increasing resting volume in response to expiratory obstruction is also preserved. The Hering-Breuer response remains unimportant under anaesthesia.

The mechanics of breathing are affected by anaesthesia. Movement from the intercostals is reduced far more than diaphragmatic movement, producing "abdominal breathing". The resting position of the diaphragm is higher in the thorax than when awake, reducing FRC. These are partially compensated for by a movement of blood from thorax to abdomen in the supine position in anaesthesia, but FRC remains reduced by about 450 ml. Paralysis does not alter FRC further.

Whether the reduction in FRC is accompanied by a fall in closing volume is uncertain. Airway calibre is reduced at lower FRC, but the increase in resistance which is expected from this is offset by the bronchodilator effect of inhalational agents. The anaesthetic circuit introduces additional resistance to breathing, particularly with small ET tubes, resistance varying inversely with greater than the fourth power of radius for turbulent flow. Without assistance, upper airway resistance is frequently very high due to obstruction by the tongue.

Compliance is reduced almost immediately upon induction of anaesthesia. The cause of this is uncertain, but the change is in pulmonary compliance, not in the chest wall. It may be due to interference with the activity of surfactant or pulmonary collapse due to the

reduction in FRC.

Metabolic rate is reduced a little by anaesthesia, particularly cerebral and cardiac oxygen consumption.

Gas exchange is impaired in anaesthesia because of the fall in minute volume in spontaneous ventilation, and because of the increase in V/Q scatter which is an unavoidable consequence of anaesthesia. The increased V/Q scatter is manifest in calculations of physiological dead space and shunt.

There is little rise in physiological dead space in spontaneous ventilation, but with paralysis, physiological dead space increases measurably. The increase occurs in alveolar dead space, anatomical dead space remaining unchanged. Alveolar ventilation is normally well-maintained as minute ventilation is increased to keep PCO_2 stable. The mechanism for the increase in dead space is thought to be maldistribution of ventilation.

Physiological shunt increases with anaesthesia from about 1-2% in healthy individuals to about 10%. This results in a substantial increase in A-a gradient. This effect is most marked in older patients and less in young adults. The cause of the increase in shunt may be impairment of the hypoxic vasoconstrictor response as well as maldistribution of ventilation or localized pulmonary collapse. The last possibility seems unlikely given the lack of benefit from PEEP in anaesthesia. PEEP may have some effect in improving ventilation, but it also reduces cardiac output, negating any improvement in oxygen flux.

B. 3 Mechanics of breathing

a. Describe the inspiratory and expiratory process involving the chest wall, diaphragm, pleura and lung parenchyma.

Inspiration

In quiet respiration, inspiration is caused by contraction of the diaphragm, innervated by the phrenic nerve from cervical segments 3-5. The dome of the diaphragm moves about 1cm caudally, increasing the volume of the chest cavity and moving the abdominal contents down. This lowers intrathoracic pressure which is transmitted through the pleural space to the lungs, expanding the lungs and causing a pressure gradient between the mouth and small airways, resulting in gas flow into the lungs.

In rapid respiration other muscles have a role in increasing the rate of gas flow into the lung. The diaphragm contracts forcefully, moving as much as 10 cm, the external intercostals lift the ribs, increasing the lateral and anteroposterior dimensions of the chest and the scalenes and sternocleidomastoid lift the first two ribs and sternum.

Expiration

Expiration is normally a passive process, relying on the elasticity of the lung parenchyma and chest wall to return the lung to its resting volume (functional residual capacity). In active expiration, the rectus abdominis, internal and external obliques and transversus contract to increase intraabdominal pressure and force the diaphragm up. The internal intercostals bring the ribs together and stiffen the intercostal spaces. These effects markedly increase intrathoracic pressure resulting in more rapid exhalation (up to a limit imposed by airway collapse).

b. Define compliance (static and dynamic) and relate this to the elastic properties of the lung.

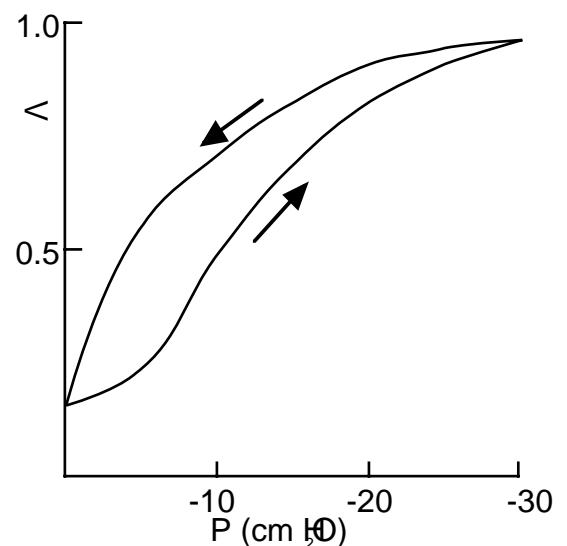
Compliance is defined as volume change per unit pressure change. This is the reciprocal of elastance. The isolated human lungs have a compliance of about 200 ml/cmH₂O in the normal pressure range of -2 to -10 cmH₂O. The lungs and chest wall as a unit have a compliance of 100 ml/cmH₂O. At higher pressures (and volumes), compliance is reduced. Compliance is less on the inspiratory than the expiratory phase of respiration. This phenomenon is called hysteresis.

Static compliance is determined at zero flow and is usually quoted as the expiratory compliance over the litre above FRC. Dynamic compliance is determined over a range of respiratory frequencies as uneven time constants of adjacent alveoli in diseased lungs reduce compliance at high frequencies. Specific compliance equals compliance divided by FRC.

Compliance is a result of the elastic properties of the lung. This is partly a result of the arrangement of fibres of collagen and elastin in the alveoli and airways and substantially a result of the surface tension in the alveoli.

Surface tension in the alveoli is modified by surfactant secreted by type II pneumocytes. It displays non-linear properties, being much greater at high volumes than low volumes and thus produces hysteresis.

Specific compliance = static compliance ÷ FRC (normal 0.05 /cmH₂O)



c. Explain the concept of time constants and relate these to “fast” and “slow”

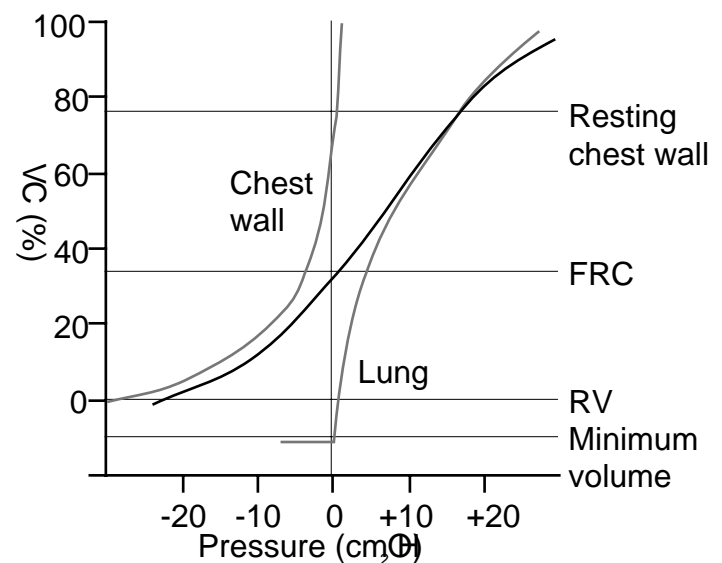
alveoli.

Compliance equals change in volume per unit pressure. Resistance equals airway pressure per unit flow. The product of compliance and resistance is the “time constant” of a component of the lung; a measure of the rate of filling of that lung unit. A large time constant can result from airway obstruction or extreme distensibility of the unit. Areas of lung with a long time constant fill more slowly than the rest of the lung during inspiration and may still be filling (from the rest of the lung) when expiration has already begun. This is called “Pendelluft”.

Lungs with a wide range of time constants among their alveoli require slow respiration to be ventilated properly. As frequency of respiration increases, “slow” alveoli fill only partially before alveolar pressure rises high enough in expiration for them to start to empty again. This reduces the tidal volume and thus the apparent compliance of the lung as the frequency of respiration increases.

d. Describe the elastic properties of the chest wall and plot the pressure-volume relationships of the lung, chest wall and total respiratory system.

The chest wall is elastic. At resting volume, it pulls against the pleural space with a pressure of about $-5 \text{ cmH}_2\text{O}$. This balances the elastic recoil of the lung, yielding a negative pleural pressure and zero pressure within the airways and outside the chest wall. Under normal circumstances the pleural space has a total volume of only a few ml. If it is opened, air is rapidly drawn in, the chest wall springs out and the lung collapses.



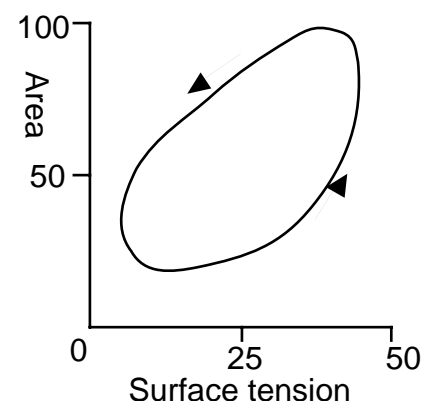
e. Describe the properties of surfactant and relate these to its role in determining respiratory mechanics.

Surfactant is secreted by type II pneumocytes. It lines the air-tissue interface of the alveoli and modifies the surface tension at the interface, preventing collapse and greatly increasing compliance. A major constituent of surfactant is dipalmitoyl phosphatidyl choline, synthesized from fatty acids. This is a long molecule with hydrophilic and hydrophobic ends.

When densely packed, DPPC molecules provide a strong repulsive force which opposes surface tension. As the surface area of an alveolus increases, the repulsion between DPPC molecules is reduced as they spread apart. At the same time, surface tension is less as it varies with the reciprocal of the radius of an alveolus.

The behaviour of surfactant is complex as it displays a greater effect as surface area is falling (during expiration) than rising. Normal detergents reduce surface tension but usually do so by a fixed amount regardless of area and do not display hysteresis.

The effect of surface tension is responsible for more than 80% of the work or inflating the lung, having a much greater effect at normal volumes than the tissue elasticity of the lung.



f. Explain the vertical gradient of pleural pressure and its significance.

In the erect position at resting volume, pleural pressure varies from -2.5 to -10 cmH₂O from base to top of the lung because of its weight. The resting volume of alveoli at the apex of the lung is much greater than at the base because of the more negative pleural pressure. However, the ventilation of the apex of the lung is proportionally less than the base during the respiratory cycle because the lung is more compliant at the lower volume and expanding pressure.

At low volumes, the pleural pressure at the base of the lung may become greater than atmospheric, resulting in airway closure and poor ventilation, while the apex benefits from a greater compliance and better ventilation. Transpulmonary pressure is defined as alveolar minus pleural pressure.

g. Explain the physics of gas flow and the significance of the relationship between resistance and pressure in the respiratory tract.

At low speeds and in smooth, small tubes, laminar flow is present, with a steady increase in flow speed from the edge to the centre of the tube. Under these circumstances, flow is described by the Poiseuille equation:

$$\dot{V} = \frac{\pi P r^4}{8 \eta l}$$

As speed and tube size increase, flow may become turbulent after a transitional phase. Turbulent flow exists when Reynolds number exceeds 2000 and laminar flow below 200. The transition from laminar to turbulent flow is not predictable. Reynolds number is given by the equation:

$$RN = \frac{v \rho d}{\eta}$$

where ρ is density, d diameter, v velocity and η viscosity. Where flow is turbulent, its relationship to the radius of the tube is not simple, being proportional to greater than the fourth power. The relationship to pressure, density and length of tube is:

$$\dot{V} \propto \sqrt{\frac{P}{l \rho}}$$

flow being unrelated to viscosity.

Resistance is equal to pressure gradient per unit flow, so each of these flow equations can be transformed into an expression of resistance.

In the respiratory tract, air flow is turbulent in the trachea, transitional in all the large airways down to the level of terminal bronchioles and probably laminar in the very small airways. The relationship between driving pressure and air flow is complex and of the form:

$$P = K_1 \dot{V} + K_2 \dot{V}^2$$

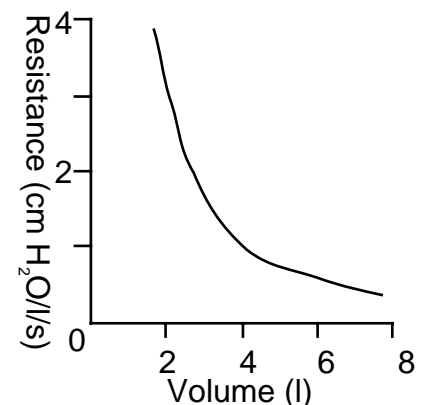
The first term reflecting laminar flow and the second turbulent flow.

h. Describe the factors affecting resistance and how to measure airway resistance.

Most of the resistance to air flow in healthy lungs is in the medium sized bronchi. Though diameter falls with each generation of airways, the total number of airways rises exponentially, reducing resistance to very low levels by the tenth generation.

Density and viscosity of inspired gas are related to resistance as described in the above equations.

Lung volume has a major effect on airway resistance.



At low lung volumes there is little support of small airways by the surrounding parenchyma and consequently high resistance, varying with the reciprocal of lung volume.

Smooth muscle tone in bronchioles can markedly increase airway resistance. The bronchioles are innervated by the vagus. Contraction can be from parasympathetic outflow, local irritant factors or systemic factors such as histamine release. Bronchiolar smooth muscle also relaxes in response to a rise in PCO_2 .

In the special case of maximal expiratory flow, resistance rises as the gradient from intrapleural pressure to airway pressure exceeds the force supporting the airways and collapse occurs. This limits flow regardless of the resistance downstream. The force supporting the airways depends on lung volume. This produces an effort-independent maximal flow envelope related only to lung volume in any individual.

Airway resistance is measured using a plethysmograph. By measuring airflow at the mouth and pressure change in the plethysmograph, having first measured lung volume, it is possible to calculate the pressure gradient between alveoli and mouth which when divided by flow equals total airway resistance.

Less satisfactorily, intrapleural pressure can be measured with an oesophageal manometer in the lower $\frac{1}{3}$ of the oesophagus when erect. If the recoil due to chest wall elasticity is reliably calculated, the pressure gradient due to both airway and tissue resistance can be determined.

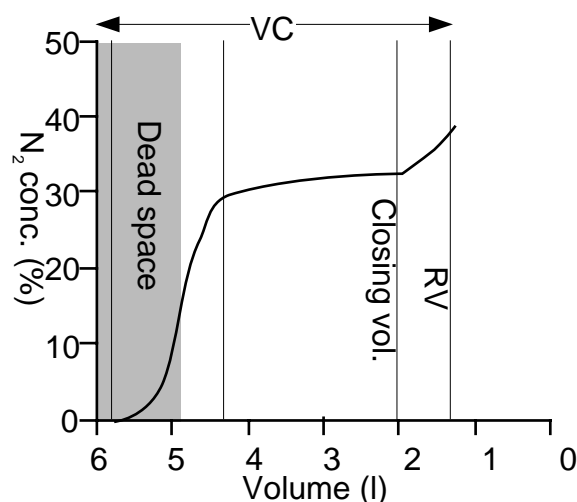
Information about resistance can also be obtained using a single forced expiration. The conventional measures are FEV_1/FVC (normal $>80\%$) and $FEF_{25-75\%}$ which is an average flow over the middle 50% of expiration (by volume). A simpler measure is PEFR, commonly used to assess the severity of obstruction in asthma.

More detailed information can be obtained from a flow-volume curve, in which the expiratory flow rates are much lower in airway obstruction and the mean volume may be increased in chronic disease.

i. Define closing capacity and its relationship to airway closure and explain its clinical significance and measurement.

In a single breath N_2 washout test, (used to measure anatomical deadspace), the exhaled nitrogen concentration rises above its alveolar plateau at a low lung volume (in healthy individuals). This represents the exhalation of alveolar gas from less well-ventilated alveoli, usually in the upper part of the lung, following closure of airways in the bottom of the lung.

The volume at which this rise starts is that at which airway closure first occurs in the more dependent part of the lung. This is about 10% of VC in healthy young adults and rises with age (45 ml/year) and airway disease to equal FRC at 45 years in the supine position and 65 years when erect. Closing capacity is also higher in infants, falling to FRC at 8 years.

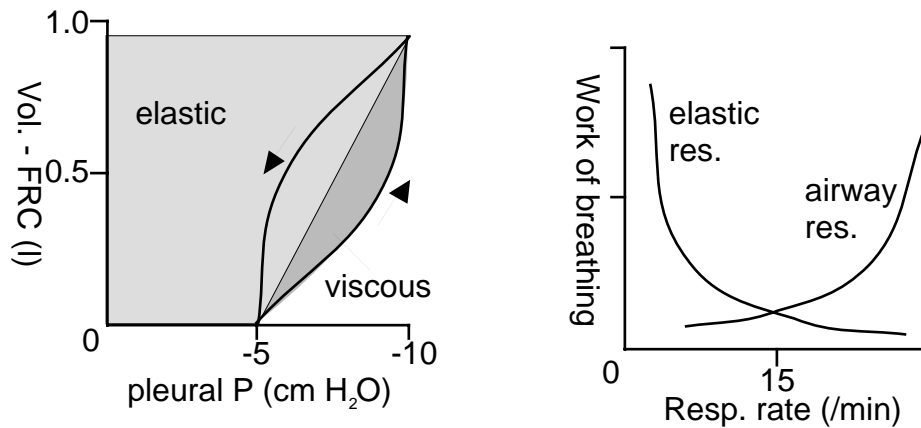


j. Describe the work of breathing and its components.

Work is equal to pressure times volume. The work of breathing may be described using a pressure-volume graph. The area of the graph represents the work of breathing; the pale part being work against elastic forces (on inspiration) and the dark area work against viscous forces such as airway resistance. On expiration, the viscous work required is less than the energy stored in elastic forces during quiet breathing.

In exercise or during rapid breathing, the work against viscous forces increases

dramatically and on expiration will exceed the work done against elastic forces on inspiration. Expiration then becomes an active process and the expiratory limb of the curve falls outside the pale area.



Work of breathing at rest is about 2% of BMR (2 W or 7.2 kJ/hr) with 10% efficiency. There is a characteristic frequency of minimal work of breathing for a given minute volume and elastic properties and airway resistance, with high elastic work at low frequencies and high airway resistance work at high frequencies. Conversely the frequency of minimum work is reduced by an increase in airway resistance and increased by a rise in elastic resistance.

k. Describe altered lung mechanics in disease states.

B. 4 Pulmonary gas volumes and ventilation

a. Explain the measurement of lung volumes and capacities and indicate the normal values.

The total volume of gas the lung can contain is total lung capacity (TLC). This is divided into the volume which can not be exhaled which is residual volume (RV) and the proportion which can be exhaled: vital capacity (VC).

The volume moved in resting ventilation is known as tidal volume (TV) and the volume remaining in the lung at the end of a normal breath is functional residual capacity (FRC). The volumes which can be inspired or exhaled in addition to TV are called inspiratory and expiratory reserve volumes (IRV and ERV)

VC, TV, IRV and ERV can easily be measured by a spirometer. FRC can be measured by helium dilution and RV and TLC derived from these measurements. Alternatively FRC can be measured by nitrogen washout with 100% oxygen over several minutes.

FRC can also be measured in a plethysmograph using a manometer to measure pressure change in the chamber and also in the airway during inspiration against a closed tube. The volume change of the chest can be derived from the pressure change in the chamber and the volume of gas in the chest determined from its volume change and pressure change. This measures the total gas volume in the chest, including areas which are not being ventilated, unlike the helium dilution method which measures the ventilated volume.

The functions of FRC are as an oxygen reserve, to prevent airway closure, to smooth alveolar gas composition and to minimize PVR, work of breathing and V/Q mismatch.

Typical values (l)

| | |
|-----|-----|
| TLC | 6 |
| VC | 4.8 |
| RV | 1.2 |
| TV | 0.5 |
| FRC | 2.4 |

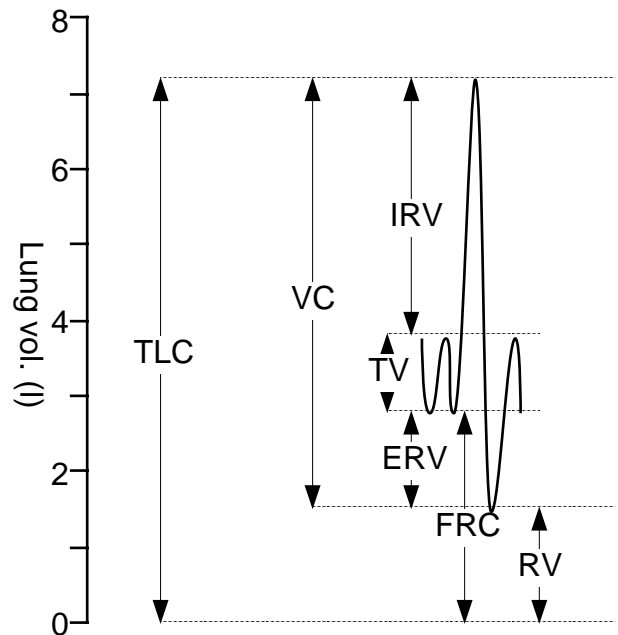
These are highly variable according to body size. The values given are for a 1.8 m male, normal VCs range from 2.5 to 7 l.

Normal ventilation at rest consists of about 15 breaths/min of a TV of 0.5 l, giving a ventilation of 7.5 l/min. Each breath ventilates an anatomic dead space (upper airways not participating in gas exchange) of about 150 ml or 2.25 l/min. This leaves 5.25 l/min of alveolar ventilation. This is roughly equal to pulmonary blood flow at rest of about 5 l/min.

These values can be measured with the spirometer except for dead space and alveolar ventilation. Dead space can be measured using a N₂ washout curve, giving anatomic dead space. Physiological dead space can be determined from the CO₂ output of the lung if tidal volume and expired and alveolar (or arterial) CO₂ are measured:

$$\begin{aligned}V_T P_{E\text{CO}_2} &= V_A P_A\text{CO}_2 \\V_D &= V_T - V_A \\V_D &= V_T (1 - P_{E\text{CO}_2} \div P_A\text{CO}_2)\end{aligned}$$

Once dead space has been measured, alveolar ventilation can be calculated.



b. Describe the factors influencing lung volumes and capacities.

Body size and sex are major determinants of lung volumes. VC varies approximately linearly with height and decreases gradually with age. These relationships are described empirically:

$$\begin{aligned}\text{male VC} &= 5.2 h - 0.022 a - 3.6 (\pm 0.58) \\ \text{female VC} &= 5.2 h - 0.018 a - 4.6 (\pm 0.42)\end{aligned}$$

where VC is in litres, h is height in metres, and a age in years. Thus VC falls about 20 ml/year.

Any disease process which occupies space in the thorax will reduce TLC and consequently VC. Pleural effusion is an example of a pathology which results in compression of the lung. Disease such as bronchial cancer within the lung may cause obstruction of ventilation to part of the lung, reducing VC. Reversible or lung volume-dependent obstruction from asthma or emphysema will increase RV dramatically without reducing TLC. This usually results from early airway closure on exhalation in obstructive disease.

Restrictive lung disease such as asbestosis can reduce TLC and VC by limiting inspiration without much change in RV.

c. Define dead space and apply the Bohr Equation and the Alveolar Gas Equation.

Dead space is the ventilated volume which does not participate in gas exchange. Anatomical dead space is the volume of the large upper airways and is measured using a N₂ washout test. Physiological or functional dead space is a similar volume in healthy individuals and can be measured using the Bohr Equation as described above.

The alveolar gas equation relates alveolar oxygen partial pressure to inspired oxygen partial pressure and CO₂ partial pressure:

$$P_{A}O_2 = P_{I}O_2 - \frac{P_{A}CO_2}{R} + P_{A}CO_2 \cdot F_{I}O_2 \cdot \frac{1 - R}{R}$$

d. Explain normal ventilation-perfusion matching including the mechanisms for these as well as the normal values.

Ventilation of the lung in the erect position is greater at the base than at the apex because of the difference in intrapleural pressure between the top and bottom of the lung. Similarly perfusion of the lung is less at the apex than at the base, largely due to the hydrostatic pressure difference between arterial pressure at the top and bottom of the lung. The difference in perfusion is greater than the difference in ventilation. Thus the ratio of ventilation to perfusion is greatest at the apex and least at the base of the lung.

The differences in ventilation and perfusion result in differences in gas concentrations:

| | Apex | Base | |
|------------------|------|------|-------|
| ventilation | 0.24 | 0.82 | l/min |
| perfusion | 0.07 | 1.29 | l/min |
| V/Q | 3.3 | 0.63 | |
| PO ₂ | 132 | 89 | mmHg |
| PCO ₂ | 28 | 42 | mmHg |
| pH | 7.51 | 7.39 | |

Matching of ventilation and perfusion is also partly due to local vascular tone. Pulmonary vessels constrict in response to high PCO₂ or low PO₂, helping to match

perfusion to ventilation. V/Q matched alveoli are far more efficient at gas exchange; over ventilated alveoli can not compensate for under ventilated ones because of the non-linear nature of the O₂ and CO₂ dissociation curves.

e. Describe the composition of ideal alveolar and mixed expired gases.

Ideal alveolar gas is described by the alveolar gas equation. It is the gas composition expected in alveoli if there were no ventilation-perfusion mismatch in the lung:

$$P_A\text{CO}_2 = P_a\text{CO}_2 = 40\text{mmHg}$$

$$P_A\text{O}_2 = P_i\text{O}_2 - \frac{P_A\text{CO}_2}{R} + P_A\text{CO}_2 \cdot F_i\text{O}_2 \cdot \frac{1 - R}{R}$$

$$= 100 \text{ mmHg}$$

Mixed expired gas is the gas sampled at the mouth during exhalation. It is a mixture of gas from the dead space and from the alveolar space from alveoli with a range of V/Q ratios. Typically:

$$P_E\text{CO}_2 = 33 \text{ mmHg}$$

$$P_E\text{O}_2 = 115 \text{ mmHg}$$

B. 5 Diffusive transfer of respiratory gases

a. Describe and explain the oxygen cascade.

The partial pressure of oxygen falls at each stage of its transport from air to peripheral tissues.

| | |
|---------------------------|-------------------------------|
| Dry air | 159 mmHg |
| Air at BTPS | 149 mmHg |
| Alveolar gas | 100 mmHg |
| Pulmonary capillary blood | 40 → <100 mmHg |
| Mean capillary blood | 40 mmHg |
| Interstitial fluid | 15-40 mmHg |
| Intracellular fluid | ≥1 mmHg for normal metabolism |

The fall from dry to saturated air results from the increase in the partial pressure of water from 0 to 47 mmHg. The pressure in inspired gas also depends upon barometric pressure.

The difference between inspired gas and ideal alveolar gas depends on ventilation and oxygen usage. With high alveolar ventilation, alveolar PO_2 approaches inspired PO_2 asymptotically. Alveolar PO_2 is also reduced by oxygen uptake and CO_2 release in the alveoli.

The gradient between alveolar gas and pulmonary capillary blood depends on the factors affecting diffusion described below. In addition it is increased by shunt and V/Q scatter. A high inspired PO_2 increases the pressure gradient because the content gradient remains constant while the content/pressure graph becomes very flat at high PO_2 . A fall in cardiac output causes a rise in the proportion of shunted blood as well as a fall in mixed venous PO_2 due to constant tissue oxygen uptake. A very marked rise in cardiac output can also increase the A-a gradient by reducing transit time in the pulmonary capillaries to the extent that oxygen uptake becomes diffusion-limited. Factors which influence the shape of the oxygen dissociation curve also affect A-a gradient: pH, temperature, and 2,3-DPG. An increase in haemoglobin concentration also reduces A-a gradient.

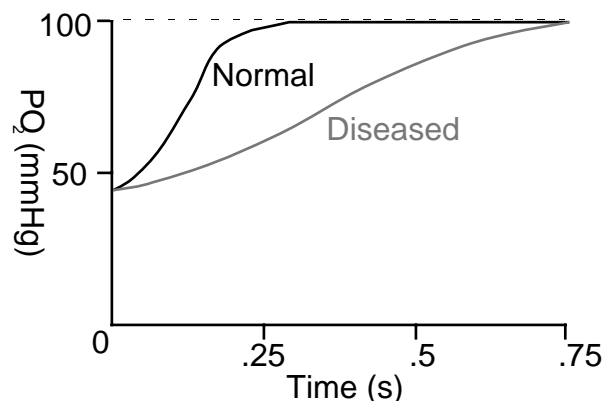
An increase in ventilation can cause a rise in A-a gradient both due to the rise in alveolar PO_2 and the fall in cardiac output which accompanies the fall in PCO_2 . If there is more than 3% shunt, increasing ventilation starts to cause a fall in arterial PO_2 because of the fall in cardiac output.

The gradient from blood to interstitial fluid to intracellular fluid differs markedly from tissue to tissue and regionally within any tissue. It is dependent on perfusion, haemoglobin concentration and oxygenation of blood. In most tissues passive diffusion carries oxygen down the concentration gradient from capillary blood to the mitochondria. Some tissues such as muscle have specialized oxygen carrying proteins (myoglobin) to improve oxygen transport and storage.

b. Explain the capillary exchange of oxygen and carbon dioxide, and the relationship of erythrocyte transit to oxygen and carbon dioxide transfer.

O_2 and CO_2 cross the blood-gas barrier by passive diffusion. The distance from alveolar lumen to erythrocyte cytoplasm is about $0.3 \mu m$.

O_2 diffuses rapidly across this barrier, equilibrating with blood in about 0.25 s. At rest, erythrocyte transit time in alveolar capillaries is about 0.75 s, however in exercise it falls to as little as 0.25 s. The time taken for diffusion can be greatly increased by lung disease which results in



thickening of the blood-gas barrier and consequent diffusion-limitation of oxygen transport. A reduction in the pressure gradient driving diffusion will also slow diffusion. This is seen at high altitude, where P_AO_2 is reduced by a greater amount than the fall in venous PO_2 .

CO_2 is much more soluble than O_2 , however the pressure gradient driving its diffusion is only 5 mmHg. In healthy lungs the time taken for alveolar gas to equilibrate with pulmonary capillary blood is about the same as with O_2 : 0.25 s.

c. Explain perfusion-limited and diffusion-limited transfer of gases.

In gas exchange at the blood-gas barrier, the rate-limiting step differs according to the gas being examined. In the case of oxygen, as described above, the partial pressure equilibrates in much less time than the blood spends in alveolar capillaries. Thus transport of oxygen is limited by the total alveolar blood flow at rest; it is perfusion-limited. N_2O is an extreme case of perfusion-limitation as it reaches equilibrium with blood in around 0.1 s. Perfusion-limitation is a characteristic of gases and anaesthetic vapours which are roughly equally soluble in the blood-gas barrier and in blood.

In exercise, when the transit time for blood is reduced substantially and if the diffusion capacity for oxygen is reduced by lung disease, the partial pressure of oxygen in pulmonary venous blood may still be much lower than in alveolar gas. CO diffuses much less readily than O_2 , with a very gradual rise in blood partial pressure. Its transport is thus almost entirely dependent on the rate of diffusion through the blood-gas barrier, hence its use in measuring diffusion capacity. This is a case of diffusion-limited gas transport and is characteristic of gases which have widely differing solubilities in the blood-gas barrier and in blood.

d. Define diffusion capacity and its measurement.

Diffusion capacity is a measure of the rate at which a gas can diffuse across the blood-gas barrier. It is described by Fick's law of diffusion. The rate of diffusion is proportional to the area (A) and pressure gradient and inversely proportional to the thickness (T) of the sheet. It is proportional to the diffusion constant which is equal to the solubility of the gas (Sol) divided by the square root of its molecular weight (MW):

$$\dot{V}_{\text{gas}} \propto \frac{A \cdot \text{Sol}(P_1 - P_2)}{T \sqrt{\text{MW}}}$$

Because area and thickness of the blood-gas barrier are not readily measurable, an empirical "diffusing capacity" for each gas is defined such that:

$$\dot{V}_{\text{gas}} = D_L \cdot (P_1 - P_2)$$

where D_L is the diffusion capacity for the gas being tested. In the case of O_2 and CO, uptake is also limited by reaction with haemoglobin. This is also included in D_L . D_L can then be split into two components, with D_M representing the conductance of the blood-gas membrane, V_C the capillary blood volume, and θ representing the rate of reaction with Hb (in ml/min/ml blood/mmHg):

$$\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{\theta \cdot V_C}$$

Diffusion capacity is conventionally measured using CO as its transport across the blood-gas barrier is diffusion-limited and its normal blood concentration is nearly zero. This can be done with a 10s single breath-hold of a 0.3% CO and 10% He containing mixture to measure both lung volume and D_LCO or using a steady-state technique with measurement of CO uptake over several breaths.

At rest D_LCO is typically 25 ml/min/mmHg. With exercise it increases by a factor of three or more due to pulmonary vasodilatation and alveolar recruitment.

e. Describe the physiological factors that alter diffusion capacity.

Increase

- blood-gas barrier area
 - lung size
 - alveolar recruitment
- alveolar gas concentration
- pulmonary vasodilatation
- uptake of CO or O₂ by Hb or buffering of CO₂

Decrease

- blood-gas barrier thickness
- systemic venous blood gas concentration
- temperature (reduces solubility)
- functional dead space

B. 6 Ventilation-perfusion inequalities

a. Describe West's zones of the lung and explain the mechanisms responsible for them.

Perfusion of the lung is not uniform in the erect position, but increases from the top to the bottom of the lung. This is a result of hydrostatic forces combined with the effect of airway pressure. Conceptually, the lung may be divided into three zones.

Zone 1 is a region at the top of the lung in which arterial pressure falls below alveolar pressure. This does not happen under normal circumstances, but can result from marked hypotension or from raised alveolar pressure in IPPV. The capillaries in this zone remain collapsed and no perfusion occurs.

Zone 2 is the region of lung where pulmonary arterial pressure is greater than alveolar pressure but venous pressure remains below alveolar pressure. Here perfusion is dependent on the gradient from arterial pressure to alveolar pressure as vessels collapse at the point where intravascular pressure has fallen below alveolar pressure, limiting flow. Pulmonary venous pressure has no influence on flow, but perfusion increases from top to bottom of zone 2 as arterial pressure rises further above alveolar pressure.

Zone 3 is where both arterial and venous pressure exceeds alveolar pressure. Now airway pressure does not influence perfusion as flow is dependent on the arterial-venous gradient. Flow increases in moving down zone 3 because the mean volume of the vessels does, as both arterial and venous pressure rise, distending the capillary bed. The pressure gradient remains the same.

A so-called zone 4 arises in areas of lung where low lung volume reduces the size of extra-alveolar vessels, increasing their resistance and reducing blood flow. This can be seen at the lung bases at low lung volumes.

b. Explain the shunt equation.

Part of the difference between mixed P_aO_2 and P_AO_2 is conceptualized as being due to "shunted" blood which circulates through the lung without being exposed to the blood-gas barrier. Part of the "shunt" blood is certainly that in the bronchial circulation and blood perfusing alveoli which are not ventilated, but the calculated value for shunted blood flow includes both anatomically shunted blood and a proportion of blood from inadequately ventilated alveoli where P_AO_2 is lower than the ideal value.

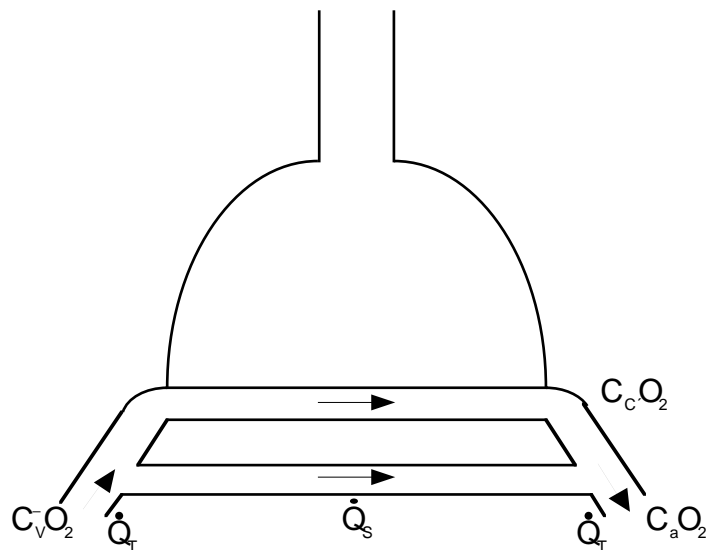
Because the total volume of oxygen carried in the pulmonary venous blood is conserved in the mixing of shunted and ventilated blood, and the alveolar and systemic venous oxygen concentrations can be measured, it is possible to calculate the proportion of pulmonary perfusion which is represented by shunted blood:

$$\dot{Q}_T \cdot C_aO_2 = \dot{Q}_S \cdot C_{\bar{v}}O_2 + (\dot{Q}_T - \dot{Q}_S) \cdot C_{C'}O_2$$

which can be rearranged to give:

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{C_{C'}O_2 - C_aO_2}{C_{C'}O_2 - C_{\bar{v}}O_2}$$

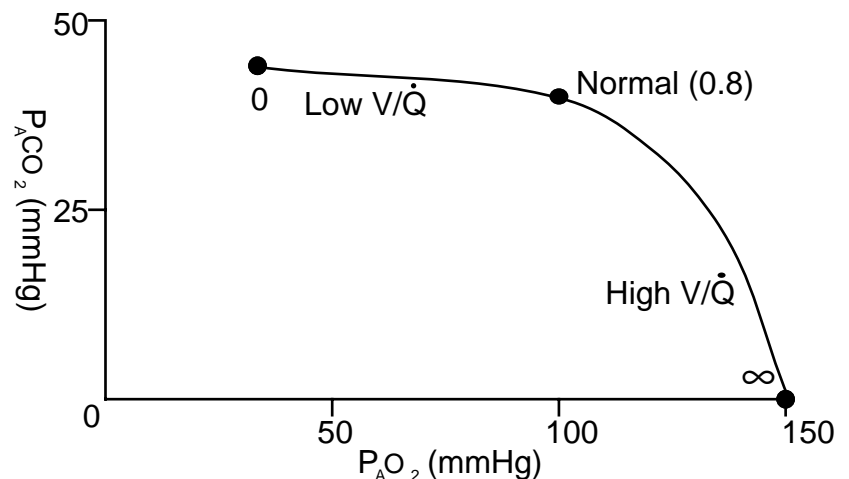
If the end-capillary blood is assumed to have equilibrated with alveolar oxygen, its oxygen concentration can be determined from the oxygen dissociation curve. The arterial and mixed venous oxygen concentrations can be measured directly, allowing for calculation of the shunt flow.



c. Describe the oxygen-carbon dioxide diagram and apply it to clinical use.

The oxygen-carbon dioxide diagram relates PCO_2 and PO_2 in the alveolus to V/Q ratio. With a V/Q ratio close to 1, PCO_2 has its normal value of around 40 mmHg and PO_2 100 mmHg. As V/Q ratio increases, the gas partial pressures approach those of inspired gas. This is the situation in functional dead space.

As V/Q ratio falls, the gas partial pressures approach those of mixed systemic venous blood; the situation of shunt. Thus the curve always runs from the values of venous blood to those of inspired gas, whatever their compositions. The composition of alveolar gas must always lie on the curve: there is a 1-1 correspondence of values for PCO_2 and PO_2 .



In a normal lung there is a spread of V/Q ratios among the alveoli, causing some alveoli (with high V/Q) to return blood with a gas composition closer to inspired gas and some (with low V/Q) to return blood which is more similar to mixed venous blood.. With disease this spread gets much wider, causing a rise in PCO_2 and a fall in PO_2 .

The normal physiological response to a fall in PCO_2 , is a rise in respiratory rate and volume. This increases the ventilation of all alveoli and shifts the distribution of V/Q ratios towards the higher end of the curve. As is clear from the curve, with increasing ventilation the PCO_2 of some units approaches 0, while the PO_2 (on air) approaches only 1.5 times normal. As a result, an increase in ventilation is much better at normalizing PCO_2 than PO_2 . This problem can also be seen in the oxygen and carbon dioxide dissociation curves; the oxygen curve is quite flat with above normal ventilation while the carbon dioxide curve remains almost linear.

d. Describe and explain regional ventilation-perfusion inequalities, their clinical importance and changes with posture.

In the upright position, V/Q ratio decreases from top to bottom of the lung. This is caused by the variation in both ventilation and perfusion resulting from pressure differences from top to bottom of the lung. Ventilation is greater at the base due to the lower mean volume at rest and thus greater compliance at the base of the lung. Perfusion is also greater at the base of the lung due to hydrostatic pressure increasing both arterial and venous pressure. The increase in perfusion at the base is greater than that in ventilation, hence the fall in V/Q .

| | Apex | Base | |
|-------------|------|------|-------|
| ventilation | 0.24 | 0.82 | l/min |
| perfusion | 0.07 | 1.29 | l/min |
| V/Q | 3.3 | 0.63 | |
| PO_2 | 132 | 89 | mmHg |
| PCO_2 | 28 | 42 | mmHg |
| pH | 7.51 | 7.39 | |

The normal V/Q scatter is responsible for a proportion of the A-a gradient. There is a greater blood flow from the base of the lung where the PO_2 is low and relatively less from the apex. The small rise in oxygen content of blood flow from the apex cannot

compensate for the larger flow from the base and so the mean PO_2 is depressed. This effect is exacerbated by the shape of the oxygen dissociation curve which is steeper below ideal PO_2 than above.

With a change to the supine position, the range of V/Q scatter is reduced because the vertical dimension of the lungs is reduced. There is a reduction in physiological dead space.

In the lateral position, the same gradient of ventilation and perfusion occurs as in the upright position, except that it extends from the superior to inferior lung. With the introduction of IPPV in the lateral position, the dependent lung is no longer much better ventilated than the upper lung, presumably due to the reduced compliance of the compressed side of the chest. Detail in [Thoracic surgery](#).

e. Outline the methods used to measure ventilation-perfusion inequalities.

To detect regional defects in ventilation or perfusion, radiolabelled tracer is used in conjunction with a gamma camera. A perfusion scan is performed using radiolabelled (Tc99m) dye. The corresponding ventilation scan uses a low concentration of radioactive gas (Xe). The images obtained show gross areas of defective perfusion or ventilation and allow differentiation between large isolated perfusion defects such as pulmonary emboli and matched defects such as pneumonia.

Physiological uniformity of ventilation can be assessed using a single- or multiple-breath N_2 washout test. The single-breath method shows a rise in N_2 concentration at the end of the alveolar plateau as inadequately ventilated alveoli are emptied. The change in N_2 concentration between 750 ml and 1250 ml expired volume is used as an indicator of uneven ventilation.

The multiple-breath method relies on the exponential washout of N_2 over multiple breaths containing no N_2 . In a perfectly ventilated lung this would result in a straight line on a semi-log plot of N_2 concentration versus breath number. Where alveoli with large time-constants delay the washout of N_2 , the curve becomes curved (concave-up). This can be quantified by modelling the shape of the curve using more than one "compartment".

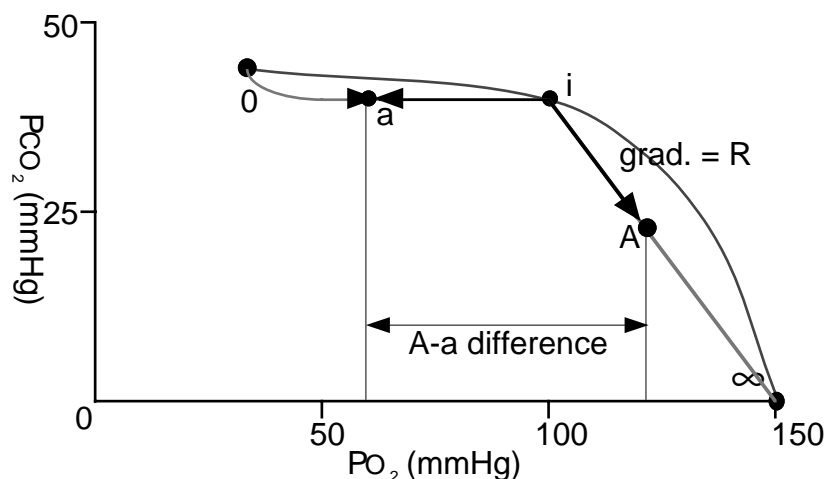
An assessment of the V/Q distribution can also be made from the PO_2 difference between ideal alveolar gas and arterial blood. Real alveolar gas PO_2 is difficult to measure unless there is completely even ventilation.

As V/Q scatter widens, the difference between the composition of alveolar gas and arterial blood widens, diverging from the point of ideal matching (i). The alveolar gas composition (A) falls on the line of gradient R, connecting i with the composition of inspired gas.

The arterial gas pressures (a) follow a line to the mixed venous composition, with PCO_2 initially held constant by the ventilatory response to any rise in PCO_2 . The point a can be measured directly with blood gases and the point A calculated from the alveolar gas equation.

Other measures of V/Q inequality include *physiological shunt* and *alveolar dead space*. These are measures of the amount of venous blood or inspired gas added to produce the measured alveolar or arterial composition from the ideal composition:

$$\frac{\dot{Q}_{PS}}{\dot{Q}_T} = \frac{C_i O_2 - C_a O_2}{C_i O_2 - C_{\bar{V}} O_2}$$



$$\frac{V_{\text{Dalv}}}{V_T} = \frac{P_i \text{CO}_2 - P_A \text{CO}_2}{P_i \text{CO}_2}$$

Alveolar dead space is difficult to calculate because of the difficulty of measuring alveolar PCO_2 , so mixed expired PCO_2 and arterial PCO_2 (to approximate ideal PCO_2) are used instead, giving *physiological dead space*.

$$\frac{V_{\text{Dphys}}}{V_T} = \frac{P_a \text{CO}_2 - P_E \text{CO}_2}{P_a \text{CO}_2}$$

f. Explain venous admixture and explain its relationship to shunt.

Venous admixture is a conceptual quantity, being the amount of mixed venous blood which would have to be added to ideal pulmonary capillary blood to produce the measured gas composition of arterial blood. In a lung where V/Q matching was perfect, it would equal the amount of shunted blood. It is also called *physiological shunt* and is a measure of the degree of V/Q mismatch. The equation for its calculation is given above.

g. Explain the clinical significance of changes in anatomical and physiological dead space.

Anatomical dead space is the volume of the conducting airways. It may be measured most commonly using an N_2 washout test or by making a cast of the airways in a cadaver or using the Bohr equation using end expiratory CO_2 and mixed expired CO_2 in the same manner as the N_2 washout test:

$$\frac{V_{\text{Danat}}}{V_T} = \frac{P_{\text{ET}} \text{CO}_2 - P_{\text{E}} \text{CO}_2}{P_{\text{ET}} \text{CO}_2}$$

Physiological dead space is the volume of airways which do not participate in CO_2 exchange and is determined from the Bohr Equation as given above. The two values are very similar in a healthy individual.

Anatomical dead space represents the difference between total ventilation and gas available for alveolar ventilation. It is typically about 150 ml and is decreased with intubation by the volume of the larynx and pharynx bypassed by the ETT or LMA. The addition of a circuit introduces *apparatus dead space* which is the volume of the circuit beyond the Y-piece in a circle system.

An increase in anatomical dead space increases the mean inspired CO_2 and reduces the mean inspired O_2 , as the first gas inspired will be of end-tidal composition. This results in an increase in minute ventilation in response to the rise in PCO_2 in a spontaneously ventilating patient. The rise in anatomical dead space required to produce significant compromise is large.

Small increases in anatomical dead space are seen with changes in posture: the erect position increasing dead space by about 50 ml over the supine position and neck extension increasing volume of the pharynx another 25 ml. Small increases are also seen with bronchodilation and with deep inspiration.

Physiological dead space increases both with an increase in volume of the conducting airways and with any increase in alveolar dead space. Alveolar dead space may increase as a result of V/Q mismatch: non-perfused alveoli, poorly perfused alveoli and non-vascular air space (in emphysema).

h. Explain the effect of ventilation-perfusion inequality on carbon dioxide elimination and oxygen transfer.

Increased V/Q mismatch impairs both CO_2 and O_2 transfer, but to different degrees. Oxygen uptake is more markedly affected because of the shape of the oxygen uptake curve. Alveoli with a low V/Q and consequently lower PO_2 cause a substantial fall in the oxygen concentration of blood leaving poorly ventilated alveoli, but alveoli with a high

V/Q and high PO_2 , produce only a small rise in oxygen concentration. If mixed venous blood contains 14.6 ml/100 ml O_2 , a normal alveolus ($V/Q = 1$) will raise this to 19.5. A V/Q ratio of 0.1 will result in a rise to only 16 and a ratio of 10 will produce an oxygen concentration of only 20 ml/100 ml.

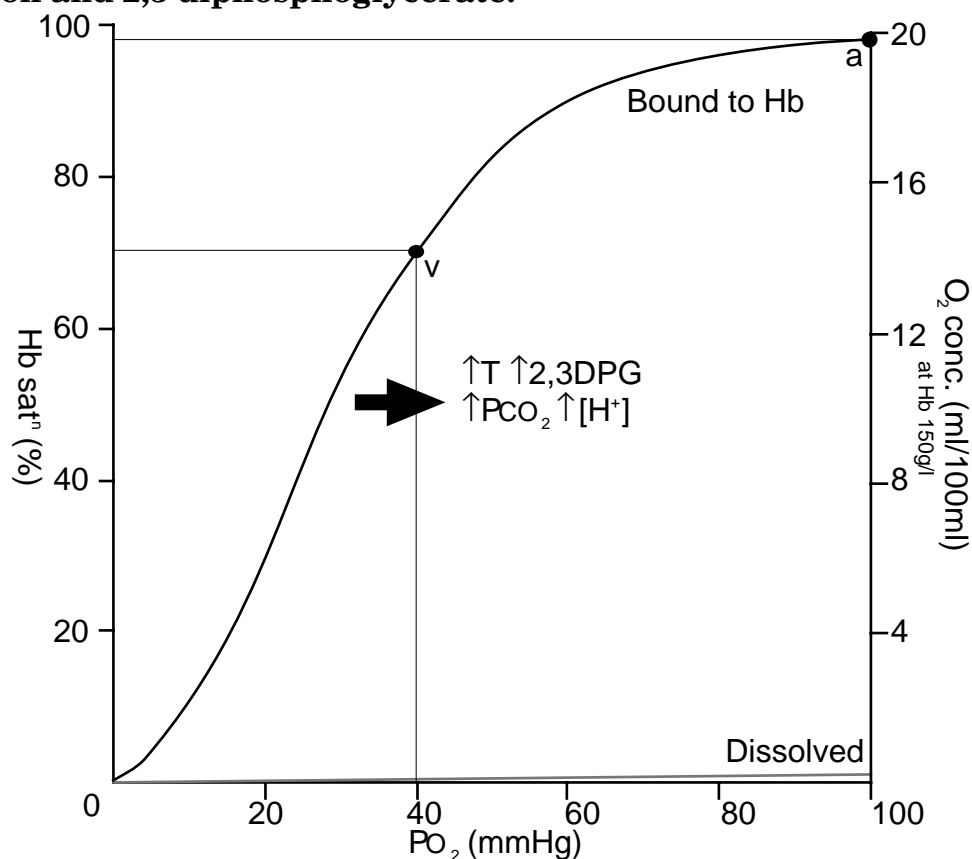
CO_2 elimination is less affected by V/Q mismatch. This is partly due to the more linear relationship between PCO_2 and CO_2 concentration and mostly due to the importance of $PaCO_2$ in determining ventilatory drive. Any rise in $PaCO_2$ resulting from V/Q mismatch will result in an increase in ventilation to normalize $PaCO_2$. A rise in total ventilation is effective in increasing the elimination of CO_2 from both well- and poorly-ventilated alveoli, so $PaCO_2$ is easily normalized.

B. 7 Gas transport in the blood

a. Describe the carriage of oxygen in blood.

Oxygen is carried either bound to haemoglobin or dissolved in solution. The solubility of oxygen in blood is 0.003 ml/100 ml/mmHg so normal arterial blood contains about 0.3 ml/100 ml. The large proportion of oxygen in the blood is bound to haemoglobin, a protein tetramer with an iron-porphyrin ring attached to each chain. Oxygen coordinates with each Fe atom, inducing a conformational change which promotes the binding of oxygen to the other Fe atoms. The total oxygen binding capacity of haemoglobin in blood (at normal pH, temperature and PCO_2) is 1.39ml/g, giving a total oxygen carrying capacity of blood with an Hb of 150 g/l of 20.8 ml/100 ml. Normal arterial blood has a PO_2 of 100 mmHg and is 97.5% saturated; venous blood has a PO_2 of 40 mmHg and is 75% saturated.

b. Explain the oxyhaemoglobin dissociation curve and factors that may alter it, such as carbon monoxide, temperature, carbon dioxide, hydrogen ion concentration and 2,3 diphosphoglycerate.



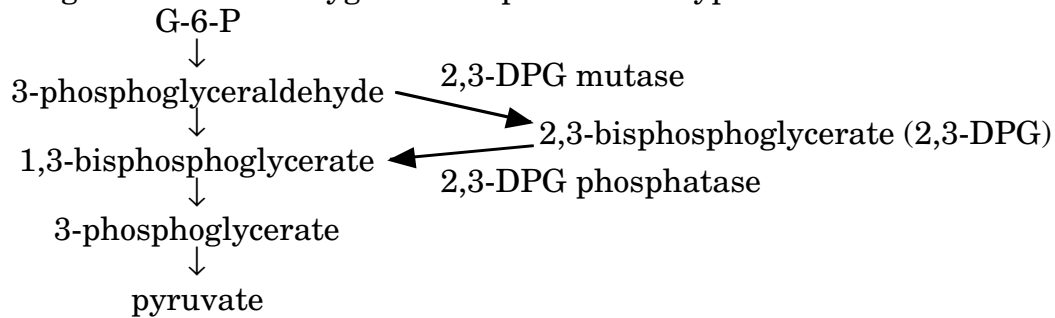
Normal adult haemoglobin (Hb A) consists of two α and two β chains composing a tetramer. Each chain surrounds a porphyrin ring and Fe^{2+} ion. An oxygen molecule can coordinate with each Fe^{2+} ion, inducing a conformational change in the tetramer from its tense (T, deoxy) to relaxed (R, oxy) state. This change requires the breakage of salt links within each chain and extrusion of 2,3 DPG (2,3 bisphosphoglycerate) from a site where it binds both β chains. The conformational changes with oxygen binding are cooperative, resulting in the sinusoidal shape of the dissociation curve.

2,3 DPG has a major effect on the affinity of Hb for oxygen. It is present within erythrocytes at approximately the same molar concentration as Hb. It is a highly negatively charged molecule:



which in the tense state of Hb occupies a site in the centre of the tetramer where it binds three positively charged sites on each β chain. This binding must be broken when Hb binds oxygen. This greatly reduces the affinity of Hb for oxygen. In the complete absence of 2,3

DPG, Hb is 50% saturated at 1 mmHg PO₂ instead of at 26 mmHg. The concentration of 2,3 DPG varies slightly in the erythrocyte, rising with glycolysis in anaerobic conditions and thus promoting the release of oxygen in the presence of hypoxia.



A rise in PCO₂ or in H⁺ ion concentration also promotes the release of oxygen (moving the dissociation curve to the right). This occurs as both CO₂ and H⁺ compete to bind to Hb, which plays a major role in pH buffering. CO₂ reacts with the α NH₃ groups of Hb, reversibly forming a carbamate which forms salt bridges and helps stabilize the T form. H⁺ similarly binds more readily to aspartate and histidine residues which display a rise in pKa with the conformational change from R to T state. This linkage of the affinity for oxygen and H⁺ and CO₂ binding sites on Hb through conformational change is known as the *Bohr Effect*.

Temperature rise reduces the affinity of Hb for oxygen, producing a right shift in tissues which are substantially above normal temperature, such as exercising muscles.

Carbon monoxide binds to Hb about 240 times as avidly as oxygen, having a P₅₀ of about 0.1 mmHg. It coordinates similarly with the Fe²⁺ ion and moves the oxygen dissociation curve to the left.

Other factors which move the curve to the left include high altitude (due to alkalosis), neonatal haemoglobin and thalassaemia. Factors which move the curve to the right include: Hb S, anaemia, hyperthyroidism and normal physiology in the infant (not neonate). More detail in [Monitoring](#) (3.B.2)

c. Describe the carbon dioxide carriage in blood including the Haldane effect and chloride shift.

CO₂ is carried in three ways in blood, as dissolved CO₂, as HCO₃⁻, and combined with proteins as carbamino compounds. It is far more soluble in blood than O₂, with about 0.06ml/100ml/mmHg dissolving. In solution it is in equilibrium with carbonic acid and bicarbonate ion:



which reacts only slowly in plasma but rapidly within red cells where carbonic anhydrase catalyzes the first reaction.

HCO₃⁻ formed within red cells diffuses easily back into plasma in exchange for Cl⁻ ion, according to the Gibbs-Donnan equilibrium in which diffusible ions distribute themselves such that their concentration ratios are equal between compartments. This movement of Cl⁻ is known as the *chloride shift*.

The H⁺ ion formed inside red cells does not diffuse readily into plasma as the cell membrane is relatively impermeable to cations. It is partly buffered by binding to deoxygenated Hb, helping to stabilize the T form. This buffering allows a greater amount of CO₂ to be carried as HCO₃⁻ than would otherwise be possible. The net increase in CO₂ carrying capacity of blood when it is deoxygenated is known as the *Haldane effect*.

Some CO₂ is also carried in combination with globin by reacting with terminal NH₂ groups to form carbamates: Hb·NH·COO⁻. This reaction is also facilitated by the deoxygenation of haemoglobin.

Of the total CO₂ content of arterial blood, 90% is as HCO₃⁻, and 5% each dissolved CO₂ and carbamino compounds. However, of the amount of CO₂ exchanged between tissues and lungs, only 60% is carried as HCO₃⁻, 30% as carbamino compounds and 10% dissolved.

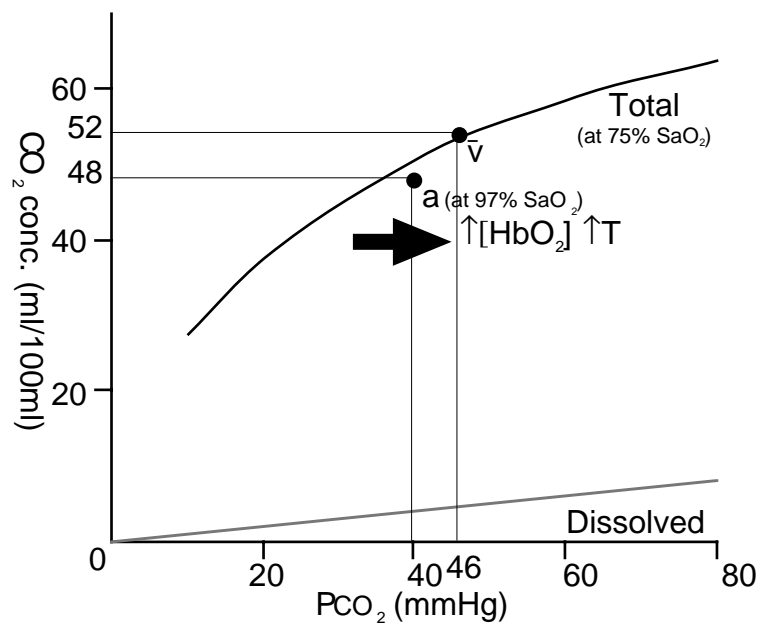
d. Explain the carbon dioxide dissociation curve and its clinical implications.

The carbon dioxide dissociation curve of blood is more evenly sloped and steeper than that of oxygen. The major component of the total CO_2 concentration is HCO_3^- ion which over the physiological range varies almost linearly with PCO_2 . The contribution of carbamino compounds varies very little with PCO_2 , but strongly with the proportion of oxyhaemoglobin, favouring the uptake of CO_2 in the tissues where PO_2 is low.

A rise in temperature reduces the solubility of CO_2 in blood.

The shape of the dissociation curve makes CO_2 transport less dependent on V/Q matching, as the contribution of high V/Q alveoli can compensate for that of low V/Q ones, as neither lies on a "plateau" on the curve.

The substantial contribution from CO_2 not bound to Hb makes CO_2 transport much less dependent upon Hb concentration than O_2 transport is.



e. Describe the oxygen and carbon dioxide stores in the body.

The total body stores of oxygen are small compared with the basal requirements for metabolism:

| | on air | on 100% O_2 |
|--------------------|--------|----------------------|
| lungs (at FRC) | 270 ml | 1800 ml |
| blood | 820 ml | 910 ml |
| interstitial fluid | 50 ml | 55 ml |
| myoglobin-bound | 200 ml | 200 ml |

thus any change in gas exchange results in a rapid change in arterial and tissue PO_2 ($t_{1/2}$ about 30 s). Breathing 100% O_2 results in an increase in the lung store, but increases the blood content by only 50 ml bound to Hb and 50 ml dissolved. O_2 consumption can be approximated using the Brody formula where BW is weight in kg and $\dot{\text{V}}\text{O}_2$ is in ml/min:

$$\dot{\text{V}}\text{O}_2 = 10.15 \cdot \text{BW}^{0.73}$$

The total body stores of carbon dioxide are very large and conform best to a multi-compartment model. The blood and interstitial fluid of well-perfused organs represents a rapid compartment which equilibrates with alveolar CO_2 in minutes. Less well perfused organs such as skeletal muscle produce a medium compartment and poorly perfused tissue (fat) and carbonates bound in bone compose the largest and very slow compartment.

The blood content of CO_2 is about 2.5 l and total body stores about 120 l. Because of the multiple compartments, arterial PCO_2 does not equilibrate as quickly following a fall in ventilation as following a rise. Hyperventilation can deplete blood CO_2 rapidly ($t_{1/2}$ about 3 min). Apnoea causes a slower rise in PCO_2 , because the normal rate of production at rest is small compared with the capacity for excretion and equilibrates into the medium compartment as well as blood and alveolar gas. PCO_2 rises 3-6 mmHg/min with a $t_{1/2}$ to equilibrium of about 15 min. In practice this allows for Ben-Jet ventilation with oxygen to provide adequate oxygenation and build up a CO_2 surplus over 15 or 20 minutes without harmful effects.

B. 8 Pulmonary circulation

a. Outline the vascular anatomy and structure of the pulmonary and bronchial circulations.

The pulmonary trunk arises from the right ventricle and branches into left and right pulmonary arteries. These pass posterolaterally to the main bronchi and follow them into the lungs. The pulmonary arteries give off multiple branches, generally following the bronchi so that bronchopulmonary segments have their own artery and bronchus without anastomosis.

Pulmonary capillaries line the walls of alveoli. They form a mesh in which the holes are smaller than the vessels themselves. The capillaries have very thin walls which are fused to the basement membrane of the alveolar epithelium.

Pulmonary veins drain oxygenated blood from the pulmonary capillaries. They are generally at the periphery of bronchopulmonary segments and drain adjacent segments. The large veins do accompany the bronchi and arteries and drain as two veins from each lung into the left atrium. The upper vein drains the upper lobe on each side and the lower vein the lower lobe. On the right, the middle lobe is drained by the upper vein.

The histology of the pulmonary arteries is different from systemic arteries of similar size. There is little smooth muscle tissue and a large amount of elastin in the artery walls. The walls overall are thin compared to the diameter of the vessels. This is consistent with the low pressures of the pulmonary circulation. The pulmonary veins are very thin-walled.

The pulmonary capillaries are lined with endothelial cells which share their basement membrane with that of the type I pneumocytes lining the alveolar air space.

The bronchial arteries arise from the thoracic aorta or from the upper intercostal arteries. There may be one or more on each side. Occasionally additional bronchial vessels arise from the descending aorta and travel in the pleural ligament. They follow the bronchi, forming a capillary plexus around the large bronchi, supplying the bronchial muscle coat and forming a second plexus in the mucosa. These plexi extend as far as the respiratory bronchioles where they anastomose with the pulmonary vessels.

The deep bronchial veins drain the bronchi within the lung and join the pulmonary veins. The superficial bronchial veins drain the bronchi near the hilum outside the pleura and join the azygous on the right and accessory hemiazygous or intercostal vein on the left.

The histology of the bronchial arteries is the same as that of other systemic arteries.

b. Describe the physiological features of the pulmonary circulation and compare them with those of the systemic circulation.

The pulmonary circulation differs from the systemic circulation in several major respects. The high-pressure side of the pulmonary circulation carries deoxygenated blood and the low-pressure side oxygenated blood. Typical pulmonary arterial pressures are much lower than in the systemic circulation:

| | Right | Left (mmHg) |
|-------------|-------|-------------|
| Ventricular | 25/0 | 120/0 |
| Arterial | 25/8 | 120/80 |
| Capillary | 12→8 | 30→10 |
| Atrial | 5 | 8 |

There is no need for higher pressures in the pulmonary circulation as there is little variation in the hydrostatic pressure to be overcome and less need for preferential perfusion of one area over another. The difference in pressure is reflected in the histology of the arterial vessels.

Flow in the pulmonary vessels is dependent not only on the arterial and venous

pressures but also on the airway pressure and lung volume as West's zones show. With high airway pressures or low venous pressure, flow is limited by the collapse of vessels where airway pressure exceeds blood pressure. At high lung volumes, the vessels are supported not only by blood pressure but by elastic forces within the lung parenchyma, allowing the effective pressure outside larger vessels to be less than intrathoracic pressure.

The volume within the pulmonary circulation is around 0.5 to 1.0 l, depending on posture, the cardiac cycle and airway pressure.

The pulmonary circulation has a number of metabolic functions which distinguish it from the systemic circulation. It is the site of synthesis of a number of hormones, including prostaglandins, histamine and kallikrein. It is the main site of conversion of angiotensin I to angiotensin II. It is a major site for removal from circulation of bradykinin, prostaglandins E_2 and $F_{2\alpha}$, leukotrienes, adenine nucleotides, serotonin, noradrenaline and acetylcholine. It is also the major site for removal of emboli from circulation and their fibrinolysis.

c. Explain the factors that affect pulmonary vascular impedance.

Impedance is the term for resistance under particular flow conditions. Resistance in a vessel equals pressure gradient per unit flow. Under normal resting circumstances, total pulmonary blood flow is about 6 l/min and the pressure drop from mean arterial to venous pressure is about 10 mmHg, giving a resistance of 1.7 mmHg/l/min (or about 100 dyne/cm⁵/s), which is about a tenth of systemic vascular resistance.

Pulmonary vascular resistance falls with an increase in arterial or venous pressure as any rise in capillary pressure causes increased distension and recruitment of capillaries and less resistance to flow. Similarly an increase in lung volume lowers large and medium vessel resistance as it increases the distending tension on the larger vessels. Capillary resistance is increased at high lung volumes as stretching of the alveolar walls compresses the capillaries. Thus total pulmonary vascular resistance is high at both very low and very high lung volumes and low between.

Smooth muscle contraction in the walls of pulmonary vessels plays some role in determining pulmonary vascular pressures, but is not as significant as in the systemic circulation. Vasoconstrictors such as noradrenaline, serotonin and histamine increase pulmonary artery pressure.

d. Describe the control of pulmonary vascular tone.

Pulmonary arterioles respond autonomously to the PO_2 in adjacent alveoli. A PO_2 below 70 mmHg results in marked vasoconstriction, largely independent of arterial oxygenation. There is little constriction above 100 mmHg. The mediator of this response has not been identified, but endothelial cells normally produce NO which acts as a vasodilator and which can relieve vasoconstriction when inhaled in low concentrations.

This response serves to direct blood flow into the best oxygenated parts of the lung when there are areas which are poorly ventilated. At high altitude, where there is a prolonged and generalized reduction in alveolar PO_2 , widespread vasospasm causes a rise in pulmonary artery pressure and may result in right heart failure and acute mountain sickness.

In the transition from foetus to newborn, this response plays a major role in allowing the changeover from 15% of cardiac output going through the hypoxic foetal lung to 90% of cardiac output passing through a much more vasodilated pulmonary circulation in the newborn after the first few breaths (with 10% shunt).

Acidosis also results in some pulmonary vasoconstriction. There is sympathetic innervation of the pulmonary arterioles with increased sympathetic outflow causing vasoconstriction.

e. Outline the mechanisms which raise pulmonary vascular resistance and describe the circulatory effects of such a rise.

Pulmonary arterial tone is raised in response to the stimuli given above. Capillary resistance rises with lung volume.

Even if total pulmonary resistance rises (for example in living at high altitude), pulmonary blood flow must still remain equal to slightly less than total systemic blood flow. In the short term this requires increased work of the right ventricle and in the long term cardiac output tends to fall. There is commonly arterio-venous shunting of blood seen within the pulmonary circulation. In persistent pulmonary vascular obstruction (as in embolism), anastomosis with the bronchial circulation increases to provide perfusion to the embolized segment.

f. Describe the pulmonary circulation in the foetus and the newborn.

The foetal circulation is substantially different from the adult, primarily because of the difference in the source of oxygenation: the foetus obtains oxygenated blood from the placenta and the newborn from the lungs. Oxygenated blood returns from the placenta in the umbilical vein which joins the portal vein and then passes through the liver into the hepatic vein or bypasses the liver in the ductus venosus and passes directly into the IVC.

Much of the blood from the IVC passes through the foramen ovale into the left atrium and then into the systemic circulation. The remainder, together with blood from the SVC, passes into the RV and then into the pulmonary trunk. In the foetus, the pulmonary circulation is of a high resistance because of the lack of oxygen in the lungs and only about a third of the RV output passes through the lungs (12% of cardiac output), the remainder being diverted through the ductus arteriosus into the arch of the aorta and the systemic circulation.

Because of the high pulmonary resistance, the pressure in the pulmonary trunk is about 5 mmHg higher than that in the aorta. The parallel operation of the right and left ventricles allows them to have substantially different outputs with the left ventricle pumping 20% more blood.

About 75% of total cardiac output ends up in the descending aorta and the majority of this flows into the umbilical arteries (over 50% of cardiac output).

The oxygen saturation of haemoglobin in the foetus is much lower than in the newborn. In the umbilical vein, the blood is about 80% saturated, falling to 62% in the LV after mixing with other venous blood. This is the saturation of the blood perfusing the head and upper body. After mixing with blood from the ductus arteriosus, saturation falls to 58% for perfusion of the remainder of the body. Foetal haemoglobin ($\alpha_2\gamma_2$) has a higher affinity for oxygen than adult haemoglobin as it binds 2,3 DPG less strongly, so in the placenta oxygen is transferred from maternal to foetal haemoglobin at the same PO_2 .

After birth, pulmonary vascular resistance falls by 90% as air enters the airways. This results in a rapid fall in right heart pressures and reversal of flow passing through the ductus arteriosus which constricts and closes over several days. The foramen ovale closes functionally as the pressure gradient between LA and RA pushes the valve shut.

In response to the trauma at delivery, the umbilical arteries constrict distal to the superior vesical arteries, and the cord is usually clamped. The cessation of flow through the umbilical vein coincides with closure of the ductus venosus which has a sphincter mechanism. The closing of the placental circulation causes a sharp rise in systemic resistance and blood pressure.

In the weeks following these changes, the muscle lining of the pulmonary vessels thins and the left ventricular wall starts to thicken to a greater extent than the right. The foramen ovale, ductus arteriosus and ductus venosus are sealed with fibrous tissue and the circulation shows the characteristics of the adult circulation.

B. 10 Clinical pulmonary function tests

a. Distinguish between obstructive and restrictive lung disorders using the family of curves measuring forced expiratory volume, peak expiratory flow rate and vital capacity.

The forced expiratory volume-time and flow-volume curves are useful in distinguishing between lung disorders. The volume-time curve which is obtained from a spirometer shows forced vital capacity (FVC) and allows reading of forced expiratory volume in 1 second (FEV_1).

FVC is a good measure of the severity of restrictive lung disease. The expected normal value can be calculated from height, sex and age and a result less than 70% of predicted is indicative of restrictive lung disease. In isolated restrictive lung disease, the FEV_1/FVC is normal or increased.

The ratio of FEV_1 to FVC is a good measure of obstructive airway disease. A value of less than 0.7 (70%) is indicative of airway obstruction limiting expiratory flow abnormally. This is independent of FVC. FVC is commonly reduced in patients with obstructive disease as many have a concomitant restrictive deficit as well.

Peak expiratory flow rate (PEFR) can be read from the flow/volume curve or measured separately with a Wright peak flow meter. In a patient with known obstructive disease it is a useful measure of the degree of obstruction and so is routinely used in asthma to assess severity and response to therapy. Normal values are calculated on height, sex and age and have a large variability.

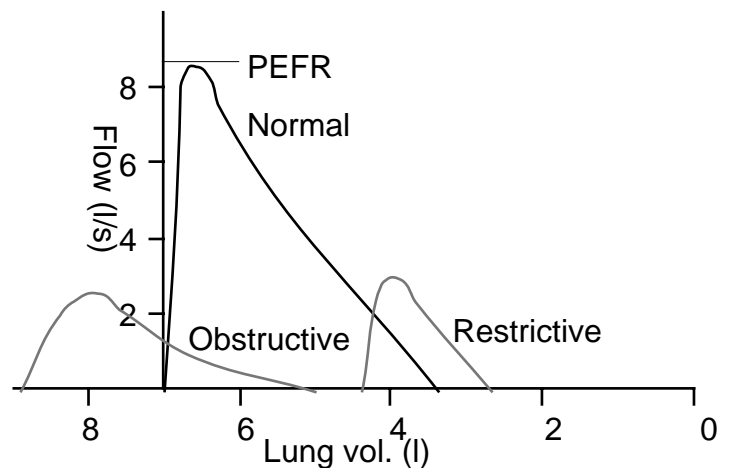
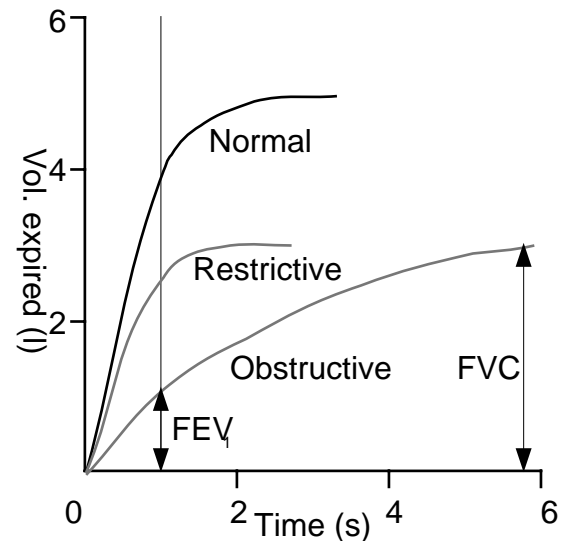
In restrictive lung disease, PEFR is similarly reduced as lung volume is the major determinant of the flow rate in the effort-independent part of the flow-volume curve. Thus PEFR alone cannot distinguish obstructive from restrictive disease.

Lung volume on the flow-volume curve is also a distinguishing feature of lung disease. In restrictive disease, FVC is lost "from the top" with inspiration limited by disease but expiratory flow rates slightly increased at low volumes because of increased elastic recoil in the lungs. In obstructive disease, FVC is lost "at the bottom" as airway closure occurs prematurely in expiration and the patient is forced to operate at higher lung volumes.

b. Outline methods used for measuring mechanics of breathing including flow-volume loops and interpret such results.

Volume-time curves are easily measured using mechanical devices such as the Benedict-Roth spirometer (traditionally) or bellows Vitalograph. The tracings produced by these devices are cumbersome to turn into flow-volume curves as the tracing needs to be differentiated with respect to time to yield flow.

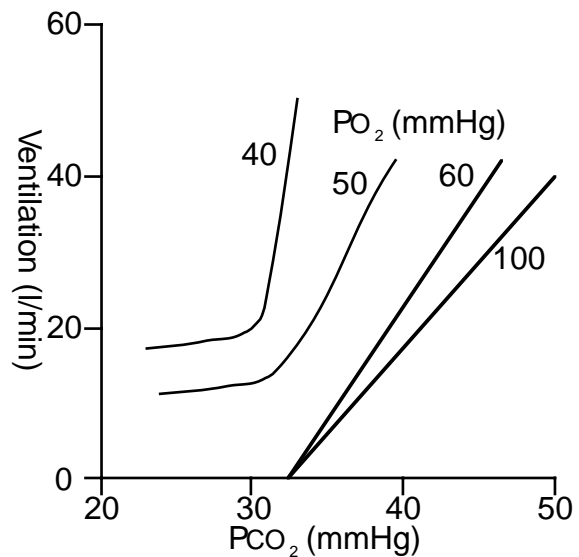
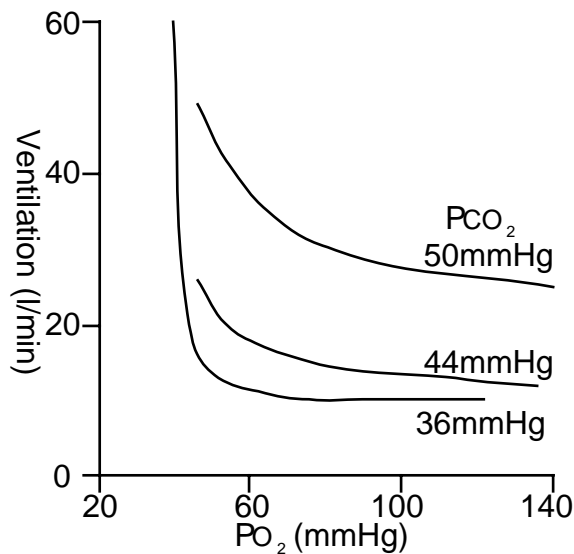
Practically, a pneumotachograph can be used to produce flow-volume curves. This is a tube with a section of fine parallel tubes in it which induce laminar flow. Pressure transducers either side of the laminar flow section measure the pressure drop across the



section of laminar flow and thus the flow rate can be calculated if the length of the section of laminar flow and the characteristics of the gas are known. This is recorded electronically and can be integrated with respect to time to yield volume expired and thus flow-volume curves.

PEFR is measured in isolation using a Wright peak flow meter. This is a chamber in which a leaf is pushed against a spring by the expiratory flow. Its excursion is calibrated to expiratory flow and it moves a pointer which remains at the point of furthest excursion of the leaf (highest flow). These devices are cheap and the results readily reproducible with practice and maximal effort.

c. Describe the carbon dioxide and oxygen response curves and how these may be used to assess the control of breathing.



d. Interpret and explain normal and abnormal blood gases

In [Acid-Base](#) (1.F)

e. Describe the measurement of lung volumes including functional residual capacity and residual volume.

In [Respiratory Mechanics](#) (1.B.3)

B. 10 Applied Respiratory Physiology

a. Describe the physiological consequences of intermittent positive pressure ventilation and positive end-expiratory pressure.

Intermittent positive pressure ventilation (IPPV) is artificial ventilation produced by imposing a positive pressure from a sealed circuit into the airway, followed by passive expiration, usually at atmospheric pressure. The major physiological difference from spontaneous ventilation is in the range of airway and intrathoracic pressures involved. Spontaneous ventilation involves small pressure excursions above and below atmospheric pressure in airway pressure. IPPV involves much higher airway pressures in inspiration, typically 15-25 mmHg in a healthy adult. Much of this pressure is transmitted to increase intrathoracic pressure.

Positive end-expiratory pressure (PEEP) is a modification of IPPV such that the expiratory airway pressure does not fall as low as atmospheric pressure. A typical level of PEEP is 5-15 mmHg.

Consequences of IPPV and PEEP:

respiratory

- end-expiratory alveolar pressure = PEEP, producing an increase in FRC according to PEEP level and compliance

- may lift FRC above closing capacity in patients with a high closing volume
- reduces airway resistance
- alters relative compliance of upper and lower parts of the lung

- reduces pulmonary shunt

- intrapleural pressure rises according to the transmural pressure gradient (increased in most pathology)

- increases dead space with prolonged application due to bronchiolar dilation

cardiac

- increased intrathoracic pressure

- reduced systemic venous return, reduced cardiac output, increased ADH, reduced ANF

- increased pulmonary capillary resistance

- increased "Zone 1" may make PCWP measurement unreliable

renal

- decreased perfusion pressure

- fluid retention

overall effect of PEEP

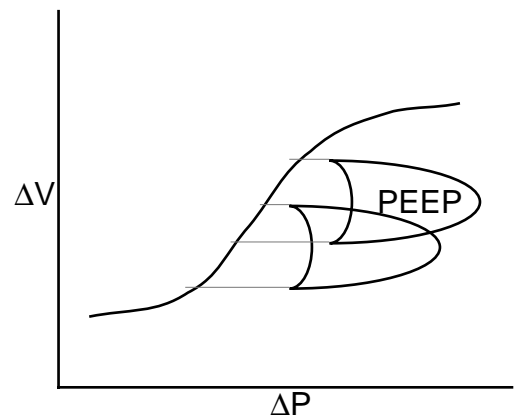
- increased P_aO_2 in diseased lung

- decreased cardiac output

- increased oxygen flux up to "best PEEP"

- not useful in healthy lungs

- mostly used in ICU setting



b. Explain the physiological consequences of hypoxaemia, hyper and hypocapnia and carbon monoxide poisoning.

Hypoxaemia

- low P_aO_2

- classified as hypoxic hypoxia (low P_aO_2), anaemia hypoxia (low O_2 carrying capacity),

stagnant hypoxia (poor tissue perfusion) and histotoxic hypoxia (failure of cellular respiration)

cellular

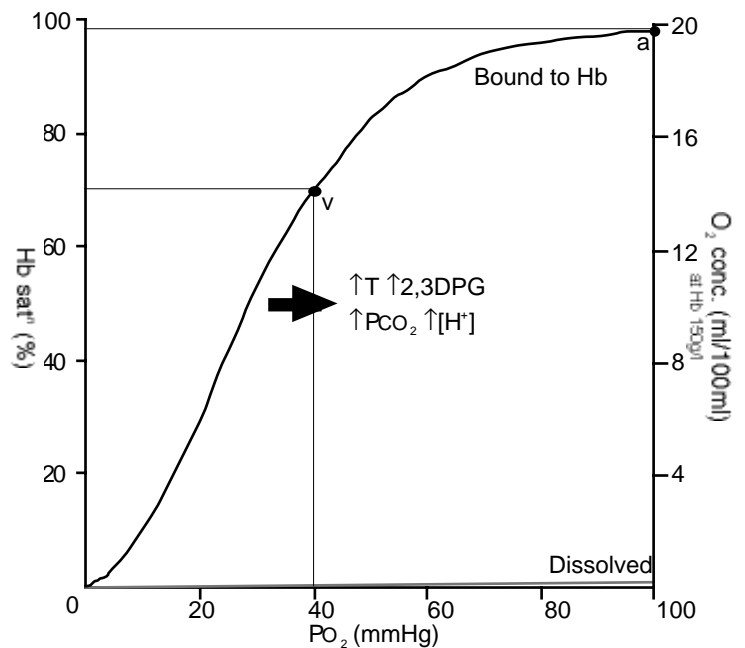
anaerobic metabolism
($P_aO_2 < 20$ mmHg or histotoxicity)
accumulation of lactate, acidosis
depletion of high energy phosphates: ATP and phosphocreatine
time to cellular “arrest” depends on energy requirements vs stores

respiratory control

hypoxia detected by peripheral chemoreceptors (carotid & aortic bodies)
hyperventilation at $P_aO_2 < 55$ mmHg, maximal at $P_aO_2 < 30$ mmHg
secondary hypocapnia
central respiratory depression with severe hypoxia
pulmonary vasoconstriction (primarily related to P_AO_2)

cardiovascular

systemic vasodilation (especially cerebral): $\uparrow CO$, $\downarrow MAP$
acidosis and increased 2,3-DPG shifts Hb- O_2 dissociation curve to the right
increased erythropoietin and haematocrit in chronic hypoxia



Hypercapnia

high P_aCO_2
causes acidosis (in blood, ECF and CSF) via carbonic anhydrase

neurological

cerebral vasodilation, $\uparrow ICP$
convulsant at high P_aCO_2
central depressant effect at high P_aCO_2 (>95 mmHg, $MAC=32\%$)
autonomic

increased sympathetic outflow
increased sensitivity to parasympathetic tone via $\downarrow AChE$ activity in acidosis

respiratory control

hypercapnia detected at central chemoreceptor (80% of sustained response) in the ventral medulla and in peripheral chemoreceptors (rapid response)
hyperventilation up to P_aCO_2 of 100-150 mmHg
pulmonary vasoconstriction (weaker effect than hypoxia)

cardiovascular

systemic vasodilation
 \uparrow contractility and heart rate via sympathetic action (direct depressant action)
arrhythmogenic
acidosis shifts Hb- O_2 dissociation curve to the right

renal

chronic hypercapnia results in renal compensation by retention of HCO_3^-

endocrine

sympathetic response raises blood glucose and K^+

Hypocapnia

low $P_a\text{CO}_2$

mainly opposite effects to those of hypercapnia

alkalosis (\downarrow free Ca^{2+})

neurological

cerebral vasoconstriction: \downarrow ICP

\uparrow neural excitability at low $P_a\text{CO}_2$

respiratory

detected at central and peripheral chemoreceptors

reduced respiratory drive (dangerous in labour)

can produce apnoea in anaesthetized patients, but not usually when conscious

pulmonary vasodilation

cardiovascular

\uparrow peripheral resistance

\downarrow cardiac output

Hb- O_2 dissociation curve shifted to the left

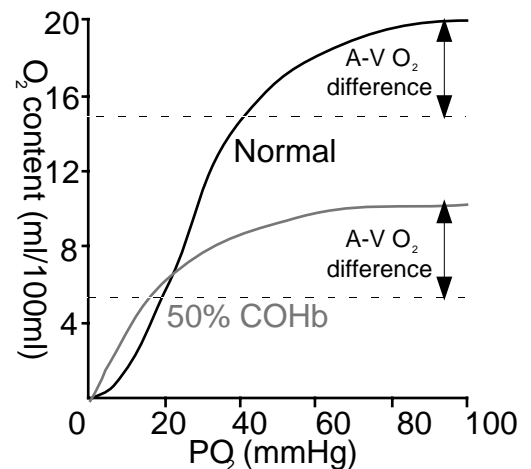
Carbon-monoxide (CO) poisoning

CO binds to haemoglobin (Hb) with approximately 270 times the affinity of oxygen under physiological conditions ($P_{50}=0.1$ mmHg). It binds at the same site and in the same manner as O_2 , so binding is cooperative with either CO or O_2 : CO poisoning moves the Hb- O_2 dissociation curve to the left. The toxicity of CO is mediated by its reduction of the oxygen carrying capacity of blood by binding with Hb and by impairing tissue oxygenation through its effect on the Hb- O_2 dissociation curve.

The reduction in oxygen concentration at a given oxygen tension results in reduced oxygen delivery and tissue hypoxia if there is sufficient reduction in oxygen concentration. The $P_a\text{O}_2$ is not reduced, but normal oxygen extraction results in a lower mixed venous PO_2 and a lower tissue PO_2 .

This reduction in oxygen carrying capacity causes hypoxaemia, and the physiological responses are given above.

CO poisoning can be reversed with removal of the source of CO, and hyperventilation with high FiO_2 to accelerate dissociation of COHb. In the conscious patient, use of a raised FiCO_2 is described as a method of increasing spontaneous ventilation.



c. Explain the effects of the supine and erect postures on ventilatory function.

Changing from erect to supine:

increased

diffusing capacity (due to reduced V/Q scatter)

decreased

FRC by 500-1000 ml, approaching closing capacity

anatomical dead space by 100-150 ml

physiological dead space by 5% (from 35% of V_T to 30%)

alveolar dead space (due to reduced V/Q scatter)

d. Define humidity and give an outline of the importance of humidification.

Absolute humidity

the mass of water vapour per unit volume of a gas.

Humidity at saturation

the maximum mass of water which can be present in a gas per unit volume at a

specified temperature.

Relative humidity

the ratio of absolute to saturation humidity at a specified temperature expressed as a percentage.

Air at 37° with a 100% relative humidity contains 44gm⁻³ of water (SVP=47 mmHg)

Inspired gas is normally humidified in the nose and mouth before entering the lower respiratory tract. Inadequate humidification of inspired gas due to use of dry gas by mask or bypassing of the upper airway by intubation results in:

acute

- impaired ciliary and mucous belt function
- tenacious mucus, crusting of secretions
- increased airway resistance and reduced compliance
- heat loss by evaporation

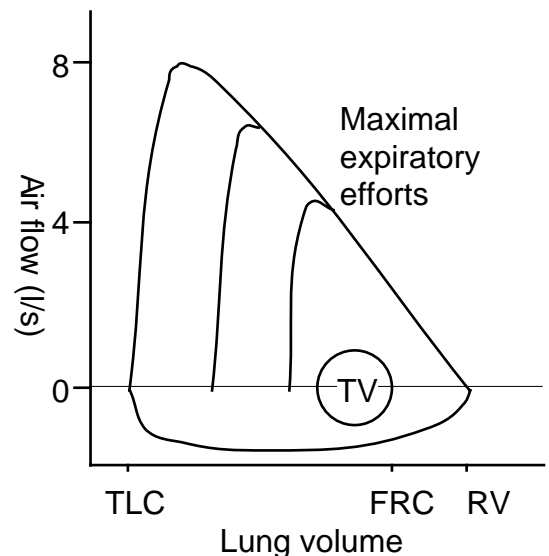
chronic

- squamous metaplasia
- ↓ FRC
- ↑ shunt
- impaired surfactant function
- atelectasis

e. Explain the importance of the cough reflex and describe the relationship between lung volume and ability to cough.

The cough reflex is the major mechanism for clearing the upper and lower airways of foreign material larger than can be carried by the mucociliary elevator. It is initiated by mechanical or chemical irritation of the airway. It consists of a deep inspiration to about $\frac{2}{3}$ of V_T followed by tight closure of the glottis and contraction of expiratory muscles causing a rise in airway pressure often in excess of 100 mmHg, then a forceful expiration through upper airways narrowed by high transmural pressure, producing a high air velocity to dislodge foreign material.

The maximum expiratory flow rate and velocity which can be generated depends on both expiratory muscle strength and lung volume. With normal strength, it is limited by lung volume due to airway closure which makes expiratory flow effort independent as lung volume decreases.



f. Explain the effects of general anaesthesia on respiratory function.

Intraoperative

Control

- Altered patterns with depth of anaesthesia and agent used
- Hyperventilation in excitatory stage
- Depressed ventilation when deep
 - ↓ response to PCO_2 with ↑ MAC value
 - abolished hypoxic response with minimal anaesthetic agent

in [Respiratory Control](#) (1.B.2)

Mechanics

- Supine position ↓ FRC
- Altered \dot{V}/Q matching with anaesthesia

- ↑ shunt, ↑ A-a gradient
 - V_D altered by position and instrumentation
- Gas exchange
 - Altered inspired gases or volatile agents
 - Second gas effect
- Defence mechanisms
 - Drying of mucosa, volatiles, tube cuff: ↓ ciliary function
- Postoperative
 - Immediate
 - Drug effects (above)
 - Diffusional hypoxia
 - ↑ O_2 requirement with shivering
 - Pain-related
 - ↓ FRC, ↓ VC most with upper abdominal surgery
 - Narcotic respiratory depression
 - Posture effects

C 1. Structure and function of the heart

a. Describe the structure and functional significance of the contractile elements of cardiac muscle and how they differ from skeletal muscle.

Cardiac muscle cells are of three types: atrial, ventricular and specialized excitatory and conductive cells.

Atrial and ventricular muscle

- cellular anatomy is similar to skeletal muscle

 - interdigitated actin and myosin filaments

 - T-tubules are opposite the Z-line rather than A-I junction

 - many mitochondria

 - cells are small and connected via intercalated disks which have many gap junctions and a very low electrical resistance. This renders cardiac muscle a functional syncytium.

- gross anatomy

 - two syncytia: the atria and the ventricles, separated by a fibrous ring around the mitral and tricuspid valves, connected only by the AV node

- electrical activity

 - resting membrane potential is -90 mV, maintained by the $\text{Na}^+\text{-K}^+$ ATPase pump

 - action potential is prolonged and divided into several phases

 - fast Na^+ channels open causing depolarization

 - slow $\text{Ca}^{2+}\text{-Na}^+$ channels open for 200-300 ms

 - K^+ conductance is inhibited while the $\text{Ca}^{2+}\text{-Na}^+$ channels are open, but rises rapidly to produce repolarization

 - excitation-contraction coupling is similar to skeletal muscle, except that metabolism is exclusively oxidative and Ca^{2+} diffuses in from the T-tubules as well as the sarcoplasmic reticulum

 - there is no summation of action potentials to produce contraction, unlike skeletal muscle

 - the refractory period is about 0.15 s in the atria and 0.3 s in the ventricles, this limits the maximum rate of contraction

 - action potentials propagate at about 0.5 m/s in muscle and between 0.02 m/s and 4 m/s in the conducting cells

C 2. Electrical properties of the heart

a. Explain the ionic basis of the spontaneous electrical activity of cardiac muscle cells (automaticity).

resting membrane potential (V_m)

maintained by Na^+ - K^+ ATPase pump and ion channels

in [Physiol G](#)

normally -90 mV

depolarization

phase 0

m-gates open over 0.2 ms around V_m -65 mV, raising g_{Na} markedly

rapid influx of Na^+ (and Ca^{2+}), V_m rises to +30 mV

h-gates close over 1 ms and g_{Na} falls again

h-gates remain closed until repolarization (refractory period)

phase 1

when V_m is positive in phase 0, K^+ efflux through i_{to} channels is increased due to electrochemical gradient

this is the i_{to} “transient outward current” of phase 1

i_{to} is pronounced in atrial cells which merge phases 1 and 3

phase 2

plateau is maintained by Ca^{2+} influx through

L channels (predominant) open at V_m +30 mV

stay open to maintain plateau

T channels open briefly at V_m -20 mV

minor effect

Ca^{2+} influx is balanced by K^+ efflux

K^+ current through i_{K1} channels is *inwardly rectified*

g_{K} is high for inward currents and low for outward currents

g_{K} is low during phase 2 and the small K^+ current balances the Ca^{2+} current

Ca^{2+} channels slowly inactivate and i_{K} channels slowly open

phase 3

delayed rectifier i_{K} channels finally open

i_{K1} current rises as V_m falls

outward K^+ current through i_{to} , i_{K1} and i_{K} repolarize cell

phase 4

Ca^{2+} concentration is restored by Ca^{2+} - Mg^{2+} ATPase pump and $\text{Ca}^{2+}/\text{Na}^+$ secondary active transport

Na^+ and K^+ gradients are maintained by Na^+ - K^+ ATPase pump

in automatic cells, specific Na^+ channels open with hyperpolarization to produce i_{f} , an inward current depolarizing the cell

when V_m becomes partly depolarized, Ca^{2+} channels open, initiating a rapid rise in V_m until an action potential is initiated

Many cardiac muscle cells display automaticity (spontaneous regular action potentials). The cells of the conducting system display the greatest automaticity; usually the SA node cells start the regular action potentials which spread to the rest of the myocardium.

The cells of the SA node have membranes which are relatively permeable to Na^+ and so have a resting membrane potential of only -55 mV to -60 mV. At this potential the fast Na^+ channels remain permanently closed and refractory. The gradual leak of Na^+ into the cell causes a progressive rise in the membrane potential until the slow Ca^{2+} channels are activated. The influx of Ca^{2+} and Na^+ generates an action potential for 100 to 150 ms before the channels close and the K^+ channels open, repolarizing the cell.

b. Describe the normal and abnormal processes of cardiac excitation.

The sinus nodal fibres fuse with the atrial cardiac muscle fibres, carrying the action potential throughout the atria. There are several conduction pathways which carry the action potential more rapidly: the anterior interatrial band and the internodal pathways which run to the AV node. The action potential reaches the AV node after 30 ms. Propagation of the action potential throughout the atria takes under 100 ms.

The AV node consists of transitional fibres from the internodal pathways, a node within the atrium and penetrating fibres connecting to the distal portion of the AV bundle in the ventricle. The fibres of the AV node conduct the action potential very slowly due to their low degree of polarization, small size and few gap junctions. This results in a delay in transmission of the action potential of about 130 ms. The AV node can conduct only one way in normal contraction.

Within the interventricular septum, the AV bundle joins the Purkinje fibres. These conducting cells are of a large diameter and have many gap junctions, transmitting the action potential rapidly throughout the ventricles. The transmission time for the entire Purkinje system is 30 ms. Propagation to the entire ventricular muscle takes another 30 ms, yielding a coordinated contraction.

Abnormalities of cardiac conduction

accessory atrioventricular muscle bundle (WPW) may lead to recurrent arrhythmias or rapid conduction of AF or flutter.

EAD

early after depolarization occurs in phase 3 at a slow heart rate
 Ca^{2+} channels recover and can be reactivated before phase 4

DAD

delayed after depolarization occurs in phase 4 at high heart rate
raised ICF $[\text{Ca}^{2+}]$ results from high rate and produces spontaneous Ca^{2+} release from sarcoplasmic reticulum

ectopic pacemaker

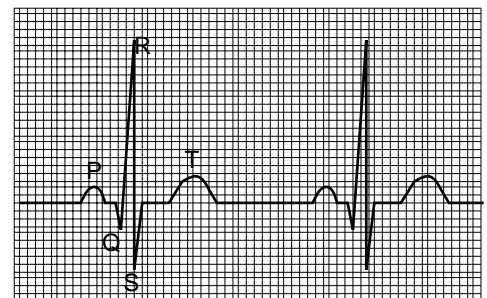
AV node or Purkinje fibres or even muscle may generate action potentials at a higher frequency than the SA node and thus become the pacemaker
If transmission of action potentials is blocked, automaticity of more distal cells will produce a continued but slow rate of contraction

fibrillation

if electrical activity in the atria or ventricles becomes uncoordinated because of high rate or abnormal conduction, a stable state of fibrillation may result
abnormal cardiac may be terminated by external initiation of action potentials
overdrive pacing
DC reversion

c. Explain the physiological basis of the ECG.

The ECG is a representation of the net electrical potential detected at the skin from the electrical events taking place in the cardiac cycle. Depolarization moving towards the observed lead gives a positive deflection as the extracellular fluid becomes more negatively charged around depolarized tissue than around polarized cells. The P wave represents atrial depolarization, the QRS complex, ventricular depolarization and the T wave ventricular



repolarization.

During the plateau phase of depolarization, there is little effect on the ECG as there is little flow of current. The initial depolarization of the ventricles produces the Q or R wave, the gradual reduction in membrane potential is represented in the ST segment and the repolarization produces the T wave.

Thus the PR interval represents the time between atrial and ventricular depolarization, usually 160 ms, and the QT interval is close to the period of ventricular contraction, about 350 ms.

The standard leads of the ECG are I, II, III, aVR, aVL, aVF and V_1 to V_6 .

Depolarization of the atria proceeds from the SA node around the walls, giving a net vector at about 60° . Repolarization of the atria takes place in the same direction, but occurs at the same time as ventricular depolarization which obscures it on the ECG.

Because depolarization of the ventricles proceeds from the septum down to the apex and around the left and right ventricles, finishing with the superior part of the left ventricle, the net electrical vector during the QRS complex is initially towards the apex (60°), then swinging to the left (-60°). Repolarization proceeds from the apex and outer surface back towards the base of the heart, generating a net vector about 40° in the frontal plane.

The QRS axis may be altered by the position of the heart. LAD is seen in expiration and in short fat people and RAD in inspiration and in tall thin people. The normal range is 20° to 100° . Ventricular hypertrophy causes axis deviation towards the hypertrophied ventricle, because of the increased muscle mass and delay in depolarization. Bundle branch block causes a delay in depolarization of one ventricle and thus results in axis deviation towards the blocked side as well as widening of the QRS complex. Bundle branch block also causes repolarization of the blocked ventricle much later than the ventricle with normal conduction, causing the axis of the T wave to deviate away from the blocked side.

The size of the QRS complex is determined by the muscle mass of the ventricles and the effective conduction of electrical potentials to the skin. Thus it is increased in ventricular hypertrophy and reduced in pericardial effusion or COAD.

When part of the ventricle is acutely injured (usually infarcted) it remains constantly depolarized. This produces an electrical vector directed away from the infarct. As the point in the ECG during which no current flows is the start of the ST segment when the entire ventricle is depolarized (J point), the ST segment is elevated relative to the TP segment in the leads over the site of injury. This is because the ST segment remains the true baseline, while the TP segment is depressed by the vector produced by the infarcted muscle while the rest of the ventricle is polarized. With reperfusion or fibrosis, this effect on the TP segment diminishes over time.

Digoxin prolongs the period of depolarization of cardiac muscle, causing changes in the T wave and ST segment in overdose as well as impairing conduction at the AV node.

d. Describe the factors that may influence cardiac electrical activity.

Na^+

gradient has little effect on resting membrane potential

high ECF $[\text{Na}^+]$ is required for phase 0 V_{max}

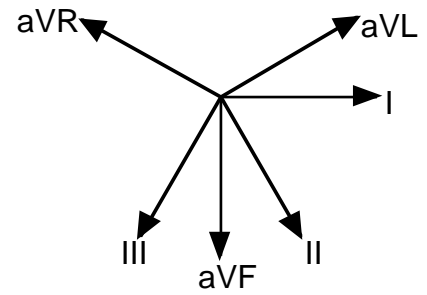
gradient required for secondary transport of Ca^{2+} out of the cell

K^+

gradient is the major determinant of resting membrane potential

low ECF $[\text{K}^+]$ is required for maintaining the electrical gradient which drives phase 0

high ECF $[\text{K}^+]$ causes low V_{max} and slow conduction



Ca^{2+}

low ECF $[\text{Ca}^{2+}]$ or blockade of Ca^{2+} channels increases the slope of phase 2 and reduces its duration, it also markedly reduces force of contraction

cycle length

i_K inactivates very slowly

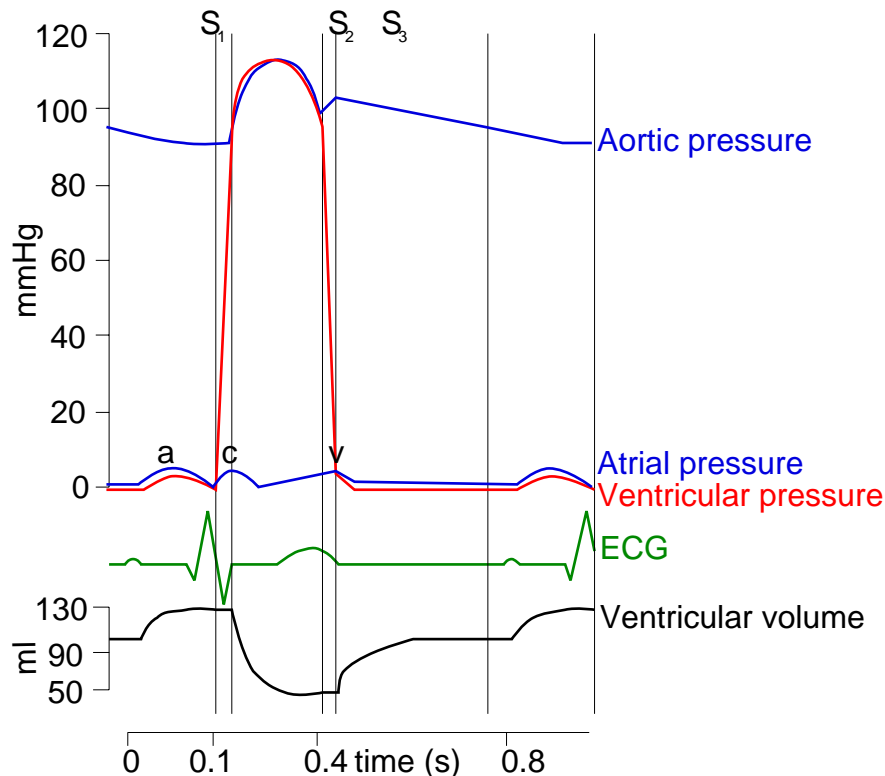
rapid heart rate results in i_K being active in phase 2

increased slope and reduced duration of phase 2 (adaptive)

Activity of the SA and AV nodes is controlled by parasympathetic and sympathetic nerves. Vagal stimulation releases acetylcholine which increases membrane permeability to K^+ and thus hyperpolarizes the cells. This reduces the rate of discharge at the SA node and delays or blocks conduction in the small fibres of the AV node.

Sympathetic nerve stimulation releases noradrenaline which increases intracellular cAMP via G-protein-linked β -receptors. A rise in protein kinase activity increases membrane permeability to Na^+ and Ca^{2+} as well as upregulating the Ca^{2+} uptake by sarcoplasmic reticulum. Increased Na^+ and Ca^{2+} permeability leads to more rapid depolarization of cells and more rapid uptake leads to quicker relaxation. These changes thus yield both chronotropic and inotropic effects.

e. Describe and explain the mechanical events of the cardiac cycle and correlate this with the electrical and ionic events.



The cardiac cycle consists of diastole and systole. During diastole, the heart initially fills with blood passively from venous return. The SA node initiates the electrical activity which drives the cardiac cycle. This leads first to atrial depolarization, which produces the P wave of the ECG and contraction which increases the end diastolic volume of the ventricles about 25% and produces the venous a wave.

After a delay of about 160 ms, the conducting system of the ventricles and the ventricles themselves depolarize, generating the QRS complex, and contract, closing the AV valves (S_1) and producing the venous c wave. Intraventricular pressure rises rapidly (isovolumetric contraction), opening the aortic and pulmonary valves at around 80 mmHg and 8 mmHg respectively.

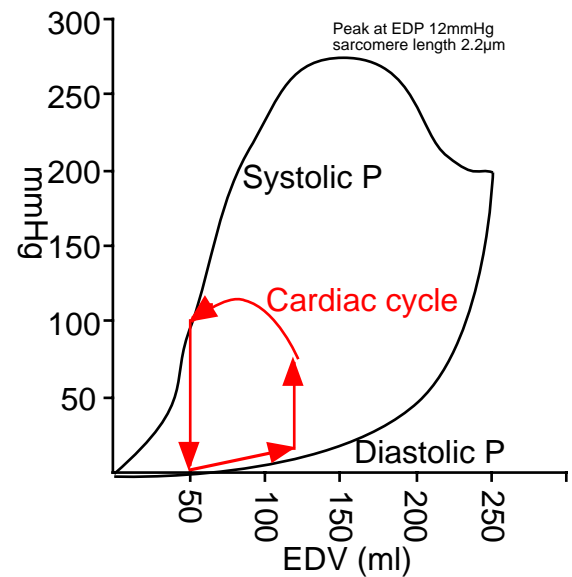
There is a period of rapid ejection in systole, followed by slower ejection and then closure of the aortic and pulmonary valves (S_2). During systole the atria have filled with venous blood, producing the v wave. Relaxation of the ventricles also coincides with the T wave of the ECG. The cycle then begins again with passive filling of the ventricles.

C 3. Determinants and control of cardiac output

a. Explain Starling's law of the heart and its relation to excitation-contraction coupling.

The Frank-Starling mechanism is the rise in developed force of contraction with increasing stretch of the myocardium with the result that within physiological limits, stroke volume rises with end diastolic volume: the heart pumps out as much blood as comes in. This mechanism is produced by the increased force of contraction developed by cardiac muscle with increasing distension of the heart producing both an increased passive tension and active contraction as the interdigitation of actin and myosin fibres is optimized up to a point by increased stretch. Stretch on the right atrial wall also produces a small direct chronotropic effect.

The pressure-volume relation was originally described in vitro as a length-energy relationship for isolated myofibrils. The energy term is interpreted as force, tension, work, pressure or cardiac output with decreasing reliability. The length term is measured as LVEDV, LVEDP, LAP, PCWP, RAP or CVP with decreasing reliability.



b. Define preload, afterload and myocardial contractility.

preload

the wall-stress of the ventricle in diastole
a description of the filling pressure of the heart
increased by

systemic filling pressure
intravascular volume, vascular compliance
posture, activity, atrial contraction

decreased by

gravity, PEEP, IPPV, tamponade, mitral stenosis
resistance to venous return (SVR)

afterload

the wall stress of the ventricle in systole
a description of the resistance against which the heart ejects blood
increased by

diastolic pressure, SVR (major determinant normally)
aortic valve impedance
circulatory impedance: elastic vessels, blood flow characteristics
ventricular inertia

decreased by

wall thickness ($T = Pr/2h$)

contractility

the force of contraction of the ventricle independent of preload and afterload
measured as dP/dt or systolic pressure curve over a range of preloads

increased by

intracellular Ca^{2+} (digoxin, Treppe & Bainbridge effects)

intracellular cAMP (β_1 stimulation, glucagon, phosphodiesterase inh.)
thyroid hormones, histamine (minor effect)
afterload (Anrep effect)
decreased by
 ischaemia

c. Describe the factors that control preload, afterload and myocardial contractility.

The stroke volume of the ventricles depends on end diastolic and end systolic volumes. EDV ranges typically from 120 ml to 180 ml and ESV from 10 ml to 50 ml. Thus cardiac output can be at least doubled by increases in stroke volume. Increases in rate can increase cardiac output by a factor of about 3 to 4 depending on fitness.

Cardiac output is determined largely by systemic factors as the Frank-Starling mechanism ensures that in most circumstances cardiac output equals venous return. Preload is determined by total venous return (in turn determined by the autoregulation of components of the systemic circulation and dependent on metabolic activity). It is also dependent upon effective function of the atria and upon the duration of diastole to allow adequate ventricular filling.

Afterload is a function of total peripheral resistance, provided there is no local problem such as aortic valve disease. Peripheral resistance is determined by arteriolar tone, much of which is autoregulated in the splanchnic circulation under resting conditions. In exercise, a substantial fall in resistance of the circulation to skeletal muscle and in hyperthermia dilatation of skin circulation can result in a big fall in TPR and consequent rise in cardiac output in order to maintain blood pressure.

Myocardial contractility is increased by preload, heart rate (force-frequency relation), circulating catecholamines acting at cardiac β_1 -receptors and inotropic agents such as digoxin and phosphodiesterase inhibitors. It is reduced by parasympathetic tone, hypoxia, hypercapnia, acidosis, myocardial depressants and loss of myocardium.

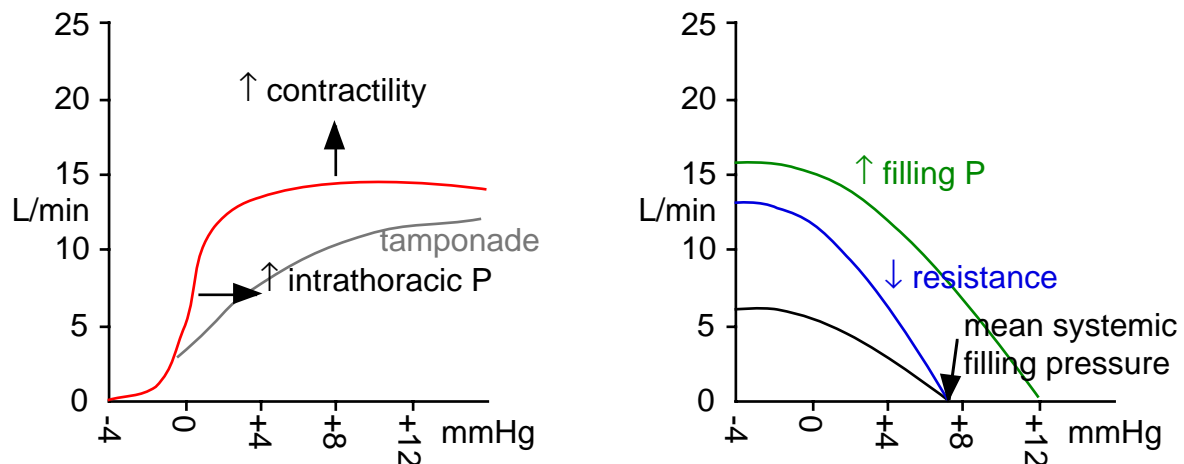
d. Describe myocardial oxygen demand and supply.

Myocardial contraction is around 20% efficient in producing physical work in pumping blood, the remainder of energy used being liberated as heat. Metabolism in cardiac muscle is almost exclusively aerobic, oxygen demand being directly related to work. The oxygen requirement is proportional to the tension-time product. Wall tension is equal to $Pr/2h$ (proportional to pressure and radius and inversely to wall thickness). Thus afterload is a major determinant of oxygen requirement as it increases the pressure derived in systole and heart rate and stroke volume are not major elements in oxygen demand.

Oxygen supply to cardiac muscle is via the coronary arteries. There is significant anatomical variation in their distribution. The usual pattern is of a right coronary supplying the right ventricle and extending around to the posterior aspect of the left ventricle and a left coronary dividing into LAD supplying the anterior of the left ventricle and a circumflex artery extending to the apex and posterior of the heart, anastomosing with the RCA territory. There is significant anastomosis of the arterial supply, allowing for retrograde perfusion in some cases of coronary stenosis or occlusion.

Resting flow is about 225 ml/min with a 70% efficiency at extracting O_2 , increasing up to about 800 ml/min in exercise. Perfusion is best in diastole, especially in the subendocardial region of the LV, where there is very little perfusion during systole.

e. Describe Guyton's cardiac output curves and explain the factors that affect them.



These are the curves for cardiac output and venous return as related to right atrial pressure. Two curves for a particular situation intersect at the cardiac output, assuming that the Frank-Starling mechanism is operating. This enables easy analysis of the effects of physiological changes which affect either curve.

The cardiac output curve shows a progressive rise in output as filling pressure rises up to a maximum level. Changes in intrathoracic pressure shift the whole curve left or right as the right atrial pressure is shifted relative to systemic venous pressure. Changes in contractility shift the maximum level of the output curve. Cardiac tamponade flattens the curve as the non-compressible fluid in the pericardial cavity makes diastolic filling unresponsive to rises in filling pressure.

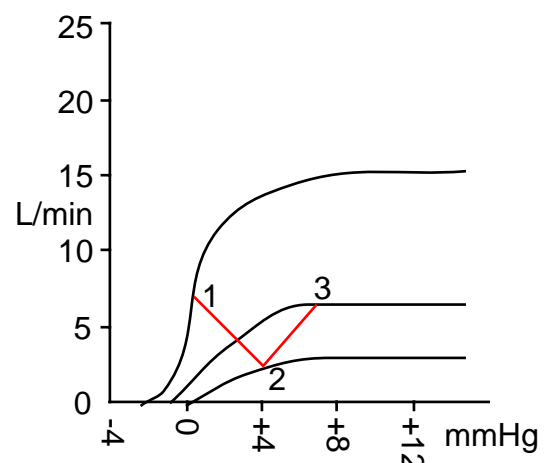
The venous return curve runs from zero where right atrial pressure is equal to systemic filling pressure back to a maximum level. Further reduction in right atrial pressure well below atmospheric pressure causes collapse of extrathoracic veins rather than any further increase in venous return. Reduced resistance to venous return, from shunting or dilatation of arteriolar or venous circulation, increases the slope of the curve. A rise in systemic filling pressure, from infusion of fluid or effective autotransfusion from vasoconstriction in response to sympathetic activity, shifts the curve up and to the right. Vasoconstriction will also increase resistance and reduce the slope of the curve.

As the cardiac output curve has quite a steep section, manipulating venous return to shift the intersection of the curves to the right can produce a very marked increase in cardiac output in the short term. Examples include transfusion, sympathomimetics and A-V shunting.

g. Describe the pressure-volume relationship of the ventricle and its clinical applications.

Acute cardiac damage from infarction or other injury results in a marked reduction in the effectiveness of contraction, with a resultant rise in right atrial pressure and fall in CO (1→2). Reflex sympathetic discharge followed by recovery (if any) and fluid retention produces a rise in contractility and in systemic filling pressure, leading to a recovery of CO at a higher right atrial (and systemic filling) pressure (2→3).

Thus a certain amount of fluid retention is adaptive in cardiac failure and is a normal response to



a fall in cardiac output. However excess fluid retention becomes maladaptive as the volume-pressure curve of the ventricle shows a fall in effectiveness of contraction at very high filling pressures, presumably as a result of distraction of actin and myosin filaments beyond their optimal interdigitation. Increased ventricular radius and wall tension also directly increases myocardial oxygen demand, further compromising the heart. Rising filling pressures lead to systemic and pulmonary oedema.

This example illustrated both the clinical usefulness of increasing circulating volume in circumstances of reduced effectiveness of contraction (AMI or spinal anaesthesia) and also of limiting circulating volume with diuretics in chronic cardiac failure.

C 4. The peripheral vascular system

a. Describe the distribution of blood volume in the various regional circulations and explain the factors that result in redistribution of blood in health and disease.

Distribution of blood volume:

| | |
|-----------------------|-----|
| Pulmonary circulation | 9% |
| Heart | 7% |
| Arteries | 13% |
| Arterioles | 2% |
| Capillaries | 5% |
| Veins | 64% |

The distribution of cardiac output to various tissues is determined largely by local factors affecting arteriolar tone and to a lesser extent by sympathetic and parasympathetic nervous activity. For laminar flow, $Q = \Delta P / R$ where R is resistance in the vessel, equal to $8\eta l / \pi r^4$. Thus:

$$Q = \frac{\pi P r^4}{8 \eta l}$$

(Poiseuille's Law)

Laminar flow occurs in situations where Reynold's number is less than 200 and turbulent flow at over 2000, with turbulent flow at branching points and other irregularities at values between 200 and 2000. Reynold's number = $vd\rho/\eta$ where ρ is density and η viscosity.

Blood flow distribution at rest:

| Tissue | %CO | ml/min | ml/min/100g | |
|---------|-----|--------|-------------|--------------|
| Brain | 14 | 700 | 50 | |
| Heart | 4 | 200 | 70 | |
| Bronchi | 2 | 100 | 25 | |
| Kidneys | 22 | 1100 | 360 | |
| Adrenal | 0.5 | 25 | 300 | |
| Liver | 27 | 1350 | 95 | (75% portal) |
| Muscle | 15 | 750 | 4 | |
| Bone | 5 | 250 | 3 | |
| Skin | 6 | 300 | 3 | |

Local control of blood flow in the short term is determined by tissue metabolism. Flow rises slower than a rise in metabolism as extraction of oxygen and nutrients is not maximal at rest. The exact mechanism of local vasodilatation is not known. Candidates as local vasodilators include adenosine (and its phosphates), CO_2 , lactate, histamine, K^+ and H^+ . It is also theorized that oxygen lack causes vasodilatation by relaxing precapillary sphincters.

These mechanisms operate from minute to minute to regulate local flow in most tissues. They also operate over a longer period after an episode of nutrient or oxygen lack, causing reactive hyperaemia after release of a tourniquet or active hyperaemia in a muscle after exercise. The net effect is a constant perfusion of most tissues at rest over a wide range of arterial pressure.

Specialized mechanism operate to regulate local flow in the renal, cerebral and coronary circulations. In the kidney, the juxtaglomerular apparatus adjusts constriction of afferent and efferent arterioles to maintain GFR. In the brain, CO_2 and H^+ ions act as potent vasodilators.

Arteriolar flow responds to local demands as a result of the release of nitric oxide (NO). Increased flow through an arteriole causes increased shearing of endothelial cells and results in the release of NO, dilating the arteriole. Many other noxious stimuli also cause the release of NO.

In the longer term, hypoxia is a stimulus for the development of new vessels in most tissues over the course of weeks and months.

b. Explain the factors which determine systemic blood pressure and its regulation.

The physiological determinant of systemic blood pressure are cardiac output and total peripheral resistance. The physical determinants are **arterial** blood volume and arterial compliance. Systemic blood pressure varies between systolic and diastolic pressures, the mean arterial pressure is the average pressure over time.

In physical terms the mean arterial pressure equals arterial volume divided by arterial compliance. Arterial volume (V_a) is determined by the cardiac output entering the arterial system (Q_h) and the peripheral flow leaving it (Q_r).

$$dV_a/dt = Q_h - Q_r$$

Peripheral resistance is defined as pressure drop divided by flow:

$$R = (P_a - P_{ra}) / Q_r$$

Compliance of the large vessels is determined by their physical composition. In the smaller arteries and arterioles, smooth muscle in the vessel walls plays a large role in determining compliance and resistance. It is defined as change in volume per unit change in pressure:

$$C_a = dV_a / dP_a$$

It is more useful in physiological terms to describe mean arterial pressure in terms of cardiac output and peripheral resistance. P_a will approach equilibrium for a given R and Q_h . The rate of approach will depend on arterial compliance:

$$dP_a/dt = (Q_h - R \cdot (P_a - P_{ra})) / C_a$$

In normal circumstances, P_{ra} is small compared with P_a . Integrating with respect to time gives an exponential equation for P_a approaching $Q_h \cdot R$ with a time constant proportional to C_a . So a non-compliant system will show rapid pressure changes in response to changes in cardiac output or peripheral resistance.

The difference between diastolic and systolic pressures is *pulse pressure*. It is determined by stroke volume and arterial compliance. As cardiac output is the product of stroke volume and heart rate, an increase in stroke volume at a fixed heart rate will increase both mean and pulse pressures. With age and atherosclerosis, arterial compliance falls, resulting in greater pulse pressure without necessarily changing mean pressure. This places greater strain on the heart as it is more efficient at volume work than pressure work.

Control in [Cardiac control](#) (1.C.5)

c. Describe total peripheral vascular resistance and the factors that affect it.

Resistance in fluid flow is defined as pressure drop per unit flow. Total peripheral resistance (R) can therefore be determined as $(P_a - P_{ra}) / Q_r$. In the systemic circulation the majority of resistance is in the arterioles. This is because of the relationship of radius to resistance in vessels:

$$R = k/r^4 \quad (k = 8\eta l/\pi)$$

Although the arterioles have a greater total cross sectional area than the large vessels, their smaller average radius more than outweighs this. In capillaries, the situation is reversed, mean radius being far smaller again, but the total number of vessels in parallel making it a low resistance section of the circulation.

Peripheral resistance is maintained largely by sympathetic tone maintaining a basal level of vasoconstriction in vascular beds in skeletal muscle and skin. Skeletal muscle constitutes the largest single vascular bed and the major determinant of total peripheral resistance. Resistance in other circulations is also partly controlled by neural factors but also by local control (especially in the brain and myocardium).

The main effect of increased sympathetic tone is vasoconstriction of the arterioles via α -receptors. Circulating adrenaline may oppose this effect by causing skeletal muscle vasodilation via β_2 -receptors at low concentrations.

Many local metabolites and transmitters affect vascular tone at a local level,

vasodilators including adenosine, H^+ , CO_2 , lactate, K^+ and phosphate, and some acting via EDRF (NO): bradykinin, histamine and leukotrienes. In anaphylaxis, sepsis or severe metabolic acidosis, circulating levels of these mediators can result in generalized vasodilation and hypotension (shock).

d. Describe the general mechanisms involved in local vascular control.

Local vasodilation results from increased metabolism via a number of mediators. The products of metabolism H^+ , CO_2 , lactate, adenosine, K^+ and phosphate all act as vasodilators, adenosine playing a key role. Oxygen may play a role as a vasoconstrictor. These factors combine to provide a negative-feedback mechanism to match blood flow and oxygen supply to tissue requirements. In the pulmonary circulation, the situation is reversed, oxygen acting as a vasodilator and CO_2 as a vasoconstrictor.

Mechanical factors play a role in local perfusion in muscle tissue. Blood flow is severely limited during contraction in both myocardial and skeletal muscle due to extrinsic compression of vessels. This effect is opposed by the myogenic mechanism in which vascular smooth muscle contracts in response to an increase in *transluminal* pressure.

Endothelium-mediated tone results in vasodilation in response to an increase in *longitudinal* pressure gradient through release of NO, allowing flow to increase with driving pressure.

e. Describe the essential features of microcirculation in relation to its structure, fluid exchange and control mechanisms present in the pre- and post-capillary sphincters.

The systemic microcirculation consists of arterioles, metarterioles, capillaries and venules. Arterioles range from $5\ \mu m$ to $100\ \mu m$ in diameter and have a media containing smooth muscle. They give rise to capillaries and metarterioles ($10\text{--}20\ \mu m$). Capillaries are around $5\ \mu m$ in diameter and $0.5\text{--}1\ mm$ long forming an interconnecting network. They rejoin to form venules.

Blood flow in the capillary network is regulated at the arteriolar-capillary junction (precapillary sphincter) and is intermittent in any one capillary, varying from zero to several mm/s. The amount of capillary flow is regulated upstream by arteriolar tone and downstream by venous pressure. Arteriolar tone responds to local factors (myogenic mechanism, EDRF, metabolites and vasodilators) and also to systemic control via sympathetic tone and circulating vasoactive mediators.

The major locally acting vasodilators are EDRF (NO) which acts via cGMP and is released in response to many agents as well as longitudinal pressure gradient and possibly PGI_2 , released in response to shear stress and acting via cAMP. Metabolites which act as direct vasodilators in adenosine, CO_2 , H^+ and K^+ .

Capillary blood has a lower haematocrit (around 15%) than arteriolar blood (more than 30%) because the obligatory cell-free boundary layer of plasma at the endothelial surface represents a significant proportion of the volume of a capillary (*Fabraeus Effect*). There is also less red cell flow into side-opening capillaries than end-opening ones with regard to arteriolar flow.

The wall of capillaries consists of a single layer of endothelial cells bounded by a basement membrane. The junctions of the endothelial cells include some pores of about $4\ nm$ which are more permeable than the rest of the lining. Some capillaries in the liver, kidney and gut have fenestrations which are large discontinuities in the endothelium covered by membrane. Pinocytotic vesicles are prominent in the endothelial cells.

The capillary wall is permeable as the function of capillaries is the transport of mediators, substrates and metabolic products to and from the periphery. Diffusion is the major transport mechanism across the capillary wall. The rate of diffusion of a substance (J) is described:

$$J = -PS \cdot (C_o - C_i)$$

Where P is the capillary permeability, S the surface area and $C_o - C_i$ the

concentration gradient. For small molecules and ions and highly lipid-soluble molecules, the capillary permeability is very high and their transport across the membrane is flow-limited. For lipid insoluble molecules, permeability falls rapidly with molecular size to almost zero at 60 kd. Thus albumin, being polar and over 60kd, shows negligible diffusion.

The equilibration of ions and molecules across the membrane is complicated somewhat by the presence of non-diffusible charged molecules such as albumin because of the Gibbs-Donnan effect.

Though most of the water movement across the capillary membrane is a result of diffusion, the net water flow is determined by capillary filtration. Water filtration or absorption across the membrane depends on the net pressure across the membrane. The components of the net pressure are hydrostatic pressure and oncotic pressure. Hydrostatic pressure within the capillary ranges from around 32 mmHg at the arterial end to 15 mmHg at the venous end. Tissue hydrostatic pressure is between -1 and -7 mmHg.

The oncotic pressure (π) depends on the concentration of non-diffusible solute (mainly albumin) and its reflection coefficient (σ , close to 1 for albumin) and absolute temperature:

$$\pi = \sigma RT \cdot (C_i - C_o) \quad (R = \text{gas constant})$$

The net water flow by filtration depends on the total pressure gradient and the filtration constant for water across the membrane (k):

$$\text{flow} = k \cdot [(P_c + \pi_i) - (P_i + \pi_p)]$$

Total flow is also proportional to the area of membrane and inversely proportional to the viscosity of water and thickness of the membrane.

In most tissues, the net flow of water out of capillaries is small, as the hydrostatic gradient from the arterial to venous end of the capillaries ensures that the rate of water loss at the arterial end is almost balanced by the water absorption at the venous end. In the glomerulus, a high hydrostatic pressure ensures filtration over the whole capillary length whereas in the intestinal mucosa, a high plasma oncotic pressure results in absorption over the entire length.

This mechanism also acts to compensate for blood loss. A fall in both arterial and venous pressure results in a lower hydrostatic pressure over the whole capillary length and consequent absorption of water from the interstitial compartment into the circulation. Similarly, a rise in venous and arterial pressures, though initially partly compensated for by increased arteriolar tone, results in extravasation of fluid: oedema. Net loss of fluid and albumin is dealt with by the lymphatics which ultimately return them to the circulation.

The last mechanism by which molecules are transferred across the capillary membrane is by pinocytosis. Small amounts of large molecules which are otherwise non-diffusible can be transferred in these vesicles.

C 5. Control of circulation

a. Describe the role of the vasomotor centre and the autonomic nervous system in the regulation of cardiac output and venous return.

The peripheral vasculature is innervated by the sympathetic nervous system, from fibres of the coeliac plexus in the abdominal viscera and from fibres from the sympathetic chain in the somatic circulation. Sympathetic activity also causes the release of systemic adrenaline and noradrenaline which act on the circulation as circulating factors. Parasympathetic innervation is significant only in the vagal innervation of the heart, where stimulation produces a reduction in rate, transmission and contractility.

Integration of the autonomic control of circulation takes place in the vasomotor centre in the medulla and lower third of the pons. Within the vasomotor centre lies the vasoconstrictor centre, anterolateral in the upper medulla, which stimulates sympathetic vasoconstrictor fibres via noradrenergic transmission. The vasodilator area lies anterolaterally in the lower medulla and acts to inhibit the vasoconstrictor area. A sensory area lies posterolaterally in the medulla and receives projections from the vagus and glossopharyngeal nerves. It projects to the vasoconstrictor and vasodilator areas and produces the baroreceptor reflex.

In the resting state there is a baseline discharge throughout the sympathetic vasoconstrictor fibres, producing vasomotor tone which is partially responsible for maintaining arterial pressure. There is also baseline tone in the sympathetic and parasympathetic innervation of the heart. Many higher centres affect activity of the vasomotor centre, especially the hypothalamus.

The vasomotor centre acts to compensate rapidly for changes in blood pressure. A fall in blood pressure, increased motor activity or a fright generates a rapid response inhibiting parasympathetic outflow, increasing sympathetic vasoconstrictor tone and releasing adrenal hormones. This produces a rise in heart rate and contractility, arteriolar constriction which increases blood pressure, and increased venous tone which increases venous return and EDV. These effects can double arterial pressure within 5 to 10 seconds. The reverse effects are produced by reducing sympathetic tone (as in spinal anaesthesia).

b. Describe the functions of baroreceptors and relate this knowledge to clinical situations.

Baroreceptors are pressure-sensitive nerve endings in the major arteries of the neck and thorax. They are particularly prominent in the carotid sinus and the aortic arch. Signals from the carotid sinuses are transmitted via Hering's nerve and IX to the tractus solitarius in the medulla. Signals from the arch of the aorta go via X to the same projection.

The firing rate from baroreceptors is extremely responsive to arterial pressure in the normal range, varying markedly from diastole to systole. They respond to both arterial pressure and the rate of rise in arterial pressure. They accommodate rapidly to changes in the baseline blood pressure. Baroreceptor firing has a strong inhibitory effect on the vasoconstrictor centre, so any sudden fall in arterial pressure (for example, from standing up), results immediately in an autonomic response to increase CO and TPR. The carotid sinus receptors have a stronger influence on the vasoconstrictor centre than those of the aortic arch.

Baroreceptors are required for the reflex responses to short-term changes in blood pressure. This is required for normal response to changes in posture and in theatre for normal response to hypotension resulting from hypovolaemia. They adapt rapidly to sustained changes in blood pressure and become less sensitive due to reduced vessel wall compliance in long-standing hypertension.

External pressure on the carotid sinus particularly can cause a marked fall in blood pressure and heart rate. This is used clinically in cases of SVT or rapid AF and is also described as causing syncope in some individuals with tight collars.

The cardiopulmonary baroreceptors are found in the atria, ventricles and pulmonary vessels. The atrial receptors are divided into A-receptors which respond to atrial tension during systole and B-receptors which respond to wall tension during atrial filling. Stimulation of these receptors results in secretion of ANF and decreased sympathetic outflow to the kidneys, increasing RBF and urine output as well as decreased sympathetic tone to the heart. ANF inhibits the release of ADH, renin and aldosterone. These effects are important in the regulation of plasma volume and blood pressure over hours to days.

c. Explain the role of the autonomic nervous system in controlling systemic vascular resistance and redistribution of blood volume.

Sympathetic innervation of the blood vessels and the adrenals plays a major role in the regulation of TPR and volume distribution. Baseline tone in sympathetic outflow from the vasoconstrictor centre maintains arteriolar and venous tone which maintain systemic blood pressure.

An increase in sympathetic tone, as a result of stimulation of the vasoconstrictor centre, results in increased arteriolar tone, increasing TPR and blood pressure and also in increased venous tone, reducing venous capacitance, rapidly increasing venous return and EDV in the short term, thus boosting CO.

Circulating noradrenaline from the adrenals acts on α receptors in vessels to produce vasoconstriction. Adrenaline at low concentrations acts on β receptors in skeletal muscle, producing vasodilatation, but at higher concentrations, its α effects predominate.

The vascular beds which are most responsive to changes in sympathetic tone are skeletal muscle and skin. Skeletal muscle overall constitutes the largest vascular bed and plays a major role in determining TPR. The splanchnic and renal circulations are less responsive to sympathetic tone and the cardiac and cerebral hardly at all.

d. Explain the neural and humoral regulation of blood volume.

Effective blood volume is affected by the compliance of the venous side of the circulation. This is reduced with an increase in sympathetic tone or by circulating α agonists resulting in increased filling pressure and increased cardiac output.

True blood volume is determined by net loss or gain from the intravascular compartment. Volume gain can result from oral fluid intake, intravenous infusion and to a minor extent from products of metabolism. Volume loss can result from bleeding, evaporative loss in expired air, secretion as sweat and enteric losses from malabsorption. Redistribution between intravascular and interstitial spaces can result from changes in hydrostatic or osmotic pressures detailed above.

Circulating volume is maintained within narrow bounds by renal loss or retention of fluid and to some extent by the hypothalamic stimulus of thirst.

Renal blood flow and consequently GFR is determined by the afferent and efferent arteriolar tone at the glomerulus, given an adequate systemic blood pressure. The main external control of renal arteriolar tone is via sympathetic innervation. An increase in stimulation of atrial baroreceptors results in a reduction in renal sympathetic tone, causing increased RBF and GFR.

e. Explain the integrated cardiovascular responses to exercise.

The response to exercise consists of central, local and baroreceptor responses. The central response starts in anticipation of exercise with inhibition of vagal output and increased sympathetic tone resulting in an increase in heart rate and contractility before exercise begins. Increased sympathetic tone also causes vasoconstriction of skin, splanchnic and renal vascular beds.

Local responses in muscle are due to local contraction and metabolites stimulating mechanoreceptors and chemoreceptors which are carried to the medulla in

type III and IV nerve fibres and result in increased sympathetic tone. The local effects of metabolites and the myogenic response are also important in increasing blood flow to working muscle. Myocardial blood flow also increases with cardiac output in response to local control of coronary vessel tone.

The baroreceptor response helps maintain sympathetic-mediated vasoconstriction of inactive beds and cardiac sympathetic outflow to maintain blood pressure. The arterial chemoreceptors play no role in exercise as arterial gases and pH are usually unchanged.

With prolonged exercise, body temperature rises and so skin vessels dilate to maintain temperature homeostasis. Local metabolites become the major determinant of active muscle vasodilation and muscle blood flow rises to a maximum of 15 to 20 times resting flow. There is still some vasoconstrictor effect from sympathetic innervation even in active muscle. Vasodilation increases capillary hydrostatic pressure and causes increased fluid movement into active tissues and increased lymphatic return. Acidosis, increased temperature and increased O_2 demand and CO_2 production in muscle move the Hb- O_2 dissociation curve to the right, enhancing O_2 extraction and lowering mixed venous PO_2 . Oxygen consumption rises to 60 times resting values.

The cardiac response to exercise is an almost linear rise in CO with workload. This is achieved mainly through a rise in heart rate to a maximum of about 180/min, accompanied by a smaller increase in stroke volume of 10%-35% depending on the level of training. The rise in CO is to a maximum of between four and six times resting output and is the limiting factor in heavy exercise.

Venous return is enhanced by the skeletal muscle pump, by reduced venous compliance with higher sympathetic tone and by the increase in respiratory effort. Blood volume is usually slightly reduced because of fluid losses into tissue, as sweat and in exhaled air. This is opposed to some extent by the increased osmotic effect of metabolites and the rise in tissue hydrostatic pressure. Renal blood flow and urine output is reduced.

There is usually a small rise in blood pressure and pulse pressure as the rise in CO is usually greater than the fall in TPR.

At the extreme of exercise, stroke volume and blood pressure fall, sympathetic tone causes cutaneous vasoconstriction resulting in a rise in temperature and blood pH begins to fall and PCO_2 to rise. These changes usually cause sufficient distress to limit exercise, but if it continues, the rise in body temperature can cause rhabdomyolysis and renal failure.

After exercise, sympathetic outflow falls abruptly, resulting in a fall in CO and BP as TPR remains low due to accumulated metabolites. This is corrected by the baroreceptor reflex.

f. Explain the integrated cardiovascular responses to pregnancy.

g. Explain the integrated cardiovascular responses to anaesthesia and regional anaesthesia/analgesia.

C. 6. Regional Circulation

a. Describe the relationship between organ blood flow and demand and the role of autoregulation.

metabolic autoregulation

products of metabolism act as vasodilators

adenosine, PGs, H^+ , CO_2 , K^+ , lactate, osmolarity...

duration of vasodilation after ischaemia depends on the duration of ischaemia

myogenic autoregulation

vascular smooth muscle contracts in response to stretch

prominent in cerebral circulation

acts over seconds

endothelium-mediated autoregulation

longitudinal shear (or flow) causes NO release from endothelium

results in \uparrow cGMP and dephosphorylation of MLCK

vascular relaxation

neural control

α receptor stimulation

\uparrow intracellular Ca^{2+} , vasoconstriction

predominantly in skin and gut

increases O_2 extraction

O_2 extraction remains constant

until critical flow is reached

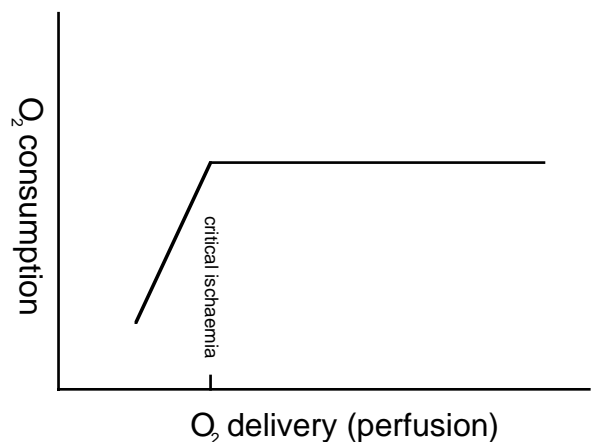
β_2 receptor stimulation

\uparrow intracellular cAMP, vasodilation

predominantly in muscle

5HT, other innervation

specialized role, active in cerebral and coronary circulations



b. Describe the features of the coronary circulation and explain the clinical significance of these.

The coronary circulation consists of the coronary arteries and veins, the arteriosinusoidal, arterioluminal and thebesian vessels. The right and left coronary arteries arise from the root of the aorta behind the right and left cusps of the aortic valve. The right coronary runs along the right A-V margin and supplies the right atrium and ventricle. The left coronary divides near its origin into the circumflex and left anterior descending arteries. They supply the left side of the heart and commonly a little of the right ventricle. Dominance of the coronary vessels is variable.

The arteriosinusoidal vessels originate from the cardiac chambers and penetrate a short distance into the myocardium where they form endothelium-lined sinuses. The arterioluminal vessels similarly arise from the chambers and the thebesian vessels are veins which drain the myocardium into the chambers. These vessels all play a minor role in supplying myocardial oxygen demands.

The major venous drainage of the heart is via the coronary veins which follow a similar distribution to the arteries except that their common drainage is to the coronary sinus on the posterior aspect of the heart, draining into the right atrium.

There is no significant anastomosis between coronary vessels in normal human hearts. Anastomoses will develop in response to gradual stenosis and occlusion of the coronary vessels but acute obstruction will result in infarction.

Cardiac muscle consumes 8-10 ml/min/100 g of oxygen at rest. O_2 extraction is quite efficient with cardiac venous blood having about 5 ml/100 ml O_2 . Thus any rise in myocardial activity must be accompanied by an increase in blood flow. As a pump it is about 18% efficient (net), but is more efficient at volume work than pressure work. This is

important in aortic stenosis and other high afterload conditions. Myocardium uses both carbohydrate and fatty acids as substrates for energy production and will use ketone bodies or lactate if they are present in high concentrations. Metabolism is aerobic in all but extreme conditions.

The coronary arteries display the same autoregulatory responses as other systemic vascular beds. Local factors are most important in regulating coronary flow. The coronary vessels are best perfused in diastole, as they are not externally compressed by ventricular contraction at this time. The left coronary displays no or retrograde flow at the start of systole as the ventricular pressure compressing the vessels is greater than aortic pressure perfusing them. Later in systole there is anterograde flow which increases dramatically after aortic valve closure and ventricular relaxation when the perfusion pressure is high and external pressure low. The coronary vessels display a very active myogenic mechanism. Right coronary artery flow is more consistent as the right ventricular pressure is lower than aortic pressure throughout the cardiac cycle.

The advantageous perfusion gradient in diastole can be enhanced further by use of an intraaortic balloon pumps. In severe hypotension, perfusion of the endocardial muscle layers is poorest, and this is the site of worst ischaemic damage following hypotension. In tachycardia, the time for perfusion in diastole is reduced, but coronary dilatation from local metabolites is sufficient to maintain perfusion.

Sympathetic innervation of the coronary vessels has a vasoconstrictor effect in isolation, but the increased CO and metabolic demand resulting from the inotropic and chronotropic effects of increased sympathetic tone result in net vasodilation in normal hearts.

c. Describe autoregulation in the cerebral circulation and the factors that may affect it.

in [Nervous system \(1.G\)](#)

d. Describe the renal circulation and explain its significance in maintaining renal function.

anatomy

- renal arteries from aorta
- interlobar, arcuate, cortical radial arteries
- afferent arterioles, glomerular capillaries, efferent arterioles
- peritubular capillaries (including *vasa recta*)
- progressive rejoining to form renal veins → IVC

renal blood flow

20% of cardiac output

dependent on CO, MAP and

low net O₂ extraction

most O₂ demand is in tubular reabsorption

countercurrent mechanism of *vasa recta* reduces medullary PO₂ to ≈20 mmHg

↑ filtrate flow → ↑ metabolic demand → medullary hypoxia

opposed by tubuloglomerular feedback

↑ macula densa flow → adenosine release → ↓ GFR

limits O₂ demand of tubules

analogous to metabolic autoregulation in other tissues

anuria is adaptive in acute stress

e. Describe the hepatic and splanchnic circulation.

anatomy

aorta → coeliac axis, superior and inferior mesenteric arteries → gut

villous countercurrent flow results in better absorption but reduced PO₂ at villus tips

→ portal venous drainage → liver → hepatic vein → IVC
blood flow
hepatic artery supplies $\frac{1}{3}$ of liver flow but 50% of oxygen delivery
portal flow supplies the remainder, total 30% of CO
oxygen extraction is constant down to a level of critical ischaemia
gut ischaemia results in bacterial translocation
hepatic failure (ischaemia) allows endotoxin to circulate
lack of monitoring options has hampered investigation of gut perfusion

f. Describe the skin circulation.

g. Describe skeletal muscle circulation.

h. Describe uteroplacental circulation.

in [Maternal physiology \(1.O\)](#).

C 7. Applied aspects of CVS physiology

a. Describe the responses to changes in posture.

standing

- venous pooling in legs and abdomen (less effect if active)
 - ↓ right heart venous return
 - ↓ right and left heart output
 - ↓ BP (also hydrostatic effect due to carotid sinus being above heart)
 - ↓ baroreceptor firing
- ↑ sympathetic tone
 - peripheral arteriolar and venous constriction
 - ↑ HR, contractility
- maintains cerebral perfusion
(or else fainting → horizontal posture)

b. Account for the cardiovascular changes seen in haemorrhage and hypovolaemia.

haemodynamic

- ↓ filling pressure
- ↓ stroke volume
- ↓ CO
- ↓ MAP

baroreceptor (response maximal at MAP 60 mmHg)

- ↓ stimulation at carotid sinus and aortic receptors
- ↓ vagal tone, ↑ sympathetic tone
 - ↑ HR, contractility
 - peripheral vasoconstriction
 - ↑ SVR, filling pressure
 - centralized blood volume

chemoreceptor

- some augmentation of sympathetic response below MAP 60 mmHg
- hypoxia, hypercapnia, acidosis stimulate carotid and aortic bodies
 - ↑ sympathetic tone
 - ↑ respiratory drive
 - minor increase in venous return

cerebral ischaemic response

- further augmentation of sympathetic tone below MAP 40 mmHg
- also ↑ vagal tone (maladaptive)

autoregulatory vascular response

- arteriolar constriction due to myogenic mechanism

reabsorption of tissue fluids

- ↓ capillary hydrostatic pressure
- reversed Starling forces
 - transfer of fluid from interstitium into circulation
 - up to 1 l/h
- transfer from ICF to interstitial fluid also occurs in response to cortisol

endogenous vasoconstrictors

- adrenaline and noradrenaline
 - from adrenal medulla and sympathetic nerves
 - responsible for acute sympathetic response

ADH

- rapid secretion from posterior pituitary in response to hypotension
- vasoconstrictor, ↑ water reabsorption from collecting ducts
- ↑ expression of vWF, VIII_c

renin

catalyzes conversion of angiotensinogen to angiotensin I

angiotensin II

vasoconstrictor

↑ ADH, aldosterone

renal conservation of fluid

low MAP reduces RBF, GFR and UO

↑ sympathetic tone causes

afferent and efferent constriction

↓ RBF, GFR

↑ renin secretion (direct and via JGA)

↑ angiotensin II causes

↑ Na⁺ reabsorption

arteriolar vasoconstriction

↑ aldosterone causes

↑ Na⁺ reabsorption from DCT and collecting ducts

ADH above

↓ ANF (minor effect)

timecourse

seconds

baroreceptor, chemoreceptor, cerebral ischaemic responses

minutes

autoregulatory, angiotensin, ADH, capillary fluid shift

hours

full effect of renal fluid retention

C 8. Measurement of CVS function

a. Outline the physics of blood flow.

b. Give a detailed account of the various methods of measuring blood pressure.

in [Physics and Measurement \(1.R\)](#).

c. Explain the various methods of measuring cardiac output as well as their limitations.

Fick principle (Adolph Fick)

pulmonary venous oxygen flux (q_3) equals pulmonary arterial oxygen flux (q_1) plus alveolar oxygen uptake (q_2)

$$\begin{aligned}q_1 + q_2 &= q_3 \\q_1 &= Q [O_2]_{pa} \\q_3 &= Q [O_2]_{pv} \\ \Rightarrow Q &= q_2 \div ([O_2]_{pv} - [O_2]_{pa})\end{aligned}$$

so cardiac output (Q) can be calculated from pulmonary O_2 uptake, and mixed venous and pulmonary venous oxygen concentrations.

Mixed venous oxygen concentration can be measured using a Swan-Ganz catheter and pulmonary venous oxygen concentration approximated with a systemic arterial sample.

This method requires determination of oxygen uptake over several minutes and so requires either a completely closed breathing circuit in anaesthesia or an approximation using mixed expired and inspired oxygen concentrations or a laboratory setting.

Indicator dilution

A known amount of an indicator is introduced into the circulation at a point where the entire cardiac output is passing.

The concentration of the marker is measured downstream before any of the flow is diverted to other vessels and its value is plotted over time. For example, the indicator might be injected in the right atrium and the sampling done from the pulmonary outflow tract.

The amount of indicator (n) is related to its mean concentration (\bar{c}), cardiac output (Q) and the time for which it is detected ($t_2 - t_1$):

$$\begin{aligned}n &= \bar{c} \dot{Q} (t_2 - t_1) \\ \bar{c} &= \frac{\int c \, dt}{t_2 - t_1} \\ \Rightarrow \dot{Q} &= \frac{n}{\int c \, dt}\end{aligned}$$

The conventional expression is in the Stewart-Hamilton equation:

$$\dot{Q} = \frac{n}{\int c \, dt} = \frac{k(T_{\text{core}} - T_{\text{indicator}})V_{\text{indicator}}}{\int_{t_1}^{t_2} -\Delta T \, dt}$$

This can be done using a dye indicator (which requires a semi-log plot to determine t_2 when recirculation occurs) or more commonly using cold saline with temperature being the “indicator”. There is an inherent inaccuracy in thermodilution when thermal exchange occurs between the blood and the vessel and structures surrounding it and when cool fluids may be being infused peripherally in a variable fashion.

Echocardiography

Cardiac output (\dot{Q}) can be calculated using the TOE probe to measure cross-sectional area (A) and flow velocity (V) over the duration of one cardiac cycle (t) at a point where the entire cardiac output is passing (e.g. pulmonary outflow tract).

$$\bar{V} = \frac{\int V \, dt}{t}$$

$$\dot{Q} = A \times \bar{V}$$

This method assumes equal flow over the whole area and it is technically difficult to perform.

d. Outline methods and principles used to measure regional blood flow.

hepatic

Fick principle with indocyanine green

cerebral

Kety-Schmidt technique

renal

PAH clearance

D. Renal physiology

a. Describe the functional anatomy of the kidneys and explain the physiology of renal blood flow.

The kidneys are paired organs located in the retroperitoneum. Each consists of a cortex, medulla and pelvis which is connected to the ureter which carries urine from the kidney to the bladder. Each kidney is supplied by a renal artery from the aorta and drained by one or more renal veins to the IVC. The medulla consists of papillae which correspond with the calyces of the collecting system. The medulla and cortex above each papilla compose a lobe.

Innervation of the kidney is by sympathetic noradrenergic nerves.

The renal artery divides into interlobar and then arcuate arteries. These divide into cortical radial arteries which run radially towards the cortical surface. Perpendicular to the cortical radial arteries arise the afferent arterioles, each of which supplies a glomerulus. The afferent arteriole is muscular and regulates flow into the glomerulus.

The glomerulus consists of a group of specialized capillaries, having fenestrated endothelium, a narrow basement membrane and a surrounding of podocytes, all of which allow filtration of fluid into the space surrounding the capillary tuft: Bowman's space.

The glomerulus is drained by the efferent arteriole which plays a regulatory role like the afferent arteriole. It supplies the peritubular capillaries which surround the cortical tubules and also vascular bundles which extend into the medulla and surround the loops of Henle (the descending and ascending *vasa recta*).

Total renal blood flow (RBF) is 1.1 l/min (20% of CO)

RBF

determined by MAP and renal vascular resistance
autoregulating over a wide MAP (90 to 200 mmHg)

myogenic mechanism

tubuloglomerular feedback

high Na^+ and Cl^- at macula densa stimulates adenosine production

↓ by constriction of either afferent or efferent arteriole

sympathetic tone (noradrenaline)

angiotensin II

response to macula densa or direct effect of flow on granular cells or
sympathetic stimulation of granular cells to increase renin secretion
from granular cells

adenosine

local mediator from JGA

afferent constrictor, efferent dilator

ADH in high concentrations

possibly thromboxanes, leukotrienes, endothelin

opposed by

renal PGE_2 and PGI_2 release

ANF from heart (afferent dilator, efferent constrictor)

possibly dopamine, bradykinin

90% to cortex, 10% to medulla

b. Describe glomerular filtration and tubular function.

Glomerular filtration

bulk flow of fluid from glomerular capillary to Bowman's space

volume = 20% of RPF (filtration fraction), ≈ 125 ml/min

barriers to filtration

endothelial fenestrae

basement membrane

podocytes

all negatively charged

composition

- water
- freely filtered solutes
 - small, unbound ions and molecules
- partly filtered solutes
 - macromolecules MW 7000 to 70000
 - less filtration if negatively charged
 - dextran 70 5-10%, albumin 0.02%

$GFR = K_f \cdot NFP$ (filtration coefficient x net filtration pressure)

$NFP = (P_{GC} + \Pi_{BC}) - (P_{BC} + \Pi_{GC})$

in capillary transit

- $\Pi_{BC} = 0$, P_{GC} and P_{BC} change little, Π_{GC} rises from 21 to 33 mmHg
- NFP falls from 24 to 10 mmHg

determinants

K_f

- decreased in disease (\downarrow glomerular surface area)

P_{GC}

- \uparrow MAP, efferent constriction
- \downarrow afferent constriction

P_{BC}

- \uparrow obstruction

Π_{GC}

- \uparrow plasma oncotic pressure, low RBF

Tubular functions

mechanisms

diffusion

- simple transfer of a substance across the tubular epithelium down its electrochemical gradient
- small lipid-soluble molecules diffuse through membranes
- ions diffuse through channels

facilitated diffusion

- transfer of molecules across the tubular epithelium down a electrochemical gradient via specific transmembrane proteins which bind and release the substrate
- displays saturability, specificity and competition

primary active transport

- transfer of ions or molecules against their electrochemical gradient via a specific transmembrane protein which consumes ATP
- four identified transporters: $Na^+ - K^+$, H^+ , $H^+ - K^+$ and Ca^{2+} -ATPase

secondary active transport

- transfer of multiple ions or molecules across a membrane by a specific transmembrane protein in which one substrate is transported down its electrochemical gradient, providing energy for the transport of the other substrates against their electrochemical gradients
- classified as cotransport or countertransport according to whether substrates travel in the same or opposite directions

endocytosis

- uptake of large molecules by invagination of the cell membrane, forming vesicles

solvent drag

- transfer of small ions or molecules by mass movement of water (solvent) through pores

sites of transport

basolateral membrane

- the only site of primary active transport

luminal membrane

site of diffusion, facilitated diffusion and secondary active transport

paracellular

diffusion across tight junctions between cells

site of Na^+ and Cl^- diffusion in parts of the tubule

c. Explain the countercurrent mechanisms in the kidney.

The loop of Henle maintains a high tissue osmolarity in the renal medulla, allowing for reabsorption of water and the production of a concentrated urine. It uses a countercurrent multiplier.

loop of Henle

descending limb

high permeability to water

low permeability to Na^+ and Cl^-

water reabsorption due to high tissue osmolarity

secondary to NaCl

reabsorption in

ascending limb

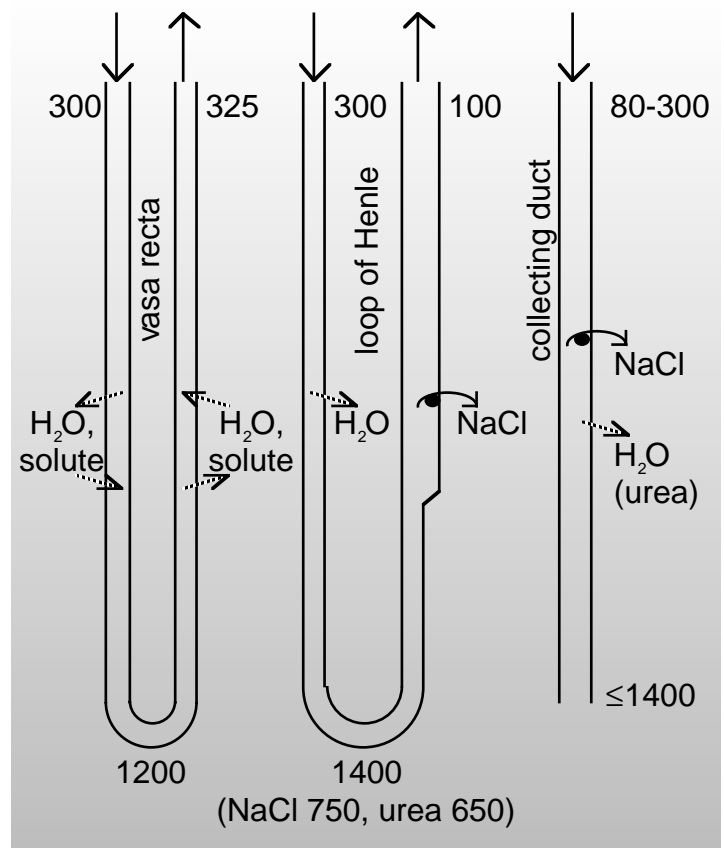
ascending limb

low permeability to water

high permeability to Na^+ and Cl^-

active reabsorption of NaCl in thick limb and passive in thin limb

a small gradient across the tubule is multiplied by the flow through the loop to produce a high tissue osmolarity in the medulla and a hypoosmotic tubular fluid at the distal end of the loop



vasa recta

medullary blood vessels travel parallel to the loop of Henle

start in cortex, run straight to medulla and return to cortex

this allows for countercurrent exchange to produce a high plasma osmolarity in the medullary part of the vasa recta and a return to close to normal on returning to the cortex

there is an overall increase in osmolarity of plasma in the vasa recta due to reabsorption of NaCl (and urea)

collecting ducts

run from cortex to medulla

variable permeability to water

increased by ADH

receive hypotonic or isotonic fluid

actively reabsorb NaCl in the cortex according to ADH and aldosterone levels

passively reabsorb water (and urea) from the medullary collecting duct due to the high tissue osmolarity (maintained by the ascending loop)

d. Explain the mechanisms involved in the regulation of renal function.

local

autoregulation

constriction of afferent arterioles maintains constant RBF for MAP 80-200 mmHg

myogenic mechanism

tubuloglomerular feedback

↑ GFR

↑ NaCl concentration at end of loop

↑ NaCl uptake by macula densa

release of adenosine

afferent constriction, efferent dilation

↓ GFR and RBF

glomerulotubular balance

reabsorption of Na⁺ is a roughly constant proportion of GFR

↑ GFR → ↑ reabsorption of Na⁺ and water in PCT

tends to stabilize tubular flow over changes in GFR

neurological

sympathetic

response to hypotension (baroreceptor), hypoxia, acidosis or stress

noradrenergic sympathetic innervation (and circulating adrenaline)

β₁ adrenergic response of granular cells

↑ renin release

α₁ adrenergic response in PCT

↑ Na⁺ reabsorption

α adrenergic vasoconstrictor response in afferent and efferent arterioles

↓ RBF, GFR

endocrine

renin

enzyme cleaved from prorenin in granular cells

released controlled by

afferent arteriolar baroreceptors (hypotension)

macula densa (↓ NaCl uptake)

sympathetic response

angiotensin II, ANF (inhibition)

cleaves circulating angiotensinogen to angiotensin I

angiotensin II

octapeptide cleaved by ACE from angiotensin I

acts at AT₁ and AT₂ receptors

vasoconstrictor of renal and other arterioles

efferent > afferent constriction (↑ K_p)

increases release of aldosterone and ADH

directly increases Na⁺ reabsorption

increases sympathetic activity

increases thirst

prostaglandins PGE₂ and PGI₂

synthesized and released in response to

sympathetic activity

angiotensin II

vasodilators limiting the local action of vasoconstrictors

ANF

peptide hormone

released from atrial cardiac muscle in response to dilation

actions (via cGMP)

↓ Na⁺ reabsorption in collecting ducts

afferent vasodilator, efferent vasoconstrictor in kidney (↑ GFR)

increases plasma filtration as lymph in spleen

↓ aldosterone, renin, ADH release

aldosterone

steroid hormone produced by *zona glomerulosa* of the adrenal cortex
released in response to

ACTH

↑ plasma K^+

angiotensin II

inhibited by ANF

acts on collecting ducts

↑ Na^+ reabsorption

↓ K^+ reabsorption

↑ H^+ secretion

also acts on all other sites of Na^+ transport (sweat, gut etc.)

ADH

peptide hormone synthesized in supraoptic and paraventricular nuclei

released from posterior pituitary neurones in response to

hypotension (7-10% volume change → low pressure baroreceptors)

↑ osmolarity (change of 1-2%)

overcome by volume effect

angiotensin II

sympathetic activity, stress

drugs (chlorpropamide, barbiturates)

actions

V_1

vasoconstrictor acting on smooth muscle

V_2

↓ collecting duct permeability to water (via ↑ cAMP)

results in insertion of aquaporin 2 in membrane

↑ release of $VIII_c$ and vWF

other vasoactive agents at the kidney (role uncertain)

TXA_2 , leukotrienes, endothelin, dopamine, bradykinin, many others

e. Outline the endocrine functions of the kidney.

Functions of the kidney

regulation of water and ion balance

removal and excretion of metabolic waste products from the blood

removal and excretion of foreign chemicals from the blood

gluconeogenesis

endocrine functions

renin secretion

from granular cells of the JGA

converts circulating angiotensinogen to angiotensin I

rate limiting step in production of angiotensin II

erythropoietin secretion

glycoprotein hormone (168 amino-acids, 4 sugar residues)

produced in interstitial renal cells

$t^{1/2}$ 5 h

release stimulated by renal hypoxaemia or hypoperfusion

stimulates maturation of erythroid precursors in bone marrow

1,25-dihydroxyvitamin D production

produced by 1-hydroxylation of 25-hydroxyvitamin D

produced in proximal tubule cells

synthesis stimulated by PTH

rate-limiting step in production of active $1,25-(OH)_2D_3$

acts to increase plasma Ca^{2+}

\uparrow bone resorption
 \uparrow tubular Ca^{2+} resorption
 \uparrow intestinal Ca^{2+} absorption
 also \uparrow tubular phosphate resorption (antagonized by PTH)

f. Describe the role of the kidneys in the maintenance of acid-base balance.

H^+ ion regulation

increased by

gain in CO_2 from metabolism
 non-volatile acids from metabolism of protein and other molecules
 loss of HCO_3^- in GIT fluid or urine

decreased by

loss of CO_2 in lungs
 metabolism of organic anions (e.g. lactate)
 loss of H^+ in GIT fluid or urine

normal determinant of H^+ flux is diet: high protein \rightarrow acid load

H^+ concentration (pH) is controlled by buffering

intracellular phosphate and proteins (greatest capacity)
 extracellular $\text{HCO}_3^-/\text{CO}_2$ (precise control)

PCO_2 controlled by respiratory system

HCO_3^- regulated by kidneys

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 \text{ PCO}_2}$$

mechanism

HCO_3^- filtered at glomerulus

actively reabsorbed in PCT (80%), ascending loop (15%) and collecting ducts

type A intercalated cells

secrete H^+ into lumen

active H^+ ATPase pump in luminal membrane

Na^+/H^+ countertransport in PCT and loop

H^+/K^+ ATPase in collecting ducts

produce HCO_3^- from CO_2 and OH^- via carbonic anhydrase

HCO_3^- moves into blood via Na^+ cotransport or Cl^- countertransport

luminal H^+ combines with HCO_3^- to form CO_2 which diffuses into cells

H^+ secretion is increased by high PCO_2 and low pH independently

minimal active HCO_3^- secretion by type B intercalated cells in collecting ducts

increased in alkalosis (?mechanism ?importance)

some secreted H^+ in collecting ducts is lost in urine, causing net addition of HCO_3^- to blood

H^+ combines with HPO_4^{2-} and may be excreted in urine

75% of HPO_4^{2-} is reabsorbed

other anions and buffers also contribute to H^+ loss

e.g. β -hydroxybutyrate or acetoacetate in DKA

bound H^+ excreted in this way is "titratable acid"

glutamine is catabolized in PCT

glutamine $\rightarrow 2 \text{NH}_4^+ + 2 \text{HCO}_3^-$

with secretion of NH_4^+ into lumen and HCO_3^- into blood

NH_4^+ mostly ends up being excreted in urine

catabolism increased in acidosis

reabsorption reduced in acidosis

compensation for acid-base disorders

respiratory

acidosis

high CO_2 and low pH

$\uparrow \text{NH}_4^+$ secretion

full HCO_3^- reabsorption (increased H^+ secretion)

\uparrow titratable acid

alkalosis

low CO_2 and high pH

$\downarrow \text{NH}_4^+$ secretion

$\downarrow \text{H}^+$ secretion causes HCO_3^- loss

no titratable acid

($\uparrow \text{HCO}_3^-$ secretion)

metabolic

acidosis

low pH and low CO_2 (low HCO_3^-)

\downarrow filtered load of HCO_3^-

full HCO_3^- reabsorption despite $\downarrow \text{H}^+$ secretion

$\uparrow \text{NH}_4^+$ secretion

\uparrow titratable acid

alkalosis

high pH and high CO_2 (high HCO_3^-)

\uparrow filtered load of HCO_3^-

HCO_3^- loss despite $\uparrow \text{H}^+$ secretion

$\downarrow \text{NH}_4^+$ secretion

($\uparrow \text{HCO}_3^-$ secretion)

generation of acid-base disorders

hypovolaemia

\uparrow aldosterone

Na^+ retention, K^+ and H^+ loss

metabolic alkalosis

Cl^- depletion

$\downarrow \text{HCO}_3^-$ secretion, $\uparrow \text{H}^+$ secretion

metabolic alkalosis

K^+ depletion

$\uparrow \text{NH}_4^+$ secretion, H^+ secretion

metabolic alkalosis

these factors combine in

diuretic use: volume depletion and K^+ depletion

prolonged vomiting: alkalosis, volume depletion, Cl^- and K^+ depletion

g. Describe the role of the kidneys in the maintenance of fluid and electrolyte balance.

normal flux

water

intake

drink 1.2 l, food 1.0 l, metabolism 350 ml

output

insensible 0.9 l, sweat ≥ 50 ml, faeces 100 ml, urine 1.5 l

NaCl

small obligatory loss in sweat and faeces

urine balances the remainder of dietary intake

both freely filtered, reabsorbed

water by osmotic pressure from solute reabsorption

Na^+ by active transport

Cl⁻ mainly passive

PCT
 reabsorbs 65% of NaCl and water **independent of GFR** (isoosmotic)
 Na⁺ reabsorbed in cotransport with glucose etc., countertransport with H⁺
 NaCl reabsorbed in coupled organic base transporter
 isotonic filtrate

loop
 passive water reabsorption
 active NaCl reabsorption (Na⁺, K⁺, 2Cl⁻ cotransport, Na⁺/H⁺ countertransport)
 produces hypotonic filtrate (80-100 mOsm/l)
 25% of Na⁺ reabsorbed

DCT
 impermeable to water
 active NaCl reabsorption (cotransporter) 5% reabsorbed
 reduces osmolarity

collecting ducts
 variable water permeability (according to ADH)
 controls free water loss
 active Na⁺ reabsorption by principal cells (according to aldosterone)
 active Cl⁻ reabsorption by B intercalated cells (with HCO₃⁻ secretion)

control
 Na⁺ content determines ECF volume and systemic filling pressure
 ANF release
 blood pressure
 baroreceptor response
 sympathetic tone, renin, AT II, aldosterone, ADH
 pressure natriuresis

pathology
 cardiac failure
 low BP, GFR
 ↑ renin, AT II, aldosterone, ADH
 inappropriate Na⁺, water retention
 opposed by ANF

nephrotic syndrome
 ↑ protein filtration, loss in urine
 ↓ oncotic pressure, loss of plasma volume to interstitium
 intravascular depletion
 Na⁺, water retention despite expanded ECF volume

primary hyperaldosteronism
 initial Na⁺ retention
 ↑ BP, GFR, ANF
 return to Na⁺ balance at higher ECF volume

potassium balance
 98% intracellular, buffers changes in ECF concentration
 movement into ICF
 ↑ by insulin, adrenaline, alkalosis

PCT
 freely filtered, 55% reabsorbed in PCT (diffusion)

loop
 active reabsorption in Na⁺, K⁺, 2Cl⁻ cotransporter
 diffusion due to transtubular potential
 30% reabsorbed

DCT, cortical collecting duct

reabsorption by H^+/K^+ countertransport in type A intercalated cells
secretion by principal cells with Na^+ reabsorption
 \uparrow by aldosterone, plasma $[K^+]$, fluid delivery to duct
 some \uparrow with ADH (opposed by \downarrow flow)

pathology

alkalosis

\uparrow intracellular K^+
 \uparrow K^+ loss from collecting ducts
 K^+ depletion

calcium balance

turnover 0.1-0.2 mmol/kg/day
free fraction filtered (45%)
 40% protein bound
 15% complexed with organic anions

PCT and loop

passive reabsorption >60% of filtered load
dependent on Na^+ reabsorption
 \uparrow Na^+ loss causes \uparrow Ca^{2+} loss

DCT

active reabsorption
 basal Ca^{2+} ATPase and Na^+/Ca^{2+} countertransporter
 secondary luminal reabsorption
 inhibited in acidosis

control

PTH

peptide hormone secreted by parathyroids
 \uparrow by low $[Ca^{2+}]$
actions
 \uparrow Ca^{2+} mobilization from bone
 \uparrow DCT Ca^{2+} reabsorption
 \downarrow phosphate reabsorption
 \uparrow vitamin D hydroxylation

1,25-(OH) $_2$ D $_3$
 above

calcitonin

peptide hormone secreted by parafollicular thyroid cells
 \uparrow by high $[Ca^{2+}]$
actions
 minor role
 \downarrow bone resorption

GH

\uparrow Ca^{2+} excretion and intestinal absorption

cortisol

\uparrow Ca^{2+} excretion and \downarrow intestinal absorption

phosphate balance

5-10% protein bound
rest freely filtered
75% of load reabsorbed in PCT (Na^+ cotransport)
 \uparrow reabsorption due to
 1,25-(OH) $_2$ D $_3$, insulin
 \downarrow reabsorption due to
 PTH, glucagon

h. Describe the role of the kidneys in the maintenance of osmolarity.

receptors

- osmoreceptors in hypothalamus (paraventricular)
- control ADH secretion from posterior pituitary
- controls free water loss and thirst

i. Describe the role of the kidney in the handling of glucose, nitrogenous products and drugs.

proteins and peptides

- little protein is present in filtrate (10 mg/l)
- endocytosis of large proteins
 - e.g. albumin, GH
 - merge with lysosomes → amino acids
 - low T_m so easily saturates if filtration of proteins increases
- small polypeptides
 - catabolized in lumen by peptidases
 - active uptake of amino acids, di- and tri-peptides
 - site of metabolism of small peptide hormones (e.g. AT II)
- damaged tubular cells release some proteins into urine

urea

- freely filtered
- 50% reabsorbed in PCT (with water)
- concentrated in filtrate in loop and DCT (impermeable)
- facilitated diffusion absorption in collecting tubule (under ADH control)

organic anions and cations (including many drugs)

- non-specific active secretion in PCT
- several carrier proteins
- displays competition and T_m

organic acids and bases

- secretion or reabsorption depends on concentration gradient of diffusible species
- acids $AH \leftrightarrow A^- + H^+$
 - acid species is diffusible
 - reabsorbed at low urine pH
 - secreted at high urine pH
 - e.g. bile salts, fatty acids, uric acid
 - acetazolamide, frusemide, penicillin, probenecid, salicylates, sulfas
- bases $B + H^+ \leftrightarrow BH^+$
 - basic species is diffusible
 - secreted at low urine pH
 - reabsorbed at high urine pH
 - e.g. ACh, choline, catecholamines, 5HT, histamine
 - atropine, cimetidine, pethidine, morphine, local anaesthetics

glucose

- freely filtered
- secondary active cotransport with Na^+ in PCT
- T_m exceeded with plasma concentration $>10\text{mmol/l}$
- T_m varies from nephron to nephron

j. Describe the principles of measurement of glomerular filtration rate and renal blood flow.

Clearance

- the volume of plasma which is completely cleared of a substance per unit time
 - $C_x = \text{rate of excretion}_x \div \text{plasma concentration}_x$
- so if a urine specimen of volume V is taken over time t and the concentration of X is

measured in plasma (P_x) and urine (U_x):

$$C_x = U_x V \div P_x t$$

GFR

if a substance is

- freely filtered

- not actively secreted or reabsorbed by tubules

- not synthesized or metabolized in tubules

its clearance must equal GFR

e.g. inulin (an exogenous polysaccharide)

- in practice inulin is inconvenient as it equilibrates throughout ECF so a long infusion time is required to yield stable plasma levels

in practice creatinine is used

- continuous production from muscle (altered by exercise)

- freely filtered

- secreted by tubules (about 10% of excreted quantity)

- slight overestimate of GFR, but plasma creatinine is also an overestimate

- a halving of GFR should result in a doubling of plasma creatinine, so a single measurement of plasma creatinine can be used to estimate GFR based on age, weight and sex using the Cockcroft-Gault equation (males):

$$\text{creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{creatinine (in mg/dl)}}$$

(creatinine in mg/dl is 11 times the level in mmol/l)

urea can also be used

- 40-60% is reabsorbed

- $2 \times C_{\text{urea}} \approx \text{GFR}$

RPF

if a substance is

- filtered and actively secreted so that its concentration in venous blood from the kidney is zero

its clearance must equal RPF

as 10-15% of RBF is supplied to non-secreting tissue, no substance can meet these criteria

a substance which is completely cleared from blood supplied to secretory tissue of the kidney is used to measure effective RPF (ERPF)

e.g. para-aminohippurate

- freely filtered and actively secreted

- not reabsorbed

- completely cleared **at low plasma concentrations**

RBF

$$\text{ERBF} = \text{ERPF} \div (1 - \text{Hct})$$

k. Describe the physiological effects and clinical assessment of renal dysfunction.

l. Explain the effects of hypovolaemia on renal function.

m. Explain the effect of general anaesthesia on renal function.

E. Body fluids and electrolytes

a. Explain the distribution of body fluids and their measurement.

total body water 60% of bodyweight (75% newborn → <50% old age)

intracellular fluid 55% of TBW

approx 2 l is in circulating cells as part of blood volume

extracellular fluid 45% of TBW

exchangeable interstitial fluid 66% of ECF (30% of TBW)

slightly lower cation concentration than plasma due to less protein

water in dense CT and bone 33% of ECF (slow exchanging)

plasma 15% of ECF

approx 3 l

lymphatic fluid

transcellular fluid 5% of ECF

small volume

CSF, gut, synovial, peritoneal, pleural, pericardial, intraocular etc.

measurement

by indicator dilution

non-toxic, rapid distribution, confined to compartment, no effect on fluid distribution

not metabolized or excreted or has predictable kinetics

TBW

tritiated or deuterium water

antipyrine

ECF

radiolabelled Na^+ , Cl^- , Br^- , SO_4^{2-} (overestimate)

inulin, mannitol (underestimate)

ICF

calculated as TBW - ECF

plasma

radiolabelled albumin, Evans blue dye, horseradish peroxidase

interstitial volume

calculated as ECF - plasma

blood volume

calculated as plasma \div (1 - Hct)

measured with ^{51}Cr labelled red cells

b. Describe the function, distribution and physiological importance of sodium, potassium, magnesium, calcium and phosphate.

Sodium

total body content 60 mmol/kg = 1.4 g/kg

distribution

ECF 50%, bone 45%, ICF 5%

70% exchangeable, 30% fixed (in bone)

concentrations

plasma, ISF 135-145 mmol/l

reflects total body tonicity due to rapid equilibration of osmolality with

ICF

ICF 15 mmol/l

with accompanying anions accounts for 86% of ECF osmolality, 92% of tonicity

NaCl is only 75% dissociated in solution

absorption

freely absorbed, typical 3 g/day (range 0-20 g/day)

control

↓ delivery to macula densa → ↑ aldosterone
↑ Na⁺ retention in DCT (and other sites of exchange)

excretion

freely filtered at glomerulus
reabsorbed in PCT, loop and DCT
also lost in all secretions

Potassium

total body content 45 mmol/kg = 1.8 g/kg

distribution

ICF 90%, bone 8%, ECF 2%
92% exchangeable

concentrations

plasma 3.5-5 mmol/l
ICF 150 mmol/l

effects

high ECF

↑ membrane potential, ↓ V_{max}
↑ T waves, ↓ Q-T, ↑ P-R, wide QRS, arrest in diastole
drowsiness

low ECF

↓ membrane potential, ↑ V_{max}
ectopics, arrhythmia, ↓ T, ↑ P-R, U waves
irritability, weakness, tetany

absorption

freely absorbed, typical 1.0 g/day

control

primarily controlled by aldosterone → increased renal loss
moves across cell membranes opposite to H⁺
↑ movement into ICF with ↑ insulin

excretion

freely filtered at glomerulus
reabsorbed in PCT, loop (part active, part due to transtubular potential)
DCT, collecting duct secretion by type A cells, absorption by principle cells.
Loss ↑ by aldosterone, ADH, plasma [K⁺], high flow

Calcium

total body content 400 mmol/kg = 15 g/kg (1.5% bodyweight)

distribution

bone 99%, ECF <1%, ICF 1%
2% exchangeable

concentrations

plasma 2.2-2.4 mmol/l
free 40%, albumen 45%, other anions 15%
ICF 10⁻⁷ mmol/l free

effects

high ECF

drowsiness, weakness, confusion, dehydration, systolic arrest

low ECF

irritability of excitable tissues

absorption

oral intake 25 mmol/day, ≈2.5 mmol absorbed

control

PTH, vit D₃, calcitonin in Physiol D

excretion

unbound fraction (55%) filtered at glomerulus
85% reabsorbed in PCT and loop
DCT reabsorption controls loss (↑ loss with PTH)

net loss ≈ 2.5 mmol/day

Magnesium

total body content 12 mmol/kg = 0.3 g/kg

distribution

ECF 1%, ICF 99%: bone 50%, muscle 20%

concentrations

ECF 0.7-1.0 mmol/l (1.4-2.0 mEq/l)

ICF 20 mmol/l

effects

intracellular cation, exchanged for Ca^{2+} at sarcoplasmic reticulum

Ca^{2+} -antagonist-like effects

cofactor in many enzymes including all ATPases

increases threshold potential

inhibits ACh release and excitation-contraction coupling

vasodilation, bronchodilation, muscle weakness, anticonvulsant activity

absorption

intake 0.4 g/day

control

excretion

unbound fraction (75%) filtered at glomerulus

25% reabsorption in PCT

60-65% controlled reabsorption in loop

c. Outline the composition and functions of lymph.

Starling forces across the capillary wall cause net transudation of fluid from plasma into the interstitial space. This fluid is collected and pumped by the lymphatic system via lymph nodes or the spleen to return to the circulation via the thoracic duct.

Starling forces

hydrostatic pressure in capillares and interstitium

mean capillary pressure 17.3 mmHg

interstitial pressure -3 mmHg

oncotic pressure in capillaries and interstitium

plasma oncotic pressure 28 mmHg

interstitial oncotic pressure 8 mmHg

mean net force is 0.3 mmHg out of capillaries

filtration coefficient 7 ml/mmHg/min for whole body

net lymph flow 2 ml/min at rest

varies widely from tissue to tissue with capillary pressure, permeability, protein concentration changes

$$J_v = K_f (\Delta P - \sigma \Delta \pi)$$

| | systemic | pulmonary | glomerular |
|---------|----------------------|---------------------|-----------------------|
| P_c | 30 \rightarrow 10 | 12 \rightarrow 6 | 60 \rightarrow 58 |
| π_c | 28 | 28 | 21 \rightarrow 33 |
| P_i | -3 | -5 | 15 |
| π_i | 8 | 12 | 0 |
| net | +13 \rightarrow -7 | +1 \rightarrow -5 | +24 \rightarrow +10 |
| K_f | 0.01/100g | ? | 12.5 |

lymph

an ultrafiltrate of plasma

includes interstitial contents

composition highly variable depending on source

e.g. splanchnic lymph after a meal can be 2% lipid and 60 g/l protein
can include bacteria
actively pumped by lymph vessels and intrathoracic pressure
foreign particles and organisms removed in lymph nodes

d. Define osmotic pressure and explain the factors that determine it.

osmotic pressure

The pressure required to prevent net diffusion of water through a membrane with differing osmolalities of the solutions on each side.
proportional to the number of osmotically active particles in solution
calculated using van't Hoff's Law

$$\pi = CRT$$

where π is osmotic pressure, C is concentration of solutes in osmoles/l, R is the gas constant and T the absolute temperature

1 mOsm/l exerts 19.3 mmHg pressure at 37°C

normal osmolarity of plasma is 282 mOsm/l (5443 mmHg)

whole-body equilibration of osmotic pressure takes less than 30 minutes

e. Outline the significance of oncotic pressure, colloid osmotic pressure and reflection coefficients.

oncotic pressure (or colloid osmotic pressure)

The osmotic pressure exerted across the capillary wall by the non-diffusible elements of plasma.

ions and small molecules diffuse readily across capillary walls (reflection coefficient close to 0)

plasma proteins have high reflection coefficients, close to 1

total plasma protein osmotic pressure is about 19 mmHg in plasma and 8 mmHg in interstitial fluid

most pressure (12 mmHg) is due to albumin as it is in high concentration and is a smaller molecule than most other plasma proteins

The Gibbs-Donnan effect results in increased cation concentration in plasma to balance anionic non-diffusible proteins. The "excluded volume" effect results from proteins not being an "ideal solute" and increases oncotic pressure. These effects increase plasma oncotic pressure by another 9 mmHg, total 28 mmHg
measured using an "oncometer"

calibrated isotonic saline solution separated from the test solution by a membrane excluding particles larger than MW 30,000 with a sensitive pressure transducer to measure the osmotic pressure generated

f. Describe the measurement of osmolality and the control mechanisms involving the regulation of osmolality.

osmolarity

number of osmotically active particles per liter of solution (not used)

osmolality

number of osmotically active particles per kilogram of solvent

measured directly by freezing point depression

1 osm/kg of water depresses freezing point by 1.86°C

approximated from electrolyte results

$2 ([Na^+] + [K^+]) + [glucose] + [urea]$

normal 280-290 mOsm/l

less than the sum of concentrations of solutes because of particle interactions
approximation is an underestimate when other solutes are present in high

concentrations
mannitol, ketoacidosis, alcohol

Control in [Renal physiology \(1.D\)](#).

F. Acid-Base Physiology

a. Explain and describe acid-base chemistry using the Henderson-Hasselbalch equation.

pH is defined as $-\log_{10}[\text{H}^+]$. Normal ECF pH is from 7.35 to 7.45 ($[\text{H}^+]$ 35-45 nmol/l). Survivable ECF pH is from 6.8 to 7.6. Acids are compounds which donate H^+ ions and bases are compounds which accept H^+ ions. Organic acid and bases in solution are partially dissociated, according to the pH of their surroundings and their pKa. pKa is defined as the pH at which half of the quantity of an acid is dissociated in solution. The relationship between pH, pKa and the dissociation of an acid or base is described by the Henderson-Hasselbalch equation:

$$\text{H}^+ + \text{A}^- \leftrightarrow \text{AH}$$
$$\text{pH} = \text{pK}_a + \log \frac{[\text{A}^-]}{[\text{AH}]}$$

Where AH is an acid and A^- its corresponding base. In ECF, examples of organic acids include many proteins such as haemoglobin, lactic acid and ketone bodies. Examples of simple acids include phosphoric and carbonic acid.

b. Describe the chemistry of buffer mechanisms and explain their relevant roles in the body.

A buffer is an acid/base pair which reversibly dissociates. A buffer acts to stabilize the pH of a solution as the introduction or removal of H^+ from a buffered solution is partially compensated for by a change in the relative concentrations of the forms of the buffer according to the Henderson-Hasselbalch equation which results in a return of the pH towards its initial value. This is most readily seen in the transformation of the equation:

$$\text{K}_a = \frac{[\text{A}^-][\text{H}^+]}{[\text{AH}]}$$

Any rise in $[\text{H}^+]$ will result in recombination of H^+ and A^- to form AH to maintain the constant K_a . ($\text{H}^+ + \text{A}^- \rightarrow \text{AH}$) A fall in H^+ or a rise in OH^- will have the opposite effect. Most organic acids are capable of acting as buffers. The maintenance of pH in a very tight range is vital for the normal function of most physiological processes. The activity of most enzymes is highly pH dependent.

The principle buffers in the blood are:

Haemoglobin which allows dissociation of some of its 38 histidine residues ($\text{HHb} \leftrightarrow \text{H}^+ + \text{Hb}^-$). This is also responsible in part for the right shift of the Hb-O_2 dissociation curve with a fall in pH.

Plasma proteins (and haemoglobin) bearing carboxyl or amine groups ($\text{RCOOH} \leftrightarrow \text{RCOO}^- + \text{H}^+$ or $\text{RNH}_3^+ \leftrightarrow \text{RNH}_2 + \text{H}^+$).

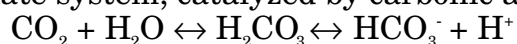
Carbonic acid which is itself in equilibrium with PCO_2 ($\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+$). This provides for the compensation for pH changes by changes in respiration.

Interstitial fluid contains little haemoglobin or protein and is buffered by carbonic acid.

Intracellular fluid is buffered by proteins as described above and also by phosphate ($\text{H}_2\text{PO}_4^- \leftrightarrow \text{HPO}_4^{2-} + \text{H}^+$).

c. Describe the regulation of acid-base balance.

The second line of regulation of pH (after buffers), is in the respiratory and renal regulation of acid-base balance. The major buffer in extracellular fluid is the carbon dioxide/carbonic acid/carbonate system, catalyzed by carbonic anhydrase:



The extracellular CO_2 concentration is regulated by respiration. If an increase in metabolic activity or a fall in pH occur, PCO_2 rises. An increase in ventilation increases the rate of elimination of CO_2 from the lungs, bringing PCO_2 back to normal and raising pH. The reverse occurs when a rise in pH causes a fall in PCO_2 .

A doubling in alveolar ventilation can compensate for a fall of 0.2 in pH and a halving for a rise of about 0.25. The capacity for changing alveolar ventilation ranges from almost 0 to 15 times normal. Reducing ventilation to compensate for a rise in pH is limited by the requirement to maintain PO_2 .

The control of ventilation is directly affected by pH. The effectiveness of the whole mechanism is 50-75% and the time to equilibrium 3-12 minutes. The system is impaired by respiratory disease, with COAD patients developing a respiratory acidosis because of their limited ventilation and a greatly impaired ability to compensate for a metabolic acidosis.

The extracellular concentrations of HCO_3^- and H^+ as well as non-volatile acids are regulated by the kidney. 80 mEq/day of H^+ are lost in association with non-volatile acids. HCO_3^- is freely filtered at the glomerulus (4320 mEq/day). In the proximal convoluted tubule and loop of Henle H^+ is secreted into the tubule by secondary transport in exchange for Na^+ . H^+ combines with filtered HCO_3^- to form CO_2 which diffuses into tubule cells and generates H^+ and HCO_3^- which diffuses back into the ECF. The net effect is resorption of HCO_3^- . This mechanism resorbs 95% of filtered HCO_3^- , but has little effect on urine pH. In the presence of a high pH or low PCO_2 , less H^+ is secreted, and HCO_3^- is lost in the urine, compensating for the alkalosis.

In the DCT, H^+ is secreted into the urine by an ATPase H^+ pump. This allows for resorption of the remaining HCO_3^- , and allows the generation of a maximally acidic urine of about pH 4.5. In the presence of a low pH or high PCO_2 , excess H^+ is secreted and combines with other buffers in the urine: HPO_4^{2-} or NH_3 . The HCO_3^- generated intracellularly by carbonic anhydrase in forming the H^+ diffuses back into the ECF as "new" HCO_3^- .

The ammonia buffer in the urine is generated by the metabolism of glutamine in PCT cells to produce 2HCO_3^- which diffuse into the ECF and 2NH_4^+ which are transported into the urine by Na^+ exchange secondary transport. A low pH stimulates the metabolism of glutamine in this way. In chronic acidosis this is the major system for renal compensation.

A minor determinant of renal H^+ secretion is the effect of aldosterone in increasing active transport of H^+ in the DCT and collecting ducts.

Infusion of acid buffering

immediate HCO_3^- buffering in plasma

ISF equilibrium in 15 minutes

ICF equilibrium in 2-4 hours

with Hb, HPO_4^{2-} , other proteins

H^+ displaces K^+ (and Na^+) from ICF → hyperkalaemia

Cl^- and HCO_3^- enter cells with H^+

physiological effects

shifts O_2 dissociation curve to the right

sensed by carotid and aortic bodies

respiratory stimulation → partial compensation

limited by initial **rise** in CSF pH

d. Explain the principles of blood gas and acid-base analysis.

measurement in [Physics and Measurement \(1.R\)](#).

normals

| | | |
|-----------------|------------|--|
| pH | 7.35-7.45 | $6.1 + \log ([\text{HCO}_3^-] \div 0.03 P_a\text{CO}_2)$ |
| p CO_2 | 36-46 mmHg | $1.5 [\text{HCO}_3^-] + 8$ |

| | | |
|-------------------------------|--------------|--|
| pO ₂ | 80-100 mmHg | P _i O ₂ - P _a CO ₂ ÷ R + F |
| HCO ₃ ⁻ | 24-30 mmol/l | |
| base excess | ±2 mmol/l | degree of <i>metabolic</i> alkalosis |
| anion gap | 12 mEq/l | [Na ⁺] + [K ⁺] - [HCO ₃ ⁻] - [Cl ⁻] |

e. Interpret blood gas analysis and its management in clinical situations.

Acid-base disorders can be categorized as acidaemia or alkalaemia, acidosis or alkalosis, respiratory or metabolic. This classification can be determined from the pH, PCO₂, and HCO₃⁻ in arterial blood. Their normal values are 7.4, 40 mmHg and 24 mEq/l respectively. A respiratory acidosis results from underventilation, resulting in increased PCO₂, low pH and compensatory rise in HCO₃⁻. A respiratory alkalosis results from overventilation, with a high pH, low PCO₂ and lowered HCO₃⁻. A metabolic acidosis displays a low pH, primary low HCO₃⁻ and compensatory low PCO₂. A metabolic alkalosis has a high pH, high HCO₃⁻ and raised PCO₂.

These problems do not always occur in isolation. Combined respiratory and metabolic acidosis is common in patients with multiple medical problems. The compensatory mechanisms require time to stabilize the pH: 6 to 12 hours for respiratory compensation and 3 to 5 days for renal compensation.

A graph of [HCO₃⁻] versus pH with PCO₂ isobars is used to readily classify acid-base disturbances. Alternatively rule-of-thumb equations can be used to relate "expected" [HCO₃⁻] and PCO₂.

Management of acid-base disturbances in the acute setting focuses primarily on the underlying cause. Respiratory acidosis can be corrected by increasing ventilation. Respiratory alkalosis can be corrected by reducing ventilation within the limits of maintaining adequate oxygenation. Sometimes, for example in neurosurgical procedures, a respiratory alkalosis is desirable and deliberately generated by hyperventilation.

Metabolic acidosis

high anion gap

ketoacidosis, lactic acidosis, ethylene glycol poisoning, renal failure

normal anion gap

loss of HCO₃⁻

GIT fluid loss (diarrhoea, drains, ureteroenterostomy)

renal tubular acidosis, interstitial disease

recovery from ketoacidosis

drugs: carbonic anhydrase inhibitors, absorbable acids

Metabolic alkalosis

renal

K⁺ depletion, Cl⁻ depletion and volume depletion all ↑ H⁺ loss

seen in diuretic use, prolonged vomiting

Conn's syndrome: ↑ aldosterone, ↑ H⁺ loss

drugs

oral (or IV) HCO₃⁻

G. Nervous system physiology

a. Explain the basic electrophysiology of neural tissue.

Cell Membrane Potential

Resting potential is maintained by active transport of ions by Na^+, K^+ ATPase against the passive diffusion of K^+ out of the cell.

Conventionally negative (inside cell) -70 to -90mV

Ion gradients in nerve cell

| | ICF | ECF | |
|---------------|-----|-----|-------|
| Na^+ | 15 | 150 | +60mV |
| K^+ | 150 | 5.5 | -90mV |
| Cl^- | 9 | 125 | -70mV |

net resting potential -70mV

relationship between gradient and potential is described by the Nernst equation:

$$E = \frac{RT}{FZ} \ln \frac{C_o}{C_i} = \frac{61.5}{Z} \log \frac{C_o}{C_i}$$

the membrane potential as a whole is described by the Goldman field equation:

$$V = \frac{RT}{F} \ln \frac{P_K[\text{K}^+]_o + P_{\text{Na}}[\text{Na}^+]_o + P_{\text{Cl}}[\text{Cl}^-]_i}{P_K[\text{K}^+]_i + P_{\text{Na}}[\text{Na}^+]_i + P_{\text{Cl}}[\text{Cl}^-]_o}$$

The membrane is much more permeable to K^+ and Cl^- than to Na^+ or Ca^{2+} . K^+ causes most of the potential, Cl^- is passively distributed according to the membrane potential.

Nerve cells

A myelinated nerve cell consists of a soma with dendrites, an axon hillock with axon attached, sheathed in Schwann cells punctuated by Nodes of Ranvier, and ending in terminal buttons.

When an electrical or other stimulus raises or lowers the resting potential of the nerve cell slightly, the normal potential is restored over 0.5 to 1 ms by K^+ and Cl^- flux. When the resting potential is raised above -63 mV, Na^+ permeability through ion channels increases, helping to sustain the electrotonic potential.

Above -55 mV, Na^+ permeability increases suddenly, flux becoming greater than the rate of transport out of the cell and an action potential results. The membrane potential spikes to +35 mV. There is a rapid reduction in Na^+ permeability and a slower increase in K^+ permeability and flux, repolarizing the cell. The Na^+ channels enter an inactivated state, causing the absolute refractory period, before returning to the resting state.

Channels are concentrated at the Nodes of Ranvier. When an action potential occurs at one node, it induces a depolarization at the adjacent node, starting another action potential if the node is not refractory. This is saltatory conduction. Because of the refractory period, saltatory conduction is unidirectional.

Extracellular Na^+ concentration does not affect excitability much as the membrane isn't very permeable. A rise in extracellular K^+ stabilizes cells by decreasing the membrane potential. A rise in extracellular Ca^{2+} stabilizes cells by increasing the depolarization required to initiate an action potential.

Ca^{2+} may play a role in the spike due to influx through Na^+ channels and also enters the cell through separate channels during the late phase of hyperpolarization.

Nerve fibres

Classified by diameter (\propto conduction velocity)

| | |
|------------------------|-------------------------------|
| $\text{A}\alpha$ (I) | proprioceptive, somatic motor |
| $\text{A}\beta$ (II) | light touch, pressure |
| $\text{A}\gamma$ | motor to muscle spindles |
| $\text{A}\delta$ (III) | pain, heat, touch |

- B preganglionic autonomic
- C (IV) pain, sympathetics

Larger fibres are more susceptible to pressure and hypoxia and less susceptible to local anaesthetics.

When bundled into nerves, the electrical behaviour seen is different from individual fibres due to a range of sensitivities and conduction velocities of the fibres in a nerve. Nerves display compound action potentials and show a ceiling response to maximal stimuli.

Synapses

Junctions between nerve cells.

May be electrical (gap junction) or chemical:

consist of a synaptic knob containing vesicles of transmitter, a 20-30 nm synaptic cleft and postsynaptic membrane.

Release of neurotransmitter is initiated by rising intracellular Ca^{2+} during action potentials causing exocytosis.

Neurotransmitter binds to receptors on the postsynaptic membrane, opening specialized Na^+ channels which raise the membrane potential (Excitatory Post-Synaptic Potential) or to Cl^- channels which lower the membrane potential (IPSP). Slow EPSPs and IPSPs are caused by transmitters which alter the permeability to K^+ .

Each neurone releases only one neurotransmitter and so is either excitatory or inhibitory. Inhibitory interneurons allow one neurone to act to generate both EPSPs and IPSPs.

If enough EPSPs sum in time and place, an action potential can be generated. There is also direct transmission of electrical potential within a single cell without action potentials.

b. Describe sensory and motor pathways.

sensation

receptors

mechano

skin (multiple types), deep tissue, muscle (spindle), tendon
others: hearing, balance, baroreceptors

temperature

warm and cold, peripheral and hypothalamic

pain

mechano and polymodal

chemo

general: taste, smell

specific: carotid/aortic bodies (O_2 and CO_2), hypothalamic (osmolarity, glucose, amino acids, fatty acids)

stimulation produces a change in discharge *frequency* which decays with adaption. Vibration and light touch require rapid adaption, pain and proprioception display minimal adaption.

afferent pathways

fibre types are specific to receptor types

Ia 17 μm annulospiral muscle spindle fibres

Ib 16 μm Golgi tendon organs

II 8 μm most skin receptors

III 3 μm crude touch and sharp pain

IV unmyelinated 0.5 μm to 2 μm pain, itch, temperature, touch

transmission from the primary afferent is often transmitted by both a fast transmitter, causing a brief depolarization and one or more slow transmitters causing a prolonged EPSP which causes sensitization to further signals

signals can also be prolonged by reverberatory circuits, or reverberatory circuits can produce a continuous rate of depolarization which is modified by inhibitory or excitatory inputs
 perception in the cord is sharpened by convergence and lateral inhibition
 excitation in the cord is limited by descending inhibitory pathways and synaptic fatigue
 ascending pathways
 dorsal column-medial lemniscal system
 primary large myelinated afferents divide into two branches
 medial runs directly to the brain in the dorsal columns
 lateral synapses in the dorsal horn to provide
 spinal reflexes
 spinocerebellar tracts
 spinocervical tract
 input to contralateral spinothalamic tract
 dorsal column fibres synapse in the cuneate and gracile nuclei, cross and ascend to the thalamus and then the cortex
 anterolateral pathway
 transmits pain, heat, cold, itch, tickle and crude touch
 primary afferents synapse in the ipsilateral dorsal horn
 secondary fibres cross to the opposite anterolateral tract and ascend as the anterior and lateral spinothalamic tracts, the spinoreticular and spinotectal tracts
 synapse in the reticular nuclei of the brainstem and the thalamus
 descending pathways

c. Describe the physiology of pain.

In [Pain Pharmacology \(2.B.3\)](#).

d. Describe the physiology of cerebrospinal fluid.

function

protection "floating" of brain and spinal cord
 constant chemical environment
 some nutrient content
 some excretory function
 transport of neurohormones within CNS

production

0.35 ml/min (500 ml/day) not affected by ICP unless CPP <70 mmHg
 total volume 150 ml
 choroid plexus produces 40-70%
 fenestrated endothelium in capillaries
 controlled secretion by epithelial cells
 Na⁺/K⁺ ATPase-driven transport of ions, glucose and nutrients
 ependyma adds 30-60% by oxidation of carbohydrates and ultrafiltration

composition

| | CSF | plasma | |
|------------------|------|--------|--------|
| pH | 7.31 | 7.41 | |
| Na ⁺ | 141 | 140 | mmol/l |
| K ⁺ | 2.9 | 4.6 | mmol/l |
| Ca ²⁺ | 1.3 | 2.5 | mmol/l |
| Mg ²⁺ | 1.2 | 0.8 | mmol/l |
| Cl ⁻ | 124 | 101 | mmol/l |
| glucose | 3.5 | 4 | mmol/l |
| protein | 0.3 | 70 | g/l |

reabsorption

90% in arachnoid villi

10% in spinal subarachnoid

determined by ICP

zero at 68mmCSF

equilibrium at 112mmCSF

drugs

diuretics ↓ production

acetazolamide reduces H^+ availability for Na^+/H^+ exchange

furosemide inhibits NaCl transport

ethacrynic acid inhibits Na^+/H^+ exchange

spironolactone inhibits Na^+ transport

steroids ↓ production

digoxin weak ↓ production from Na^+, K^+ ATPase inhibition

volatile agents

most ↓ absorption

some ↓ production (halothane, sevoflurane)

e. Describe the autonomic nervous system and explain its role in controlling body function.

In [Thoracic Anatomy \(3.G.1\)](#).

f. Describe neurotransmitters and their physiological role.

released from presynaptic neuron

synthesis

only one type of fast transmitter in one neuron

ACh

choline + acetyl-CoA

amines

synthesized in cytoplasm

e.g. tyrosine → DOPA → dopamine → noradrenaline → adrenaline

glutamate → GABA

tryptophan → 5-OH trp → 5HT

histidine → histamine

amino acids are derived from uptake from blood and transamination

NO

synthesized from arginine by NO synthase

neuropeptides

synthesized in RER

very small quantities

transported to terminals by axonal transport

much more potent but act slowly and for a prolonged period

storage

vesicles near the synaptic junction for all transmitters except NO

release

in response to action potential

detail above and in Physiol H and Pharm B VII

metabolism

ACh

cholinesterase

amines

reuptake by pre- and post-synaptic membrane transport

MAO and COMT

GABA transaminated by GABA-T → succinic semialdehyde → succinate

rapid

Class I

acetylcholine

Class II (amines)

noradrenaline

adrenaline

dopamine

serotonin

histamine

Class III (amino acids)

γ -aminobutyric acid

glycine

glutamate

aspartate

Class IV

NO

lipids

arachadonic acid derivatives

neurosteroids

slow

hypothalamic

TRH

LHRH

somatostatin

pituitary

β -endorphin

MSH

prolactin

LH

TSH

GH

ADH

oxytocin

gut and brain

leu-enkephalin

met-enkephalin

substance P

CGRP

gastrin

cholecystokinin

VIP

neurotensin

insulin

glucagon

others

angiotensin II

bradykinin

carnosine

sleep peptides

calcitonin

receptor types (not dealt with elsewhere)

GABA_A

pentameric transmembrane ligand-gated Cl⁻ channel

multiple subunit types (α , β , γ , δ , ρ) \rightarrow hundreds of receptor subtypes

several binding sites

GABA → opens Cl^- channel, IPSP
BDZ requires α , β , γ subunits, binds α → ↑ GABA binding
several subtypes of BDZ binding site
 β -carboline binds at BDZ site → ↓ GABA binding (inverse agonist)
alcohol, barbiturates, progesterone also facilitate GABA transmission

GABA_B

G-protein linked receptor
↑ K^+ conductance, ↓ Ca^{2+} conductance
presynaptic inhibitory role in pain transmission and elsewhere
activated by baclofen, midazolam → analgesia

other GABA receptor roles

monocyte chemotaxis
 β cells in the pancreas

glutamate receptors

AMPA, kainate
ligand-gated Na^+ channels
4 or 5 subunits, multiple subunit types, hundreds of channel subtypes
fast excitatory response

NMDA

complex receptor, Ca^{2+} channel when activated
normally inactive with Mg^{2+} in channel
inhibited by ketamine, phencyclidine binding in channel
binding of glycine *facilitates* activation
prolonged depolarization causes escape of Mg^{2+}
activation causes ↑ Ca^{2+} conductance
prolonged activation causes NO production, c-fos expression
may play a role in neuronal death (↑ glutamate released from ischaemic nerve cells)

glycine

pentameric Cl^- channel → IPSP
 α and β subunits
antagonized by strychnine → convulsions

g. Explain the physiology of the control of intracranial and intraocular pressure.

ICP

uniform pressure within cranial vault
normal range 5-13 mmHg at rest
rises with intrathoracic pressure due to transmission of BP changes
determined by
brain volume
blood volume
CSF volume
changing one must alter the others (Monroe-Kellie Doctrine) as volume is constant
measurement
qualitative
MRI, CT
quantitative
catheter in ventricle/cerebrum/subarachnoid/extradural space
transducer outside or at tip of catheter

cerebral circulation

Circle of Willis supplied by ICA and basilar arteries
grey matter 80 ml/100 g/min, white 20 ml/100 g/min, total 50 ml/100 g/min
slightly less in cord

measurement

Kety-Schmidt technique

uses Fick principle

uptake of tracer = perfusion x extraction

$$Q_b = F \int (C_a - C_v) dt$$

$$Q_b = C_b \cdot \text{Mass}_b$$

$$C_b = C_v \cdot \lambda \text{ (at equilibrium)}$$

$$\frac{F}{\text{Mass}_b} = \frac{C_v \lambda}{\int (C_a - C_v) dt}$$

N₂O at low concentration is the tracer used

C_a and C_v are measured continuously

at radial artery and IJV

until equilibrium

λ is assumed to be 1 for N₂O

result is expressed in ml/100 g/min

radioactive tracers

¹³³Xe, ⁸⁵Kr as gases

organic compounds including ¹¹C, ¹⁵O, ¹³N or ¹⁸F

detected by scintigraphy, PET, autoradiography

flow probes

doppler, electromagnetic

MRA

O₂ extraction monitoring

jugular bulb oximetry

near IR spectroscopy

flow is autoregulating

CPP 50-150 mmHg (CPP = MAP - ICP)

largely myogenic and gas pressure determined

PCO₂ causes linear response in CBF over 20-70 mmHg

1-2 ml/100 g/min/mmHg

due to pH change, so attenuated with buffering over time

PO₂ causes rise in CBF below 50 mmHg

no change at 60-300 mmHg

small fall >300 mmHg

vessels are innervated by sympathetic, parasympathetic, trigeminal and

intrinsic nerves which have little effect

if BBB is impaired: α agonists ↓ CBF, β agonists ↑ CBF

requirements

22 ml/100 g/min EEG changes

15 ml/100 g/min isoelectric EEG

6 ml/100 g/min cell death

directly related to O₂ requirement (CMRO₂)

normal 3-3.5 ml/100 g/min

5-10 s reserve before unconsciousness

reduced by

cerebral depressants (barbiturates etc) up to 60% reduction

hypothermia up to 90% reduction at 17°

h. Describe the integration of central nervous system activity via the cerebellum, hypothalamus and limbic system.

i. Describe the physiology of sleep.

j. Outline the basis of the electroencephalogram.

In [Monitoring \(3.B.2\)](#).

H. Muscle Physiology

a. Describe the muscle spindle and explain its physiological role. Use this knowledge to describe the integration of voluntary movement.

A muscle spindle consists of 3 to 12 specialized fusiform myocytes attached at their ends to the normal muscle cells of a skeletal muscle. There are two types of spindle cell: nuclear bag and nuclear chain. The cells have contractile units at their ends innervated by γ motor neurones independently of the extrafusal muscle. The central portion of the myocytes has no contractile filaments but generates sensory signals depending on the stretching of the spindle (either by lengthening of the muscle or contraction of the spindle cells).

The sensory innervation of the spindle cells is dual: a Ia annulospiral fibre surrounding the central portion of all cells and II fibres away from the centre and surrounding only the nuclear chain cells.

The response characteristics of the muscle spindle are of two types. The static response is generated by the nuclear chain cells and is a signal with a frequency related to stretch of the spindle and persistent for several minutes after stretching. The dynamic response is a response to rapid change in the length of the spindle with a big rise in impulse frequency with lengthening and reduction with shortening. It is produced by the nuclear bag cells and is seen only in the Ia fibres.

The γ innervation is also divided into static and dynamic components, each producing an increase in sensitivity of the respective response. These compose 31% of all motor neurones, the rest being A α fibres. The γ fibres are stimulated at the same time as A α fibres in voluntary movement, maintaining coordination between the length of the muscle spindle and the muscle as a whole. Coordination of this effect is primarily in the bulboreticular facilitatory area of the brain stem with secondary input from the cerebellum, basal ganglia and cortex.

In the spinal cord, the Ia afferent neurones synapse directly with motor neurones supplying the same muscle, providing the monosynaptic spinal reflex (jerk reflexes and clonus). The IIa fibres produce a weaker but more sustained reflex in response to continued stretch rather than “jerks”. These reflexes have an important application in smoothing the motor neurone (and muscle) response to the very uneven signals from higher centres and compensating for the sudden forces involved in walking or running. Muscle spindles in antagonist muscles are stimulated to stabilize a joint for precise movement.

b. Describe the physiology of the neuromuscular junction and its receptors.

The neuromuscular junction is the interface between lower motor neurones and skeletal muscle cells. Motor neurones end in multiple terminals which interdigitate with the muscle cell membrane, forming a motor end-plate. The space between the cells is the synaptic cleft and is 20-30 nm across.

The nerve terminals contain mitochondria and vesicles of acetylcholine. When an action potential reaches the terminal, about 125 (of the 300,000) vesicles are released or their contents diffuse through the cell membrane. This process is mediated by influx of Ca^{2+} through voltage dependent channels. Acetylcholine binds to nicotinic receptors which are transmembrane proteins in the muscle cell's subneural clefts.

Nicotinic post-junctional receptors are grouped at the “shoulders” of the subneural clefts. The receptor is a cone-shaped protein consisting of five subunits which binds with two molecules of acetylcholine. The ion channel when opened allows passage of Na^+ , K^+ and Ca^{2+} , but the main effect at the time of opening is influx of Na^+ .

The receptor is a pentamer composed of four different units ($\alpha_2\beta\gamma\delta$) all of which span the cell membrane. The ACh receptor sites are on the α subunits. There is a central ion

channel which opens due to conformational changes when both receptor sites are occupied by agonists.

The nicotinic receptors on nerve tissue are composed of a different combination of units ($\alpha_2\beta_3$).

Opening of ACh-gated ion channels generates an excitatory end plate potential which triggers an action potential by opening voltage-dependent Na^+ channels if it lifts the membrane potential above the threshold potential, about -70mV.

The acetylcholine is broken down within a few milliseconds by acetylcholinesterase. The action potential lasts 1-5ms and propagates down the T-tubules at 3-5m/s. The generation of the action potential is the same as in nerve tissue with influx of Na^+ followed by efflux of K^+ repolarizing the cell.

The action potential triggers voltage-dependent Ca^{2+} channels in the sarcoplasmic reticulum which open, allowing an influx of Ca^{2+} into the intracellular space. Ca^{2+} binds to troponin C, causing a conformational change which allows the active site of actin to bind to adjacent myosin heads, initiating muscle contraction. The Ca^{2+} is rapidly transported back into the sarcoplasmic reticulum within 50ms in skeletal muscle (300ms in cardiac muscle) and contraction ends unless a further action potential is received.

c. Describe the comparative physiology of skeletal, smooth and cardiac muscle.

Muscle tissue

Skeletal

Cellular anatomy

striated, not functionally syncytial

Composed of sarcomeres (Z line to Z line) A band is thick myosin filaments, the I band is thin filaments of actin, troponin and tropomyosin.

Fibrils are surrounded by the sarcotubular system of transverse tubules, continuous with the cell membrane, and sarcoplasmic reticulum. Two T-tubules per sarcomere.

Electrical activity

Nerve endings at the motor end plate release acetylcholine which opens Na^+ channels to initiate the action potential.

Membrane potential is -90 mV, action potential is 2-4 ms and propagates at 5m/s. It is transmitted along the transverse tubules.

This starts release of Ca^{2+} from sarcoplasmic reticulum which binds to troponin C, releasing the myosin-binding sites on actin.

The myosin cross-bridges swing, lysing ATP and shortening the fibril.

The contraction takes several ms, the refractory period of the muscle is less, so repeated action potentials result in tetanic muscle contraction.

ATP for muscle contraction is derived from hydrolysis of phosphocreatine near the myosin heads and from anaerobic and aerobic glycolysis and from oxidation of free fatty acids, depending on the activity of the muscle and availability of oxygen. ATP will supply tetanic contraction for 1-2 s, phosphocreatine for 5-8 s, and glycolysis for 1-2 minutes in skeletal muscle.

ATP is also required for relaxation of muscle as it drives the Ca^{2+} , Mg^{2+} ATPase pump which returns Ca^{2+} to the sarcoplasmic reticulum.

Muscle structure

Muscles fibres are classified as types I, IIB and IIA (few in humans). I are slow contracting with high oxidative capacity and are most common in postural muscles. IIB and fast and support more glycolytic metabolism and are more common in "quick" muscles such as the extraocular muscles. All muscles have a varying proportion of fibre types. Fibre type is determined by the pattern of discharge from the

motor neuron innervating a particular motor unit.

Cardiac Muscle

Cellular anatomy

striated, functionally syncytial

Composed of sarcomeres, but fibrils branch and attach at the ends with intercalated disks and membrane fusion with gap junctions.

The transverse tubules are aligned with the Z lines (one per sarcomere).

Fibres are "slow" type with high oxidative capacity and many mitochondria. Myosin type and consequently ATPase activity are determined by thyroid hormone levels.

Electrical activity

Membrane potential is -80 mV

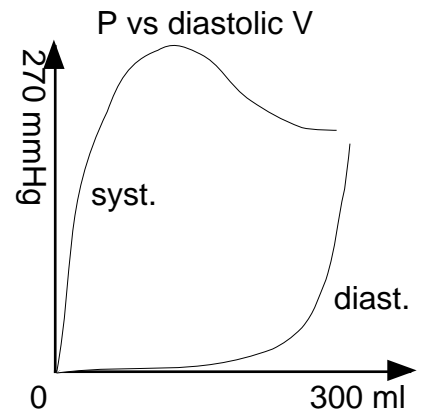
Depolarization is started by (fast) Na^+ channels opening for a few ms, then maintained by (slow) Ca^{2+} channels which remain open for 150-250 ms, depending on rate. K^+ channels open at the same time and remain open to repolarize the cell.

Muscle contraction is initiated by Ca^{2+} from both sarcoplasmic reticulum and ECF and lasts 1.5 times as long as the action potential. There is no tetanic contraction. Ca^{2+} release from sarcoplasmic reticulum is Ca^{2+} -mediated rather than voltage-gated as in skeletal muscle.

In specialized pacemaker cells, the membrane potential rises due to falling K^+ permeability, initiating repeated action potentials. These cells compose the SA node and conducting bundles.

Muscle behaviour

Force of contraction is determined by diastolic filling (graph)
 β agonism increasing Ca^{2+} influx mediated by cAMP (also shortens systole)
digoxin inhibiting Na^+-K^+ ATPase leading to a higher intracellular $[\text{Ca}^{2+}]$



Smooth Muscle

Cellular anatomy

not striated, functionally syncytial

Cells contain actin, myosin and tropomyosin but no troponin. Fibres are not organized. There are few mitochondria; cells rely on glycolysis.

There is no sarcotubular system.

Visceral smooth muscle is found in the walls of viscera. Cells have low-resistance junctions.

Multi-unit smooth muscle is found in the iris. Cells are not linked.

Electrical activity

Membrane potential varies continually with spontaneous action potentials at irregular intervals. Action potentials propagate through the muscle and initiate contractions lasting seconds.

Myosin links to actin only after phosphorylation by myosin light-chain kinase which is activated by calmodulin-bound Ca^{2+} .

Muscle behaviour

The spontaneous variation in membrane potential is affected by hormones. The response varies with the location of the smooth muscle. Acetylcholine, cold and stretch all increase frequency and strength of contraction.

Smooth muscle is plastic in response to prolonged stretch.

I. Liver Physiology

a. Describe the storage, synthetic, metabolic, and excretory functions of the liver and identify the physiological consequences of hepatic disease.

The liver is composed of lobules, 0.8 to 2 mm in diameter. They comprise a central vein (which drains to the hepatic vein) surrounded by plates of hepatocytes sandwiching bile canaliculi and surrounded by the space of Disse (which drains to lymphatics). Between the plates are sinusoids filled with blood derived from the hepatic artery (350 ml/min) and portal vein (1.1 l/min).

The liver receives a total of 29% of resting cardiac output. It is a low-resistance circulation, the portal vein being at 9 mmHg and hepatic vein at 0 mmHg. In cirrhosis the vascular resistance is increased. In right heart failure, venous pooling in the liver can amount to 2 l (normal 450 ml). With high intrahepatic capillary pressure, fluid is rapidly transudated into lymph and directly into the abdominal cavity as ascites. This involves loss of plasma protein.

Kupffer cells in the sinusoids are part of the mononuclear phagocytosing system, removing bacteria from portal blood very effectively.

Carbohydrate metabolism (glucose buffering)

glycogen synthesis

polymerized from UDP-glucose

hydrolyzed by phosphorylase to glucose 1-PO₄. Phosphorylase is activated by adrenaline or glucagon via cAMP and enzyme intermediates.

represents up to 8% of hepatocytes' weight

conversion of galactose and fructose to glucose

galactose (+ATP) → ~ 1-PO₄ ↔ UDP ~ ↔ UDP glucose → glycogen

fructose (+ATP) → ~ 6-PO₄ ↔ glucose 6-PO₄ ↔ ~ 1-PO₄ ↔ UDP ~

Only glucose is readily released back into blood by the action of glucose phosphatase on glucose 6-PO₄.

gluconeogenesis

from glycerol released from fats or by deamination and conversion of many amino-acids (e.g. alanine → pyruvic acid + NH₃). This is promoted by glucocorticoids via liberation of amino-acids from protein catabolism in peripheral tissues.

Fat metabolism

oxidation of fatty acids

Triglycerides are split into glycerol (→ gluconeogenesis) and fatty acids. Fatty acids are split by β oxidation into a shorter fatty acid, acetyl-CoA, FADH₂, NADH and H⁺. The net gain from oxidation of a molecule of stearic acid (C₁₇H₃₅COOH) is 146 ATP. Acetyl-CoA can enter the TCAC or is converted to acetoacetic acid which circulates to peripheral tissues as acetoacetic acid, β-hydroxybutyrate and acetone (ketone bodies). These are converted back to acetyl-CoA in cells and enter the TCAC *provided that there is adequate oxaloacetic acid* (derived from carbohydrate metabolism), otherwise ketosis develops.

synthesis of lipoproteins

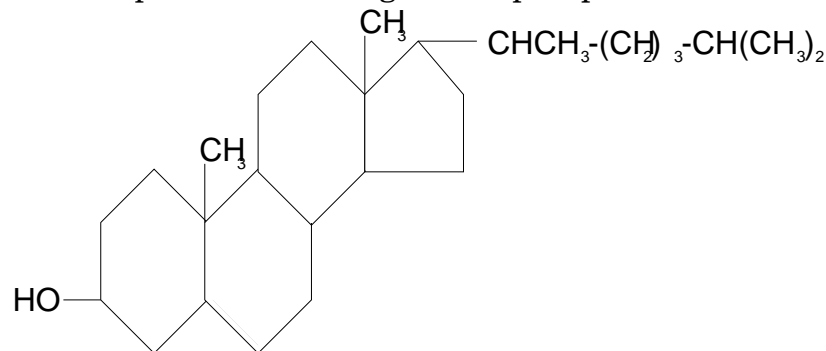
The liver synthesizes VLDL, a lipoprotein containing large amount of triglyceride and some cholesterol and bearing the apoprotein B-100 marker. VLDL circulates to the periphery where lipoprotein lipase hydrolyzes the triglycerides, allowing free fatty acids and glycerol to be taken up by peripheral tissue. The VLDL thus becomes IDL and then LDL, containing mainly cholesterol esters. IDL and LDL are taken up by the liver and by peripheral tissue by pinocytosis following binding of apo B-100 to its receptor.

HDL is formed in the liver and bears apo A-I or A-II on its surface. It is thought to absorb cholesterol from vessels. The details of its circulation are not

fully known.

synthesis of cholesterol and phospholipids

90% of phospholipids are synthesized in the liver and transported via lipoproteins. They are a heterogeneous group of compounds, all containing fatty acids and at least one phosphoric acid radical; most also contain a quaternary nitrogen. They include lecithins, cephalins and sphingomyelin and are required for the formation of cell membranes, lipoproteins, and in specialized applications such as sphingomyelin in nerve sheaths, thromboplastin in clotting and as phosphate donors.

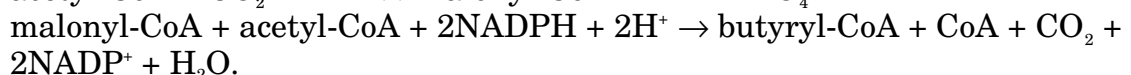
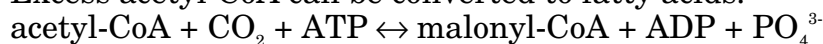


Cholesterol is synthesized de novo in the liver from acetyl-CoA. The rate-limiting step in synthesis is at hydroxymethylglutaryl-CoA reductase which is directly inhibited by cholesterol and by statin drugs. The plasma level of cholesterol is determined partly by dietary intake and substantially by the availability of acetyl-CoA in the liver (which is determined by dietary saturated fat intake).

Most cholesterol in the body is in cell membranes where it affects fluidity of the membrane and also deposits in the stratum corneum to improve the waterproofing of the skin. The majority of non-membranous cholesterol is converted to cholic acid in the liver and conjugated with glycine or taurine to form bile salts which solublize fats in the gut and are reabsorbed (enterohepatic circulation). A small amount is used in the synthesis of steroid hormones.

synthesis of fatty acids from glucose or amino-acids

Excess acetyl-CoA can be converted to fatty acids.



This process is repeated until the fatty acid is 14-18 carbons long, when the fatty acids are condensed with glycerol to form triglycerides. This process is about 85% efficient in storing energy from glucose. Triglycerides are stored in the liver or transported to peripheral fat cells via lipoproteins.

Protein metabolism

storage of amino acids

After absorption from the gut, amino acids are rapidly taken up by cells in the liver and throughout the body by active transport and facilitate diffusion. They are rapidly incorporated into proteins. Intracellular protein is in equilibrium with free amino acids and so is readily broken down for release of amino acids back into the circulation or for their metabolism.

Uptake of amino acids and synthesis of protein is promoted by GH and insulin and antagonized by glucocorticoids.

Albumin is also taken up directly by phagocytosing cells and broken down to amino acids which are then released into circulation.

transamination of amino acids

Nonessential amino acids are formed in the liver primarily by the synthesis of the appropriate α -keto acid followed by transfer of an amino radical from glutamine, glutamate, aspartate or asparagine.

glutamine + pyruvic a. \rightarrow α -ketoglutaric a. + alanine

Several of the aminotransferase enzymes which catalyze these reactions are derivatives of pyridoxine (B_6).

deamination of amino acids

Deamination predominantly occurs by the same pathway as transamination, with the amino radical transferred from an amino acid to α -ketoglutaric acid and subsequent deamination of glutamine:

glutamine + NAD^+ + H_2O \rightarrow α -ketoglutaric a. + $NADH$ + H^+ + NH_3

The α -ketoacid derived from the amino acid which was deaminated can be oxidized, usually through the TCAC.

formation of urea

The NH_3 generated by deamination is toxic and so is used to synthesize urea:

ornithine + CO_2 + NH_3 \rightarrow citrulline + H_2O

citrulline + NH_3 \rightarrow arginine + H_2O \rightarrow urea + ornithine

net: $2NH_3$ + CO_2 \rightarrow $H_2N-CO-NH_2$ + H_2O

Urea is cleared by the kidneys.

synthesis of plasma proteins

90% of plasma proteins are formed in the liver (the remainder are mainly immunoglobulins). Albumin, fibrinogen and globulins as well as clotting factors and some hormones are formed in the liver. The rate of synthesis is 15-50g/day.

Secretion of bile

The liver secretes 600-1200 ml of bile a day. It forms in the bile canaliculi between plates of hepatocytes and passes into collecting ducts, hepatic ducts and the bile duct. The lining of these ducts add volume, Na^+ and HCO_3^- to the bile in response to secretin. Some empties directly into the duodenum and the remainder is temporarily stored in the gall bladder where it is concentrated.

Bile contains plasma electrolytes, bile salts, bilirubin, cholesterol, fatty acids and lecithin. It is relatively alkaline. The mixture may become supersaturated with cholesterol or bile salts, leading to the formation of stones. Emptying of the gallbladder is initiated by cholecystokinin after a meal.

Other functions

The liver stores vitamins A, D and B_{12} .

It stores excess iron by binding with apoferritin to form ferritin, as well as synthesizing transferrin for the transport and absorption of iron.

Detoxification of many drugs and metabolism of many hormones occurs in the liver. Many compounds are oxidized or demethylated by the cytochrome P450 system of enzymes, others are conjugated with UDP by glucuronyl transferase, competing with bilirubin for this pathway.

Excretion of bilirubin

Bilirubin is derived from the breakdown of haem in tissue macrophages. It circulates bound to albumin and is absorbed into hepatocytes. Here it is conjugated with glucuronic acid (80%), sulfate (10%) or other compounds and excreted by active transport into the bile.

In the gut, some conjugated bilirubin is converted to urobilinogen by bacteria which is reabsorbed and filtered by the kidneys, appearing in the urine where it is oxidized to urobilin. Urobilinogen which is not absorbed in the gut is converted to stercobilinogen and oxidized to stercobilin.

Physiological consequences of hepatic disease

Carbohydrate metabolism

- reduced ability to metabolize a glucose load
- reduced sensitivity to insulin both in the liver and peripherally
- reduced ability to metabolize lactate
- reduced glycogen stores

Protein metabolism

- disrupted metabolism of non-branched-chain amino acids, leading to elevation

- in circulating levels of aromatic amino acids
- impairment of the urea cycle and a rise in plasma ammonia
- secondary rise in ammonia due to poor excretion of urea and NH_3 by the kidneys with enterohepatic circulation of urea (converted in the gut to NH_3)
- and potentiation of the effect of NH_3 because of alkalosis.

Lipid metabolism

- the pathogenesis of fatty liver is uncertain
- possibly reduced synthesis of apoproteins, causes accumulation of triglycerides
- possibly increased synthesis of lipids
- longstanding cholestatic disease causes increased LDL and cholesterol and reduced HDL

Synthetic functions

- reduced albumin synthesis, reducing plasma oncotic pressure and binding sites
- reduced clotting factor synthesis (II, V, VII, IX, X) except for fibrinogen

Metabolism of drugs and hormones

- portosystemic shunting
- decreased phase I and II reactions
- ↑ insulin, glucagon, oestrogens

b. Describe the clinical laboratory assessment of liver function and hepatic failure.

Assessment of liver function with laboratory tests requires serial measurements of parameters related to different hepatic functions, interpreted in a clinical context.

Bilirubin metabolism is assessed by plasma conjugated and unconjugated bilirubin, assessing the conjugation and excretion functions. Elevated conjugated bilirubin can also be detected by dipstick testing of urine.

Hepatocellular enzyme levels in plasma are used to assess cellular injury. Aminotransferases (AST and ALT) reflect cellular injury. ALT is more specific to liver tissue and is less elevated in alcoholic hepatitis. Alkaline phosphatase is not specific to liver tissue but is elevated in cholestasis of any cause. γ -Glutamyl transferase is a sensitive indicator of biliary disease and is elevated by all causes of induction of microsomal enzymes.

Serum proteins provide an indicator of the synthetic function of the liver. Albumin has a half-life of about 20 days and is reduced in severe cirrhosis, and also by malnutrition, nephrotic syndrome and other causes. Clotting factors II, VII, IX, X, V and fibrinogen are produced in the liver. A prolonged INR may indicate a failure of synthesis of these factors (especially VII) due to hepatic failure or vitamin K malabsorption.

Other tests include blood ammonia, which is elevated in hepatic failure due to impairment of the urea cycle and correlates with encephalopathy. Elevated triglycerides and abnormal lipoproteins may also reflect impaired lipid metabolism.

Specific tests for causes of liver disease include hepatitis serology, antimicrosomal antibody (PBC), antinuclear antibodies (SLE), α -fetoprotein (hepatoma), Fe studies (haemochromatosis), ceruloplasmin (Wilson's disease), and dozens of other specific tests.

c. Describe the handling of bilirubin in the body.

Bilirubin is derived from the breakdown of haem in tissue macrophages. It circulates bound to albumin and is absorbed into hepatocytes. Here it is conjugated with glucuronic acid (80%), sulfate (10%) or other compounds and excreted by active transport into the bile.

In the gut, some conjugated bilirubin is converted to urobilinogen by bacteria which is reabsorbed and filtered by the kidneys, appearing in the urine where it is oxidized to urobilin. Urobilinogen which is not absorbed in the gut is converted to stercobilinogen and oxidized to stercobilin.

d. Describe the anatomical and physiological considerations in hepatic blood flow, and the changes that occur with anaesthesia.

e. Outline the reticulo-endothelial functions of the liver.

The venous sinusoids in the liver are lined with Kupffer cells, the mononuclear phagocytosing cells of the liver. Portal blood usually contains significant numbers of enteric organisms, especially gram negative bacteria, and Kupffer cells phagocytose foreign organisms, preventing them from entering the systemic circulation.

f. Explain the protective function of the liver between the gut and body.

The liver provides a barrier between the portal and systemic circulations. In its reticulo-endothelial functions it acts as an effective barrier against infection. It also acts as a metabolic buffer between the highly variable contents of the gut and portal blood and the tightly controlled systemic circulation.

By absorbing, storing and releasing glucose, fat and amino acids, the liver plays a vital role in homeostasis. It also stores and releases vitamins A, D and B₁₂. It metabolizes or deactivates most of the biologically active compounds absorbed from the gut, such as drugs and bacterial toxins. It performs many of the same functions in systemic blood entering from the hepatic artery, processing a total of 29% of cardiac output.

g. Describe the portal circulation and its significance.

The gut receives its blood supply from the coeliac axis, superior and inferior mesenteric arteries. Venous drainage from the gut from the level of the lower oesophagus to the anal canal ultimately drains into the portal vein and into the liver. The total flow from the portal vein is about 1.1 l/min at about 9 mmHg. All substances absorbed from the gut, with the exception of lipids which pass into the lymph, must pass through the liver before entering the systemic circulation.

Cirrhosis or right heart failure cause an increased resistance to flow in the liver, leading to a rise in pressure in the portal venous system. This causes transudation of fluid into the gut and peritoneal cavity, and in the long term, dilatation of veins at the sites of portosystemic anastomosis: the lower oesophagus, bare area of the liver, umbilicus and anal canal.

J. Haematology

a. Explain the origin and importance of blood groups.

ABO blood groups are determined by an autosomal gene. Each copy may express A, B or no antigen on the surface of erythrocytes. Blood is thus classified as O (45%), A (41%), B (10%) or AB (4%) according to whether none, one or both antigens are expressed. The A antigen can be further subtyped as A₂ (plain A) or A₁ (A and A₁) and other rare groups.

People normally express IgG and IgM against the AB antigens not expressed on their own red cells. Thus if blood expressing an antigen against which a high IgM titre is present is transfused, rapid agglutination of the infused red cells occurs with activation of complement and rapid haemolysis: a major transfusion reaction. This leads to circulatory collapse and renal failure. In the presence of a lower titre of IgM or IgG, agglutination and haemolysis occurs more slowly. Prior to any matched transfusion, donor and recipient blood are mixed in vitro and checked for agglutination.

Rhesus antigens are expressed on all red cells. They are of three classes: C, D, and E and each antigen is expressed as one of two types (C or c, D or d etc.) The C and E antigens are not strongly antigenic. The D antigen is most antigenic so RhD is described as “Rhesus positive” and Rhd as “Rhesus negative”. RhD has an 85% prevalence in Caucasians and higher in negros.

Anti-D IgG is usually only formed in Rh negative people in response to exposure to Rh positive blood. This can occur through unmatched transfusion or more commonly through carriage of an Rh positive foetus with foetal-maternal haemorrhage at delivery or earlier. Sensitization to D antigen results in expression of anti-D IgG in the mother. As IgG is transferred across the placenta, this results in haemolysis in any subsequent Rh positive foetus, called *Erythroblastosis foetalis*. This can be prevented by the administration of anti-D antibody at the time of likely foetal-maternal haemorrhage to remove any Rh positive blood from the mother's circulation before antibodies are expressed.

b. Outline the constituents and functions of plasma.

Plasma comprises about 18% of extracellular fluid, or 5% of bodyweight. It is the non-cellular part of the blood, being about 60% of blood volume. It is 0.7% solids, so measured concentrations of ions *per litre plasma* are lower than the actual concentrations per litre of water present.

The ionic composition of plasma is similar to that of interstitial fluid, except for a higher protein concentration and (because of the Gibbs-Donnan equilibrium) a slightly higher concentration of diffusible cations. Typical constituents (in mOsm/l) are:

| | |
|-------------------------------|-----|
| Na ⁺ | 142 |
| K ⁺ | 4.2 |
| Ca ²⁺ | 1.3 |
| Mg ²⁺ | 0.8 |
| Cl ⁻ | 108 |
| HCO ₃ ⁻ | 24 |
| phosphates | 2 |
| SO ₄ ⁻ | 0.5 |
| amino acids | 2 |
| creatine | 0.2 |
| lactate | 1.2 |
| glucose | 5.6 |
| protein | 1.2 |
| urea | 4 |
| other ions | 4.8 |

The osmolality of protein in plasma is low but the high molecular weight of proteins means that they are a major constituent of plasma when measured by weight.

The protein constituent of plasma can be fractionated by electrophoresis into albumin and α , β and γ globulins and other proteins such as fibrinogen. Albumin makes up over half the protein content by weight and 75% of the oncotic pressure. It and a number of globulin proteins bind circulating hormones and drugs. Albumin also provides a source of amino-acids to tissues.

The globulin proteins include many specialized binding proteins, the immunoglobulins and enzymes such as the clotting factors. Fibrinogen plays an important role in blood clotting.

c. Describe platelets and their role in coagulation.

Platelets are non-nucleated membrane-bound elements of blood 2-4 μm in diameter derived from megakaryocytes in the marrow. They are normally present in blood at $150\text{--}300 \times 10^9/\text{l}$ with a half life of 8-12 days. Though they have no nucleus, they do have contractile elements (actin, myosin and thrombosthenin), SER and Golgi apparatus and mitochondria and are capable of synthesizing prostaglandins and thromboxane, peptides and other messengers.

Function

adhesion

- to damaged endothelium via vWF to group Ib, IX receptors
- to collagen via group IV receptors
- to each other via IIb, IIIa receptors

activation and shape change

- release of ATP, ADP, serotonin (activate other platelets)
- vWF, factor Va, VIIIa, phospholipid, βTG (activate coagulation)
- synthesize TXA_2
- express receptors for aggregation (IIb, IIIa)

aggregation

- via receptors and fibrin
- activation of factor XIII to crosslink fibrin
- activation of contractile elements

d. Describe the coagulation cascade.

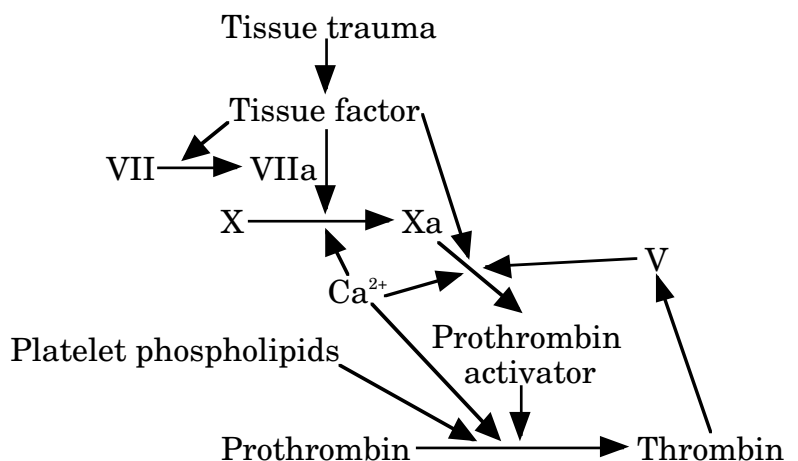
The coagulation cascade is described in two pathways: extrinsic and intrinsic, which converge on the activation of factor X and the common pathway.

The extrinsic pathway is the simpler and, in vivo, more rapid. Traumatized tissue releases a tissue-specific combination of compounds called tissue thromboplastin. This activates factor VII which, together with Ca^{2+} , activates factor X.

Prothrombin activator is formed as a complex of Xa, V and phospholipids from tissue or platelets in the presence of Ca^{2+} .

The factor V is initially inactive, but once prothrombin activator converts prothrombin to thrombin, this activates factor V and greatly accelerates the action of prothrombin activator.

The intrinsic pathway is a slower clotting mechanism which does not require initiation from tissue damage. Exposure of the blood to a wettable surface such as glass or collagen will both activate platelets and factor XII. The cascade of



clotting factor activation proceeds through factors XI and IX.

Activation of factor X requires the presence of not only factor IX but also VIII, Ca^{2+} and phospholipids from activated platelets or damaged tissue.

Factor Xa participates in the formation of prothrombin activator as in the extrinsic pathway. There are a number of inherited defects of clotting factors which impair clotting on the intrinsic pathway: haemophilia A (VIII), haemophilia B (IX), von Willebrand's disease (VIII cofactor) and other rarer conditions.

The common pathway is the means by which prothrombin activator leads to clot formation. In the presence of activated platelets, prothrombin is bound to the platelet surface where it is more readily cleaved to form thrombin.

Thrombin cleaves fibrinogen, exposing its reactive sites for polymerization which occurs spontaneously, forming long fibres. These are weakly bound until activated factor XIII, derived from platelets catalyzes the covalent cross-linking of fibrin.

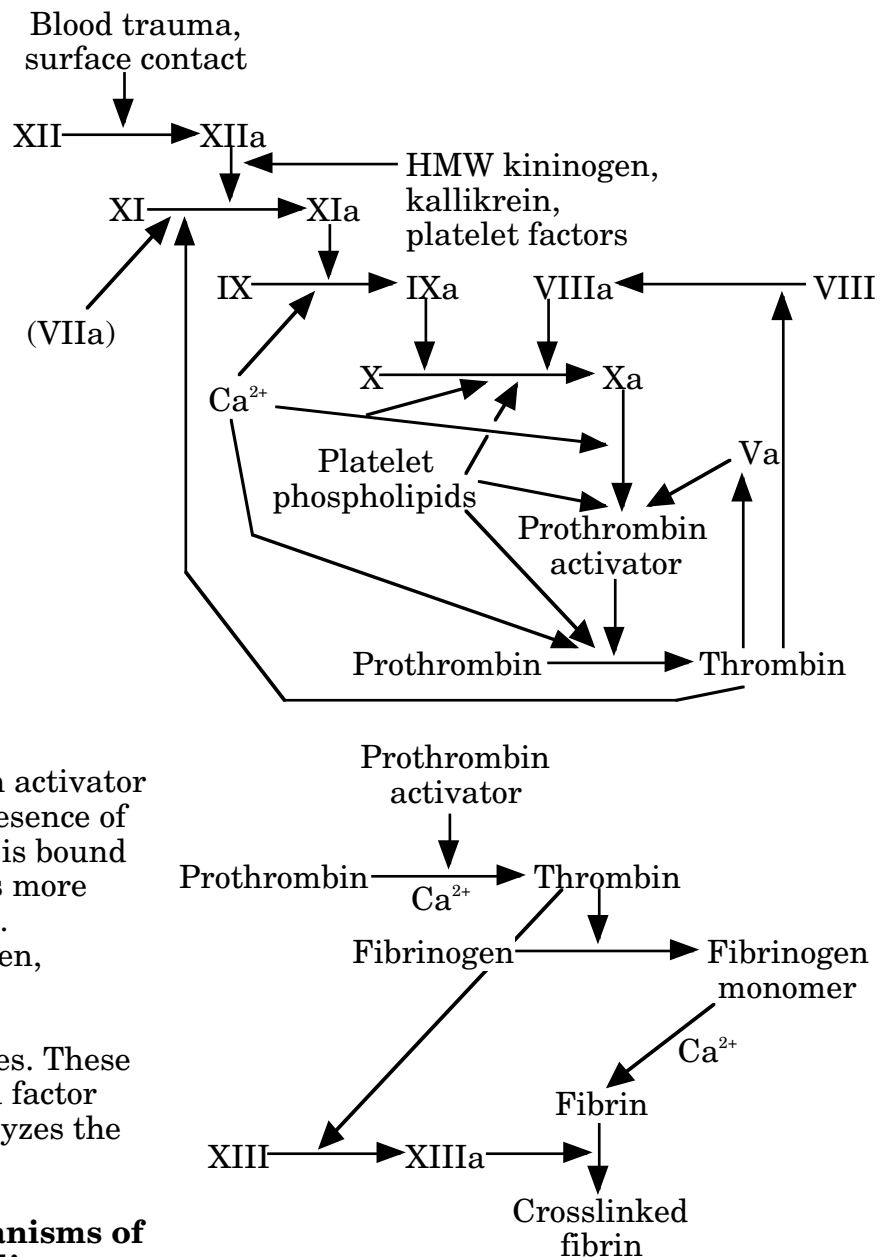
e. Describe the normal mechanisms of preventing thrombosis including endothelial factors and natural anticoagulants.

Endothelium absorbs mediators involved in inflammatory response and coagulation: PGF_2 , serotonin, adenosine, histamine, complement and other mediators. It synthesizes or releases plasminogen activator, proteoglycan, PGI_2 , heparin and protein C which play an inhibitory role in coagulation as well as factor VIII, von Willebrand factor and tissue factor. Antithrombin III is synthesized in the liver and circulates in the plasma.

Because normal blood coagulation is a positive-feedback process, there are mechanisms to prevent inappropriate spontaneous coagulation and limit the spread of clot. The endothelium is smooth and lined with glycocalyx which repels platelets and clotting factors. Thrombomodulin is bound to the endothelial membrane. It binds thrombin and, when thrombin is bound, activates protein C and protein S which inactivate factors V and VIII.

The release of PGI_2 from the endothelium inhibits thrombus formation. It acts via intracellular cAMP on endothelial smooth muscle to produce vasodilation and platelets to inhibit aggregation and the production of phospholipid.

In the process of clot formation, thrombin is strongly bound to fibrin fibres, limiting its range of action. The plasma protein antithrombin III binds circulating thrombin and



inactivates it. The action of antithrombin III is greatly enhanced by binding of antithrombin III to heparin. Heparin-antithrombin III complex also binds activated factors XII, XI, IX and X. Small amounts of heparin are released from mast cells and basophils and this presumably plays a role in the lysis of small pulmonary emboli, but systemic anticoagulation is rapidly induced using large IV doses of heparin derived from animal tissues.

Heparin is a collection of polysaccharides of different molecular weights, all of which are highly negatively charged. Fractions of the range of heparin molecules are used clinically. The effect of heparin can be titrated using protamine, a highly positively charged molecule which binds circulating heparin and prevents it from acting as an anticoagulant.

Alpha₂-macroglobulin is a plasma protein which binds activated clotting factors but does not inactivate them.

f. Describe fibrinolysis and its regulation.

Plasminogen is a plasma protein which is trapped in the formation of a clot. Tissue plasminogen activator (tPA) is slowly released from injured endothelium and tissues and activates plasminogen to form plasmin. Kallikrein also activates plasmin. Plasmin is a protease which degrades fibrin, factors V, VIII and XII, thrombin and fibrinogen, causing lysis of the clot. This typically occurs hours to days following clot formation.

The action of plasmin is limited by PAI-1 and 2 and circulating alpha₂-antiplasmin which prevents any low levels of circulating plasmin from lysing clots. tPA or the similar enzyme streptokinase can be used to initiate the lysis of clots in the coronary or cerebral circulation as a therapeutic intervention. It is also used for clearing clot from long-term indwelling central lines.

g. Outline methods for assessing coagulation, platelet function and fibrinolysis.

A functional test of clotting is a bleeding time. A standardized cut is made on the skin and the time of bleeding measured. Unfortunately this is a difficult test to calibrate. It is a good test of platelet function as the formation of a platelet plug is usually the reaction limiting the duration of bleeding, but if the time is prolonged, it does not indicate the nature of the clotting defect.

A platelet count has good predictive value of the risk of bleeding if the platelets are known to be of normal function. A count below $50 \times 10^9/l$ is associated with substantially prolonged bleeding time and below $20 \times 10^9/l$ is associated with dangerous spontaneous haemorrhages.

The function of the extrinsic and common pathways is assessed by prothrombin time (or INR). A specimen of plasma at 37° is citrated (to bind any ionized Ca^{2+}) and an excess of tissue factor and Ca^{2+} are added as a timer is started. The time taken to coagulate is an most commonly used to assess the effect of coumarin anticoagulants which impair synthesis of factors VII, IX, X and prothrombin.

The function of the intrinsic and common pathways is commonly measured using activated partial thromboplastin time (APTT). Citrated plasma at 37° is combined with kaolin and cephalin before an excess of Ca^{2+} is added and the time taken to coagulate is measured. This screens for the adequacy of factors XII, XI, IX, VII, PK and HMWK as well as the common pathway. It is used to adjust the dose of heparin used for anticoagulation.

The common pathway is assessed using a thrombin time (TT). Thrombin as added to plasma and the time taken to coagulate measured. Ca^{2+} is not required for coagulation in this test.

In cardiopulmonary bypass, large doses of heparin are used, and clotting is assessed using the activated clotting time (ACT), an automated device optimized for assessing supratherapeutic heparinization. ACT is in excess of 400 s for bypass.

None of these tests will detect factor XIII or alpha₂-antiplasmin deficiency and they may miss vWF deficiency which can be cyclical, so they cannot exclude the possibility of excessive bleeding. There is also a substantial functional reserve in the concentration of

most clotting factors. In haemophilia A, symptoms are uncommon while the factor VIII level is above 5% of normal.

To determine a specific cause for defective clotting, it is necessary to do specific factor assays and test for the presence of anticoagulant factors such as anti-factor antibodies.

The function of the fibrinolytic system can be assessed by clot lysis time. This is shortened in α_2 -antiplasmin deficiency. Circulating fibrin degradation products can be assayed and give some information about the amount of clot lysis occurring. Fibrin cross-linking can be assessed by clot solubility in 5 M urea, which is increased in factor XIII deficiency.

h. Explain the physiological consequences of acute and chronic anaemia.

Anaemia is defined as a reduction in red cell mass below the normal range. The normal range differs with age, sex, environment and pregnancy. Acute blood loss, as in surgery, results in rapid fluid shift from the interstitial compartment to the intravascular compartment, usually supplemented by IV fluid. This results in a rapid fall in red cell count due to dilution.

The immediate effects of an acute fall in red cell mass are a reduction in the viscosity of blood and a reduction in the oxygen carrying capacity of blood. The majority of the oxygen carrying capacity is made up by haemoglobin, so a fall in Hb from 150 g/l to 100 g/l results in a fall in oxygen carrying capacity from 20 ml/100 ml to 14 ml/100 ml. If metabolic rate is unchanged, this requires a lower mixed venous PO_2 or increased cardiac output to maintain oxygen flux. Both of these changes occur, the rise in CO being facilitated by the reduction in viscosity. Impaired tissue oxygenation also results in increased production of 2,3DPG which facilitates oxygen transfer by moving the dissociation curve to the right. Dyspnoea results in increased ventilation with some increase in P_{AO_2} .

Within hours of acute blood loss, red cell production rises, stimulated by the impairment of tissue oxygenation causing release of erythropoietin. A rise in reticulocyte count to 10-15% over a week and a rise in platelet and white cell counts occur as they are mobilized from marginal sites.

The physiological changes in chronic anaemia depend partly on the cause of the anaemia. Reduction in oxygen carrying capacity is always present and results in the same physiological responses as acute anaemia: increased ventilation, CO, 2,3DPG and reduced mixed venous PO_2 .

The haematological changes depend on the cause of the anaemia which can be classified as haemorrhagic, aplastic or haemolytic and subclassified in more detail.

i. Outline the production of blood constituents including red blood cells, haemoglobin and plasma proteins.

The cellular elements of blood are derived from the bone marrow and lymphoid tissue (and liver and spleen in the neonate). Putative pluripotent stem cells in the marrow give rise to lymphoid and myeloid stem cells. Lymphoid stem cells differentiate into pro-T and pro-B lymphoid cells which mature in the thymus or lymph nodes into T and B lymphocytes (and plasma cells). Lymphoid cell lines are distinguishable only by cell surface markers.

Myeloid stem cells differentiate into colony forming units (CFU) of the eosinophil (CFU-Eo), granulocyte/monocyte (CFU G/M) or erythroid/megakaryocyte (E/Mega) lines which further differentiate into five distinct lineages. The committed stem cells (pro-lymphoid and CFU cells) are capable of self-replication and this is the level at which the marrow population of stem cells is maintained. The replication and differentiation of the precursor cells is regulated by stimulating factors (erythropoietin, G-CSF, GM-CSF and others).

The myeloid and erythroid cell lines differentiate through several morphologically distinct stages. The erythroid line begins with the proerythroblast, a nucleated cell devoid of haemoglobin which gradually increases its haemoglobin content and reduces its size, finally losing all cytoplasmic organelles as a reticulocyte. The differentiation from stem cell

to erythrocyte takes about a week.

Haemoglobin is synthesized in erythroid cells from the proerythroblast stage. It consists of four globin chains ($\alpha_2\beta_2$ in adult Hb) each covalently linked to a haem molecule. Haem is synthesized from glycine, succinyl-SCoA and Fe^{2+} . Synthesis is commonly limited by Fe deficiency, resulting in hypochromic microcytic anaemia. The rate-limiting step in haem synthesis is the condensation of succinyl-SCoA and glycine to form δ -aminolaevulinic acid. This step also requires pyridoxine. 2 δ -aminolaevulinic acid molecules are condensed to form a pyrrole ring, 4 of which are required to form protoporphyrin IX. This coordinates with four of the six coordination points on Fe^{2+} , to form haem.

The globin chains are synthesized in the RER of erythroid cells, each having a molecular weight of about 16,000. 97% of haemoglobin in normal adults is Hb A ($\alpha_2\beta_2$), most of the remaining 3% is Hb A₂ ($\alpha_2\delta_2$), with very small amounts of Hb F ($\alpha_2\gamma_2$). These proportions are different in thalassaemia, where the production of one chain type is disordered.

Plasma proteins can be subdivided by electrophoresis into α_1 , α_2 , β_1 , β_2 and γ fractions and fibrinogen. All the fractions are produced almost entirely in the liver, with the exception of γ -globulins which are produced in lymph nodes and small quantities of other proteins and peptide hormones which are produced in many different organs.

Albumin turnover is about 200-400 mg/kg/day from a total pool of 4-5 g/kg.

j. Outline the constituents of blood products, their source, role and risks.

Whole blood

Rarely used in Australia. A single donation of 450 ml of whole blood in 63 ml acid-citrate-dextrose anticoagulant including all cellular and plasma protein elements. Donors are screened by questionnaire and blood is screened for HIV, HTLV, Hep B, Hep C, CMV, syphilis and other antibodies. There is still a risk of infective blood being taken prior to seroconversion. This is a serious problem with hepatitis C and there remains a 0.01% risk of contracting hepatitis C from donor blood. There is also a smaller risk of contracting other hepatitides (hep B $1/_{250,000}$) or theoretically HIV. All blood transfusions must be ABO matched and other antigens are matched if possible to minimize the risk of transfusion reaction.

Packed red cells

A single donation of blood with most of the plasma removed and resuspended in isotonic solution, giving a volume of about 350 ml. The infection and reaction risks are the same as for whole blood. PRBC are typically deficient in white cells, clotting factors (especially V and VIII) and platelets, increasing the risk of bleeding following large transfusions. Transfusion also has a general immunosuppressive effect, possibly increasing the risk of infection or metastasis.

Used for replacement of blood loss if the loss of red cell mass is likely to cause problems with oxygen transport (not just for volume expansion).

There are special preparations of packed cells: neonatal and paediatric volumes, CMV negative, washed, irradiated and phenotyped units.

Platelets

The platelet fraction of a single donation of blood in plasma (30-60 ml). Usually 5×10^{10} platelets. Rise in platelet count is highly variable. Platelets lose function rapidly and so are kept agitated at 20°C and used within 5 days. Small numbers of white cells remain in the plasma fraction and carry the risk of febrile reactions, CMV infection and also GVH disease in marrow transplant patients.

Platelets express HLA antigens and so transfusions will provide a more sustained rise if major HLA antigen matching is performed. This is not common practice. Febrile reactions and rigors are common (20%) with platelet transfusion.

Platelet transfusion is used in well patients with a count below $10 \times 10^9/l$ as they risk spontaneous haemorrhage and in patients undergoing unavoidable surgical procedures with a count less than $80 \times 10^9/l$ or dysfunctional platelets.

one unit should raise platelet count by $10 \times 10^9/l$

most common source of bacterial contamination in transfusion

FFP

Fresh frozen plasma is the plasma fraction of a single blood donation (180-240 ml), frozen to maintain function of clotting factors and other plasma proteins. It is thawed immediately before use.

Infection risk as for whole blood

FFP is used in patients with multiple clotting factor deficiencies who are at risk of serious bleeding (e.g. DIC, warfarin overdose).

cryoprecipitate

a fraction of about 10 ml which precipitates when a unit of FFP is thawed contains high concentrations of factors VIII, XIII, vWF, fibronectin and fibrinogen, though less than a unit of FFP

previously used for factor VIII deficiency

used in fibrinogen deficiency induced by massive transfusion and some chemotherapy agents

probably does not require ABO matching, but may cause alloimmunization

factors

Heat-treated fractions of pooled human plasma containing high concentrations of factor VIII or IX are used for haemophilia. These solutions no longer carry HIV, but did prior to 1988.

Intragam

60 g/l solution of human IgG fraction. Used for ITP, myasthenia gravis, CFS (controversial) and immune deficiencies.

Other immunoglobulins

Human immunoglobulin fractions are available for specific purposes: hepatitis B, rabies, CMV, Rh D, tetanus and zoster IgG solutions are available for patients with high-risk exposures or immune deficiency. These are all heat-treated.

Some animal-derived immunoglobulin fractions are used as antisera for envenomations. They are sheep, horse or rabbit derived and often cause hypersensitivity reactions. There is unlikely to be any risk of infection transmission from other species.

Albumex

Heat-treated human albumin solution available as 40 g/l (500 ml) and 200 g/l (100 ml). Used as a plasma expander or for priming bypass equipment, an (expensive) alternative to Haemaccel. Derived from pooled plasma, but should carry no risk of infection as it is heat-treated.

A number of other hormone preparations are still blood- or tissue-derived.

k. Describe the changes during blood storage and the problems of massive blood transfusion and their management.

At the time of collection, a blood donation is a normal venous sample. In the production of packed cells, most of the plasma and plasma proteins are removed and the remaining cells and fluid are sealed in a sterile plastic bag in an isotonic solution and stored at $1-6^\circ\text{C}$. This is an anaerobic environment in which red cell metabolism continues, though at a greatly reduced rate due to the low temperature. Hypoxia results in progressive depletion of ATP from red cells and consequent failure of the Na^+/K^+ -ATPase pump, resulting in unopposed leakage of K^+ from the cells. Red cells have a mean lifetime of 120 days, so a small proportion of the cells will lyse within the storage period. Almost all the white cells and platelets remaining within the unit will lyse within a few days.

| | Collection | 35 days old |
|------------------|--------------|----------------------|
| pH | 6.8 | 6.3 |
| PCO ₂ | 45 mmHg | ≈200 mmHg |
| PO ₂ | 40 mmHg | <1 mmHg |
| 2,3 DPG | 10 μmol/g Hb | 0 |
| Na ⁺ | 145 mM | 100 mM |
| K ⁺ | 1.7 mM | 26 mM |
| Ca ²⁺ | citrated | citrated |
| Hct | 60% | (70% viable for 24h) |
| free Hb | 10 mg/l | 1000 mg/l |

The gas and electrolyte changes in packed cells are usually rapidly compensated for on transfusion. Respiratory compensation occurs for the high PCO₂ and low PO₂. Citrate and lactate enter the TCAC, releasing Ca²⁺. The red cell Na⁺/K⁺-ATPase pump restarts and sequesters much of the K⁺ load.

Erythrocytes can also be frozen. This requires preparation in glycerol and storage at –65°C for up to 3 years. There is little change in frozen preparations from the time of freezing and near-normal function on thawing and deglycerolization. The cost of this sort of storage restricts its use to rare blood types.

Problems associated with massive blood transfusion

defined as replacement of blood volume in under 24 hours

problems with any blood transfusion: acute and delayed reactions

volume

difficulty maintaining normal volume status (monitor CVP, PCWP, UO)

hypothermia from infusion below body temperature (blood warmer, monitor T)

dilution of any drugs in the circulating compartment

electrolytes

CO₂ and acid load causes transient acidosis

K⁺ load may cause hyperkalaemia, arrhythmia (monitor ECG, gases)

citrate load requires hepatic metabolism to avoid hypocalcaemia

citrate is metabolized to pyruvate and HCO₃⁻, raising pH a little

red cells

poor oxygen carrying capacity on infusion (high FiO₂, monitor SaO₂)

free haemoglobin from lysed cells may cause renal failure

iron load

clotting

dilution and consumption of platelets and clotting factors results in coagulopathy

treat with FFP for clotting factors and platelets

other

increased risk of blood-borne virus infection

alloimmunization (minor RBC antigen or HLA)

haemolytic or febrile reactions

adenine metabolites may cause renal impairment (>60 units required)

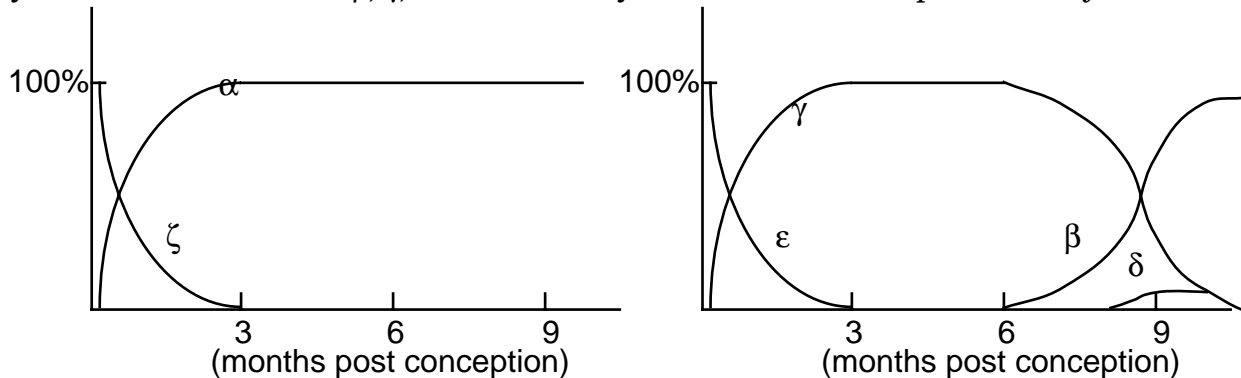
1. Describe the breakdown of haemoglobin.

When red cells break down in circulation, most commonly in the sinusoids of the spleen, their haemoglobin is phagocytosed by mononuclear cells. The globin chains are metabolized as are any proteins to amino acids which are returned to circulation. The Fe is split from haem and bound to ferritin where it is again available for metabolism or transport bound to transferrin. The porphyrin ring is oxidized to biliverdin and carbon monoxide and then to bilirubin which is transported bound to albumin.

Unconjugated bilirubin is conjugated in the liver with UDP glucuronate, this more soluble conjugate is excreted in bile. Some of the excreted bilirubin is converted by gut organisms to urobilinogen which is reabsorbed across the mucosa and renally excreted as urobilin. Urobilinogen which is not absorbed may be converted to stercobilinogen and stercobilin, colouring the faeces.

m. Describe abnormal haemoglobins and their clinical significance.

There are over 500 haemoglobin variants described, most of which are rare and of little clinical significance. The genes coding for globin chains are on chromosomes 16 (α and ζ) and chromosome 11 (β , γ , δ and ϵ). The ζ and ϵ chains are expressed only in the embryo.



Many Hb variants are single amino acid substitutions in the β chain. In Hb S, valine is substituted for glutamic acid in position 6. This results in Hb which when deoxygenated will polymerize via hydrophobic bonding between two loci on the β chain. The polymerized crystals of Hb S and Hb A result in cell rupture and infarction of tissue as well as haemolytic anaemia.

Homozygotes for Hb S have a reduced life expectancy and persistent anaemia due to a red cell survival time of only 10-15 days. They suffer multiple painful infarcts, particularly to the renal medulla and spleen, and may have aplastic crises precipitated by folate deficiency or by infection. Hb S has a reduced affinity for oxygen, so homozygotes have reduced saturation for their PO_2 and display increased physiological shunt. Crises are precipitated by hypoxia, hypovolaemia and cold.

Heterozygotes for Hb S will also express normal β chains and so have a mixture of Hb SS, AS and AA. They suffer the same complications of sickling, but a much lower PO_2 is required to induce sickling, so symptoms are less frequent and severe.

Hb C is the result of a substitution in the β chain of lysine for glutamic acid at position 6. It is largely asymptomatic in the Hb AC heterozygote. In SC heterozygotes, symptoms similar to mild Hb SS disease are seen, with ocular complications prominent. CC homozygotes have a mild haemolytic anaemia and splenomegaly with target cells on the blood film due to intracellular water and potassium depletion.

Hb E ($\beta 26 \text{ Glu} \rightarrow \text{Lys}$) is more common in SE Asians. It results in decreased Hb synthesis but normal oxygen binding. It is asymptomatic and causes a microcytosis on blood film.

Many other Hb variants are poorly soluble but have normal oxygen affinity. These are asymptomatic, but cause Heinz bodies on the blood film.

Some Hb variants have increased oxygen affinity, resulting in reduced tissue oxygenation and secondary polycythaemia.

Rare Hb variants such as Hb M have decreased oxygen affinity which is manifest as familial cyanosis.

Thalassaemias are manifestations of defective α or β chain genes, resulting in an abnormal proportion of globin chains in erythrocytes. There are normally four α and two β genes.

α thalassaemia is clinically manifest when there is only one functional α gene. The excess of β chains results in precipitates of Hb H (β_4) seen as Heinz bodies. There is anaemia

with microcytosis and hypochromia and many target cells. α thalassaemia is most common in negroes and Mediterranean groups. The complete absence of functional α genes results in hydrops foetalis, which is incompatible with life as Hb Barts (γ_4) is the only foetal Hb produced.

β thalassaemia is more common in SE Asians and Southern Italians. Those with one non-functioning β gene show a mild anaemia with an increased red cell count and marked microcytosis. There is mild splenomegaly and no clinical signs. Hb electrophoresis shows increased Hb A₂.

Homozygotes (thalassaemia major) develop severe anaemia from 4-6 months of age as production of Hb A should be increasing. They develop delayed growth and maturation with abnormal bone growth from marrow expansion. Splenectomy, transfusion and possibly bone marrow transplantation are required for survival if there is no production of Hb A. Some homozygotes have sufficiently increased Hb A₂ and Hb F to reduce their symptoms somewhat or have reduced rather than absent β chain synthesis.

All the possible heterozygote states have been described: Hb S/ β thal etc. and show varying severity and range of symptoms.

K. Nutrition and Metabolism

a. Define basal metabolic rate and describe its measurement.

The rate of energy expended by the body at rest at room temperature 12 hours after a meal. Normal value is expressed divided by surface area: 40 kcal/m²/hr (50 W/m²)

Measured directly using an Atwater-Benedict chamber (calorimeter).

Measured indirectly using O₂ consumption at rest and assuming 4.82 kcal/lO₂ (20 kJ/lO₂). A more accurate measure can be obtained from measuring CO₂ production concurrently and calculating R or allowing for dietary constituents.

b. Describe the factors that influence basal metabolic rate.

sex males 10-15% more than females

age

BMR double adult value per unit bodyweight at birth
falls to a plateau through adulthood and falls further in old age

increased

fever, hyperthyroidism, ↑ GH, sympathetic stimulation

ingestion of food, especially protein

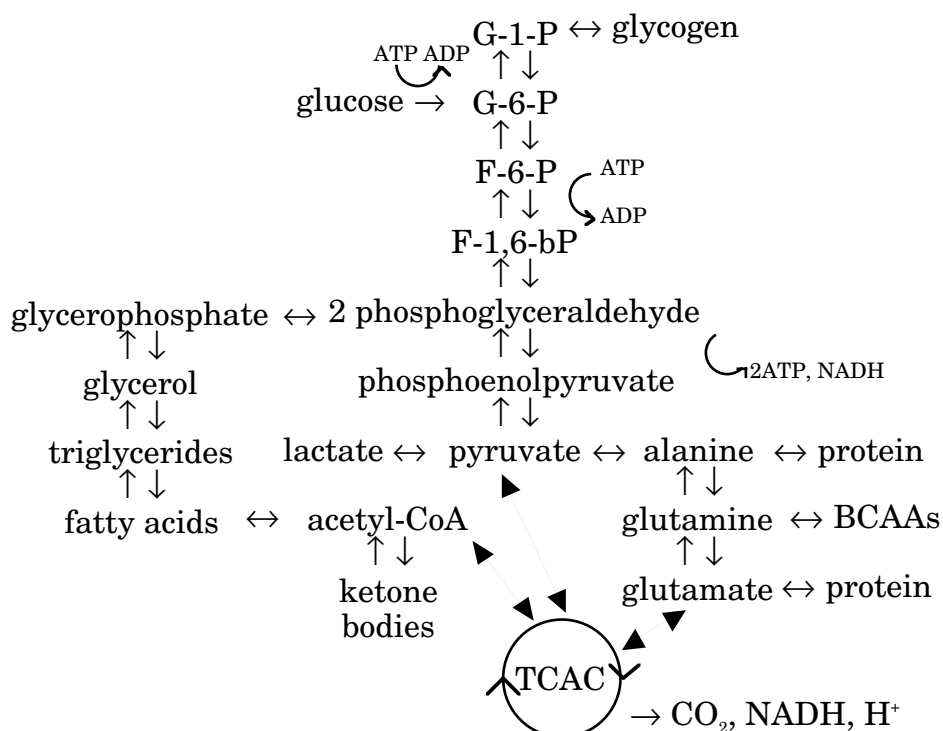
activity

decreased

sleep (by 10-15%)

starvation

c. Describe relevant cellular biochemical pathways and the control of fat, carbohydrate and protein metabolism including the role of vitamins and trace elements.



yield

| | |
|------------|---|
| acetyl-CoA | 12 ATP per turn of the TCAC |
| glucose | 2 ATP anaerobic, 38 ATP aerobic |
| G-6-P | 3 ATP anaerobic, 39 ATP aerobic |
| fats | 17 ATP per 2 C unit less 7 ATP overhead |

energy value

| | |
|--------------|----------|
| carbohydrate | 4 kcal/g |
| protein | 4 kcal/g |
| ethanol | 7 kcal/g |
| fat | 9 kcal/g |

d. Explain the physiological principles of parenteral nutrition.

acute stress

responses below

TPN will not help as excess energy substrate is already being mobilized
just increases CO₂ load, urinary N load and risk of fatty liver

after several days

benefits from providing energy substrates to reduce protein catabolism

fat up to 1 g/kg/day as Intralipid (omega-6-fa → immunosuppression)

carbohydrate up to 4 g/kg/day

monitored with metabolic cart

measures RER

normal 0.85

>1 suggests fat synthesis (→ ↓ carbohydrate intake)

nitrogen around 0.2 g/kg/day (= a.a. 1.3 g/kg/day)

depends on nitrogen balance

= $\text{urea}_{\text{urine}} \div 16.7 \times 28/60 - \Delta \text{urea}_{\text{plasma}} \times 0.6 \times \text{weight}$

increased N increases urinary solute load

some units tie caloric input to N input (possibly obsolete)

total energy intake typically 1700 kcal/day (usage ≈ 2500 kcal/day)

hypocaloric nutrition is practised in some units

electrolytes must be monitored separately

tendency to loss of K⁺ and Cl⁻ resulting in alkalosis

intracellular K⁺ deficit reflected in ↓ [Na⁺]_{plasma} due to osmolarity effect

starved patients

small glucose load in first few days until ketosis resolves

then fat

trace element and vitamin deficiencies are unmasked by nutrition

e. Describe the consequences of anaerobic metabolism.

glucose → 2 pyruvate → 2 lactate yields net 2 ATP per glucose molecule

does not require O₂ or NAD⁺ or mitochondrial e⁻ transport function

does not produce CO₂

results in ↑ lactate ↓ pH

subsequent metabolism of lactate to glucose (Cori cycle) requires O₂ (oxygen debt)

f. Describe the physiological consequences of starvation.

reserves

| | | |
|----------|-------|-------------------------|
| fat | 15 kg | 141,000 kcal |
| protein | 6 kg | 24,000 kcal (available) |
| glycogen | 75 g | 300 kcal |

muscle glycogen cannot be liberated as glucose

liver glycogen provides for a few hours of metabolism

some tissues are glucose-dependent

RBC, marrow, renal medulla, peripheral nerves

the brain requires some glucose, but can also use ketones

during starvation, adaption gradually reduces the glucose requirement to a minimum

obligatory glucose use requires protein breakdown and nitrogen loss

initial rapid protein breakdown until adaption occurs

nitrogen loss falls after two days

ketone bodies rise for two to three weeks

renal ketone excretion is titrated with NH_4^+

↑ glutamine use by the kidney

supplemental glucose or glycerol (in fat) reduces protein breakdown

gluconeogenesis

transamination of pyruvate yields alanine and α -ketoglutarate yields glutamate and glutamine (mainly from muscle)

branched-chain amino-acids are used to provide amine groups and their keto-acids enter the TCAC

alanine and glutamine enter the gluconeogenic pathway in liver and kidney, yielding glucose and urea

glycerol from triglyceride breakdown also provides a substrate for gluconeogenesis
capacity: 85 g/day (20 g from protein, 15 g from glycerol, rest from recycling lactate etc.)

ketosis

low intracellular glucose → low pyruvate, oxaloacetate (carrier for TCAC)

acetyl-CoA cannot enter the TCAC (lack of oxaloacetate)

→ acetoacetyl-CoA → acetoacetate, β -hydroxybutyrate (in liver)

circulating ketone bodies can be taken up by other cells and enter the TCAC

g. Describe the metabolic consequences of sepsis, burns and trauma, as well as the effects of anaesthesia in this setting.

stress response

local mediators

tissue damage

inflammatory mediators: PGs, bradykinin, substance P, serotonin, histamine, cytokines

nociceptive afferents (A δ and C fibres) → anterolateral and dorsal columns

central mediators

↑ ACTH, GH, prolactin, ADH

↑ sympathetic outflow

produces endocrine and metabolic responses

endocrine

steroid response

↑ cortisol, aldosterone

↑ renin-angiotensin

↑ insulin, ↑ glucagon

inflammatory mediators

NO, 20-HETE, $\text{PGF}_{2\alpha}$, TXA_2 , PAF, LTs, ILs

expression of cellular iNOS

metabolic

↑ MR, T, O_2 consumption, CO_2 output

mediators alter distribution of blood flow: ↓ α response, vasodilation

catabolism of protein, fats and carbohydrate stores

↑ plasma glucose, rapid glucose turnover in anaerobic metabolism
catabolism of muscle protein for gluconeogenesis and synthesis of protein
inflammatory mediators

does not fall after a few days if stress continues (unlike starvation)

↓ synthesis of albumin, prealbumin, transferrin

rapid cycling of triglycerides to fatty acids and back again in the liver

inadequate VLDL production causes fatty liver

excess exogenous glucose worsens futile cycling and fatty liver

modification by anaesthesia

volatiles: little effect

intravenous: only etomidate has any effect (↓ cortisol)

opioids: ablate response in very high dose

regional

spinal, epidural LA

ablate the response from lower body surgery

attenuate response to upper abdominal & thoracic surgery

spinal opioids

no effect despite analgesia

L. Thermoregulation

a. Outline the mechanisms for heat transfer between the body and its environment.

radiation

by electromagnetic radiation

dependent on difference of fourth power of T of body and surroundings

evaporation

by vaporization of water

dependent on T of body, sweating, air flow, humidity

convection

by transfer to or from fluids (usually air)

dependent on air flow and T

conduction

by direct transfer to solids

from body contact with cold surfaces

mass transfer

loss of warm fluids (urine, blood)

infusion of cold or warm fluids (IV, irrigation, soup)

b. Describe the mechanisms by which heat is produced by the body.

heat production by metabolism of energy substrates

carbohydrate, protein, fat + $O_2 \rightarrow CO_2 + H_2O$

Basal Metabolic Rate (BMR) \approx 100 W or 2000 kcal/day

must be dissipated exactly to maintain a constant temperature

c. Describe the mechanisms by which heat is lost from the body.

above

in an anaesthetized patient losses are approximately

radiation 50%

evaporation 30%

convection 10%

conduction 10%

d. Explain the processes used for conserving as well as generating heat under situations of lowered environmental temperature and the effects of anaesthesia on these processes.

e. Explain the processes used for losing heat as well as increasing heat loss under situations of raised environmental temperature and the effects of anaesthesia on these processes.

afferent

peripheral

skin, viscera

central

spinal cord, preoptic nuclei of hypothalamus, midbrain, great vessels

pathways

peripheral cold (10° - 40° C) and warm (30° - 45° C) sensors

90% of skin thermoreceptors are cold receptors

nociceptors activated at $<10^\circ$ C or $>45^\circ$ C

A δ fibres carry cold sensation only

C fibres carry warm and cold

- spinal and ascending pathway similar to pain pathway
- integration
 - preoptic hypothalamic nuclei
 - interthreshold range maintained in hypothalamus
 - narrow range ($\pm 0.2^{\circ}\text{C}$) within which no response is triggered
 - altered by
 - circadian rhythm, menstrual cycle, exercise, food, infection, thyroid function, sex (F > M), drugs, climatic adaption
- efferent
 - cold
 - sympathetic
 - cutaneous vasoconstriction (400 \rightarrow 50 ml/min)
 - centralizes circulation, maintains core temperature and allows periphery to cool
 - piloerection
 - nonshivering thermogenesis
 - brown fat \uparrow heat production 10% in adult (100% in neonate)
 - central
 - shivering
 - \uparrow heat production 100% (adults only)
 - behavioural responses
 - heat
 - sympathetic cholinergic
 - sweating
 - up to 0.7-1.5 l/h, 0.58 kcal/g water evaporated
 - cutaneous vasodilation
 - 400 \rightarrow 2500 ml/min (increases heat loss by factor of 8)
 - central
 - behavioural responses
- anaesthesia
 - afferents
 - regional anaesthesia blocks afferent “cold” transmission
 - increases central perception of warmth
 - integration
 - general anaesthesia broadens interthreshold range
 - vasoconstriction threshold falls $3^{\circ}\text{C}/\text{MAC}$ for all agents
 - sweating threshold rises $1^{\circ}\text{C}/\text{MAC}$ for volatiles, no rise for propofol
 - gain is preserved for all responses
 - efferents
 - regional anaesthesia directly blocks sympathetic outflow \rightarrow vasodilation
 - direct vasodilation and \downarrow sympathetic tone increase peripheral circulation
 - typical response is triphasic
 - initial rapid fall in core temperature due to vasodilation and redistribution of heat (not heat loss) typically 1°C
 - continued slow fall in core temperature due to loss > production
 - plateau as thermoregulatory responses are elicited $\approx 34^{\circ}\text{C}$
 - plateau is higher if effective warming is used
 - due to heat loss = production + gain
 - not due to regulatory responses
 - monitoring
 - best with a central probe: PA, oesophagus, tympanic, nasopharynx
 - preservation of heat
 - prewarming of peripheral compartment reduces redistribution fall in T
 - high ambient temperature can prevent hypothermia, but impractical
 - radiant warmers effective for babies only
 - warming IV fluids prevents a fall of $\approx 0.25^{\circ}\text{C}/\text{l}$ in adults

HME or humidification prevents 10% of loss in adults, more in babies
blankets prevent $\leq 30\%$ of loss (proportional to % coverage)
water heated mattress covers are ineffective
forced warm air blankets are the most effective method
transfer up to 50 W

f. Define thermoneutral zone.

The ambient temperature range within which a stable core temperature can be maintained with minimal rise in metabolic rate.

| | |
|-----------|---------|
| adult | 22-24°C |
| neonate | 32-34°C |
| premature | 33-35°C |

g. Explain how the neonate differs in the regulation of body temperature compared with the adult and explain the physical and physiological reasons for these differences.

more rapid loss

- high SA to weight ratio

- high BMR (double adult rate per unit SA)

impaired responses

- poor vasoconstriction, little peripheral compartment

- no shivering

- no sweating

- limited behavioural responses

increased response

- non-shivering thermogenesis from brown fat is effective in doubling MR

mild intraoperative hypothermia

advantages

- cerebral and tissue ischaemic protection from \downarrow metabolic rate

- \downarrow MAC requirement

- \downarrow triggering of MH?

disadvantages

- \uparrow oxygen demand due to hypothermic responses during cooling

- \uparrow risk of AMI, arrhythmia

- impaired clotting, immunity, wound healing

- slowed drug metabolism (e.g. atracurium)

Hypothermia in more detail in [Metabolic \(3.C.5\)](#).

M. Immunology

a. Use basic immunological principles to explain how the body defends against infection.

Immune organs

thymus

- develops from third and fourth pharyngeal pouches
- active from early fetal life, necessary until 20 weeks
- site of development of self recognition of T lymphocytes
- atrophies from 3-6 months (T cells are seeded peripherally)

marrow

- site of development of most circulating cells from birth
- site of development of lymphocyte precursors

spleen

- major site of clearance of opsonized and antigen-coated particles
- many B cells, site of Ig production, phagocytosing cells

lymph nodes

- contain follicles of lymphocytes (B and T) and antigen-presenting cells
- major site of Ig response

other lymphoid tissue

- associated with gut, bronchi, skin

Immune cells

T lymphocytes

- develop in thymus in early life
- differentiate into CD4 and CD8
 - cytotoxic T cells (CD8)
 - lyse cells bearing viral antigen and MHC I
 - suppressor T cells (CD8)
 - modulate T and B cell response
 - regulator/helper T cells (CD4)
 - recognize antigen with MHC II
 - control B and T cell proliferation via cytokines

B lymphocytes

- express surface Ig
- activated by antigen and T helpers to transform into plasma cells
- initially produce IgM when activated, then IgG (or A or E if stimulated by IL-4 or IL-5)

phagocytes (monocytes, macrophages etc.)

- engulf opsonized particles without specific recognition
- produce cytokines
- present antigens

NK cells (lymphocytes without T or B cell markers)

Innate immune mechanisms

barriers

skin

- dry, hydrophobic *stratum corneum*
- fatty acids from glands

mucosae

- mucus
- cilia
- IgA

flora

- skin, gut, pharynx, vagina etc.

- specialized defences
 - gastric acid

specialized cells

phagocytes: neutrophils and macrophages

NK cells

macrophages have multiple functions

activation of lymphocytes, complement and chemotactic secretion

direct toxicity to tumour and microbial cells

secretion of tissue reorganization factors

plasma proteins

complement

ABO antibodies (not provoked by antigen)

individual

susceptibility to particular diseases: TB, candida

Adaptive (acquired, anamnestic) immunity

antigen binds to surface Ig on B lymphocytes

induces proliferation and memory cells

phagocytosed and presented to T helper cells

antigen also can be presented by mononuclear phagocytes or dendritic cells

T helper cells modulate the response of

T cytotoxics, NKs, macrophages, granulocytes, B cells and ADC cells via cytokines

T suppressor cells influence T and B lymphocytes

macrophages also produce cytokines which affect NK, ADC and granulocyte cells

antigen presented to B lymphocyte

production of specific antibody (requires stimulation: IL, T_h, APC)

clonal expansion on reexposure

b. Identify effects of anaesthesia and critical illness on immune function.

Difficult situation to analyze due to

premorbid illnesses

drugs

age

surgical trauma

stress response

post-op nutrition

infection

pain

Cell-mediated immunity

↓ chemotactic migration

↓ oxygen radical production, impaired phagocytosis

↑ WCC

↓ NK cells (less antitumour effect)

↓ T cell proliferation

Humoral immunity

↓ B cell proliferation

no change to Ig levels

↓ complement

Effects worsened by

hypothermia

increased wound infection

decreased oxygen tension in wound

blood loss

↓ NK cell function

reduced effect if volume is replaced

transfusion

immunosuppressive (NK, T-helper)
stress response
anxiety, starvation, tissue trauma, pain
result in catabolism, hyperglycaemia, hypercoagulability, immunosuppression

Specific agents

halothane: effects above
N₂O: impaired B₁₂ metabolism, haematopoietic dysfunction
propofol: better maintenance of T cell numbers
etomidate: inhibits 11-β hydroxylase, reduces stress response
opioids
↓ NK cells, ↓ polymorph function, transient ablation of stress response

Regional

attenuates stress response
less impairment of phagocytes and NK cells

c. Explain the immunological basis and pathophysiological effects of hypersensitivity.

I IgE cross-linking on mast cells (e.g. penicillin anaphylaxis on reexposure)
II Ig-mediated cell lysis (e.g. haemolytic transfusion reactions, HITS)
III antigen-antibody complex deposition (e.g. Farmer's lung)
IV cell-mediated hypersensitivity (e.g. contact allergies)
V stimulation by Ig directed against cell receptors (e.g. Graves' disease)
anaphylactoid
reaction clinically similar to type I without being IgE-mediated
e.g. direct activation of complement and mast cells by drugs

d. Outline the principles of management strategies for anaphylactic and anaphylactoid reactions.

e. Describe the role of complement.

Complement

complex group of 20 or more plasma proteins
alternative pathway
C3 circulates in plasma at 1.2 mg/ml
spontaneous cleavage to C3b, binding to factor B and Mg²⁺ (C3bB), activation by factor D to C3bBb which catalyzes C3 breakdown
limited by factors H and I (inactivators)
C3bBb may bind to microorganism surfaces via a thioester, protecting it from factor H and causing runaway C3b formation
C3b complexes C5 which is cleaved to C5b
C5b complexes C6, C7 and C8
C9 is bound and undergoes conformation change, yielding the membrane attack complex
MAC opens a channel permeable to Na⁺ in the cell membrane, usually causing lysis
classical pathway
bound antibody complexes with C1q which activates C1r and C1s to form C1qrs
this cleaves C4 to C4b which complexes C2 and Mg²⁺ (C4b2)
C1qrs activates C4b2 to C4b2a
this activates C3 as in the alternative pathway
C4b can also bind to a microorganism via a thioester bond
promotion of phagocytosis

C3b and C3bi bind to receptors on phagocytes, producing phagocytosis of organisms to which they are bound
C3a and C5a stimulate granulocytes and degranulate mast cells

f. Describe the role of cytokines.

O. Maternal Physiology

a. Explain the cardiovascular and respiratory changes during pregnancy and their consequences.

cardiovascular

blood

- volume \uparrow 35% (1-2 l) from 12 weeks to term
 - partly due to \uparrow aldosterone, ADH
- red cell mass \uparrow 20%
- anaemia common due to high iron requirement of mother and fetus
 - Hb 140 \rightarrow 120 g/l (lower without iron supplementation)
- \uparrow platelets (usually)
- \uparrow clotting factors (except XIII), \uparrow fibrinogen (3 g/l \rightarrow 5 g/l)
- \downarrow albumin

peripheral

- 700 ml/min through uterus (80% to placenta)
- >1 l/min through the uterus in labour
- \uparrow flow to skin, breasts and uterus
- \downarrow SVR by 20%, BP \approx 100/70 (fall of 15 mmHg)
- potential for aortocaval compression
- dilation of epidural veins, reduction of epidural space

cardiac

- \uparrow venous compliance, CVP unchanged
- CO rises to 40% above normal by 32 weeks and plateaus
 - SV \uparrow 30%, HR \uparrow 15%
 - acute rise in labour up to a further 65%
 - contractions produce autotransfusion of 500 ml
 - \uparrow CVP, BP, CSF and epidural pressure
- heart position altered by enlarged uterus, LAD on ECG

respiratory

mechanical

airway

- weight gain, fluid retention and vasodilation causes difficult airway
- resistance \downarrow 36%, unchanged work of breathing

diaphragm

- rises 4cm
 - \downarrow RV (20%), FRC (20%), reduced oxygen reserve

chest wall

- increased AP and transverse diameters
- \uparrow IRC (5%) so VC unchanged, \downarrow TLC (5%)

metabolic

- BMR rises 20% over pregnancy
- VO_2 \uparrow 20%
- increased respiratory drive due to progesterone increasing PCO_2 sensitivity
 - \uparrow TV (40%), RR (15%)
 - PaCO_2 32-34 mmHg by end of first trimester
 - compensatory low HCO_3^- (20 mmol/l)
 - reduced buffering ability
- during labour minute volume doubles, PaCO_2 swings as low as 20 mmHg
 - \downarrow CO, \uparrow pH, \downarrow respiratory drive
 - typically followed by hypoventilation and fall in PaO_2

gastrointestinal

mechanical

- pressure on stomach and diaphragm from uterus
 - \uparrow gastric pressure, reflux

aspiration risk from 16 weeks

hormonal

progesterone slows gastric emptying

↑ gastrin reduces pH

↓ hepatic metabolism of drugs, PlChE ↓ 30%

renal

↑ RBF and GFR parallel rise in CO

↓ urea, creatinine

↑ aldosterone

↓ renal threshold for glucose

uterus may obstruct ureters

other

relaxin softens connective tissue

progesterone ↓ MAC (by 40% for halothane, 15% for isoflurane)

↓ volume of epidural space, ↑ pressure

b. Explain the consequences of the supine posture during pregnancy.

gastrointestinal

increased gastric pressure, reflux

respiratory

diaphragmatic splinting

cardiovascular

aortocaval compression

may occur from second trimester, peaks at 36-38 weeks

greatly reduced IVC flow, venous return and CO

reduced aortic flow to pelvic organs (including uterus)

venous diversion through azygous and vertebral systems

prevented by 15° tilt when supine

c. Outline the functions of the placenta

structure

forms from the trophoblast tissue which invades the endometrial decidua

circulation begins at the 16th day from fertilization

consists of placental villi from the trophoblast and blood sinuses from the endometrium

surface area of 1.8 m², thickness 3.5 μm

function

diffusion of nutrients from mother to fetus

oxygen

simple diffusion from 50 mmHg to 30 mmHg

30 mmHg is adequate for the fetus because of

higher haematocrit

higher affinity of HbF for oxygen (P₅₀=19 mmHg)

double Bohr effect

PCO₂ falls in fetal circulation and rises in maternal circulation through the placenta

secondary pH change decreases affinity for oxygen in maternal blood and increases affinity in fetal blood

total capacity 1.2 ml/min/mmHg gradient

glucose

facilitated diffusion via carrier molecule

main energy source for fetus

fat

simple diffusion

- amino acids, vitamins, Ca^{2+} , Fe^{2+}
 - active transport
- other substance also exchanged by simple diffusion include
 - ketone bodies, Na^+ , K^+ , Cl^- ,
- diffusion of excretory products from fetus to mother
 - carbon dioxide
 - simple diffusion down a 2-3 mmHg gradient
 - diffusion capacity 20 times that of oxygen
 - Haldane effect
 - deoxygenation of Hb in the maternal circulation increases its H^+ binding affinity and consequently the HCO_3^- carrying capacity of red cells, facilitating CO_2 removal
 - the reverse occurs in the fetal circulation
- non-protein nitrogen
 - urea, uric acid, creatinine transferred by simple diffusion
- endocrine function
 - secretion of hCG by syncytiotrophoblast cells
 - results in secretion of relaxin, oestrogens and progesterone by corpus luteum
 - relaxin softens ligaments and the cervix at the time of delivery
 - results in secretion of testosterone by testes in male fetuses
 - stimulates maternal thyroid
 - secretion of oestrogens by syncytiotrophoblast cells
 - mostly oestriol (low potency)
 - derived from maternal and fetal DHEA and 16-OH DHEA
 - produces maternal physical changes in pregnancy
 - enlargement of uterus, breasts
 - relaxation of ligaments
 - secretion of progesterone by syncytiotrophoblast cells
 - maintains decidua
 - ↓ uterine contractility
 - plays a role in lactation
 - ↓ gastric motility
 - ↓ SVR (smooth muscle tone)
 - ↓ MAC by 40%
 - secretion of human chorionic somatomammotrophin (HPL)
 - weak prolactin and GH-like activity
 - decreases maternal insulin sensitivity
 - promotes free fatty acid mobilization
 - secretion of human chorionic thyrotropin
 - stimulates maternal thyroid
 - secretion of gastrin
 - ↓ gastric pH

d. Describe the transfer of gases between the mother and fetus including the double Bohr and Haldane effects.

placenta

- area 1.8 m^2 for exchange (11 m^2 total villous area)

- thickness $3.5 \mu\text{m}$

- diffusing capacity

- O_2 1.2 ml/min/mmHg

- CO_2 25 ml/min/mmHg

- maternal

- uterine perfusion 700 ml/min (80% placental)

- reduced by contractions, α agonists, hypotension, abruption

| | | | |
|-------|--|---|-------------------------------------|
| fetal | PO ₂ | 100 → 40 mmHg | content falls 4 ml/100 ml (16 → 12) |
| | PCO ₂ | 32 → 45 mmHg | |
| | pH | 7.42 → 7.3 | |
| | placental perfusion 300 ml/min (50% of cardiac output) | | |
| | | reduced by cord compression, α agonists, hypoxia, hypoglycaemia | |
| | PO ₂ | 18 → 28 mmHg | content rises 6 ml/100 ml (10 → 16) |
| | PCO ₂ | 55 → 40 mmHg | |
| | pH | 7.21 → 7.32 | |

e. Describe the endocrine changes that occur during pregnancy and their consequences.

Placental hormones outlined above.

pituitary

50% enlargement of anterior pituitary
suppression of LH, FSH due to high oestrogen and progesterone levels
increased secretion of ACTH, TSH, MSH and prolactin

adrenal cortex

cortisol

moderately increased throughout pregnancy
increases amino acid mobilization and raises blood glucose

aldosterone

rises to double normal levels by the end of pregnancy
increases Na⁺ and water retention

thyroid

enlarges up to 50% in pregnancy and increases T₃ and T₄ release

parathyroid

enlarge and increase PTH secretion (continues during lactation)
increases Ca²⁺ mobilization and absorption for fetal use

ovaries

corpus luteum

relaxin, progesterone and oestrogens as above

weight gain

| | | |
|--------------|---------------|---------------|
| fetus | 3 kg | |
| other POC | 2 kg | |
| uterus | 1 kg | |
| breasts | 1 kg | |
| ECF | 2.5 kg | |
| fat | <u>1.5 kg</u> | |
| total | 11 kg | range 0-35 kg |

f. Describe the haematological changes with pregnancy.

proteins

↓ albumin and γ globulin due to dilution
↑ α and β globulin
↑ clotting factors, fibrinogen and plasminogen
↓ fibrinolytic activity

g. Describe the physiology of labour.

P. Fetal and neonatal physiology

a. Describe the fetal circulation

The fetal circulation is substantially different from the adult, primarily because of the difference in the source of oxygenation: the fetus obtains oxygenated blood from the placenta and the newborn from the lungs. Oxygenated blood returns from the placenta in the umbilical vein which joins the portal vein and then passes through the liver into the hepatic vein or bypasses the liver in the ductus venosus and passes directly into the IVC.

Much of the blood from the IVC passes through the foramen ovale into the left atrium and then into the systemic circulation. The remainder, together with blood from the SVC, passes into the RV and then into the pulmonary trunk. In the fetus, the pulmonary circulation is of a high resistance because of the lack of oxygen in the lungs and only about a third of the RV output passes through the lungs (12% of cardiac output), the remainder being diverted through the ductus arteriosus into the arch of the aorta and the systemic circulation.

Because of the high pulmonary resistance, the pressure in the pulmonary trunk is about 5 mmHg higher than that in the aorta. The parallel operation of the right and left ventricles allows them to have substantially different outputs with the left ventricle pumping 20% more blood.

About 75% of total cardiac output ends up in the descending aorta and the majority of this flows into the umbilical arteries (over 50% of cardiac output).

The oxygen saturation of haemoglobin in the fetus is much lower than in the newborn. In the umbilical vein, the blood is about 80% saturated, falling to 62% in the LV after mixing with other venous blood. This is the saturation of the blood perfusing the head and upper body. After mixing with blood from the ductus arteriosus, saturation falls to 58% for perfusion of the remainder of the body. fetal haemoglobin ($\alpha_2\gamma_2$) has a higher affinity for oxygen than adult haemoglobin ($P_{50}=19$ mmHg) as it binds 2,3 DPG less strongly, so in the placenta oxygen is transferred from maternal to fetal haemoglobin at the same PO_2 . The Bohr and Haldane effects also operate at the placenta to facilitate transfer of oxygen from mother to fetus.

After birth, pulmonary vascular resistance falls by 90% as air enters the airways. This results in a rapid fall in right heart pressures and reversal of pressure gradient between LA and RA which pushes the foramen ovale shut. The rise in arterial oxygen tension and reversal of flow initiate constriction and closure of the ductus arteriosus (may be prostaglandin-mediated).

In response to the trauma at delivery, the umbilical arteries constrict distal to the superior vesical arteries, and the cord is usually clamped. The cessation of flow through the umbilical vein coincides with closure of the ductus venosus which has a sphincter mechanism. The closing of the placental circulation causes a sharp rise in systemic resistance and blood pressure.

In the weeks following these changes, the muscle lining of the pulmonary vessels thins and the left ventricular wall starts to thicken to a greater extent than the right. The foramen ovale, ductus arteriosus and ductus venosus are sealed with fibrous tissue and the circulation shows the characteristics of the adult circulation.

Hypoxia in the neonate can produce pulmonary vasoconstriction and raise right side pressures enough to cause the reopening of the ductus arteriosus and foramen ovale ("transitional circulation"). The shunting produced by this circulation tends to worsen and prolong desaturation despite administration of oxygen. It can be reversed with continued oxygen administration or by inhalation of NO.

Neonatal heart

HR 120-160

systolic 70-90 mmHg, MAP 45-65 mmHg

PAP labile (with hypoxia or hypercapnea)

CO 180-240 ml/min/kg

- low compliance
 - dependent on preload and rate to maintain output
 - poor tolerance of hypovolaemia or bradycardia
- equal muscularity of left and right ventricles
- little sympathetic activity
 - bradycardia easily provoked
 - little change in vascular tone with spinal or caudal

Lungs

- not viable before 24 weeks
 - inadequate surface area, inadequate surfactant, immature control
- airway
 - jaw angle 140°, high larynx (C3-4), long epiglottis, narrow cricoid
 - short trachea (4 cm), large nasal airway
- first breath
 - results from stimulation at birth, ?reset of chemoreceptors with \uparrow SVR
 - from “zero” volume, requires >60 cmH₂O transpulmonary pressure
 - volume rises and transpulmonary pressure falls over first few breaths
- control
 - high rate minimizes work of breathing
 - increased response to \uparrow PCO₂
 - unreliable response to hypoxia
 - transient apnoea is normal
 - true apnoea: >15 s, \downarrow PO₂, \downarrow HR
- values
 - same as adult
 - TV 7 ml/kg, V_D 2.2 ml/kg, FRC 30 ml/kg, spf comp 0.05 /cmH₂O
 - different
 - VC 35 ml/kg (55), resistance 27 cmH₂O/l/s (1.6), RR 35 /min (14)
 - minute vol 125 ml/min/kg (60), O₂ uptake 6.8 ml/min/kg (3.3)
 - P_aO₂ 65-80 mmHg, P_aCO₂ 35 mmHg
 - low P_aO₂ due to CC>FRC (\rightarrow airway closure) and shunt
 - very compliant chest wall limits transpulmonary pressure
 - chest compliance 260 ml/cmH₂O
 - lung compliance 5 ml/cmH₂O

c. Explain temperature regulation in the neonate and how this differs from the adult.

d. Compare the physiological differences in organ function between the neonate and the adult.

Renal

- immature at birth
 - GFR/SA 15 ml/m² at birth, 35 at 2 months, 70 at 2 years (adult)
 - concentrating ability 600 mOsm/l (1200 in adult)
 - protein synthesis is a major contributor to nitrogen metabolism
- hepatic metabolism
 - conjugation less developed than phase 1 reactions

e. Explain the control of body fluids in the neonate and how the control and composition differ from the adult.

R. Principles of Measurement

<http://www.netspace.net.au/~jam/anaesth/measurement.html>

a. Explain mathematical concepts such as exponential functions, integration and differentiation.

Any process in which the rate of change of a quantity is proportional to the quantity is an exponential function. An example is the emptying of a bath: the rate of change of the volume of the bath (the plug-hole flow) is proportional to the volume remaining in the bath (which determines the pressure at the plug-hole):

$$\dot{V} = -kV$$

Integrating with respect to time gives the exponential function:

$$V_t = V_{t=0}e^{-kt}$$

This situation is analogous to the elimination of a drug which demonstrates first-order kinetics, such as the washout curve of an inhaled anaesthetic. It is also analogous to the natural expiration from the lungs where $-k$ equals the rate constant of expiration, the reciprocal of the time constant (compliance times resistance).

Integration is the derivation of a function which expresses the area under a function $y = f(x)$ from $x = 0$ to any value of x .

Differentiation is the reverse process: deriving a function which expresses the rate of change of $f(x)$.

b. Explain electrical concepts such as current, potential difference, resistance, impedance and capacitance as they relate to biomedical apparatus.

Current is the flow of charged particles resulting from a potential difference or changing magnetic field. Most commonly this is a flow of electrons through a metal or other conductor (such as graphite) which has freely mobile electrons. A current can also flow through solutions containing charged particles. All body fluids contain ions and so are capable of conducting current. The unit of current is the Ampere (1 Coulomb/second). Many quantities in monitoring devices are measured indirectly as electrical current. Nerve stimulators are calibrated to deliver a determined current through the tissue between the electrodes.

Solids which do not contain many unbound electrons and solutions with few ions are poor conductors and are known as insulators.

Semiconductors contain electrons which are loosely bound and may conduct a current if electrons are given enough energy to become unbound. This effect is seen in thermistors and photodetectors used in monitoring equipment. It is also the basis for transistors and silicon-based integrated circuits which are universally present in electronic equipment.

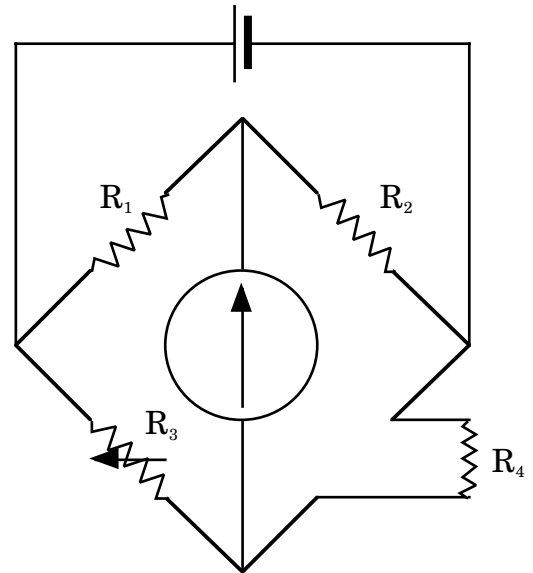
Potential difference is the difference in electrical energy between two points. Its unit is the Volt (1 Joule/Coulomb) and it generates an electromotive force which drives a current of charged particles.

Resistance is a measure of the electromotive force required to drive a current through a material. Its unit is the Ohm (1 Volt/Ampere). Thermistors display a change in resistance over a range of temperature and so with calibration the current flow for a specified voltage can be measured and used to determine temperature. Similarly some materials display an increase in resistance as they are stretched, allowing for tension or pressure to be measured indirectly.

When a small change in resistance is to be measured, a Wheatstone Bridge circuit is commonly employed. Classically, R_4 is measured by adjusting R_3 until the galvanometer reads 0. In this situation, $R_1/R_2 = R_3/R_4$. In practice, a monitor is set up so that R_1 and R_4 vary together and inversely to R_2 and R_3 . The deflection of the galvanometer is then read as output.

Impedance is the resistance of a component or circuit with a specified characteristic current flowing. Resistance of many components (capacitors and inductors) varies with frequency of alternating current. In a surgical diathermy device, a capacitor is part of the circuit, providing low impedance at the high frequency typically used (1 MHz), but high impedance to low frequency currents likely to cause arrhythmias (50 Hz).

Capacitance is a measure of the charge a device can hold. Its unit is the Farad (1 Coulomb/Volt). Defibrillators are based on a capacitor which is charged with a calibrated voltage to provide a determined energy output for DC reversion. The energy stored in a capacitor is $0.5 \times \text{charge} \times \text{potential}$. A typical output of 360 J is usually produced by about 5000 V across about 150 mC. An inductor is used to slow the discharge of the defibrillator.



c. Explain the SI system of units.

Seven basic SI units from which all other units are derived

| | |
|---------------------|-----|
| mass | kg |
| time | s |
| distance | m |
| current | A |
| temperature | K |
| luminous intensity | cd |
| amount of substance | mol |

Derived SI units (some of them)

| | | |
|--------------------|---------|--|
| temperature | °C | K - 273.15 |
| force | N | kg m s ⁻² |
| pressure | Pa | N m ⁻² |
| energy | J | N m |
| power | W | J s ⁻¹ |
| frequency | Hz | s ⁻¹ |
| volume | l | 10 ⁻³ m ³ |
| charge | C | A s |
| potential | V | W A ⁻¹ or J C ⁻¹ |
| capacitance | F | C V ⁻¹ |
| resistance | Ω | V A ⁻¹ |
| magnetic flux | Wb | V s |
| radiation dose | Gy | J kg ⁻¹ water |
| radiation exposure | Sievert | Gy · tissue factor · radiation type factor |

Prefixes (multipliers)

| | | |
|-------|-------|------------|
| atto | a | 10^{-18} |
| femto | f | 10^{-15} |
| pico | p | 10^{-12} |
| nano | n | 10^{-9} |
| micro | μ | 10^{-6} |
| milli | m | 10^{-3} |
| kilo | k | 10^3 |
| mega | M | 10^6 |
| giga | G | 10^9 |
| tera | T | 10^{12} |
| peta | P | 10^{15} |
| exa | E | 10^{18} |

Some non-SI units with conversions

| | | |
|---------------|-------------------------|--------------------------------------|
| pressure | mmHg | 132 Pa |
| | cmH ₂ O | 98 Pa |
| | atm | 101.325 kPa |
| | psi | 6.89 kPa |
| energy | calorie | 4.18 J |
| resistance | dyne s cm ⁻⁵ | 80 mmHg l ⁻¹ min |
| catheter size | French | external circumference in mm |
| | Gauge | 20 (1 – log external diameter in mm) |
| glucose | mg/dl | mmol/l x 18 |

d. Outline the conversion between different units of pressure measurement.

Given above.

e. Describe the laws governing the behaviour of fluids.

Fluids are gases or liquids. They exhibit flow, which is defined as quantity (Q) moved per unit time (t):

$$\dot{Q} = \frac{Q}{t}$$

Flow is characterized as laminar or turbulent. In laminar flow, fluid moves without eddies and flow is equal to pressure (P) over resistance (R):

$$\dot{Q} = \frac{P}{R}$$

In a cylindrical tube, resistance to flow is related to radius (r) and length (l) of the tube and viscosity (η) of the fluid, yielding the Hagen-Poiseuille equation:

$$\dot{Q} = \frac{\pi P r^4}{8 \eta l}$$

Above a critical speed, laminar flow changes to turbulent flow. For a smooth cylindrical tube, the transition occurs when Reynolds number is approximately 2000. For rough or bent tubes, the transition occurs at lower numbers. Reynolds number (RN) is defined in terms of speed (v), density (ρ) and viscosity (η) of the fluid and diameter (d) of the tube:

$$RN = \frac{v \rho d}{\eta}$$

For turbulent flow, the relationship determining flow is described empirically:

$$\dot{Q} \propto \sqrt{\frac{P}{l \rho}}$$

The relationship with tube diameter is complex and roughly related to slightly

greater than diameter to the power four.

The behaviour of gases is described by the gas laws. Because gases are composed of small molecules or atoms widely spaced, their physical properties are very similar regardless of the identity of the molecules or atoms.

Boyle's Law states that for a constant quantity of gas at a constant temperature, the absolute pressure is inversely proportional to the volume. Charles's Law states that for a constant quantity of gas at a constant pressure, the absolute temperature of the gas is proportional to its volume. Avogadro's Hypothesis states that equal volumes of gas at the same temperature and pressure contain the same number of molecules. One mole of gas occupies 22.4 dm³ at s.t.p. (273.15 K, 101.325 kPa). These laws combine to give the relation:

$$PV=nRT$$

Where R is the universal gas constant.

Real gases all have a temperature at which they condense into liquids (boiling point at standard pressure). Over a range of pressures, the temperature at which a gas will condense varies below the critical temperature (the temperature at which the gas will condense at critical pressure and above which it will not condense). At a temperature well below critical temperature, a gas will start to condense with decreasing volume, maintaining a constant pressure over a range of volume until it is entirely condensed.

With gas mixtures, separation of the constituents by condensation of one into the liquid phase may occur below the "pseudo-critical" temperature over a range of pressures.

f. Describe the principles of measurement employed by apparatus in clinical use, including transducers and describe their calibration.

Resonance

All oscillating systems display resonance with a peak resonant frequency (f_0)

$$f_0 = \frac{1}{2\pi} \sqrt{\frac{\text{stiffness}}{\text{mass}}}$$

Frequencies close to the resonant frequency will be distorted in the absence of damping

High resonant frequency allows accurate reproduction of waveforms

Damping

The property of a system which diminishes resonance

Damping ratio is the ratio of the amplitude of successive resonant peaks following a "square-wave" stimulus ($D_2 \div D_1$)

Damping coefficient is derived from damping ratio

$$\beta = \sqrt{\frac{(\ln \frac{D_2}{D_1})^2}{\pi^2 + (\ln \frac{D_2}{D_1})^2}}$$

$\beta = 0.64$ is the coefficient for optimal damping

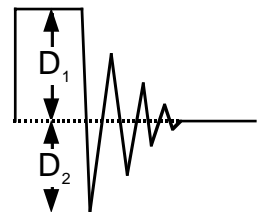
Corresponds to a damping ratio of about 0.07

Eliminates phase lag

Allows accurate reproduction of frequencies up to $\frac{2}{3}$ of the resonant frequency

Underdamped systems (small β , damping ratio close to 1) respond rapidly but overshoot, so they oscillate around their final value e.g. bathroom scales

Overdamped systems (β close to 1, damping ratio close to 0) move slowly to their final value and do not overshoot e.g. thermometer, arterial line with bubbles.



g. Describe the measurement of flow, pressure and velocity in fluids.

Flow is the change of volume over time. In gases it may be most simply be measured by a device which records volume against a time baseline, such as the Benedict Roth spirometer in which a sealed drum moves up as it is filled with gas, recording directly

onto a chart moved with time, or with a bellows which moves a pen with its expansion as in the Vitalograph more commonly used for spirometry.

For the measurement of continuous flows, an alternating bellows device is used in gas and water supplies, with the direction of flow into the bellows alternating as it is filled. In anaesthesia, the Wright respirometer connects in series with the circuit and records tidal volume with each breath. A set of slits generates a circular flow inside the meter which spins a vane connected directly to a rotating dial via a gearing system. It is not accurate for continuous flow.

Most commonly in anaesthesia, tidal volume and flow is measured using an electronic flow meter. Sets of blades cause the flow of gas to spin a mounted vane which interrupts a light beam shone through the housing of the device. Electronic processing of the frequency and duration of the interruption of the light beam allows calculation of flow (Ohmeda). Alternatively the cooling of a fine heated wire across the gas flow can be used to calculate flow (Dräger). These devices all measure gas flows at ambient temperature and pressure.

Measurement of continuous flow also occurs in the flowmeters of the anaesthetic machine. These consist of a calibrated glass tube of variable internal diameter in which a grooved bobbin is suspended by the flow of gas. The flow through a flowmeter tube is complex and dependent on the characteristics of the particular gas being measured, so they are calibrated empirically for a specific gas or mixture at a specific temperature and pressure. The pressure drop across the bobbin is constant and determined by the weight of the bobbin. The size of the orifice around the bobbin increases as it moves up the glass tube, allowing more gas flow for the fixed pressure drop. This is a “fixed pressure, variable orifice” flowmeter.

Highly variable flows may be measured with specific devices such as the peak flow meter. In this a ratcheted marker is moved against a variable resistance as the patient breathes out forcefully. The maximum displacement of the marker is calibrated to show the peak flow rate. This measurement is highly effort-dependent.

For constant measurement of respiratory flows, a pneumotachograph may be used. In this device a heated gauze screen maintains a region of laminar flow which provides a fixed resistance which results in a pressure drop across the gauze proportional to flow. By electronically integrating this pressure drop against time, the device can calculate the flow continuously.

Measurement of flow in liquids is simpler than gases because the variations in volume with temperature and pressure are much less. In IV giving sets, flow may be measured using a calibrated drop chamber in which the drop rate is counted either manually or electronically. The accuracy of this method depends on the composition of the fluid.

More common in slow infusions is the use of volumetric pumps. These incorporate an electric pump in the infusion line which is calibrated to deliver a controlled volume and operated at a rate programmed into the pump.

For small volumes, a mechanical syringe-driver operated by a stepper motor is used. Combined with calibrated syringes, this can deliver very accurate flows of small volumes over extended periods, such as in subcutaneous infusion of narcotics by portable battery-driven devices.

Measurement of liquid flow in the body is generally by indirect methods with the exception of dialysis and bypass devices where mechanical or electromagnetic methods can be used. Dilution of a marker such as fluorescent dye, radioactive tracer or thermal dilution with cold crystalloid produces a washout curve when introduced into a fluid flow. The curve can be integrated to calculate flow rate. This technique is used to measure cardiac output.

Flow can also be deduced from concentration changes in a marker across an organ if the rate of excretion or absorption of the marker can be separately measured. This is the Fick principle and is used in the calculation of cardiac output from the rate of oxygen uptake from the lungs and the change from mixed venous to arterial oxygen concentration. It is also used in the calculation of GFR from creatinine output.

An approximation of flow can be determined from ultrasound Doppler studies of

fluid velocity and vessel area. This is used to estimate flows across heart valves.

h. Describe and compare the methods of measuring temperature.

Heat

The quantity of thermal energy contained in a substance.

Temperature

An expression of the *specific heat* of a substance and the amount of thermal energy in it.

Determines the direction of flow of thermal energy (from hotter to cooler).

Specific heat

The thermal energy required to produce a given temperature rise in a substance.

Mercury thermometer

A bulb contains mercury which expands to force its way up a narrow calibrated column containing a vacuum. To produce a maximum-reading thermometer, a constriction just above the bulb splits the column when it contracts. Alternatively, a metal index sits above the column.

It is slow to equilibrate (with the time constant of equilibration being printed on the side), fragile and cannot read temperatures below -39°C .

Bimetallic thermometer

A coiled strip of two metals turns a pointer as the two metals expand at different rates with heat. It is slow to equilibrate.

Bourdon thermometer

A pressure-measuring device in which expansion of a fluid turns a dial. It is slow and sensitive to pressure changes.

Resistance thermometer

A piece of wire displays increasing resistance linearly with a rise in temperature. A Wheatstone bridge provides accurate measurement of the resistance. The changes in resistance over a useful clinical range are very small.

Thermistor

Many metal oxides display large resistance changes over small temperature ranges. These provide for accurate measurement in the clinical range using a very small probe. It is sensitive to heat damage from sterilization.

Thermocouple

Different metals generate an electrical potential when in contact which is related to their temperature. This allows for thin needle probes to be made to measure temperature. Their disadvantage is that the reference electrode must be kept at a fixed temperature, or compensation made for its temperature.

In practice

In the anaesthetized patient, the most practical method of measuring temperature is a small probe (thermistor) inserted into the nasopharynx, oesophagus or rectum.

i. Describe and compare the methods of measuring humidity.

Humidity

The amount of water vapour present in air or another gas

Absolute (gm^{-3}) or relative (% of saturation) terms

Saturation humidity of air is highly dependent on temperature

17 gm^{-3} at 20° , 44 gm^{-3} at 37°

Hair hygrometer

A hair stretches more readily as it becomes moist. If balanced against a spring, a simple hygrometer is formed. This is a primitive device, accurate over a limited range.

Wet and dry bulb hygrometer

Evaporation of water from around the bulb of a constantly moistened thermometer cools the thermometer an amount dependent upon the relative humidity and air flow over the bulb. If the air flow is constant, the relative humidity can be determined from the ambient temperature and this cooling effect.

Regnault's hygrometer

Air is blown through ether in a tube until condensation occurs on the outside of the tube. The temperature at which this occurs is the "dew point": the temperature at which the current absolute humidity represents 100% relative humidity. From this temperature, the absolute humidity can be determined and the relative humidity derived from knowledge of the saturated vapour pressure at ambient temperature. This is an impractical device as it involves ether and measurement of the dew-point with precision is difficult.

Other devices

Electrical measures of humidity depend on probes whose resistance or capacitance depends on their water-content.

Ultraviolet absorbance spectrophotometry can measure absolute humidity as can mass spectrometry. These are more precise and rapid methods of measuring humidity.

j. Explain in detail the principles of pulse oximetry including calibration, sources of errors and limitations.

Pulse oximeter

Device which measures functional saturation of haemoglobin by spectrophotometry through intact tissue.

Haemoglobin species absorb light of different wavelengths with different intensities

Oxyhaemoglobin absorbs less red light and more infrared than deoxyHb

Beer-Lambert Law describes absorption of light in a fluid

$$I_{\text{transmitted}} = I_{\text{incident}} e^{-dC\epsilon}$$

where I is light intensity, d is path length, C is concentration, ϵ is extinction coefficient

Practical application

Two wavelengths: 660 nm (red) and 940 nm (infrared)

Rapidly alternating LEDs, one on at a time

I_{incident} known

Single photodetector for both wavelengths measures $I_{\text{transmitted}}$

Constant absorbance due to tissue, venous and capillary blood

Variation in $I_{\text{transmitted}}$ for each wavelength assumed to be due to arterial pulsation

Rate of pulsation read as heart rate

Ratio of pulsatile to constant proportions at different wavelengths is calculated

$$R = \frac{\text{pulse}_{660} \div \text{const}_{660}}{\text{pulse}_{940} \div \text{const}_{940}}$$

Functional saturation varies with R (non-linear)

100% corresponds to R=0.4, 85% to 1.0 and 0% to about 3.4

Functional saturation

Saturation assuming

HbO₂ and deoxyHb are the only species present

Dissociation curve is not markedly shifted (pH, temp normal)

$$\text{Functional SaO}_2 = \frac{[\text{HbO}_2]}{[\text{HbO}_2] + [\text{Hb}]}$$

Fractional saturation

Percentage of total Hb present which is HbO₂.

Measured in arterial sample with co-oximeter (typically 7 wavelengths used)

Sources of error

Sensor

- Inadequate light transmitted (nail polish, onychomycosis)
- Extraneous light
- Movement or diathermy causing “noise” in received signal
- Processing
 - Human calibration only for $\text{SpO}_2 > 80\%$
 - Increasingly unreliable with low SpO_2
- Haemoglobin
 - High concentration of MetHb (\downarrow to 85%), COHb (\uparrow) or other species
 - Other light-absorbing species in blood (methylene blue, other dyes)
- Blood flow
 - Poor perfusion (vasoconstriction, hypothermia, BP cuff)
 - Pulsatile venous flow (tricuspid regurgitation)

The clinical usefulness of pulse oximetry diminishes with high haematocrit, as an adequate PO_2 may yield a lower saturation than expected. The peripheral placement of the probe reduces its usefulness in cold or peripherally vasoconstricted patients as the oxygen saturation in the central circulation may be substantially higher than in the fingertips.

k. Explain the principles involved in the analysis of gases using ultraviolet or infrared absorption, paramagnetic analysis, gas chromatography, mass spectrometry and Raman scattering.

Absorption spectrophotometry
covered in j. and l.

Paramagnetic analysis

Most gases are diamagnetic, being repelled by a magnetic field, because of the characteristics of their outer shell electrons. Oxygen is paramagnetic because of its unpaired outer shell electrons and so is attracted by a magnetic field. This effect is used to produce a paramagnetic analyzer to determine oxygen concentration.

In a paramagnetic analyzer, a dried gas sample flows through a chamber in which a nitrogen-filled dumbbell is balanced in a magnetic field. The dumbbell is displaced by the paramagnetic force on the oxygen in the sample and either its displacement against a torsion spring or else the force required to keep it in position is measured.

By calibrating the device with 100% nitrogen and 100% oxygen, a very accurate measurement of the oxygen concentration in a gas sample may be made.

A more modern design of paramagnetic analyzer uses an alternating magnetic field at the junction of two gas streams (sample and reference). A pressure wave is induced by the change in magnetic field and a pressure transducer between the gas streams can detect differential pressure and allows calculation of the oxygen concentration of the sample rapidly and continuously.

Gas chromatography

Chromatography relies on the separation of compounds by their different affinities for a stationary and mobile phase in a chromatography column. In the case of gas chromatography, the mobile phase is usually an unreactive gas such as nitrogen or argon and the stationary phase is a fine crystalline material such as silica coated in polyethylene glycol or silicone oil. The column is kept at a constant temperature and the sample to be analyzed is injected into the gas flow before the column.

At the end of the column a detector records the appearance of the components of the sample against the time since injection. The detector may be a flame ionization detector, a thermal conductivity detector (suitable for inorganic gases) or an electron capture detector (best for halogenated compounds).

Control samples are used to determine the chromatographic characteristics of known gases. These are compared with the unknown sample's trace to determine its constituents. The detector can also be calibrated for quantitative analysis of the sample.

Gas chromatography is suitable for analysis of all gases and many compounds which can be made to yield volatile products.

Mass spectrometry

Mass spectrometry separates molecules or atoms according to their mass and charge after stripping their outer electrons. A sample is allowed to leak very slowly into an ionization chamber in which an electron beam is used to ionize the sample. The ions are accelerated and focussed through an electric field and then deflected either using a strong magnetic field or an oscillating electric field between four rods ("quadrupole mass spectrometer").

The ions are separated according to their mass and charge and so the components of the sample can be determined quantitatively by analyzing the composition of the ionized sample which will include breakdown products of the components of the sample. This analysis is simple for small molecules and difficult for mixtures of several larger molecules because of the wide variety of breakdown products.

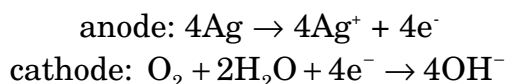
Mass spectrometry can measure very small concentrations in very small samples and can be made to have a response time as little as 0.1 s, but it remains a complex and expensive analysis tool.

Raman scattering

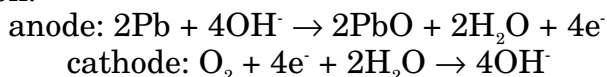
The Raman effect occurs when gas molecules absorb energy from photons resulting in quantized changes in vibrational or rotational states. Light is re-emitted with further changes in state producing a spectrum of wavelengths characteristic of the molecules involved. Spectral analysis allows identification of known compounds by comparison with their Raman spectra. This is a technique of similar accuracy to mass spectrometry.

Oxygen electrodes

The Clarke oxygen electrode is a polarographic electrode. Oxygen from the sample fluid equilibrates across a membrane with a buffered KCl solution surrounding a glass electrode. The electrode has a platinum cathode and a Ag/AgCl anode. With between 0.5 V and 0.9 V applied across the electrode, the consumption of O₂ at the cathode and hence the current in the circuit is dependent on the O₂ concentration in the solution which rapidly equilibrates with the sample. In practice, 0.68 V is used. Performance is affected by N₂O and halothane.



The fuel cell detector operates on the same principle as the Clarke electrode, but using a lead anode which is oxidized in the operation of the cell. It is oxygen-powered with a voltage output proportional to the oxygen concentration in the electrolyte. In this case the electrolyte is KOH solution.



Both these devices require temperature and pH compensation and have limited lifespans.

Blood gas electrodes

Arterial sample stored on ice in lithium heparin tube and analyzed quickly

PO₂, PCO₂ and pH are measured directly

PO₂ using a Clark electrode

pH using a pH electrode

Ag/AgCl or Hg/Hg₂Cl₂ reference electrode in contact with sample via KCl solution and membrane

solution and membrane

Buffer solution of 0.1 M $[H^+]$ in contact with sample via H^+ -sensitive glass

Voltage generated by H^+ gradient converted to pH reading

PCO_2 using a Severinghaus electrode

Similar to pH electrode except H^+ -sensitive glass is surrounded by $NaHCO_3$

solution in contact with sample via CO_2 -permeable membrane

CO_2 equilibrates across membrane, changing pH of buffer solution

pH change read by glass electrode and converted to PCO_2 reading

HCO_3^- (mmol/l) calculated from pH and PCO_2 (mmHg)

$$pH = 6.1 + \log_{10} \frac{[HCO_3^-]}{0.03 PCO_2}$$

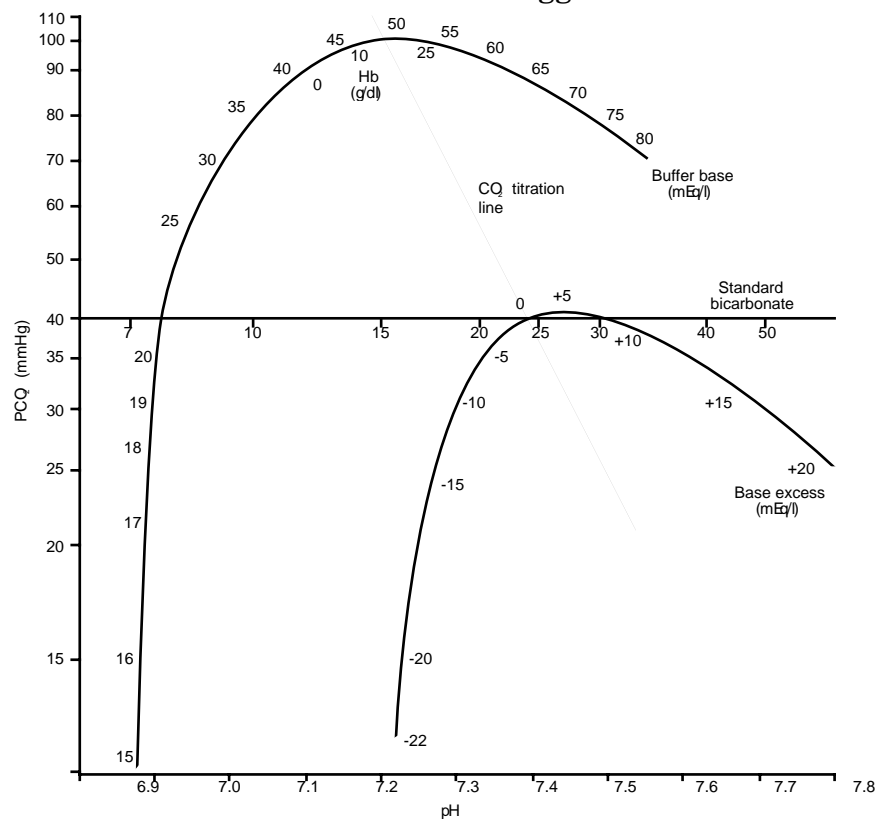
$$\Rightarrow [HCO_3^-] = 0.03 PCO_2 \cdot 10^{pH-6.1}$$

Base excess is measured by determining the sample's buffering capacity

Sample is equilibrated to two known PCO_2 values

pH is measured at each PCO_2

These two points fall on a "titration line" on the Siggaard-Andersen curve nomogram



Nomogram is a graph of $\log(PCO_2)$ versus pH

Intersection of the titration line with the $PCO_2 = 40$ mmHg line gives a value for "standard bicarbonate" which represents what the $[HCO_3^-]$ would be without respiratory compensation

Titration line also intersects two curves on the nomogram, reading "buffer base" (concentration of proton acceptors in the blood, normal 48 mEq/l) and "base excess" (mEq/l of H^+ required to correct blood to pH 7.4 at PCO_2 40 mmHg)

Other values commonly measured by blood gas machines

Na^+ , K^+ , Ca^{2+} using sensitive glass electrodes

Hb, glucose, lactate

1. Explain in detail the principles of capnography including calibration, sources of errors and limitations.

Capnography is the continuous measurement of PCO_2 in a gas sample. It is used in anaesthesia to monitor respiration and, by measuring $\text{P}_{\text{ET}}\text{CO}_2$, to give information about acid-base status and adequacy of gas exchange. Capnographs are usually set up either as “main stream” with a sensor on the circuit or “side stream” with gas sampled from the circuit at around 150 ml/min and analyzed separately. Side stream circuits are more common as they are cheaper and more robust.

Capnographs measure the CO_2 content of gas by infrared spectrophotometry. CO_2 molecules absorb infrared light at a $4.28\text{ }\mu\text{m}$ by altering their vibration and rotation. Infrared radiation is shone through the sample chamber containing a continuous flow of sampled gas at a controlled pressure. The absorbance at the specified wavelength may be compared with that in a calibration cell containing no CO_2 and must also be calibrated periodically to zero. The absolute amount of absorbance may be increased by using a reflected beam which passes through the sample chamber many times.

Some capnographs use multiple light wavelengths and so are able to measure the concentration of volatile anaesthetics and other gases such as NO_2 .

There are several potential problems with capnography. Side stream capnography has an increased response time as gas from the circuit must be drawn through the sampling line. There is potential for leakage at each connection of the sample line, reducing the CO_2 concentration. The gas drawn from the circuit is not a true end-tidal sample even at the end of expiration because of the dead-space in the large airways and circuit, and so there is always an underestimate of $\text{P}_\text{A}\text{CO}_2$. Mixing within the sample chamber will “blunt” changes in the CO_2 trace. Pressure changes in the sample chamber either as a result of airway pressure changes or constriction of the sample line will alter the absolute CO_2 concentration in the chamber. Physiological derangements such as V/Q mismatch may result in a wide disparity between $\text{P}_{\text{ET}}\text{CO}_2$ and $\text{P}_\text{a}\text{CO}_2$ (an increased A-a gradient), reducing the usefulness of capnography.

Main stream capnographs avoid the problems associated with the sample line but are more prone to pressure changes and as the sample chamber windows are made of sapphire, they are very expensive if damaged in handling or cleaning.

Measurement of cardiac output

Fick principle (Adolph Fick)

Pulmonary venous oxygen flux (q_3) equals pulmonary arterial oxygen flux (q_1) plus alveolar oxygen uptake (q_2)

$$\begin{aligned}q_1 + q_2 &= q_3 \\q_1 &= Q [\text{O}_2]_{\text{pa}} \\q_3 &= Q [\text{O}_2]_{\text{pv}} \\ \Rightarrow Q &= q_2 \div ([\text{O}_2]_{\text{pv}} - [\text{O}_2]_{\text{pa}})\end{aligned}$$

so cardiac output (Q) can be calculated from pulmonary O_2 uptake, and mixed venous and pulmonary venous oxygen concentrations.

Mixed venous oxygen concentration can be measured using a Swan-Ganz catheter and pulmonary venous oxygen concentration approximated with a systemic arterial sample.

This method requires determination of oxygen uptake over several minutes and so requires either a completely closed breathing circuit in anaesthesia or an approximation using mixed expired and inspired oxygen concentrations or a laboratory setting.

Indicator dilution

A known amount of an indicator is introduced into the circulation at a point where the entire cardiac output is passing.

The concentration of the marker is measured downstream after mixing has occurred and its value is plotted over time. The entire cardiac output need not be passing the

sampling point so long as no other blood flow has been added. For example, the indicator might be injected in the right atrium and the sampling done from the pulmonary circulation.

The amount of indicator (n) is related to its mean concentration (\bar{c}), cardiac output (\dot{Q}) and the time for which it is detected ($t_2 - t_1$):

$$n = \bar{c} \dot{Q} (t_2 - t_1)$$

$$\bar{c} = \frac{\int c \, dt}{t_2 - t_1}$$

$$\Rightarrow \dot{Q} = \frac{n}{\int c \, dt}$$

The conventional expression is in the Stewart-Hamilton equation:

$$\dot{Q} = \frac{n}{\int c \, dt} = \frac{k(T_{\text{core}} - T_{\text{indicator}}) V_{\text{indicator}}}{\int_{t_1}^{t_2} -\Delta T \, dt}$$

This can be done using a dye indicator (which requires a semi-log plot to determine t_2 when recirculation occurs) or more commonly using cold saline with temperature being the “indicator”. There is an inherent inaccuracy in thermodilution when thermal exchange occurs between the blood and the vessel and structures surrounding it and when cool fluids may be being infused peripherally in a variable fashion.

Echocardiography

Cardiac output (\dot{Q}) can be calculated using the TOE probe to measure cross-sectional area (A) and flow velocity (V) over the duration of one cardiac cycle (t) at a point where the entire cardiac output is passing (e.g. pulmonary outflow tract).

$$\bar{V} = \frac{\int V \, dt}{t}$$

$$\dot{Q} = A \times \bar{V}$$

This method assumes equal flow over the whole area and it is technically difficult to perform. With continuous wave Doppler and a multiplane probe this method should have a bias of zero and limit of agreement of 1 l/min compared to thermodilution.

Outline methods and principles used to measure regional blood flow.

Cerebral

Kety-Schmidt technique

Uses Fick principle

Total uptake of tracer = perfusion x extraction

$$Q_b = F \int (C_a - C_v) \, dt$$

$$Q_b = C_b \text{ Mass}_b$$

$$C_b = C_v \lambda \text{ (at equilibrium)}$$

$$\frac{F}{\text{Mass}_b} = \frac{C_v \lambda}{\int (C_a - C_v) \, dt}$$

N_2O at low concentration is the tracer used

C_a (arterial concentration) and C_v (venous concentration) are measured continuously at radial artery and IJV until equilibrium

λ is assumed to be 1 for N_2O

Total quantity of tracer in brain (Q_b), total brain blood flow (F) and brain mass (Mass_b) don't need to be known to calculate brain blood flow per unit mass.

Result is expressed in ml/100 g/min

Radioactive tracers

^{133}Xe , ^{85}Kr as gases

Organic compounds including ^{11}C , ^{15}O , ^{13}N or ^{18}F

Detected by scintigraphy, PET, autoradiography

Flow probes

Doppler, electromagnetic

MRA

O_2 extraction monitoring

Jugular bulb oximetry

Near IR spectroscopy

Hepatic

Fick principle with indocyanine green

Renal

PAH clearance

Ultrasound

Physical principles

Intermittent pulses of sound waves

2.5 to 7.5 MHz generated by piezoelectric quartz crystals

\uparrow frequency $\rightarrow \uparrow$ resolution (to 1 mm), \downarrow penetration (10-25 cm)

Sound waves passing through tissue of differing densities causes reflection of part of the sound energy

Loudness of reflection is interpreted as intensity

Delay of reflection is interpreted as distance from the probe

Sound assumed to travel at 1540 m/s in tissue at 37°C

A-mode ("Amplitude")

Brief ultrasound pulses in a single direction

Amplitude of reflected ultrasound is graphed against time (50-300 μs) for each pulse

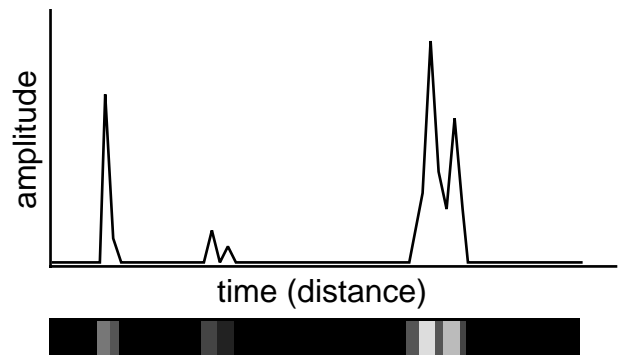
Peaks in amplitude correspond to reflective interfaces

Time taken before reflection corresponds to distance from the probe

Used to measure eye axial length ("A-scan")

B-mode ("Brightness")

Same as A-mode, but one dimensional graphical display with brightness corresponding to amplitude of reflected sound



M-mode ("Motion")

B-mode scan with repeated pulses graphed against a time-base

Up to 1000 pulses per second: excellent time resolution

Provides a one-dimensional image of tissue against a time-base

Useful for valve motion

2-D

Multiple crystals (linear or phased-array) or moving crystal

Sequential B-mode pulses sweeping up to 90° across a plane

Displayed as a single image

Up to 30 images per second (dozens of pulses per image)

Moving in real-time

Pulsed wave Doppler

Doppler shift is an alteration in the frequency of reflected sound depending on the velocity of the source of the reflection

Velocity (V) of the source of reflection (e.g. blood cells) can be calculated

$$V = \frac{F_d C}{2F_0 \cos \theta}$$

where F_d is the Doppler shift, C is the speed of sound, F_0 is the ultrasound frequency and θ is the angle between the direction of flow and the sound wave

An area of the 2-D scan is specified and the Doppler shift in reflections from that area is used to provide a graph of velocity versus time

Limitations

If θ is small ($<15^\circ$) it can be ignored, if large the results are imprecise

Flow faster than the Nyquist limit (0.4-0.6 m/s) cannot be unambiguously measured because of the intermittent sampling causing “aliasing”

Continuous wave Doppler

Separate crystals are used to emit and receive ultrasound continuously along a single axis

The frequency spectrum of reflected sound is related to the velocity of all interfaces along the axis

A graph of the range of velocities against time is produced

Advantages

Can measure very fast flows

Used to calculate valve gradients ($=4V^2$ where V is peak velocity)

Limitations

θ must be small

No pulses, so no information about location of measured velocities

Colour Doppler

Pulsed wave Doppler used on an area of a 2-D scan

Velocity is depicted as a colour in each pixel of the area

Advantages

Easy visualization of flows across valves or shunts

Limitations

Above the Nyquist limit, colour reversal is seen

Rapid turbulent flow produces “colour jets”

TOE probe

Phased-array 2-D probe with 64 crystals

May be monoplane, biplane (2 arrays) or multiplane (array can rotate)

Mounted on 9 mm gastroscope

A. 1 Pharmacodynamics

a. Explain the concept of drug action with respect to receptor theory, enzyme interactions and physico-chemical interactions.

Drug action may occur by one of several means. A drug-receptor interaction occurs where a drug binds to a specific ligand for an endogenous regulatory substance, inducing or blocking a conformational change in the receptor which initiates a series of cellular changes which characterize the effect of the drug. Many specific receptors have been characterized and specific agonist and antagonist drugs are available (e.g. β_2 adrenoreceptors). The effect of a drug reflects its concentration, affinity for receptors, the concentration of receptors (affected by up- or down-regulation) and the inherent agonist or antagonist potency of the drug.

Some drugs act by interaction with the active or other site on enzymes, exerting an effect by blocking the action of the enzyme and the metabolic pathway of which it forms part (e.g. allopurinol).

At a molecular level, drug action occurs by physico-chemical interaction. This may be by covalent bonding (e.g. organophosphates), ionic bonds, hydrogen bonds or van der Waals forces. These interactions may be between drug and receptor or between a drug and other compounds, e.g. chelating agents, antacids. Drugs operating by physico-chemical interaction usually have non-specific effects, are less potent and are without specific antagonists (e.g. ethanol).

b. Explain receptor activity with regard to: ionic fluxes, second messengers and G proteins, nucleic acid synthesis, evidence for the presence of receptors, regulation of receptor number and activity.

serpentine receptors

- cell-surface receptors

- seven transmembrane domains

- amine terminal extracellular, carboxyl terminal intracellular

- loop between domains V and VI (intracellular) is the binding site for G-proteins

- C-terminal chain is phosphorylated to alter sensitivity (e.g. β -ARK)

 - phosphorylated chain binds β -arrestin, inhibiting G-protein activation

- agonist binding site is between the clustered transmembrane domains

G-proteins

evidence for receptors

- drug action is tissue-specific

- log(dose)-response curve is sigmoid

- ceiling effect suggests saturation of receptors

- response is molecule-specific e.g. stereo-specific

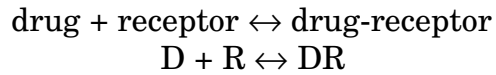
- antagonism is drug-specific

c. Define and explain dose-effect relationships of drugs, especially: graded and quantal response, therapeutic index, potency and efficacy, competitive and non-competitive antagonists, partial agonists, mixed agonist-antagonists and inverse agonists.

d. Compare efficacy and potency on the basis of dose-effect curves.

e. Explain the Law of Mass Action and apply this to pharmacodynamics to understand affinity and dissociation constants, the Hill plot and the Lineweaver-Burke plot.

assuming no interaction between receptors and one drug molecule per receptor:



$$[R] + [DR] = [R_{\text{total}}]$$

$$K_D = \frac{[D][R]}{[DR]}$$

$$K_D[DR] = [D] \cdot ([R_{\text{total}}] - [DR])$$

$$K_D + [D] = \frac{[D][R_{\text{total}}]}{[DR]}$$

$$\frac{[D]}{K_D + [D]} = \frac{[DR]}{[R_{\text{total}}]}$$

= proportion of receptors occupied = "effect"

$$\text{Effect} = E_{\text{max}} \frac{[D]}{K_D + [D]}$$

plot of log (dose) vs effect is approximately linear for effect 20%-80% of E_{max} .

Lineweaver-Burke plot

plot of 1/dose vs 1/effect is linear

$$\frac{1}{\text{Effect}} = \frac{1}{E_{\text{max}}} + \frac{K_D}{E_{\text{max}}[D]}$$

$$= \frac{1}{E_{\text{max}}} + \frac{K_D}{E_{\text{max}}} \cdot \frac{1}{[D]}$$

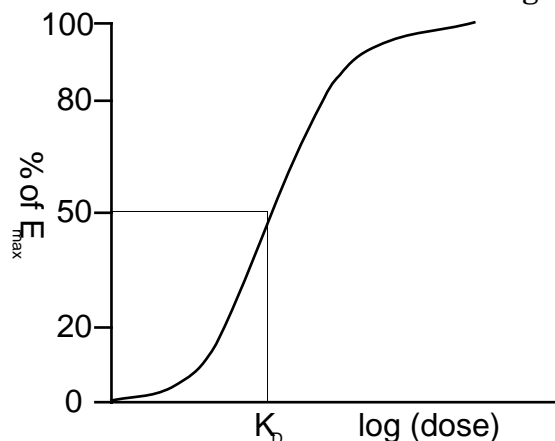
with y-intercept $1/E_{\text{max}}$, x-intercept $-1/K_D$ and gradient K_D/E_{max} .

Hill plot

plot of log (dose) vs $\log \frac{E}{E_{\text{max}} - E}$ is linear:

$$\log \frac{E}{E_{\text{max}} - E} = n \cdot \log(\text{dose}) - \log K_D$$

where n is the number of molecules binding to each receptor



for competitive antagonists, pA_2 expresses their affinity with a receptor

$pA_2 = -\log_{10} [\text{antagonist}]$ required to produce a doubling of K_D for an agonist

f. Explain theories of action of general anaesthetic agents.

g. Explain the concept of side effects.

h. Explain the concept of toxicity.

A. 2 Pharmacokinetics

a. Explain the concept of pharmacokinetic modelling of single and multiple compartment models and define: half-life, clearance, volume of distribution, bioavailability, area under the “plasma concentration-time curve”, extraction ratio.

Half-life

The time taken for the plasma concentration of a drug to fall by 50% when first-order kinetics are observed

Many drugs have an initial redistribution phase with a short half-life ($t_{1/2\alpha}$) followed by an elimination phase with a longer half-life ($t_{1/2\beta}$)

Clearance

The apparent volume of plasma from which a drug is entirely removed per unit time

Usually expressed in proportion to bodyweight or surface area

Volume of distribution

The volume into which a drug appears to be uniformly distributed at the concentration measured in plasma

Usually a steady state volume of distribution equal to the amount of drug in the body (n) divided by the plasma concentration (C)

$$V_d = \frac{n}{C}$$

Also equal clearance (Cl) times elimination half-life divided by $\ln 2$

$$V_d = \frac{1}{\ln 2} Cl \cdot t_{1/2}$$

Bioavailability

The proportion of a dose of a specified drug preparation entering the systemic circulation after administration by a specified route
Usually used to mean “oral bioavailability”: the ratio of the areas under the plasma concentration-time curves of intravenous and oral administration of the same dose of a drug

Area under plasma concentration-time curve

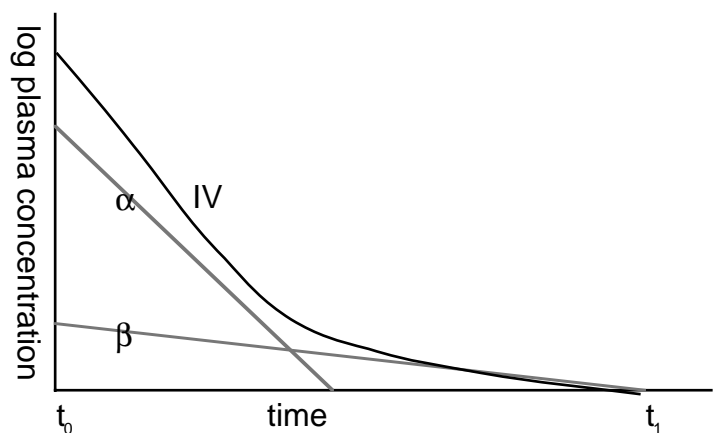
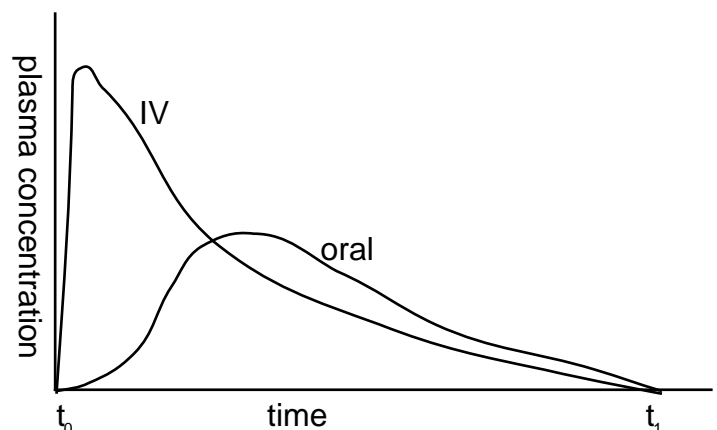
The integral of plasma concentration with respect to time from the time of administration to the time of no detectable drug is equal to the amount of drug appearing in the systemic circulation. This is used in calculating bioavailability.

A semi-logarithmic plot gives more information about the kinetics of a drug's distribution and elimination as first-order (exponential) curves become straight lines.

This allows easier calculation of distribution and elimination half-lives (proportional to gradients of lines α and β in the graph).

Extraction ratio

The proportion of a drug removed from blood by a single pass through the liver.



Equal to 1 - bioavailability.

A high extraction ratio indicates perfusion-dependent hepatic metabolism. A low ratio suggests enzyme activity dependent metabolism.

b. Apply Fick's Law to absorption of drugs by enteric, sublingual, rectal, nasal, intramuscular, subcutaneous, transmucosal and transdermal routes.

Fick's Law

relates rate of diffusion (J) to permeability coefficient (P), thickness (T), area (A) and concentration gradient ($C_1 - C_2$) for a drug diffusing across a membrane.

$$J = \frac{PA(C_1 - C_2)}{T}$$

permeability coefficient is related to solubility of the drug in the tissue between the site of administration and the blood draining the tissue

concentration gradient is maintained by a high concentration of drug at the site of administration and rapid blood flow

diffusion is also accelerated by a rise in temperature

c. Explain factors influencing the distribution of drugs and apply these in disease states.

Distribution occurs by several processes, the effect of each is determined by aspects of the drug involved.

bulk flow

drugs of MW < 200 flow with water through intercellular pores

facilitated diffusion

some drugs bind specific membrane receptors which facilitate transport across the membrane. This mechanism displays saturability and competition.

active transport

secondary active transport of many organic molecules

e.g. glucose, amino acids active uptake from gut

diffusion

determined by solubility in water

hydrophilic groups

molecule size

membrane penetration is related to lipid solubility

reduced with ionization

depends on pH for basic or acidic drugs

other polar groups

reduced with increasing size

protein binding

most drugs which are protein bound, bind either albumin or α_1 -acid glycoprotein according to their pK_a

some bind specialized proteins e.g. steroid binding globulin, transcortin etc

increases V_d and reduces free fraction of drug

reduces renal clearance by filtration but not active secretion

is a source of interactions

albumin

the largest component of plasma proteins

has three major binding sites

warfarin, bilirubin, salicylates, phenytoin, sulfonamides

benzodiazepine, NSAIDs, penicillin

digoxin, verapamil, quinidine

level is reduced by

catabolic states: burns, malignancy, renal/hepatic disease

pregnancy, old age, neonates
 α_1 -acid glycoprotein
 level increased in
 catabolic states: burns, renal transplant, malignancy, trauma
 inflammatory diseases: RA, UC, Crohn's
 myocardial infarct
 level decreased in
 pregnancy, neonates

d. Identify the mechanisms of hepatic and non-hepatic metabolism of drugs.

hepatic

phase I

microsomal

mixed function oxidases (including cytochrome P450)
 reaction with active oxygen species derived from O_2 and NADPH
 oxidation, dealkylation, hydroxylation, deamination, desulfuration,
 some reductions, dehydrogenation
 activity is unregulated by many drugs
 barbiturates, rifampicin
 inhibited by a few drugs
 cimetidine

increase polarity of drugs

phase II

conjugation with polar groups which increase renal and biliary secretion
 glucuronide, sulfate, acetate, amino acids

First order kinetics

elimination is proportional to concentration, clearance is constant

$$Cl = V_d \cdot k_{el}$$

where k_{el} is the elimination constant

so for a single compartment, concentration falls exponentially

$$C_t = C_0 \cdot e^{-kt}$$

where k is the rate constant, equal to $\ln 2 \div t_{1/2}$

in a two compartment model, with both distribution and elimination

$$C_t = Ae^{\alpha t} + Be^{-\beta t}$$

where A and B are the intercepts on the log plasma concentration-time graph and α and β are the gradients of the lines drawn to approximate the two compartments at a steady state with repeat dosing

dose rate = elimination rate

dose x bioavailability \div time interval = mean concentration x clearance

$$\frac{n F}{t} = C_{ss} V_d k_{el}$$

$$C_{ss} = \frac{n F}{V_d k_{el} t}$$

e. Explain the mechanics and significance of drug absorption and elimination such as first-order and zero-order kinetic processes and factors affecting renal excretion of drugs.

f. Explain and apply concepts related to infusion kinetics as well as absorption and distribution of drugs following epidural and spinal administration.

g. Calculate loading and maintenance dosage regimens.

h. Explain clinical drug monitoring with regard to peak and trough concentrations, minimum therapeutic concentration and toxicity.

A. 3 Pharmacokinetics of inhalational agents

a. Define and explain the concept of partition coefficients, boiling point and saturated vapour pressure.

partition coefficient

the ratio of the amount of substance present in one phase compared with another, the two phases being of equal volume and in equilibrium at a specified temperature.

The partition coefficient is a measure of the relative solubility of a compound in two specified phases (gas, liquid or solid). For example, the blood-gas partition coefficient of N₂O at 37°C is 0.47. That is, at equilibrium, the concentration of N₂O in blood is 0.47 times that of N₂O in a gas in contact with the blood.

This is a useful measure of how quickly one phase can become saturated and of the quantity of compound which will be taken up by one phase over time. It is applied to volatile anaesthetic agents and gases in partition with blood, tissues and the materials in the anaesthetic circuit. It is also applied in other solution equilibria such as in chromatography.

boiling point

the temperature at which a compound changes entirely from liquid to gas at standard pressure (101.325 kPa).

At boiling point the mean kinetic energy of individual molecules in a liquid is sufficient to overcome the attractive forces between them, allowing them to separate into a gas.

saturated vapour pressure

the pressure at which (at a specified temperature) a compound begins to condense from gas into liquid.

At any temperature below the critical temperature, a gas can be liquefied by compression. As the saturated vapour pressure is reached, the volume of the gas and liquid can be reduced without further increase in pressure until all the gas is condensed to liquid.

Any sealed container of liquid contains in the space above the liquid, gas at saturated vapour pressure, this pressure being dependent on temperature. In the case of N₂O at 20°C, the SVP is 5.25 MPa, in the case of water at 37°C, it is 47 mmHg.

b. Define MAC, MAC_{awake}, MAC-hr and MAC-BAR and outline their value and limitations of each as well as describe the factors affecting them and how they are measured.

MAC

Minimum Alveolar Concentration of an agent at equilibrium at 1 atmosphere pressure in oxygen needed to suppress purposeful movement in response to a standard surgical stimulus in 50% of subjects.

MAC is a useful measure of the relative potency of inhaled anaesthetic agents and a guide to the concentration required to eliminate awareness. It is also used to standardize comparable doses of inhaled agents for research purposes.

Its limitations are that it is a population mean which is not representative of the response of an individual to an inhaled agent and it requires measurement of alveolar gas which can only be approximated by clinical monitors. The sedative response to 1 MAC is standardized, but EEG findings at higher MAC levels differ between agents; it is an oversimplification of the response to inhaled agents.

Increased

infants, hyperthermia, thyrotoxicosis, alcoholism, central stimulants

Decreased

old age, pregnancy, hypothermia, MAP < 40 mmHg, PaCO₂ > 95 mmHg, PO₂ < 38 mmHg, sedative or anaesthetic drugs

MAC is measured in humans with a skin incision in the forearm and in animals using other standards. It is approximated in individual patients by analysis of end-expiratory gas for concentrations of N₂O and volatile agents.

MAC_{awake}

The MAC needed to abolish eye opening on command in 50% of subjects.
≈ 0.5 MAC

Subject to the same limitations and influencing variables as MAC. It is used as a means of comparing the sedative effect of inhaled agents.

MAC-hr

The integral of MAC by time for exposure of an individual patient to an inhaled agent.

Exposure to 1.5 MAC of an agent for 30 minutes represents 0.75 MAC-hr exposure. This is used as a comparative measure of exposure to an inhaled agent in calculation of adverse effects of inhaled agents and for setting dose-limits.

It is easily calculated but if used in setting safe doses, does not take into account differences in metabolism and effects which may occur at different concentrations, nor the effects of other factors in an agent's safety such as the level of fresh gas flow and flushing of metabolites from the circuit.

MAC-BAR

The MAC needed to abolish the sympathetic response to a surgical stimulus in 50% of patients.
≈ 1.5 MAC

Sympathetic response is measured as changes in heart rate or blood pressure or plasma noradrenaline levels.

c. Explain and apply the concepts of the concentration effect and the second gas effect.

d. Explain how uptake is affected by factors such as alveolar ventilation, cardiac output, shock states and ventilation-perfusion inequalities.

e. Explain the significance of the distribution of cardiac output and tissue partition coefficient on uptake and distribution of volatile agents.

f. Explain how patients recover from volatile agents by describing recovery curves and the factors affecting the rate of recovery.

g. Describe diffusion hypoxia and explain its significance.

A. 4 Variability in drug response

a. Define tachyphylaxis, idiosyncrasy, tolerance, addiction and habituation.

Tachyphylaxis is a rapid diminution in responsiveness following administration of a drug. e.g. GTN

An idiosyncratic reaction is an unusual adverse reaction, sensitivity or resistance to a drug, usually genetically determined. An example is suxamethonium apnoea in pseudocholinesterase deficiency.

Tolerance is a reduced effect or increased dose requirement after repeated administration of a drug. It may be due to receptor down-regulation or increased metabolism. e.g. opiates, barbiturates

Addiction is a state of physical or psychological dependence on a drug. Physical dependence is manifest as pathological signs or symptoms on withdrawal of a drug. Psychological dependence is manifest as compulsive drug-seeking behaviour which compromises physical wellbeing or social function.

Habituation is the neural mechanism by which a response is gradually reduced or eliminated following repeated stimuli.

b. Explain alteration in drug response due to the physiological consequences of age, pregnancy and other factors including obesity, altered total body water, hypoproteinaemia and various other disease states.

Elderly

Absorption is unchanged with age except by intercurrent disease and concurrent use of multiple medications.

Distribution is affected by reduced lean body mass, reduced total body water and increased fat percentage. Binding is altered by a decrease in plasma albumin and increase in α -acid glycoprotein (which increases the V_d of basic drugs).

Metabolism is slowed for most drugs, partly by a reduced hepatic blood flow and reduced capacity of the microsomal enzyme system. The ability to conjugate compounds (phase II reactions) is substantially unchanged with age. Hepatic function tends also to be diminished by other illnesses such as CCF or malnutrition. The reduction of hepatic oxidation of drugs is most apparent in drugs such as diazepam which have a long half-life and active metabolites.

Elimination by renal clearance is slowed by a progressive reduction in creatinine clearance with age. The Cockcroft-Gault equation relates clearance to age in males, the female result being multiplied by 0.85:

$$\text{creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{creatinine (in mg/dl)}}$$

(creatinine in mg/dl is 11 times the level in mmol/l)

Absorption and elimination of drugs via the lungs is also impaired in the elderly because of progressive reduction in FVC and DLCO as well as more damage from prolonged smoking.

Pharmacodynamic changes in the elderly are less important than pharmacokinetic ones. There is an increased responsiveness to some sedatives and hypnotics which may be receptor-mediated and a decrease in responsiveness to β -adrenoceptor agonists and antagonists. Many homeostatic mechanisms are impaired in the elderly: functional reserve in cardiac output to maintain blood pressure is limited with increased incidence of hypotension, glucose tolerance is often impaired and temperature regulation may also be impaired, with particular susceptibility to

hypothermia.

Specific examples of common drugs:

Benzodiazepines have increased volume of distribution (if lipid soluble), reduced metabolism and clearance and possibly increased receptor sensitivity. Motor functions may be particularly impaired in the elderly.

Narcotics show variable changes in pharmacokinetics. The major concern is that physiological reduction in respiratory capacity makes patients more susceptible to hypoventilation.

Drugs with anticholinergic effects (including phenothiazines, butyrophenones and most antihistamines) are more likely to cause confusion or acute brain syndrome in the elderly, especially in those with dementia.

Foetus

Pharmacokinetic factors

Lipid solubility increases placental penetration; ionized drugs do not cross the placenta easily.

Molecules larger than 1000 Dalton cross poorly except for immunoglobulins and some hormones.

Protein binding affects transfer. Some drugs are bound with different affinities to maternal and foetal proteins.

Metabolism in the placenta is limited to a few oxidation reactions. The foetal liver has a reduced metabolic capacity.

Pharmacokinetic factors

Effects on the mother are substantially the same in pregnancy, except for effects of greater circulating volume, and sometimes impaired glucose tolerance and susceptibility to cardiac failure.

Some drug effects are specific for foetal life: steroids to accelerate lung maturation and folate to prevent neural tube defects.

Some drug toxicities are predictable in foetal life: ACE inhibitors causing renal impairment and opiates causing dependence.

Teratogenic effects are usually specific to a drug and a time of gestation: thalidomide causing phocomelia when exposure occurs in weeks 4 to 7.

Paediatric

Absorption

Intramuscular administration is made unpredictable in neonates by small muscle mass and variable blood flow if cold.

Oral absorption is altered by the absence of gastric acid in premature babies for several days.

Gut motility is unpredictable in neonates, with gastric emptying commonly delayed.

Pancreatic enzymes and bile salts are present in reduced amounts up to 4 months of age.

Distribution

Total body water is 75% and ECF 40% of bodyweight in neonates. Diuresis in the first few days reduces the ECF compartment substantially.

Body fat is low in premature infants, rising to 15% at term.

Plasma protein binding is reduced in the neonate. With neonatal jaundice this effect is increased by competition of bilirubin for albumin binding sites.

Metabolism

Hepatic metabolism of drugs by both P450 and conjugation reactions is reduced in the neonate unless enzyme-inducing drugs have been given antenatally. They reach adult levels (per kg) by about three years.

Elimination

GFR/SA in the neonate is about 35% of adult values, rising to 50% at three weeks

and 100% at 6 to 12 months. This substantially alters the dose requirement of drugs such as penicillins and aminoglycosides which are renally cleared.

Pharmacodynamics

Some drugs have specific effects in neonates, particularly indomethacin for closing and PGE₁ for maintaining patency of the ductus arteriosus.

Dosing

Dosage calculations are often based on weight or surface area. Doses in adolescents should not exceed the adult dose except in some isolated cases such as theophylline where metabolism in children may be more rapid than in adults.

Equations for scaling doses include Young's rule: $\text{age}/(\text{age}+12)$ and Clarks' rule: $\text{weight}/70 \text{ kg}$, but in infants and adolescents these rules are not useful.

Obesity, dehydration, hypoproteinaemia

c. Classify drug interactions and the principles involved.

Physicochemical

- in vitro incompatibility
- binding
- precipitation

Pharmacokinetic

- Absorption (affecting extent and rate of absorption)
 - adsorption (cholestyramine, charcoal)
 - chelation or binding (resonium)
 - alter gastric pH (ranitidine)
 - alter motility (narcotics)
 - second gas effect (NO₂, volatile agents)

Distribution

- competition for protein binding (phenytoin)
- competition for tissue binding (digoxin & quinidine)
- direct binding (heparin & protamine)

Metabolism

- induction of microsomal enzymes (rifampicin, phenytoin)
- inhibition of microsomal enzymes (cimetidine, allopurinol)

Excretion

- urinary pH
- renal function in tubular secretion
- second gas effect

Pharmacodynamic

- potentiation
 - additive or synergistic effect
 - same or different receptors or multiple points in one pathway
- antagonism
 - direct antagonism (naloxone) or partial agonism (pentazocine)
- combined toxicity
 - predictable combination of adverse effects (NSAID & gentamicin → renal impairment)
 - potentiation of adverse effects by otherwise safe drugs (ketoconazole & terfenadine → prolonged QT interval)

d. Explain the mechanisms and significance of malignant hyperpyrexia, porphyria, atypical cholinesterase, slow acetylators and G6P-D deficiency.

Malignant hyperpyrexia is a genetically determined condition (1 in 20000, AD, long arm of chromosome 19) involving an abnormality of the ryanodine Ca²⁺ channel. In the presence of a triggering agent, commonly halothane or suxamethonium, Ca²⁺ is not

taken up by the sarcoplasmic reticulum after release, resulting in persistent contraction and thus lactic acidosis and hyperthermia (a late sign). Prevention is by taking a detailed history of anaesthetic complications, including a family history. Detection is by muscle biopsy for halothane/caffeine contraction testing or by chromosome analysis. Specific treatment is by elimination of the trigger agent: a clean anaesthetic machine, chilled intravenous fluids, and by intravenous use of dantrolene 1 mg/kg up to 10 mg/kg which inhibits Ca^{2+} release.

dantrolene

- lipid soluble hydantoin

pharmacokinetics

- low water solubility

- 20% oral bioavailability

- V_d 0.5 l/kg

- clearance 0.6 ml/min/kg

- $t_{1/2\beta}$ 12h

- therapeutic concentration $>3 \mu\text{g/ml}$

- metabolized to 5-OH dantrolene (50% potency)

pharmacodynamics

- inhibits Ca^{2+} release from sarcoplasmic reticulum

- limits excitation-contraction coupling in skeletal muscle

adverse effects

- muscle weakness

- negative inotrope

- $\uparrow [\text{K}^+]$

- electrolyte and volume disturbance due to water and mannitol load

indications

- malignant hyperpyrexia

- also used in

 - neuroleptic malignant syndrome

 - MDMA overdose, serotonin syndrome with hyperpyrexia

 - muscle cramps

clinical use

- ampoules of 20 mg with 3 g mannitol, pH 9.5

- dissolved in 60 ml water \rightarrow 1 mg/3 ml

- dose 1 mg/kg up to 10 mg/kg

 - = up to 30 ml/kg free water, 1.5 g/kg mannitol

Hepatic porphyria is an AD condition resulting from a defect in the HMB synthase gene. Symptoms are triggered by exposure to agents causing an increase in porphyrin synthesis, resulting in acute crampy abdominal pain, nausea, hypertension and neurological symptoms including axonal degeneration causing sensory loss peripherally and proximal motor weakness. Surgery itself can be a trigger, but many drugs are identified as precipitating attacks. These include: barbiturates, sulfonamides, phenytoin, carbamazepine, valproate, ergots, sex steroids and alcohol. Prevention is by history taking and avoidance of precipitating drugs. Between attacks, excretion of porphobilinogen and δ -amino laevulinic acid is normal, but erythrocyte HMB synthase is low. Treatment of attacks is initially symptomatic: narcotics, phenothiazines, and benzodiazepines. Intravenous haem therapy reduces the duration of an attack.

Atypical (plasma) cholinesterase is an AR condition. The genes has been well-characterized and comes in one normal and three atypical variants: dibucaine-resistant, fluoride-resistant and silent. Patients who have neither gene normal show markedly increased duration of action of suxamethonium as it is not effectively metabolized. This results in prolonged apnoea. Some heterozygous "normal" patients also have mildly prolonged duration of apnoea. Activity is also depressed by many other chronic illnesses,

burns and in neonates. There is a rare C5 variant which results in increased plasma cholinesterase. Prevention is by history taking and avoiding suxamethonium. Treatment is by mechanical ventilation until the paralysis ceases (often up to 5 hours). The incidence of significant suxamethonium apnoea is 1:2800.

N-acetylation of isoniazid and hydralazine varies in the normal population with a bimodal distribution. Slow acetylation is an AR condition with an incidence variable by race (rare in Asians and Inuit, more common in Northern Europeans). Slow acetylators metabolize these drugs much more slowly due to low levels of normal enzyme. There are no anaesthetic consequences of this condition.

Similar conditions have been described in metabolism of other drugs, much less commonly.

Glucose-6-Phosphate Dehydrogenase deficiency is an X-linked enzyme deficiency. There are many gene defects described, the common ones being A- in 11% of blacks and variants in Eastern Mediterranean (Favism) and Chinese populations. G6PD activity falls in red cells with age, and cells with very low activity will haemolyse in the presence of an oxidant drug. Drugs inducing haemolysis include: antimalarials, sulfonamides, nitrofurantoin and many others. An acute drop in haematocrit with a rise in plasma haemoglobin and unconjugated bilirubin results from haemolysis. Because younger red cells are less susceptible, the haemolysis is usually self-limiting, even with continued exposure. Prevention is by history taking and screening for red cell G6PD (which may not be low immediately after a crisis) and avoidance of oxidant drugs. Treatment is focussed primarily on avoiding renal damage; transfusion is usually not necessary.

e. Describe immune mechanisms in anaphylactoid and anaphylactic drug reactions in general and as applied to anaesthetic drugs.

Anaphylactic (type I) hypersensitivity reactions require an initial sensitizing exposure to the allergen. This causes the synthesis of IgE which binds to the surface of mast cells and basophils by its Fc region. On re-exposure to the allergen, the Fab regions of the IgE molecules bind the allergen and become cross-linked, triggering the degranulation of mast cells (mediated by phospholipase c and Ca^{2+}), releasing histamine, heparin, chemotactic factors and PAF and the synthesis of leukotrienes B_4 , C_4 and D_4 , prostaglandins and thromboxane. These are collectively known as SRSA.

The immediate effects include vasodilatation, bronchoconstriction and an increase in capillary permeability. If localized, these effects may lead to rhinorrhoea, asthma, rash with urticaria, localized oedema or diarrhoea. If generalized, these effects lead to circulatory collapse and respiratory compromise, requiring immediate treatment, initially with adrenaline.

Type I hypersensitivity can occur with any anaesthetic drugs, but is most common with large molecules which patients are likely to have been exposed to before, especially β -lactams and cephalosporins and some anaesthetic agents, notably thiopentone and suxamethonium. A history of a localized type I reaction to a drug is a contraindication to its use. Patients with a serum IgE $> 1 \mu\text{g/ml}$ are at a high risk of atopy.

Anaphylactoid reactions occur as a result of complement activation and subsequent mast cell degranulation on first exposure to the antigen. They are similar to but generally not as severe or long-lasting as anaphylactic reactions. Cremaphor (polyoxyethylated castor oil), a solubilizing agent, is noted for causing these reactions.

f. Explain alteration in drug response due to due to consequences of pathological changes such as liver disease, cardiac failure or renal failure.

A. 5 Pharmaceutical aspects

a. Define shelf life and outline factors that may influence drug potency during storage.

The period over which a drug loses 10% of its potency or its guarantee of sterility when stored according to the manufacturer's specifications.

b. Describe methods of preserving shelf-life of drugs

Suitable method depends on the nature of the reactions which would degrade the drug.

physical

- sealed containers

- temperature

 - refrigeration or freezing to reduce the rate of degrading reactions

 - e.g. sux, atracurium, blood products

- light

 - dark or opaque containers minimize light-induced changes

 - e.g. halothane, nitroprusside

- drying

 - dried to powder to reduce reaction rates

 - e.g. thio, vec, many antibiotics

chemical

- controlled pH

 - many drugs in solution have NaOH or HCl and buffer added

- reducing or oxidizing agents in solution

 - usually reducing agents, may cause reactions (e.g. sulfites, nitrites)

- reaction with or adsorption to a carrier

 - sugar glasses in phase IIb trials for α_1 -antitrypsin

- controlled atmosphere (N_2) or vacuum

 - thio, some antibiotics

microbiological

- pretreatment to sterilize drug

 - heat, radiation, ethylene oxide

- risk of contamination minimized by physical and chemical methods which remove water (and oxygen)

- anti-microbials

 - added to many oral agents

 - e.g. alcohol, benzalkonium chloride

c. Describe the mechanisms of action and potential toxic effects of buffers, anti-oxidants, anti-microbials and solubilizing agents added to drugs.

additives

- buffers

 - commonly NaOH, KOH, HCl used to control pH

 - carbonate buffers in LA solutions, methohexitone, thio...

 - phosphate buffers

 - benzenesulfonic acid in atracurium

- osmolal agents

 - mannitol in dantrolene, vecuronium

 - glucose in spinal LA solutions

- stabilizing agents

 - antioxidants

 - Na metabisulphite in catecholamine solutions: neurotoxicity

- other agents
 - thymol in halothane prevents light inactivation
 - N₂ atmosphere in thiopentone
- antimicrobials
 - methylparabens used in multidose vials, cause hypersensitivity
 - methyl- and propyl-hydroxybenzoate in topical and IV solutions
 - benzalkonium chloride in nebulizer solutions
 - benzyl alcohol in some water preparations
- solubilizing agents
 - lipid solutions
 - Cremaphor EL: polyoxyethylated castor oil, hypersensitivity
 - Intralipid: soybean oil, egg phospholipid, glycerol
 - high omega-6-fa content
 - propylene glycol & alcohols solution e.g. diazepam
 - polyethylene glycol in temazepam gelcaps (phlebitis if injected)
- propellants
 - chlorofluorocarbons in inhalers may be replaced with other agents e.g. N₂
- pharmacokinetic alteration
 - binding agents: protamine in insulin
 - uptake: adrenaline in LA
- compliance
 - flavouring, colouring etc.

d. Outline the variations in generic nomenclature of commonly used drugs.

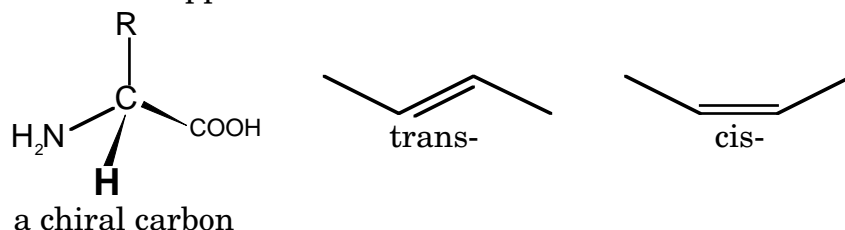
| Not approved | Approved name | Not approved | Approved name |
|----------------------|----------------------|-----------------------|----------------------------|
| acetaminophen | paracetamol | laevulose | fructose |
| albuterol | salbutamol | levarterenol | noradrenaline |
| aminoacetic acid | glycine | levothyroxine | thyroxine |
| aminoacridine | aminacrine | lidocaine | lignocaine |
| amobarbital | amylobarbitone | meperidine | pethidine |
| aneurine | thiamine | mephobarbital | methylphenobarbitone |
| anthralin | dithranol | methenamine | hexamine |
| asparaginase | colaspase | niacin | nicotinic acid |
| azidothymidine | zidovudine | nitroglycerine | glyceryl trinitrate |
| calciferol | ergocalciferol | norephedrine | phenylpropanolamine |
| carvomenthenol | terpineol | norepinephrine | noradrenaline |
| chlormethin | mustine | norethisterone | norethisterone |
| cortisol | hydrocortisone | omadine | pyrithione |
| cromolyn | cromoglycate | penicillin G | benzylpenicillin |
| dextrose | glucose | penicillin V | phenoxymethylpenicillin |
| dibucaine | cinchocaine | phytonadione | phytomenadione |
| epinephrine | adrenaline | pizotyline | pizotifen |
| ergonovine | ergometrine | propoxyphene | dextropropoxyphene |
| furosemide | frusemide | pyrilamine | mepyramine |
| glyburide | glibenclamide | tetracaine | amethocaine |
| hexamurium | distigmine | trolamine | triethanolamine |
| isoprotenerol | isoprenaline | tromethamine | trometamol |

e. Define isomerism, provide a classification with examples and explain its significance.

Isomers are molecules having the same empirical formula but different structures. Chemical isomers have completely different atom to atom bonds, for example enflurane and isoflurane or edrophonium and ephedrine HCl. Stereoisomers or enantiomers have the

same bond arrangements but differ in three-dimensional structure due to the presence of chiral centres (atoms bonded to four different groups) which may exist in two mirror-image arrangements or bonds without rotational freedom such as unsaturated carbon-carbon bonds with the two carbon atoms each bonded to different groups.

Chiral centres are present in all amino-acids and many other organic compounds including sugars. They are usually designed D- or L- or d- or l- or R- or S- or (+) or (-) isomers according to their configuration or effect on the polarization of light. Unsaturated bonds are present in many lipids and other molecules and are designated cis- or trans-isomers (Z- or E-) according to whether the major functional groups on the carbon atoms involved are on the same or opposite sides.



Many organic compounds include multiple chiral centres (e.g. atracurium) or unsaturated bonds (e.g. retinoic acid), yielding multiple optical isomers. As the isomers are different in three dimensional structure, they often bind with different affinities to receptor sites with specific three-dimensional structure and are degraded by enzymes at different rates.

Examples (optical isomers)

- isomers equally active
- isomers have slightly different potencies and metabolism, e.g. atracurium, ropivacaine
- isomers have different actions, e.g. quinine/quinidine
- one isomer is active and drug is administered as a racemic mix, e.g. verapamil
 - makes blood levels misleading (active L-verapamil is cleared more rapidly)
- one isomer is active and is administered alone, e.g. l-DOPA

f. Describe the process by which new drugs are approved for research and clinical use in Australia and outline the phases of human drug trials.

Safety tests in animals/tissue culture

- acute toxicity
 - LD₅₀ in animals (2 species, 2 routes), “no effect” dose
- subacute toxicity
 - up to 6 months use in three dose ranges in 2 species
- chronic toxicity
 - 1-2 years if prolonged use is planned in humans
- specific testing
 - reproduction, carcinogenesis, mutagenicity (Ames test), investigative toxicology

Human evaluation

- phase I
 - establish dose-effect relationship in healthy volunteers or diseases volunteers
 - not blinded, establishes predictable adverse effects and pharmacokinetics
 - phase II
 - small single-blind trials in diseased patients with placebo and positive controls
 - phase III
 - large, usually multicentre, double-blind or crossover trials
 - phase IV
 - on-going surveillance for adverse effects during marketing
- Phases I trials often start more than 4 years after initial synthesis and phase III may

not be completed until 8 years after initial synthesis. Some drugs are made available for life-threatening or serious diseases without completion of phase III or even phase II trials, e.g. some antiretrovirals.

Australian approval is distinct from overseas approval and applies similar criteria of safety and efficacy as in the US and UK. PBS listing and approval for hospital pharmacopoeia availability depends on cost-effectiveness as well.

The detection of rare adverse effects requires more subjects than are available in phase III trials. For example, to detect the doubling in incidence of a 1/1000 adverse effect requires 18000 subjects ($\beta=0.20$, $\alpha=0.05$). Thus most rare or unpredictable adverse effects will not be detected prior to marketing.

List the plants from which commonly used drugs are derived.

| | |
|------------------------------------|--|
| <i>Claviceps purpurea</i> | ergotamine |
| <i>Erythroxylon coca</i> | cocaine |
| <i>Papavertum somniferum</i> | morphine, codeine, thebaine, papaverine etc. |
| <i>Digitalis purpurea, lantana</i> | digoxin |
| <i>Rauwolfia serpentina</i> | reserpine |
| <i>Atropa belladonna</i> | atropine |
| <i>Hyocyamus niger</i> | hyoscine |

B. 1 Sedative-hypnotic drugs

a. Define and distinguish: sedation, hypnosis, anxiolysis, tolerance, REM and non-REM sleep, physical and psychological dependence.

b. Identify the major chemical classes of sedatives, hypnotics and anxiolytics.

c. Describe the pharmacodynamics of the barbiturate and non-barbiturate sedatives.

d. Describe the pharmacokinetics of commonly used barbiturates and benzodiazepines and indicate how differences between them may be applied clinically.

e. Describe individual sedative-hypnotic agents.

ethanol

clear colourless liquid, miscible with water

usually given orally, can be administered IV

some is metabolized by gastric alcohol dehydrogenase (more in men)

small $V_d = 0.7$ l/kg

metabolized in the liver to acetaldehyde and acetic acid

alcohol dehydrogenase active at low BAC (< 0.10)

microsomal oxidation at high BAC

limited by NAD^+ , $NADP^+$ availability

zero-order kinetics (~ 8 g/h)

dissolves in membranes decreasing viscosity and affecting many receptors and ion channels

CNS depression (many complex actions)

↓ cardiac contractility, smooth muscle tone, uterine contraction, platelet aggregation

teratogenic

long term effects are difficult to separate from confounding variables (nutrition, smoking, social status, premorbid problems)

interacts with other drugs acutely by reducing hepatic metabolism and with chronic use by inducing hepatic metabolism

tolerance mainly results from cellular adaption, not increased metabolism

cross-tolerance with other sedatives

little therapeutic use: acute methanol poisoning, prevention of withdrawal

dose: 10g per standard drink

dependent users 100-750 g/day

thiopentone

0.5 g in 20 ml glass ampoule

yellow power, sodium salt

stabilized with anhydrous sodium carbonate 60 mg/g

prepared with water or saline to 25 mg/ml solution

pH 11-12. Precipitates in neutral or acid solution

administered IV

rapid onset of effect in CNS followed by redistribution

hepatic metabolism

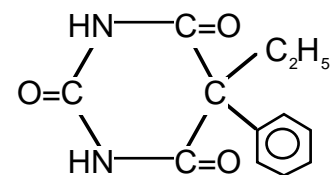
binds GABA receptors, increasing the duration of Cl^- channel opening

methohexitone

500 mg in 50 ml glass ampoule

white/yellow powder, sodium salt

stabilized with anhydrous sodium carbonate



mostly α L and α D isomers. β isomers increase involuntary movement.
prepared with water or saline
pH 10.6-11.6
pharmacokinetics and actions similar to thiopentone

phenobarbitone

200 mg in 1ml ampoule
30 mg tablets
the oldest anticonvulsant
pKa = 7.4
undergoes hepatic oxidation of the C5 functional groups and conjugation with renal clearance. 25% is excreted unchanged.
 $t_{1/2}\beta$ = 4 days
binds GABA receptors increasing Cl^- conductance, AMPA receptors blocking glutamate transmission
sedative and anticonvulsant

propofol

10 mg/ml in 20, 50 and 100 ml ampoules
white aqueous isotonic emulsion
solubilized with 2.25% glycerol, 1% soybean oil, 1% purified egg phospholipid
previously solubilized in Cremaphor EL \rightarrow anaphylaxis
pH 6.0 to 8.5
administered IV
rapid onset of effect in CNS followed by redistribution
rapid metabolism in liver ($t_{1/2}\beta$ 0.5-1.5 h)

diazepam

Diazemuls

1 ml of 5 mg/ml glass ampoule
solubilized in soybean oil

Diazepam USP

2 ml of 5 mg/ml brown glass ampoule
clear yellow solution
dissolved in 40% propylene glycol, 10% ethyl alcohol, 5% Na benzoate

midazolam

5 ml of 1 mg/ml or 1, 3 or 10 ml of 5 mg/ml glass ampoules
clear aqueous solution
buffered to pH 3.3
precipitates in strongly alkaline solutions

clonazepam

1 mg in 1 ml glass ampoule
2.5 mg/ml oral solution
0.5 mg and 2 mg tablets
long $t_{1/2}\beta$ ~36 h

zopiclone

7.5 mg tablets
structurally unrelated to benzodiazepines, but binds at the same site on the GABA receptor

chloral hydrate

no longer on the Australian market
prodrug metabolized to trichloroethanol
non-specific membrane stabilizer
hepatic metabolism produces trichloroacetic acid which accumulates
possibly carcinogenic
dose 0.5-1.0 g (of 100 mg/ml solution)

chlormethiazole

8 mg/ml oral solution
192 mg capsules

5-20% bioavailability
 65% protein bound
 pKa 3.2
 related to vitamin B₁
 ?GABAergic, unknown mechanism

agents affecting CMR and CBF

| | CBF | CMR | ICP | autoregulation |
|-------------------|-----|-----|-----|----------------|
| N ₂ O | ↑ | ↓ | ↑ | 0 |
| halothane | ↑ | ↓ | ↑ | ↓ |
| enflurane | ↑ | ↓ | ↑ | ↓ |
| isoflurane 0.5MAC | ↓ | ↓ | 0 | 0 |
| isoflurane 2MAC | ↑ | ↓ | ↑ | ↓ |
| barbiturates | ↓ | ↓ | ↓ | 0 |
| benzodiazepines | ↓ | ↓ | 0 | 0 |
| ketamine | ↑ | 0 | ↑ | 0 |

f. Describe the anticonvulsant and proconvulsant properties of the agents.

B. 2 Opioid agonists and antagonists

a. Provide a brief overview of the history of morphine.

| | |
|----------|---|
| 300 BC | juice extracted from <i>papavertum somniferum</i> described by Theophrastus contains phenanthrines and isoquinolones (noscapine, papverine) |
| 1400s | repopularized in Europe |
| 1806 | morphine isolated by Serturner |
| 1853 | syringe invented, morphine used with ether or chloroform GA |
| late C19 | morphine-scopolamine anaesthesia tried, high mortality wave of dependence/abuse |
| 1940s | semisynthetic opioids introduced: pethidine, methadone, nalorphine balanced anaesthesia and neurolept anaesthesia introduced |
| 1970s | opioid receptors differentiated |

b. Explain the structure-activity relationships of the opioid agonists and antagonists.

All L isomers

Phenolic ring, quaternary carbon, 2 more carbons, amine group (highlighted)

4.55 Å from centre of phenol to N

Substitution of a larger group than OH at C3 reduces μ activity

Alkyl group at N produces an antagonist

Br or OH at C14 produces an antagonist

phenanthrines

extracted from *papavertum somniferum*

5 rings: morphine, thebaine, codeine

substitutions

3,6 diacetyl \uparrow lipid solubility: heroin

3 methoxy \downarrow μ agonism: codeine

6 keto, $\text{NCH}_2\text{CH}=\text{CH}_2$, 14OH, 7-8 saturated: naloxone

morphinans

4 rings (no ether linkage): levorphanol, dextromethorphan (has NMDA antagonist activity)

benzmorphans

3 rings (C6, 7 & 8 removed): pentazocine

phenylpiperidines

2 rings: pethidine, fentanyl, ~fentanils

5.66 Å from ring to N

lipophilic chains on active N \uparrow lipid solubility

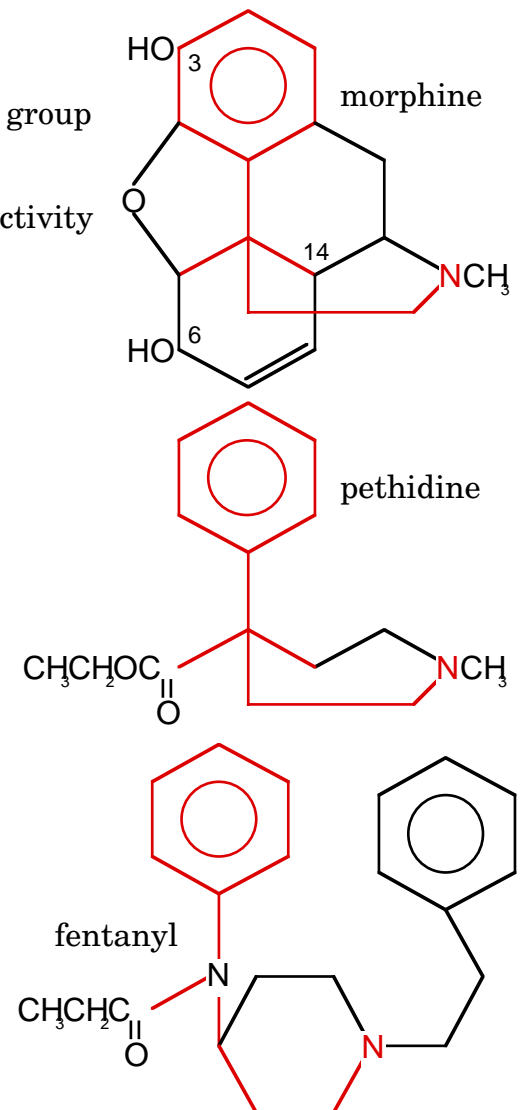
peptides

endogenous opioid agonists

synthesized in endocrine and neural tissue

products all contain the same pentapeptide at the N terminal which is the opioid core

three precursors: pro-opiomelanocortin (produces hormones: ACTH, MSH, β -endorphin), pro-enkephalin and pro-dynorphin (produce neurotransmitters)



c. Explain the physiological nature and types of opioid receptors and the action of agonists, partial agonists, mixed agonist-antagonists and antagonists.

μ_1

stimulated by opiates and opioid peptides
 β -endorphin > dynorphin > enkephalins
endogenous ligand: met-enkephalin
exogenous agonists: morphine, fentanyl
G protein linked: \uparrow K^+ conductance, \downarrow cAMP
protein kinase C activation \uparrow wind-up
supraspinal analgesia
 \downarrow prolactin, ACTH release, \uparrow ADH, ACh turnover, catalepsy, feeding

μ_2

stimulated by morphine
G protein linked
respiratory depression, \downarrow gut motility, CVS depression (central)
dopamine turnover, feeding, \downarrow GH release

δ

stimulated by enkephalins
 β -endorphin = enkephalins > dynorphin
G-protein linked: \uparrow K^+ conductance, \downarrow cAMP
spinal analgesia
GH release

$\kappa_{1,2,3}$

stimulated by opiates and dynorphin
dynorphin \gg β -endorphin \gg enkephalins
endogenous ligand: dynorphin
exogenous agonists: ketocyclazocine, pentazocine
 \downarrow Ca^{2+} channel conductance
spinal analgesia
 \downarrow ADH, sedation, feeding

ϵ

stimulated by β -endorphin
endocrine role, \downarrow immune function

σ

no longer classified as an opioid receptor
so-called agonists turned out to be NMDA agonists
psychotomimetic effects
morphine-3-glucuronide is an NMDA agonist
 \uparrow pain with high dose morphine, responsive to ketamine

mixed agonist-antagonists

nalbuphene: μ antagonist, κ agonist

may reverse respiratory depression without fully reversing analgesia

slow dissociating partial agonist

buprenorphine: μ partial agonist, high potency, slow dissociation

d. Explain the pharmacokinetics of the opioids and apply them to clinical useage, including infusion kinetics, transdermal, epidural, spinal and intramuscular useage.

| | protein binding | $t_{1/2\alpha}$ (min) | $t_{1/2\beta}$ (h) | V_d (l/kg) | clearance (ml/min/kg) | pKa | lipid solubility |
|--------------|-----------------|-----------------------|--------------------|--------------|-----------------------|------------|------------------|
| morphine | 35% | 1.65 | 3.0 | 3.2 | 15.0 | 7.9 | 1.4 |
| pethidine | 65% | 4-11 | 3-8 | 4.4 | 7.5-16.0 | 8.7 | 39 |
| fentanyl | 80% | 13 | 3.6 | 4.0 | 13.0 | 8.4 | 860 |
| alfentanil | 90% | 11.6 | 1.6 | 0.86 | 6.4 | 6.5 | 130 |
| sufentanil | 92% | 17.7 | 2.7 | 1.7 | 13.0 | 8.0 | 1778 |
| remifentanil | 70% | 6 | 10min | 0.35 | 40.0 | | |
| pentazocine | 60% | | 3.3-5.7 | 4.3-5.6 | 10.9-17.8 | 7.9 | |
| methadone | 90% | n/a | 8- 36 | 6 | ~0.5 | 8.6 | 115 |
| codeine | | n/a | 3 | | | 8.2 | |
| naloxone | | 1.5 | 1.0-2.5 | 3.6 | 27-35 | 7.9 | high |

Morphine is used intravenously, intramuscularly, subcutaneously, orally, intraarticular and occasionally nebulized. Its plasma levels do not correlate with clinical effect as its low lipid solubility causes slow equilibration across the blood-brain barrier. It has a high hepatic extraction ratio and so an oral bioavailability of only 30%. It is metabolized in the liver by glucuronide conjugation to morphine-3-glucuronide which is inactive and morphine-6-glucuronide which is active. These metabolites are renally cleared, so clinical effect of morphine is increased in renal failure though clearance remains constant. Metabolism is limited by hepatic blood flow.

Parenteral administration is commonly by intramuscular injection (0.1-0.2 mg/kg 3-4 hourly) or intravenous infusion for more constant plasma levels. Infusion is commonly at 1-5 mg/h in adults but a loading dose is required to achieve initial analgesia, typically 5-15 mg. Morphine is suitable for PCA. Epidural and spinal use are described but morphine is not the most suitable narcotic for this purpose as its low lipid solubility slows distribution, increasing the risk of central respiratory depression.

Pethidine is used intravenously, intramuscularly, epidurally and occasionally orally. It has an oral bioavailability of about 60%. It is metabolized in the liver to active and inactive metabolites, the most important of which is norpethidine which is a convulsant. Pethidine and its metabolites are renally cleared resulting in accumulation of metabolites in renal impairment. Its elimination half-life is prolonged in hepatic impairment.

Absorption from intramuscular injection is impaired in cold or vasoconstricted patients. When used epidurally, pethidine crosses the dura rapidly with CSF concentration peaking at about 15 minutes at the same time as plasma concentrations. It also crosses the placenta readily and has an elimination half-life in the newborn of 24 hours.

Dosing IV and IM is similar to morphine, with pethidine being about $1/_{10}$ as potent. Epidural use is in the same dose range as IV use.

Fentanyl has a high lipid solubility and is used intravenously, epidurally and transdermally and can be used by other routes. In small doses its duration of action is determined by redistribution rather than elimination. Plasma concentrations correlate well with effect as it crosses the blood-brain barrier readily. It is metabolized in the liver by demethylation and hydroxylation to inactive metabolites which are renally cleared. A small amount may be secreted unchanged into the stomach and undergo recirculation.

Intravenous use is in two dose-ranges: 1-2 μ g/kg as a coinduction or sedative agent and for brief duration analgesia and 30-100 μ g/kg as an induction agent for cardiac anaesthesia alone or with N_2O . In the high dose range, its elimination half-life determines the duration of action. It can be combined with droperidol in neurolept anaesthesia.

Epidural use is common either alone or with a local anaesthetic agent. The dose range is 10-60 μ g/h in adults. Fentanyl readily diffuses across the dura and also into blood.

Its high lipid solubility allows for transdermal use via patches (S-100) which deliver 50-100 $\mu\text{g/h}$. There is a long delay in reaching therapeutic plasma levels, so another analgesic is required to cover the first 6-8 hours. There is also a depot effect in the skin after a patch is removed. Use by intravenous infusion or intramuscular injection is uncommon as fentanyl is not well-suited to these uses because of its cost and short half-life.

Alfentanil is used intravenously. It is less lipid soluble than fentanyl but its low pKa results in most of the drug being in the unionized (basic) form at physiological pH, resulting in rapid diffusion across the blood-brain barrier. This, combined with a smaller V_d results in a more rapid onset of effect than fentanyl. Its elimination half-life is brief, so an infusion is required if it is to be used for anaesthesia.

It is metabolized in the liver to inactive metabolites by demethylation and dealkylation.

Sufentanil is pharmacokinetically similar to fentanyl.

Pentazocine is an opioid agonist(κ)-partial agonist(μ). It is used IM, IV and orally. It has a high extraction ratio and a bioavailability of 20%. Its hepatic metabolism is variable from patient to patient and is sensitive to hepatic impairment, with bioavailability rising to 70%. It is rarely used.

Codeine (3-methyl morphine) is used orally for analgesia and diarrhoea. It undergoes hepatic metabolism to inactive metabolites and also to morphine. Typical doses range from 8mg to 60mg q4h in adults.

Methadone is used orally for chronic pain and narcotic dependence and can be used IV. Its elimination half-life is markedly prolonged in chronic oral use. It has a low clearance by hepatic metabolism and so a low extraction ratio

Buprenorphine can be used IM, IV and sublingually.

Naloxone is an opioid receptor antagonist. It is used IM and IV for narcotic overdose. It is highly lipid soluble and has a short elimination half-life. It is metabolized in the liver by conjugation to glucuronide. Because its half-life is much shorter than most of the opioid agonists, repeat IM injection or IV infusion is required for treatment of overdose. Typical dose is 20-70 $\mu\text{g/kg}$ IM or 5-10 $\mu\text{g/kg/h}$ IV. Smaller doses are used to antagonize adverse effects of narcotic epidural infusions such as itch.

Naltrexone is an opioid antagonist with a lower extraction ratio than naloxone and so is used orally. It is used in an oral dose of 50 mg daily to help maintain alcohol and narcotic abstinence in dependent users who have withdrawn.

In principle, the loading dose and infusion rate of the narcotics used by IV infusion can be calculated from MEAC, V_d and clearance. In practice the dose is titrated against pain.

$$\begin{aligned}\text{Loading dose} &= \text{MEAC} \times V_d \\ \text{Infusion rate} &= \text{MEAC} \times \text{clearance}\end{aligned}$$

e. Provide a detailed systematic description of the actions and pharmacodynamics of individual drugs: morphine, pethidine, pentazocine, diamorphine, methadone, fentanyl, alfentanil, sufentanil, codeine.

morphine
pharmacokinetics above
epidural, spinal use
slow distribution into spinal cord (10-15 min spinal, 15-60 min epidural)

- prolonged duration due to low lipid solubility (12-20 h epidural)
 - late respiratory depression described
 - conjugated to morphine-6-glucuronide (potent analgesic)
 - and morphine-3-glucuronide (NMDA agonist)
 - also sulfated and N-demethylated
- pharmacodynamics
 - potent μ and κ agonist
- actions
 - supraspinal
 - cortex
 - anxiolysis, sedation, inhibition of REM sleep
 - EEG: \uparrow voltage, \downarrow frequency
 - mood effects: euphoria, dysphoria
 - stiffness
 - μ effect from inhibition of descending inhibitory motor pathway
 - from caudate nucleus
 - brainstem
 - respiratory depression
 - \downarrow CO_2 , O_2 sensitivity (2° \uparrow ICP if hypercapnia develops)
 - \downarrow cough reflex
 - CTZ: nausea, emesis
 - autonomic centres
 - \uparrow vagal tone (bradycardia)
 - \downarrow sympathetic tone
 - analgesia
 - opiate receptors in periaqueductal grey, NRPG
 - descending inhibitory pathways in DLF
 - spinal
 - inhibit slow EPSP resulting from C fibre stimulation
 - most potent as **preemptive analgesia**
 - itch: from either altered threshold or direct stimulation
 - peripheral
 - analgesic activity in periphery e.g. intraarticular use
 - cardiovascular
 - direct effect on SA node to \downarrow rate
 - haematological
 - direct effect on mast cells to degranulate and release histamine
 - gastrointestinal
 - smooth muscle spasm, damages anastomoses
 - \downarrow LOS tone, \downarrow motility
 - genitourinary
 - \downarrow urine output (via ADH)
 - \uparrow detrusor and sphincter tone
 - endocrine (? via D_2 agonism)
 - \downarrow ACTH, prolactin, GHRH
 - \uparrow ADH
 - clinical use
 - MEAC ≈ 16 ng/ml
 - administered by all routes except rectal, transdermal and topical
- pethidine
 - synthetic opioid developed as an anticholinergic (1939)
- pharmacokinetics above
 - N-demethylated to norpethidine
 - 50% analgesic potency, cerebral irritant

then hydrolyzed to normeperidinic acid

$t_{1/2\beta}$ 24 h in the neonate, fetal:maternal concentration ratio ≤ 1.0

epidural use

plasma levels peak after 10-15 min, rapid CSF penetration 15-30 min

pharmacodynamics

10% potency of morphine

μ and κ agonist

local anaesthetic, type I antidysrhythmic

anticholinergic

actions

as for morphine except:

cerebral

irritation and convulsions with accumulation of norpethidine

less miosis due to anticholinergic effect

respiratory

same reduction in ventilation, but \downarrow TV with little fall in rate

cardiovascular

not suitable for cardiac use because of membrane stabilizing effect

mild vasodilator

gastrointestinal

less spasm and constipation than morphine, but still \downarrow motility

clinical use

MEAC $\approx 0.5 \mu\text{g/ml}$

fentanyl

synthetic phenylpiperidine-related opioid

alfentanil and sufentanil differ only in potency and pharmacokinetics

pharmacokinetics

rapid redistribution and slow elimination

high hepatic extraction ratio

metabolized by N-dealkylation and hydroxylation

pharmacodynamics

potent μ and κ agonist

100 times potency of morphine

actions

similar to morphine except:

cardiovascular

little effect alone, no histamine release

hypotension in large doses in conjunction with diazepam

endocrine

suppresses stress response

clinical use

MEAC 3 ng/ml

anaesthesia $> 20 \text{ ng/ml}$

two dose ranges

coinduction 1-2 $\mu\text{g/kg}$

cardiac 30-100 $\mu\text{g/kg}$

pharmacokinetics unpredictable at intermediate doses

transdermal use occasionally

skin produces a 12-hour depot "compartment"

pentazocine

a benzomorphan

only the L-isomer is active, but it is supplied as a racemic mixture

pharmacokinetics

20% bioavailable

- high extraction ratio
- oxidized and glucuronidated
- metabolism greatly impaired in alcoholism
- pharmacodynamics
 - μ partial agonist, κ agonist, NMDA agonist
 - approximately 30% as effective as morphine as an analgesic
- actions
 - similar to morphine except
 - respiratory
 - ceiling to μ effects: respiratory depression and supraspinal analgesia
 - cardiovascular
 - \uparrow sympathetic outflow, mild \uparrow MAP and HR

B. 3. Pain

a. Define pain.

An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

Fast and slow pain: fast pain is sharp, well-localized and is conducted via A δ afferent nerve fibres. Slow pain is dull, poorly localized and conducted via C fibres.

Somatic and visceral pain: somatic pain is conducted via spinal nerves and is localized to the site of the stimulus. Visceral pain is conducted via autonomic fibres and localizes to the dermatomal level of the organ innervated where it can produce secondary hyperalgesia. It is provoked by stretch or ischaemia and is not associated with protective reflexes.

Deep and superficial pain: superficial pain is somatic, well-localized and unpleasant. Deep pain may be somatic, but is poorly localized and is associated with nausea, sweating, muscle spasm and blood pressure changes.

Allodynia

Pain perceived in response to a stimulus which does not usually cause pain

Analgesia

Absence of pain in response to a normally painful stimulus

Anaesthesia dolorosa

Pain in an area that is anaesthetic

Causalgia (CRPS II)

Sustained burning pain, allodynia and hyperpathia after traumatic nerve injury, often accompanied by vasomotor, sudomotor and trophic changes

Dysaesthesia

An unpleasant or painful sensation

Hyperalgesia

Increased response to a normally painful stimulus

Hyperaesthesia

Increased sensitivity to stimuli

Hyperpathia

A painful syndrome with increased reaction to a stimulus, especially a repetitive one, and increased threshold

Neuralgia

Pain in the distribution of a nerve

Paraesthesia

An abnormal sensation

b. Describe pain mediators and pain pathways and display an appreciation of the gate control theory and the concept of preemptive therapy.

receptors

mechanosensitive

respond to mechanical stimuli

A δ conduction (myelinated)

mechanothermal

mechanical stimuli and temperatures over 43°C

A δ conduction

polymodal

mechanical, thermal and chemical stimuli

ACh, bradykinin, histamine, PGs, K⁺

C conduction (unmyelinated)

- all high threshold
- do not show adaption (unlike most receptors)
- sensitized by chemical mediators
- dorsal horn transmission
 - A δ fibres synapse in the dorsal horn Rexed laminae I (nociceptor specific) and V (wide dynamic range)
 - C fibres synapse in the dorsal horn laminae I and II (*substantia gelatinosa*)
 - dorsal horn transmission displays long term potentiation resulting from repeat stimuli
 - slow depolarizing response to substance P
 - enhanced NMDA transmission
 - activation of NO synthase, c-fos expression, \uparrow dynorphin, \uparrow NGF which induces new neurite growth (A β \rightarrow WDR)
 - transmission is sensitized by substance P even while anaesthetized, hence preoperative local and intraoperative opioids for **preemptive analgesia**
 - substantia gelatinosa*
 - inhibited by A δ and C nociceptive afferents
 - stimulated by A β mechanoreceptor afferents and descending pathways
 - short inhibitory interneurons project to laminae I and V, inhibiting pain transmission (**Gate Control**)
- spinal motor neurones
 - withdrawal reflex
 - ?guarding
- ascending pathways
 - contralateral spinothalamic tract
 - posterior thalamus produces localization
 - medial thalamus produces unpleasant experience and autonomic response
 - thalamus projects to somatosensory cortex (SI and II) and cingulate gyrus (emotional response)
 - also projects to *nucleus reticularis paragigantocellularis*
 - multisynaptic system
 - fasciculi proprii* and Lissauer's tracts project to reticular formation and thalamus
 - slower transmission
 - periaqueductal grey matter
 - opioid receptors stimulate descending pathways which inhibit transmission in the dorsal horn (transmitter may be serotonin)
 - hypothalamus
 - spinoreticular tract (brainstem)
 - stimulation of reticular activating system
 - thalamic projection
- Visceral afferents probably both converge on and facilitate transmission in somatic pathways, producing referred pain. Experience influences the site of projection of referred pain (i.e. preferentially to traumatized sites).
- descending pathways
 - locus ceruleus*
 - inhibitory descending projection to dorsal horn
 - noradrenaline inhibitory neurones
 - periaqueductal grey matter
 - input from cortex, thalamus, hypothalamus
 - opioid receptors
 - stimulates *nucleus raphe magnus*
 - nucleus raphe magnus*
 - input from periaqueductal grey matter and *nucleus reticularis paragigantocellularis*

descending projection in dorsolateral funiculus to dorsal horn
serotonin and enkephalin inhibitory neurones

transmitters

glutamate

primary afferent transmitter

fast transmission via AMPA ((R,S) α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) receptors & others

\uparrow Na⁺, K⁺ conductance

slow potentiation via NMDA (N-methyl-D-aspartate) receptors

Ca²⁺, Mg²⁺, Na⁺, K⁺ channels

NMDA antagonists such as ketamine may prevent \uparrow Ca²⁺, NO production, c-fos expression, neuropeptide Y release and development of aberrant A β fibres which activate WDR neurones in response to mechanical stimuli, causing a pain syndrome.

substance P, CGRP and somatostatin

primary afferent transmitters

cause slow and prolonged depolarization (LTP) via NK₁ and NK₂ receptors

phospholipase C, IP₃, DAG \rightarrow \uparrow Ca²⁺ \rightarrow K⁺ efflux

2^o messengers inhibited by some gangliosides

sensitizes primary nociceptors in the periphery

activate WDR neurones to respond to all stimuli (A β mechanoreceptive etc. \rightarrow "pain")

enkephalins, endorphins and dynorphin

receptors in the periaqueductal grey matter, *nucleus reticularis*

paragigantocellularis and other central sites stimulate descending inhibitory pathways from the *nucleus raphe magnus*

opioid receptors are also present in the *substantia gelatinosa* and **may** act as presynaptic inhibitors of substance P release

play a role in placebo analgesia and stress analgesia (antagonized by naloxone)
role in "resting" state is controversial

serotonin

strong direct stimulation of nociceptors

transmitter in descending inhibitory pathways

inhibits substance P transmission in dorsal horn (mechanism uncertain)

noradrenaline

inhibitory transmitter at dorsal horn via α_2 (clonidine analgesia)

injured cells may express α -receptors (?pathology)

may stimulate dorsal ganglion afferent fibres directly in reflex sympathetic dystrophy

NO

enhances dorsal column transmission (via c-fos)

bradykinin

direct stimulation of nociceptors (G-linked receptor)

stimulates PGE₂ release (and possibly other PGs) which potentiates bradykinin response

GABA

inhibitory GABA_A receptors on WDR neurones

presynaptic GABA_B inhibition of excitatory neurotransmitter release

GABAergic drugs used in neuropathic pain

glycine

NMDA agonist

blockers used for specific therapy ***

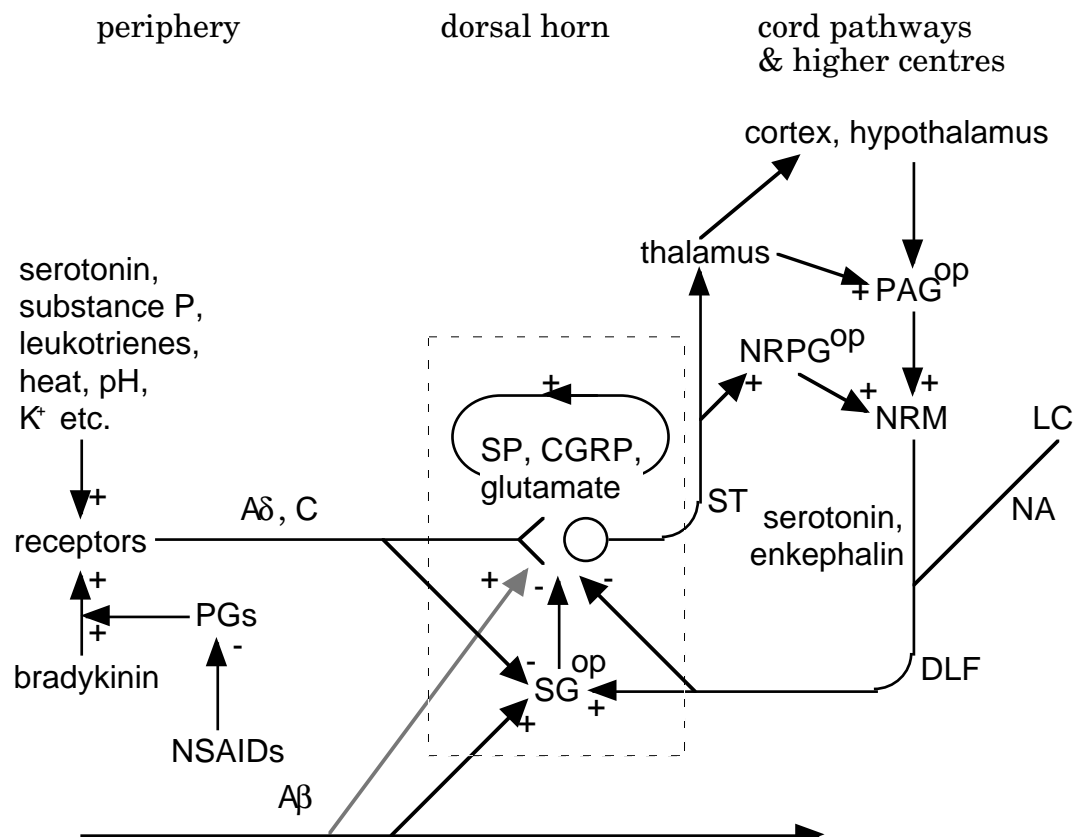
capsaicin

not an endogenous transmitter

acts on Ca²⁺ channel linked receptors

stimulates substance P release acutely

depletes substance P with repeat use
destroys C fibres in the newborn
other inhibitory transmitters
somatostatin, galanin, adenosine, cholecystokinin



| | |
|--------|---|
| Aβ | mechanoreceptive afferent fibres |
| Aδ, C | nociceptive afferent fibres |
| CGRP | calcitonin gene-related peptide |
| DLF | dorsolateral funiculus |
| LC | locus ceruleus |
| NA | noradrenaline |
| NRM | nucleus raphe magnus |
| NRPG | nucleus reticularis paragigantocellularis |
| NSAIDs | non-steroidal anti-inflammatory drugs |
| op | opiate receptors |
| PAG | periaqueductal grey matter |
| PGs | prostaglandins |
| SG | substantia gelatinosa |
| SP | substance P |
| ST | spinothalamic tract |

c. Describe the role in analgesia of α_2 agonists, inhalational alagesics, NMDA antagonists, non-steroidal anti-inflammatory drugs, serotonergic agents and activators of adrenergic inhibition (tramadol).

Some sites of action detailed above. Details under specific drugs.

d. Describe and evaluate methods in the assessment and measurement of pain in animal models and patients.

B. 4 Non-steroidal anti-inflammatory analgesic drugs

a. Describe the prostaglandin pathway

Prostaglandins and other eicosanoids (thromboxanes, leukotrienes, lipoxins, hydroperoxyeicosatetraenoic acids etc.) are synthesized from saturated membrane phospholipids derived from dietary linoleic and linolenic acid. They are not stored, but are synthesized as required either by cleavage of phospholipids by phospholipase A₂ (which can also give rise to PAF) or by phospholipase C and diacylglycerol lipase. The production of arachadonic acid is the rate-limiting step in the production of prostaglandins. Production of arachadonic acid may be stimulated either by specific receptors in some tissues or by general cell damage.

Arachadonic acid is oxidized to PGG₂ by cyclooxygenase and then reduced to PGH₂ by peroxidase. These steps are both catalyzed by prostaglandin endoperoxide synthetase. Which prostaglandins are synthesized from PGH₂ depends on the enzymes present in the tissue. In platelets thromboxane synthetase produces TXA₂, in endothelium prostacyclin synthetase produces PGI₂, in macrophages predominantly PGE₂ is formed. The subscript 2 refers to the number of saturated bonds in the fatty acid backbone of the molecule. Small quantities of prostaglandins are synthesized from dihomo- γ -linolenic acid or eicosapentanoic acid, giving one or three saturated bonds.

In lung, platelets and leukocytes, lipoxygenases convert arachadonic acid to 5-HPETE and then LTA₄ which is subsequently converted to other leukotrienes: important chemotactic factors.

Prostaglandins are metabolized either by specific uptake and inactivation in the lung (in the case of PGE₂), renal metabolism (in the case of PGI₂) or spontaneous decay to inactive substances (TXA₂ \rightarrow TXB₂).

b. Classify the non-steroidal anti-inflammatory drugs

The NSAIDs are classified by chemical structure

salicylic acids

aspirin, diflunisal

propionic acids

naproxen, ibuprofen, ketoprofen

acetic acids

indomethacin, sulindac, diclofenac

fenamates

mefenamic acid, meclofenamic acid

oxicams

piroxicam, tenoxicam

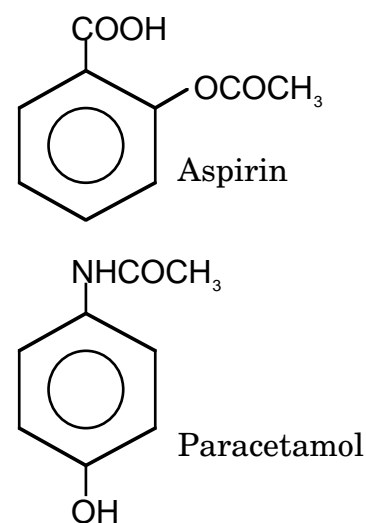
pyrazolones

phenylbutazone, azopropazone

COX-II selective

celecoxib

paracetamol



c. Describe the effects of paracetamol and its toxicity

Class

Paracetamol is an analgesic and antipyretic with no anti-inflammatory effect. It is a weak prostaglandin inhibitor. It is the most commonly used analgesic and is available without prescription.

History

Physical

a white powder, sparingly soluble in water

Chemical

structural formula above, empirical formula $C_8H_9N_2O_2$, a para-aminophenol derivative

Pharmacokinetics

administered orally or rectally (variable absorption)
IV preparation available overseas: proparacetamol
bioavailability close to 100%
peak concentration 30-60 min
 V_d 1 l/kg
little protein binding (20-50%)
plasma $t_{1/2}$ 2-4 h
clearance 5 ml/kg/min
eliminated by conjugation and hydroxylation in the liver followed by renal excretion
metabolism pathway is saturated in overdose, resulting in production of N-acetyl-p-benzoquinone which is hepatotoxic in the absence of glutathione. N-acetyl-cysteine administration within 8 hours of overdose is protective by regenerating hepatic glutathione.

Pharmacodynamics

little effect on peripheral prostaglandin synthesis
no antiinflammatory action
no gastric/renal toxicity
no antiplatelet activity
central effect, presumably prostaglandin moderated
analgesic
antipyretic

Clinical uses

dosage 10-30 mg/kg orally, less in hepatic impairment
up to 100 mg/kg/day in children, up to 40 mg/kg PR
duration of action around 4 hours
analgesic of choice for mild musculoskeletal or superficial pain without an inflammatory component
synergistic with opiates in severe pain
antipyretic of choice in children
no significant interactions

Adverse effects

hepatotoxicity in overdose
some constipation

d. Describe the actions of aspirin on prostaglandin synthesis in high and low doses and compare it with other NSAIDs

Class

the prototype non-steroidal anti-inflammatory drug

History

salicylates are present in willow bark, a traditional antipyretic described in 1763
aspirin was synthesized in 1853 and sold commercially from 1899

Physical/Chemical

a white powder sparingly soluble in water
calcium salts are readily soluble
structure above: acetylsalicylic acid
acidic pKa (3.5)

Pharmacokinetics

orally administered
high bioavailability
absorbed from stomach and small bowel, best in acidic conditions
hydrolyzed in the liver to salicylate $t_{1/2}$ 15 min
salicylate is protein bound 80-90%

salicylate is conjugated with glycine in the liver

$t_{1/2}$ 2 h at low dose, up to 20 h at high dose

both are renally excreted; unchanged drug is excreted rapidly in alkaline urine

Pharmacodynamics

irreversibly acetylates cyclooxygenase

inhibits production of PGI_2 , thromboxanes, other PGs

impaired platelet function, analgesic, antipyretic

salicylic acid reversibly inhibits cyclooxygenase

high doses result in

PG-mediated

local gastric irritation or ulceration

CNS stimulation

seizures, hyperventilation, respiratory alkalosis

reduced GFR, Na^+ and water retention, renal papillary necrosis

prolongation of labour

closure of PDA

hepatotoxicity

inner ear toxicity, tinnitus

reduced prothrombin synthesis, increasing INR

decoupling oxidative phosphorylation

metabolic acidosis, hyperthermia, dehydration

anaphylactoid reactions are most common in asthmatics

cross-reactivity with other NSAIDs is common

Clinical use

dosage

for anti-platelet activity 100 mg daily

single dose for mild pain 300-600 mg

anti-inflammatory dose 4-6 g/day

toxicity

as above, plus

protein-binding interactions, especially with warfarin

Reye's syndrome in children

marrow suppression

blood levels are closely related to toxicity

<10 mg/dl analgesic, antiplatelet

10-40 mg/dl anti-inflammatory

50-80 mg/dl tinnitus, hyperventilation

80-100 mg/dl acidosis

>100 mg/dl hypoprothrombinaemia, renal failure, coma

indications

antiplatelet: IHD, carotid disease, CVA risk

analgesic: mild pain, with or without inflammatory component

synergistic with opiates

contraindications

not generally used in children

Reye's syndrome: hepatic failure associated with viral illness

bleeding risk (e.g. proliferative retinopathy, warfarin)

renal impairment or hypovolaemia

peptic ulcer disease

asthma a relative contraindication

gout (reduces uric acid excretion in low dose)

overdose management

gastric lavage & charcoal

correction of pH disturbance, dehydration or hyperthermia

alkalinized diuresis

Other NSAIDs

Inhibit cyclooxygenase reversibly, so have less prolonged antiplatelet effect and are not known to be effective at low dose.

exhibit the same adverse effects with variation according to selectivity for COX-I or COX-II. COX-II inhibition results in better selectivity for anti-inflammatory activity.

Potency, metabolism, excretion and half life vary widely.

e. Describe the actions of parenterally administered NSAIDs and their side-effects.

Ketorolac

parenteral NSAID

propionic acid derivative

Pharmacokinetics

administered intramuscularly (sometimes IV)

oral bioavailability 80%

peak concentration 45 min after IM injection

99% protein bound

clearance 30 ml/kg/min

hepatic glucuronidation and renal clearance

$t_{1/2}$ 5h

Pharmacodynamics

similar to other NSAIDs

analgesic potency: 30 mg ketorolac \approx 12 mg morphine

f. Outline the pharmacology of acetic acid derivatives and propionic acid derivatives including their side-effects.

B. 5 Intravenous anaesthetic agents

a. List the ideal properties of an intravenous induction agent.

Definition

A drug or combination of drugs which will induce anaesthesia safely and reversibly when injected in sufficient doses and which could also be used intermittently or by infusion for maintenance of anaesthesia.

Classification

rapid acting

barbiturates, imidazoles, phenols, steroids, eugenols

slower acting

phencyclidines, benzodiazepines, opioids, neurolept combinations

Ideal properties

simple preparation

compatible with other agents and IV fluids

painless on administration

high potency and efficacy

predictable action within one circulation time

minimal cardiovascular effects or other toxicity

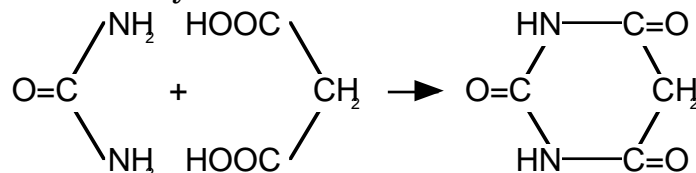
depression of airway reflexes for intubation

rapid and predictable offset of effect

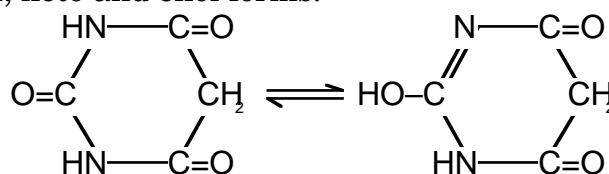
rapid metabolism for minimal hangover

b. Describe the structure-activity relationship of the barbiturates.

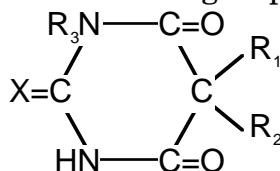
Barbituric acid is formed by the condensation of urea and malonic acid:



it is insoluble in water and has no activity in vivo. Barbiturates have two structural isomers which are in equilibrium, keto and enol forms:



The barbiturates have substitutions of functional groups of barbituric acid:



X is oxygen (oxybarbiturates) or sulfur (thiobarbiturates). The thiobarbiturates such as thiopentone are generally more lipid-soluble and so have a more rapid onset of action. R₃ is usually hydrogen, but in the case of methohexitone a methyl group is substituted which increases convulsive effect and shortens elimination half-life. The R₁ and R₂ groups can be short alkyl or aryl chains in the hypnotic barbiturates or longer (more than 5 carbon) chains in the anticonvulsants. Branched chains give greater hypnotic than anticonvulsant effect. Phenobarbitone has phenol and ethyl groups at R₁ and R₂ and is an anticonvulsant.

| | R ₁ | R ₂ | R ₃ | X |
|----------------|------------------------------------|--|-----------------|---|
| thiopentone | ethyl | 1-methyl-butyl | H | S |
| pentobarbitone | ethyl | 1-methyl-butyl | H | O |
| methohexitone | CH ₂ CH=CH ₂ | CH(CH ₃)C≡CC ₂ H ₅ | CH ₃ | O |
| phenobarbitone | ethyl | phenyl | H | O |

c. Describe the pharmacology of propofol, thiopentone and methohexitone and the factors which influence their effects.

thiopentone

pharmaceutics

presented as the Na⁺ salt of the enol form

0.5 g in 20 ml ampoule with N₂, Na₂CO₃ 30 mg to pH 11

prepared with water or saline to 25 mg/ml solution

pH 11-12 precipitates in neutral or acid solution

stable (<7% loss of potency) for 5 days at 25°C or 45 days at 5°C

pharmacokinetics

distribution

pKa 7.6

85% protein bound

V_{dss} 1-2 l/kg

metabolism

t_{1/2}α fast 8 min, slow 60 min, t_{1/2}β 11 h

clearance 3 ml/min/kg

rapid redistribution from VRG into muscle (30 min peak) and fat

slow hepatic metabolism, easily saturated in infusion

pentobarbitone is one metabolite

pharmacodynamics

CNS

potentiates GABA_A transmission, prolongs channel opening

may depress excitatory transmission by inhibiting Ca²⁺ transport

acts at reticular formation, hypothalamus and limbic

brief stimulatory phase before sleep

anticonvulsant at hypnotic doses

↓ CMRO₂, CBF, vasoconstrictor (may cause inverse steal)

not analgesic

CVS

effects depend on dose and rate of administration and filling

venodilator: ↓ LVEDV

myocardial depressant at high doses: ↓ SV, CO, MAP

but ↑ myocardial O₂ demand in anaesthetic doses

not an arterial vasodilator: baroreceptor reflex ↑ SVR

respiratory

central depressant

↓ rate, ↑ V_T followed by apnoea

↓ CO₂ sensitivity

↓ upper airway reflexes when deep

renal, hepatic

minimal ↓ function

uterine

crosses placenta readily, no effect on tone

local

thrombophlebitis, pain, thrombosis

intraarterial injection causes vasospasm

due to endogenous vasoconstrictor release

adverse effects

above plus anaphylaxis (1/14000), anaphylactoid

clinical use

induction of general anaesthesia around 4 mg/kg

cerebral protection (5 mg/kg + 5 mg/kg/h)

contraindicated

no IV access, no airway support equipment

respiratory obstruction (croup, epiglottitis)

allergy

porphyria

relative contraindications

cardiac disease

septicaemia, acidosis

adrenocortical insufficiency

methohexitone

pharmaceutics

500 mg in 50 ml glass ampoule

white/yellow powder, sodium salt

stabilized with anhydrous sodium carbonate

mostly α L and α D isomers. β isomers increase involuntary movement.

prepared with water or saline

pH 10.6-11.6

pharmacokinetics

pKa 7.2

70% protein bound

V_{dss} 1l/kg

$t^{1/2}\alpha$ fast 6 min, slow 60 min, $t^{1/2}\beta$ 2-4 h

clearance 11 ml/min/kg

pharmacodynamics

excitatory phenomena

more irritant to vessels

dose 1-1.5 mg/kg

propofol

pharmaceutics

10 mg/ml in 20, 50 and 100 ml ampoules

white aqueous isotonic emulsion

solubilized with 2.25% glycerol, 10% soybean oil, 1.2% purified egg

phospholipid

previously solubilized in Cremaphor EL \rightarrow anaphylaxis

pH 6.0 to 8.5

pharmacokinetics

weak organic acid, pKa 11

98% protein bound

V_{dss} 10 l/kg

metabolism by conjugation in liver

three compartment model

$t^{1/2}\alpha$ 2 min, $t^{1/2}\beta$ 45 min, $t^{1/2}\gamma$ 4 h

pharmacodynamics

similar to thiopentone

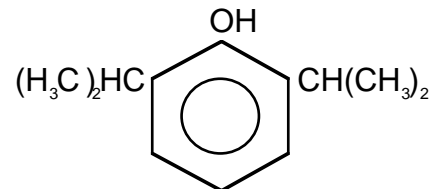
GABA_A transmission effect may be its mechanism of action

CNS

excitatory effect, but anticonvulsant

? analgesic

little psychomotor effect after awakening



PNS: potentiates effect of NMJ blockers
respiratory: greater incidence of apnoea
CVS: ↓ SVR, SV, MAP

clinical use

induction 2-2.5 mg/kg (less in elderly or hypovolaemic)

maintenance 0.1-0.2 mg/kg/min

levels (µg/ml)

0.3 psychomotor effects

1.0 sleep

3 minor surgery

4 major surgery

ketamine

pharmaceutics

500 mg/10 ml, 100 mg/ml 10 ml, 2 ml vials

benzethonium chloride preservative

pH 3.5-5.5

(+) isomer 3-5 times more potent

pharmacokinetics

V_d 3 l/kg

hepatic metabolism hydroxylation or N-demethylation, conjugation
norketamine has 20% potency

clearance 18 ml/kg/min

$t_{1/2\alpha}$ 10 min, $t_{1/2\beta}$ 3 h

pharmacodynamics

NMDA antagonist

CNS

dissociative anaesthesia

inhibits thalamic transmission to cortex

↑ CBF, ICP, IOP

hallucinations on emergence

CVS

↑ sympathetic tone (central and ↓ NA uptake)

↑ HR, MAP, PVR

direct cardiac depressant

respiratory

retention of airway reflexes in low dose

↑ secretions, bronchodilation

muscle: ↑ tone, movements, inhibits PIChE

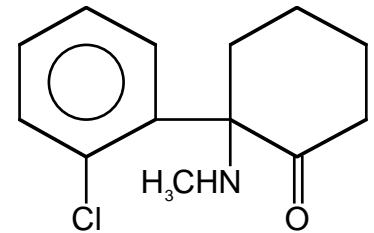
clinical use

induction 1-2 mg/kg IV (4-6 mg/kg IM)

maintenance 5-30 µg/kg/min

analgesia 150 ng/ml

anaesthesia 1000 ng/ml



Althesin

alphaxolone and alphadolone (3α-hydroxy steroids)

not available

pharmaceutics

alphaxolone 9 mg/ml, alphadolone 3 mg/ml in Cremaphor EL

pharmacokinetics

rapid induction of anaesthesia in one circulation time

pharmacodynamics

alphaxolone is twice as potent as alphadolone

high therapeutic index (30.6)

excitatory movements common

cardiodepressant → hypotension

propanidid

pharmaceutics

eugenol derivative

50 mg/ml in Cremaphor EL

pharmacokinetics

rapidly metabolized by pseudocholinesterase

competes with suxamethonium

pharmacodynamics

excitatory movements common

marked hyperventilation in induction

hypotension, tachycardia

d. Describe the formulation of thiopentone, methohexitone, propofol, diazepam and midazolam.

Diazepam

Diazemuls

1 ml of 5 mg/ml glass ampoule

solubilized in soybean oil

Diazepam USP

2 ml of 5 mg/ml brown glass ampoule

clear yellow solution

dissolved in 40% propylene glycol, 10% ethyl alcohol, 5% Na benzoate

pH 6.6-6.9

Midazolam

5 ml of 1 mg/ml or 1, 3 or 10 ml of 5 mg/ml glass ampoules

clear aqueous solution

buffered to pH 3.3

precipitates in strongly alkaline solutions

e. Compare the pharmacokinetic and pharmacodynamic differences between thiopentone, methohexitone, midazolam, diazepam, ketamine, etomidate and the steroid anaesthetics.

Thiopentone and methohexitone are barbiturate induction agents used intravenously. Their brief duration of action results from rapid distribution from the vessel-rich group into skeletal muscle and then fat. Methohexitone is slightly less dependent on redistribution for its duration of action as its rate of hepatic metabolism and renal clearance is significantly higher.

| | Rapid Distribution $t_{1/2}$ | Slow Distribution $t_{1/2}$ | Elimination $t_{1/2}$ | Clearance (ml/min/kg) | V_{dist} (l/kg) |
|---------------|---------------------------------|--------------------------------|--------------------------|--------------------------|----------------------|
| thiopentone | 8.5 min | 62.7 min | 11.6 h | 3.4 | 2.5 |
| methohexitone | 5.6 min | 58.3 min | 3.9 h | 10.9 | 2.2 |

Both are highly protein-bound, lipid soluble and metabolized by hepatic oxidation (and desulfuration in the case of thiopentone) to inactive and less lipid-soluble metabolites which are renally cleared. Elimination half-life is shortened in children and patients with induced liver enzymes.

Barbiturates act by depressing the reticular activating system, possibly by inhibiting the dissociation of GABA from its receptors. Tolerance develops rapidly with continuous use.

Diazepam and midazolam are benzodiazepines which are active orally, transmucosally, intravenously, and in the case of midazolam, epidurally. Midazolam is used as a sedative and coinduction agent. They are both highly lipid soluble and 96–98% protein

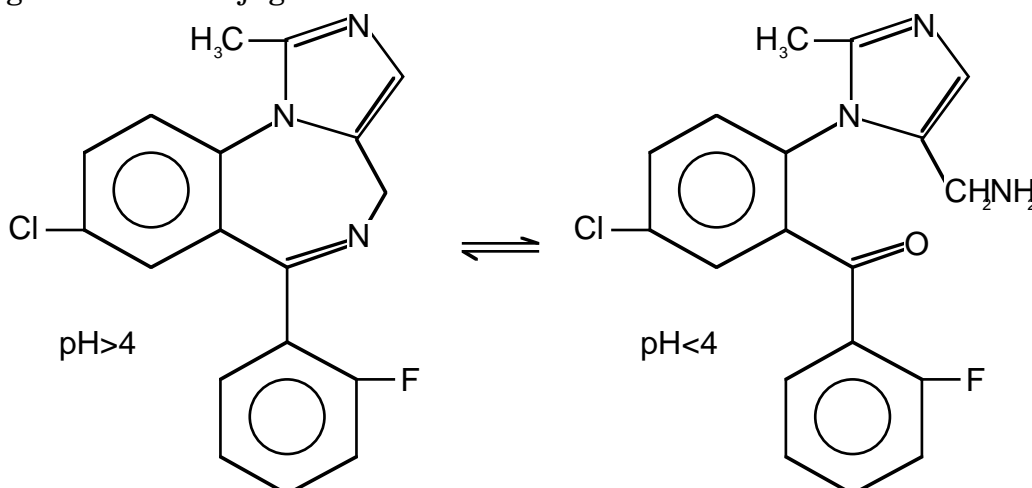
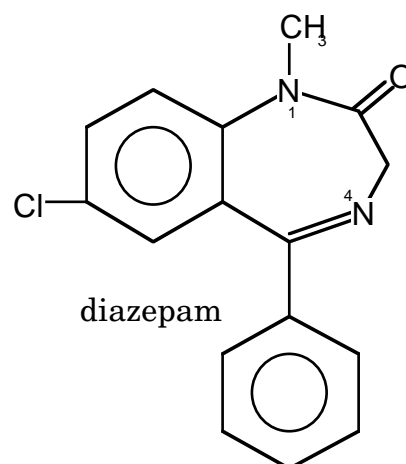
bound. They have similar volumes of distribution but differ in metabolism.

| | Elimination $t_{1/2}$ | Clearance (ml/min/kg) | V_{dist} (l/kg) | Oral bioavailability |
|-----------|--------------------------|--------------------------|----------------------|-------------------------|
| diazepam | 21-37 h | 0.2-0.5 | 1-1.5 | 94% |
| midazolam | 1-4 h | 6-8 | 1-1.5 | 50% |

Diazepam is oxidized in the liver to desmethyldiazepam, oxazepam and temazepam all of which are active. Desmethyldiazepam has an elimination half-time of 48-96 hours, greatly prolonging the clinical effect of diazepam. The elimination half-time of diazepam increases with age and hepatic impairment to over 100 h in the elderly. The effective duration of action depends on both metabolism and initially on redistribution into fat.

Midazolam spontaneously converts to a water-soluble form at acidic pH due to a reversible ring-opening reaction and possibly due to ionization of the imidazole nitrogen. This allows preparation of a buffered (pH 3.5) water-based solution for intravenous use.

Midazolam is metabolized by hepatic microsomal enzymes to 1-hydroxymidazolam and 4-hydroxymidazolam both of which are excreted renally as glucuronide conjugates.



Benzodiazepines act by binding to a specific receptor site on GABA receptors, facilitating GABAergic transmission. In the CNS, it acts predominantly in the cortex; the concentration of GABA receptors being less in the more primitive parts of the CNS. There are GABA receptors on spinal motor interneurons, which may account for the activity of diazepam in reducing muscle tone.

Ketamine is a phencyclidine derivative used to induce dissociative anaesthesia.

| | Elimination $t_{1/2}$ | Clearance (ml/min/kg) | V_{dist} (l/kg) |
|-----------|--------------------------|--------------------------|----------------------|
| ketamine | 1-2 h | 16-18 | 2.5-3.5 |
| etomidate | 2-5 h | 10-20 | 2.2-4.5 |
| propofol | 4 h | 30-60 | 10 |

Ketamine is active intravenously, intramuscularly, epidurally and intrathecally. It is not significantly protein-bound. It is extremely lipid soluble and when administered IV is rapidly redistributed into the vessel-rich group including the brain, with slower redistribution to muscle and fat. It is demethylated by cytochrome p450 enzymes to norketamine (active) and hydroxylated and excreted renally as a glucuronide conjugate. Its

metabolism is slowed by the administration of halothane or diazepam. Ketamine induces the enzymes responsible for its metabolism so tolerance and dependence are seen.

Ketamine is thought to interact with opioid receptors in the CNS. Its analgesic effects exhibit cross-tolerance with opiates. It inhibits reuptake of catecholamines, causing an indirect sympathomimetic effect. It blocks glutamic acid NMDA transmission in the CNS. Its direct effect on the heart is depressant, intact sympathetic activity is required for its effect in increasing cardiac output. It enhances the activity of non-depolarizing muscle relaxants and inhibits plasma cholinesterase, prolonging the effect of suxamethonium.

Etomidate is an imidazole containing compound which can be used as an induction agent. It is water-soluble at acidic pH and is used intravenously. Its brief duration of action is a result of redistribution as with thiopentone. It is moderately lipid-soluble at physiological pH. It is 76% protein bound.

Etomidate is metabolized by hydrolysis by hepatic microsomal enzymes and plasma esterases. Its metabolism is more rapid than thiopentone. Metabolites are inactive and renally cleared.

Etomidate probably acts to increase GABA transmission. Like methohexitone lowers the seizure threshold and causes myoclonic movements. It acts to inhibit 11- β -hydroxylase in the adrenal, reducing synthesis of cortisol and inhibiting the normal stress response. It is not used in Australia.

gamma-hydroxybutyrate

water soluble hydrocarbon

high dose (50 mg/kg for induction)

slow onset (3 min)

long duration

bradycardia, emesis and hallucinations

pregnanolone

steroid

solubilized in intralipid

rapid onset, short duration

$t_{1/2\alpha}$ 10 min, $t_{1/2\beta}$ 1 h

V_{dss} 4 l/kg

clearance 30-60 ml/kg/min

dose 0.6 mg/kg

may produce "steroid pyrogen fever"

similar thrombophlebitis to barbiturates

f. Describe the undesirable systemic effects of individual agents.

g. Describe the toxic and adverse reactions to intravenous agents.

B. 6 Inhalational anaesthetic agents

a. Describe the properties of an ideal inhalational anaesthetic agent.

preparation

- easily administered
 - boiling point above ambient temperature
 - low latent heat of vaporization
 - simple apparatus
- chemically stable
 - long shelf-life, compatible with soda-lime, metals and plastics
 - not flammable
 - cheap

pharmacokinetic

- low solubility
 - rapid onset, rapid offset, adjustable depth
- minimal metabolism
- predictable in all age groups

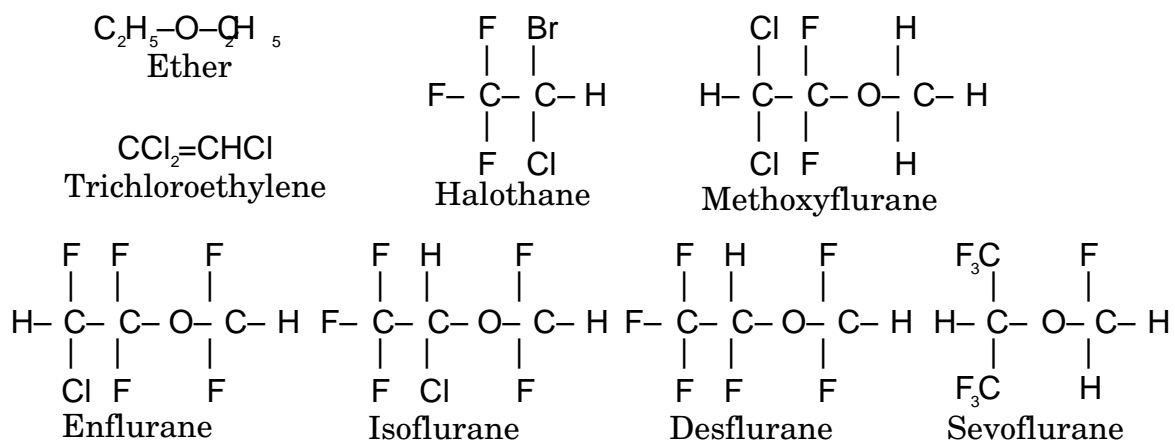
pharmacodynamic

- high potency
 - allows high FiO_2
- high therapeutic index
- analgesic

adverse actions

- minimal toxicity
- minimal unwanted effects
 - nausea, vomiting, cardiac arrhythmogenicity
- no toxicity with chronic low-level exposure of staff

b. Describe the structure-activity relationships of the volatile agents.



Structure-activity relationships for the volatile anaesthetic agents apply to their physical and chemical properties and to their metabolism.

physical

- low molecular weight and non-polar structure produce low boiling point, high vapour pressure

chemical

- large number of hydrogen atoms increases flammability
- high fluorine content minimizes flammability
- CF_2H moiety can liberate CO in reaction with dry soda-lime

pharmacokinetics

- fluorine content reduces solubility in blood and fat
- hydrolysis of ethers is most rapid when the adjacent carbon atoms are not halogenated
- hydrolysis produces a halogenated acetic acid and halogenated methanol which can release some halides
- fluorine on the 1-carbon of methyl-ethyl-ethers can be liberated as F⁻

pharmacodynamics

- chlorine and hydrogen content increases potency
- fluorine content reduces potency

c. Provide a brief overview of the history of nitrous oxide, cyclopropane, ether and chloroform.

- 1772 N₂O first prepared by Priestly
- 1779 Humphrey Davy suggested N₂O had anaesthetic and analgesic properties
- 1844 N₂O demonstrated by Horace Wells for dental extraction
- 1846 ether demonstrated by Morton at Massachusetts General
- 1847 chloroform introduced, used by Queen Victoria
- 1880s ethyl chloride introduced
- 1930s cyclopropane and trichloroethylene introduced
 - cyclopropane used for single-breath gas inductions (MAC 9%)
 - trichloroethylene (Trilene) blue coloured agent with good analgesic properties
- 1951 halothane synthesized
 - fluroxene enters clinical use
- 1956 halothane enters clinical use
- 1960 methoxyflurane enters clinical use
- 1963 enflurane synthesized
- 1965 isoflurane, desflurane synthesized
- 1966 enflurane enters clinical use
- 1968 sevoflurane synthesized
- 1971 isoflurane enters clinical use
- 1990 sevoflurane enters clinical use
- 1992 desflurane enters clinical use

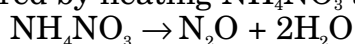
d. Describe the preparation of nitrous oxide and Entonox and outline their physical properties.

nitrous oxide

physical properties

- MW 44.02
- BP -88.5°C
- SG 1.53 kg/l

prepared by heating NH₄NO₃ at 245-270°C



small amounts of NH₃ and HNO₃ produced recombine to NH₄NO₃ on cooling

small amounts of NO and NO₂ are also produced

can cause methaemoglobinaemia, pulmonary oedema if inspired

N₂O must be purified to remove these contaminants

Entonox™

- 50% O₂, 50% N₂O supplied in cylinders at 138 bar
- maximum pseudo-critical temperature -5.5°C at 117 bar
 - separation of constituents occurs below pseudo-critical temperature
- analgesic for labour and brief procedures

e. Describe the undesirable effects of nitrous oxide.

pharmaceutic

contamination in manufacture

NO₂, NO, HNO₃

physiological

cardiovascular

haematological

↑ P₅₀ by 1.6 mmHg

inhibition of thymidylate synthetase and methionine synthetase by oxidation of cobalt ion on B₁₂

megaloblastic anaemia

neuropathy

teratogenicity

CNS

↑ muscle tone, rigidity especially with opiates

physical

flammability

not flammable, but will support combustion

gas spaces

partition into physiological spaces

middle ear, gut ? → nausea

other spaces

expansion of pneumothorax, gas emboli, tube cuffs

hypoxia

low potency requires high Fi, potential for hypoxic gas mix

rapid flow of N₂O into alveoli on ceasing administration causes diffusional hypoxia unless supplemental oxygen is inhaled

f. Describe the comparative pharmacology of halothane, enflurane, isoflurane, methoxyflurane, desflurane and sevoflurane.

| | BP (°C) | MW | SVP (mmHg) | blood: gas | blood: brain | MAC (%) | metab. (%) |
|-------------------|------------|-----|-------------------|------------|--------------|------------|---------------|
| N ₂ O | -88.5 | 44 | 4x10 ⁴ | 0.46 | 1.0 | 105 | 0.004 |
| desflurane | 23.5 | 168 | 669 | 0.45 | 1.3 | 6.0 | 0.02 |
| sevoflurane | 58.5 | 200 | 170 | 0.65 | 1.7 | 2.0 | 3.0 |
| isoflurane | 48.5 | 184 | 240 | 1.4 | 1.6 | 1.15 | 0.2 |
| enflurane | 56.5 | 184 | 172 | 1.8 | 1.5 | 1.7 | 2.4 |
| halothane | 50.2 | 197 | 244 | 2.4 | 1.9 | 0.75 | 20 |
| methoxyflurane | 105 | 165 | 22.5 | 12 | 2.0 | 0.15 | 50 |
| ether | 35 | 74 | 440 | 12 | | 1.9 | high |
| trichloroethylene | 87 | 131 | 59 | 9.1 | | 0.17 | |
| cyclopropane | -33 | 42 | 6x10 ⁴ | 0.42 | | 9.2 | 0 |

oil:gas partition ≈ 150 ÷ MAC

g. Describe the physiological effects of the volatile agents.

CNS

anaesthesia

facts

anaesthetics act at millimolar concentrations (high)

lipid solubility increases potency for most agents

(Meyer-Overton relationship)

some stereospecificity is displayed by chiral agents

lipid fluidity changes induced by agents are very small
inhibition of intracellular Ca^{2+} release occurs

several theories

unitary vs degenerate

agents act at a single site or at multiple sites

lipid vs protein

agents act by altering lipid fluidity or binding lipophilic regions of proteins

likely explanation

binding to lipophilic protein regions (differing slightly for different agents) alters ligand-gated ion channel activity, altering some or all of ACh, GABA, NMDA, AMPA and KA transmission

analgesia

uncertain mechanism of action, probably related to anaesthetic actions

EEG ↓ frequency ↑ voltage from 0.4MAC (asleep)

I, S, D burst suppression at 1.5MAC, silence at 2MAC

H silence at 3.5MAC (impractical)

E seizure activity (↑ by low PCO_2)

evoked potentials ↓ amplitude ↑ latency

CSF volume E ↑ I ↓

CBF loss of autoregulation → vasodilation

H from 0.6MAC

E > I from 1.0MAC

CVS

↓ contractility H, E > I, S, D

↑ RAP H, E > I

↓ SVR I, S, D > E > H (I can cause coronary steal, no tachycardia with S)

catecholamine sensitization H > I, S, D > E

respiratory

↓ hypoxic response markedly from 0.1MAC

↓ hypercapnic response: E, S > I > H

↓ TV

↑ RR up to 1MAC, then I ↓ H, E ↑

bronchodilation (↓ vagal tone, smooth muscle relaxation)

GIT

hepatotoxicity

all ↓ portal flow

hepatic artery flow H ↓ I ↑

renal

F⁻ ion toxicity (below)

E ↓ RBF and GFR

I, H, D maintain RBF and GFR

muscle

relaxant due to

↓ central outflow, ↑ blood flow, ↓ post junctional sensitivity, ↓ Ca^{2+} flux

E, I > H

trigger for malignant hyperpyrexia

H > E > I

obstetric

↓ contractility, vasodilation (↑ blood loss), depression in fetus

immune, haematological

H ↓ platelet aggregation

impair neutrophil activity

N_2O > volatiles

teratogenic

h. Describe the metabolism of the volatile agents and the role of their metabolites in toxicity.

halothane

oxidation (most metabolism if hepatic oxygen delivery is adequate)

→ trifluoroacetic acid, Br⁻, Cl⁻ → conjugates of TFA

inhibited by cimetidine, isoflurane, ischaemia

reduction (0.1-0.5%)

→ Br⁻ + CF₃CH₂Cl → HF + F₂C=CHCl → conjugates

toxicity

alkane volatiles are more arrhythmogenic than ethers

Br⁻ direct sedative

F⁻ nephrotoxicity (but very little liberated)

dose- and hepatic blood flow-related hepatotoxicity

mild ↑ ALT, AST

incidence ≈20%

associated with increased reductive metabolism

autoimmune fulminant hepatic necrosis

1:30000

accompanied by eosinophilia, rash

associated with oxidative metabolites modifying hepatic proteins

may also be associated with other volatiles more rarely

fluoride ion liberation

most severe with α-carbon fluorinated ethers

M >> S > E >> I > D

systemic [F⁻] > 50 μmol/l associated with high output renal failure

sevoflurane is metabolized by cytochrome p450 E1 in liver

methoxyflurane and enflurane are metabolized by p450 in kidney, producing higher local F⁻ concentrations

sevoflurane may also alter renal handling of amino-acids and glucose

i. Describe the interaction of soda-lime with trichloroethylene, halothane and sevoflurane.

sevoflurane

forms compound A (PIFE) on reaction with warm soda-lime

sevoflurane → HF + FH₂C-O-C(CF₃)=CF₂ (a vinyl ether)

other compounds formed in very small quantities

compound A causes nephrotoxicity in rats at 150-200 ppm (LD₅₀ 1000 ppm)

normal levels in human anaesthesia don't exceed 30 ppm

reduced by gas flow (>2 l/min recommended)

halothane

forms a vinyl compound in soda-lime

halothane → HF + F₂C=CBrCl

greater toxicity in rats than compound A (LD₅₀ 250 ppm)

normal levels in high flow anaesthesia 4-6 ppm

trichloroethylene

forms toxic compounds with soda-lime

trichloroethylene → dichloroacetylene → phosgene (Cl₂C=O) + CO

dichloroacetylene causes neurotoxicity

esp. cranial nerves V, VII, VIII

phosgene causes pulmonary toxicity

phosgene + H₂O → 2HCl + CO₂

(never to be used with soda-lime; rarely used anyway)

B. 7 Neuromuscular blocking agents

a. Explain the physiology of neuromuscular transmission and how this may be interfered with to produce muscle relaxation.

Acetylcholine is the neurotransmitter of the NMJ. Choline is synthesized in the liver and actively taken-up by nerve cells. It is condensed with acetyl-CoA derived from the TCAC which is present in the cell cytoplasm. This reaction is catalyzed by choline acetyltransferase present in the nerve terminal which is inhibited by acetylcholine and acetylcholinesterase. ACh is stored in vesicles in the nerve terminal.

Vesicles are grouped in the nerve terminal away from the junctional surface and move to sites adjacent to the junction where they are bound to synapsin. The mobilization and release of vesicles is promoted by stimulation of the prejunctional nicotinic receptor and inhibited by stimulation of the prejunctional muscarinic receptor.

In response to the rise in intracellular Ca^{2+} , protein kinase II dephosphorylates synapsin and allows vesicles to bind to synaptophysin which results in release of their contents. There is continuous slow release of the contents of vesicles from the nerve terminal, resulting in miniature end-plate potentials (MEPPs). ACh is hydrolyzed to choline and acetate by cholinesterase in the synaptic cleft. These are then reabsorbed by the nerve terminal.

The neuromuscular junction consists of a nerve terminal (of a motor neurone) adjacent to an end plate on skeletal muscle. The nerve terminal contains around 300,000 vesicles containing acetylcholine. When an action potential arrives at the nerve terminal, an influx of Ca^{2+} triggers the release of the contents of around 125 vesicles of acetylcholine into the synaptic cleft. The acetylcholine diffuses rapidly to its receptors on the end plate where it opens ion channels in the muscle cell membrane, allowing a rapid influx of Na^+ , generating an EPSP and triggering an action potential (by opening voltage-dependent channels) which propagates through the T-tubule system and causes a release of Ca^{2+} from the sarcoplasmic reticulum. This intracellular Ca^{2+} binds to troponin C, allowing binding of actin to tropomyosin and contraction of muscle fibrils with the hydrolysis of ATP.

The influx of Ca^{2+} lasts around 50 ms in skeletal muscle. The action potential lasts only 1-5 ms and the acetylcholine is broken down within a few milliseconds by acetylcholinesterase in the subneural clefts. The low intracellular concentration of Ca^{2+} is rapidly restored by active transport of the Ca^{2+} back into the sarcoplasmic reticulum. A single action potential generates only a brief contraction of skeletal muscle. A sustained (tetanic) contraction requires summation of a rapid series of action potentials.

The pharmacological methods by which neuromuscular transmission is blocked include competitive blockade of the acetylcholine receptor with an antagonist (non-depolarizing block) or non-competitive blockade with an agonist which is not broken down by acetylcholinesterase (depolarizing). Non-competitive blockade works to prevent muscle contraction initially by maintaining the end plate in a depolarized state and blocking the ion channel at the receptor, thereby blocking the repeated action potentials required to produce sustained contraction (phase I block). Prolonged exposure to depolarizing blockers causes a desensitization of the end plate resulting in a phase II block similar to that caused by the non-depolarizing blockers.

Transmission can also be interfered with at other stages. Latrotoxin (Red-back spider venom) increases vesicle release, depleting ACh. Botulinum toxin inhibits vesicle release from the nerve terminal.

After blockade, transmission can be enhanced ("reversed") by cholinesterase inhibiting drugs which increase the life of ACh in the synaptic cleft. Higher doses of these drugs inhibit transmission by causing a depolarizing block. 4-aminopyridine and tetraethylammonium block K^+ channels in the nerve terminal, delaying repolarization and increasing the amount of ACh released.

Open channel block is produced by depolarizing muscle relaxants but can also be produced by NDBs if a depolarizing agent is given while a high concentration of NDB is present. The NDB binds in the open channel of the ACh receptor, producing a prolonged

block. This is a clinical problem if a reversal agent is given while the patient is deeply paralyzed.

There is substantial redundancy in transmission at the NMJ. The quantity of ACh released and the number of nicotinic receptors are both in large excess. Normal VC and TOFC 0 is seen despite block of 75% of receptors by an NDB. Normal inspiratory force is observed with 50% blocked and sustained head lift with 33% blocked.

b. Describe the post-junctional receptor.

Nicotinic post-junctional receptors are grouped at the “shoulders” of the subneural clefts. The receptor is a cone-shaped protein consisting of five subunits which binds with two molecules of acetylcholine. The ion channel when opened admits Na^+ , K^+ and Ca^{2+} , but the main effect at the time of opening is influx of Na^+ .

The receptor is a pentamer composed of four different units ($\alpha_2\beta\epsilon\delta$) all of which span the cell membrane. The ACh receptor sites are on the α subunits. There is a central ion channel which opens due to conformational changes with both receptor sites are occupied by agonists.

The nicotinic receptors on nerve tissue are composed of a different combination of units ($\alpha_2\beta_3$) as are fetal receptors ($\alpha_2\beta\gamma\delta$), which are found on the muscle cell surface away from the neuromuscular junction and are also expressed in denervated muscle.

c. Outline the properties of an ideal neuromuscular blocking agent.

- Non-depolarizing action
- Rapid onset (within one circulation time)
- Short duration, suitable for infusion
- Rapid metabolism to inactive products
- Antagonized by cholinesterase inhibitors
- Actions confined to the NMJ
- Not transferred across the placenta or blood-brain barrier
- No local or systemic side-effects
- Compatibility with other drugs and solutions
- Long shelf life without refrigeration
- Cheap
- Made by chemical synthesis
- Sterilizable

d. Apprise different methods of monitoring the neuromuscular junction.

A transcutaneous nerve stimulator placed over the ulnar nerve, producing contraction of *adductor pollicis* is commonly used to assess the degree of neuromuscular junction block. Other sites used include the phrenic, facial, posterior tibial and lateral popliteal nerves. Other skeletal muscles have different sensitivities to neuromuscular blocking agents from the diaphragm. The ulnar nerve is the best validated.

Skin is prepared by removal of excess hair, abrasion to remove some of the *stratum corneum* and cleaning with alcohol. Pregelled electrodes are placed over the ulnar nerve, distally at the lateral border of FCU 1-2 cm proximal to the proximal skin crease at the wrist and proximally as close as practical to the distal electrode in the line of the nerve. The positive electrode is proximal.

An initial threshold for stimulation is established with 1 Hz stimuli: the minimum current required to produce a twitch in the thumb. This current is tripled (minimum 20 mA) to determine a supramaximal stimulus which should stimulate all fibres in the ulnar nerve.

The most common method of assessment is the “train-of-four”. A train of four impulses at 0.5 s intervals is applied to the ulnar nerve and the contraction of adductor pollicis is palpated or measured with a force transducer. The result is quantified as a count

(TOFC) or a T4/T1 ratio (TOFR). Without a junction blocker, the four twitches are of equal strength, at TOFR ≥ 0.7 , spontaneous ventilation is safe. With a count of 1 or 0, intubation should be possible. Reversal should be given with a TOFC of 3 or 4, a TOFC of 1 or 2 increases the risk of inadequate reversal in recovery.

In recovery or when TOFC is 4 with little fade, double-burst stimulation of two brief 50 Hz stimuli 0.75 s apart gives a more readily palpable fade for manual monitoring of residual paralysis. Fade is due to blockade of presynaptic nicotinic receptors causing a failure of the normal increase in ACh mobilization following a stimulus.

With deep paralysis all four twitches become absent, and a post-tetanic count allows monitoring of paralysis: a 5 s 50 Hz stimulus is followed by a 3 second pause and then stimuli every second, the number before complete fade being counted. Repetitive stimuli increase synthesis and release of ACh, producing post-tetanic facilitation. Some facilitation will be present for five minutes following a PTC. To guarantee no coughing or diaphragmatic movement on intubation, a PTC of 1 or 0 is required. A PTC of 9 is equivalent to a TOFC of 1. The time from PTC 1 to TOFC 1 is documented for most relaxants (pancuronium 40 min, atracurium 9 min)

Clinical assessment of the degree of relaxation is also made by the surgeon, particularly in intraabdominal surgery and in recovery with assessment of head lift for 5 s.

e. Give a detailed account of the pharmacology of suxamethonium including its undesirable properties.

Class

depolarizing neuromuscular blocking agent, used to achieve rapid, brief paralysis of skeletal muscle.

History

This class of agent was discovered in the late 1940s by Paton & Zaimis, who initially investigated decamethonium, a similar compound without ester linkages.

Physical

The structure of suxamethonium is two ACh molecules linked through the acetate methyl groups: $(\text{CH}_3)_3\text{N}^+(\text{CH}_2)_2\text{-O-OC-CH}_2\text{-CH}_2\text{-CO-O-}(\text{CH}_2)_2\text{-N}^+(\text{CH}_3)_3$.

Chemical

Presentation is as a 2 ml vial containing 100 mg in solution. Storage is at 4°C, with 5% loss of potency over 3 months at 20°. It is a small polar molecule, readily soluble in water.

Pharmacokinetics

administered as IV injection

rapid distribution to ECF

rapid hydrolysis by plasma cholinesterase. 90% hydrolyzed before distribution to the NMJ. \rightarrow succinylmonocholine (+ choline) \rightarrow succinic acid + choline. 14% of succinylmonocholine is renally cleared. Spontaneously hydrolyzes slowly at physiological pH.

inactive genetic variants of plasma cholinesterase produce a greatly prolonged half life: $t_{1/2}$ 1 h.

Pharmacodynamics

binds to post-synaptic nicotinic ACh receptors at the NMJ, resulting in the fixing open of the associated Na^+ channel. This produces a brief depolarization, seen as fasciculation, particularly in the face, and then blocks transmission of normal impulses to the muscle until the suxamethonium is hydrolyzed. Fasciculation may also result from antidromic conduction. The blockade is not competitive. This is known as phase I block.

minimal affinity for preganglionic nicotinic receptors.

repeated or prolonged administration produces a state of phase II block: a more prolonged block with features similar to non-depolarizing blockade: fade on train-of-four, recovery with neostigmine administration.

Clinical use

dosage: 1 to 2 mg/kg IV, with a higher dose required if a NDB has been given first.
Higher dose in neonates and children.

onset of action: one circulation time

duration: 3-5 minutes (except in suxamethonium apnoea)

advantages

- rapid, complete relaxation with a standard dose

- clinical signs of onset: fasciculations

- brief duration

- cheap

disadvantages

common

- post operative muscle pains, common in younger patients. bradycardia from vagotonic effect

- increased intraabdominal pressure

- increased intraocular pressure

- increased intracranial pressure (all prevented with NDB)

- release of K^+

 - rise of 0.5-0.7 mmol/l in normal patients

 - due to depolarization and trauma with fasciculation

 - extrajunctional ACh receptors

 - seen in burns, denervation, prolonged immobility

 - rise up to 9 mmol/l described

 - in muscle trauma rise of 3-4 mmol/l described

 - period of danger is quoted variously

 - burns 1-12 weeks or 1 day to 6 months

 - prevention attempted with NDB (ineffective)

 - salbutamol has some effect

uncommon

- abnormal plasma cholinesterase results in very prolonged action: suxamethonium apnoea

- may trigger malignant hyperpyrexia, masseter spasm

- development of phase II block with repeated use

Plasma cholinesterase

coded for by autosomal gene

variants

- N normal

- D dibucaine (cinchocaine) resistant

- F fluoride resistant

- S silent

- C₅ increased activity (coded at a different locus)

- D, F and S types have reduced (or no) activity in hydrolysing suxamethonium

- 95% of people are NN

assays

- direct assay of PlChE activity using benzoylcholine as the substrate

- dibucaine number

 - % inhibition by 10^{-5} mol/l cinchocaine in vitro (low in D)

- fluoride number

 - % inhibition by 5×10^{-5} mol/l fluoride in vitro (low in F and D)

- scoline number

 - activity assay (?method) high with normal hydrolysis

| genotype | dibucaine number | fluoride number | scoline number | incidence |
|----------|---------------------|--------------------|-------------------|-----------|
| NN | 80 | 60 | 90 | 95% |
| ND | 60 | 50 | 65 | 4% |

| | | | | |
|----|----|----|----|----------|
| DD | 20 | 20 | 15 | 1:3000 |
| NF | 75 | 50 | 90 | 1:200 |
| NS | 80 | 60 | 90 | 1:200 |
| DF | 50 | 35 | 55 | 1:20000 |
| DS | 20 | 20 | 15 | 1:30000 |
| FF | 67 | 40 | 0 | 1:150000 |
| FS | 67 | 40 | 80 | 1:100000 |
| SS | 0 | 0 | 0 | 1:10000 |

f. Describe the structure-activity relationships of the non-depolarizing muscle relaxants including the newer steroidal and benzyl-isoquinolinium muscle relaxants.

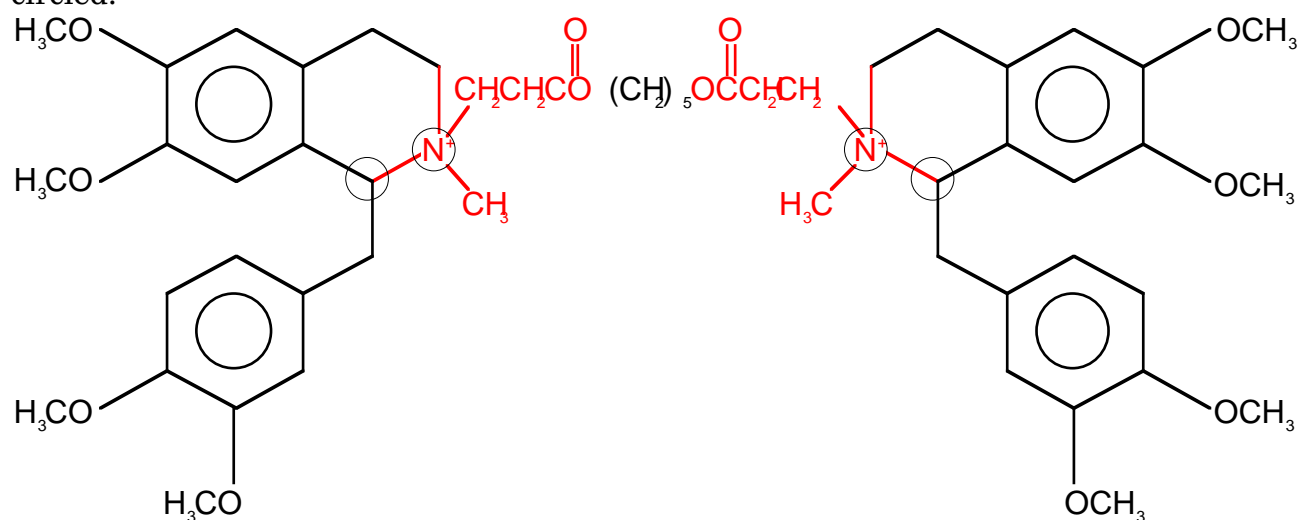
Most of the muscle relaxants bear a resemblance to acetyl choline in part of their structure. This is most obvious in suxamethonium which consists of two ACh molecules joined by their acetate methyl groups. Chain length determines specificity for neuromuscular rather than ganglionic synapses.

Most of the non-depolarizing agents can be grouped into steroids and isoquinolinium derivatives. The steroid agents include pancuronium, vecuronium, rocuronium. They each have two ACh-like regions at each end of the molecule:

This is pancuronium. Removal of the 2 β -methyl group yields vecuronium.

Other substitutions of the end rings give rocuronium and pipecuronium.

The isoquinolinium muscle relaxants consist of large rigid functional groups at either end of a chain resembling suxamethonium. This is atracurium. Its chiral centres are circled.



Doxacurium and mivacurium have different lengths in the central chain and extra functional groups. Not all neuromuscular blocking agents have a quaternary nitrogen

atom nor a region resembling ACh e.g. β -erythroidine.

g. Describe the pharmacokinetics of non-depolarizing muscle relaxants and the role of prejunctional receptors as well as the effects of renal and hepatic disease.

| | V_d ml/kg | $t_{1/2\alpha}$ min | $t_{1/2\beta}$ min | clearance ml/min/kg | elimination | in urine % | induction mg/kg |
|---------------|----------------|------------------------|-----------------------|------------------------|---------------|---------------|--------------------|
| atracurium | 160 | 2.0 | 20 | 5 | spont | | 0.5 |
| cisatracurium | 160 | | 25 | 5 | spont | | 0.15 |
| mivacurium | | | | | Pl ChE | | 0.16 |
| rocuronium | 250 | 15 | 100 | 5 | hepatic | 15-30 | 0.6 |
| vecuronium | 250 | 7.5 | 25-90 | 5 | hepatic | 10-25 | 0.08 |
| pancuronium | 250 | 12 | 120 | 2 | renal/hepatic | 46 | 0.1 |
| suxamethonium | n/a | n/a | short | | Pl ChE | 0 | 1-2 |

The non-depolarizing muscle relaxants are administered by intravenous injection or infusion. They are polar compounds and so have a limited V_d . Blood levels fall rapidly initially with redistribution.

The older agents tubocurarine, metocurine and gallamine are not metabolized, but excreted unchanged, gallamine by renal clearance and the others 50-60% by renal clearance.

The steroidal agents are hydroxylated in the 3 and 17 positions in the liver with some reduction in potency. The long-acting agents, pancuronium, doxacurium and pipecuronium are predominantly renally excreted (60-90%) while the shorter-acting agents vecuronium and rocuronium are predominantly excreted in bile (75-90%) either unchanged or as 3-hydroxy derivatives.

The isoquinolinium agents are hydrolyzed either spontaneously (atracurium) or by plasma cholinesterase (mivacurium) to inactive metabolites. The action of these agents is still affected by renal failure (which lowers plasma cholinesterase activity) and hepatic failure (due to hepatic metabolism of metabolites of atracurium).

Effective durations of action range from around 15 minutes for mivacurium, 20-35 minutes for vecuronium, rocuronium and atracurium to more than 35 minutes for pancuronium and tubocurarine.

Hepatic impairment increases the V_d and $t_{1/2\beta}$ (of agents undergoing hepatic metabolism or excretion) and reduces their clearance. This increases the initial dose requirement but prolongs the duration of action.

Renal impairment greatly reduces the clearance of renally cleared agents (e.g. pancuronium) and so increases the duration of action. It is also associated with a reduction in plasma cholinesterase activity and so slows metabolism of mivacurium and suxamethonium and reduces their dose requirements.

Non-depolarizing agents exert their action predominantly by acting as competitive antagonists to ACh at the nicotinic receptor site. At high doses they may also cause direct blockade of the ion channel. On the prejunctional cell membrane they block sodium channels, inhibiting the depolarization of the membrane and the release of ACh. They also block prejunctional nicotinic receptors, inhibiting the mobilization of ACh vesicles.

h. Describe the factors that may modify responses to muscle relaxants.

The factors which affect response to suxamethonium are given above: primarily factors affecting plasma cholinesterase activity and the degree of K^+ release with administration of suxamethonium.

Pharmacokinetic

adequate circulation required for distribution: determines rate of onset.

- reduced V_d in elderly
- rate of metabolism dependent on
 - plasma cholinesterase for mivacurium, suxamethonium
 - ↓ in pregnancy, burns
 - hepatic function for vecuronium and rocuronium
 - ↑ metabolism with enzyme induction
- elimination dependent on
 - renal function for many agents, especially tubocurarine and gallamine
 - temperature
 - perfusion
 - blood loss may be a significant contributor in some cases

Pharmacodynamic

- receptors
 - deficiency in myasthenia gravis
 - up-regulation in UMN lesions
- drugs
 - open channel block
 - aminoglycosides, Ca^{2+} channel blockers, local anaesthetics, Li^+
 - closed channel block
 - quinidine, tricyclics, naloxone
 - Mg^{2+} decreases ACh release
 - block antagonized by
 - cholinesterase inhibitors
- also increased block in
 - hypothermia, acidosis, hypokalaemia, hypercalcaemia

Other

- reduced motor neurone activity due to volatile anaesthetics (isoflurane >> halothane). Isoflurane also acts at the NMJ.
- other drugs
 - diuretics, ganglion blockers

i. Describe the systemic side effects of muscle relaxants.

The adverse effects of suxamethonium are given above.

Administration of non-depolarizing muscle relaxants causes weakness and then paralysis of skeletal muscle, acting most rapidly on small, fast-twitch muscles and last on the postural muscles and diaphragm.

Cardiovascular

- isoquinolinium agents other than doxacurium cause histamine release and thus vasodilation and hypotension
- gallamine and pancuronium antagonize cardiac muscarinic receptors, causing an increase in heart rate
- in high doses, tubocurarine causes blockade of autonomic ganglia, leading to hypotension and reduced intestinal motility

Histamine release

- the obsolete agents dTC and metocurine showed strong histamine release
- mivacurium causes marked histamine release
- suxamethonium and atracurium cause some histamine release
- causes flushing, hypotension and bronchoconstriction

B. 8 Anticholinesterase drugs

a. Classify the anticholinesterase drugs in relation to mechanism of action.

anionic site of action

competitive inhibitors of binding of quaternary nitrogen of ACh

edrophonium

tetraethylammonium

esteratic (and anionic) site of action

transfer acidic group onto the esteratic site (carbamate or phosphate)

slow dissociation (minutes to weeks)

carbamates

neostigmine

pyridostigmine

physostigmine

organophosphates

ecothiopate

parathion

b. Describe structure-activity relationships of these drugs.

quaternary ammonium group

binds to anionic site by electrostatic force

reduces lipid solubility

poor oral bioavailability

don't cross BBB

electrophilic group

carbamate or phosphate

distance from N⁺ affects potency

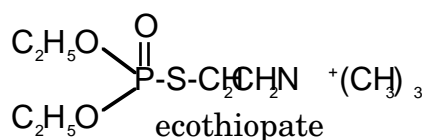
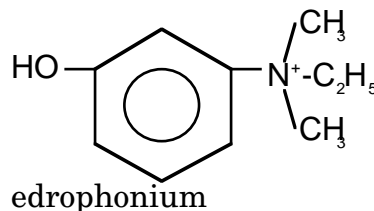
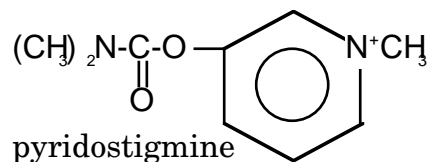
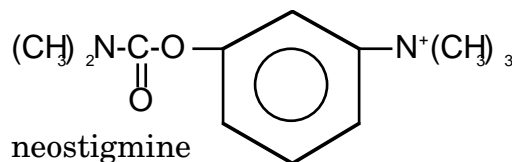
reacts covalently with serine -OH at esteratic site

slow dissociation determines duration of action

thiophosphates

require activation by substitution of oxygen for sulfur atom

very lipid soluble



c. Compare and contrast the pharmacodynamics and pharmacokinetics of neostigmine, edrophonium, pyridostigmine, physostigmine and tacrine.

absorption

quaternary amines have low bioavailability 10-20%

physostigmine and tacrine have higher bioavailability

lipophilic organophosphates have high bioavailability even transdermally

distribution

quaternary amine reduces V_d and lipid solubility

- prevents penetration into CNS
- metabolism and elimination
 - esters are hydrolysed by cholinesterase and pseudocholinesterase
 - quaternary amines have high renal clearance
 - edrophonium is conjugated with glucuronide

| | V_d (l/kg) | $t_{1/2\alpha}$ (min) | $t_{1/2\beta}$ (min) | duration (min) | reversing dose (mg/kg) |
|----------------|-----------------|--------------------------|-------------------------|-------------------|---------------------------|
| neostigmine | 0.7 | 3.5 | 80 | 80 | 0.04 |
| edrophonium | 1.1 | 7.2 | 110 | 60 | 0.5-1 |
| pyridostigmine | 1.1 | 6.8 | 112 | 120 | 0.2 |
| physostigmine | | | 25 | | 0.15 |
| tacrine | | | | | |

Onset of action is determined by rate of diffusion and depth of NDB blockade.
 Duration of action is determined by rate of dissociation from AChE of carbamates and phosphates or by conjugation and clearance for edrophonium.
 For reversal, the duration of action of neostigmine and pyridostigmine is well-matched by glycopyrrolate ($5 \mu\text{g/kg}$) and that of edrophonium by atropine ($7 \mu\text{g/kg}$).

mechanism

- esteratic site agents prevent hydrolysis of ACh
 - \uparrow ACh concentration in synaptic cleft
 - competitive antagonism of NDB
- edrophonium
 - direct cholinomimetic activity
 - some competitive inhibition of hydrolysis of ACh

d. Outline the effects and treatment of poisoning with organophosphate compounds.

organophosphates transfer phosphate to esteratic site of AChE
 hydrolysis takes weeks
 prolonged \uparrow in ACh at muscarinic and nicotinic synapses

effects

- muscarinic (apparent first)
 - potent cholinomimetic effect
 - salivation, lacrimation, \uparrow gut motility, miosis
 - bradycardia
 - bronchoconstriction
- nicotinic
 - initial tetany, then depolarizing blockade
 - weakness, paralysis
 - minor preganglionic sympathetic actions
- CNS (apparent last)
 - excitation, convulsions

treatment

- management of acute effects
 - ventilation, sympathomimetics, pacing
 - anticonvulsants
- regeneration of AChE
 - pralidoxime accelerates hydrolysis
- blockade of autonomic effects
 - atropine

B. 9 Anticholinergic drugs

- a. Describe the structure-activity relationship of anticholinergic drugs.
- b. Compare and contrast the pharmacokinetics and pharmacodynamics of atropine, hyoscine and glycopyrrolate.
- c. Describe the effects of overdose of anticholinergic drugs and its management.

peripheral cholinergic transmission

muscarinic: mostly post-ganglionic parasympathetic

nicotinic: autonomic ganglia and the neuromuscular junction

NMJ covered in [Relaxants](#) (2.B.7)

antimuscarinic effects

↓ secretions (tears, saliva, bronchial, gut)

mydriasis, cycloplegia, ↑ IOP

↑ heart rate

↓ motility, urinary retention

general structure

natural alkaloids

tertiary amines containing tropic acid

l- and d- isomers, l- isomers active

selective for muscarinic receptors

penetrate CNS

synthetic agents

quaternary amines containing mandelic acid

poor penetration of CNS

some activity at nicotinic receptors → ganglion blockade

atropine

derived from *A. belladonna* (deadly nightshade)

pharmacokinetics

oral, rectal bioavailability 25%

similar for ocular administration

rapid distribution $t_{1/2} \alpha$ 1min

V_d 3 l/kg

crosses placenta

metabolized by hydrolysis to tropine and tropic acid

50% excreted unchanged in urine

$t_{1/2} \beta$ 2 h

pharmacodynamics

selective competitive muscarinic antagonist

CNS

stimulation at high doses

↑ cardioinhibitory centre, ↑ vagal tone (transient)

↓ CTZ transmission (weak antiemetic)

mydriasis, cycloplegia, ↑ IOP

CVS

initial ↓ HR followed by ↑ due to muscarinic blockade

little change in CO

blocks vasodilating actions of exogenous ACh analogues

Respiratory

↓ secretions, bronchodilation

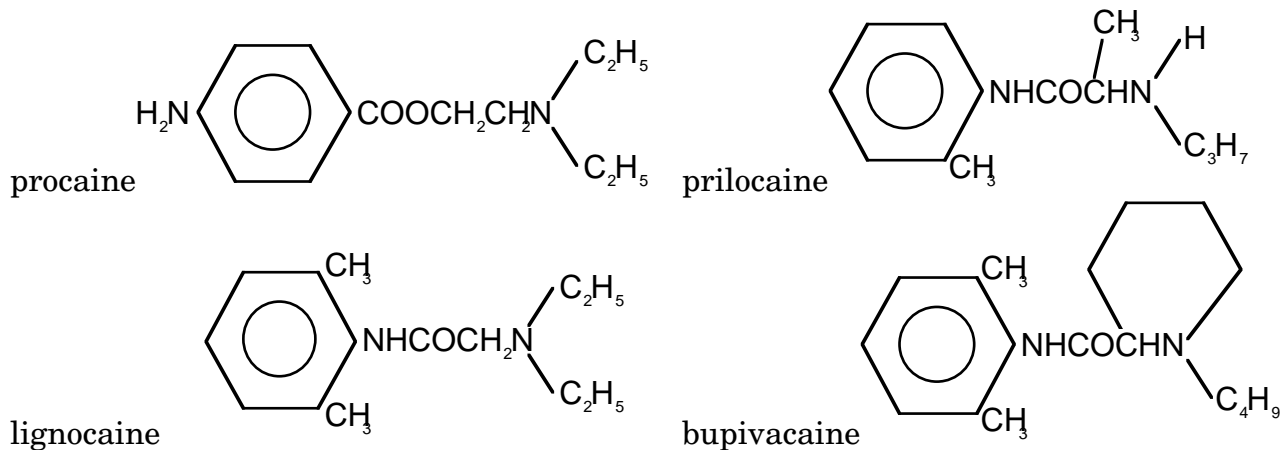
GIT

- ↓ LOS tone
 - other
 - ↓ sweating
- clinical use
 - premedication 0.4-0.6 mg (largely obsolete)
 - prophylaxis against bradycardia
 - in children at induction 10-50 $\mu\text{g/kg}$
 - with neostigmine for reversal 15-20 $\mu\text{g/kg}$
 - treatment of bradycardia or sinus arrest 0.4-1.2 mg
- adverse effects
 - above, plus myocardial ischaemia due to \uparrow HR
 - narrow-angle glaucoma
 - confusion and delirium in the elderly
- hyoscine
 - similar to atropine
- pharmacokinetics
 - bioavailability 25%
 - V_d 1.5-3 l/kg
 - clearance 7-15 ml/kg/min
 - 5% excreted unchanged in urine
 - $t_{1/2\beta}$ 2-3 h
- pharmacodynamics
 - less CVS effect
 - more \downarrow secretions, ocular effects, antiemetic effect
- clinical use
 - transdermal antiemetic for motion-sickness
 - 0.14 mg + 5 $\mu\text{g/h}$
- glycopyrrolate
 - synthetic anticholinergic
- pharmacokinetics
 - much longer duration of action than atropine: 6-8 h
- pharmacodynamics
 - similar to atropine except
 - less penetration into CNS
 - greater potency in \downarrow secretions
 - less tachycardia
- clinical use
 - prevention of bradycardia, salivation with neostigmine: 5-6 $\mu\text{g/kg}$
- other anticholinergics
 - ipratropium nebulized for asthma, COAD
 - benztropine, benzhexol for dystonia, Parkinsonism
 - propantheline for gut, bladder spasm
 - tropicamide in topical ophthalmic use

B. 10 Local anaesthetic drugs

a. Describe the structure-activity relationships of local anaesthetic drugs.

composed of lipophilic end, chain and hydrophilic end
saturated groups at hydrophilic end increase lipid solubility, decrease water solubility, increase protein binding and potency, increase time to onset
 pK_a reduced by amide rather than ester linkage



Bupivacaine is N-**butyl**pipecolic xylidide. Mepivacaine is N-**methyl**~ and ropivacaine is (S) N-**propyl**~.

Benzocaine has no hydrophilic group and does not display frequency-dependent block.

b. Classify local anaesthetic drugs and list them under the appropriate group.

esters

cocaine (from *Erythroxylon coca*)

procaine

nesacaine

amethocaine

benzocaine

carbamoyl

cinchocaine

amides

prilocaine

lignocaine

etidocaine

mepivacaine

bupivacaine

ropivacaine

other agents with LA activity

barbiturates

pethidine

β -blockers

phenol (6% for neurolytic block)

c. Describe the mechanism of action of local anaesthetic drugs.

diffuse through cell membrane in basic form

ionized at intracellular pH

bind to voltage-gated Na^+ channels in the open state

channel consists of α , β_1 and β_2 subunits

α subunit has four homologous domains which form the channel
 each domain has six subunits S₁₋₆
 S₅ and S₆ form the m-gate
 local anaesthetics bind to α domain 4 S₆ in the open and inactivated states
 cause stabilization of the inactive state
 bind most rapidly with repetitive firing (frequency dependence)

lignocaine: fast dissociation
 bupivacaine: slow dissociation
 benzocaine: probably another mechanism

prevent channel opening
 ↑ threshold voltage, refractory period
 ↓ V_{max}
 nerve

resistant to depolarization
 B > C > Aδ - Aα

cardiac
 wide QRS, long PR
 ↓ contractility

d. Explain the principles of the pharmacokinetics of local anaesthetic drugs and apply this knowledge to use in clinical practice.

| | pK _a | bound (%) | t _{1/2β} (h) | onset | duration (h) | hepatic extraction | V _d (l/kg) | lipid sol. |
|-----------------|-----------------|-----------|-----------------------|--------|--------------|--------------------|-----------------------|------------|
| lignocaine | 7.9 | 70 | 1.6 | fast | 1-2 | 68% | 1.3 | 2.9 |
| bupivacaine | 8.1 | 96 | 2.4 | medium | 2-6 | 37% | 1.0 | 28 |
| (S) ropivacaine | 8.1 | 94 | 1.8 | medium | 4-6 | 40% | 0.6 | 8.4 |
| prilocaine | 7.7 | 55 | 1.5 | fast | 1-2 | high | 2.7 | 0.9 |
| procaine | 8.9 | 3 | 1-10min | medium | .5-.75 | low | | 0.02 |
| cocaine | 8.6 | | 1-2 | fast | topical | 80% | | |
| etidocaine | 7.7 | 94 | 2.4 | fast | 2-6 | 73% | 1.9 | 141 |

absorption

all weak bases B + H⁺ ↔ BH⁺
 pK_a falls with a rise in temperature (↑ unionized form)
 distributed as acid solution of HCl salt
 unionized species diffuses readily
 high pH → rapid diffusion
 hence addition of bicarbonate to solutions
 intracellular pH is lower
 more ionized
 ionized species is pharmacologically active
 systemic absorption depends on site of administration
 intravascular > intercostal > tracheal > caudal > epidural > plexus > local
 speed of injection increases peak level slightly (epidural and plexus)

distribution

dependent on
 route
 lipid solubility (↓ onset time), water solubility
 protein binding (↑ duration)
 pH: acidosis ↓ diffusion
 temperature
 perfusion
 adrenaline reduces blood flow, intensifies motor block
 ropivacaine is a vasoconstrictor

susceptibility of nerve

B > C > A

age

children: rapid tracheal uptake, slow caudal uptake

spinal

rapid uptake into spinal cord

grey > white

dorsal root > ventral

removal by partition into blood

minor spread in CSF

$t_{1/2\alpha}$

lignocaine 1 h

bupivacaine 2 compartment 30% 1 h, 70% 6 h

epidural

rapid diffusion into CSF (10-20 min)

spread into spinal nerves by 30 min

also spread into cord by diffusion into spinal arteries

sequestered in epidural fat

blood level peaks at 15-30 min

brachial plexus

penetration of nerves from outside (distal, motor) to inside (proximal, sensory)

clearance in similar sequence due to greater perfusion of outside

circulation

distribution into lung tissue smooths arterial peak after IV injection

cross placenta readily

rapid arterial injection can cause retrograde flow to cerebral circulation

bound to α_1 acid glycoprotein

low level in pregnancy \uparrow free fraction

high level in

renal failure (and low pH) \downarrow action

post op, trauma or AMI

cancer

may result in "toxic" total plasma concentration from infusion

post-op with unchanged free concentration due to increased

binding

metabolism and excretion below

e. Explain the factors that determine the clinical effects of local anaesthetic drugs.

f. Describe the metabolism of local anaesthetic drugs.

metabolism

esters

hydrolysed by plasma cholinesterase

both in circulation and at site of action

cocaine \rightarrow benzoylecgonine \rightarrow ecgonine

procaine \rightarrow diethylamino ethanol + para-amino benzoic acid

amides

minimal metabolism at site of action

hepatic metabolism by hydrolysis, dealkylation and hydroxylation

perfusion limited except bupivacaine (\downarrow β -blockers, general anaesthesia)

metabolism in immature in the neonate $t_{1/2\beta}$ 2-3 times longer

obesity prolongs $t_{1/2\beta}$ due to slower redistribution

bupivacaine < lignocaine < etidocaine < prilocaine

lignocaine

N-deethylation → glycine xylidide (LA)

amide hydrolysis → xylidine

3' and 4' hydroxylation are minor pathways

prilocaine

hydrolysis → o-toluidine + N-propylalanine in kidneys, liver and lung

→ methaemoglobin + 4- and 6-hydroxytoluidine

methaemoglobin is very slowly reduced in neonates

MetHb reduced to Hb with methylene blue 1-2 mg/kg

bupivacaine

poorly characterized metabolism

hydrolysis, 3'- and 4'- hydroxylation

ropivacaine

3'-hydroxylation, glucuronidation and renal excretion (40%)

minor N-dealkylation and 4'-hydroxylation

$t_{1/2\beta}$ 1.8 h, E 0.4, clearance 6 ml/kg/min, V_d 0.6 ml/kg

$t_{1/2}$ from epidural space 4.8 h

excretion

renal

filtration of free fraction and tubular secretion

1-6% excreted unchanged (increased in acidic urine)

hepatic metabolites are renally cleared

enteral

small amount of gastric secretion and intestinal reabsorption

coexistent disease

cardiac failure

↓ V_d , clearance

hepatic failure

↑ V_d , $t_{1/2\beta}$, ↓ clearance

renal failure, pulmonary disease

little change to kinetics

drug interactions

general anaesthesia

↓ hepatic blood flow, ↑ $t_{1/2\beta}$

adrenaline

↑ hepatic blood flow, ↓ $t_{1/2\beta}$

β-blockers

propranolol → 40% reduction in pulmonary uptake of lignocaine

enzyme inducing and inhibiting agents

hepatic

cholinesterase (for esters)

g. Describe the management of overdose of local anaesthetic drugs.

| | safe dose (mg/kg) | toxic level (μg/ml) |
|-------------|----------------------|------------------------|
| lignocaine | 5 | 6-8 |
| bupivacaine | 2 | 2 |
| ropivacaine | 3 | |
| prilocaine | 6 | 7 |
| procaine | 5 | 7-10 |

“Safe dose” is for infiltration or regional block, not IV or spinal dose

40-50% higher dose for local infiltration with adrenaline

lower safe dose with ↓ protein binding, ↓ pH, ↑ HR in neonates

lower safe dose with ↓ protein binding, ↓ pH, ↑ HR in neonates

cardiac:CNS toxicity ratio is a measure of safety

lignocaine 7:1

bupivacaine 3.7:1 (with slow offset of action)

central mechanism for some arrhythmias

L-bupivacaine is less toxic

lignocaine

| level ($\mu\text{g/ml}$) | effect |
|-------------------------------|--|
| 2 | anticonvulsant, antidysrhythmic |
| 4 | positive inotrope, tinnitus, lightheadedness |
| 6 | vision disturbance |
| 8 | twitching |
| 10 | convulsions |
| 15 | coma |
| 20 | respiratory arrest |
| 26 | cardiac arrest |

cardiac

reentrant arrhythmias → VF

refractory to DCR

brain

tinnitus, drowsiness, convulsions, coma

worsened by acidosis and hypercarbia due to ion trapping

local neurotoxicity

may be due to preservatives (sodium bisulfite causes permanent damage)

management

correction of acute disturbances

ventilation, oxygen

cardiac massage, DCR, bretylium/lignocaine/clonidine/amiodarone, bypass

correction of acidosis (allows diffusion away from site of action)

control of seizures with benzodiazepine or barbiturate

B. 11 Pharmacology of the autonomic nervous system.

a. Describe the physiological roles of the sympathetic and parasympathetic nervous systems.

sympathetic

thoracolumbar outflow T₁ to L₃

efferent: cell body in grey matter of cord, ventral root, white ramus to sympathetic chain or grey ramus to spinal nerves

afferent: sympathetic chain, white ramus, dorsal root (body in ganglion), dorsal horn

preganglionic fibres are B type myelinated nicotinic

synapse in chain and ganglia (cervical, coeliac, mesenteric and sacral) and adrenal medulla

postganglionic

adrenergic secretory cells in adrenal medulla

noradrenergic postganglionic fibres

mydriasis, distant vision accommodation, vasoconstriction/dilation, bronchodilation, inotropy, chronotropy, ↓ gut motility, ↑ renin, detrusor relaxation, trigone contraction, ejaculation, ↑ glucagon, ↑ glucose & lipid mobilization. lipolysis

muscarinic postganglionic fibres

sweating, piloerection, some vasodilation

parasympathetic

craniosacral outflow (III, VII, IX, X, S₂ to S₄) 75% in vagus

efferent: cell body in CNS, peripheral ganglia (ciliary, sphenopalatine, otic, local synapses in organs)

preganglionic fibres are nicotinic

postganglionic fibres are muscarinic

III miosis, near vision accommodation

VII lacrimation, submandibular gland secretion

IX parotid gland secretion

X ↑ gut secretions, ↑ motility, palmar sweating, negative inotropy & chronotropy, bronchoconstriction

sacral detrusor contraction, trigone relaxation, erection, defaecation

afferent

minor component

substance P, peptide neurotransmitters including glutamate

b. Describe the physiological actions of adrenergic, cholinergic and dopaminergic receptors including their subtypes, and their molecular effects.

α and β receptors differentiated by Alquist (1948)

β subtypes identified by Lands (1967)

cotransmitters found at probably all sites of autonomic transmission

noradrenaline ± dopamine, NO, neuropeptide Y...

ACh ± substance P, VIP...

α_{1A,B,C,D}

G-protein linked, ↑ IP₃, DAG except possibly α_{1A} which ↑ Ca²⁺ conductance
vasoconstriction, ↑ contractility, glycogenolysis, mydriasis, piloerection, apocrine sweating, salivation, uterine contraction, bladder neck contraction, ejaculation, detumescence

α_{2A,B,C}

G-protein linked, ↓ cAMP

central functions (sedation, descending inhibitory pathways, ↓ CO₂ response)

platelet activation, vasoconstriction, ↓ lipolysis, ↓ insulin
presynaptic inhibition at postganglionic sympathetic terminals
↓ renin, ADH, ↓ stress response

β_1

G-protein linked, ↑ cAMP
↑ contractility, ↑ HR, ↑ conduction velocity, ↑ diastolic relaxation
↑ renin

β_2

G-protein linked, ↑ cAMP
bronchodilation, vasodilation, uterine relaxation, ↑ HR
↑ K^+ uptake by skeletal muscle, ↑ glycogenolysis, ↑ insulin

β_3

G-protein linked, ↑ cAMP
↑ lipolysis

D_1

G-protein linked, ↑ cAMP
vasodilation: renal, splanchnic, coronary, cerebral

D_2

G-protein linked, ↓ cAMP, ↑ K^+ conductance, ↑ Ca^{2+} conductance
? presynaptic inhibition

D_4

G-protein linked, ↓ cAMP
possible site of action of clozapine (with $5HT_7$)

D_5

G-protein linked, ↑ cAMP

M_1

G-protein linked, ↑ IP_3 , DAG, Ca^{2+}
CNS neurotransmission
sympathetic postganglionic
↑ gut motility
presynaptic

M_2

G-protein linked, open K^+ channels, ↓ cAMP
myocardial and vascular innervation of vagus
preganglionic function (site of action of pancuronium and gallamine)

M_3

G-protein linked, ↑ IP_3 , DAG, Ca^{2+}
exocrine glands, vasodilation via NO & cGMP, miosis
bronchoconstriction
↑ gut motility, defaecation, urination

N_N

gated ion channel, ↑ Na^+ , Ca^{2+} flux
presynaptic potentiation at NMJ
CNS

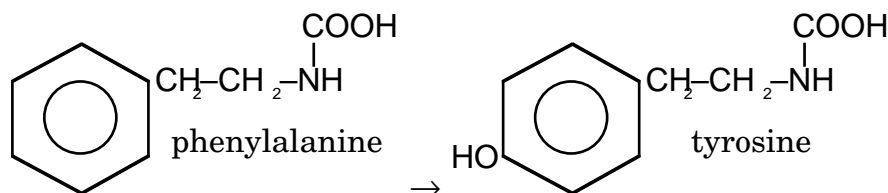
N_M

gated ion channel, ↑ Na^+ , Ca^{2+} flux
neuromuscular junction

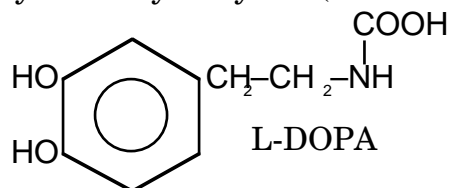
c. Describe the synthesis, release and fate of adrenergic and cholinergic transmitters.

catecholamines

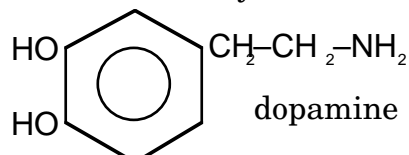
synthesized from tyrosine (or phenylalanine if tyrosine is unavailable)



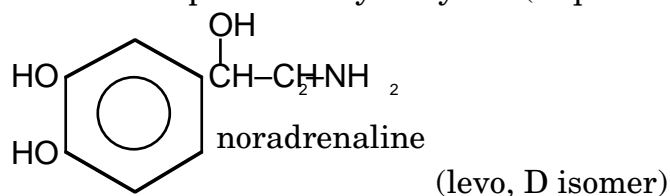
tyrosine hydroxylase (rate limiting step, requires biopterine) →



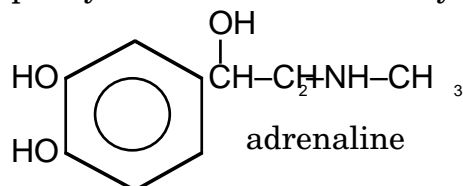
DOPA decarboxylase (inhibited by disulfiram, requires pyridoxal phosphate) →



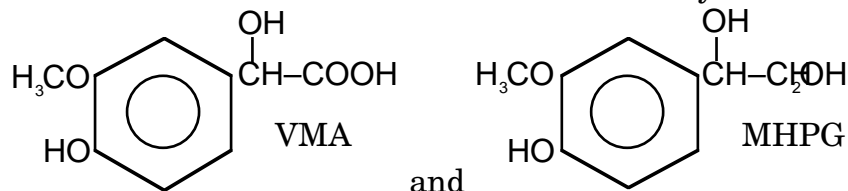
vesicular dopamine β-hydroxylase (requires ascorbate) →



phenylethanolamine N-methyl transferase (requires 5-adenosyl methionine) →

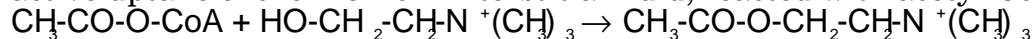


adrenaline or noradrenaline are metabolized by MAO and COMT to



acetylcholine

active uptake of choline from interstitial fluid, reacted with acetyl-CoA:



breakdown is by hydrolysis due to acetylcholinesterase, with recycling of choline and return of acetate to the TCAC

d. Describe the structure-activity relationships of adrenergic and cholinergic drugs

adrenergic

ligands bind in their ionized form

receptor affinity

β-OH or 3-OH required for direct activity

4-OH or > methyl group on N: ↑ β affinity, potency

> isopropyl group on N or α or 3 sidechain: β₂ selective

imidazole group: α selectivity (α₂ > α₁)

distribution, metabolism

few OH, no N⁺: enters CNS
 > methyl on N: not a substrate for uptake 1 (no indirect action)
 > methyl on N or α methyl: not a substrate for MAO
 3,4 di-OH required for COMT
 all bind to the receptor in the ionized form

cholinergic

similar to ACh, all have N⁺ except pilocarpine
 receptor affinity
 side groups on chain: muscarinic selective
 metabolism
 no acetyl group (e.g. carbamoyl): not a substrate for AChE

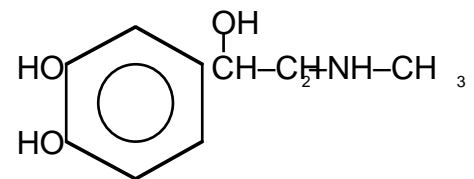
e. Compare and contrast the mechanism of action and effects of sympathomimetic and cholinomimetic agents used clinically.

f. Describe α₁, α₂, β₁ and β₂ adrenergic agonists and their clinical applications.

Endogenous (direct acting catecholamines)

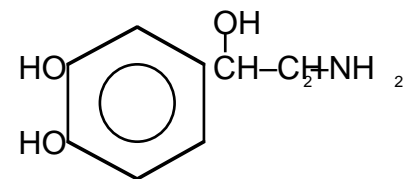
adrenaline

β > α, not α or β selective
 ↑ **CO**, **HR**, MAP, CNS activity, blood glucose
 ↓ RBF, airway resistance
 arrhythmogenic
 vasoconstrictor in local anaesthetics
 used for anaphylaxis, asystole (100 μg-1 mg),
 inotrope, nebulized for croup



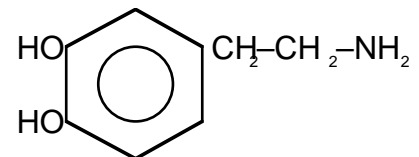
noradrenaline

α > β₁ >> β₂ not a selective
 ↑ **TPR**, MAP
 ↓ **RBF**
 used as an inotrope (5-15 μg/min)



dopamine

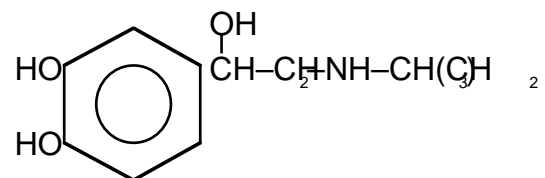
D₁ > β₁ > α₁ > β₂ > α₂
 ↑ **CO**, **HR**, **TPR**, **MAP**, **RBF**
 suppresses hypoxic drive
 used for renal "protection" (low dose), inotrope (high dose) 2-20 μg/kg/min



Exogenous catecholamines (direct acting)

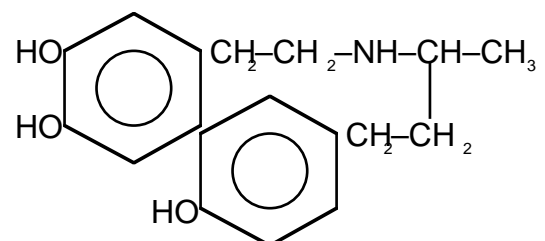
isoprenaline (isopropyl noradrenaline)

non-selective β
 ↑ **HR**, **CO**, CNS activity
 ↓ **TPR**, airway resistance
 arrhythmogenic
 reduces pulmonary vascular resistance
 used as an inotrope (1-5 μg/min),
 bronchodilator (obsolete)



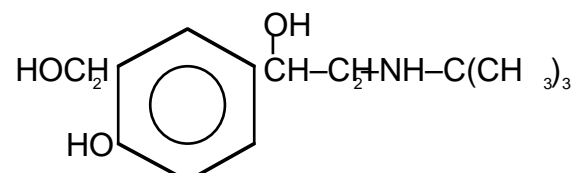
dobutamine

selective β₁ (not dopaminergic)
 ↑ **CO**, **HR**, **MAP**, **RBF**
 used as an inotrope without
 vasoconstrictor effects



salbutamol (and terbutaline, fenoterol and orciprenaline)

selective β₂
 ↑ **HR**, CNS activity
 ↓ airway resistance, labour



used for bronchodilation (IV, oral or nebulized), chronotrope, tocolytic

dopexamine

selective D_2 ($>\beta$) agonist

Direct acting non-catecholamines

phenylephrine (and methoxamine)

selective α_1

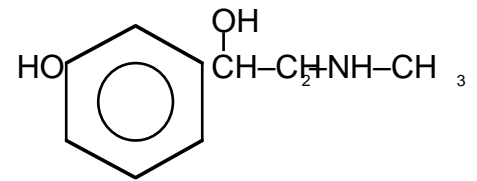
↑ **TPR, MAP** (methoxamine is a more potent arteriolar constrictor)

↓ **RBF**

arrhythmogenic (methoxamine is mildly antidysrhythmic)

used for hypotension (20-50 $\mu\text{g}/\text{min}$ IV)

topical mydriatic, nasal decongestant



clonidine

α_2 selective, imidazoline antagonist

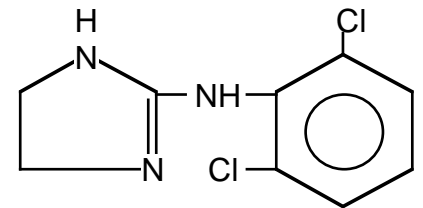
↓ HR, CO, TPR, MAP, CNS activity

used for hypertension, reduces sympathetic outflow

sedative, reduced anaesthetic & opiate requirements

spinal/epidural analgesic (inhibits substance P release)

reduces opiate withdrawal symptoms



BRL37344

β_3 selective

↑ lipolysis

? fat-loss agent

Indirect acting non-catecholamines

ephedrine (β -OH methamphetamine)

$\alpha > \beta$ (non selective, has some direct activity)

↑ HR, CO, TPR, MAP, CNS activity

↓ RBF

used short-term for hypotension (5-25 mg IV/IM)

does not reduce uterine blood flow

abused as CNS stimulant, anorectic

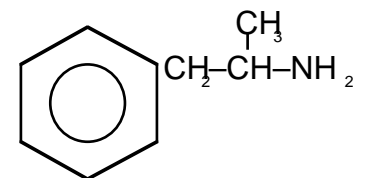
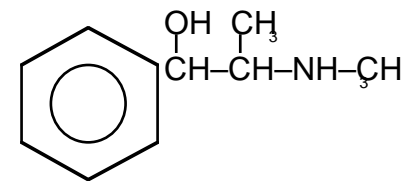
amphetamine (and dexamphetamine, methamphetamine, methylphenidate)

alphamethylphenylethylamine

non selective, enter CNS rapidly, displaces noradrenaline

↑ **CNS activity**, HR, CO, TPR

used for ADHD (oral), widely abused orally and IV.



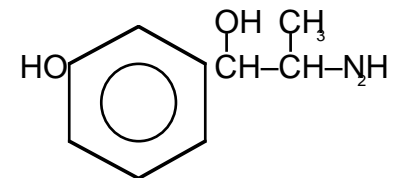
metaraminol

$\alpha \gg \beta$ (direct and indirect), weak false transmitter

↑ **TPR, MAP** (reflex ↓ HR)

↓ **RBF**

used for hypotension (0.5-5 mg IV 40-500 $\mu\text{g}/\text{min}$)



g. Describe the drugs used as inotropic and vasoactive agents including the phosphodiesterase inhibitors.

phosphodiesterase inhibitors

bipyridines include milrinone, amrinone, vesarinone etc.

flosequinan is a fluoroquinolone

milrinone

pharmacokinetics

orally active

$t_{1/2\beta}$ 2-3 h

50% renal excretion

pharmacodynamics

selective inhibitor of phosphodiesterase III

onset of action over 15 minutes

↑ intracellular cAMP in cardiac and smooth muscle

↑ Ca^{2+} release in cardiac muscle

inotrope, ↑ HR, diastolic compliance & proportion of cycle

↑ phosphorylation of MLCK in smooth muscle (↓ activity)

↓ MLC phosphate, ↓ contraction

systemic, coronary and pulmonary vasodilation

net ↑ MAP

adverse effects

amrinone

nausea, vomiting, hepatotoxicity, thrombocytopenia, arrhythmogenic

milrinone

less adverse effects but same risk of arrhythmia

clinical use

milrinone: 50 $\mu\text{g}/\text{kg}$ load, 0.25-0.75 $\mu\text{g}/\text{kg}/\text{min}$ infusion

intensive monitoring required

used for short term inotropy, especially where vasoconstriction is to be avoided

h. Outline the interactions with drugs used in the perioperative period.

B. 12 Adrenoceptor blocking agents

a. Explain the mechanisms and physiological consequences of α_1 , α_2 , β_1 and β_2 receptor blockade.

b. Classify α and β receptor blocking agents according to their actions, reversibility and chemical groups.

c. Describe the pharmacokinetics of α receptor blocking agents and apply this to their clinical use.

prazosin

competitive α_1 blocker (predominantly α_{1A})

high extraction ratio, 50% bioavailable

$t_{1/2}\beta$ 3 h hepatic metabolism, unaffected by renal impairment

used for hypertension, afterload reduction, urinary retention (low dose)

1-10 mg o tds

terazosin

similar to prazosin

high bioavailability

$t_{1/2}\beta$ 12 h

5-20 mg o daily

doxazosin

similar to prazosin

$t_{1/2}\beta$ 22 h

1-16 mg a daily

yohimbine

competitive α_2 blocker

used in idiopathic orthostatic hypotension (not in Australia)

? improves impotence

more selective α_2 blockers are under development

phentolamine

competitive non-selective α blocker

onset of action within 2 minutes

effective duration 10-15 minutes

used for acute hypertension (2-5 mg IV) esp. in phaeochromocytoma surgery

does not affect autoregulated circulations (unlike nitrates)

also combined with papaverine in impotence

adverse effects due to muscarinic, H_1 and H_2 agonism and reflex β stimulation

phenoxybenzamine

non-competitive non-selective α blocker ($\alpha_1 > \alpha_2$)

low bioavailability

pro-drug converted to ethylene ammonium compound

slow onset: over 60 min to peak effect

binds covalently to receptors

also binds H_1 , ACh and serotonin receptors

offset of action as receptors are renewed ($t_{1/2}\beta$ 24 h irrelevant)

used in hypertension (phaeo) and Raynaud's syndrome

10-30 mg o bd

ergot derivatives, phenothiazines and butyrophenones also have α antagonist activity

d. Describe the pharmacodynamic and pharmacokinetic features of β receptor blocking agents.

e. Describe the clinical uses of β receptor blocking agents and their side effects.

all competitive antagonists at β receptors

pharmacokinetics

| agent | absorbed (%) | bioavailability (%) | protein bound (%) | $t_{1/2\beta}$ (h) | metabolism/excretion |
|-------------|--------------|---------------------|-------------------|--------------------|----------------------|
| atenolol | 50 | 55 | 0 | 6 | urinary |
| esmolol | | | 50 | 9 min | hydrolysis |
| metoprolol | 100 | 50 | 10 | 4 | oxidation |
| pindolol | 100 | 100 | 50 | 4 | conj/oxid |
| propranolol | 100 | 33 | 90 | 5 | oxidation |
| sotalol | 100 | 60 | 0 | 10 | urinary |

Agents fall into broad categories of renally cleared, hepatically metabolized and esmolol which is hydrolyzed in red cells. Elimination kinetics are correspondingly affected by renal or hepatic disease.

Hepatic metabolism is also reduced in the elderly and increased in smokers. The elderly are less susceptible to β blockade, so increased plasma levels are not necessarily toxic.

pharmacodynamics

| agent | potency | selective for β_1 | membrane stabilizing | partial agonist |
|-------------|-----------|-------------------------|----------------------|-----------------|
| atenolol | 1 | + | - | - |
| esmolol | 0.01-0.02 | + | - | - |
| metoprolol | 1 | + | + | - |
| pindolol | 6 | - | + | + |
| propranolol | 1 | - | + | - |
| sotalol | 0.3 | - | - | - |

β_1 selectivity is relative, at high doses β_2 antagonism is seen

most display differing potencies of enantiomers

membrane stabilizing (local anaesthetic) effect is independent of β blocking activity

adverse effects

predictable from β receptor functions

β_1 ↓ CO, masks hypoglycaemic symptom of tachycardia

β_2 bronchospasm, peripheral vasospasm, ↓ glucose tolerance (via ↓ insulin secretion)

clinical use

hypertension

↓ CO, ↓ renin release, central effect

IHD

↓ CO, greater ↓ in myocardial O_2 demand, proven mortality benefits

↓ HR at lower doses than ↓ contractility

thyrotoxicosis, pheochromocytoma

symptomatic relief

SVT, AF

second line drugs for reducing AV conduction

glaucoma

↓ IOP in open-angle glaucoma (topical use)

esmolol

specific use for suppressing short-term sympathetic response e.g. at laryngoscopy and reducing tachycardia from nitroprusside infusion

B. 13 Antihypertensive drugs

a. Classify the modes of action of the antihypertensive drugs.

- central sympathetic tone inhibitors
 - α_2 agonists
 - β antagonists
- peripheral sympathetic antagonists
 - α blockers
 - adrenergic neurone blockers (obsolete)
- vasodilators
 - arteriolar
 - Ca^{2+} blockers
 - others
 - arteriolar and venous
 - nitrates
- ACE inhibitors
- ATII₁ receptor antagonists
- diuretics

b. Describe the pharmacology of centrally acting agents such as clonidine and α -methyldopa.

clonidine

- a selective α_2 antagonist with central, spinal and peripheral actions
- available as oral, transdermal, IV, epidural and intrathecal preparations
- a weak base
- pharmacokinetics
 - 95% bioavailable, 20% protein bound, V_d 2 l/kg, $t_{1/2}$ 8-12 h
 - lipid soluble, diffuses readily into the CNS
 - renally cleared 50% unchanged
- pharmacodynamics
 - binds α_2 receptors, imidazoline receptors
 - presynaptic effect in periphery inhibits noradrenaline release
 - central effect
 - reduces sympathetic tone
 - increases parasympathetic tone
 - accentuates baroreceptor reflex
 - sedative, depressant (blocked by tricyclics)
 - rebound hypertension and anxiety on withdrawal
- dose 0.2-1.2 mg/d orally

α -methyldopa

- false transmitter substrate with central α_2 agonist effect
- administered orally
- pharmacokinetics
 - metabolized on the same pathway as DOPA, yielding α -methylnoradrenaline, an α_2 agonist
 - 50% bioavailable, 15% protein bound, duration of effect ~24 h
- pharmacodynamics
 - central effects similar to clonidine with less \downarrow CO
 - antagonizes dopaminergic transmission
 - extrapyramidal effects
 - galactorrhoea
 - hepatic necrosis
 - Coomb's test positive in 20%

other central α_2 agonists, guanfacine and guanabenz are similar to clonidine

c. Describe the actions of ganglion blocking agents and the pharmacology of trimetaphan.

Ganglion blocking agents include tetraethylammonium, hexamethonium, meclizine and trimetaphan. They are all selective nicotinic-N antagonists, blocking transmission at all autonomic ganglia, the adrenal medulla and sites in the CNS (though the quaternary ammonium compounds do not penetrate the CNS readily). They are all obsolete.

trimetaphan

- competitive nicotinic antagonist acting predominantly at autonomic ganglia
- administered IV

- pharmacokinetics

 - rapid onset and brief action

 - IV infusion allows titration of blood pressure

- pharmacodynamics

 - binds nicotinic receptors in autonomic ganglia

 - reduces sympathetic transmission

 - marked postural hypotension

 - impotence

 - sedation

 - reduces parasympathetic transmission

 - constipation

 - urinary retention

 - dry mouth

 - glaucoma, blurred vision

d. Describe the pharmacology of agents which block the release of transmitters at the adrenergic nerve ending.

guanethidine

- an anti-sympathetic agent which inhibits noradrenaline release

- similar to bethanecol and debrisoquin

- pharmacokinetics

 - variable bioavailability (3-50%), large V_d , $t_{1/2}$ 5 days

 - dose adjustment cannot be made more than fortnightly

 - requires uptake 1 for action (blocked by cocaine, tricyclics)

- pharmacodynamics

 - transported into adrenergic neurones by uptake 1

 - concentrated in noradrenaline vesicles

 - displaces noradrenaline and depletes stores

 - has no effect at receptors

 - results in gradual onset of sympathetic blockade

 - hypotension (especially postural)

 - shock in overdose

 - impotence

 - diarrhoea

 - upregulation of adrenergic receptors \uparrow sensitivity

- dose starts at 10 mg/d (obsolete)

reserpine

- plant-derived alkaloid from *Rauwolfia serpentina* formerly used as an anti-hypertensive

- oral and IV preparations

- pharmacokinetics

poorly elucidated, duration of action is unrelated to plasma half-life
 pharmacodynamics
 interferes with uptake and storage of endogenous amines in vesicles
 depletes noradrenaline, dopamine and serotonin (and adrenaline)
 acts both peripherally and in the CNS
 ?mostly central effect at low doses
 reduced sympathetic tone
 sedation, depression
 extrapyramidal effects
 diarrhoea
 ↑ gastric acid secretion
 dose 0.25 mg to 1 mg as a single dose (obsolete)

e. Appraise the use of β -receptor blocking agents, α -receptor blocking agents and calcium antagonists in the treatment of hypertension.

β -blockers

antihypertensive and antidysrhythmic drugs also used for glaucoma and sedation
 classification
 non-selective (propranolol), β_1 selective (metoprolol, atenolol, esmolol), α and β antagonist (labetalol)
 membrane-stabilizing (propranolol, labetalol)
 partial agonist (pindolol, alprenolol)
 pharmacokinetics
 oral, ophthalmic and IV preparations
 bioavailability and binding vary from drug to drug
 half-lives are mostly 3-6 h except esmolol which is short-acting and a few long-acting drugs (penbutolol, nadolol)
 metabolism
 responsible for variability in plasma levels in hepatic or renal disease
 hepatic oxidation or conjugation
 labetalol, metoprolol, propranolol, most others
 renal excretion
 atenolol, sotalol
 hydrolysis
 esmolol

| | bioavailability | protein bound | $t_{1/2\beta}$ | metabolism |
|-------------|-----------------|---------------|----------------|-------------------|
| atenolol | 50% | <5% | 6-7 h | renal excretion |
| propranolol | 33% | 90% | 4-6 h | hepatic oxidation |
| metoprolol | 50% | 10% | 3-4 h | hepatic oxidation |
| esmolol | n/a | 50% | 9 min | hydrolysis |

pharmacodynamics

some have (class Ia) membrane stabilizing activity
 competitive antagonists at β -adrenoceptors
 can always be overcome with sufficient catecholamines
 β_1 effects
 ↓ HR, contractility, renin secretion
 β_2 effects
 ↑ airway tone, vasomotor tone
 ↓ insulin release

adverse effects

bronchospasm, asthma
 cardiac failure, heart block

impaired glucose tolerance and mask hypoglycaemia
indications

hypertension

more effective in high renin setting
acts both by ↓ renin release and ↓ CO

angina (and cardiac/major surgery)

↓ CO, myocardial oxygen demand
↑ duration of diastole, myocardial perfusion

AMI

proven to reduce mortality
acutely via anti-anginal effects
also antidysrhythmic

arrhythmia

slow atrial rate
slow AV conduction

glaucoma, hyperthyroidism

Calcium channel blockers

vasodilating and antidysrhythmic drugs

verapamil

type I Ca^{2+} channel blocker: phenylalkylamine
inhibits opening of both fast Na^{+} channels and slow Ca^{2+} channels
oral and IV preparations

pharmacokinetics

10-20% bioavailable
90% protein bound (albumin and AAG)
hepatic metabolism
 $t_{1/2}$ 5 h L isomer more rapidly metabolized
slower clearance with prolonged use

pharmacodynamics

L- (active) and D-isomers
type Ia and IV antidysrhythmic effects at low dose
negative inotrope at higher dose
vasodilator
both Ca^{2+} channel and α -antagonist effects
weak bronchodilator
sedative (↓ MAC)

indications

AF, SVT: slows A-V nodal conduction
hypertension
improves diastolic compliance in hypertrophic cardiomyopathy

adverse actions

complete heart block
especially with β -blockers or halothane/enflurane
myocardial depression
constipation
impaired glucose tolerance
potentiate neuromuscular blockers and local anaesthetic effects
causes hyperkalaemia when given with dantrolene

nifedipine

dihydropyridine Ca^{2+} channel blocker
oral, slow release and IV preparations

pharmacokinetics

poor absorption sublingually
50% bioavailable (oral)

90% protein bound (albumin and AAG)
 $t_{1/2}$ 2h (slow release oral preparations available)
hepatic metabolism

pharmacodynamics

potent peripheral and weak coronary vasodilator
direct negative inotrope
site of action is dependent on pharmacokinetics
nimodipine has more cerebral effect
reflex (baroreceptor-mediated) tachycardia, \uparrow CO
 \uparrow risk of ischaemia
minimal effect on conduction

indications

hypertension
Raynaud's phenomenon

adverse actions

vasodilation
headache, flushing, peripheral oedema
constipation
hypotension

nimodipine

dihydropyridine with cerebral vasodilating activity
 \downarrow risk of vasospasm and ischaemia in SAH
 \downarrow Ca^{2+} entry to neurones may reduce cell death
light sensitive
administered IV 0.4-2 mg/h

diltiazem

benzothiazepine Ca^{2+} channel blocker active at both cardiac and peripheral sites
oral preparations

pharmacokinetics

40% bioavailable
80% protein bound
hepatic metabolism
 $t_{1/2}$ 4 h but complex kinetics result from enterohepatic circulation

pharmacodynamics

similar to other Ca^{2+} blockers but fairly selective for coronary vessels
improves subendocardial perfusion
some antidysrhythmic effect

indications

angina
hypertension

f. Describe the mechanism of action of vasodilators such as hydralazine, ACE inhibitors and diazoxide.

Direct vasodilators are potent in reducing blood pressure acutely, but have little effect on blood pressure when used long term. Reflex responses to arteriolar vasodilation include immediate increase in cardiac output and venous return and baroreceptor-mediated increase in sympathetic tone causing tachycardia, increased contractility and reduced venous pooling. Reduced renal perfusion pressure and sympathetic outflow results in increased renin, angiotensin II and aldosterone levels and consequent fluid retention. These effects result in a maintenance of blood pressure with increased intravascular volume and myocardial workload.

hydralazine

a directly acting arteriolar vasodilator

- oral and IV preparations
- pharmacokinetics
 - 25% bioavailability
 - bimodal metabolism by hepatic acetylation
 - $t_{1/2}\beta$ 2-4 h
- pharmacodynamics
 - binds to vascular tissue, effect longer than $t_{1/2}\beta$
 - direct vasodilator via NO synthesis
- adverse actions
 - vasodilation
 - headache, flushing, palpitations
 - sympathetic tone
 - anorexia, sweating, nausea
 - sporadic
 - SLE-like syndrome, neuropathy, fever
- clinical use
 - 5 mg bolus, titrated to effect
 - onset over 20 minutes

minoxidil

- oral (and topical) preparations
- pharmacokinetics
 - high bioavailability
 - low protein binding
 - prodrug: sulfate is the active metabolite (long $t_{1/2}\beta$)
 - $t_{1/2}\beta$ 4 h
- pharmacodynamics
 - sulfate binds to K^+ channels in smooth muscle
 - increased K^+ conductance
 - hyperpolarized membrane
 - direct arteriolar vasodilator
- adverse effects
 - major reflex increase in sympathetic tone
 - pretreatment with propranolol required
 - hair growth

diazoxide

- a thiazide without diuretic actions
- IV preparation
- pharmacokinetics
 - onset of action 5 min
 - high protein binding
 - metabolism uncharacterized
 - some excreted unchanged
 - $t_{1/2}\beta$ ~24 h (duration of effect 4-12 h)
- pharmacodynamics and effects
 - as for minoxidil except without hirsutism

ACE inhibitors

- effective in high renin hypertension (as are β -blockers)

pharmacokinetics

- most are prodrugs, deesterified in the liver

| | bioavail. (%) | $t_{1/2}\beta$ (h) | daily dose (mg) |
|------------|---------------|--------------------|-----------------|
| captopril | 40-70 | 3 | 15-75 |
| enalapril | | 11 | 10-20 |
| lisinopril | | 12 | 10-80 |

- all renally cleared except fosinopril

pharmacodynamics

antagonize peptidyl dipeptidase
normally converts AT I to AT II and metabolizes bradykinin
↓ AT II, ↑ bradykinin
↓ aldosterone, ↑ Na⁺ and water loss
vasodilation

adverse effects

cardiovascular

initial hypotension, intraoperative hypotension
potent effect on fetal blood pressure

renal

precipitate failure with or without renovascular hypertension
K⁺ retention

other

dry cough (bradykinin-mediated)
neutropenia
altered taste, allergies

diuretics

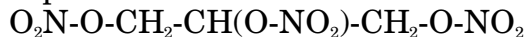
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g. Describe in detail the pharmacokinetics and pharmacodynamics of sodium nitroprusside and glyceryl trinitrate including their toxic side-effects.

glyceryl trinitrate

direct vasodilator described in 1879

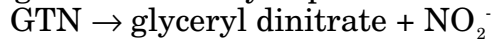
explosive



pharmacokinetics

binds to PVC, reduces predictability of dose

prodrug metabolized by hepatic nitrate reductase, $t_{1/2}$ 2 min



nitrite can release NO, but glyceryl di- and mono-nitrate are the main active drugs

NO is liberated from the nitrates by an unknown reaction which displays saturability, causing rapid tolerance

pharmacodynamics

NO diffuses into cells, ↑ cGMP to produce effects

smooth muscle: promotes dephosphorylation of myosin light chain

↓ phosphorylated myosin → relaxation

CVS: coronary vasodilation, ↑ endocardial perfusion

venodilation > arteriolar dilation, ↓ MAP, ↓ myocardial work

↓ platelet aggregation, ↑ MetHb

respiratory: pulmonary vasodilation, bronchodilation

GIT, uterine relaxation

clinical use

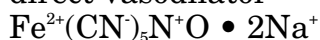
75-150 μg/min IV, up to 500 μg/min

adverse actions

hypotension, headache, tolerance, methaemoglobinaemia

nitroprusside

direct vasodilator



light sensitive

pharmacokinetics

rapid metabolism in red cells releases NO and CN⁻

CN⁻ metabolized to thiocyanate and renally cleared ($t_{1/2}$ 4-7 days)

short $t_{1/2}$: offset of action within 10 min

pharmacodynamics

vasodilator in all tissues

more arteriolar dilation than GTN

pulmonary vasodilation

loss of coronary autoregulation: potential for steal

clinical use

0.5 to 10 $\mu\text{g/kg/min}$ (up to 2 $\mu\text{g/kg/min}$ for sustained use)

adverse effects

cyanide toxicity if inadequate metabolism or sulfur donors

causes cellular hypoxia

treated with thiosulfate (\uparrow thiocyanate) or hydroxycobalamin

thiocyanate accumulation

neurological toxicity: weakness, disorientation, fits

inhibits iodide uptake: hypothyroidism

methaemoglobinaemia, hypotension, headache, tolerance

some patients are resistant or display unacceptable tachyphylaxis

h. Describe the pharmacological significance of nitric oxide, its mode of action and toxic effects.

Molecule of the Year 1992

pharmacokinetics

synthesized by nitric oxide synthetase

arginine + O_2 (+ NADPH, Ca^{2+} , calmodulin) \rightarrow citrulline + NO

subtypes of NO synthetase

I brain, platelets in cytosol. Ca^{2+} , calmodulin dependent

\uparrow by NMDA stimulation

\downarrow by IV induction agents

II macrophage. Prolonged production after induction and activation

responds to γ -interferon, cytokines, endotoxin

III vascular endothelium. Ca^{2+} , calmodulin dependent

responds to shear, bradykinin, ACh, 5HT, hydralazine...

can be administered in inspired gas at 0.1-40 ppm

metabolism

highly reactive, spontaneous degradation with O_2 to NO_2 , NO_2^- and NO_3^-

strong oxidant: Hb \rightarrow MetHb

$t_{1/2}$ 3 seconds

pharmacodynamics

vascular smooth muscle

activates guanylate cyclase, \uparrow cGMP, \uparrow protein kinase activity, \downarrow Ca^{2+} ,

relaxation

macrophages

oxidizes bacterial respiratory enzymes \rightarrow death

neurones

neurotransmitter via \uparrow cGMP, excitatory

role in peripheral and central analgesia, pain wind-up, memory

neurotoxic in non-NO neurones

clinical use

inhaled pulmonary vasodilator

improved V/Q matching (distributed according to ventilation)

used in ARDS, neonatal hypoxic pulmonary vasoconstriction

administered in N_2 to minimize NO_2 exposure

potential for specific NOS inhibitors in septic shock

adverse actions

methaemoglobinaemia

NO_2 causes pulmonary oedema

i. Describe the pharmacology of ketanserin

ketanserin

vasodilator, antihypertensive

not marketed in Australia

pharmacokinetics

$t_{1/2}$ 15 h

pharmacodynamics

5HT_{1c}, 5HT₂ antagonist

↓ platelet aggregation

vasodilation

weak α_1 antagonist

clinical use

adverse effects

CNS: headache, drowsiness

CVS: ↑ QT interval, *torsade de pointes*

B. 14 Antidysrhythmic drugs

a. Classify antidysrhythmics by their electrophysiological actions.

Vaughan-Williams classification

- I membrane stabilizers
 - all \uparrow ERP, \uparrow ERP/APD, all except c \uparrow APD
 - classified by rate of dissociation
 - a medium
 - \uparrow QT, QRS
 - quinidine, procainamide, disopyramide
 - b fast
 - \downarrow QT
 - lignocaine, mexiletine, tocainide
 - c slow
 - \uparrow PR, QT, QRS
 - flecainide, encainide, others
- II β -blockers
 - in Antihypertensives (2.B.13)
 - \downarrow HR, \uparrow PR
- III drugs prolonging repolarization
 - \uparrow APD, \uparrow ERP
 - \uparrow QT, \downarrow HR
 - amiodarone, sotalol, bretylium
- IV Ca^{2+} channel blockers
 - in Antihypertensives (2.B.13)
 - \downarrow HR, \uparrow PR
- others
 - adenosine, digoxin, alinidine, phenytoin etc.

arrhythmia classification

abnormal impulse formation

- early afterdepolarizations
 - occur in phase 3
 - more likely at slow heart rates, long QT interval
 - worse with class Ia, Ic and III drugs
- delayed afterdepolarizations
 - occur in phase 4
 - due to $\uparrow \text{Ca}^{2+}$, more likely in fast heart rates
 - worse with digoxin, catecholamines, ischaemia, hypercalcaemia

abnormal impulse conduction

- AV block
 - three degrees
 - worse with \uparrow vagal tone, β -blockers, Ca^{2+} channel blockers
- reentry
 - area of no conduction adjacent to area of one-way conduction
 - circuit long enough to avoid refractory period
 - source of tachyarrhythmias
 - improved with either increased or decreased conduction
- other abnormal conduction pathways
 - Wolf-Parkinson-White
 - other accessory pathways

b, c, e. Describe the pharmacodynamics and pharmacokinetics of the antidysrhythmic drugs. Describe the side effects and problems associated with the use of antidysrhythmic drugs during anaesthesia.

potassium

↑ plasma $[K^+]$ causes ↓ E_K and ↑ P_K
more effect in non-pacemaker cells (↑ V_m)
less effect on pacemaker cells

magnesium

acts on Na^+/K^+ ATPase, Na^+ , K^+ and Ca^{2+} channels
mechanism of action uncertain
used in *torsade* and digoxin toxicity
effective in paediatric acute asthma (25-50 mg/kg of $MgSO_4$)

adenosine in New Developments (2.B.24)

quinidine

stereoisomer of quinine

pharmacokinetics

high bioavailability
80% protein bound (competes with digoxin)
hepatic metabolism and renal clearance
 $t_{1/2} \beta$ 6 h
IV preparation also used for malaria

pharmacodynamics

α antagonist, antimuscarinic
may cause ↑ AV conduction
decompensation in AF or flutter due to ↑ ventricular rate
prolonged QT and APD predispose to *torsade*
nausea, vomiting, cinchonism, ↑ digoxin levels

procainamide

procaine with an amide instead of ester linkage
75% bioavailable
metabolized to N-acetyl procainamide (type III → *torsade*)
ganglion blocker
negative inotrope
long term SLE syndrome

disopyramide

50% bioavailable
 $t_{1/2} \beta$ 6 h
potent antimuscarinic (full range of atropine effects)
negative inotrope

imipramine

class Ia activity (not used for this purpose)

amiodarone

iodine-containing tertiary amine

pharmacokinetics

high oral bioavailability
concentrated in cardiac tissue
large V_d → loading time 15-30 days
 $t_{1/2} \beta$ weeks to months

pharmacodynamics

α , β antagonist, Ca^{2+} channel blocker (type II and IV)

binds Na^+ channels in the inactive state (type I)

probably blocks K^+ channels (type III)

effects

cardiac

\uparrow APD, ERP, QT

bradycardia, AV block

adverse

corneal deposits (100%)

pulmonary fibrosis (5-15%)

skin discolouration (5%)

photosensitivity (25%)

neurological problems

hyper- or hypo-thyroidism (5%)

constipation (20%)

hepatocellular necrosis

interactions

\downarrow clearance of warfarin, theophylline, quinidine, procainamide...

clinical use

effective in most arrhythmias including WPW (\downarrow accessory conduction)

phenytoin

Na^+ and Ca^{2+} blocker

\downarrow automaticity

effective in digoxin toxicity

flecainide

Na^+ channel blocker (type Ic)

suppresses PVCs

caused doubled mortality in CAST trial for asymptomatic PVCs

bretylium

inhibits catecholamine release after initial release \rightarrow hypotension

prolongs action potential

previously used in resuscitation and for LA toxicity

no longer available in Australia

sotalol

L isomer non selective β blocker

D & L isomers prolong action potential

d. Describe the pharmacological basis of the antidysrhythmic properties of lignocaine, including its pharmacokinetics.

lignocaine

diethyl glycine xylidide

class Ib antidysrhythmic

pharmacokinetics

3% bioavailable orally (tocainide and mexiletine are oral congeners)

pK_a 7.9

70% bound to α_1 acid glycoprotein

$t_{1/2} \alpha$ 8 min

V_d 1.3 l/kg

hepatic metabolism (E = 68%)

N deethylation, hydrolysis, 3' and 4' hydroxylation

clearance 15 ml/kg/min

$t_{1/2\beta}$ 90 min

renal excretion

pharmacodynamics

binds $S_6 \alpha_4$ domain of voltage-gated Na^+ channel in open state

rapid release from binding site in inactivated and resting states

prevents Na^+ flux

reduces V_{max} , prolongs QRS

binds open and inactivated Na^+ channels

rapid dissociation in resting state, so little effect on normal tissue

Na^+ channels in tissue with prolonged depolarization stay in inactive state

→ preferential binding in ischaemic or digoxin toxic tissue

positive inotrope at low dose

exacerbates arrhythmias in <10% (good)

clinical use

local anaesthetic use in Local Anaesthetics (2.B.11)

antidysrhythmic use

agent of choice in ventricular arrhythmias

loading dose: 1.5 mg/kg followed by 3×0.7 mg/kg at 10 minute intervals

infusion: 20-60 μ g/kg/min

infusion rate depends on clearance (\downarrow in hepatic disease, CCF)

adverse effects

| level (μ g/ml) | effect |
|------------------------|--|
| 2 | anticonvulsant, antidysrhythmic |
| 4 | positive inotrope, tinnitus, lightheadedness |
| 6 | vision disturbance |
| 8 | twitching |
| 10 | convulsions |
| 15 | coma |
| 20 | respiratory arrest |
| 26 | cardiac arrest |

f. Describe the pharmacological basis of the use of digoxin as an antidysrhythmic and its toxic effects.

digoxin

glycoside derived from *Digitalis purpurea*

consists of lactone, steroid and sugars

lactone and steroid are the active part (aglycone or genin)

other similar agents: digitoxin and ouabain are not used in Australia

pharmacokinetics

75% bioavailable (less with certain gut flora)

30% protein bound

V_d 6 l/kg, concentrated in heart, liver and kidney

renal excretion unchanged

$t_{1/2\beta}$ 40h

pharmacodynamics

binds to and inhibits Na^+/K^+ ATPase pump

different affinities in different tissues

binding competes with K^+ (\uparrow effect with hypokalaemia)

less negative membrane potential

reduced activity of Na^+ -dependent pumps (Na^+/Ca^{2+} exchanger)

effects

cardiac

\uparrow intracellular Ca^{2+}

↓ $\text{Na}^+/\text{Ca}^{2+}$ exchange, ↑ Ca^{2+} entry via channels, ↑ SR release
results in ↑ contractility, ↑ automaticity, no change in rate, ↑ K^+
conductance
↓ AP duration
at high Ca^{2+} levels, delayed afterdepolarizations occur → bigeminy
↑ toxicity with hypercalcaemia, any arrhythmia

neuro

↑ vagal tone at low dose: ↓ HR

CTZ stimulation

vision changes

GIT

nausea, anorexia, vomiting, diarrhoea

other

gynaecomastia

clinical use

IV or oral administration

B. 15 Antiemetic drugs

Definitions

nausea

unpleasant sensation referred to the pharynx and upper abdomen associated with the desire to vomit.

vomiting

forceful expulsion of gastric contents via the mouth (and nose).

retching

activation of the muscles involved in vomiting without expulsion of stomach contents.

regurgitation

return of gastric contents into the mouth without effort.

Mechanism of vomiting

detectors

peripheral

visceral afferents in the vagus (vagus is 80-90% afferent fibres)
mechanoreceptors responding to stretch
chemoreceptors in enterochromaffin cells
serotonergic transmission (5HT₃)
project to CTZ and *nucleus tractus solitarius* (muscarinic and H₁)

central

chemoreceptor trigger zone (CTZ)
in the area postrema, caudal part of the floor of the fourth ventricle
outside the blood-brain barrier
D₂ and 5HT₃ transmission

vestibular system

in inner ear
detects movement and position of the head
cholinergic and H₁ transmission
integrated with visual and proprioceptive inputs in the cortex
project to CTZ

vision

can induce nausea alone if perception of motion does not match vestibular input

taste, smell

both directly and by association with memories

touch at the back of the pharynx

the gag reflex mediated by the glossopharyngeal nerve

cortex

memories, emotions and thought can induce or facilitate nausea
probable site of action of benzodiazepines

integration

medullary emetic centre (vomiting centre) in the brainstem
receives inputs from CTZ, cortex and *nucleus tractus solitarius*
predominantly muscarinic cholinergic and NK₁
operates a coordinated motor program acting on
dorsal motor vagal nucleus
nucleus ambiguus
dorsal and ventral respiratory groups
presympathetic neurones

effectors

sympathetic

cutaneous vasoconstriction, sweating, mydriasis, tachycardia

- parasympathetic and enteric
 - gastric relaxation, ↓ gastric secretion
 - retrograde peristalsis from mid small bowel
 - relaxation of oesophageal sphincters
- somatic
 - respiratory
 - diaphragm relaxed
 - glottis closed, soft palate elevated
 - abdominal
 - rectus contracts rhythmically
 - flexed posture

a. Describe the pharmacokinetics and pharmacodynamics of dopamine antagonists, anticholinergic agents and serotonin antagonists.

metoclopramide

substituted benzamide:

methoxychloroprocainamide

pharmacokinetics

- 75% oral bioavailability
- crosses BBB
- hepatic conjugation to glucuronide and sulfate
- renal excretion 25% unchanged
- excreted in breast milk
- crosses placenta
- $t_{1/2\beta}$ 3-5 h, more rapid redistribution

pharmacodynamics

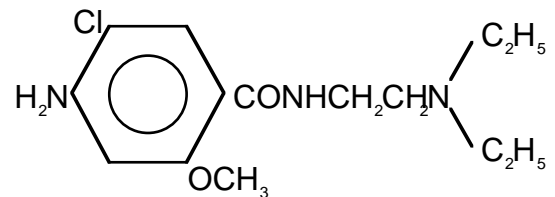
- D_2 antagonist and $5HT_4$ agonist
- $5HT_3$ antagonist at high dose
- sites of action
 - central: CTZ
 - gut: ↑ motility, LOS tone (centrally mediated)

adverse actions

- central D_1 effects: restlessness, drowsiness
- extrapyramidal effects: dystonia, akathisia
- ↑ prolactin, aldosterone secretion
- inhibits plasma cholinesterase

clinical use

- IV dose 0.15 mg/kg (up to 3 mg/kg in some centres)
- for prevention and treatment of PONV, chemotherapy nausea
- not effective for vestibular problems: vertigo, ENT surgery



prochlorperazine (similar to other phenothiazines)

phenothiazine (7 times as potent as chlorpromazine)

pharmacokinetics

- high oral bioavailability
- lipid soluble
- crosses BBB

pharmacodynamics

- predominant D_2 antagonist
- also antagonist at α -adrenergic, muscarinic, histamine and serotonin receptors

adverse actions

- as for all phenothiazines

clinical use

- oily solution for IM injection

used IV (not approved)
effective in vertigo and ENT surgery

droperidol

butyrophenone

pharmacokinetics

used IV

90% protein bound

crosses BBB

$t_{1/2}$ 2-3 h

pharmacodynamics

potent D_2 antagonist

some α -antagonist, histamine and serotonin antagonist activity

most potent in apomorphine-induced emesis

adverse actions

hypotension, sedation, dysphoria

extrapyramidal effects

↑ prolactin

clinical use

10-20 $\mu\text{g/kg}$ IV in adults, 50-75 $\mu\text{g/kg}$ in children (e.g. squint surgery)

ondansetron

pharmacokinetics

oral bioavailability $\approx 50\%$

75% protein bound

hepatic metabolism

$t_{1/2}$ 4 h

pharmacodynamics

specific 5HT_3 antagonist

acts at gut chemoreceptors and CTZ

potent antiemetic

adverse actions (rare)

headache, flushing

hypotension, bradycardia

involuntary movements

clinical use

4-8 mg IV or oral for adults

best agent for PONV and chemotherapy nausea

not good for opiate-induced nausea

other antiemetics in other sections

antihistamines

anticholinergics

benzodiazepines

steroids

cannabinoids

ephedrine

NK_1 blockers in phase II trials may be better than 5HT_3 antagonists

b. Critically appraise the clinical usage of these drugs.

decision to use preventively depends on patient's risk

increased by

school-age children, female sex, anxiety, pregnancy

history of PONV or motion sickness

full stomach, raised ICP

specific surgery (squints, gynae, ENT...)

choice of drug depends on likely cause

eliminate drugs from previous anaesthetics likely to have caused PONV

consider TIVA

spinal/epidural-induced nausea is often low CO, esp. in Caesars

treat with posture, fluid, ephedrine

ENT surgery: prochlorperazine, droperidol affect both dopamine and serotonin

opiate induced: droperidol probably best

other: high dose metoclopramide may be as effective as ondansetron

in susceptible patients, hypnosis or acupuncture are safest

B. 16 Histamine and serotonin

a. Describe the roles of histamine and serotonin receptor subtypes.

histamine

production

histidine is decarboxylated by histidine decarboxylase
in nerve cells, mast cells and basophils

stored in granules with

acidic protein, heparin and chemotactic factors

metabolized by

histamine N-methyl transferase

MAO

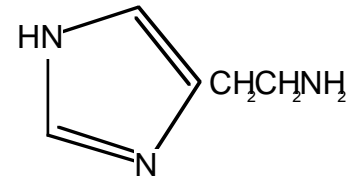
release from mast cells in response to

IgE crosslinking (via phospholipase C)

activated complement binding

direct drug actions

morphine, atracurium, others



receptors

H₁

act via phospholipase C

bronchoconstriction, colic

vascular triple response (vasodilation via NO, ↑ permeability, leukocyte activation)

central neurotransmitter

hypothalamus, thalamus, cerebellum and cortex

temperature regulation, ADH, BP control, pain transmission

H₂

act via adenylyl cyclase, lower affinity than H₁

parietal cells of the stomach ↑ acid secretion

vasodilation, bronchodilation

minor cardiac effects (↑ rate at SA node)

H₃

G protein-linked

central & peripheral presynaptic inhibition at histamine synapses

serotonin

production from L-tryptophan

5-hydroxylated, decarboxylated

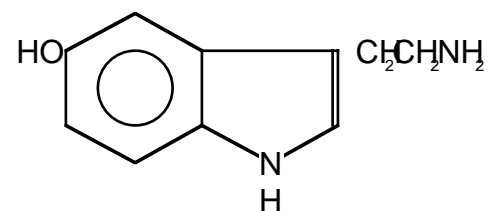
in platelets, gut

CNS: retina, pineal, midline raphe of pons

and upper medulla, elsewhere

metabolized by

MAO, aldehyde dehydrogenase to 5HIAA



receptors

5HT_{1A}

via ↓ adenylyl cyclase

central inhibitory transmission

behavioural and homeostatic actions

5HT_{1B}

via ↓ adenylyl cyclase

central presynaptic inhibition

5HT_{1Da, Db, E and F}

via ↓ adenylyl cyclase

present on cerebral blood vessels

cerebral vasoconstriction

- 5HT_{2A}
 - via ↑ phospholipase C
 - platelet aggregation
 - bronchoconstriction
 - gut contraction
 - systemic vasoconstriction or dilation
 - central behavioural effects
- 5HT_{2B}
 - via ↑ phospholipase C
 - contraction of gastric fundus
- 5HT_{2C}
 - via ↑ phospholipase C
 - increased CSF secretion at choroid plexus
- 5HT₃
 - gated ion channel
 - CTZ transmission
 - central excitation
 - behavioural effects
 - peripheral autonomic activation, nociception
- 5HT₄
 - via ↑ adenylyl cyclase
 - ↑ gut motility
 - central excitation
- 5HT_{5a, 5b, 6 and 7}
 - via ↑ adenylyl cyclase
 - in brain
 - 5HT₇ is inhibited by clozapine

b. Describe the pharmacodynamics, pharmacokinetics and side effects of H₂ antagonists, serotonin agonists and antagonists and outline their applications.

H₁ antagonists (“antihistamines”)

- many agents of different chemical classes
- available in OTC preparations
- most have antimuscarinic, α blocking, antiserotonergic and local anaesthetic activity
- well absorbed orally, IM and IV
- adverse actions
 - sedation or disinhibition (less with piperidines and loratidine)
- clinical use
 - allergic rhinitis
 - not effective in drug reactions as reaction is sustained by other mediators
 - motion sickness
 - nausea in pregnancy (category A: chlorpheniramine)

H₂ antagonists

- ranitidine
- pharmacokinetics
 - 30-90% bioavailable
 - V_d 1.5 l/kg
 - t_{1/2β} 2 h
 - renal elimination
- pharmacodynamics
 - competitive antagonist at H₂ receptors
 - suppresses gastric acid secretion

high dose: ↓ cardiac output, confusion

adverse effects

(cimetidine inhibits p450 enzymes, competes at androgen receptors)

ranitidine reduces gastric alcohol dehydrogenase activity

↑ alcohol bioavailability by 40%

ergotamine

alkaloid produced by *Claviceps purpurea* fungus in grain

pharmacodynamics

partial agonist at α and 5HT receptors peripherally and in CNS

slow dissociation

hallucinations

prolonged vasospasm, including cerebral and coronary vessels

prolonged uterine contraction

nausea, vomiting, diarrhoea

clinical use (largely replaced by similar alkaloids)

migraine (replaced by sumatriptan, dihydroergotamine)

hyperprolactinaemia (bromocriptine)

PPH (ergometrine)

sumatriptan

specific 5HT_{1D} agonist

orally active (low bioavailability), also sc

$t_{1/2\beta} < 2$ h

causes selective vasoconstriction

relieves migraine, cluster headache

may cause coronary vasospasm

injection site reaction

dose 50-100 mg o, 6 mg sc

ondansetron

specific 5HT₃ antagonist

50% oral bioavailability

acts at CTZ and in gut

dose 0.1-0.2 mg/kg

potent antiemetic

may cause hypotension, headache, flushing, abnormal movement, constipation

B. 17 Diuretics

a. Outline the physiological basis of classifying diuretics, related to their site of action.

Site of action

PCT

osmotic and carbonic anhydrase inhibitors (predominantly)

loop

loop diuretics

cortical part of loop, DCT

thiazides

collecting ducts

potassium-sparing diuretics

ADH antagonists (demeclocycline, Li^+ , alcohol)

b. Describe the actions of mannitol, frusemide, thiazides, aldosterone antagonists and carbonic anhydrase inhibitors.

c. Outline the side effects of the diuretics.

d. Describe the major applications and toxicities of the thiazides, loop diuretics and potassium-sparing diuretics.

mannitol

a sugar alcohol

osmotically active but not metabolized

pharmacokinetics

not absorbed orally → diarrhoea

administered IV

distributed throughout ECF

not metabolized

renal excretion by filtration

pharmacodynamics

expands plasma volume

↑ RBF, GFR

filtered at glomerulus

exerts osmotic pressure to prevent PCT reabsorption of Na^+ and water

high flow in loop “washes out” countercurrent multiplier

produces dilute urine

adverse actions

water loss in excess of Na^+ loss → hypernatremia

excess K^+ loss, particularly if aldosterone is high

clinical use

rapid diuresis for reduction of intracranial or intraocular pressure

frusemide

loop diuretic

sulfonamide derivative

pharmacokinetics

high oral bioavailability

96% protein bound

V_d 0.1 l/kg (circulation)

$t_{1/2\beta}$ 1 h

urinary filtration and secretion

acts from tubular lumen

pharmacodynamics

inhibits Na^+ , K^+ , 2Cl^- transporter in ascending loop

↓ medullary gradient

↓ lumen-positive potential

Ca^{2+} , Mg^{2+} , K^+ loss

vasodilation of renal vessels and systemic veins (?mechanism)

adverse actions

cation loss

dehydration → renal failure, gout

↑ aldosterone and DCT flow → K^+ and H^+ loss

hypokalaemic metabolic alkalosis

ototoxicity

sulfonamide allergy

clinical use

acute pulmonary oedema (venodilation)

hypercalcaemia

overdose of anions: Br^- , F^- and I^-

thiazides

sulfonamide derivatives

some have carbonic anhydrase inhibiting activity

pharmacokinetics (chlorothiazide)

high oral bioavailability

95% protein bound

V_d 0.2 l/kg

$t_{1/2\beta}$ 1.5 h

renal excretion by organic acid mechanism

pharmacodynamics

inhibit DCT NaCl uptake

↑ Ca^{2+} uptake

adverse actions

hypokalaemic metabolic alkalosis

hyponatraemia

↓ glucose tolerance, lipids

sulfonamide allergy

clinical use

cardiac failure

hypercalciuria

spironolactone

synthetic steroid

pharmacokinetics

hepatic metabolism

pharmacodynamics

competitive inhibitor at aldosterone receptor

↓ Na^+ reabsorption, ↑ K^+ , H^+ reabsorption

adverse actions

steroid effects: gynaecomastia, prostate enlargement

hyperkalaemia, acidosis (esp. with NSAIDs, ACE inhibitors)

amiloride

pharmacokinetics

urinary excretion unchanged

pharmacodynamics

inhibits Na^+ transport in luminal membrane

acts in lumen

adverse effects

hyperkalaemia, acidosis

acetazolamide

sulfonamide, carbonic anhydrase inhibitor

pharmacokinetics

well absorbed orally

not metabolized

weak acid actively secreted in PCT

eliminated within 12 h

pharmacodynamics

prevents secretion of H^+ in PCT to reabsorb HCO_3^-

results in alkaline diuresis

inhibition of carbonic anhydrase in ciliary body and choroid plexus causes reduced volume and more acidic aqueous humor and CSF

adverse effects

HCO_3^- depletion and acidosis result in reduced diuretic effect

increased urinary phosphate and Ca^{2+} can cause calculi

K^+ depletion due to increased luminal electronegativity

reduced urinary NH_4^+ excretion in alkaline urine (reabsorbed as NH_3)

exacerbates hepatic encephalopathy

↓ renal clearance can result in toxic levels in renal impairment

cross-sensitivity with other sulfonamides

clinical use

glaucoma (not for diuretic effect)

acute mountain sickness (alkalosis, ↑ ICP)

alkalinizing urine in drug overdose (e.g. salicylate)

B. 18 Drugs used in coagulation disorders

a. Classify the anticoagulants.

oral agents inhibiting vitamin K metabolism
 warfarin
parenteral anticoagulants
 heparin, low-molecular-weight fractions, hirudin
platelet inhibitors
 aspirin, NSAIDs, dipyridamole, ticlopidine, abciximab
thrombolytics
 tPA, streptokinase, urokinase
fibrinogen-depleting agents
 ancrod
in vitro agents
 citrate, EDTA

pro-coagulants
 ↑ clotting factor synthesis
 vitamin K
platelet activators
 DDAVP
plasminogen activation inhibitors
 EACA, tranexamic acid
plasmin inhibitors
 aprotinin (EACA, tranexamic acid)

b. Describe the pharmacodynamic and pharmacokinetics of heparin and low-molecular-weight heparins including their side effects.

heparin
 parenteral anticoagulant
 used IV and SC
 derived from porcine & bovine gut and other tissues
 anionic mucopolysaccharides synthesized in mast cells
 MW 5000-30000
 up to 50 saccharides
 quantitated by anticoagulant activity
 bioassay of anticoagulant effect on animal blood
 1 ml sheep blood with 0.2 ml 1% CaCl₂ anticoagulated for 1 hour
pharmacokinetics
 not absorbed orally
 t_{1/2} of effect 0.5-3 h saturable kinetics
 taken up by reticuloendothelial cells (high affinity, low capacity)
 absorbed by epithelium
 hepatic metabolism by heparinase
 some renal clearance
 administered by IV infusion (rate according to APTT) following loading dose
 active subcutaneously at low dose (5000 U bd - 7500 U tds) for DVT prophylaxis
 late rise in heparin levels observed after reversal with protamine
pharmacodynamics
 binds to antithrombin III, greatly increasing its affinity for thrombin
 thrombin activity rises rapidly from 8-13 saccharides
 increases anti factor Xa activity of antithrombin III
 only 5 saccharides required for Xa activity
 some antiplatelet activity

adverse actions

- bleeding
- hypersensitivity
- thrombocytopenia
 - dose-related in prolonged use
 - immune-mediated HITS
- osteoporosis
- alopecia

Low molecular weight heparins (dalteparin “Fragmin”, enoxaparin “Clexane”, nandoparin “Fraxiparine”, danaparoid “Orgaran”)

- low molecular weight fractions of heparin produced by depolymerization
- MW 2000-9000
- polysaccharide with 13-22 sugars
- quantitated by anti factor Xa activity
- used in prophylaxis and heparin sensitivity

pharmacokinetics

- 90% available by subcutaneous injection
- $t_{1/2}$ 2 h IV (3-4 h sc)

pharmacodynamics

- binds antithrombin
 - promotes inactivation of factors IXa, Xa, XIa and kallikrein
 - little effect on thrombin
- little platelet binding
- anti factor Xa activity is **not** reversed by protamine

adverse actions

- bleeding
- hypersensitivity
- osteoporosis
- thrombocytopenia

hirudin

- leech anticoagulant prepared by rDNA techniques
- direct antithrombin activity

c. Describe the mode of action and side effects of protamine

protamine

- basic protein (cationic)
- derived from salmon testes

pharmacokinetics

- administered slowly IV
- binds heparin immediately in circulation

pharmacodynamics

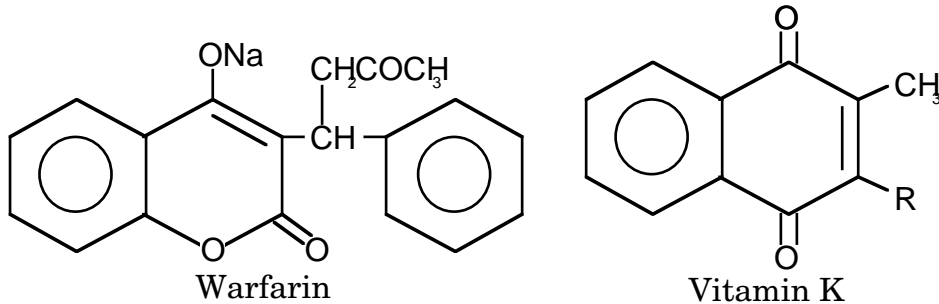
- binds heparin in circulation to form inactive complexes (1.3 mg protamine to 100 U heparin)
- complexes are cleared by the reticuloendothelial system

adverse actions

- hypotension
 - systemic vasodilation from rapid administration, especially via CVC
 - due to histamine release from cationic drug
 - minimized by slow injection (5 mg/min) into peripheral line
- type I hypersensitivity
 - more common in patients with fish allergy and diabetics using protamine-containing insulin

- theoretical risk in vasectomized men
- anaphylactoid reactions
 - complement activation by heparin-protamine complexes in lungs
 - possible role of IgG
 - protamine inhibits plasma carboxypeptidase
 - responsible for inactivating many cytokines
 - increased risk if ACE is also inhibited
 - transient pulmonary vasoconstriction due to TXA₂ release
- anticoagulant activity in large overdose
 - ? mechanism

d. Describe the chemistry, mechanism of action and toxicity of the coumarin anticoagulants.



warfarin

- discovered accidentally in spoiled sweet clover silage
- oral anticoagulant of choice
- racemic mixture (L-warfarin is four times as potent as D-warfarin)

pharmacokinetics

- 100% bioavailable
- 99% protein bound
- V_d small
- t_{1/2} 36 h
- hepatic metabolism

pharmacodynamics

- a competitive inhibitor of the reduction of vitamin K from epoxide to hydroquinone form
 - vitamin K hydroquinone is required for γ -carboxylation in the synthesis of factors II, VII, IX and X (and protein C)
- factors II, VII, IX and X have half-lives of 60, 6, 24 and 40 h, resulting in a clinical effect from about 30 h and full effect from about 72 h
- antagonism with vitamin K (dietary and intentionally administered)
- can also be reversed with FFP

interactions

pharmacokinetic

- enzyme induction or inhibition
- protein binding

pharmacodynamic

- other inhibitors of clot formation, especially NSAIDs which interact via displacement from protein binding, impaired metabolism and synergistic anti-platelet activity (phenylbutazone)
- some patients (and rats) have a hereditary abnormality of vitamin K metabolism and are resistant to warfarin

adverse actions

- bleeding
- teratogenicity

- warfarin crosses the placenta readily

- γ -carboxylation is required in the normal synthesis of bone and other tissues in

the foetus

protein C deficiency can result in hypercoagulability in some patients, with skin necrosis and multiple infarcts
alopecia

The other oral anticoagulants include dicoumarol and phenindione. They have less predictable absorption and phenindione causes hepatic and renal impairment in some patients.

e. Describe the fibrinolytic pathway and mechanisms of action of thrombolytic agents.

Plasminogen is a plasma protein which is trapped in the formation of a clot. Tissue plasminogen activator (tPA) is slowly released from injured endothelium and tissues and activates plasminogen to form plasmin. Plasmin is a protease which degrades fibrin, factors V, VIII and XII, thrombin and fibrinogen, causing lysis of the clot. This typically occurs over hours to days following clot formation.

The action of plasmin is limited by circulating α_2 -antiplasmin which prevents any low levels of circulating plasmin from lysing clots.

Fibrinolytic agents include streptokinase and anisoylated plasminogen-streptokinase activator complex (derived from bacteria), urokinase (derived from the kidney) and recombinant tPA and SCU-PA. All act by binding to proactivator plasminogen which then catalyzes the formation of plasmin from plasminogen.

Streptokinase and urokinase bind to circulating as well as bound plasminogen and so result not only in clot lysis but depletion of circulating fibrinogen. APSAC binds to fibrin and is deacylated to yield active streptokinase. r-tPA and r-SCU-PA preferentially activate bound plasmin, theoretically producing more selective fibrinolysis, but in practice there is little difference between their fibrinolytic effects.

Streptokinase and APSAC differ from the human-derived agents in that they are more antigenic. An immune response typically begins within 5 days of administration and hypersensitivity reactions can result from sensitization by streptococcal infection.

Benefit from thrombolytic therapy is proven in early treatment of suitable patients with AMI. There is no proven advantage in using any one agent. Treatment for cerebral infarcts, pulmonary embolism and DVT is indicated under specific circumstances. Use in clearing clot from long-term CVCs is safe and effective.

f. Describe the action of antifibrinolytic agents such as ϵ -aminocaproic acid (EACA).

EACA and tranexamic acid are competitive inhibitors of plasminogen activation and have minor anti-plasmin activity. EACA is $\text{H}_2\text{N}(\text{CH}_2)_5\text{COOH}$.

pharmacokinetics

high oral bioavailability

rapid renal clearance unchanged

$V_d \sim 0.5 \text{ l/kg}$

$t_{1/2} \sim 2 \text{ h}$

EACA dosage: 5 g over 30 minutes, 1 g/h for therapeutic plasma levels (130 mg/l)
post-TURP: 0.25 g/h as EACA is concentrated in urine

pharmacodynamics

?binds plasminogen activator and plasmin

clinical application

useful in the treatment of bleeding postoperatively due to primary fibrinolysis
bleeding in DIC (secondary fibrinolysis) is greatly exacerbated by EACA

g. Describe the action and pharmacological role of anti-platelet drugs

aspirin and other NSAIDs

discussed previously (2.B.4)

dipyridamole

phosphodiesterase inhibitor

increases platelet cAMP

impairs adhesion and activation

increases myocardial oxygen requirement

ticlopidine

inhibits ADP-mediated platelet activation

proven benefit over placebo in TIAs, unstable angina

not demonstrated to be better than aspirin

adverse effects

20% nausea, diarrhoea

5% bleeding

1% leukopenia

abciximab

preparation for intravascular use in PTCA

Fab fragment directed against platelet receptors

inhibits platelet aggregation by binding IIIa receptors

h. Describe the actions of aprotinin

Plasma prekallikrein is activated by trypsin, factor XIIa and kallikrein itself to form kallikrein which activates high-molecular-weight kininogen to form bradykinin. This promotes activation of the intrinsic pathway and mediates a vasodilator and chemotactic response. Kinins act via B₁ and B₂ receptors (B for bradykinin). There are multiple B₂ subtypes, which are G-protein linked. Bradykinin promotes tissue release of t-PA. Kallikrein also converts prorenin to renin, C1 to C1 and plasminogen to plasmin.

Aprotinin inhibits kallikrein, reducing production of bradykinin and plasmin. It also inhibits plasmin's fibrinolytic activity and reduces the inactivation of PAI by protein C.

additional

Classify and describe transfusion reactions.

haemolytic

acute

ABO incompatibility causes immediate intravascular haemolysis

0.004% incidence

recipient IgM binds to donor RBC antigens

complement activation, CMI activation, chemotactic factors

life-threatening: 25% mortality

shock

DIC

renal failure

usually due to clerical error

volume dependent

management

cease transfusion, return to blood bank with recipient sample

support circulation

maintain renal function

detect and treat DIC

maintain ventilation

delayed

minor recipient Ab to donor antigens causes extravascular haemolysis

e.g. Rhesus

0.06%

IgG coating of RBC, haemolysis in reticuloendothelial system

gradual onset

fever, malaise

jaundice, haemoglobinuria

fall in haematocrit

not haemolytic

acute

anaphylaxis

IgA-deficient recipient Ab to donor IgA

0.005%

tiny volume required

type I hypersensitivity

pulmonary oedema

donor Ab to recipient lymphocytes

complement activation

rare

urticaria

recipient Ab to donor plasma proteins or other constituents (e.g. food, drugs)

2-3%

type I or III hypersensitivity

fever

recipient Ab to donor granulocytes

1% with packed cells, 20% with platelets

complement and recipient leukocyte activation

treated with pethidine, steroids

delayed

purpura

recipient antiplatelet Ab

rare

GVH disease

engraftment of donor lymphocytes in immunosuppressed recipient
life threatening

B. 19 Obstetric pharmacology

a. Explain the physiological consequences of pregnancy and its pharmacological implications.

In Maternal Physiology (1.0)

b. Describe the mechanism of action and side effects of oxytocics, tocolytic agents, magnesium trisilicate and prostaglandins used in obstetrics.

α agonists

- ↑ uterine tone and contractions
- vasoconstriction

β_2 agonists

- ↓ uterine tone and contractions
- salbutamol used in large doses
- accompanying tachycardia, excitation

ergometrine

- tonic contraction of uterus
- onset within 40 s, lasts hours
- adverse effects
 - vasoconstriction → hypertension, coronary spasm
 - emesis
- dose 0.25 mg

oxytocin

- low dose produces normal contractions, milk let-down
- high dose produces tonic contraction
- direct systemic vasodilator, pulmonary vasoconstrictor
- reflex tachycardia
- ADH-like effect on collecting ducts
- half-life of minutes

PGF_{2 α}

- cervical relaxation, uterine contraction
 - direct myometrial injection for atonic uterus in PPH
- bronchoconstrictor, vasoconstrictor in most beds
- prokinetic: nausea, vomiting, diarrhoea

PGE₂

- uterine contraction, abortion
- bronchodilation, vasodilation
- prokinetic: diarrhoea
- ↓ gastric acid secretion

magnesium salts

- trisilicate, hydroxide, other salts
- used in antacids

sulfate

- pharmaceutics

 - 10 mmol (2.5 g) in 5 ml ampoule

- pharmacokinetics

 - normal plasma level 0.8-1.1 mmol/l

 - anticonvulsant level 2-3 mmol/l

 - paralysis at 7.5 mmol/l

 - 99% intracellular, 25% protein bound

 - eliminated by glomerular filtration and controlled reabsorption

- pharmacodynamics

 - reduces ACh release, desensitizes post junctional membranes

- adverse effects

potentiates relaxants
↓ muscle tone in newborn
clinical use
preeclampsia: bolus 4 g followed by 1-2 g/h, monitoring levels
arrhythmia: 0.15 mmol/kg + 0.1 mmol/kg/h

c. Outline the effects on the fetus of those drugs crossing the placenta.

e. Explain the factors which influence the transfer of drugs across the placenta to the fetus.

placental transfer

Fick's law of diffusion:

$$J = \frac{k \Delta C A \text{ Sol}}{T \sqrt{MW}}$$

where k is a constant, ΔC is concentration gradient, A is area of interface, Sol is solubility, T is temperature and MW is molecular weight

concentration gradient

maternal and fetal plasma levels

speed of metabolism in mother and fetus

shunt past fetal liver, recirculation (e.g. alcohol)

degree of protein binding

solubility

lipid solubility

molecule size, reflection coefficient

examples

narcotics

rapid transfer of lipid soluble agents (pethidine etc.)

long $t_{1/2}$ in neonate → bradycardia from pethidine

thiopentone

rapid transfer and redistribution

little effect by the time of delivery at Caesarean

propofol

demonstrated reduction in Apgar and neurobehavioural tests at >2.8 mg/kg

ketamine

increased uterine contractions, fetal depression and increased muscle tone

volatile agents

rapid transfer, higher MAC in fetus

uterine relaxation at >1.5 MAC

local anaesthetics

transfer dependent on protein binding

free fraction similar in mother and fetus (\uparrow protein binding → \downarrow f:m ratio)

relaxants

highly polar so little transfer

f:m ratios: atracurium 0.07, vecuronium 0.11, rocuronium 0.16

B. 20 Endocrine pharmacology

a. Describe the pharmacology of insulin preparations and their use.

insulin

pharmaceutics

51 amino-acid polypeptide composed of two chains linked by disulfide bonds
synthesized by β cells of the pancreas as proinsulin

proinsulin is cleaved into insulin and C-protein before secretion

endogenous production 1 unit/h plus 10-20 units/day after food

synthetic preparations were formerly bovine or porcine, now recombinant

standard solution 100 U/ml only

controlled release preparations by complexing with zinc or protamine

pharmacokinetics

zero oral bioavailability

administered by subcutaneous injection for fast or slow-release preparations

non-complexed preparations also administered IV by infusion

| | onset | peak | duration |
|--------------|--------|------|----------|
| soluble (sc) | 15 min | 3 h | 6 h |
| semilente | 1 h | 5 h | 15 h |
| lente | 2 h | 10 h | 20 h |
| ultralente | 4 h | 18 h | 30 h |

metabolized by hydrolysis of the disulfide bonds in the liver and kidney

$t_{1/2}$ 3-5 min

pharmacodynamics

binds specific cell-surface receptors

2 α and 2 β subunits, binds to α unit, β unit is a tyrosine kinase

causes a cascade of protein phosphorylations

activates GLUT 4 glucose uptake transporter in muscle and fat

↑ synthesis of fat, proteins, glycogen (↓ breakdown)

↑ K^+ uptake

↓ ketone production

↑ growth

adverse effects

hypoglycaemia

hypersensitivity to components of insulin

worst with animal-derived

allergy to protamine

lipodystrophy at the site of injection

clinical use

for type I diabetes as replacement therapy

commonly basal long-acting plus short-acting boluses before meals

perioperatively stabilized with infusion IV plus glucose and K^+

type II diabetes with resistance to oral therapy

much higher doses

generally normal glucose while fasting perioperatively without therapy

b. Describe the pharmacodynamics and pharmacokinetics of the oral hypoglycaemic agents with their clinical implications and side effects.

biguanides

metformin is the only agent available

pharmacokinetics

high oral bioavailability

high protein binding

renal excretion unchanged

$t_{1/2\beta}$ 1-2 h, effect 5-6 h

pharmacodynamics

uncertain mechanism of action
reduce fasting and post-prandial blood glucose
do not produce hypoglycaemia

adverse effects

increased lactic acidosis
nausea

sulfonylureas

pharmacokinetics

| | potency | $t_{1/2\beta}$ | metabolism |
|----------------|---------|----------------|-----------------|
| tolbutamide | 1 | 4-10 | hepatic |
| chlorpropamide | 6 | 24-42 | renal > hepatic |
| glibenclamide | 150 | 10-16 | hepatic |
| glipizide | 100 | 3-7 | hepatic |

pharmacodynamics

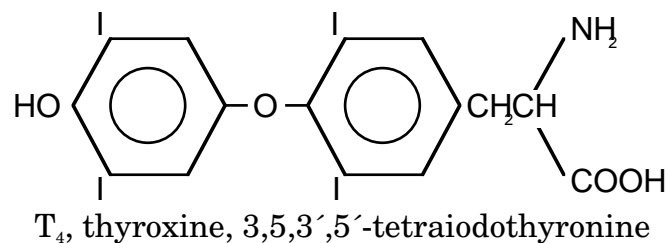
bind receptors on β cells \downarrow K^+ conductance, \uparrow insulin release
this effect is opposed by thiazide diuretics (\downarrow glucose tolerance)
 \downarrow glucagon secretion (mechanism uncertain)
? increase tissue sensitivity to insulin

adverse effects

hypoglycaemia
sulfonamide allergy (rash, type I)
flushing with alcohol use
chlorpropamide: \uparrow ADH release and effect

c. Describe the mode of action and adverse effects of thyroid hormones and antithyroid drugs.

thyroxine



pharmacokinetics

oral bioavailability T_4 80%, T_3 95%
synthesized in the colloid of the thyroid follicles
 I^- uptake and oxidation to I^o
reaction with tyrosine residues of thyroglobulin to form MIT and DIT
condensation of MIT and DIT to form T_3 and T_4 (bound to thyroglobulin)
hydrolysis of thyroglobulin to liberate MIT, DIT, T_3 and T_4
release of T_3 (17%) and T_4 (83%), deiodination of MIT and DIT
activation of T_4 to T_3 in the periphery ($1/3$)
inactivation of T_4 by conversion to rT_3 3,3',5'-triiodothyronine ($1/2$)
rapid clearance of free T_3 and rT_3
highly protein-bound to TBG, TBPA and albumin (T_4 0.04% free, T_3 0.4% free)
 \uparrow binding in pregnancy
autoregulated by negative feedback of **free** concentration on TSH, TRH

pharmacodynamics

binds to intracellular receptors (similar to steroid, vitamin A and D receptors)
 \uparrow RNA polymerase

- ↑ mitochondrial activity
- ↑ metabolic rate
- ↑ catecholamine responsiveness

clinical use

- replacement therapy
- 25-100 $\mu\text{g/day}$ thyroxine orally

antithyroid agents

I⁻ uptake inhibitors

- many anions
- SCN^- , BF_4^- , NO_3^- , ClO_4^- ...
- relevant only as toxic metabolites (e.g. nitroprusside), not used clinically

thioamides

- propylthiouracil, carbimazole
- contain -N-C=S moiety
- high oral bioavailability
- short plasma $t_{1/2}$
- concentrated in thyroid, prolonging effect
- inhibit I organification, tyrosine coupling and peripheral deiodination
- can cause autoimmune syndromes and agranulocytosis
- cross the placenta

iodides

- high dose I⁻ cause inhibition of T₄ release and deiodination
- marked rebound on withdrawal

I¹³¹

- β -ray emitter ($t_{1/2}$ 5 days)
- ablates hyperactive thyroid

physiological antagonists

- non-selective β -blockers reduce symptoms of hyperthyroidism (e.g. propranolol)

d. Describe the glucocorticoid and mineralocorticoid activities of steroid drugs and their adverse effects.

glucocorticoids

- analogues of cortisol (hydrocortisone)

hydrocortisone

pharmacokinetics

- synthesized in the adrenal cortex from cholesterol in response to ACTH
- diurnal variation in levels
- circulates 75% bound to CBG (an α_2 -globulin)
- synthetic glucocorticoids are albumin-bound
- metabolism to cortisone in kidney (20%) which has 80% potency
- inactivation in liver to multiple metabolites
- $t_{1/2}$ 60-90 min

pharmacodynamics

- binds intracellular receptor
- promotes or inhibits gene expression
- some effects are too fast to be gene-mediated
- metabolic
 - ↑ gluconeogenesis, glycogen synthesis
 - ↑ muscle catabolism, bone reabsorption
 - ↑ insulin synthesis, lipogenesis
- adrenal suppression by exogenous steroids

immune

- inhibit cyclooxygenase II, phospholipase A₂, IL-1 & 2 synthesis

↑ circulating neutrophils, ↓ other leukocytes
↑ susceptibility to infection

CNS

↑ ICP (minor)
↓ ACTH, TSH, FSH
psychosis, cataracts

GIT

↑ acid, pepsin secretion
↑ fat absorption
↓ Ca²⁺ absorption (oppose vitamin D)

fetus

speed maturation and surfactant production

connective tissue

acne, fine hair, striae, bruising
aseptic necrosis of the femoral head

aldosterone

mineralocorticoid synthesized in the *zona glomerulosa* of the adrenal cortex
similar to cortisol
details in [Renal Physiology \(1.D\)](#)
exogenous analogue: fludrocortisone

| | antiinflammatory | mineralocorticoid |
|--------------------|------------------|-------------------|
| hydrocortisone | 1 | 1 |
| cortisone | 0.8 | 0.8 |
| prednisolone | 4 | 0.3 |
| methylprednisolone | 5 | 0 |
| dexamethasone | 30 | 0 |
| fludrocortisone | 10 | 250 |

e. Describe the pharmacology of glucagon.

glucagon

29 amino-acid protein

pharmaceutics

recombinant preparation
1 mg (100 U) glass ampoule with water for reconstitution

pharmacokinetics

synthesized by the α cells of the pancreas
rapid hydrolysis in plasma and in the liver and kidney
 $t_{1/2}$ 3-6 min
similar proteins synthesized by the gut including GLP which stimulates insulin release

pharmacodynamics

N-terminal binds specific cell-surface receptors
↑ cAMP
initiates cascade of protein dephosphorylation
↑ glycogenolysis, ketogenesis, gluconeogenesis
↑ insulin, catecholamine, calcitonin release
positive inotrope
↓ gut motility

adverse effects

nausea, vomiting

clinical use

acute treatment of hypoglycaemia
effect limited by hepatic glycogen stores

relaxation of gut sphincters (e.g. ERCP)

f. Describe the pharmacology of vasopressin and its analogues.

ADH

nonapeptide hormone synthesized in supraoptic and paraventricular nuclei
released from posterior pituitary neurones in response to

hypotension (7-10% volume change → low pressure baroreceptors)

↑ osmolarity (change of 1-2%)

overcome by volume effect

angiotensin II

sympathetic activity, stress

drugs (chlorpropamide, barbiturates, carbamazepine, clofibrate)

pharmacokinetics

exogenous analogue DDVAP (1-desamino-8-D-arginine vasopressin)

selective V_2 agonist used for bleeding and anti-diuretic effect

administered nasally, sc, IM and IV

$t_{1/2}$ 20 min renal and hepatic hydrolysis of peptide and disulfide bonds

pharmacodynamics

V_1

vasoconstrictor acting on smooth muscle

V_2

↓ collecting duct permeability to water (via ↑ cAMP)

results in insertion of aquaporin 2 in membrane

↑ release of $VIII_c$ and vWF (V_2 -like receptors on endothelium)

B. 21 Gastrointestinal pharmacology

a. Describe the mode of action and comparative pharmacology of sodium citrate and magnesium trisilicate.

sodium citrate

non-particulate antacid

presented as 30 ml of 0.3 mol/l solution

raises gastric pH above 3 for 2-3 hours

given prophylactically to reduce the incidence of pneumonitis if aspiration occurs

effectiveness depends on gastric volume, pH and motility

most effective with low volume, poor motility

100% bioavailable

citrate is metabolized by the TCAC

represents a small alkaline load (equivalent to 27 mmol HCO_3^-)

magnesium trisilicate

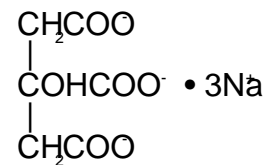
particulate, relatively insoluble antacid

similar to magnesium carbonate, aluminium hydroxide, others

present in many proprietary preparations

raises gastric pH similar to citrate

not bioavailable, minimal absorption



b. Describe the mode of action and side effects of omeprazole.

omeprazole (and lansoprazole, pantoprazole...)

a substituted benzimidazole

pharmacokinetics

prodrug activated by low pH in parietal cell canaliculi

high oral bioavailability

plasma $t_{1/2}$ 1-2h

duration of effect 1-2days due to local concentration

pharmacodynamics

direct inhibitor of H^+ , K^+ ATP-ase in parietal cells

adverse effects

complete suppression of acid secretion

altered bacterial flora

loss of barrier to infection posed by acid environment

upregulation of gastrin secretion (? risk of carcinoid gastrinoma)

clinical use

60 mg oral daily

c. Describe the mode of action and side effects of the H_2 antagonists.

ranitidine (cimetidine, famotidine, nizatidine...)

pharmacokinetics

30-90% bioavailable

V_d 1.5 l/kg

$t_{1/2}$ 2 h

renal elimination

pharmacodynamics

competitive antagonist at H_2 receptors

suppresses gastric acid secretion

high dose: ↓ cardiac output, confusion

adverse effects

(cimetidine inhibits p450 enzymes, competes at androgen receptors)

ranitidine reduces gastric alcohol dehydrogenase activity

↑ alcohol bioavailability by 40%

B. 22 Intravenous fluids

a. Describe the composition, pH and osmolality of crystalloids and colloids used in clinical practice.

0.9% NaCl

| | |
|-----------------|------------|
| Na ⁺ | 150 mmol/l |
| Cl ⁻ | 150 mmol/l |
| | 300 mOsm/l |
| pH | 4-7 |

Hartmann's solution

| | |
|------------------|------------|
| Na ⁺ | 129 mmol/l |
| K ⁺ | 5 mmol/l |
| Cl ⁻ | 109 mmol/l |
| Ca ²⁺ | 2 mmol/l |
| lactate | 29 mmol/l |
| | 274 mOsm/l |
| pH | 5-7 |

5% dextrose

| | |
|---------|------------|
| glucose | 278 mmol/l |
| | 278 mOsm/l |
| pH | 3.5-6.5 |

4% dextrose 1/5 normal saline

| | |
|-----------------|------------|
| Na ⁺ | 30 mmol/l |
| Cl ⁻ | 30 mmol/l |
| glucose | 222 mmol/l |
| | 282 mOsm/l |
| pH | 3.5-6.5 |

mannitol

12.5%, 20% and 25% solutions

dextrans

40 and 70 in 5% glucose or 0.9% NaCl

polygeline (Haemaccel™)

| | |
|---|-------------|
| Na ⁺ | 145 mmol/l |
| K ⁺ | 5.1 mmol/l |
| Cl ⁻ | 145 mmol/l |
| Ca ²⁺ | 6.25 mmol/l |
| PO ₄ ³⁻ , SO ₄ ²⁻ | trace |
| polygeline | 35 g/l |
| | 293 mOsm/l |
| pH | 7.3±0.3 |

succinylated gelatin (Gelofusine™)

| | |
|------------------|--------------|
| Na ⁺ | 154 mmol/l |
| Cl ⁻ | 120 mmol/l |
| Ca ²⁺ | <0.04 mmol/l |
| gelatin | 40 g/l |
| | 274 mOsm/l |
| pH | 7.4±0.3 |

hetastarch

Albumex 4

| | |
|-----------------|------------|
| Na ⁺ | 140 mmol/l |
| Cl ⁻ | 128 mmol/l |
| octanoate | 6.4 mmol/l |
| albumin | 40 g/l |
| | 260 mOsm/l |
| pH | 7±0.3 |

Packed red blood cells (300 ml)

| | |
|-----------------|---------------------|
| erythrocytes | 200 ml |
| albumin | 4 g |
| globulin | 2 g |
| total protein | 36 g |
| Na ⁺ | 15 mmol |
| K ⁺ | 4 mmol (≈40 mmol/l) |

other blood products in [Haematology \(1.J\)](#)

b. Evaluate their effects and fate when used in volume replacement.

c. Compare the pharmacology of colloids with crystalloids.

crystalloids

t_{1/2} 20 min

free water (dextrose solution)

55% ICF, 38% ISF, 7% plasma

↓ total body tonicity (↓ [Na⁺]_{pl})

isotonic solutions

85% ISF, 15% plasma

colloids

remain in circulating compartment

| | $t^{1/2}$ circ. | $t^{1/2}\beta$ |
|------------|-----------------|----------------|
| polygeline | 1-2 h | ?4-6 h |
| Gelofusine | 2-3 h | |
| dextran 40 | 4-6 h | 2-6 h |
| dextran 70 | 12 h | 12 h |
| Albumex 5 | 24 h | 21 d |
| hetastarch | 36 h | 36 d |

increased incidence of hypersensitivity (>1/10,000)

B. 23 Antimicrobials

a. Describe the pharmacology of antimicrobial drugs.

inhibit cell wall synthesis

- cell wall is composed of peptidoglycan

- polysaccharide and polypeptide chains

- crosslinked by transpeptidase acting on pentaglycine chains

- penicillins, cephalosporins

- β -lactams inhibit transpeptidase enzymes "PBP"s (multiple subtypes)

- cleaved by β -lactamase (plasmid-mediated resistance)

- some agents resist β -lactamase (methicillin, ceftiofur)

- some agents inhibit β -lactamase (clavulanate)

- some PBPs have low affinity for antimicrobials

- vancomycin (glycopeptide)

- prevents synthesis of peptidoglycan chains (before crosslinking)

- bacitracin

- cycloserine

- inhibits peptidoglycan synthesis (false substrate)

alter cell membrane permeability

- cell membrane has lipids characteristic of the organism

- selective detergents can disrupt the membrane

- low therapeutic index

- amphotericin B, polyenes

- active against fungi

- azoles

- inhibit fungal membrane lipid synthesis

- e.g. imidazole, ketoconazole

- polymyxins

- active against gram negatives

inhibit protein synthesis

- aminoglycosides

- attach to ribosomes

- block transcription of correct amino-acids

- disperse polysomes (groups of ribosomes)

- require active uptake into cells (aerobic metabolism dependent)

- resistance due to ↓ uptake, inactivating enzymes, deletion of receptor

- tetracyclines

- cause reversible inhibition of protein transcription, bacteriostatic

- require active uptake

- macrolides, lincomycins

- prevent polypeptide formation

- resistance due to absent binding site

- chloramphenicol

- reversibly inhibits amino-acid linking in peptide synthesis

- resistance due to inactivating enzymes

inhibit nucleic acid synthesis

- quinolones

- inhibit DNA gyrase (uncoils supercoiled DNA)

- sulfonamides

- PABA analogues inhibits folate synthesis (required for nucleotide synth.)

- p-aminosalicylic acid acts similarly in mycobacteria

- inherently resistant to PABA

- trimethoprim

- selective inhibitor of bacterial tetrahydrofolate reductase

- pyrimethamine

- selective inhibitor of protozoal dihydrofolate reductase

- rifampicin

- inhibits RNA polymerase

- resistance due to altered binding site

- antiviral nucleic acid analogues

- AZT, DDI, DDC etc. impair DNA transcription

- penicillin

- 1929 described by Fleming

- 1940s purified by Florey & Chain

- addition of other functional groups alter β -lactamase resistance and spectrum

- pharmacokinetics

- administered IV, IM, orally (different radicals provide oral stability)

- quantitated by units (10^6 units = 0.6 g)

- high oral bioavailability of oral preparations

- elimination by renal excretion (90% active)

- up to 2 g/h (saturable kinetics)

- inhibited by probenecid, renal failure

- hepatic metabolism for some analogues, especially halogenated

- excreted in milk, sputum

- spectrum

- penicillin most active against gram positives

- semisynthetic agents \uparrow gram negative cover (ticarcillin, piperacillin)

- no cover for cell-wall deficient bacteria

b. Outline the interactions between antimicrobials and anaesthetic agents.

- aminoglycosides

- prolong and potentiate non-depolarizing block

- direct nephrotoxins

- erythromycin

- induced nausea and \uparrow motility via motilin₁ receptors

c. Explain the principles of antimicrobial prophylaxis.

d. Chemotherapeutic agents

- cycle specific

- antimetabolites

- methotrexate, citarabine, 5FU, mercaptopurine, thioguanine

- most interfere with purine or pyrimidine metabolism

- antibiotics

- bleomycin

- binds to DNA

- podophyllin alkaloids

- etoposide (VP-16)

- inhibit topoisomerase II

- plant alkaloids

- vincristine, vinblastine, paclitaxel

- interfere with spindle formation

- cycle non-specific

- alkylating agents

- busulfan, cyclophosphamide, melphalan, thiotepa

- metabolized intracellularly to reactive agents

- metabolism (and toxicity) may be tissue-specific

- donate alkyl groups to many molecules, especially guanine

- result in DNA crosslinking or breakage

- antibiotics
 - daunorubicin, doxorubicin, mitomycin
 - different action
- cisplatin, carboplatin
 - probably an alkylating agent
- nitrosoureas (mustards)
 - BCNU, CCNU
 - act as alkylating agents
- endocrine agents
 - anti-oestrogens and anti-androgens
- other agents
 - asparaginase, hydroxyurea, all-*trans*-retinoic acid, interferons...

B. 24 Developments in pharmacology

a. Describe the developing pharmacology in relation to the cytokines.

cytokines

| | |
|------------------|---|
| IFN- α | antiviral, antiproliferative |
| IFN- β | antiviral, antiproliferative |
| IFN- γ | \uparrow cytokines, leukocyte activity |
| IL-1 | inflammatory mediator, "endogenous pyrogen", \uparrow marrow activity produced by macrophages, lymphocytes and fibroblasts |
| IL-2 | \uparrow T cell activity, NK cells, produced by CD4 and CD8 T cells |
| IL-3 | multi-CSF |
| IL-4 | \uparrow antigen-primed T and B cells, IgE, IgG ₁ |
| IL-5 | \uparrow eosinophils |
| IL-6 | \uparrow plasma cells and early marrow cells, \uparrow hepatic mediator synth. |
| IL-7 | \uparrow proliferation and differentiation of early cell progenitors |
| IL-8 | neutrophil chemotactic factor |
| IL-9 | mast cell growth-enhancing factor |
| IL-10 | immune suppressant |
| TNF (α) | mobilizes Ca ²⁺ from bone, similar to TNF β |
| TNF β | antiparasitic, endotoxic shock reaction, antitumour, \uparrow B cells |
| GM-CSF | \uparrow granulocyte, neutrophil, monocyte-macrophage and eosinophil proliferation and differentiation |
| G-CSF | \uparrow granulocyte proliferation and differentiation |
| M-CSF | \uparrow monocyte-macrophage proliferation and differentiation |

Cytokines are available as pharmaceuticals through the use of recombinant DNA techniques. Most are administered as subcutaneous injections. Interferon- α is used in the treatment of some malignancies and hepatitis C. Interferon- β 1b may be effective in relapsing multiple sclerosis. Interferon- γ is used in chronic granulomatous disease. IL-2 is effective in metastatic renal cell carcinoma. Use of interleukins or interferons as vaccine adjuvants is possible but expensive.

G-CSF and GM-CSF are used to reduce the period of severe neutropenia following chemotherapy and may be used in future in other situations of poor leukocyte response.

Inhibition of the action of cytokines in conditions where they are thought to contribute to pathology is under on-going investigation. The preparations used are monoclonal antibodies against cytokines and soluble receptors (both available for IL-1 and TNF). Endogenous IL-1Ra, an IL-1 antagonist has been synthesized. These preparations are in phase III trials in patients with septic shock and may be trialled in ulcerative colitis, rheumatoid arthritis and CML.

Alteration in the endogenous production of cytokines is a mechanism of action of several established drugs.

Glucocorticoids inhibit production of IL-1 and thus IL-2 and IFN- γ . They also inhibit the production of many other inflammatory mediators, cause sequestration of lymphocytes in lymphoid tissue and impair margination of granulocytes.

Cyclosporin inhibits the gene transcription of IL-2, 3 and IFN- γ as well as other factors produced by activated T cells. It acts as a potent inhibitor of the cell-mediated immune response and is used in prevention of transplant rejection. It also prolongs the "honeymoon" period in Type I diabetes and has been trialled in rheumatoid arthritis and other autoimmune diseases. It is 20-50% bioavailable and has a $t_{1/2}$ of 24h with hepatic metabolism and excretion in the bile.

Tacrolimus is a macrolide antibiotic with similar actions to cyclosporin but greater potency. Sirolimus (rapamycin) binds to the same intracellular site as tacrolimus but blocks response to cytokines rather than their expression.

A₁

adenosine receptor

G protein linked: ↓ adenylyate cyclase

actions

renal: afferent vasoconstriction, efferent vasodilation

cardiac: ↓ AV conduction, ↓ contractility

bronchi: constriction

CNS: pre- and post-synaptic inhibition (↑ K⁺ conductance)

neuroprotective (↓ glutamate release)

↓ dopamine release (↓ nausea)

benzodiazepines inhibit uptake

antagonists

methylxanthines (as well as ↓ phosphodiesterase)

A₂

adenosine receptor

G protein linked: ↑ adenylyate cyclase

actions

platelets: ↓ aggregation

PNS: ↑ nociceptive afferents (?transmitter of angina)

P₂

ATP/ADP/AMP receptors

several subclasses (P₁ are adenosine receptors)

agonists

ATP

most P₂ receptors are most sensitive to ATP (>ADP>AMP)

cotransmitter in noradrenergic and cholinergic transmission

especially gut relaxation, bladder contraction

fast transmitter in CNS and autonomic ganglia

ADP

platelet P₂ receptors are most sensitive to ADP

causes platelet aggregation (antagonized by adenosine)

antagonists

suramin (P_{2X} only)

Adenosine

nucleoside which occurs naturally

used intravenously

pharmacokinetics

t_{1/2}β ≈ 10 s

distribution is not relevant

metabolized to inosine or AMP in circulation

pharmacodynamics

binds specific receptors on cardiac and smooth muscle

slows AV nodal conduction

reduces SA node discharge rate slightly (may cause asystole)

vasodilates

antagonized by methylxanthines

potentiated by dipyridamole (uptake inhibition)

adverse actions

flushing

bronchoconstriction

hypotension, nausea, headache

infusion may induce gout

use

6-12 mg IV bolus for SVT or VT

c. Other newish drugs.

losartan (and irbesartan)

- non-peptide angiotensin II antagonist
- oral and IV preparations

pharmacokinetics

- well-absorbed orally

pharmacodynamics

- potent competitive antagonist at the AT₁ receptor
 - AT₁ receptor is present in vascular smooth muscle and other tissues
 - G protein linked via IP₃ and DAG in vascular smooth muscle
- may lower cholesterol (?mechanism)

adverse actions

advantages

- no bradykinin/renin/angiotensin II effects
 - cough, hormonal "escape", renal vasodilation

use

- 100 mg daily oral dose in essential hypertension
- IV bolus 25 mg in CHF
- expensive

rocuronium

- quaternary aminosteroid analogue of vecuronium
- non-depolarizing muscle relaxant

pharmacokinetics

- V_d 0.2 l/kg
- clearance 3.9 ml/min/kg
- t_{1/2} π 2 min, α 15 min, β 100 min
 - slightly prolonged in hepatic disease
 - shorter in children (t_{1/2} β 50 min 3-8 years)
- hepatic clearance 40% unchanged in bile
- renal clearance 15-30% unchanged

pharmacodynamics

- competitive blocker at nicotinic receptors

adverse actions

- minimal vagolytic effect in high doses (>0.9 mg/kg)
- not known to cause MH
- rare histamine release

clinical use

- ED₉₀ 0.3 mg/kg
- induction 0.6 mg/kg
- duration of action 35 min
- supplemental 0.15 mg/kg
- infusion 5-10 μ g/kg/min

cisatracurium

- isomer of atracurium, a benzyliisoquinolinium agent
- non-depolarizing muscle relaxant

pharmacokinetics

- V_d 0.15 l/kg
- clearance 5 ml/kg/min
- t_{1/2} β 25 min
- elimination largely Hoffman → laudanosine and monoquaternary acrylate
- some hydrolysis

- unaffected by age, renal or hepatic disease
- metabolites have no NDB effect
- metabolites are renally and hepatically cleared
- pharmacodynamics
 - competitive antagonist at nicotinic receptors
- adverse actions
 - uncommon histamine release
- clinical use
 - ED₉₅ 0.05 mg/kg
 - induction 0.15 mg/kg
 - duration of action 55 min
 - supplemental 0.03 mg/kg
 - infusion 1-2 $\mu\text{g/kg/min}$
- remifentanyl
 - synthetic opioid
 - fentanyl derivative with ester linkage
 - formulated in glycine (not for intrathecal use)
- pharmacokinetics
 - V_{dss} 25-40 l
 - clearance 5 l/min
 - t_{1/2 β} 10-21 min
 - context t_{1/2} after infusion 3 min
 - hydrolysed by non-specific esterases
 - metabolite potency 0.2%
- pharmacodynamics
 - μ agonist, equal potency to fentanyl
- clinical use
 - load with 0.5-1 $\mu\text{g/kg/min}$, maintain 0.1-0.2 $\mu\text{g/kg/min}$

B. 25 Psychotropic agents

MAO inhibitors

MAO A

intestinal mucosa, peripheral noradrenergic nerves, placenta, liver

30% of brain MAO

highest affinity for noradrenaline, serotonin

MAO B

liver, dopaminergic neurones, platelets

70% of brain MAO

higher affinity for dopamine, tyramine, phenylethylamine

non selective

phenelzine, tranylcypromine

non competitive

inhibit both MAO A and B

cause "cheese reaction"

indirect sympathomimetics cross intestinal mucosa and liver due to lack of MAO

enter noradrenergic neurones via uptake 1

displace noradrenaline from vesicles

cytoplasmic noradrenaline is normally metabolized by MAO A but instead

diffuses into synaptic cleft via uptake 1 (in reverse)

MAO A selective

moclobemide

competitive inhibitor of MAO A

minor potentiation of indirect sympathomimetics

MAO B selective

selegiline

inhibitor of MAO B

potentiates dopaminergic transmission in CNS

used in Parkinsonism

Selective serotonin reuptake inhibitors

Pharmaceutics

Chemically diverse

Prozac (fluoxetine), Zoloft (sertraline), Aropax (paroxetine), Cipramil (citalopram), Luvox (fluvoxamine), Efexor (venlafaxine) and generics

Oral preparations only

Pharmacokinetics

Oral bioavailability >90% with repeat dosing

Lower on first dose due to saturable first-pass metabolism

Highly protein bound (95%) except fluvoxamine (77%)

Large V_d (20 l/kg) due to high lipid solubility and tissue binding

$t_{1/2}$ 15 h (fluvoxamine) to 4-7 days (fluoxetine)

Hepatic metabolism, some active metabolites (fluoxetine, sertraline)

Renal or hepatic excretion

Pharmacodynamics

Selective inhibition of presynaptic serotonin reuptake

Increased serotonin in synaptic cleft

Inhibition of serotonergic firing by presynaptic inhibitory receptor

Delayed desensitization of presynaptic receptor over two weeks

Subsequent increased serotonin release and antidepressant effect

Adverse effects

Mild inhibition of dopamine and noradrenaline uptake

Venlafaxine is a potent inhibitor of noradrenaline reuptake

Paroxetine is also antimuscarinic

Inhibition of various cytochrome p450 enzymes

Multiple interactions

↑ effect of diazepam, warfarin, lipophilic β -blockers

Common symptoms

Nausea, vomiting, diarrhoea, insomnia, agitation, tremor, headache, impotence

SIADH, hyponatraemia

Depletion of platelet serotonin, impaired aggregation

Serotonin syndrome

↑ serotonin in brainstem and spinal cord (5HT_{1A} mediated)

Caused by combination with serotonergic drugs

MAOI, carbamazepine, pentazocine, tricyclics, pethidine

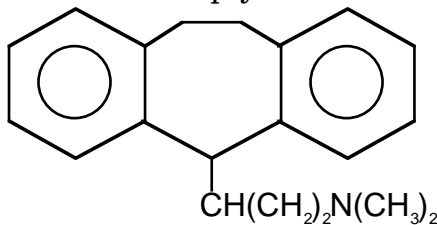
Confusion, agitation, coma, rigidity, myoclonus, opisthotonus, myoglobinuria,

Autonomic instability, DIC

May mimic neuroleptic malignant syndrome

Tricyclics

Amitriptyline



Chemistry

Three ring nucleus

Developed as antihistamines

Pharmacokinetics

High oral bioavailability, first-pass metabolism

Highly protein bound, high lipid solubility

Hepatic metabolism

Ring hydroxylation, conjugation

Chain demethylation → active metabolites

Pharmacodynamics

Block noradrenaline and serotonin reuptake

Also antihistaminic, antimuscarinic, α -blocker

Compensatory response to uptake inhibition results in delayed antidepressant effect

Overdose

Clinical features

CNS: irritability, seizures, unconsciousness, respiratory depression, fever

PNS: urinary retention, gut paralysis

CVS: arrhythmias, refractory SVT, VT, VF

Management

Activated charcoal, ABC

Arrhythmia: lignocaine, propranolol, phenytoin, pacing

Acidosis, decrease toxicity: HCO₃⁻, K⁺

C. Statistics

a. Describe the stages in the design of a clinical trial, taking into account the: research questions and hypothesis, literature review, statistical advice, choice of study protocol, ethical issues, data collection and processing.

b. Explain concepts in statistics such as: distribution of data and frequency distributions, measures of central tendency and dispersion of data and the appropriate selection and application of non-parametric and parametric tests in statistical inference.

data types

nominal

a list of possible results

e.g. death/discharge/transfer to another institution

ordinal

an ordered grouping of results on a scale with discrete points

e.g. ASA status, Duke's staging

numerical

interval

equal intervals between values but no absolute zero

e.g. temperature in °C

ratio

a linear scale from an absolute zero

e.g. mean arterial pressure

parametric

data which are distributed normally

variable

a measurement of a sample

parameter

a measurement of the population

measurement of central tendency

mean

arithmetic

the average of numerical data: $\bar{X} = \frac{\sum X_i}{n}$

geometric

the n^{th} root of the product of numerical data

$GM = \sqrt[n]{X_1 X_2 \dots X_n}$ or $\ln GM = \sum \frac{\ln X_i}{n}$

not applicable to nominal or ordinal data

affected by outliers

median

the middle result in rank order

mode

the most common result in data on a discrete scale

distributions may have more than one mode

measurement of variability

range

the difference between largest and smallest values

interquartile (25%-75%) or 5%-95% ranges are sometimes quoted

suitable for ordinal or interval data

variance

$$\text{var} = \frac{\sum (X - \bar{X})^2}{n}$$

suitable for interval data only
standard deviation

$$s = \sqrt{\frac{\sum (X - \bar{X})^2}{n - 1}}$$

n is used for descriptions of a sample and n-1 for descriptions of a population derived from a sample

both variance and standard deviation are a function of the population and do not change with sample size

comparing variances of samples is a test to see if they are from the same population: "F test"

coefficient of variation

the standard deviation as a percentage of the mean

allows comparison of the degree of variance between measurements of different quantities

independent of sample size and mean value

$$CV = s \div \bar{X}$$

F-test

variances of data sets can also be compared using the F-test

larger variance is divided by smaller variance

tables provide a confidence limit for the ratio obtained that the data sets are from the same population

standard error of the mean

describes the relationship between the sample mean and the population mean

$$SEM = s \div \sqrt{n}$$

for a normally distributed data set, the population mean has a probability of 96% of falling within 2xSEM of the sample mean

this is used to provide confidence intervals from sample data

confidence intervals are now preferred to p values

SEM falls with increasing sample size

hypothesis testing

null hypothesis (H_0)

"there is no difference between groups studied"

alternate hypothesis (H_1)

"there is a difference between groups studied"

type I error

false conclusion that H_0 is false based on sample
(spurious "significant" result)

probability of a type I error in a given study is called " α "

probability that a type I error has occurred is called "p"

type II error

false conclusion that H_0 is true based on sample
(missing a real difference)

probability of a type II error in a given study is called " β "

β varies inversely with α , depending on study design

significance

an arbitrary decision as to the maximum p value acceptable as evidence that H_0 is false

typically 0.05 for biological studies

power

probability of finding H_0 is false given that it really is false
(finding a real difference)

$$\text{power} = 1 - \beta$$

increases with sample size, α , parametric (>non-parametric) analysis

distributions

binomial

describes the probability distribution for
 a fixed number of independent events
 with two possible outcomes of constant probability
 probability of x successes each of probability π from n trials is

$$P(x; n, \pi) = {}^nC_x \pi^x (1 - \pi)^{n-x}$$

 for large values of n , this approaches normal distribution

poisson

describes distribution of results where an event occurs with a known frequency
 (λ) at random intervals

normal

a symmetrical distribution representing the limit of the binomial distribution
 as n approaches ∞

parametric tests

require

normal distribution
 similar variance between data sets (F-test)
 independent data sets

Student's t-test

compares two groups from the same population to detect a difference in means
 at a specified level of significance

$$t = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{SE_{\bar{X}_1}^2 + SE_{\bar{X}_2}^2}} \text{ or}$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\text{var}_p (\frac{1}{n_1} + \frac{1}{n_2})}} \text{ where } \text{var}_p = \sqrt{\frac{\text{var}_1 + \text{var}_2}{(n_1 - 1) + (n_2 - 1)}}$$

in principle, t is a mean divided by a SEM

t is an expression of the spread of the SEM distribution for a given sample size
 (degrees of freedom). There is a 95% probability that the population mean lies
 within $t \times \text{SEM}$ of the sample mean. t approaches 1.96 as sample size
 approaches ∞ , and is approximated to 1.96 for $n > 30$.

the result t is compared with tables giving minimum values of t for specified
 significance and degrees of freedom

can be performed on paired (dependent) or unpaired data, one- or two-tailed
 depending on whether the alternative hypothesis postulates a direction for
 change of the mean

ANOVA (analysis of variance)

compares the variance of multiple groups
 against the "independent variable" (one-way ANOVA)
 or against each other (Multiple ANOVA)

by calculating an F-ratio

= between-groups variance \div within-groups variance

this identifies the presence of a difference but not which groups cause it

multiple comparison tests

used to identify different groups from ANOVA

based on t-test but modified to diminish the risk of type I error

many eponymous varieties

Bonferroni, Newman-Keuls, Duncan, Dunnett, Dunn, Tukey, Scheffe,
 Least significant difference etc.

non-parametric tests

suitable for ordinal data and data which is not normally distributed

less power than parametric tests

Wilcoxon signed ranks test \approx paired t-test

Mann-Whitney u test \approx 2-tailed t-test

two data sets to compare

all data are ranked 1 to $n_1 + n_2 \rightarrow$ rank sums R_1 and R_2

$$U = n_1 n_2 + \frac{1}{2}(n_1(n_1 + 1)) - R_i$$

U is compared with values for a specified α and degrees of freedom

Kruskall Wallis test \approx ANOVA

Friedman's test \approx Multiple ANOVA

Spearman rank order r

χ^2 test

used for nominal data

compares rates of independent events for significant difference

requires expected rates of more than 5 events in $\geq 80\%$ of cells

(otherwise use Fisher's Exact Test)

$\chi^2 = \sum \frac{(O - E)^2}{E}$ where E is the expected number and O the observed number of events

tables of χ^2 values for levels of significance and degrees of freedom

degrees of freedom = (interventions - 1) x (outcomes - 1)

| | Vomiting | No Vomiting | Total |
|------------|----------|-------------|-------|
| Antiemetic | 10 | 90 | 100 |
| Placebo | 30 | 70 | 100 |
| Total | 40 | 160 | 200 |

$E_{\text{vomiting}} = 20$ in each group, $E_{\text{no vomiting}} = 80$ in each group

$\chi^2 = 5 + 5 + 1.25 + 1.25 = 12.5$, df = 1

Yates correction for 2x2 matrices with fewer than 40 trials reduces the magnitude of (O - E) by 0.5 for each term in χ^2

Fisher's exact test for small sample sizes in 2x2 matrices calculates p regardless of df using the binomial distribution

$$p = \frac{R_1! R_2! C_1! C_2!}{n! n_{11}! n_{12}! n_{21}! n_{22}!}$$

for the example p=0.000248

onerous to calculate for large n

McNemar's test is used for matched data.

odds ratio

the ratio of the incidence of an outcome in an exposed group versus a control group in a case-control study

called a "risk ratio" in a prospective cohort study

a confidence interval associated with an odds ratio does not span 1 if the correlation is significant

odds ratio describes the strength of association as well as its presence

regression and correlation

regression is a mathematical description of the association between two variables the dependent variable is plotted on the Y axis

linear regression produces a relationship $y = ax + b$ such that

$\sum (Y_i - aX_i + b)^2$ for the set of data points is minimized

correlation is a description of the tightness with which a data set matches a regression

$$a = \frac{\sum (X_i - \bar{X})(Y_i - \bar{Y})}{\sum (X_i - \bar{X})^2}$$

$$b = \bar{Y} - a\bar{X}$$

the coefficient of determination, r^2 expresses strength of correlation (from 0 to 1)

$$r^2 = \frac{\sum (aX_i + b - \bar{Y})^2}{\sum (Y_i - \bar{Y})^2}$$

the correlation coefficient is r (varying from -1 to +1)

r^2 expresses the proportion of the value of the dependent variable attributable to the independent variable

Regression assumes a constant variance over the range of data. If variance is not

constant, a correction factor is added to the “least squares” calculation.

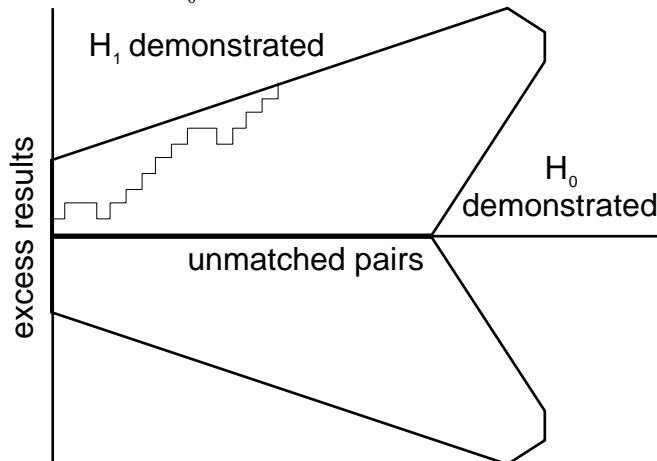
Where the nature of the relationship between dependent and independent variables is known to be of a non-linear nature (e.g. dose-response), a transform can be applied to the data to render the relationship linear (e.g. Hill plot or Lineweaver-Burke plot).

sequential analysis

suitable for paired subjects giving nominal results

e.g. drug vs placebo: vomiting or no vomiting

a curve can be drawn on a graph of “number of untied pairs” versus “excess outcomes”, the boundaries of which mark statistical significance at a specified p value and H_0 demonstrated:



allows termination of a trial as soon as significance is achieved

largely obsolete technique, replaced by interim analysis (with a low p)

Ratio

the number of one of two possible results divided by that of the other
used for comparison between data sets

Rate

the number of one result divided by the total number of data points
applicable to ordinal and nominative data

c. Explain the principles of errors of statistical inference and describe techniques to minimize such errors through good study design.

d. Describe the features of a diagnostic test, including the concepts: sensitivity, specificity, positive and negative predictive value and how these are influenced by the prevalence of the disease in question.

sensitivity

a property of a test, regardless of the population tested

the proportion of subjects having the attribute being tested for who show a positive result for the test

e.g. proportion of hepatitis B infected patients testing positive for hepatitis B surface antigen (HBsAg)

= true positives ÷ (true positives + false negatives)

specificity

the proportion of subjects not having the attribute being tested for who show a negative result for the test

e.g. proportion of patients without hepatitis B testing negative for HBsAg

= true negatives ÷ (true negatives + false positives)

Assessment

[Who is suitable for day surgery?](#)

[Routine preoperative testing](#)

[Risk assessment](#)

[Airway assessment](#)

Who is suitable for day surgery?

Patient

Willing to have the procedure performed and has the understanding to follow discharge instructions

ASA 1 or 2; stable ASA 3 or 4 if the anaesthetist accepts them

Term infants over 12 weeks or ex-prems more than 12 weeks post due date with prior anaesthetic consultation

Surgery

Minimal risk of postoperative bleeding

Minimal risk of postoperative airway compromise

Postoperative pain which can be managed as an outpatient

No special monitoring or nursing requirements

Rapid return to normal oral intake

Social

Responsible person available to transport the patient home in a suitable vehicle

Responsible person at home for the first postoperative night

Preoperative screening tests (Miller Ch. 23)

History and examination are more efficient and safer than routine screening.
No amount of laboratory investigation replaces a pre-anaesthetic consultation.

Young ASA 1 patients almost certainly suffer net harm from screening investigations.

Partly determined by nature of surgery

- Minimally invasive (D&C, cataract, arthroscopy)
- Moderately invasive (laparoscopic surgery, TURP, CEA)
- Highly invasive (cardiac, neuro, major laparotomy)

CXR

- Almost never indicated in asymptomatic patients
- Symptomatic or previously diagnosed pulmonary malignancy, infection
- Symptomatic congestive cardiac failure
- Exposure to tuberculosis
- Disease likely to involve the trachea: e.g. large goitre

ECG

- Asymptomatic, no risk factors: over 45 y (men) or 55 y (women)
- Major surgery, specific risk factors for IHD (smoking, diabetes, hypertension, family history, hypercholesterolaemia): threshold 5-10 y earlier
- Previous abnormal ECG more than 2 months old
- Clinical arrhythmia or symptoms suggesting arrhythmia or ischaemia

FBE

- Surgery requiring group and hold or crossmatch
- Known haematological disorder
- Clinical anaemia or significant bleeding
- Condition associated with thrombocytopenia: PET, chemotherapy

U&E

- Disease associated with renal impairment, e.g. diabetes
- Diuretic or electrolyte therapy

LFT

- Known or symptomatic hepatitis or jaundice
- Alcoholism or suspected drug abuse
- Symptomatic coagulopathy
- Suspected malignancy

Blood glucose

- Diabetes, steroid therapy
- Risk of cerebral ischaemia intraoperatively

APTT, INR

- Symptomatic abnormal bleeding
- Anticoagulant therapy
- Disease associated with coagulopathy: hepatic dysfunction, PET, SLE, ESRF, malnutrition

Urinalysis

- Probably not relevant to anaesthesia

Serology

βhCG

- Possible undiagnosed pregnancy

Hepatitis B, C, HIV

- Established risk factors for blood-borne virus transmission and with patient counselling and consent

Risk assessment

Goldman criteria

Independent predictors of perioperative morbidity

- Age >70 y
- MI in previous 6 months
- S₃ or gallop or ↑ JVP
- Rhythm other than sinus
- Aortic stenosis
- Abnormal ABG, U&E
- Emergency thoracic or abdominal surgery

Cardiovascular risk

Dipyridamole thallium imaging

- Useful in vascular patients if one or two of
 - Q waves, VEs, diabetes, age >70 y, angina (Eagle et al.)
- Where positive result carries RR of 10 of cardiac morbidity
- No risk factors → little contribution to risk assessment
- Three or more → coronary angiography indicated

Ambulatory ECG

- Similar predictive value to DTI
- Highest risk patients often have baseline abnormalities which preclude testing

Dobutamine stress echo

- Similar to DTI, possibly better predictive value

Cardiac catheterization

- In PVD patients
 - 8.5% normal coronaries
 - 60% >70% stenosis

Cardiopulmonary exercise testing

- Basal $\dot{V}O_2$ commonly 3.5 ml/kg/min
- Postoperative $\dot{V}O_2$ requirement 5-7 ml/kg/min
 - Poor O₂ extraction in healing tissue, so equivalent to 8.5-11 ml/kg/min
- Testing involves measuring $\dot{V}O_2$ and $\dot{V}CO_2$ over a range of exercise load
 - Rise together up to anaerobic threshold ($\dot{V}O_2$ at onset of anaerobic metabolism)
 - Onset of anaerobic metabolism causes $\dot{V}CO_2$ to rise in excess of $\dot{V}O_2$
 - Point of flexion on graph of $\dot{V}O_2$ vs $\dot{V}CO_2$
- AT <11 ml/kg/min moderate risk, <8 ml/kg/min high risk
- Claimed RR of 42 for myocardial event in high risk patients

History

- CABG with no symptoms: similar to never had symptoms
- PTCA or stents: little evidence

Pulmonary risk

Airway assessment

Views of the pharynx (Mallampati)

With head in neutral position and tongue inside mouth:

- I tonsillar and pharyngeal folds visible
- II tonsillar folds and all of soft palate visible
- III part of soft palate visible
- IV hard palate only visible

Higher grade is associated with greater difficulty in intubation as are poor neck mobility, small jaw, large tongue, long narrow mouth and thyromental distance <6.5 cm.

Sensitivity and specificity of MP ≥ 3 as a predictor of difficult intubation (CL ≥ 3) is 60-70%

Combination scoring systems (including weight, TMD, mouth opening etc.) approach 95% sensitivity and specificity

Views of the cords (Cormack and Lehane)

- I cords totally visible
- II posterior part of cords visible
- III epiglottis visible but not cords
- IV epiglottis not visible

Higher grade is associated with difficulty in intubation.

Complications

[Intraoperative hypotension](#)

[Anaesthesia Related Mortality in Australia 1994-96](#)

[Postoperative confusion](#)

[Pulmonary aspiration in anaesthesia](#)

[Perioperative stroke](#)

[Respiratory depression under GA](#)

[Adverse effects of laryngoscopy](#)

[Complications of, benefits of, indications for IVs, CVCs, PA catheters, arterial lines](#)

[Perioperative myocardial ischaemia](#)

[Arrest protocol](#)

[Malignant hyperthermia](#)

[Post-operative nausea and vomiting](#)

[Crisis Management in Anaesthesia](#)

Intraoperative hypotension

Differential diagnosis

Airway and breathing

- Desaturation, hypoxia

- Pneumothorax

- High circuit pressure

Cardiac

- Arrest

- Arrhythmia with low output

- Failure

- Ischaemia or infarction

- Vagally mediated bradycardia

Circulation

- Hypovolaemia

- Obstructed venous return

- Sepsis with vasodilatation

Drugs

- Induction agents, volatile agents, vasodilators

- Incorrect dose or rate of infusion

- Regional technique: sympathetic blockade, local anaesthetic toxicity

- Anaphylaxis

Equipment

- Drug administration equipment failure

 - Anaesthetic machine, syringe pumps

- Monitoring equipment failure: artifact

Fluids, electrolytes, metabolism

- Transfusion reaction, Haemaccel reaction

- Hypoglycaemia, Addisonian crisis...

- Hypothermia

Surgical

- Blood loss

- Embolism: air, fat, cement

- Obstruction to venous return

- Specific surgical complications

 - Clamp release, great vessel surgery, cardiac compression

Anaesthesia Related Mortality in Australia 1994-96

Classification

- Deaths attributable wholly or partly to anaesthesia
 - Under anaesthetist's control
 - Doubtful whether under anaesthetist's control
 - Combined anaesthetic and surgical factors
- Deaths in which anaesthesia played no part
 - Entirely due to surgical factors
 - Inevitable deaths despite correct anaesthetic and surgical management
 - Fortuitous deaths
- Unassessable deaths
 - Despite considerable data
 - Due to inadequate data

1994-96

Deaths in Australia 1875 106.8 per million population
Related to anaesthesia 135 7.7 per million population
7.2% of deaths considered
15.9 per million procedures (1/63,000)

Major factors

| | |
|-----------------------------------|----|
| Anaesthetic technique | |
| Airway | 16 |
| Ventilation | 9 |
| Other | 48 |
| Anaesthetic drugs | |
| Dosage | 45 |
| Selection | 18 |
| Inadequate reversal | 3 |
| Adverse reaction | 2 |
| Preoperative | |
| Assessment | 40 |
| Management | 13 |
| Anaesthetic management | |
| Crisis management | 21 |
| Inadequate monitoring | 12 |
| Equipment failure | 3 |
| Inadequate supervision/assistance | 19 |
| PA catheter | 5 |

Gender

Male 77, female 58

Age

≤40 y 6 (4.4%)
>60 y 117 (86.7%)

ASA status

| | |
|---|----|
| 1 | 0 |
| 2 | 13 |
| 3 | 66 |
| 4 | 45 |
| 5 | 11 |

Postoperative confusion

Differential diagnosis

- Respiratory failure: hypoxia

- Cardiovascular

 - Hypotension, arrhythmia, cardiac ischaemia, anaemia

- Neurological

 - Cerebral bleed, embolic event, long-standing dementia or degenerative disease particularly in unfamiliar environment and in pain

- GIT

 - Hepatic decompensation, gut ischaemia

- Renal

 - Acute renal failure, uraemia

- Endocrine or metabolic

 - Electrolyte disturbance, hypoglycaemia, Cushing's syndrome, hypercalcaemia

- Septic

 - Infection: respiratory or urinary most characteristic

- Drug-related

 - Withdrawal of benzodiazepines, narcotics, alcohol, other sedatives

 - Administration of sedatives, analgesics, antiemetics

 - Adverse reaction to anaesthetic agents

History

Examination

- HR, BP, T, RR, SpO₂

- General examination focussing on signs of sepsis or cardiorespiratory problems

- Neurological examination for focal signs and to assess degree of confusion

Investigation

- Directed by history and examination findings

- FBE, U&E, LFT, glucose, ABG, CXR, ECG, urine dipstick

- Consider CT head if no other cause found

Management

- Correction of cause

- Acutely: supportive care, reassurance, prevention of self-harm or wandering

Pathophysiology

- Particle related

- Acid related

 - Critical pH 2.5 and volume 0.4 ml/kg may be untrue

 - HCl LD₅₀ 1.0 ml/kg in monkeys

- Process

 - Burn within 5 s

 - Neutralized by 15 s

 - Desquamation with 6 h

 - Alveolar type II cells most sensitive

 - Second phase: inflammatory mediators

 - Local effect ARDS, systemic effects

- Bacterial related

 - Mixed aerobes and anaerobes

 - Klebsiella*, *P. aeruginosa*, *E. coli*, *S. aureus*

Detection

- No specific tests if aspiration is not witnessed and no gastric contents from ETT

- Bronchoscopy, lavage, brushing may yield evidence

- CXR may show signs after hours

- V/Q scanning in children

Incidence

- 1 in 2000-3000

- Swedish study of 185385 GAs

 - Four fatalities

 - One ASA IV ICU patient, two failed intubation during resuscitation and one kyphoscoliosis

 - Non fatal: 47% pneumonitis, 17% ventilation

- Mayo Clinic study of 215488 GAs

 - Three fatalities in ASA III-IV

- Obstetric patients

 - Incidence around 1 in 900 for Caesarean section

 - Negligible mortality (denominator unknown)

Prevention

- No useful correlation with BMI, smoking, fasting, alcohol use, volume, pH

- Fasting

 - Intermediate markers used in studies (volume and pH)

- Drugs

 - Intermediate markers used

 - Cost-benefit analysis impossible

 - Likely minimal effect on morbidity or mortality

- Anaesthetic technique

 - Rapid sequence induction recommended

 - Quality of cricoid pressure is variable

 - Overuse of the LMA has potential to increase incidence of aspiration

Treatment

- Head-down, suctioning, intubation, tracheal suctioning

- Ventilation with 100% oxygen

- No proof for steroids or antibiotics

Conclusion

- Minimal demonstrated mortality or morbidity

- Changes in anaesthetic practice have probably contributed to this

- No proven benefit from prophylactic measures

Perioperative stroke

Kam PC, Calcroft RM. Peri-operative stroke in general surgical patients. *Anaesthesia* 1997 **52**: 879-883.

Stroke

Rapidly developing episode of focal or global loss of cerebral function with symptoms lasting more than 24 hours or leading to death

Less than 24 hours: TIA

Peri-operative stroke commonly defined as occurring intra-operatively or within 3-30 days postoperatively

Epidemiology

Third most common cause of death

Annual incidence 1-2 per 1000 population

Rises with age: 3 per 1000 at 60 y, 10-25 per 1000 at 80 y

Acute mortality 15-30%, 45% independent after 1 year

Surgery

Incidence

General surgery 0.2-0.7% (six times background risk)

With previous stroke 2.9%

Peripheral vascular surgery 1-3%

Carotid surgery 3-5%

Usually between 2 and 10 days postop

Natural history

Acute mortality 26%

Aetiology

42% emboli of cardiac origin (33% AF)

Vascular emboli from plaque

In situ thrombosis (hypercoagulable state)

Risk factors

Hypertension, cardiac disease (AF), PVD, diabetes, age

Carotid disease has not been established as a risk factor for periop stroke

Prevention

Preoperative

Identify risk factors and modify if possible (e.g. revert AF, anticoagulate)

Consider heparinization of patients on warfarin

Delay surgery 4-6 weeks after a stroke

Intraoperative

Maintain oxygen delivery

Normotension, maintain Hb, high PaO₂, normocapnia

Normal blood sugar

Avoid excessive neck rotation or extension

Anaesthetic technique has not been shown to cause a difference

Postoperative

Avoid hypotension

Avoid dehydration and hypercoagulability

Control anticoagulation

Respiratory depression under GA

Definition

Inadequate ventilation caused by an abnormality in control of respiration
Manifest as rising PaCO₂ or falling PaO₂

Respiratory control

Afferent

Peripheral chemoreceptors predominantly for PaO₂

Carotid bodies via IX

Aortic bodies via X

Central chemoreceptors for PaCO₂ (via CSF pH)

Lung receptors

Pulmonary stretch receptors, irritant receptors, J receptors

Other receptors

Nose and upper airway

Joint and muscle, γ afferents

Arterial baroreceptors

Pain and temperature sensation

Efferent

Central integration: cortex, hypothalamus, pons, medulla

Spinal cord: dorsolateral UMN system

Anterior horn cells: α and γ fibres

Muscles

Diaphragm, intercostals, accessory muscles

Signs

Spontaneously ventilating anaesthetized patient

↑ ETCO₂, ↓ SpO₂, ABG findings

Ventilated patient (underventilation)

Same gas changes

Mild hypercapnia: sympathetic stimulation

Profound hypoventilation

Myocardial irritability and depression, cyanosis, circulatory collapse

Causes

Anaesthetic

Drugs

Central

Induction agents, volatiles, opioids

All ↓ response to PaCO₂

Supplemental O₂ in patients reliant on hypoxic drive

Spinal cord

High block, total spinal

Peripheral nerve

LA blockade of phrenic nerve (e.g. deep cervical block)

Neuromuscular

Muscle relaxants, volatiles, Mg²⁺ etc

Physiological change

Hypothermia, hypoglycaemia

Hyperventilation

Surgical

Interruption of any part of reflex control e.g. brainstem

Mechanical disruption of thorax

Airway obstruction, pulmonary blood flow obstruction

Patient

OSA

CVA

Apnoea of newborn

Adverse effects of laryngoscopy

Mechanical

- Trauma to teeth, dental work, tongue, pharynx, epiglottis
- Compression of soft tissues: lip, gums
- Eye injury
- Cervical spine injury if preexisting instability

Physiological

Airway

- Coughing with inadequate anaesthesia
 - ↑ ICP, IOP
 - Damage if open eye injury or cerebral vascular anomaly
- Laryngospasm
- Vomiting, aspiration

Neurological

- ↑ CBF together with ↑ ICP
- May cause vagal response
- Commonly causes sympathetic response

Cardiovascular

- Usually tachycardia, hypertension
 - ↑ myocardial O₂ demand, risk of ischaemia
- Bradycardia if vagal response, more common in children

Pulmonary

- Bronchospasm

Drug-related

- Hypnotics and muscle relaxants

Failure to secure the airway

- Hypoxia, aspiration, death

Minimizing adverse effect

Patient selection

- Airway assessment
- Alternative anaesthetic techniques if laryngoscopy is likely to be problematic
- Removal of dentures

Equipment

- Suitable sized and well-maintained airway equipment
- Gentle use of laryngoscope

Drugs

- Blunt airway response
 - Local anaesthetic to upper airway
 - Nerve blocks to IX, superior laryngeal nerve
 - Prophylactic IV lignocaine, opioid
- Blunt haemodynamic response
 - β-blocker, clonidine, vasodilators
- Reduce airway reactivity
 - β₂ agonists, anticholinergics, steroids
- Induction agents
 - Suitable doses and adequate time for muscle relaxant to work

Complications of, benefits of, indications for IVs, CVCs, PA catheters, arterial lines.

IV

Complications

Cannula and insertion

- Pain of insertion

- Vessel damage, thrombosis, haematoma, haemorrhage, local irritation

Through the cannula

- Infection, septicaemia

Fluids

- Fluid overload, incorrect fluid: electrolyte disturbance, transfusion reaction, hypothermia

Drugs

- Incorrect drug or dose, incorrect route of administration, administration too rapidly

- Extravasation with vessel damage or cannula misplacement

Dressing

- Skin reactions, allergy

Benefits

Drug administration

- Rapid, 100% of drug delivered, more secure and reliable than oral or PR administration

- Suitable for emergency and resuscitation drugs

Fluids

- In fasting patients or patient with ileus, allows hydration and electrolyte supplementation, nutrition possible

Other uses

- May allow blood sampling with large cannula or in infants

Indications

- Requirement for parenteral fluids or drugs where

- Rapid effect is required

- Volume is too large or agent unsuitable to give subcutaneously

- Possible requirement for resuscitation drugs e.g. during mask anaesthetic

CVC

As for IV, plus

Complications

Cannula and insertion

Insertion technique

- Arterial or other vessel damage

- Damage to nerves or other viscera (e.g. femoral insertion)

- Pneumothorax

- Arrhythmia related to wire or cannula irritating endocardium

- Loss of guidewire

Cannula

- Vessel wall damage: haemothorax, pericardial tamponade

- Misplacement into cerebral or other vessels

Benefits

Drug administration

- Highly secure access

- Suitable for irritant or hypertonic agents requiring rapid mixing

Fluids

- Suitable for TPN

Measurement of CVP provides information to guide fluid management

Other

Suitable for venous blood sampling, normovolaemic haemodilution

Useable for 7 days up to months depending on cannula type

Indications

Secure IV access (e.g. TIVA)

Prolonged access (e.g. chemotherapy)

Need for CVP measurement (e.g. large fluid shifts with major laparotomy)

Inadequate access elsewhere

PA catheter

As for CVC, plus

Complications

Cannula and insertion

Large sheath increases risk of vessel damage

Greater risk of arrhythmia

Potential for injury to right heart, PA, smaller pulmonary vessels

Balloon

May injure surrounding vessel

Expands with N₂O

Site of entry of gas into circulation

Through the cannula

Cardiac output boluses risk bolus injection of other agents

Benefits

Measurements

CVP, PAP, PAOP, CO, S_mvO₂, SVR, PVR, MRO₂

May guide fluid and inotrope management

No proven benefit

Fluids

Sheath allows rapid infusion

Indications

Requirement for measuring PA pressures or cardiac output or SVR

e.g. pulmonary hypertension, septic shock

Perioperative myocardial ischaemia

Epidemiology

- Most common cause of perioperative (and non-periop.) death
- Occurs most frequently postoperatively (peak day 3)
- Symptoms obscured by surgical pain or analgesia (silent)

Myocardial oxygen balance

Demand

- Heart rate
- Diastolic volume (preload)
- Contractility
- Blood pressure (afterload)

Supply

- Coronary blood flow
 - Diastolic duration
 - Coronary perfusion pressure
 - Coronary vessel size and patency
- Oxygen content
 - Haematocrit
 - PaO₂

Triggers

Tachycardia

Anaemia

- Some evidence for maintaining Hb >90 g/l in CAD patients
- Hb ≥70 g/l well-tolerated in normal patients

Monitoring

ECG

Subendocardial ischaemia causes ST elevation

Transmural ischaemia causes ST elevation

Criteria for ischaemia

- Horizontal or downsloping ST depression ≥1 mm, 60-80 ms after J point
- Duration ≥1 min
- Separation from other episodes by ≥1 min of normal baseline

Sensitivity (intraoperative)

| | |
|-------------------------------------|-----|
| V ₅ | 75% |
| II, V ₅ | 80% |
| II, V ₄ , V ₅ | 96% |

Advantages

- Least expensive, most automated

Limitations

- RBBB, LBBB, AF, LVH with strain interfere with interpretation

TOE

Segmental wall motion abnormality with ischaemia

Advantages

- Most sensitive: earlier signs and more sensitive than ECG
- Information about regional ischaemia, valve function, CO

Limitations

- Expensive equipment and experienced operator required
- Not well-tolerated without sedation

PA catheter

Rise in PAOP or change in waveform (e.g. mitral regurgitation) with ischaemia

Advantages

- Information about CO

Limitations

- Less sensitive than ECG or TOE
- Expensive, invasive

Arrest protocol

Cardiac arrest

BLS algorithm

Secure airway, ventilate with 100% O₂

Praecordial thump

Attach defibrillator/monitor, IV access

Assess rhythm and pulse

VF or pulseless VT

Defibrillate up to 3 times

200 J, 300 J, 360 J first time

360 J subsequent times (4 J/kg)

CPR up to 1 min, then reassess rhythm and pulse

non VF/VT

CPR up to 3 min, then reassess rhythm and pulse

During CPR

Verify electrode, paddle and ETT placement

IV access if not present

Adrenaline 1 mg every 3 min

Consider atropine, K⁺, lignocaine, bicarbonate if indicated

Consider reversible causes

Hypoxia, hypovolaemia, hypothermia, K⁺, Mg²⁺, Ca²⁺, tension pneumothorax, tamponade, drug toxicity, thromboembolism

Malignant Hyperthermia

Miller 5th Edition Chapter 27

History

- 1929 Ombredanne's syndrome: post-op hyperthermia and pallor
- 1960 Denborough & Lovell case report in Australia
- 1966 Stress-susceptible swine described
- 1975 Dantrolene use described in swine and trialled in humans

Epidemiology

- 1 in 62,000 anaesthetics with triggering agents

Aetiology

Normal excitation-contraction coupling

- ACh binds to nicotinic receptors and opens cation channels
- Na⁺ influx raises membrane potential
- Voltage-gated Na⁺ channels open: depolarization
- Voltage-gated Ca²⁺ channels in T tubules open (L-type channels or DHPR)
- Physical linkage to sarcoplasmic reticulum ryanodine receptor (Ca²⁺ channel)
- Ca²⁺ released from SR activates myofibril contraction
- Rapid reuptake of Ca²⁺ into SR and binding to calsequestrin
- Termination of contraction

MH defect

- Ry₁ coded on chromosome 19 in humans
 - Multiple mutations described covering fewer than 50% of MH families
- Defects also described on chromosome 17 (Na⁺ channel, L-type Ca²⁺ channel), chromosome 7 (L-type Ca²⁺ channel), chromosome 1 (DHPR)
- Functional abnormality is complex at a molecular level
 - Increased tendency for Ca²⁺ release from SR
 - Decreased inhibition by Mg²⁺ and Ca²⁺
- Sustained high sarcoplasmic Ca²⁺ level causes sustained contraction, aerobic and glycolytic metabolism and thus rigidity, acidosis, hyperkalemia...

Risk factors

- Family history of MH
- King-Denborough syndrome, central core disease

Clinical Features

- Triggered by volatile anaesthetics or suxamethonium, but not consistently
 - Rise in muscle intracellular Ca²⁺, rigidity
 - Venous ↓ pH, ↓ PO₂, ↑ PCO₂, ↑ lactate, ↑ [K⁺]
 - Subsequent ↑ HR, ↑ BP, ↑ T
 - Temperature rise up to 1°C per 5 min
- Secondary DIC, neurological dysfunction, renal and cardiac failure and arrest
- Clinical syndrome may be indistinguishable from other causes of hypermetabolism
- Masseter spasm
 - Caused by suxamethonium
 - Present to a variable extent in most patients
 - Due to slow tonic fibres in masseters and lateral pterygoids
 - Increased risk of MH

Acute treatment

- Institution protocol
- Call for assistance
- Clean anaesthetic machine, hyperventilate with 100% O₂
- Cold fluids and packs
- Curtail surgery
- Dantrolene
 - Lipid soluble hydantoin
- Pharmacokinetics

Low water solubility
20% oral bioavailability
 V_d 0.5 l/kg
Clearance 0.6 ml/min/kg
 $t_{1/2\beta}$ 12 h
Therapeutic concentration $>3 \mu\text{g/ml}$
Metabolized to 5-OH dantrolene (50% potency)

Pharmacodynamics

Molecular action uncertain
Inhibits Ca^{2+} release from sarcoplasmic reticulum without inhibiting uptake
Limits excitation-contraction coupling in skeletal muscle

Adverse effects

Muscle weakness
Negative inotrope
 $\uparrow [\text{K}^+]$
Electrolyte and volume disturbance due to water and mannitol load

Indications

Malignant hyperpyrexia
Also used in
Neuroleptic malignant syndrome
MDMA overdose, serotonin syndrome with hyperpyrexia
Muscle cramps

Clinical use

Ampoules of 20 mg with 3 g mannitol, pH 9.5
Dissolved in 60 ml water \rightarrow 1 mg/3 ml
Dose 1 mg/kg up to 10 mg/kg
= up to 30 ml/kg free water, 1.5 g/kg mannitol

Post-operative ICU, supportive treatment of other abnormalities

MH-safe anaesthesia

Safe agents

Regional (amide LA almost certainly safe)
 N_2O , non-depolarizing relaxants, propofol, barbiturates, etomidate, ketamine, opioids, benzodiazepines

Follow up

Testing family members (through RMH)
Two protocols (North American and European) for muscle biopsies
 Ry_1 testing not sufficient because of heterogeneity in humans
<http://www.mhaus.org/>

Postoperative nausea and vomiting (PONV)

Preoperative

Assessment

- Detailed history of previous anaesthetic problems and nature of surgery
- Severity of PONV, duration, delay in discharge
- Examine previous anaesthetic charts if available
 - Particularly if there has been a nausea-free anaesthetic
- History of drug sensitivity, particularly narcotic analgesics

Preparation

- Minimal safe fasting time
- Preoperative hydration
- Reassurance

Premedication

- Anxiolytic, antiemetic
 - Lorazepam, ranitidine, metoclopramide
 - Consider anticholinergic e.g. scopolamine (risk of dysphoria)

Transport

- Gentle ride, sitting up
- Consider walking to theatre

Intraoperative

- Avoid GA if feasible: regional blockade
 - But also avoid hypotension
- Avoid N₂O, opioids, volatile agents
 - Propofol TIVA may be best choice for GA
- Avoid muscle relaxation if possible, in order to avoid neostigmine
 - If neostigmine unavoidable, give slowly
- Avoid specific emetogenic drugs: e.g. ergometrine
- Give prophylactic antiemetic
 - Ondansetron and dexamethasone
- Give adequate hydration
- Empty stomach and deflate insufflated gas prior to awakening

Postoperative

- Regional blockade for analgesia
 - Otherwise aim for opioid-free analgesic regimen
 - Paracetamol, NSAID, ketamine
- Regular antiemetic, rescue therapy available
- Continue IV hydration

Crisis Management in Anaesthesia

COVER algorithm derived by Runciman from AIMS reports (<http://www.apsf.net.au/>)

Based on incident reports collected since 1988

Performs better than the anaesthetist in 20-30% of incidents

Performs worse in 1%

Not always the best strategy if the cause of a problem is obvious

Must be considered at the same time as resuscitation/ABCD

C

Circulation

Pulse, BP, ECG

Colour

Saturation, skin colour

O

Oxygen flow

100% O₂, increase flow

Oxygen concentration

Oxygen monitor, gas analyzer

V

Vaporizer

Turn off (also remember intravenous drug infusions)

Ventilation

Change to manual ventilation, feel compliance and flow

E

Endotracheal tube

Check position, cuff

Eliminate machine

Change to Laerdal bag

R

Recheck monitors

Review

Causes of incidents

30% equipment/human interface problems

14% contributed to by haste

8% drug problems

8% equipment failures

Vigilance mnemonic (SCARE)

Scan every five minutes

Check on the unexpected

Alert &

Ready if a problem is suspected

Emergency mode in a deteriorating situation

Pain

[Complex Regional Pain Syndromes](#)

[Problems related to pain management](#)

[Chronic pain](#)

Complex Regional Pain Syndromes

Reflex sympathetic dystrophy (CRPS Type I)

Continuous pain in a portion of an extremity after trauma which may include a fracture but does not involve a major nerve (causalgia), associated with sympathetic hyperactivity.

Aetiology

Probably peripheral nervous system disorder, possible CNS component

Presentation

Usually follows mild trauma to an extremity

Weeks later continuous and burning pain exacerbated by movement, touch or stress

Initial vasodilation, hyperhydrosis and oedema

Skin atrophy, cool, red skin may be present

Underlying bone may undergo disuse atrophy ("Sudeck's atrophy")

Late vasospastic features: cool, pale, cyanosed, atrophic, Raynaud's phenomenon, joint stiffness

Spontaneous remission is rare

Therapy

Pharmacological

Sympathetic blockade with LA

Early high-dose steroids

Surgical

Sympathectomy

Physical

Physiotherapy

Psychological

Depression a common complication

Causalgia (CRPS Type II)

Similar to type I except a major nerve is injured

Problems related to pain management

respiratory

local pain and muscle spasm ↓ ventilation
ileus, other surgical cause → diaphragmatic splinting
↓ FRC, ↑ airway closure, basal collapse, shunt, infection
“autoPEEP” with grunting respirations ↑ intrathoracic pressure
↑ venous stasis, ↓ venous return

cardiovascular

↑ sympathetic outflow
↑ HR, contractility, myocardial O₂ demand, risk of ischaemia
↑ coagulability (stress response)

GIT

ileus exacerbated by opiates, not by epidural LA

urinary

retention from epidural or systemic opiates

neuroendocrine

stress response
↑ cortisol, aldosterone, glucagon, ADH etc.
adaptive value uncertain

musculoskeletal

persistent spasm → alteration in function, less effective rehabilitation

CNS

depression, anxiety, poor sleep
chronic pain syndromes

Chronic pain

Definition and transmission details in [Pain Pharmacology \(2.B.3\)](#).

Components of pain

- Noxious stimulus mediated by patient factors and modified by emotional state
- Influenced by situation and behaviour
- Stimulus-response relationship is modified at many levels
 - Periphery, cord, brainstem, cortex
 - Multiple stages of processing → multiple sites of therapy

Aetiology

- Usually arises from acute pain
- High-risk scenarios
 - Post-herpetic, multitrauma, thoracotomy, amputation, mastectomy

Evidence-based practice

- Very little evidence, little concordance with practice
 - TENS, guanethidine IVRA: proven ineffective
 - Articular steroids, spinal cord stimulators: no evidence
 - NSAIDs, epidural steroids, radio-frequency neurotomy, CBT: positive evidence

Management approach

- Multidisciplinary assessment usually appropriate
 - Patients usually have had multiple opinions
- Medical, physio, psychological...
- Coordinated plan
 - Pharmacology, nerve blockade, nerve stimulation, surgery, psychology
- Medical model can relieve pain without affecting suffering or function
- CBT can improve suffering and function without change in pain

Specific therapies

- Conversion of narcotics
 - Morphine
 - 0.1 mg IT = 30 mg IM = 100 mg po
 - Acute pain (surgery) with chronic morphine use: approx. triple dose
- Neuropathic pain
 - Anticonvulsants, tricyclics often effective
 - Gabapentin > baclofen > valproate > phenytoin, carbamazepine
 - Amitriptyline useful coanalgesic
 - Calcitonin highly effective for phantom pain in first 48 hours
 - 3 U/kg over 30 min q8h for 3 doses, check Ca^{2+} levels
 - Sympathetic blocks often effective early (stellate, coeliac, lumbar, others)
 - Type I agents may be effective (lignocaine, mexiletine)

Miscellaneous anaesthesia

[Position](#)

[Sterilization](#)

[Pros and cons of anaesthetic rooms](#)

[Intravenous anaesthesia](#)

Trendelenberg Position (head-down)

Adverse effects

CVS

↑ CVP, ↑ HR, ↑ CO

May precipitate failure, APO

May cause hypotension on return to level position

Respiratory

Abdominal contents press on diaphragm

↓ FRC, ↓ VC, ↓ compliance

↑ ventilation pressures in IPPV

↑ V/Q mismatch

PEEP may be helpful

Neurological

Neuropraxia from pressure

Shoulder rests for steep Trendelenberg

Brachial plexus and accessory nerve

Stirrups in gynae laparoscopy

Superficial peroneal nerve

Sterilization

Why

- Prevention of disease transmission
- Medicolegal responsibilities
- Recent cases: HIV, Hep C transmission by anaesthetic techniques
- Protection of patients and staff

Crossinfection

- Requires sufficient numbers of organisms transferred from patient to patient
- Wet equipment usually harbours sufficient pathogenic organisms
- Transfer has been shown to occur in the past
 - e.g. *Pseudomonas*, *Streptococcus* from humidifiers

High risk areas

- Equipment close to airway
- Organisms up to 1 m down tubing, mass transfer with droplets of sputum or vomitus
- Immune suppression related to anaesthesia and surgery: cellular, humoral and mechanical protection broken down.
- Some techniques limited by practicalities: airway handling and anaesthetic machine operation
- Cross infection is nonetheless rare

Risks of universal precautions

- Reassembly errors, misconnections, mechanical wear
- Latex allergy, exposure to antiseptic agents
- Cost

Sterilization techniques

- Disposable equipment: expensive, wasteful, poor quality
- Filters
- Good handling practices
- Cleaning and sterilization between cases
 - Sterilization produces known rates of elimination of all organisms
 - Disinfection is a gentler cleaning process without guaranteed sterility

Sterilization

- First step is cleaning: manual or dishwasher in a designated "dirty" area by dedicated staff
- Sterilization by heat or gas (ethylene oxide) or radiation
- Moist heat is autoclaving: for all reusable metal and plastic components
 - Cheap, quick, non-toxic
 - Specifications: commonly 134°C for 3 minutes with high pressure steam
 - Pre-wrapping in packs which can then be stored
 - Degrades: sharp edges, drugs, electrical circuits

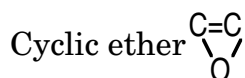
Dry heat

- 150-180°C with convection for 30-60 min
- Less blunting of needles

Gamma radiation

- Co⁶⁰ emits γ rays
- Suitable for packaged items which may be heat-labile
- Used commercially

Ethylene oxide used in industry for sensitive equipment



- Toxic, explosive, requires dry equipment, airing after sterilization
- Contamination causes burns to mucous membranes

Disinfection

- By moist heat (Pasteurization) or liquid chemicals
- Pasteurization: hot water 70-90°C for specified time, drying with hot air

Suitable for more delicate equipment: laryngeal masks (can also be sterilized)
Liquid chemicals: last resort for equipment which can't be sterilized
Cleaning surfaces, scopes
Common agents: glutaraldehyde, 70% alcohol, sodium hypochlorite
Requires cleaning of surfaces first, rinsing afterwards
Fairly cheap and quick, corrosive to metals, alcohol flammable, toxic fumes

Filters

Not 100% effective, particularly if wet
Hygroscopic: large pore, high resistance if wet
Hydrophobic: small pores, allow fluids to pass in small quantities, larger dead space
Can obstruct the circuit
Can't be used with heated humidifiers
Troublesome in prolonged prone cases: secretions into filter causes obstruction

Housekeeping practices

Hand washing
Between cases, after patient contact, before drawing up next patient's drugs
Gloves
Worn for all patient contact and removed immediately afterwards with hand washing between
Clothing
Should be changed if dirty or between lists
Masks
Partly for self-protection: e.g. orthopaedics
Placement of dirty items
Airway equipment tray separate from drug tray
Multiuse of ampoules
Requires one operator and rigid procedure (if at all)
Sharps handling
Direct from use to sharps container

Where is cleaning done?

Preliminary cleaning by tech in theatre
Sterilization either in CSSD or in theatre (depending on required turnaround time)
Verification system needs to be in place

Some things are just washed

T-piece scavenge, laryngoscope handles, anaesthetic machine
Some soda lime cannisters

Pros and cons of anaesthetic rooms.

Advantages

- Allows preparation of the next patient while the theatre is in use, reducing turnaround time
 - Preanaesthetic consultation (if not previously completed)
 - Insertion of lines and application of monitoring
 - Establishment of blocks
- Allows performance of minor procedures during a case
 - CVC insertion, lumbar puncture etc.
- Allows induction of anaesthesia in a less noisy and threatening environment than the OR

Disadvantages

- Requires duplication of monitoring and some equipment
 - If general anaesthesia is induced, extensive monitoring is mandated by college policy
- May require extra staffing for either sedation or general anaesthesia
- If used for induction, transport into theatre requires a period of apnoea and inadequate monitoring

College Policy (relevant bits)

Recommended Minimum Facilities for Safe Anaesthetic Practice in Operating Suites (T1)

- Anaesthetic machine for each anaesthetizing location
 - Safety devices required on every machine
- Separate emergency ventilating device
- Suction
- Monitoring, airway, IV... equipment
- Availability of difficult intubation, emergency... equipment

Sedation for Diagnostic and Minor Surgical Procedures (P9)

- Provided that **rational verbal communication** to and from the patient is continuously possible during the procedure, the operator may provide the sedation and be responsible for the care of the patient.
- Continuous pulse oximetry with alarms must be used on patients undergoing intravenous sedation.

Intravenous anaesthesia

Closed-loop control

Drug infusion → patient → effect → monitor of effect → pharmacokinetic model ↩

Feasible for muscle relaxants, blood-pressure control

“Monitor” is difficult to build for hypnotic agents

Median EEG frequency, evoked potentials, bispectral index...

Computed pharmacokinetic model is substituted in target-controlled infusion devices

Pharmacokinetic models

Polyexponential model used for drug elimination

$$C(t) = I(t) * \sum_{i=1}^n A_i e^{-\lambda_i t}$$

where C is concentration, I is infused drug, t is time

Usually not more than three compartments required

Compartments do not necessarily represent physiological spaces

Pharmacodynamic modelling

Relating an effect to putative biophase concentration

$$D_{\text{biophase}}(t) = \frac{F(E(t), P)}{C_{\text{plasma}}(t)}$$

where D is disposition, E is effect, F is a function relating effect and other parameters (P) to C_{biophase} .

$D_{\text{biophase}}(t)$ is modelled as a single term exponential equation

$$D_{\text{biophase}}(t) = k_{e0} e^{-k_{e0} t}$$

So effect over time of a bolus of drug can be modelled using “time to peak effect” and $t^{1/2} k_{e0}$.

Application

By deconvoluting the functions for pharmacokinetic and pharmacodynamic modelling and limiting the solutions to those involving only positive infusion rates ($I(t) > 0$), it is possible to derive an function for infusion rates to target a plasma concentration or end-effect

Determining target plasma levels

An equivalent to the MAC of volatile agents for use with intravenous agents has been difficult to determine.

MIR is minimum infusion rate for a given effect in 50% of a population

Dependent on infusion duration for most agents

C_{50} is a steady-state plasma concentration for a given effect in 50% of a population

Difficult to determine as steady-state plasma levels take a long time to achieve

Instead commonly based on pseudo-steady-state using mathematical modelling

Plasma concentration required for a given reduction in MAC

Determined for opioids for hypnotic and analgesic end-points

More useful for practical application

Calculating initial bolus

Bolus dose can be based on desired concentration and volume of distribution

Using the Vd for the central compartment produces a dose which achieves the desired concentration only for an instant

Using the Vd_{ss} gives a much larger dose with gross overshoot at the time of peak effect

Vd_{pe} , the calculated effective Vd at the time of peak effect, gives a reasonable dose for an initial bolus

Vd_{pe} for fentanyl is about 1 l/kg, propofol 0.5 l/kg, remifentanyl 0.25 l/kg

Calculating infusion rate

At $t = \infty$, maintenance infusion rate = target conc. x clearance

At any earlier time, rate must be higher to account for redistribution

Can be calculated from multicompartment distribution model

Or from nomogram based on model

Time to recovery

At $t = \infty$, recovery time is determined by terminal elimination half-life and total drug in body

At any earlier time, recovery is faster because of redistribution

Context-sensitive half-time is a function of infusion duration and pharmacokinetics

Describes time required for 50% decrease in plasma level

Least dependent on infusion duration for drugs with short elimination half-lives

Synergistic combinations of drugs for anaesthesia allow more rapid emergence because of lower concentrations of both drugs

e.g. fentanyl 1-1.5 ng/ml plus propofol 3 μ g/ml provides most rapid emergence of any combination of the two drugs

Specific drugs

All regimens require titration to surgical stimulus

Fentanyl

with volatile or propofol 1.5-3 μ g/kg 0.01-0.04 μ g/kg/min

with N₂O 5-15 μ g/kg 0.03-0.1 μ g/kg/min

Remifentanyl

with volatile or propofol 0.5-1 μ g/kg/min 0.1-0.2 μ g/kg/min

Ketamine

alone 1-2 mg/kg 30-100 μ g/kg/min

with N₂O 10-50 μ g/kg/min

with propofol 5-20 μ g/kg/min

Propofol

with opiate or N₂O 1 mg/kg 10,8,6 mg/kg/h (\downarrow every 10 min)

Monitoring

[ECG features](#)

[Pulse Oximetry](#)

[Neurological monitoring](#)

[Neuromuscular monitoring](#)

[College requirements](#)

ECG features

| Lead | Location |
|------|----------|
|------|----------|

| | |
|----|--|
| RA | Right wrist |
| RL | Right ankle |
| LA | Left wrist |
| LL | Left ankle |
| V1 | 4th intercostal space, right of sternum |
| V2 | 4th intercostal space, left of sternum |
| V3 | Between V2 and V4 |
| V4 | 5th intercostal space, left midclavicular line |
| V5 | 5th intercostal space, left anterior axillary line |
| V6 | 5th intercostal space, left midaxillary line |

| Change | ECG Response |
|--------|--------------|
|--------|--------------|

| | |
|---------------|--|
| Hypokalemia | ST segment depression T wave flattening and inversion Tall U wave |
| Hyperkalemia | Tall T wave PR interval prolongation ST segment depression QRS widening Ventricular fibrillation |
| Hypocalcemia | Prolonged Q-T interval |
| Hypercalcemia | Short Q-T interval ST segment may disappear |
| Hypothermia | Bradycardia, prolonged PR, QRS and QT Below 33°C: J wave, T inversion, 1° AVB, AF Below 30°C: 3° AVB Below 28°C: VF increasingly common Below 20°C: asystole |
| Digoxin | Prolonged PR, short QT, ST depression “scooped” Small or inverted T |

| ECG feature | Diagnosis |
|-------------|-----------|
|-------------|-----------|

| | |
|---------------------------|--------------------------|
| Upsloping ST depression | Likely ischaemia |
| Downsloping ST depression | Definite ischaemia |
| Inverted T wave | Subendocardial ischaemia |
| ST elevation | Transmural ischaemia |
| Q wave >0.03 s | Infarction |

Pulse Oximetry

Artefacts in SpO₂

| | |
|---|---|
| COHb, HbH | slight ↓ SpO ₂ (appears as deoxyHb) |
| MetHb | approaches 85% |
| SulfHb | appears as MetHb on co-oximetry |
| HbKöln | ↓ by 8-10% |
| Dyes | ↓ variable severity |
| | methylene blue > isosulfan blue > indigo carmine, indocyanine green |
| Anaemia | increasing underreading with hypoxia |
| Venous pulsation, vasodilatation | |
| | ↓ SpO ₂ due to venous pulsation |
| Black henna, dark nail polish, deep pigmentation, tape, vasoconstriction | |
| | reduced signal |
| HbF, HbS, Hb substitutes, fluorescein, polycythaemia, red henna, jaundice | |
| | no effect |

Neurological monitoring

EEG

Electrodes

“10-20 system”

20 electrodes in a standard arrangement

< 5 k Ω resistance

Intraoperative use usually a smaller subset

Signal

10-50 μ V, 4-20 Hz

β >13 Hz

α 8-13 Hz

θ 4-8 Hz

δ 4 Hz

Processing

Full EEG is 16-20 channels

Processed EEG

Power analysis (simple spectral analysis)

Spectral Edge Frequency 95% (95th centile frequency)

Median Frequency

Relative Delta Power (% in δ band)

Bispectral analysis

Includes phase data in analysis

Bispectral Index (BIS)

0-100, 50% unconscious at 67, 95% at 50

Validity for amnesia, unconsciousness, prevention of response to surgery depends on the anaesthetic technique

Change with anaesthesia

Standard pattern with increasing depth

Activation, frontal spindles, 1-3 Hz activity, burst suppression, silence

Produced by barbiturates, propofol, etomidate, benzodiazepines (no silence), volatiles (except epileptiform activity with enflurane)

Opioids

↓ frequency, ↑ amplitude

Ketamine

Frontal θ activity with ↑ amplitude

Higher doses, δ and β activity

No silence, slow recovery of normal pattern

N₂O

Potentiates standard agents

Alone produces frontal >30 Hz activity

Hypoxia

Slowing, silence with severe hypoxia

Hypotension

Severe hypotension required for clear effects: low frequencies

Hypothermia

Slowing, silence at 15-18°C

Transcranial Doppler ultrasound

Principle

Continuous wave Doppler ultrasound

Applied to temples

Aligned with middle cerebral artery

Function

Display of velocity spectrum against time

Derived values for an index of cerebral blood flow and pulsatility

Detection of emboli, vasospasm

Assessment of autoregulatory function by monitoring blood flow over a range of perfusion pressures

Jugular bulb oximetry

Principle

Oximeter inserted percutaneously into internal jugular vein

Function

Measured SvO₂ of venous drainage of brain

Combined with SaO₂ allows calculation of an index of O₂ extraction

Maximal O₂ extraction suggests ischaemia

Problems

Careful calibration required

Assessment only of global perfusion

Significant variability from side to side

Bilateral placement might be necessary

Cerebral oximetry

Principle

Pulse oximeter applied to scalp

Function

Output related to scalp perfusion, no useful information about cerebral ischaemia

Evoked potentials

Applications

Cerebral injury: carotid surgery, craniotomy, CPA surgery

Spinal injury: AAA, spinal cord and column surgery

Peripheral nerve injury: parotidectomy...

Visual evoked potentials

Goggles with flashing patterns, occipital EEG

Test retina, optic nerve, chiasm, radiation, occipital cortex

Rarely used

Somatosensory evoked potentials

Transcutaneous nerve stimulation (20 Hz, 100-400 V)

EEG monitoring (frequency tuned 1-2 μ V amplitude)

Measured: waveform amplitude and latency

Latency \uparrow 15%, amplitude \downarrow 50% suggests injury

Tests nerve, dorsal and ventrolateral tracts, cortex

Median nerve \rightarrow MCA territory

Posterior tibial nerve \rightarrow ACA territory

Interference

Drugs

N₂O > volatile > propofol: \downarrow amplitude

opioids: minimal \uparrow latency

Hypothermia: \uparrow latency 1.15 ms (5%) per °C

Neuromuscular monitoring

At 60 Hz

| | |
|------------|---------------------------|
| 0.05 mA | microshock current for VF |
| 0.3-0.5 mA | threshold of perception |
| 0.1-2.5 mA | macroshock current for VF |
| 1-2 mA | pain |
| 8-20 mA | “cannot let go” |

Vaporizers & gas delivery

[Outline hazards of anaesthetic machines](#)

[Outline arrangements of flow meters on the anaesthetic machine](#)

[Outline vaporizer arrangements on the anaesthetic machine](#)

[Classify breathing systems](#)

[Briefly outline the protocol for checking the anaesthetic machine](#)

[Vaporizers](#)

[Oxygen therapy](#)

[Gas cylinders](#)

[Suction ports](#)

Outline hazards of anaesthetic machines.

Physical design

- Mobile and able to fall over
- Must be stable at up to 8° tilt

Medical gas supply

- Misconnection: pipeline, wall outlet, cylinder
- Contamination
 - Wrong gas due to backflow from mixing devices
 - Errors in gas manufacture and processing
 - Solvents or particulate matter from welding

Gas regulators

- Cooling with gas expansion may freeze valve seats
- Heating with rapid pressurization on opening gas cylinders may ignite grease
- Regulators may allow transition from pipeline to cylinder supply without alarm

Rotameters

- Bobbin & tube mismatched
 - Transposed in servicing, over- or under-read
- Gas leak
 - Test with application of soapy water
- Selective oxygen leak
 - Reason for oxygen mixing downstream
 - Can still occur with leak in flowmeter before bypass tube
- Mechanical failure
 - Damage to bobbin, stops, needle valve
- CO₂-related incidents
 - If CO₂ rotameter is fitted
- Contamination of flowmeter assembly
- Float not visible at top of tube
 - Flowmeter fully open but not noticed

Valves

- Resistance, obstruction, incompetence
 - Due to wear, moisture, misassembly, damage

Vaporizers

- Agent impurities, breakdown products
- Mounting problems
 - Leaks, interlock failure
- Output control problems
- Filling problems
 - Incorrect agent, overfilling, underfilling
- Free-standing vaporizers
 - Tipping, misconnection
 - Placement after oxygen flush
- Thymol accumulation

Breathing systems

- All systems
 - Leaks
 - Potential infection risk
 - Humidifier disconnection or overheating
- Circle system
 - Valve failure
 - Rebreathing, high circuit pressure
 - Absorber problems
 - Leaks, reaction with volatile agents, inhalation of dust, streaming of flow, exhaustion of soda lime
 - Condensation in circuit: inadvertent PEEP

- Uncertainty in gas composition at low flows without agent monitoring
 - Mapleson systems
 - Potential for significant rebreathing at low flows
- Ventilators
 - Hazards are model-specific
 - Pressure
 - Delivery of high airway pressures
 - Gas composition
 - Contamination of circuit gas with driver gas
 - Leak of circuit gas
 - Flow
 - Under- or over-ventilation
 - Failure to deliver adequate volume in pressure-cycled modes
 - Alarms
 - Failure to detect disconnection due to resistance in breathing system
 - Inadvertent inactivation
 - Failure or absence of power failure or “off” alarm
 - Potential disease transmission
- Monitoring systems
 - Electrical safety
 - Patient isolation
 - Power backup
 - Alarms
 - Failure due to inactivation or inappropriate settings
 - Injury associated with monitor placement
 - e.g. Temperature probe epistaxis, BP cuff bruising
 - Misreading
 - Monitor misplacement or device failure

Outline arrangements of flow meters on the anaesthetic machine.

Flowmeter

A device to control and indicate flow of medical gases accurately.

Standard requirements

Flow control knob should be adjacent to flow indicator

Oxygen control knob has a characteristic profile: 8 equally spaced flutes

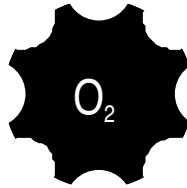
Oxygen flowmeter must be on the left (UK, Europe, Australia) or right (US)

Axial pressure on the knob must not greatly alter flow

Only one flow control for each gas

Oxygen must be delivered downstream in the flowmeter manifold

Mixer must not deliver <25% O₂



Outline vaporizer arrangements on the anaesthetic machine.

Principle

- Vaporizer delivers a calibrated concentration of anaesthetic vapour into gas passing through the device
- Gas is divided into bypass and vaporization chambers
 - Gas in bypass chamber remains unchanged
 - Gas in vaporization chamber is saturated with anaesthetic vapour
- Delivery is dependent on flow, temperature and gas pressure
 - Temperature compensation is integral in modern vaporizers
 - Output falls at high flows
 - Pumping effect is prevented by vaporizer design
 - Pressure effect is minor

Classification

- Draw-over vs plenum (plenum: uses vapour-saturated gas)
- Variable bypass vs measured flow
- Vaporization method
- Location (in-circuit vs out-of-circuit)
- Temperature compensation
- Pressure compensation
- Resistance
- Agent specificity

Position

- Historically in-circuit or out-of-circuit
- Now usually placed out-of-circuit between flowmeters and common gas outlet or replaced by electronic direct injection of vapour
- Interlock to prevent multiple vaporizers being on concurrently
 - Prevents transfer of vapour from upstream to downstream vaporizer
 - Reduced output of upstream agent
 - Contamination of downstream vaporizer
- Contamination also minimized by placing higher SVP agent downstream

Modern plenum vaporizers

- Variable bypass, VOC, temperature compensated, backpressure resistant, high resistance, agent specific
- Most use wick vaporization except TEC6, Engstrom Elsa, Datex ADU

Models

- Ohmeda TEC series
- Penlon PPV Σ and Σ Elite
- Blease Datum
- Vapamasta
- Dräger 19.3

Classify breathing systems.

Rebreathing

Mapleson A

Magill

Most efficient for SV, requiring 70% of MV as FGF
3 x MV required for IPPV

Lack

Mapleson A with coaxial expiratory tubing

Mapleson B, C

Rarely used, closed bag requires high FGF

Mapleson D

Bain

Low resistance, single tube, FGF 70-80 ml/kg/min

Mapleson E

Replaced by Mapleson F (Jackson-Rees' modification)

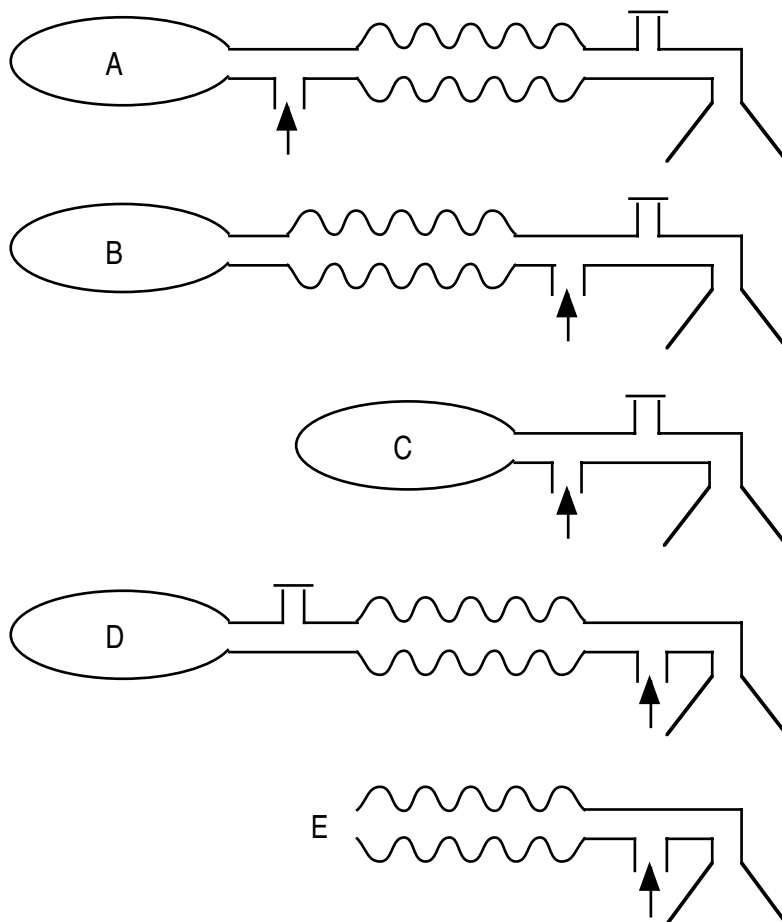
Mapleson F

Common use for paediatric anaesthesia

FGF 2-3 times MV

Switchable devices

Several varieties for switchable A/D circuit types



Non-rebreathing valve systems

Laerdal bag

Triservice apparatus

T-piece oxygen/air inlet, drawover vaporizers, self-inflating bag, non-rebreathing valve

CO₂ absorption systems

Water's to-and-fro system

Mapleson C with absorber near patient, obsolete

Circle systems

- Many configurations

- Commonly

 - APL valve in expiratory limb before absorber

 - FGF in inspiratory limb after absorber

- Nomenclature depends on component arrangements

 - VIC/VOC, closed/semi-closed, coaxial/not-coaxial

- Advantages

 - Economical of gases and vapour

 - Hypocarbica easy to achieve

 - Good heat and water conservation

- Disadvantages

 - Large number of parts, risk of faults, complex ventilator required

 - Bulky, cleaning difficult

 - Soda lime dust can be inhaled

 - Trichloroethylene cannot be used

Briefly outline the protocol for checking the anaesthetic machine.

Level 1

Detailed service check by manufacturer's personnel or technician

Detailed documentation of checking and calibration

Label visible to anaesthetist of next scheduled check

Gas delivery

Quantify and minimize leaks, exclude crossed pipelines, check valves, check O₂ failure device

Accuracy of vaporizers

Compliance with Standards

Level 2

Anaesthetist or technician check at the start of a list

High pressure system

Cylinder and pipeline supply, cylinders off

Single gas test for oxygen

Low pressure system

Control valves and flowmeters

Hypoxic interlock device

Vaporizers

Filled, ports closed, correctly seated, no leak on or off, electricity supply

Precircuit leak test

Breathing system

Check connections

Leak test (<300 ml/min at 30 cmH₂O)

Check valves: one way and APL

Ventilator, function, leak, alarms

Scavenging at correct pressure

Spare self-inflating bag

Other apparatus

Intubation equipment, suction, gas analysis, monitoring, IV infusion, warming, humidifier, filters

Final check

Vaporizers off, purge with oxygen or air

Level 3

Brief check before each case

If vaporizer or breathing circuit is changed, recheck

Recheck other apparatus

Vaporizers

Tec 6

- Separate gas and vapour circuits

- Fresh gas flow passes a fixed resistance in vaporizer

 - Pressure upstream of the resistance is “working pressure”

 - Proportional to gas flow

- Desflurane is heated to 39°C (1300 mmHg absolute)

 - Pressure downregulated to “working pressure” by differential pressure transducer, electronics and regulating valve

 - Desflurane passes through a variable resistance controlled by the concentration dial on the vaporizer

 - Desflurane output varies with working pressure and concentration selected

- Carrier gas affects working pressure

 - Lower desflurane output with N₂O

- Altitude does not affect concentration delivered (unlike variable bypass vaporizers)

 - Lower partial pressure delivered at lower ambient pressure

 - Potential for awareness

 - Vaporizer requires adjustment for ambient pressure

Oxygen therapy

Fixed performance

High flow Venturi masks

O₂ flow of 6-8 l/min entrains air

Total flow 40-60 l/min, FiO₂ 25-60%

Anaesthetic circuits, CPAP or PEEP machines

Require air-tight fit

Reservoir allows fixed FiO₂ (20-100%)

Variable performance

No capacity

Nasal catheters

FiO₂ depends on flow rate and PIFR

Small capacity

Simple face masks (e.g. Hudson mask)

O₂ flow and PIFR determine FiO₂

| O ₂ flow | FiO ₂ (approx.) |
|---------------------|----------------------------|
|---------------------|----------------------------|

| | |
|---|------|
| 4 | 0.35 |
|---|------|

| | |
|---|------|
| 6 | 0.50 |
|---|------|

| | |
|---|------|
| 8 | 0.55 |
|---|------|

| | |
|----|------|
| 10 | 0.60 |
|----|------|

| | |
|----|------|
| 12 | 0.65 |
|----|------|

| | |
|----|------|
| 15 | 0.70 |
|----|------|

Tracheostomy masks, T-piece circuit, face tent (soft bowl-shaped mask)

Large capacity

Face masks with reservoir bags

Higher FiO₂, risk of rebreathing if disconnected

Head boxes, incubators, tents

Gas cylinders

Markings specified by AS2030 (1977)

Requirements

ID number

Owner's mark

CIG, LAA, MD, NZIG

Water capacity

Mass of water required to fill cylinder at 15°C

Test pressure

Testing station mark and date



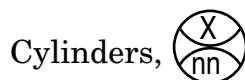
British Tube Mills,



Australia Liquid Air,



Gas



Cylinders, CIG (X location, nn year),



Tubemakers,



Luxfer



Holdings, National Vulcan Engineering Insurance Group

Manufacturer's mark

May be combined with testing station mark

Standards specification mark

For cylinder type e.g. AS B114 for alloy steel cylinders

Tare mass

Weight of empty cylinder without valve

Name or symbol of gas and colouring to identify contents

ISO standard

| Gas | Pins | Colour |
|-------------------------------|--------|---|
| CO ₂ | 1,6 | grey |
| O ₂ | 2,5 | black (with white shoulder for medical O ₂) |
| air | 1,5 | grey with black and white shoulder |
| N ₂ O | 3,5 | blue |
| He | 4,6 | brown |
| C ₃ H ₆ | 3,6 | orange |
| N ₂ | | grey with black shoulder |
| Entonox | single | blue with blue and white shoulder |
| Heliox | 4,6 | brown with black and white shoulder |
| Carbogen | 2,6 | black with grey and white shoulder |

Aluminium ring on neck of cylinders containing liquifiable gas

Tare weight with valve, date, test station, number and "ET" if eductor tube present

Plastic tab on some aluminium cylinders to detect excessive heat exposure

Star indicates use for dry gas only

Filling ratio

Used for liquifiable gases: N₂O, CO₂, C₃H₆

Ratio of mass of gas to water capacity at 15°C

Specification to ensure pressure does not exceed 80% of test pressure at 65°C

Suction ports

AS 2896, AS 2120.3

Number of ports

| | |
|---------------------------------------|----------------|
| OR | 4 |
| PACU, ICU | 3 |
| Delivery | 2 + 1 for baby |
| Resus | 2 |
| Coronary care, anaesthetic room, etc. | 1 |

Each port

40 l/min free flow
-60 kPa (-500 mmHg, -600 cmH₂O)
Time constant ≤ 4 s

Central vacuum source

At least two pumps with automatic switching
Each capable of meeting peak demand
Reservoir tank

Venturi suction

Dry gas flow entrains gas from suction device
Obstruction of gas flow outlet can result in high positive pressure
Large venturis have a safety device to prevent pressurization
Twin-O-Vac commonly used for portable suction
16 l/min or -55 kPa (using 22 l/min O₂)
Not up to AS 2120, but better than nothing
No protection against pressurization

Scavenging

Must be separate from suction (different sleeve index)
30 mm or 19 mm connections
Usually pink 30 mm hose

Passive

Simple hose from circuit to external vent (with fluid trap)
Able to transfer 75 l/min with acceptable back-pressure (≈ 0.5 cmH₂O)
Must be gas-tight
Obstruction may cause raised circuit pressure

Active

Suction applied to 3 l reservoir with indicator for 20-30 l/min flow through vents
30 mm tubing to circuit
Able to absorb 4 l bolus of exhaust without contamination of theatre
Multiple vents on reservoir to prevent negative circuit pressure with occlusion

Miscellaneous Equipment

[Fires & Explosions](#)

[Lasers](#)

Fires & Explosions

Explosion

Combustion fast enough to produce sound waves

Most likely with a stoichiometric combination of substances

Detonation

Combustion fast enough to produce compression waves initiating further ignition

Flammability limits

Concentrations between which combustion is supported

Lower flammability limits for volatiles (theoretical)

| Agent | 100% O₂ | 1:4 O₂:N₂O | 1:2 O₂:N₂O |
|--------------|---------------------------|---|---|
| Halothane | | <u>3.25%</u> | 4.75% |
| Enflurane | 5.2% | 4.25% | 5.75% |
| Isoflurane | 8.75% | 5.25% | 7.0% |

Flammability index

Fractional O₂ or N₂O flow in N₂ which supports sustained combustion

PVC > silicone > red rubber

Sources of ignition

Static electricity

Prevented with conductive flooring, earthing, high humidity

Electrical switches

Shielded or placed above "Five foot line"

Diathermy

Avoid in close proximity to airway or bowel gases

Laser, fibreoptic light sources

Adiabatic compression

Combustible things in theatre

Gases and vapours

Anaesthetic agents withdrawn

Alcoholic prep.

Bowel gases

Drapes

Papers and plastics

Lasers

Laser

Light Amplification by Stimulated Emission of Radiation

Source of coherent, monochromatic, collimated light

Lasing medium (gas, liquid or crystal) with mirrors at each end, pumping source

Delivery system

Aperture, guide, frequency doubler if necessary

Applicator: lenses, contact tip, diffuser

Mode of delivery

Continuous wave, pulsed, quality-switched, mode-locked

Extinction length (EL)

Depth of tissue for 90% absorption

Popular types

Carbon dioxide (CO₂)

10600 nm absorbed by water

Used for superficial lesions (EL 0.03 mm)

Neodymium-yttrium-aluminium garnet (Nd-YAG)

1064 nm (near IR) absorbed by water

High power, deep penetration (EL 3 mm)

Addition of potassium-titanyl-phosphate (KTP) frequency doubler produces 532 nm (green) laser

Argon (Ag)

458-515 nm (blue green)

Absorbed by Hb, photocoagulation

Suitable for retinal work

Helium-neon (HeNe)

632 nm (red)

Low power red laser used for aligning invisible lasers

Safe use (AS 4173, AS 2211)

Equipment design

Control key to lock machine, warning signs, shutters, safety interlocks and emergency shut-off

Protocols

Laser safety committee and officer

Closed theatre with blinds and signs

Eye protection

Appropriately trained staff

Eye examinations

Drill for fire management

Anaesthetic issues

Difficulty reading displays through tinted glasses

Fire risk with drapes, and especially with [shared airway](#)

Smoke plume removal to avoid inhalation or viral transmission

Potential for gas embolism with gas-cooled lasers

Cardiology

[Aortic incompetence](#)

[Mitral stenosis](#)

[Pacemaker management](#)

[Heart block management](#)

Aortic incompetence

Aetiology

Acute

Endocarditis, aortic dissection, connective tissue disease, trauma

Pathophysiology

Acute

Sudden volume load on LV

↑ LVEDP, PAOP

Sympathetic response: ↑ HR, vasoconstriction

May cause acute decompensation and failure

Chronic

Progressive LV enlargement and hypertrophy

High compliance, high output

Late decompensation (10-20 years)

Classification

Regurgitant flow: < 3 l/min mild, 3-6 l/min moderate, > 6 l/min severe

Or by contrast findings on aortogram

Features

Tachycardia: ↓ regurgitation, LVEDV, ↑ coronary perfusion

Relatively little increase in myocardial O₂ demand until late

Volume work increases O₂ demand less than pressure work

Management

Responsive to pressors, but vasodilators may increase forward flow

Diastolic hypotension and bradycardia to be avoided (↓ coronary perfusion)

IABP contraindicated (enhances retrograde flow)

Valve replacement

Retrograde flow of pump blood may distend LV until aortic clamping

Anterograde cardioplegia may be difficult

Mitral stenosis

Aetiology

Usually rheumatic heart disease

Clinical features

Symptomatic early, slow progression

Marked worsening with ↑ demand for CO (pregnancy) or development of AF

Severity

Pressure gradient not useful (dependent on HR, CO...)

Valve area (normal 4-6 cm²)

Mild 1.5-2.5 cm²

Moderate 1-1.5 cm²

Severe <1 cm²

Anaesthetic management

Heart rate maintained low-normal in sinus rhythm

Bradycardia → ↓ CO due to low SV

Tachycardia → ↓ CO due to slow diastolic filling

AF → sudden decompensation, especially with rapid ventricular rate

Maximal tolerated LAP without pulmonary oedema

Risk of complications from PA catheter

Pulmonary hypertension: ↑ risk of PA rupture, unreliable PAOP

Risk of RV failure with pulmonary hypertension

Septal deviation impairs LV filling

Prevent with NO, lowering PVR

Pacemaker management

Identification code (5 letters)

Chamber paced: O, Atrium, Ventricle, Dual

Chamber sensed: O, Atrium, Ventricle, Dual

Mode of response: O, Triggered, Inhibited, Dual

Antitachycardic function: O, Pacing, Shock, Dual

Programmability: O, Program, Multi-program, Communicating, Rate-response

Modes

Asynchronous

AOO, VOO, DOO: pacing regardless of underlying activity

Fall-back mode only as wasteful of battery and may compete with intrinsic rhythm

Single chamber demand

AAI, VVI: single chamber pacing inhibited by intrinsic activity

Simple single-lead pacemakers

AAI requires intact A-V conduction

VVI does not maintain A-V synchrony

Dual chamber

A-V synchronous (VAT, VDD)

A-V sequential (DVI)

Universal (DDD)

Operate in AAI, VDD or DVI as required

A-V inhibited (DDI)

Used where atrial tachycardia causes rapid ventricular pacing in DDD

Rate responsive

Provide exercise response in patient who are pacemaker-dependent

Various sensors used

Temperature, SvO₂, respiratory rate or minute volume, QT interval, vibration, acceleration

Antitachycardia functions

Simple shock devices

Recognize sustained tachycardia

Deliver 25-30 J shocks up to five times

Tiered (dual) therapy devices

Pacing for bradycardia

Overdrive pacing for atrial tachycardia

Low energy cardioversion for VT

High energy defibrillation for VF

Generate palpable but not dangerous voltage at the body surface

Issues

Maintain stable heart rate and rhythm throughout surgery

Preoperative

History

Reason for pacemaker insertion

Symptomatic arrhythmias or IHD

Medications

Other illnesses

Type of pacemaker, who manages it, last tested, history of problems

Previous anaesthetics

Examination

Routine, focussing on cardiorespiratory examination

Identify location of box

Investigation

ECG

Identify rhythm, presence of pacing spikes

Consultation

Cardiologist to determine pacing mode, rate-responsiveness

Rate-responsiveness and antitachycardia functions must be switched off prior to surgery

Premedication

Continue cardiac medications

Transport

Avoid excess movement if movement-responsive

Preparation

Chronotropic medications available, external pacemaker may be available

Atropine, isoprenaline

Routine access and monitoring

Additional heart rate monitor not susceptible to diathermy interference

Precordial stethoscope or palpable pulse

ECG leads short: can act as antennae

“Cardiac protected” theatre required

Intraoperative

Sensing pacemakers can be affected by myopotentials, movement, diathermy

Induction

Suxamethonium fasciculations produce myopotentials

Excess ventilation simulates exercise in movement-responsive pacemakers

No requirement for prophylactic antibiotics

Maintenance

Position so that pacemaker is not a pressure area

Diathermy

Problems

Direct damage to pacemaker from current

Microshock (VF) from current through lead

Inhibition of pacemaker by current if in demand mode

Precautions

No diathermy within 15 cm of pacemaker

Brief bursts of diathermy if interfering with pacing

Preferably bipolar diathermy with minimal current

Consider changing mode to asynchronous

Diathermy current distant from and at 90° to pacemaker

Grounding plate distant, but not if head & neck surgery

Avoidance of N₂O with a recently implanted pacemaker

Expanding a gas pocket around the generator can cause loss of anode contact with a unipolar generator

Maintain temperature to avoid post-op shivering

Emergencies

Use of a ring magnet

In VVI will set a fixed rate

Effect is not predictable in programmable pacemakers

“Pacemaker syndrome”

Activation of VVI pacemaker causes hypotension

Loss of AV synchrony or retrograde conduction causes fall in CO

Atrial stretch causes reflex vasodilatation

Pacemaker failure

Interference from electrical activity or muscle potentials

Failure to capture due to electrolyte disturbance or drugs

Hypoxia, hypercarbia, ↑ intracellular K⁺, hypernatremia

Verapamil, β-blockers, quinidine

Defibrillation

Paddles at least 12 cm from generator, orientated at 90° to AICD electrodes

Management of heart block

Issues

- Risk of development of AV block with bradycardia
 - Is a prophylactic pacemaker required?
- Risk of associated cardiac disease

Preoperative

Assessment

Conduction defect

- Symptoms: dizziness, drop attacks, palpitations
- Cardiac examination: BP and HR, arrhythmia
- Previous investigation: conduction studies, ECG
- Stability of disease

Associated disease

- History of Lev's or Lenegre's disease
 - Fibrosis of His bundle or terminal fibres
- Cardiac surgery or His ablation
- Cardiomyopathy
- IHD
- Previous investigations: stress test, echo, coronary angiogram etc.
- Drug therapy either treating or causing block
 - e.g. digoxin, propranolol, quinidine, procainamide, verapamil

General assessment

- Level of function
- Routine anaesthetic assessment

Investigation

- ECG, U&E, specific investigations as indicated

Consultation

- Discussion with treating cardiologist
- Optimize medication regimen
 - Defer surgery if time is needed
- Decision whether preoperative pacing is required
 - Not usually necessary unless unstable and symptomatic
 - If unstable, insert transvenous pacing wire under LA

Premedication

- Continue usual cardiac drugs
- Anxiolytic, sedative premedication

Consent

- Discuss possible requirement for temporary pacing
- Anaesthetic plan
 - Regional with avoidance of hypotension preferable to GA

Intraoperative

Preparation

- Routine anaesthetic equipment prepared
- Drugs and equipment for rapid conversion to GA if necessary
- Chronotropes available for CHB: atropine, isoprenaline
- Transvenous or external pacing equipment available

Monitoring

- Routine, plus
- 5 lead ECG monitor prior to block insertion
- Large bore IV access

Induction

- Low spinal or epidural catheter
 - Depending on likely duration of surgery and stability of disease
- Preloading with fluid

Pressors drawn up

Emergencies

- Heart block with nodal rhythm
 - Usually responsive to atropine
- Heart block with ventricular escape
 - Usually accompanied by bradycardia, hypotension
 - Immediate transvenous or external pacing if available
- Otherwise
 - Airway control and ventilation with 100% O₂ if unconscious
 - IV fluid
 - Rate support with isoprenaline and atropine until
 - Insertion of transvenous pacing wire

Endocrinology

[Diabetes](#)

[Perioperative corticosteroid supplementation](#)

Diabetes

Classification

Type I

Autoimmune disease, 40-50% concordance, β -cell destruction, ? viral or environmental trigger, insulin deficiency

Prone to diabetic ketoacidosis

Presents at an early age

Require insulin replacement

Type II

100% genetic concordance, increased in obese, insulin resistance

Not prone to DKA, but may develop hyperglycaemic hyperosmolar coma

Presents in middle aged or elderly (except MODY)

Initial therapy often with diet, exercise, oral agents, later insulin

Insulin

Synthesized in endocrine pancreas (islets of Langerhans) by β -cells

α -cells secrete glucagon, δ -cells secrete somatostatin, F cells secrete pancreatic polypeptide

Normal secretion 1 U/kg/day, peaks after meals, $t_{1/2}$ 5 min

Release stimulated by

Plasma glucose and fructose, amino acids, glucagon, gastrin, secretin, CPK, ACh, catechols via β receptors

GH increases insulin responsiveness

Release inhibited by

Somatostatin, catechols via α -receptors

Perioperative management

Evidence

Diabetics are at increased risk of complications

Due to secondary effects of diabetes (IHD, renal disease...) **not** due to hyperglycaemia

Tight control of blood sugar

Reduces chronic complications of diabetes

Benefits foetus in pregnancy

Less macrosomia

Beneficial during cardiopulmonary bypass

More responsive to inotropes

Stress response produces hyperglycaemia

Hypothermia diminishes insulin sensitivity

Beneficial during cerebral ischaemia

Lower risk of neurological damage

Otherwise little evidence for advantages in tight perioperative control

Major risks in the diabetic patient

Cardiovascular: IHD, PVD, microvascular disease

Renal impairment

Neuropathies

Impaired cellular immunity

Joint collagen abnormality (jaw stiffness, poor deep wound healing)

Resuscitation of the DKA patient for emergency surgery

Usually time for fluid replacement, electrolyte correction

Fluid deficit 3-10 l (Saline 5-10 ml/kg plus 1-4 l/h)

Potassium deficit 3-10 mmol/kg (KCl 10-20 mmol/l fluid)

Insulin deficit

Correct $K^+ < 3$ mmol/l first

10 U bolus plus 5-10 U/h titrated against blood sugar

- Add 5% dextrose to fluids when glucose < 15 mmol/l
- Hourly ABG and glucose
- Aim for glucose 10-14 mmol/l, pH > 7.35, Na⁺ < 155 mmol/l, K⁺ 3-5 mmol/l
- Also phosphate, magnesium deficient
- Classic “non-tight control” regimen
 - Fast from midnight for morning surgery
 - 5% dextrose 125 ml/h IV from 6am
 - Half normal morning dose of insulin
 - Check BSL 1-4 hourly
 - Sliding scale insulin from recovery until return to normal diet
- “Tight” regimen
 - Check fasting glucose day before surgery
 - 5% dextrose 50 ml/h IV
 - Initial insulin IV rate (U/h) = BSL/8.3 (mmol/l) (or BSL/5.5 if on steroids)
 - Titrate insulin rate to BSL 5.5-11.1 mmol/l
 - Check BSL at start of surgery and every 1-2 h for 24 h
- Other perioperative concerns
 - Autonomic neuropathy
 - ↑ gastric emptying time, risk of aspiration
 - Painless myocardial ischaemia
 - Signs include hypertension, lack of sweating, lack of R-R variability, postural hypotension, peripheral neuropathy
 - Microvascular disease
 - ? ↑ risk of neuropraxia with regional

Perioperative corticosteroid supplementation

Evidence

- Few patients with adrenocortical suppression have problems even without steroid cover: documented cases are rare
- Acute adrenal insufficiency is life-threatening
- Perioperative steroid cover carries minimal risks
- Primate study found no difference between physiologic and supraphysiologic doses

Physiology

- Maximum adrenal cortisol output 200-500 mg/d
- Normal 25 mg/d

Risks of supplementation

Possible

- Minor impairment of wound healing (antagonized by vitamin A)
- Impaired immune function
- Hypertension, fluid retention, stress ulcers, psychosis
- Aseptic necrosis of head of femur

Recommended regimen

- Indicated for all patients receiving steroids within past year
- Not less than usual preoperative dose equivalent
- Hydrocortisone 200 mg/d for 70 kg adult (100 mg for minor procedures)
- Reducing 25% per day until oral steroids resumed

Haematology

[Outline management of a sickle-cell patient for appendicectomy](#)

[Review of paediatric transfusion](#)

[Deep vein thrombosis](#)

Outline management of a sickle-cell patient for appendicectomy.

Appendicectomy

Urgent operation, moderate risk

Patient factors

Sickle cell anaemia

May be trait, sickle cell disease or Hb SC or other variants

Severity of disease determined by Hb type

Hb SS

Anaemic Hb 70-80 g/l

Vaso-occlusive crises cause organ infarction

Especially spleen, renal papillae, skin (if cold), CNS

Complications

Poor spleen function, encapsulated organism susceptibility

Hepatomegaly

Impaired renal function

May cause "acute abdomen", confused with appendicitis

Appendicitis

Causes fever, acidosis: ↑ risk of sickle crisis

Patient not fasted, commonly with an ileus: risk of aspiration

Preoperative

Assessment

Usual patient assessment: clinical, baseline investigations

Severity of sickle cell disease

FBE, history, abdominal and skin examination

Resuscitation status

Needs to be warm, well-filled, supplemental oxygen

Premedication

Usually avoided as may cause hypoventilation

Oxygen by face mask, prewarming with forced-air warmer

Intraoperative

Objectives: normothermia, avoid hypoxaemia and acidosis to minimize risk of sickling

Monitoring

Usual monitoring

ECG, NIBP, SpO₂, gas analysis, airway pressure, urinary catheter, temp

Anaesthetic technique

General anaesthesia: balanced technique with muscle relaxation

Induction

Rapid sequence induction

Check equipment, difficult airway equipment available

Preoxygenation, cricoid pressure

Thiopentone (3-4 mg/kg), suxamethonium (1-1.5 mg/kg)

Reduce thiopentone dose if underfilled to avoid hypotension

Secure airway with cuffed ETT

Maintenance

Ventilate with increased FiO₂, normocapnia

Analgesia with local anaesthetic in wound plus narcotic as necessary

More likely to require transfusion if significant blood loss

Avoid hypothermia aggressively if necessary (often febrile)

Emergence

Extubation awake in lateral position

Postoperative

Maintain supplemental oxygen, keep warm

Narcotic analgesia will be required, but hypoventilation is a risk

Review of paediatric transfusion (RCH 1999)

Prompted by HIV transmission case

Transmission would have occurred once the infected unit had passed the screening process. Directed transfusion would only have caused a different child to be infected.

Risks of transfusion

Cause of death associated with transfusion (FDA, 1990)

| | |
|-------------------------------------|-----|
| ABO incompatibility | 50% |
| Pulmonary oedema | 14% |
| Hepatitis C | 12% |
| Hepatitis B | 7% |
| Bacterial infection | 7% |
| Delayed reaction, anaphylaxis, GVHD | 9% |
| HIV | 1% |

Risk of viral transmission

Lowest in volunteer repeat donors

Minimized by screening questionnaire and serology

Estimate of risk of "window period" donation

| | |
|-------|---|
| HIV | 1 in 1.2 million in Australia (twice as high in US) |
| Hep B | 1 in 370,000 |
| Hep C | 1 in 250,000 |

Risk in children

5% of transfusions are given to children

20% of paediatric transfusion is for elective surgery

Expected incidence of HIV transmission from elective paediatric surgical transfusion in Australia is 1 per 100 years.

Reducing risks

Transfuse only for specific clinical indications

Whole blood

Massive transfusion, exchange transfusion, CPB or ECMO

Packed cells

Under 4 months of age

Hb <130 g/l in neonates <24 h old or with severe pulmonary disease, cyanotic heart disease or heart failure

Acute loss of $\geq 10\%$ of blood volume

Phlebotomy loss of 5-10% of blood volume

Hb <80 g/l with symptomatic anaemia

Over 4 months of age

Operative blood loss $\geq 15\%$ of blood volume

Post-op Hb <80 g/l with symptoms

Hb <130 g/l with severe pulmonary disease requiring ventilation

Hb <80 g/l or symptomatic Hb <100 g/l without response to medical therapy

Suppression of endogenous erythropoiesis in some thalassaemia and sickle-cell patients

Prior to renal transplant

Autologous transfusion

Available at RCH from 40 kg up

20-30 cases per year

90% of elective surgery requiring transfusion is in ineligible children

Toronto HSC from 18 kg up

100 cases per year, >50% discarded

Directed transfusion

Specific indications

Kidney transplant recipient preparation

Bone marrow transplant

- Rare phenotype red cells
- HLA-compatible platelet transfusion
- Parent to neonate transfusion for alloimmune thrombocytopenia, neutropenia or haemolytic disease of the newborn

Other countries

- UK prohibited
- Canada available if parents insist
- US some states prohibited, some mandate offering directed transfusion
 - In California, 2-3% of donations are directed
 - Early 1980s HIV risk from donor blood in CA was 1/200-1/300

Practice

- 88% chance of compatibility if both parents available, 72% for one parent (84% and 50% if identical group required for cardiac surgery)
- 5 days notice required
- 31% of donations are used
- More expensive than random donor transfusions

Safety

- Viral markers *may* be slightly more prevalent in directed donations
- 22% of donors might modify answers to screening questions to allow donation
- No studies of long-term outcomes in children
 - 50% of blood is transfused to patients who are dead within one year

GVHD

- Near HLA-match allows lymphocyte engraftment in immunocompetent recipient
- Risk 1 in 17-39,000 in Caucasians for random donor, 20 times higher if parent to child donation

TRALI

- Donor neutrophil or HLA antibodies cause acute respiratory distress
- May be more common in maternal plasma in the first few months after childbirth

HLA isoimmunization

- Increased risk of rejection of subsequent marrow transplant

Ethical complications

- Coercion of an unwilling donor, false screening declarations
 - 3% of donors feel forced to donate
- Potentially worse therapy used based on parental desire
 - No conclusive evidence that directed donation is less safe
- Potential for discovering a different biological parent
- False positive viral screening tests
 - Positive threshold is set low for donor units
 - High false positive rate, donor counselling required
- Impact on volunteer donor pool
- Use of finite resources
- Parental desire to help their children

Cost-effectiveness recommendations (Health Ministers, 1999)

- Minimize blood loss
- Autologous donation should be available but should not be promoted
- Acute normovolaemic haemodilution should not be encouraged
- Erythropoietin and desmopressin use should not be encouraged
- Cell salvage should be evaluated
- Aprotinin use should be actively supported

Conclusions

- No evidence to ban directed donation
- Should not be encouraged because of increased cost and possible increased risk
- Should be permitted in defined circumstances

Deep Vein Thrombosis

Pathogenesis

- venous stasis
 - no activity of muscle pump mechanism
 - decreased venous return with IPPV or pneumoperitoneum
 - patient position can affect venous return
- vascular injury
 - direct trauma
 - endothelial activation due to cytokines released in surgery
 - increased tissue factor and PAI-1
 - reduced thrombomodulin
- activation of coagulation
 - local activation with vessel trauma
 - systemic increase in coagulability with surgery or stress
- known risk factors
 - age > 60
 - previous DVT
 - major surgery
 - surgical duration
 - orthopaedic surgery to the hip or knee
 - fractured pelvis, femur or tibia
 - surgery for malignant disease
 - immobility in the perioperative period
 - medical conditions
 - cardiac failure
 - sepsis
 - inflammatory bowel disease
 - myocardial infarction
 - varicose veins
 - obesity

Natural History

- site
 - most commonly superficial veins and deep veins of the calf
 - proximal spread to involve popliteal, femoral and iliac veins
 - other sites are uncommon
- symptoms and signs
 - calf vein DVT is usually asymptomatic
 - proximal DVT causes impaired venous drainage, perivascular inflammation, symptomatic PE
 - postthrombotic syndrome may occur in the long term
- prognosis
 - untreated
 - 30% of small calf DVTs will spread proximally if untreated
 - proximal spread is associated with 40-50% risk of PE
 - historical mortality from PE was 20%
 - treated
 - proximal DVT associated with 5% incidence of significant events
 - recurrent DVT after treatment
 - 5-10% at one year (4% for post-surgical DVT)
 - 30% at 8 years
 - risk of recurrence is greatest in DVT associated with a non-reversible cause (i.e. malignancy or coagulation disorder)
 - postthrombotic syndrome
 - incidence 25% after treated DVT

- caused by increased venous pressure
 - incompetent valves
 - outflow obstruction
- oedema, pain, venous ulceration
- “thromboneurosis”

Prophylaxis

- proven cost-effective for high-risk patients
- prevent venous stasis
 - pneumatic calf compression
 - calf compression is as effective as low-dose heparin in abdominal surgery
 - TEDS stockings
 - effective adjunct in the postoperative period
- modulate coagulation
 - low-dose heparin
 - cost-effective for general surgery
 - reduces DVT risk by 50-70%
 - warfarin, adjusted dose heparin, LMWH
 - LMWH is most effective in major orthopaedic surgery
- low risk
 - age < 40, uncomplicated surgery, mobile post-op risks
 - calf DVT 2%, proximal DVT 0.4%, fatal PE <0.02%
 - prophylaxis
 - early mobilization
- moderate risk
 - age > 40, medical risk factors, immobility (e.g. leg fracture) risks
 - calf DVT 10-20%, proximal DVT 2-4%, fatal PE 0.2-0.5%
 - prophylaxis
 - low dose heparin or pneumatic calf compression
- high risk
 - high risk surgery, previous DVT risks
 - calf DVT 40-70%, proximal DVT 10-20%, fatal PE 1-5%
 - prophylaxis
 - LMWH or warfarin or adjusted dose heparin
- neurosurgery, ophthalmic surgery
 - if anticoagulation is contraindicated, pneumatic compression and stockings are safe

Diagnosis

- venography
 - gold-standard for diagnosis
 - operator dependent
 - may be misleading in recurrent DVT
- venous ultrasound
 - operator dependent
 - inadequate resolution for calf veins
- impedance plethysmography
 - fails to detect calf thrombi
- predictive value of tests is greatly influenced by clinical probability

| Ultrasound result | Clinical probability | Likelihood of DVT | Management |
|--------------------------|-----------------------------|--------------------------|----------------------|
| positive | high | 100% | treat |
| positive | intermediate | 96% | treat |
| positive | low | 63% | venography |
| negative | high | 24% | venography or retest |
| negative | intermediate | 5% | retest |
| negative | low | <1% | no treatment |

diagnosis of pulmonary embolism

clinical features are non-specific

shortness of breath (increased dead space)

pain, haemoptysis, sudden death

diagnostic tests

pulmonary angiography

gold-standard test

highly invasive

ventilation/perfusion scan

interpreted in combination with clinical impression

“high probability” scan result means

PE in 96% of patients with high clinical suspicion

PE in 85% with intermediate clinical suspicion

PE in 50% with low clinical suspicion

“low probability” scan means

PE in <6% with low clinical suspicion

testing for the presence of a DVT may determine management

ECG

significant negative predictive value if other pathology (e.g. pericarditis, infarction)

may show right heart strain

CXR

useful positive diagnostic signs are uncommon

may show effusion, infarction, regional oligoemia, prominent

pulmonary vessels at the hilum

ABG

non-specific

may show hypoxaemia, hypocarbia in large PE in an awake patient

Treatment

anticoagulation

heparin

promotes inhibition of thrombin and factor Xa via AT-III

high concentrations required to affect clot-bound thrombin

warfarin

inhibits synthesis of factors requiring γ -carboxylation

thrombin, VII, IX, X

usual regimen

therapeutic heparin, followed by

warfarin to INR 2-3 for 3-6 months

shorter duration is more appropriate if there is no on-going predisposing factor

patients with a thrombotic condition (e.g. antiphospholipid antibody) may require lifetime therapy

overlap period should be about 4 days as INR rises as factor VII level falls ($t_{1/2}$ 7 h) but full anticoagulant effect requires a fall in factor II ($t_{1/2}$

- 60 h)
- sc LMWH may be an alternative to IV heparin
- thrombolysis
 - usually contraindicated in the postoperative period
- surgery
 - caval interruption
 - intracaval devices
 - thrombectomy

Pregnancy

- diagnosis
 - leg pain and swelling are frequent without DVT
 - venography, V/Q scanning are relatively contraindicated
- management
 - heparin is safe in pregnancy
 - warfarin is teratogenic at 6-12 weeks and contraindicated at term
 - women on prophylactic warfarin are changed to heparin or LMWH before 6 weeks gestation (or before conception)
 - heparin is ceased at the onset of labour

Children

- DVT is relatively rare
- highest risk surgery has <1% incidence of clinical DVT
- 80% of neonatal and 40% of childhood DVTs are associated with CVCs

Perioperative management of anticoagulants

- “low” risk patients on warfarin
 - risk of thromboembolism from AF or prosthetic valves without anticoagulation is about 10% per year
 - ceasing warfarin 4-5 days before surgery should carry <0.1% risk of thromboembolism
- “high” risk patients on warfarin (e.g. recurrent thromboembolism)
 - reduction in INR to 1.5 for surgery
 - replacement of warfarin with heparin
 - ceased 4-6 hours before surgery
 - recommenced 12 hours after surgery

Metabolic

[Hypothermia](#)

[Obesity](#)

Hypothermia

Definition

Body temperature below normal

Normal 36.7-37.0°C

Mild 34-36.5°C, moderate 27-34°C, deep 17-27°C, profound <17°C

Mild hypothermia

Benefits

Cerebral and myocardial protection, ↓ risk of MH, ↓ MAC requirement

Risks

↑ O₂ demand during cooling, myocardial ischaemia, arrhythmia, impaired immunity, pharmacokinetic changes, discomfort

Effects in detail

Regulation in [Thermoregulation \(1.L\)](#)

Neurological

↓ CBF, CMRO₂ (7% per °C), EEG activity, MAC requirement, IOP

Neuroprotection via ↓ neurotransmitter release, membrane stabilization, effects on response to ischaemia

Impaired conscious state at 33°C, coma at 30°C (dilated pupils)

↑ neuromuscular blockade

via ↓ axonal depolarization, ↑ ACh release, ↓ excitation-contraction coupling

↓ TOFC (causing overestimate of paralysis)

CVS

↑ myocardial O₂ demand if shivering, ↓ CO if anaesthetized

severe: arrhythmias, ↓ HR, O₂ consumption

contractility and SV relatively preserved

vasoconstriction, poor peripheral perfusion, ↑ SVR, CVP

ECG

SB, ↑ \overline{PR} , wide QRS, prolonged \overline{QT}

<32°C: J wave in II, V₆, then anterior leads

nodal rhythms, PVCs, AV block, fibrillation

Respiratory

↑ $\dot{V}O_2$ with shivering (up to 300%)

↑ PVR, \dot{V}/Q mismatch, impaired hypoxic vasoconstriction

↓ ventilatory drive, ↓ bronchial tone, ↑ dead space

↑ gas solubility

Renal

↓ RBF, GFR directly due to ↑ sympathetic tone, ↓ CO

Cold diuresis due to ↓ Na⁺ reabsorption

Hepatic, GIT

↓ blood flow, metabolic and excretory functions

↓ gut motility

Haematological

↓ platelet function, ↑ visceral sequestration

↓ coagulation, ↑ fibrinolysis

↑ haematocrit, rouleaux formation, left shift of Hb-O₂ dissociation curve

Endocrine and metabolic

↓ BMR 5-7% per °C if not shivering (↓ PCO₂, ↑ glucose)

Metabolic acidosis, pH and PCO₂ changes (α-stat)

Acute rise in K⁺ with rewarming

↓ insulin, insulin resistance, hyperglycaemia with ↑ sympathetic tone

↑ thyroid hormone secretion (long term)

Pharmacokinetic

↓ metabolism and excretion (hepatic and renal)
↑ protein binding, ↓ V_d of circulating compartment

Obesity

Definition

BMI (height in m \div weight in kg squared)
> 25 overweight, > 30 obese

Waist-hip ratio
0.8 ideal, > 1.0 overweight

Risks

↑ perioperative morbidity and mortality, average hospital stay

Associated diseases

Respiratory

↓ FRC, ↑ closing capacity

Hypoventilation, OSA

Cardiovascular

↑ CO 0.1 l/min/kg fat

HT, LVH

Cor pulmonale

Other

Diabetes, cholelithiasis, cirrhosis

30% overweight → 40% ↑ in IHD mortality, 50% ↑ in CVA mortality

Anaesthetic risks

Reduced physiological reserve

↑ difficult intubation

↓ FRC, ↑ ventilatory pressures

↑ fasting gastric volume

75% have > 25 ml, pH < 2.5 at 140 kg

Pressure areas

Monitoring difficulties, vascular access

Larger fat compartment in pharmacokinetics

Postoperative risks

Postoperative hypoxia

Wound infection

DVT, PE

Neurology

[Brain death](#)

[Tests](#)

[EEG in Monitoring 3.B.2](#)

[Neuromuscular disorders and anaesthesia](#)

Brain death

- Coma GCS < 8, potential for recovery

- Persistent coma

 - Persistent vegetative state: brainstem function intact

 - Brain death: brainstem function lost (no spontaneous ventilation)

- Death: "Irreversible cessation of circulatory and respiratory functions or irreversible cessation of all functions of the entire brain, including the brainstem."

Diagnostic criteria of brain death

- Deep coma

 - confirm clearance of depressant drugs

 - normal body temperature

 - no gross electrolyte or metabolic disturbance

- Apnoea

 - no relaxants, opioids or other depressants

 - raised PaCO₂, normal PaO₂

- Irreversible structural brain damage

Procedure

- Pupillary response to light absent

- Corneal touch reflex absent

- Vestibulo-ocular reflexes absent

 - 20 ml ice cold water in ear canals, no eye movement

- Facial motor response to trigeminal distribution pain absent

- Gag and cough reflexes absent

- Apnoea in the presence of PaCO₂ > 60 mmHg, pH < 7.30

- Two examinations at least 2 h apart by separate qualified doctors

- Angiography required if no diagnosis or tests incomplete (e.g. eye injury)

- Modified criteria < 1 year of age due to greater recovery potential

Tests

Flicker fusion test

- Increasing frequency of flashing light

- Frequency at which light appears steady is recorded

- Used to assess degree of hypotension producing significant cerebral ischaemia

Neuromuscular disorders and anaesthesia

Literature

- Little high-quality evidence
- Many case reports, few series
- Small numbers for all conditions except myasthenia gravis (thymectomy)

General concerns

Pre-op assessment

Weakness

- Respiratory failure
- Upper airway maintenance
 - Assessment of need for back-up ventilated bed
- Decreased fitness and exercise tolerance
- Possible myocardial involvement
- Documentation of functional state before anaesthesia

Deformity

- Airway assessment
- Likely ease of intubation
- Positioning

Investigations

- Respiratory function testing
- Blood gas analysis
- ECG, echocardiography if indicated

Intra-op management

- Risk of aspiration
- Decision regarding need for muscle relaxants
- Altered sensitivity to relaxants, need for NMJ monitoring
- Variable distribution of weakness makes relaxant monitoring unreliable
- Appropriate management of steroids or other drugs

Post-op

- Careful monitoring of recovery to adequate tidal volume
- Monitoring for respiratory failure post-extubation
- Possible ICU ventilation

Motor neurone disorders

Multiple Sclerosis

Aetiology

- Unknown, environmental and genetic associations
- Patchy demyelination in the CNS

Features

Signs

- Typical onset in females 20-40 years of age
- Variation in severity over minutes to years
- Common involvement of optic nerve and oculomotor pathways
- Exacerbated by
 - Parturition, elevated temperature, other stresses
- Progression to motor weakness of limbs

Investigations

- MRI shows "plaques"
- Abnormal sensory evoked potentials
- CSF IgG and myelin basic protein elevated

Treatment

- Steroids, ACTH, immunosuppressants used with some effect

Anaesthetic considerations

Hyperthermia may cause exacerbation of weakness
Induction agents, volatiles, relaxants (including suxamethonium) all known to be safe

Relaxants may exacerbate weakness directly

Regional

Possible increased permeability of blood-brain barrier

Increased risk of CNS toxicity from local anaesthetics

Possible increased risk of histotoxicity from spinal local anaesthetic

Not supported by clinical data

Guillain-Barré syndrome

Aetiology

Cell-mediated autoimmune response

Causes demyelination of peripheral nerves

Commonly post-viral (herpes viruses, influenza, para-'flu, HIV)

Possibly post-vaccination (TB, tetanus, typhoid)

Features

Signs

Progressive motor weakness or more than one limb

Areflexia or hyporeflexia

Symmetrical and progressive

Results in flaccid paralysis

Mild sensory involvement, mostly vibration and proprioception

Cranial nerve involvement in 45%

Autonomic dysfunction

Circulatory instability: hypo- and hyper-tension

Bradycardia, tachyarrhythmias

Ileus, urinary retention

Investigations

CSF: low WCC, high protein

Abnormal nerve conduction studies

Timecourse

Recovery 2-4 weeks after onset

Treatment

Plasma exchange proven effective

Immunoglobulin therapy is as effective, but more relapses

Steroids commonly used but unproven

Supportive management: ventilation etc.

Anaesthetic considerations

Increased aspiration risk with bulbar palsy

Respiratory muscle weakness

Circulatory instability on induction

Exaggerated response to pressors and vasodilators

Suxamethonium contraindicated

Motor neurone disease

Aetiology

Some inherited, most sporadic (amyotrophic lateral sclerosis)

Progressive degeneration of upper and lower motor neurones

Features

Signs

Sensory and autonomic pathways spared

Cerebral function largely spared

Several patterns of progression

Cranial vs somatic

Upper vs lower

- Similar to post-polio syndrome
- Investigations
 - None specific
 - EMG shows denervation
- Anaesthetic considerations
 - Upper airway and respiratory muscle weakness
 - Lack of specific treatment raises ethical problems
 - Suxamethonium contraindicated due to potassium release

Neuromuscular junction disorders

Myasthenia gravis

Aetiology

- Autoantibodies (IgG) to α -subunit of ACh receptors on skeletal muscle
- Thymic abnormalities in 75% of patients
- Associated with other autoimmune diseases
 - Hypothyroidism, RA, SLE, pernicious anaemia
- Neonatal variants
 - Children of myasthenic mothers
 - Transient weakness from maternal IgG
 - Hereditary myasthenia
 - No autoantibodies, structurally abnormal receptors

Paraneoplastic variant (Eaton-Lambert syndrome)

- Autoantibodies against voltage-gated Ca^{2+} channels
- Decreased ACh release from nerve terminals
- Association with autonomic dysfunction, reduced gastric motility
- Predominantly limb involvement
- Little bulbar involvement

Features

Signs

- Ocular involvement first: ptosis and diplopia
- Commonly bulbar weakness
- Asymmetrical trunk and limb involvement

Investigations

- Edrophonium (TensilonTM) test
 - 1 mg-6 mg edrophonium, 0.6mg atropine
- Autoantibody assay
 - False positives in RA and some family of affected patients
 - False negative immediately after anaesthesia

Treatment

- Anticholinesterase drugs
 - Pyridostigmine 60 mg qid (up to 750 mg/day)
- Plasma exchange
- Immunoglobulin (unknown mechanism)
- High dose corticosteroids
- Azathioprine, cyclophosphamide, cyclosporin
- Thymectomy after medical optimization gives the best results

Anaesthetic considerations

- Decision to continue anticholinesterase drugs depends on severity
- Anticholinergic agents may be required to cover bowel anastomoses
- Myasthenic crisis (acute exacerbation)
 - Described worsening with local anaesthetics, muscle relaxants, narcotics, ether, aminoglycosides
- Weakness can also be due to anticholinesterase overdose
- Regional anaesthesia is well tolerated
- General anaesthesia

- Propofol plus opioid, or
- Volatile only
 - Produces 50% twitch fade at 1.0 MAC
- Suxamethonium is safe
 - Possibly decreased sensitivity
 - Decreased metabolism if on high anticholinesterase dose
 - High incidence of phase II block at normal dose
- Non-depolarizing agents are usually avoided
 - Increased sensitivity, difficulty reversing

Muscle disorders

Myotonia dystrophia

Aetiology

- Disorder of relaxation of skeletal muscle (AD 19q)
 - Slow reuptake of Ca^{2+} into sarcoplasmic reticulum
 - Multiple tissues affected
- Myotonia congenita variant present from birth
- Paramyotonia variant manifest only with cold

Features

Signs

- Weakness with myotonia
 - Involving pharyngeal muscles as well as limbs and face
- Cataracts
- Frontal balding
- Variable intellectual disability, somnolence
- Cardiomyopathy, conduction abnormalities
- Testicular failure
- Reduced gastric motility

Investigations

- ECG increased PR interval, atrial flutter, other arrhythmias
- RFT marked reduction in maximal expiratory pressure, small reduction in VC

Treatment

- Myotonia can be treated with phenytoin, but is not usually a problem
- Atrophy is not treatable

Anaesthetic considerations

- Prolonged contraction in response to depolarizing relaxants
 - Suxamethonium absolutely contraindicated
 - Also triggered by propranolol, clofibrate, K^+
- Prolonged contraction with shivering
 - Aim to maintain normothermia
 - Relative contraindication to volatiles
- Myotonia provoked by mechanical stimulus and diathermy
- Increased risk of apnoea with sedative drugs
- Myotonia antagonized only by intramuscular local anaesthetic
- Some relief with quinine, procainamide or phenytoin
- Non-depolarizing relaxants are effective at normal doses
 - Reversal appears to be safe despite theoretical risk of myotonia
- Intravenous regional anaesthesia should be effective

Muscular dystrophy

Aetiology

Familial

- Duchenne (X-linked), Limb girdle (AR), Facioscapulohumeral (AD)
- Atrophy of skeletal muscle with fatty infiltration and fibrosis

Features

Signs

- Progressive limb weakness
- Diaphragm function relatively preserved
- Late cardiomyopathy, arrhythmias, mitral valve prolapse
- Kyphoscoliosis with respiratory compromise common

Investigations

- CK typically elevated
- ECG abnormalities (RSR' in V₁, deep Q in lateral V leads, arrhythmias)
- RFT VC<30% predicted indicated high risk with GA

Anaesthetic considerations

- Progressive disease so earlier operation is preferable
- Increased incidence of malignant hyperthermia
- Suxamethonium contraindicated due to potassium release
- Decreased margin of safety with non-depolarizing relaxants
- Gastroparesis reported pre- and post-operatively
- Increased risk of aspiration with bulbar weakness
- Avoid tachycardia as increased risk of arrhythmia
- Rhabdomyolysis and renal failure

[Malignant hyperthermia](#) in Complications 3.A.4

Neuroleptic malignant syndrome

Respiratory

[Management of anaesthesia for a teenager with cystic fibrosis](#)

[Smoking](#)

Management of anaesthesia for a teenager with cystic fibrosis

Cystic fibrosis

AR inherited condition: 1/2500 Caucasians

Chromosome 7 mutation, multiple abnormalities described

Expressed as defective Cl⁻ channels

High Cl⁻ concentration in secretions, increased viscosity

Sweat Cl⁻ > 60 mmol/l

Resultant respiratory, pancreatic, biliary dysfunction

Clinical problems

Respiratory

Impaired clearance of secretions, mucociliary dysfunction

Chronic infection, bronchiectasis, dyspnoea, excessive sputum

Air-trapping due to mucous plugging: COAD-like picture

Nasal polyps, chronic sinusitis

Complications

Respiratory failure: cyanosis, CO₂ retention

Haemoptysis, pneumothorax, cor pulmonale

GIT

Pancreatic exocrine failure

Malabsorption, malnutrition without enzyme supplementation

Chronic pancreatitis, acute exacerbations

Secondary endocrine failure: diabetes mellitus

Bile secretion impaired

Fat and fat-soluble vitamin malabsorption

Later cirrhosis and portal hypertension

Neonatal meconium ileus

Psychological

Many admissions and procedures

Chronic illness, medicalization

Longer survival resulting in more adult presentations

Assessment

Routine, plus

History related to CF

Admissions, current therapy, respiratory disease, diabetic control

Previous anaesthesia

Examination

General appearance, respiratory, cardiac focus

Signs of respiratory failure, right heart failure

Investigation

CXR, RFT, ABG

FBE, U&E, LFT, glucose

Recent cultures of sputum

Optimize

Consult with treating physician to achieve best respiratory function

Bronchodilators, saline nebs, antibiotics, physiotherapy

Technique

Regional avoids the need for intubation and risk of worsening infection

If GA required by nature of surgery, regional analgesia may result in better respiratory function postoperatively

Airway

Humidified gases, nebulized saline may be of benefit

Frequent suctioning

Avoid nasal intubation

Ventilation

As for COAD: long I:E, minimize airway pressures, slow rate

Increased FiO₂

Vigilance for pneumothorax

Circulation

Consider invasive monitoring if cor pulmonale: arterial line ± PA catheter

Other considerations

Management of diabetes: fasting, glucose monitoring

Choice of drugs suitable for impaired hepatic function

Postoperative

Level of care determined by severity of disease and extent of surgery

Active physiotherapy and early mobilization

Smoking

Miscellaneous medicine

[Short case history](#)

[Short case examination](#)

[Anaesthesia and connective tissue disease](#)

Short case history

General history

- Presenting symptoms

- History of the presenting illness

 - Symptoms: duration, site and radiation, character, severity, onset, aggravating and relieving factors, associated symptoms, treatment

- Past history

- Social history

- Family history

- Systems review

 - Cardiovascular, respiratory, gastrointestinal, hepatobiliary, haematological, genitourinary, musculoskeletal, neurological, endocrine

Cardiovascular history

- Symptoms

 - Chest pain (nature, stable or unstable), dyspnoea (exertional, postural, nocturnal), ankle swelling, palpitations, syncope, claudication, fatigue

- Risk factors

 - Family history, smoking, hypertension, hypercholesterolaemia, diabetes, obesity, sex and age

- Past history

 - Angina, AMI, rheumatic fever, chorea, preeclampsia, investigations

- Treatment

 - Drugs, revascularization

- Social history

 - Work, exercise tolerance, smoking

- Family history

Respiratory history

- Symptoms

 - Cough, sputum, haemoptysis, dyspnoea, wheeze, chest pain, sinusitis, hoarseness, night sweats

- Past history

 - Pneumonia, tuberculosis, bronchitis, allergies

- Treatment

 - Steroids, bronchodilators, antibiotics

- Social history

 - Occupation, hobbies (exposures), smoking, alcohol

- Family history

 - Tuberculosis, asthma, emphysema (e.g. cystic fibrosis)

Gastrointestinal history

- Symptoms

 - Pain, nausea, vomiting, bleeding, reflux, dysphagia, appetite and weight change, diarrhoea, constipation, mouth ulcers, fever

- Past history

 - Peptic ulcer, colitis, carcinoma

- Treatment

 - Steroids, NSAIDs, antibiotics, diet

- Social history

 - Alcohol, smoking, travel, occupation

- Family history

 - Bowel cancer, IBD, coeliac disease, polyposis coli

Hepatobiliary history

- Symptoms

 - Jaundice, dark urine, pale stools, fever, pruritus

- Past history

 - Jaundice, surgery, hepatitis, transfusion, blood-borne virus risks

- Treatment
 - Drugs, especially sex steroids and other hepatotoxic drugs
- Social history
 - Alcohol, viral exposure (travel, contacts, sex, occupation, drug use)
- Family history
 - Genetic disease (Wilson's disease, haemochromatosis...), family contacts
- Haematological history
 - Symptoms
 - Blood loss, bruising, infection, gland enlargement, bone pain, symptoms of anaemia, paraesthesia, rash
 - Past history
 - Gastric surgery, colitis, malabsorption, rheumatoid arthritis, uraemia, transfusion
 - Treatment
 - Anticoagulants, immunosuppressants, anticonvulsants
 - Social history
 - Diet, alcohol
 - Family history
 - Genetic disease (haemophilia, thalassaemia, sickle cell, pernicious anaemia, haemolytic anaemia)
- Genitourinary history
 - Symptoms
 - Infection
 - Dysuria, frequency, urgency, fever, loin pain, urethral discharge
 - Renal failure
 - Anuria, nocturia, polyuria, anorexia, vomiting, fatigue, hiccough, itch, bruising, oedema
 - Obstruction
 - Reduced stream, hesitancy, dribbling
 - Menses
 - Onset, regularity, last period, dysmenorrhoea, menorrhagia, parity, discharge
 - Past history
 - Infections, stones, surgery, proteinuria, nephritis, diabetes, gout, hypertension, preeclampsia
 - Social history
 - Analgesic use
 - Family history
 - Polycystic kidneys
- Musculoskeletal history
 - Symptoms
 - Pain, stiffness, swelling, loss of function, nodules, dry eyes or mouth, red eyes, rash, fever, fatigue, weight loss, mucosal ulcers, Raynaud's
 - Past history
 - Trauma, infection, IBD
 - Treatment
 - Physiotherapy, analgesics, NSAIDs, steroids, DMARDs, surgery
 - Social history
 - Home arrangements, work, carer, STDs
 - Family history
 - Arthritis, gout, psoriasis, IBD
- Neurological history
 - Symptoms
 - Headache, pain, paraesthesia, anaesthesia, weakness, disturbance of sphincter control, special senses, loss of consciousness, dizziness, ataxia, tremor, speech disturbance
 - Risk factors for stroke

- Hypertension, family history, smoking
- Past history
 - Meningitis, head or spinal injury, convulsions, operations, STDs
- Treatment
 - Anticonvulsants, anti-Parkinsonian agents, steroids, antihypertensives
- Social history
 - Alcohol, drugs, work, travel
- Family history
 - Neurological disease, consanguinity
- Endocrine history
 - Symptoms
 - Hyperthyroid
 - Goitre, heat intolerance, weight loss, increased appetite, palpitations, sweating, anxiety, diarrhoea
 - Hypothyroid
 - Goitre, cold intolerance, lethargy, eyelid swelling, hoarse voice, constipation, coarse skin
 - Diabetes
 - Polyuria, polydipsia, thirst, blurred vision, weakness, infections
 - Past history
 - Thyroid surgery, irradiation, diabetic complications, hypertension
 - Treatment
 - Iodine, antithyroid drugs, hormone replacement (thyroxine, steroids, insulin...)
 - Social history
 - Impotence
 - Family history
 - Thyroid disease, diabetes, endocrine adenomatosis

Short case examination

General

Position

Patient supine in bed, examined from right side
Fully exposed (with consideration to modesty)

Overview

Facies, skin colour, hair, body habitus, hydration
HR, BP, temperature

Cardiovascular

Position

Supine at 45° on pillows

General appearance

Pallor, dyspnoea, fatigue, cachexia
Characteristic appearance (Marfan's, Down's...)

Hands

Clubbing, nailbeds, finger pulps

Pulse

Rate, rhythm, character and volume, radiofemoral delay

Blood pressure, postural effects

Face

Sclerae (pallor, jaundice), mitral facies, mouth (arched palate)

Neck

Carotid pulse, JVP (level, waveform, Kussmaul's sign, hepatojugular reflex)

Praecordium

Inspection: scars, pacemaker, apex beat (5 ICS, 1 cm medial to MCL)

Palpation: apex beat size and character, left sternal heave, palpable P2, thrill

Auscultation

Bell at apex: mitral stenosis or S3

Diaphragm at apex: Mitral regurgitation or S4

5L ICS (tricuspid)

2L ICS (pulmonary)

2R ICS (aortic)

Carotids or axilla as indicated

Sit forward

Inspiration: right-sided murmurs louder

Expiration: left-sided murmurs louder (esp. AI)

Valsalva: HOCM louder or MVP earlier (↓ LV volume)

Squatting: murmurs except HOCM, MVP louder (↑ LV volume, CO)

Back

Lung bases, sacral oedema

Abdomen

Hepatomegaly, splenomegaly, ascites

Legs

Femoral pulses and auscultation

Distal pulses and oedema

Buerger's test: pallor on elevation (poor perfusion), cyanosis on dependence

DVT, PVD signs

Varicose veins

Other

Urinalysis, fundoscopy

Respiratory

Position

Sitting

General

Sputum mug, cough, rate and depth of respiration, accessory muscle use

Hands

Colour (cyanosis, tar), clubbing, wasting, tenderness (HPO), pulse, tremor

Chest

Inspect

Shape (kyphosis), scars

Palpate

Expansion, nodes, fremitus, breasts

Percuss, auscultate (breath sounds, resonance, adventitious sounds)

Pemberton's sign

Cardiac examination if indicated

JVP, pulmonary hypertension...

Face

Horner's syndrome, jaundice, pallor, cyanosis

Hoarseness

Tracheal deviation

Other

Tests: FET, PEFr, counting tests

Signs of malignancy elsewhere

Temperature

Anaesthesia and Connective Tissue Diseases

Ankylosing Spondylitis

Epidemiology

- 0.5 to 4 per 1000
- male:female 10:1
- HLA-B27 related
- onset between 15 and 40

Pathology and Clinical Findings

- progressive inflammatory synovitis
 - sacroiliac, intervertebral, costovertebral, hip, shoulder and other joints
- fibrosis and ossification, especially of the *annulus fibrosus*
 - “bamboo spine”
 - may impinge spinal cord, nerve roots, vertebral arteries
- aortic root involvement may cause aortic incompetence (3%)
- fibrosis of the AV bundle may cause conduction defects
- pulmonary fibrosis, especially upper lobe, can cause massive haemoptysis
- uveitis in 20-30%

Treatment

- symptomatic treatment with NSAIDs
- no disease-modifying therapy

Anaesthetic Considerations

- may present with
 - orthopaedic procedures (joint replacement, spinal wedge resection)
 - NSAID-associated gastric ulcer disease
 - aortic incompetence, haemoptysis
- spine involvement limits neck mobility
 - may be difficult intubation
 - high incidence of cervical fractures with minimal trauma
 - fixed neck flexion may preclude cricothyroidotomy or tracheostomy
- TMJ involvement limits mouth-opening in 10%
- cricoarytenoid arthritis rarely causes vocal cord fixation
- costovertebral involvement limits chest expansion
 - increased incidence of post-op pulmonary complications
 - external cardiac massage is often ineffective
- neuraxial anaesthesia has an increased failure rate
 - Can J Anaesth 1996 case series:
 - 3 of 13 of spinals and 3 of 3 of epidurals unsuccessful
 - case report analysis suggests epidural haematoma is more likely

Anaesthetic Management

- investigation
 - radiological and clinical assessment of cervical spine and airway
 - ECG
- induction
 - likely difficult intubation
 - cervical manipulation may be dangerous
 - awake fiberoptic intubation or avoidance of intubation may be safest
 - diaphragmatic splinting postoperatively is more likely to cause respiratory failure
- regional
 - spinal or epidural is likely to be even more difficult than GA

Rheumatoid Arthritis

Epidemiology

- approx. 1% of population
- female:male 3:1

prevalence increases with age
onset usually between 35 and 50
associated with HLA-DR4 in some populations

Pathology and Clinical Findings

aetiology uncertain
persistent inflammatory synovitis with symmetric polyarthritis
cartilage destruction and bone erosion
pain and stiffness usually worst in the morning
joints affected
 most commonly pip, mcp, wrist, knee, elbow
 most other synovial joints
 axial involvement limited to cervical spine
 atlanto-axial subluxation
 TMJ and cricoarytenoid joints may be involved
 articular swelling may cause nerve entrapment
 median, ulnar, radial interosseous br., anterior tibial
extraarticular involvement
 rheumatoid nodules in 25%
 vasculitis can cause several complications
 polyneuropathy, skin necrosis, distal gangrene, visceral infarction, renal impairment
 pleuropulmonary nodules and pulmonary fibrosis
 pericarditis and pericardial effusion (present in 50% but subclinical)
 episcleritis and scleritis (1%)
 increased incidence of dysphagia

Treatment

disease-modifying
 gold: thrombocytopenia, granulocytopenia, proteinuria
 D-penicillamine: thrombocytopenia, granulocytopenia, proteinuria
 hydroxychloroquine: retinopathy
symptomatic
 simple analgesics
 NSAIDs
 corticosteroids
immunosuppressants
 azathioprine, cyclophosphamide: marrow suppression, ?malignancy
 methotrexate: abnormal LFTs
surgery
 synovectomy, joint replacement, nerve releases

Anaesthetic Considerations

cervical spine
 cervical spine instability in 25%, usually atlanto-axial
 most asymptomatic
 case reports of spinal cord damage in relaxed patients
 occipito-cervical fusion increases the incidence of lower instability
larynx
 odontoid migration is associated with laryngeal displacement
 usually anteriorly and to the left
mouth opening
 limited by TMJ involvement
 more common in juvenile arthritis
cardiac function
 pericardial effusion and valve involvement
pulmonary fibrosis
drug-related complications

Anaesthetic Management

- investigation
 - clinical and x-ray assessment of cervical spine in flexion and extension
 - investigation for drug complications (FBE, U&E)
 - RFT if pulmonary involvement
- induction
 - cervical collar if unstable
 - intubation with fiberoptic scope or laryngeal mask
 - cricoid cartilage involvement may necessitate a smaller tube

Progressive Systemic Sclerosis (“Scleroderma”), CREST syndrome

Epidemiology

- female > male
- onset 30-50 years
- variation in severity over time

Pathology and Clinical Findings

- increased production of normal collagen
 - cutaneous, gastrointestinal, cardiac, renal, other organs
- possibly due to endothelial damage in small vessels causing an inflammatory response, antinuclear antibodies are usually present
- cutaneous
 - taut, shiny skin tethered to underlying tissue
 - contractures of joints and the mouth may occur (bird-like facies)
- peripheral vascular spasm causes Raynaud’s phenomenon
- gastrointestinal
 - involvement spares the upper third of the oesophagus
 - remainder of the small bowel affected
 - diverticulae in large bowel
 - dysphagia and dysmotility, malabsorption
- pulmonary
 - vascular involvement may cause pulmonary hypertension
 - interstitial fibrosis usually lower $2/3$
- cardiac
 - fibrosis of myocardium and conducting system (56%)
 - fibrinous pericarditis, effusion (28%)
- renal
 - cortical infarction and glomerulosclerosis in >50%
 - temperature-sensitive vasospasm
- symmetric polyarthritides
- hypothyroidism due to fibrosis

Treatment

- D-penicillamine, aspirin used without evidence
- vasodilators for Raynaud’s (and avoidance of cold)
- symptomatic H_2 antagonists
- antihypertensives may delay renal failure

Anaesthetic Considerations

- periphery
 - difficult venous access
 - increased risk of fingertip ischaemia or ulceration
 - telangiectasia may bleed
- airway
 - mouth contractures
 - increased reflux risk
- cardiovascular
 - hypertension, LV failure, arrhythmias
 - cold-induced vasospasm
- pulmonary

- constrictive chest wall, alveolitis
- regional
 - case reports of prolonged sensory loss after local anaesthetic
- Anaesthetic Management
 - investigation
 - assessment of airway and any contractures
 - assessment of pulmonary function
 - CXR may show prominent PA in pulmonary hypertension
 - pre-op
 - warming, possible need for CVC or cut-down for IV access
 - increased risk of distal ischaemia with arterial cannulation
 - induction
 - protection from reflux risk

Systemic Lupus Erythematosus

- Epidemiology
 - 15 to 50 per 100,000
 - female:male 10:1
 - onset 20-50 years
 - racial differences in prevalence
 - association with multiple autoantibodies and HLA types
- Pathology and Clinical Findings
 - type III immune complex disease
 - aetiology uncertain
 - drug-induced variant from hydralazine or procainamide
 - abnormal immune activation against self antigens
 - skin
 - “butterfly” rash, photosensitivity, vasculitis, ulceration, alopecia
 - arthritis
 - painful pip and mcp joints, tenosynovitis
 - ischaemic necrosis of bone
 - renal
 - immune complex deposition causes glomerulosclerosis
 - may cause renal failure requiring dialysis
 - neurological
 - CNS involvement, ?personality changes, psychosis, fitting
 - neuropathies, including cranial nerves
 - vascular, haematological
 - thrombotic tendency (Lupus anticoagulant)
 - binds phospholipids in prothrombin-activator complex
 - persistent vasculitis predisposes to coronary and peripheral vascular disease
 - commonly require anticoagulant prophylaxis
 - may develop anti-VIII or IX antibodies, causing bleeding
 - thrombocytopenia is common
 - cardiac
 - pericarditis, myocarditis are uncommon
 - endocarditis can involve mitral or aortic valves, causing incompetence
 - pulmonary
 - pleural effusions are common, infiltrates are most commonly infective
 - gastrointestinal
 - vasculitis may cause gut ischaemia or perforation
 - eyes
 - retinal vasculitis, infarcts, blindness
 - pregnancy
 - normal fertility, increased spontaneous abortion rate
 - SLE commonly exacerbated from first trimester

neonates may display complete heart block or discoid lupus rash

Treatment

30% mortality over 10 years from diagnosis, related to severity

symptomatic treatment of inflammation with NSAIDs

rash may respond to hydroxychloroquine

severe disease responds to high-dose corticosteroids

immunosuppressants sometimes used: azathioprine, cyclophosphamide, chlorambucil

Anaesthetic Considerations

pulmonary involvement may cause restrictive lung deficit

thrombotic tendency, but abnormally prolonged APTT with Lupus anticoagulant

commonly thrombocytopenic

commonly present during pregnancy

Anaesthetic Management

investigation

RFT for pulmonary disease

assessment of cardiac involvement and renal function

coagulation testing, platelet count

test for Lupus anticoagulant

regional

difficult risk-benefit assessment for epidural analgesia in labour

Cardiac surgery

[Management of pericardial tamponade post bypass surgery](#)

[Preparation for going onto and coming off cardiopulmonary bypass](#)

[Post-bypass bleeding](#)

[Patient assessment for cardiac surgery](#)

[Anaesthesia for cardiac surgery](#)

[Priorities in valve disease](#)

[Doses](#)

[Anaesthesia in the post-transplant patient](#)

Management of pericardial tamponade post bypass surgery

Issues

- Emergency complication of bypass surgery requiring immediate surgical consultation
- Simultaneous diagnosis and management
- Accumulation of blood in enclosed pericardial space limits atrial and ventricular filling

Features

- Fall in cardiac output
 - Hypotension, narrow pulse pressure
- High filling pressures
 - ↑ PAOP, CVP
- Failure of mediastinal drainage
 - Large volume drainage early followed by clots

Management

- ABCDE priorities
 - Secure airway, ventilate with 100% O₂
 - Support circulation
 - High filling pressures, tachycardia
- Surgical intervention
 - Remove clot from pericardium in theatre if there is time for transfer

Anaesthesia

- Reanaesthetizing post-bypass patient

Preparation

- Routine check of anaesthetic machine and equipment
- Pressor and dilator drugs, heparin for bypass
- Check Hb, platelets, coagulation status, acid-base status
- Notify blood bank
- Haemodynamic support
 - IV fluid, pacing to 90-140 min⁻¹
 - Continue inotropes from ICU

Monitoring

- Invasive monitoring (arterial and PA catheter) usually in situ
- TOE may give useful information about tamponade and ventricular function

Induction

- Fentanyl 10-20 µg/kg, pancuronium
 - Consider sux if reintubation required (may be difficult)
- Small dose of thiopentone or ketamine

Maintenance

- High degree of vigilance for complications, arrhythmias
- May require going onto bypass
- Monitoring of Hb, ABG, coagulation

Postoperative

- Return to ICU intubated and ventilated

Preparation for going onto and coming off cardiopulmonary bypass

Check list for bypass

Before cannulation

Anticoagulation

Heparin dose 300-400 U/kg

ACT > 300 s

Haemodynamics

Systolic BP < 100 mmHg

ECG recorded

CVP adequate for caval cannulation

Ventilation

Compliance recorded

ABG and acid-base satisfactory

Before running on CPB

Anaesthesia and paralysis confirmed

CPB circuit has no bubbles, correctly connected and clamps off

IV fluid ceased and urine recorded

First minutes of CPB

Adequate flows and pressures

Obvious oxygenation of aortic cannula blood

Cease ventilation when arrested

Continue ABG, ACT measurement

During CPB

Anticoagulation

Maintain ACT > 400 s

Inspect circuit and reservoir for fibrin

ABG, acid-base

ABG normal (α stat)

$P\bar{v}O_2$ > 40 mmHg, $S\bar{v}O_2$ > 60%

Hct 18-22%

Haemodynamics

MAP 40-90 mmHg, PAP < 15 mmHg, CVP < 0

Quiescent ECG

Temperature

Monitor hypothermia and rewarming

Neurological

Facial oedema, pupils, EEG (if monitored), paralysis

Renal

UO > 1 ml/kg/h, no haemolysis

Pump

Pressure and flow appropriate

Venous return appropriate

Fluid balance

Coming off CPB

Rewarming

Neurological unresponsiveness

Adequate ACT, normal ABG, pH, electrolytes

Vasodilation for even rewarming

Defibrillation \pm pacing

Prior to coming off

ABG, Hct, K^+

Core and peripheral temperatures

Suitable rhythm

Controlled MAP

Filling, vasodilation, CVP, PAP

- Reinflate lungs, Valsalva
- Vent arterial air, verify with TOE
- Weaning CPB
 - Preload
 - CVP, PAOP
 - Filling and vasodilation
 - Ventricular function
 - dP/dt on arterial trace
 - CO, TOE
 - Inotropes if indicated
 - Return of reservoir blood \pm haemodilution blood
- After discontinuation
 - Protamine to normalize ACT
 - Correction of coagulopathy, thrombocytopenia if indicated
 - Haemodynamic management (pacing, filling, inotropes, vasodilation)
 - Maintenance of anaesthesia
 - Preparation for ICU transfer

Post-bypass bleeding

Issues

Postoperative patient with multiple possible causes of impaired haemostasis
Usually in ICU setting
May be an emergency depending on severity: simultaneous diagnosis and management

Priorities

ABCDE if necessary (tamponade, rapid bleed)
Aim for haemodynamic stability, assessment, correction of abnormalities
In practice, treatment may be empirical in order to achieve stability

Assessment

History

Medical problems (e.g. renal failure, hepatic dysfunction)
Preoperative drug therapy (e.g. aspirin, warfarin)
Operative detail: duration of CPB, transfusion requirement

Examination

Rate, source and nature of bleeding (general vs localized, arterial vs haemoserous)
Relation to position if drain tube losses only

Tests

ACT prior to leaving theatre
APTT, INR, platelets
DIC screen
Thromboelastography

Management

Surgical haemostasis
Reversal of residual heparinization
Replacement of platelets and desmopressin
Replacement of clotting factors
Prevention of secondary fibrinolysis, DIC

Patient assessment for cardiac surgery

Epidemiology

IHD in 20% of adult surgical patients, 70% of vascular patients

Perioperative AMI has 15-70% mortality

Cardiovascular

History, examination

Angina, exercise tolerance, dyspnoea, palpitations

Hypertension

Medication, previous procedures

Other vascular disease: aneurysms, carotid or peripheral disease

Signs of cardiac failure or valve dysfunction

ECG, exercise ECG

HR and BP at which ischaemia was evident

Leads which showed ischaemia best

Evidence of ventricular dysfunction

Echocardiography

Condition of aorta and coronaries, LV function, valve function

Regional wall motion abnormalities

Stress echo has good discriminatory power

Coronary angiogram

Static test, no indication of exercise ischaemia

Location of lesions → ECG leads to monitor

Results of previous revascularization procedures

LVgram indicates LV function (not best test)

Radionuclide angiocardigraphy

Perfusion defects ± stress, ventricular ejection

Cardiac catheter

Valve function and gradients, ventricular pressure, output

Quantification of shunts

Other tests

FBE, U&E, LFT, XM, ABG (sometimes at induction)

Of questionable value: clotting, urinalysis

Noncardiac disease of interest

Condition should be optimized before elective surgery

Endocrine

Obesity, thyroid dysfunction, adrenal dysfunction, phaeo

Diabetes

Autonomic lability, silent ischaemia, slowed gastric emptying

Haematological

Anaemia, coagulopathy, haemolytic conditions

Respiratory

Smoking, asthma, COAD, infection, pulmonary embolism

Other

Renal failure, cirrhosis, peptic ulcer disease, drug dependence, connective tissue diseases

Medications

Decision to continue or cease in consultation with cardiologist

Continue

Antianginals, β -blockers, antidysrhythmics, most antihypertensives

Usually continue

Aspirin, Ca^{2+} channel blockers, digoxin, most other agents

Maybe cease

ACE inhibitors (worsen hypotension)

Usually cease

Diuretics, oral hypoglycaemics (substitute insulin)

Other preparation
Consent
Height, weight, BSA
Washing, shaving, fasting

Anaesthesia for cardiac surgery

Premedication

- Anxiolytic and sedative, avoid hypotension and marked hypercarbia
 - Diazepam 0.1-0.2 mg/kg plus morphine 0.1 mg/kg
 - or lorazepam and fentanyl, or Omnopon and scopolamine
- Reduced risk of ischaemia
 - Nitrate, β -blocker, clonidine

Monitoring

Routine

- SpO₂, ECG with ST analysis, arterial line, PA catheter (CVC in some units), temperature (core and peripheral), IDC with burette, large peripheral IV
- All in place before induction
- Priorities: volume status and contractility assessment to guide therapy

If indicated

- Oesophageal stethoscope can monitor HR, breathing without interference
- PA catheter (unless routine) for CO, PAOP
- TOE
- Cerebral function monitor for deep hypothermia

Bedside tests

- ABG, Na⁺, K⁺, Hb, glucose, ACT (? thromboelastography)

Induction

Traditional

- Fentanyl 10-30 μ g/kg, pancuronium 0.1 mg/kg, propofol minimum required dose

Additional drugs

- Antibiotics, ϵ -aminocaproic acid or aprotinin, Mg²⁺
- Heparin pre-bypass
- Pressors and vasodilators as required

“Fast track”

- Propofol, isoflurane, fentanyl or remifentanyl
- Requires normothermia, haemodynamic stability and coagulation at end of case

Thoracic epidural

- Improved analgesia, \downarrow stress response
- Risks unknown, may be no better than β -blockade

Off-bypass CAGS

- Conventional anaesthetic, grafts performed on beating heart
- Requires low CO, low O₂ demand during grafting as coronary vessel is occluded
- Fill, posture head down, reduce heart rate

Maintenance

- Usually air, O₂, isoflurane \pm propofol infusion for bypass

Bypass

[Going onto and coming off bypass](#)

- Venous return usually from SVC and IVC

Total or partial bypass

- Additional input from sucker and LV vent if present
- Reservoir in bypass machine
- Oxygenator (membrane or bubble)
- Heat exchanger
- Pump (usually non-occlusive roller)
- Bubble catcher and filter
- Arterial infusion usually ascending aorta

- Output commonly set at typical CO for patient (\approx 5 l/min)
- MAP set by dilator/pressor infusion (\approx 70 mmHg)

Management of pH, PCO₂

No temperature correction (alpha-stat) is conventional

Postoperative

Transfer to ICU

Oxygen and means of ventilation

Continuous monitoring (ECG, SpO₂, BP), pacemaker if necessary

Infusion devices for drugs

Assistance for emergencies

Sedative, analgesic and resuscitation drugs

Advance notice to ICU

Analgesia

Narcotic infusion, PCA, oral adjuvant agents

Doses

| | Bolus | Infusion | Prepare |
|---------------------|------------------|-------------------------|----------------------|
| Pressors | | | |
| Methoxamine | 2-100 mg | | |
| Phenylephrine | 50-100 μ g | | |
| Metaraminol | 0.1-2 mg | 40-500 μ g/min | 10 mg in 20 ml |
| Ephedrine | 5-30 mg | | 30 mg in 6 ml |
| Noradrenaline | 1-10 μ g | 1-60 μ g/min | 1.5 mg in 25 ml |
| Inotropes | | | |
| Dobutamine | | 2-20 μ g/kg/min | 3·BW mg in 50 ml |
| Dopamine | | 2-15 μ g/kg/min | 3·BW mg in 50 ml |
| Isoprenaline | 1-5 μ g | 0.5-5 μ g/min | 200 μ g in 20 ml |
| Adrenaline | 2-50 μ g | 1-60 μ g/min | 1.5 mg in 25 ml |
| Milrinone | 50-75 μ g/kg | 0.4-0.8 μ g/kg/min | |
| CaCl ₂ | 0.25-1 g | | |
| Glucagon | 3-10 mg | | |
| Vasodilators | | | |
| GTN | | 50-500 μ g/min | 15 mg in 25 ml |
| SNP | | 0.2-8 μ g/kg/min | 50 mg in 500 ml |
| Phentolamine | 1 mg | 0.5-7 μ g/kg/min | |
| PGE ₁ | | 0.05-0.5 μ g/kg/min | |
| Hydralazine | 5 mg | <40 mg/h | |

Priorities in valve disease

Mitral stenosis

Severity by valve area: normal 4-6 cm², mild 1.5-2.5 cm², moderate 1-1.5 cm², severe ≤1 cm²

Sinus rhythm and normal heart rate are vital for output

Maximize LA pressure without pulmonary oedema

↑ risks with PA catheter in pulmonary hypertension

Pulmonary HT may cause RV failure

Mitral regurgitation

Severity by regurgitant fraction: >0.6 severe

Heart rate normal to high

Low SVR increases forward flow (limited by hypotension)

Maintain contractility without high preload (dilates LV)

Risk of ventricular rupture coming off bypass

Loss of *chorda tendinae* bracing ventricle and ↑ pressure work

IABP may be helpful

Aortic regurgitation

LV volume overload, gradual hypertrophy, sudden decompensation

Severity by regurgitant volume: mild 1-3 l/min, moderate 3-5 l/min, severe >6 l/min

Tachycardia reduces LV distension

Low SVR increases forward flow (limited by hypotension)

Contractility usually impaired

Aortic cross-clamp or LV vent may be required

Antegrade cardioplegia may be impossible

IABP contraindicated

Aortic stenosis

Severity by valve area (<1 cm² severe) or pressure gradient

High LVEDP (PAOP) to fill non-compliant ventricle

Sinus rhythm a high priority, normal heart rate

Myocardial O₂ balance is impaired by LV hypertrophy and low aortic root pressure

Vasodilation may severely impair coronary and cerebral perfusion

HOCM

Dynamic functional aortic outflow obstruction due to septal hypertrophy

Obstruction improves with reduced pressure gradient

Vasoconstriction, β-blockade, myocardial depressants

Maintain high preload

High incidence of arrhythmia

Anaesthesia in the post-transplant patient (BJA 1991; 67: 772-778)

Transplant types

Heart, heart-lung, single lung

Complications

Arrhythmia: including fatal VT, sign of rejection

Infection related to immunosuppression

CMV, HSV, pneumonia with *Pneumocystis carinii*

Neoplasia related to immunosuppression

Depression, anxiety, thought disorder

May lead to rejection due to medication non-compliance

Coronary vessel disease

Common (46% at 2 years) without pain (denervated)

Presents with lethargy and dyspnoea

Routine screening angiography and biopsies for rejection

Lung rejection

Symptoms similar to infection: desturation, fever, leukocytosis, opacification

Anaesthesia issues

Denervated heart

Rate 90-100 /min, no vagal or sympathetic response

Normal response to circulating catecholamines

No rate response to baroreceptors, Valsalva, carotid sinus, hypovolaemia, light anaesthesia

Dependent on intrinsic regulation of cardiac output

Preload dependent → stroke volume

Must maintain filling pressure

Cardiac pharmacology

Little effect from cholinergic agents: atropine, neostigmine, suxamethonium

β adrenergic agents and glucagon remain effective

Antidysrhythmics and DC reversion remain effective

Denervated lung

Relatively normal respiratory pattern and maintenance of gases

PCO₂ response may be blunted

No cough in response to irritation of bronchi

Extubate awake, encourage active physio

Uneven V/Q distribution

Bronchoconstriction *can* occur

Usual drug regimen

Immunosuppression

Must be continued perioperatively

Steroid requires supplementation

Azathioprine

Cyclosporin: nephrotoxicity, hepatotoxicity, hypertension, ↑ NDB effect

Evaluation

Consult with treating unit

Routine preoperative assessment

Technique

GA or regional **provided filling maintained**

Meticulous aseptic technique

Routine prophylactic antibiotics (? also for line insertion)

Isoprenaline for bradycardia (not atropine)

Minimize lines, avoid right IJV (used for biopsies)

Vigorous physio post-op

Vascular

[Carotid endarterectomy](#)

[Preoperative assessment of a patient for carotid endarterectomy](#)

[Abdominal aortic aneuysm](#)

[Thoracic aortic aneurysms](#)

Carotid endarterectomy

Indication

- Symptomatic carotid disease > 70% occlusion: proven benefit in long-term stroke rate
- Asymptomatic disease > 50-60% occlusion: reduces ipsilateral stroke rate

Perioperative morbidity

- Stroke 3-5%, most postoperatively (> 50% after 4 hours post-op)

 - Risk factors: previous stroke, poor BP control post-op

- AMI 0-4%

Preparation

- Cardiac investigation indicated only for unstable angina, recent MI or decompensated CCF

- 70% of patients have silent IHD, diagnosis does not alter management

- Relative priority of CAGS is undetermined

Anaesthetic management

Objectives

- Cardiac and neurological protection from ischaemia

- Cardiovascular stability

- Early postoperative neurological examination

Monitoring

- Routine plus ST segment monitoring, arterial line, large IV

- Arterial line in arm with highest BP on examination

- CVC generally avoided

GA

- Fairly routine

- Consider propofol “book-end” technique for rapid awakening

- O₂, N₂O, isoflurane maintenance

- Ready availability of pressors and nitrates for BP control

- Continued BP control with emergence and post-op

- Maintain normocapnia and normoglycaemia

- Cerebral protection: high dose barbiturates for burst-suppression

Regional

- Deep and superficial cervical plexus block

 - Exclude contraindications, monitor, IV access, assistant

 - Detail of [technique](#)

Advantages

- Continuous functional neurological monitoring

- High level of patient acceptance: 92% would have again

- Possible lower risk of perioperative stroke

- Possible lower risk of cardiopulmonary complications

- Less BP lability intra- and post-operatively

- No instability on “wake-up”

Disadvantages

- High plasma levels of LA

- Phrenic nerve block

- Higher catecholamine levels, ? more tachycardia

Clamping

- Order: ICA, CCA, ECA

- Observe neurological findings for 2-3 minutes (regional) or BP, stump pressure, other monitors (GA)

Unclamping

- Order: ICA (flush), clamp ICA, ECA, CCA, ICA

Postoperative complications

Neurological complications

- Usually due to intraoperative embolization or hypoperfusion or endarterectomy site embolization or thrombosis

Some due to intracerebral haemorrhage (0.4-2%) or hyperperfusion

Rate strongly correlates with surgical technique

Hypertension, hypotension

Usually due to carotid sinus baroreceptor dysfunction but hypoventilation, pain, bladder distension should be excluded

Treated aggressively to minimize risk of cerebral or myocardial injury

Nerve injury

Commonly recurrent laryngeal, superior laryngeal, hypoglossal or marginal mandibular

Wound haematoma requires prompt drainage if airway compromised

Preoperative assessment of a patient for carotid endarterectomy.

Surgery

Elective, high risk

1-2% mortality, 4-10% morbidity

Issues

Access to airway

Cerebral protection

Assessment

Identify myself and patient, confirm procedure, explain role

History

CVS

Symptoms of cerebrovascular disease

Hypertension, usual BP as basis for intraoperative aim

Coronary vascular disease

MI, angina, SOB, symptoms of failure

Peripheral vascular disease symptoms

NYHA functional classification

Respiratory disease

Commonly smokers, COAD

Other illnesses

Diabetes. renal impairment

Examination

Focussed on cardiac and respiratory complications

Document neurological status

Medications

Decision whether to continue or withhold

Commonly on multiple medications

Antiplatelet, β -blockers, diuretics, ACEI, others

Investigation

ECG: high incidence of IHD

U&E, FBE

If IHD, consider echo, thallium scan or angiography

Carotid disease is generally treated before CAGS

But other revascularization options may be considered

Overall

Diseases unstable or stable, optimized or not

Plan for risk minimization

Consult

Appropriate referral for optimization of function

Consent

Anaesthetic plan: GA or regional

Regional requires detailed explanation in advance

Risks

General: allergy, aspiration, blood transfusion, cardiac event, dental injury, death, awareness

Specific: stroke risk

Postoperative plan

Ward or HDU

Analgesia

Premedicate

Aiming for normotension, normocapnia, anxiolysis

Usual antihypertensives, antiplatelet drugs as per surgeon's instructions

Anxiolytic: temazepam

Abdominal aortic aneurysm

Natural history

Progressive enlargement and rupture

5 y rupture rate

4-7 cm 25%

7-10 cm 45%

>10 cm 60%

Risk of rupture rises with diameter and rate of expansion

Greater than risk of surgery at ≥ 5 cm or $\uparrow \geq 0.5$ cm in 6 months

Preoperative

Assessment

Similar to [endarterectomy](#)

Intraoperative

Monitoring

Routine, plus arterial line, multiple large IVs, CVC or Swan sheath

Cell-saver for large anticipated blood loss

Consider nasopharyngeal airway placement prior to heparinization if extubation planned

Induction

GA with minimized BP rise, epidural catheter or

Spinal or CSE for endoluminal repair

Crossclamping

Effects depend on level of clamping, collateral circulation and physiological reserve

Little effect from infrarenal clamp, major changes with thoracic clamp

Haemodynamic

\uparrow SVR (direct): \uparrow BP, \downarrow ejection fraction, \downarrow CO, \uparrow LVEDV,

\uparrow contractility, \uparrow coronary flow

reflex \uparrow sympathetic tone: \uparrow SVR, \uparrow venous return, \uparrow PAOP & CVP,

\uparrow LVEDV, \uparrow CO (if good myocardial function)

If coronary stenosis: segmental wall motion abnormality, ischaemia or LV failure

Wall motion abnormalities in 40% of infrarenal and 90% of supraceliac clamps

Metabolic

Distal ischaemia: $\downarrow \dot{V}O_2$, \downarrow CO_2 excretion, \uparrow $S\bar{v}O_2$, \uparrow catecholamines

Metabolic acidosis, if ventilated: respiratory alkalosis

Intervention

Afterload reduction

SNP, volatiles, amrinone, epidural, remifentanyl

Preload reduction

GTN, epidural, shunt or left heart bypass

Renal protection

Mannitol, dopamine, fluids

Suprarenal clamp \rightarrow 90% reduction in RBF

Infrarenal clamp \rightarrow 40% reduction in RBF

Unclamping

Haemodynamic

\downarrow SVR, \downarrow CVP, \downarrow CO, \downarrow BP, \downarrow contractility

Metabolic

$\uparrow \dot{V}O_2$, $\downarrow S\bar{v}O_2$, \uparrow lactate, PGs, activated complement, myocardial depressants

Intervention

\downarrow vasodilators & volatiles, IV filling, pressors

Reapply crossclamp if unacceptable hypotension
Emergence
Extubate on table if stable: normothermia, normal ABG, no massive
transfusion

Thoracic aortic aneurysms

Classification

DeBakey

- I thoracoabdominal
- II ascending and arch
- III descending ± abdominal

Crawford I-IV

Risk with surgery

- Mortality 5-15%
- Paraplegia 5-40%
- ARF 3-30%

All depending on extent of aneurysm

Issues

Planned technique

- Extracorporeal circulation
- One-lung ventilation

Monitoring

- Spinal cord function

Protection

- Spinal cord, renal, cerebral, myocardial

Preoperative

Assessment

- As any vascular or thoracic patient, plus anatomical detail of aneurysm
- Respiratory function if OLV planned

Intraoperative

Monitoring

- Routine, plus
- IV access: 8.5 Fr x 3 (PA catheter and 2 rapid infusers)
- Arterial line in right radial ± femoral if femoral bypass
- Temperature (core and periphery), TOE, SSEPs

Induction

- Minimizing hypertension with cardiac-type induction
- Left-sided DLT for **left** lung deflation (minimizes risk of occluding RUL)

Maintenance

Bypass

- Full bypass with flow into ascending aorta
- Partial bypass with flow LA → femoral artery
- Passive shunt around clamped aorta
- No bypass “clamp and run”
- Clamp duration
 - 30 min 10% paraplegia
 - 60 min 90% paraplegia
- Deep hypothermic circulatory arrest (DHCA) for arch aneurysms
± cold oxygenated retrograde cerebral perfusion

Spinal protection

- CSF drainage, hypothermia, intrathecal papaverine

Renal protection

- Dopamine, mannitol, fluid loading, frusemide

Myocardial protection

- Clamping and unclamping: compensate for haemodynamic changes with vasoactive drugs

Emergence

- Change DLT for single-lumen tube with changing catheter
- Transfer ventilated to ICU

Neurosurgery

[Positioning for neurosurgery](#)

[Venous air embolism](#)

[Problems associated with raised ICP](#)

[Transsphenoidal surgery for acromegaly](#)

[Paediatric neurosurgery](#)

[Surgery following subarachnoid haemorrhage](#)

[Awake craniotomy](#)

Positioning for neurosurgery

General considerations

- Usually prolonged surgery
- Careful identification of pressure areas
- Avoidance of traction on nerves
- Thromboembolic precautions

Supine

- Used for frontal, temporal or parietal access
- Extreme of head rotation may cause venous obstruction, carotid dissection
- Slight head-up usually desirable for venous drainage
- Hip and knee flexion reduces back strain: beach-chair position

Semilateral ("Jannetta")

- Used for retromastoid procedures
- Table tilted 10-20°, shoulder roll, head rotation
- Avoid extreme head rotation

Lateral

- Used for posterior parietal and occipital access
- Axillary roll to prevent brachial plexus injury
- Stabilization with vacuum bean-bag or lateral rests (potential pressure areas)

Prone

- Used for spinal, occipital, cranial suture and posterior fossa procedures
- For cervical spine and posterior fossa usually head-up and neck flexed
- Requires planning for turning
 - Secure airway and lines, 100% O₂, removal of most monitoring
 - Unstable cervical spine may require awake intubation and positioning
- Facial support must not cause eye compression and retinal ischaemia
- Other pressure areas: elbows, breasts, iliac crests, genitalia, knees, toes
- Avoid pressure on abdomen: ↑ PAW, IVC obstruction
- Neck flexion may cause compression of base of tongue and pharynx
 - Especially with instrumentation: ETT, TOE

Sitting

- Used for some posterior fossa and cervical spine surgery
- Possibly greater dangers than alternative positions
 - Hypotension, cerebral ischaemia (↓ venous return, ↓ CPP)
 - Perfusion pressure should be measured at ear level
 - Lightly anaesthetized patients may compensate with ↑ SVR, ↓ CO
 - Volume loading and pressors to maintain CPP ≥60 mmHg
 - TEDs stockings or calf compression devices
 - Tongue and pharynx compression or spinal injury from neck flexion
 - Pressure areas: buttocks, potential brachial plexus distraction
 - Venous air embolism ± paradoxical embolism
 - Pneumocephalus
 - May be worsened by N₂O diffusion after dural closure
 - Cease N₂O with dural closure
 - PA catheter tip may be in West's zone 1 (alveolar pressure > PA pressure)
 - Surgery in this position may involve the brainstem
 - Haemodynamic, respiratory, homeostatic disturbance
- Some advantages
 - Better venous and CSF drainage, possibly better access

Venous air embolism

Incidence

- Depends on procedure, position and method of detection
- Sitting position posterior fossa surgery with TOE: 76%
- Less for other positions, surgery and monitors

Aetiology

- Open vessels at lower than ambient pressure
 - Cerebral sinuses, emissary veins, diploic vessels in head-up position
 - Gas under pressure in ventricles, subdural space
 - Gas under pressure in non-neurosurgical procedures: laparoscopy, hysteroscopy, gas-cooled lasers

Detection

- High sensitivity
 - TOE, praecordial Doppler (right sternal edge 3rd-6th intercostal spaces)
- Lower sensitivity, indication of severity and recovery
 - ETCO₂, PAP
- Low sensitivity, indication of incipient arrest
 - BP, ECG, SpO₂

Management

- ABC
- Prevent further air entry
 - Notify surgeon, flood field
 - Jugular compression, lower head
- Manage intravascular air
 - 100% O₂, cease N₂O, cease PEEP
 - Aspirate right heart catheter if present
 - Circulatory support: fluid, pressors, chest compression
 - Head-down right lateral position theoretically advantageous
 - Not feasible in most neurosurgery, no evidence for efficacy

Paradoxical embolism

- Requires PFO (25% prevalence) and transient RAP > LAP
 - PFO may be detected by TOE after induction
- RAP to LAP gradient
 - Transiently positive during cardiac cycle
 - Increased by PEEP, greatest with release of Valsalva manoeuvre
 - Reduced by fluid loading

Problems associated with raised ICP

ICP

Intracranial pressure

Usually measured with LP in lateral position or intraventricular catheter

Used to calculate cerebral perfusion pressure

$$CPP = MAP - \text{greater of JVP and ICP}$$

Rises with intracranial expansile mass

Monro-Kellie Doctrine: volume of cranium is constant

Initial compensation by reduced venous blood volume

Then rapidly rising ICP, \uparrow capillary pressure increases cerebral oedema

CBF becomes pressure-passive

Potential for herniation through tentorium

Cerebral blood flow (CBF)

Autoregulated under normal conditions

CPP 60-160 mmHg

Affected by PaO_2 , $PaCO_2$, cerebral metabolic activity ($CMRO_2$)

Surgery

To relieve intracranial pressure

Craniotomy, resection of lesion, drainage of haematoma

Incidental

Trauma patient with head injury and other injuries

Chronic intracranial hypertension

Assessment

Routine, plus

Neurological findings

Headache, nausea, vomiting, visual disturbance, cranial nerve lesions, irritability and confusion

Intracranial pathology: malignancy, haemorrhage

Timecourse of symptoms

Cardiorespiratory history

Usual blood pressure (baseline for autoregulation of CBF)

Specific diseases

Diabetes, pituitary dysfunction, trauma

Medications

Steroids, anticonvulsants, antihypertensives, mannitol, frusemide

Airway assessment, risk of aspiration

Usual investigations plus imaging

Preoperative

Premedication

Avoid hypercapnia, so no opiates

Usual machine and equipment checking

Monitoring

Routine, plus

ECG arrhythmias common

Arterial line, CVC or long line

IDC, temperature

Intraoperative

Induction

Most agents suitable except ketamine

Barbiturates, propofol reduce $CMRO_2$, CBF and ICP

Non-depolarizing relaxants safe

Histamine release should be avoided

Suxamethonium relatively contraindicated

ICP rise is small and blocked by pre-dosing with NDB

Lignocaine 1.5 mg/kg may reduce ICP rise at intubation

- Protect eyes and face
- Use armoured tube
- Maintenance
 - Continuous deep muscle relaxation
 - TIVA or inhalational techniques
 - All agents except ketamine cause \downarrow CMR, \downarrow CBF in parallel
 - High concentration of volatiles impair autoregulation ($H \gg E > I, S, D$)
 - N_2O is a cerebral vasodilator alone (\uparrow CBF, \downarrow CMRO₂)
 - Probably safe in balanced techniques
 - Propofol TIVA is probably best
 - Techniques to reduce ICP (in consultation with surgeon)
 - Cellular
 - Surgical resection
 - ICF, ECF
 - Osmotic diuretics (mannitol 0.25-2 g/kg)
 - Limited by serum osmolarity ≤ 320 mOsm/l
 - May cause rebound swelling, hypovolaemia, hypotension
 - Loop diuretics
 - \downarrow ECF and impair idiogenic osmole formation
 - May reduce rebound swelling
 - Fluid restriction
 - Steroids
 - \downarrow ICP over 48-72 h, may worsen outcome overall
 - CSF
 - Surgical drainage
 - Blood
 - Head-up position (also reduces perfusion pressure)
 - Lower CMR (with intact autoregulation)
 - Barbiturates, anticonvulsants, hypothermia
 - Acute hyperventilation (controversial)
 - Transient response, risk of ischaemia, rebound on cessation
 - Avoid agents which impair autoregulation
 - High dose volatiles, vasodilators
 - Avoid coughing, straining or high PAW \rightarrow venous pressure
 - Hypotension for vascular lesions
 - Worsens cerebral perfusion
 - Once the head is open, CPP is a higher priority
 - Support MAP
 - Neuroprotection
 - Drugs: barbiturates
 - Hypothermia

Transsphenoidal surgery in acromegaly.

Acromegaly

- Excessive growth hormone secretion

- >99% due to pituitary adenomas

- Gradual onset of clinical features

 - Pre-puberty: pituitary gigantism, ↑ linear growth plus adult features

 - Adult

 - Continued growth of facial, hand and foot bones

 - Hypertrophy of soft tissues, viscera, skin tags, mucosal polyps

 - Cardiomyopathy, hypertension, IHD

 - Diabetes

 - Proximal myopathy

 - Local effects

 - Failure of other pituitary secretion: LH, FSH, ACTH...

 - Headache

 - Bitemporal hemianopia

- Usually diagnosed in 3rd or 4th decade

- Medical therapy with bromocriptine, octreotide, radiation

- Surgical excision usually curative

Surgery

- Elective, moderate risk

- Performed through the nose or an incision under the upper lip

- Shared airway, commonly soiled by surgery

Preoperative

- Assessment

 - Routine, plus

 - Features of acromegaly

 - Airway compromise: large tongue and jaw, nasal polyps, mucosal folds, recurrent laryngeal nerve palsy

 - Cardiorespiratory complications

 - Other disease complications

 - Diabetes, IHD

 - Pituitary tumours

 - Commonly secrete prolactin, occasionally GH, ACTH or TSH

 - Compress normal tissue with loss of other hormone secretion

 - Supplement hypoadrenalism (hyponatraemia, hypovolaemia) or hypothyroidism

- Investigation

 - Routine bloods, glucose, crossmatch

 - Imaging of the head may give information about the airway

- Premedication

 - Important if fiberoptic intubation planned

Intraoperative

- Monitoring

 - Routine plus arterial line, but 50% positive Allen test

 - Large IV

- Induction

 - Large mask required, mask ventilation may be difficult

 - Oral intubation, consider awake FOB if likely to be very difficult

 - Small tube due to incidence of subglottic narrowing

 - Armoured tube plus throat pack

 - Positioning

 - May be heavy, nerve hypertrophy increases risk to ulnar nerve

 - Head-up reduces bleeding but may cause air embolism

- Maintenance

- Neuro-type balanced technique
- Vigilance for complications
 - Disconnection
 - Dissection into cavernous sinus with haemorrhage
 - Pressure on face or eyes
- Antiemetic
- Emergence
 - Clear blood or CSF from airway
 - Aim to minimize coughing
- Postoperative
 - Ward care
 - Attention to complications
 - Diabetes insipidus (usually transient)
 - Panhypopituitarism
 - Analgesia
 - Oral ± IM narcotic

Paediatric neurosurgery

Positions

- supine, prone, sitting, lateral/park bench, knee-chest
- purpose
 - surgical access, physiological effect (ICP, bleeding control)
- considerations
 - airway
 - usually IPPV with oral ETT
 - raises CVP, ICP
 - compensate with head-up, minimize airway P using deep paralysis, long inspiratory time, improve compliance with position (e.g. pressure off abdomen)
 - SV occasionally in brainstem surgery, still ETT
- access
- monitoring
- pressure areas
 - especially eyes
- specific complications
 - air embolism in sitting position
 - diagnosis by TOE, fall in CO_2 , fall in SpO_2 , calibrate arterial pressure at head level for hypotension
 - manage Valsalva, 100% O_2 , flood field, neck tourniquet, aspirate CVC

Control of ICP

- Monroe Kellie doctrine
 - volume of cranium is constant
 - true after closure of sutures
- physiologic control
 - normal 5-15 cmCSF
 - remains constant due to redistribution of CSF and venous blood volume
 - rises sharply after critical point in elastance curve as intracranial "mass" expands

Physiologic interventions

- positioning
 - head up reduces both ICP and CPP
- hypovolaemia, hypotension
- PCO_2
 - fall causes transient fall in ICP due to vasoconstriction
 - not used below 30 mmHg as may impair CPP
 - effect is transient
- opening the cranium: surgery

Pharmacologic interventions

- reducing mass effect
 - steroids reduce reactive oedema
- diuretic agents
 - mannitol (acute volume-expanding effect)
 - furosemide
 - IDC required
 - can also reduce MAP
- agents to reduce CBF, CMRO_2
 - general anaesthesia, barbiturates
- avoiding agents which raise ICP
 - high PCO_2 , Valsalva, coughing
 - drugs: suxamethonium (but commonly indicated in trauma etc.)

agents which impair autoregulation: volatiles

Protection of the patient

positioning

pressure areas, joint hyperextension or malposition

vascular compromise

neuropraxia

temperature

conservation and warming

neuroprotection

drugs

maintain cerebral autoregulation, reducing CMRO₂

barbiturates, volatiles, propofol

hypothermia

Surgery following subarachnoid haemorrhage

Subarachnoid haemorrhage

Aetiology, natural history

Rupture of arterial aneurysm or bleed from AVM

40% immediate major morbidity or mortality

30% major morbidity or mortality after surgery

Grading

| Grade | GCS | ICP (cmH ₂ O) | Mortality |
|-------|-----------------------------|--------------------------|-----------|
| I | 15 | <10 | 2% |
| II | 13-14 without motor deficit | <10 | 5% |
| III | 13-14 with motor deficit | 15-20 | 5% |
| IV | 7-12 | >25 | 35% |
| V | 3-6 | >25 | 50% |

Surgical management

Operation before 72 h or after 14 days (reduced risk of vasospasm)

Ischaemia managed with fluid loading and hypertension

Nimodipine

Believed to reduce vasospasm, probably cell protection

Requires CVC administration

May cause hypotension

Anaesthetic priorities

Avoid acute hypertension

Intraoperative brain "relaxation"

Maintain high-normal CPP

Preparation for BP manipulation at clipping or rupture

Preoperative

Assessment

Routine, plus

Neurological assessment

Complications of SAH

SIADH or salt-wasting (hyponatraemia, hypovolaemia, high urine Na⁺)

Vasospasm related to clot around Circle of Willis

ECG abnormalities: T inversion, QT prolongation, ST depression, U waves

No correlation with LV function

No specific therapy unless ischaemic pattern

Premedication

No sedation (may raise PCO₂)

Monitoring

Routine, plus

Arterial line, long line for central venous access, large bore IV, IDC, temperature, nerve stimulator

Intraoperative

Induction

Aim to minimize BP rise

Rebleeding at induction (1%) is usually fatal

Vasodilator and pressor agents drawn up

Topical anaesthesia to airway

Lignocaine, β -blocker, narcotic to smooth intubation

Suxamethonium probably safe

Maintenance

Air, O₂, propofol probably causes least cerebral vasodilation in "tight" cases

Volatile, N₂O probably safe for elective cases

Maintain low-normal PCO₂, check on ABG

BP manipulation

- Blunting response to pinning (as for intubation)
- Maintained planned CPP (e.g. 70 mmHg)
- Induced hypotension for uncontrolled bleeding: SNP fastest agent
- Induced hypertension for temporary occlusion: metaraminol or phenylephrine
- ICP manipulation
 - Hypocapnia controversial
 - Lumbar CSF drain, mannitol may be requested by surgeon
- Cerebral protection
 - Propofol commonly used
 - Thiopentone proven effective but delays awakening so not common
 - Consider bolus 5 mg/kg for temporary occlusion
 - Mild hypothermia 32-34°C
- AVM surgery
 - “Perfusion pressure breakthrough”
 - Closure of AVM and loss of shunt causes sudden increase in perfusion of adjacent brain which has always been vasodilated
 - Failure of autoregulation response causes rapid oedema of brain
- Other considerations
 - EEG monitoring, angiography with femoral access
- Emergence
 - Avoidance of hypertension, coughing
 - Consider extubation deep if fasted
- Postoperative
 - Maintain slight head-up position or as required by surgeons
 - Close monitoring of haemodynamic and neurological status
 - ICU or HDU level of care

Awake craniotomy

Surgery

Usually for an epileptogenic focus in the temporal lobe

Preoperative

Assessment

Routine, plus

Detailed history of epilepsy

Nature of aura and seizures for intraoperative recognition

Medication and complications

Investigation

Wada test

Unilateral carotid injection of sodium amytal

Determines lateralization of speech, short term memory

Videotelemetry

Continuous EEG with subdural, parenchymal or *foramen ovale* electrodes to localize focus of seizures

Premedication

Anticonvulsant agents avoided (benzodiazepines)

Monitoring

Routine, plus

Gas analysis to confirm airway patency

Continuous neurological assessment

Careful attention to patient comfort and warming

Intraoperative

Sedation, analgesia

Must allow patient responsiveness during cortical stimulation

Must not inhibit seizure activity

Drug regimens

Local anaesthetic block and infiltration for pins and incision

Droperidol 2.5-7.5 mg plus narcotic

alfentanil 5-10 $\mu\text{g/kg}$ plus 0.25-0.5 $\mu\text{g/kg/min}$, or

fentanyl 0.7 $\mu\text{g/kg}$ plus 0.7 $\mu\text{g/kg/h}$

Propofol infusion or PCA plus narcotic

If provoking agent is required for seizures, methohexitone 0.3 mg/kg

For seizure termination if necessary, thiopentone 1 mg/kg

Surgery

Usually prolonged

Pin placement (if necessary) and craniotomy are painful

Brain parenchyma is insensate

Airway access may be difficult, especially if head is pinned

Orthopaedics

[Total hip replacement](#)

[Other orthopaedic surgery](#)

[Tourniquets](#)

[Anaesthesia for a patient with unstable cervical spine fracture for fixation](#)

Total hip replacement

Surgery

Ranges in complexity from simple cementless arthroplasty to re-do with bone grafting, revision of acetabular protrusion etc.
Moderate to high risk

Issues

Choice of anaesthetic technique
Positioning
Blood loss
Cement
Thromboprophylaxis

Preoperative

Assessment

Patient

Typically old patient, may have multi-system disease
Exercise tolerance difficult to assess if limited by hip pain
Discussion of anaesthetic technique

Surgery

Complexity and likelihood of blood loss
Suitability or desire for autologous predonation
Likely requirement for haemodilution, cell-saver

Monitoring

Simple surgery

Routine SpO₂, ECG, NIBP, large IV

Complex surgery, GA, induced hypotension

Temperature, IDC, arterial line, CVC

Intraoperative

Spinal or CSE

Lumbar placement

Plain (hypobaric) bupivacaine if lateral position
3-4 ml 0.5% spinal dose

GA

Relaxant technique if complex procedure
Consider use of induced hypotension
Reduces blood loss 30-50% (as does spinal)

Either

Intraoperative forced-air warming, avoid hypothermia

Position

Commonly lateral

\dot{V} / \dot{Q} mismatch in ventilated patients
Pressure on dependent brachial plexus, axillary artery
Lateral rest may press on femoral canal
Pressure necrosis more likely with hypotension

Reaming and cementing

Sudden profound hypotension, hypoxaemia or arrest may follow reaming or cemented prosthesis insertion
Associated with \uparrow PA pressure
Possibly due to methyl methacrylate or fat, air and marrow emboli
May be delayed by femoral vein obstruction with leg position

Postoperative

Analgesia

Epidural not commonly used because of incidence of urinary retention
Systemic narcotic plus paracetamol and NSAID (if not contraindicated)

Level of care

Usually ward unless high-risk

Other orthopaedic surgery

Total knee replacement

Surgery

- Unilateral or bilateral

- Higher incidence of complications if bilateral and HDU care may be required

- Commonly done below a tourniquet

Issues

- Cement associated hypotension with femoral component

- Blood loss

- Tourniquet

- Antifibrinolytics (ϵ -aminocaproic acid)

- Postoperative analgesia

- Epidural catheter

- Femoral catheter

- Spinal morphine

- Femoral, sciatic, obturator blocks

Spinal surgery

Surgery

- Major surgery, commonly in prone position

Issues

- Patient deformity and respiratory or neuromuscular disease

- Positioning

- Spinal cord monitoring: SSEP, wake-up test

- Blood loss and conservation techniques

- Duration, temperature conservation

Tourniquets

Inflation

Local

Folds or lines under tourniquet may cause bruising or pressure necrosis of skin

Metabolic

By 8 min mitochondrial PO_2 approaches 0

Anaerobic metabolism

↓ ATP, NAD^+ , CP, ↓ pH

Release of myoglobin, K^+ , intracellular enzymes, thromboxane

Tissue oedema develops after 60 min

Tissue temperature approaches room temperature

Haemodynamic

Exsanguination ↑ CVP, PAP

Inflation ↑ SVR, BP

45-60 min hypertension “tourniquet pain” unresponsive to anaesthesia

Not prevented by axial blockade

May be prevented or delayed by plexus blockade

Neurological

Conduction ceases by 30 min

Neuropraxia may be due to ischaemia or shear forces

Prevented by periodic deflation

Release

Metabolic

Rapid washout of metabolic products and equilibration of temperature

↓ core temperature, SvO_2 falls to 20%, ↑ PCO_2

Haemodynamic

Direct: ↓ SVR, ↓ CVP

Metabolites: marked vasodilation, myocardial depression

Potential embolisation of distal venous clot or debris

Anaesthesia for a patient with unstable cervical spine fracture for fixation.

Halo traction

Emergency surgery in a trauma patient at high risk of catastrophic neurological injury

Issues

Cervical immobilization

Other injuries

Minimizing anaesthetic intervention

Preoperative

Assessment

Routine, plus

Trauma patient

ABC priorities

Conscious state, and fluctuation

Other injuries, particularly head and airway

Careful airway assessment

Neurological state

Documentation of any defect

Optimization

Urgency of surgery usually does not allow much time

Cervical spine immobilization

Hard collar, sand bags, spinal board

Premedication

None

Detailed explanation of procedure

Transport

Supine on spinal board

Transfers on board or lifting frame

Log-rolling for turning

Intraoperative

Preferred anaesthetic technique is local infiltration for bolts and no sedation

Monitoring and access

Large bore IV access, routine monitors

Induction

Drugs available for induction of general anaesthesia

Emergency drugs for CVS support

Difficult airway equipment available

GA only if unmanageable otherwise

Aim to minimize cervical spine movement

In-line immobilization for laryngoscopy or use of FOB or Fastrach or

Bullard if appropriate

Postoperative

Traction frame bed or body-harness

Minimal analgesia required

ENT

[Management of airway fire in laser microlaryngoscopy](#)

[Pharyngeal pouch](#)

[Local anaesthetic for tonsillectomy](#)

Management of airway fire in laser microlaryngoscopy. How can this be avoided.

Laser microlaryngoscopy

High energy laser (CO₂ or Nd-YAG) used along side the ETT

0.5%-1.5% incidence of airway fire

Usually laser igniting ETT or swabs

Minimizing risk

Surgeon

Control of laser direction and operation

Non-reflective instruments

Moistened swabs

Copious sterile water on setup

Fire drill should be agreed or rehearsed

Choice of ETT

Metal tube: Mallinkrodt "Laser Flex"

Metal coated silicone tube: Xomed "Laser Shield"

Metal tape coating on regular tube

Flammability silicone < rubber < PVC

Toxic debris silicone > PVC > rubber

Cuff is still vulnerable

Fill with saline ± methylene blue

Second cuff on Laser Flex

Distal placement of cuff (out of sight)

?Place moist swabs on wires above cuff

Metal can be ignited or cut by Nd-YAG laser

Consider jet ventilation or oscillator

Airway gases

Minimize use of oxidant gases

Minimal required FiO₂

No N₂O

Helium retards ignition

Air available for ventilation in case of fire

Maintenance

Immobility required: deep anaesthesia or paralysis

High level of vigilance for fire

Good communication with surgeon

Managing fire

Remove source of fire and extinguish with water

Stop ventilation, turn off O₂

Mask ventilate with air, then 100% O₂ once fire is extinguished

Laryngoscopy and rigid bronchoscopy to remove debris

Lavage and fiberoptic bronchoscopy if indicated by airway injury

Common pattern is worst injury at the surgical site and little distal injury

If severe injury

Maintain ventilation

Consider low tracheostomy

IV corticosteroids may be helpful

CXR, ABG with co-oximetry for smoke inhalation assessment

Outline management of anaesthesia for resection of pharyngeal pouch.

Surgery

- Elective, moderate risk
- High risk of aspiration
- Close to major structures in neck

Assessment

- Routine plus
- History
 - Dysphagia, regurgitation and aspiration of food
 - Positional or on waking

Examination

- Complications of lesion
- Malnutrition, pneumonia

Investigations

- Imaging of pouch: contrast studies, CT

Preoperative

- Premedication to reduce aspiration risk: H₂ blocker

Monitoring

- Routine plus
- Arterial line, CVC
- Epidural if thoracic incision

Induction

- Rapid sequence induction with cricoid pressure
- Pharynx may need to be suctioned
- Avoid high-pressure mask ventilation
 - Risks distension ± rupture of pouch
- Consider cervical plexus block if neck incision

Maintenance

- Usually supine with head turned to side
- If lateral, increased risk of pressure areas
- No nasogastric before surgery
 - May pass into pouch

Emergence

- Aim for extubation when awake
- Usually do not require HDU care

Local anaesthetic for tonsillectomy

Anatomy

Tonsil innervated by branches of glossopharyngeal n. which runs along stylopharyngeus and anterior palatal arch

Technique

Initial topical anaesthesia to pharyngeal arches with lignocaine

Tongue depressed with spatula

Infiltration of posterior palatal arch, then anterior palatal arch (IX n.)

Tonsil grasped with forceps and drawn medially

Tonsillar attachment infiltrated

Careful aspiration at all points because of proximity of ICA

Local anaesthetic

Lignocaine 0.5% 10-15 ml each side

Thoracic surgery

[Anaesthetic management of bronchopleural fistula](#)

[Outline your approach to tracheal stenosis surgery](#)

[Preparation for lung surgery](#)

[One lung ventilation](#)

[Mediastinoscopy](#)

Anaesthetic management of bronchopleural fistula

Bronchopleural fistula

- Communication from major bronchus to pleural space

- Commonly associated with pneumonectomy, trauma, abscess or empyema

- Relevant complications

 - Pus may contaminate other lung

 - Associated injuries with trauma

Surgery

- Usually semi-elective

- Resuturing of bronchial stump, muscle flap to stump, drainage of abscess

 - High risk surgery requiring GA and one-lung ventilation

- If incidental surgery, GA may be avoided, regional preferred

 - Positioning still important to avoid soiling

Patient

- Commonly debilitated, may have coexistent medical problems

- Respiratory function assessed

 - Clinical, spirometry, ABGs

- Routine assessment for thoracic surgery

 - Consideration of epidural

Decision to proceed

- Respiratory function optimized

- Chest drain inserted to avoid tension pneumothorax and drain pleural collection

Induction

- Objectives

 - Maintain oxygenation and ventilation, avoid tension pneumothorax

 - Avoid soiling good lung

- Protection of lung requires DLT, bronchial lumen to good side

- Small leak without infection may be manageable with single-lumen ETT

- Paediatric patients are typically too small for DLT or FOB \Rightarrow blocker or endobronchial intubation

- Fistula reduces effectiveness of mask IPPV, so spontaneous ventilation

- Ideally awake DLT intubation

 - Topical local anaesthetic to airway

 - Position head-up and bad side down

 - Sedation for intubation

- Alternatively spontaneously ventilating GA with DLT insertion when deep

- Verification of DLT position with differential ventilation or FOB

Maintenance

- IPPV to healthy lung

- Lung with fistula may benefit from small V_T ventilation or CPAP below critical pressure for fistula or HFJV

Emergence

- Avoid high airway pressures if fistula has been repaired

 - Hand ventilation or SIMV

Postoperative

- Epidural analgesia

- HDU monitoring post-op

 - High incidence of arrhythmia post-thoracotomy

Outline your approach to tracheal stenosis surgery.

Surgery

- Elective, high risk
- Cervical level: neck incision
- More distal stenosis: thoracotomy or sternotomy

Stenosis

- Extrinsic compression e.g. goitre
 - Usually tracheomalacia: soft tracheal stenosis
 - May be easily splinted with ETT
 - Surgery may not involve opening trachea

Scarring

- Usually firm fibrous stenosis

Assessment

- Routine plus
- History
 - Symptoms of airway compromise: positional dyspnoea, sleeping position
- Examination
 - Respiratory examination: upper airway sounds
- Investigations
 - Pulse oximetry, ABG if obvious compromise
 - Spirometry: may be only slightly blunted by significant stenosis
 - Tomography or CT: define anatomy

Preoperative

- Sedative premedication may worsen function as may anxiety
- Aspiration prophylaxis: H₂ blocker
- Anticholinergic to reduce secretions

Monitoring

- Routine plus
- Left radial arterial line (compression of innominate artery during surgery)

Induction

- Technique depends on degree of stenosis and airway control
- Mild, flexible stenosis with little compromise
 - Conventional IV induction
- Tracheostomy in situ
 - IV induction and armoured tube in tracheostomy
 - Replacement by surgeon with sterile tube
- Critical stenosis
 - Inhalational induction with potent volatile agent in 100% O₂
 - May take 20 min to achieve anaesthesia
 - e.g. sevoflurane in O₂ plus BP support if required

Intraoperative

- Rigid bronchoscopy should delineate degree of stenosis
 - Allow decision about method of ventilation
- Ventilation options
 - Conventional IPPV
 - Armoured ETT or DLT passing stenosis: sterile or non-sterile
 - Reinforced ETT above stenosis, sterile tube across surgical field
 - Jet ventilation using small catheter
 - Cardiopulmonary bypass
 - Deep hypothermic arrest
- Head is usually in flexion at the end of the surgery, may be sutured chin-to-chest

Emergence

- Aim for extubation to minimize tension on tracheal anastomoses
- Spontaneous ventilation, suctioning, extubation either deep to minimize coughing or light with adequate narcotics

Fibreoptic scope available in case of need for reintubation

Preparation for lung surgery

Assessment

Associated disease: IHD, PVD, COAD

History

Exposures (smoking, occupation)

Symptoms

Bronchopulmonary, extrapulmonary

Intrathoracic, extrathoracic

Metastatic, non-metastatic

Examination

Investigation

FBE, U&E, enzymes

CXR, CT

Pulmonary function testing

Whole lung: ABG, spirometry, diffusing capacity

Single lung: \dot{V}/Q testing, split function testing

Simulation: occlusion of main stem bronchus or pulmonary artery

Exercise testing

Risk factors for poor outcome

$\text{PaCO}_2 > 45$ mmHg, MBC or $\text{FEV}_1 < 50\%$ predicted, $\text{RV} > 50\%$ of VC, raised PVR (> 190 dyne.s.cm⁻⁵)

Requirements for surgery

Predicted postop: $\text{FEV}_1 > 0.85$ l, PAP < 40 mmHg, $\text{PaCO}_2 < 60$ mmHg, $\text{PaO}_2 > 45$ mmHg

Preparation

Optimize respiratory function

Cease [smoking](#), bronchodilate, treat infection, mobilize sputum, educate for physio

Optimize associated diseases

Intraoperative

Monitoring

Tiered approach

Routine

FiO_2 , O_2 fail, SpO_2 , gas analysis, NIBP, ECG, airway P, disconnect, nerve stimulator, temperature

Sick patient or major procedure

Arterial line, gases, spirometry and derived measurements, CVC

Sick patient and major procedure

PA catheter and derived measurements, SvO_2 and derived measurements

Lateral position

Placement of PA catheter may need to be verified on II (if in deflated lung, CO and SvO_2 measures are inaccurate)

One lung ventilation

Physiology

Hypoxic pulmonary vasoconstriction

PVR is locally responsive to PO_2

Reduced shunt fraction in lung which is partially hypoxic

Most effective in reducing fall in PaO_2 when 30-70% of lung is hypoxic

Inhibited by some agents

Volatiles inhibit HPV *in vitro* but not significantly in humans

No intravenous anaesthetics inhibit HPV

Direct arterial dilators inhibit HPV (SNP, GTN, Ca^{2+} antagonists, β agonists), though aminophylline and hydralazine may be safe

Distribution of blood flow

Lateral positioning reduced lung blood flow by 10% of CO

Non-ventilation reduces lung blood flow by 50% due to HPV

1 MAC of isoflurane inhibits HPV to 40% reduction in flow

The inhibition of HPV by volatiles is difficult to detect in practice

No significant difference from TIVA

| Position | Left | Right |
|-------------------|------|-------|
| Upright or supine | 45% | 55% |
| Right lateral | 35% | 65% |
| OLV | 18% | 82% |
| +1 MAC iso | 21% | 79% |
| Left lateral | 55% | 45% |
| OLV | 77% | 23% |
| +1 MAC iso | 73% | 27% |

Anaesthetic technique

Recommendations

High FiO_2 , precludes N_2O use

Potent volatile or propofol reduces airway reactivity

Narcotic analgesia or thoracic epidural diminishes hypnotic requirement

Intubation

Response blunted with adequate anaesthesia, narcotic and lignocaine

Indications for DLT

Absolute

Lung isolation for bronchopleural fistula, bullous disease, bleeding, infection, bronchopulmonary lavage

Conducting airway surgery or trauma

VATS

Relative

Surgical exposure: aortic, lung, mediastinal, oesophageal, vertebral surgery

Differential lung ventilation following unilateral massive PE thrombectomy or with unilateral lung disease

DLT insertion

Types

Carlens left with hook

Robertshaw left or right

26, 28, 35, 37, 39 or 41 Fr (4.0 to 6.5 mm lumen diameter)

Left side most commonly used unless proximal left main lesion

Protocol

Check cuffs and connections

Conventional laryngoscopy

Tip passed with curvature concave-forward

Rotated if hook present so hook passes anteriorly through larynx

Rotated so tip points to side to be endobronchially intubated and

- head turned to opposite side
 - Advanced until resistance is met (typically at 29 cm + 1 cm per 10 cm height over 170 cm)
 - Tracheal cuff inflated and bilateral lung ventilation verified
 - If unilateral, may be in too far, withdraw until bilateral
 - Bronchial cuff inflated, bronchial lumen ventilated
 - If bilateral lung inflation \pm leak from tracheal lumen, tube is not advanced far enough
 - If lower lobe inflation only, tube is advanced too far
 - If right lung isolation, tube is in right bronchus
 - Verify lung isolation
 - Tracheal lumen ventilated
 - If no apparent ventilation, tube may be too far advanced in either bronchus or entirely in the trachea so deflate bronchial cuff and ventilate to determine position
 - Verify lung isolation
 - Verify position with tracheal lumen fibreoptic bronchoscopy, particularly with right-sided tubes to verify upper lobe bronchus position relative to cuff
 - Verify isolation again after patient positioning
- Other methods to verify position
 - X-ray, differential capnography or flow-volume loops, surgical palpation
 - Underwater bubble test to verify total lung isolation
- Other lung isolation techniques
 - Univent, bronchial blockers
 - Place with FOB assistance
- Ventilation
 - Principles
 - Maintain two-lung ventilation as long as possible
 - High FiO_2
 - Initial OLV V_T of 10 ml/kg
 - Titrate ventilation to normal PaCO_2
 - Strategy to maximize HPV in non-ventilated lung
 - Avoid vasodilation in non-ventilated lung due to
 - Systemic vasodilators, \uparrow PA pressure, \uparrow $\text{P}\bar{\text{v}}\text{O}_2$, \downarrow PCO_2
 - Avoid vasoconstriction in ventilated lung due to
 - Hypoxia, \downarrow PA pressure, \uparrow PCO_2 , high PEEP
 - Managing falling PaO_2
 - Low PEEP to ventilated lung
 - CPAP with 100% O_2 to non-ventilated lung
 - Intermittent two-lung ventilation
 - Early PA clamping if lung resection
 - Other options
 - HFPPV, HFJV
 - Lower mean airway pressures
 - Less movement
 - Low flow apnoeic ventilation
 - Theoretically feasible for up to 20 minutes
 - High PaCO_2 and severe respiratory acidosis

Mediastinoscopy

Surgery

- Suprasternal notch incision

- Blunt dissection anterior to trachea, posterior to aortic arch down to carina

Intraoperative

Monitoring

- Routine, plus

- Right radial arterial line (for great vessel compression) and left NIBP

- Large bore IV access in arm and leg (in case of SVC disruption)

Induction

- Conventional relaxant GA (reduced risk of air embolus)

- Reinforced ETT

Maintenance

- Extreme vigilance required

- Head-up position reduces bleeding but increases risk of air embolus

Complications

- Massive haemorrhage requiring sternotomy

- Have rapid infusion device available and blood crossmatched

- Venous disruption may cause air embolus and require lower limb access for drug administration

- Pneumothorax

- Common postoperatively, usually small

- Recurrent laryngeal nerve injury

- 50% permanent

- Compression of aortic arch branches

- Especially right innominate: cerebral ischaemia

- Detect with right arm arterial line or pulse oximeter

- Autonomic reflexes

- Especially bradycardia, hypotension

Postoperative

- CXR to detect pneumothorax

- Repeat mediastinoscopy is usually impossible due to scarring

Upper GI surgery

[Management of a 60yo for laparoscopic cholecystectomy](#)

[Outline basic management of liver transplant surgery](#)

[Anaesthesia with portal hypertension for shunt insertion](#)

Management of a 60yo for laparoscopic cholecystectomy.

Laparoscopy

- Intraperitoneal insufflation with gas through a paraumbilical Veress needle

- Pressure 12-15 mmHg

- Usually CO₂ used

Surgery

- Elective, moderate risk

Preoperative

Assessment

- Routine, plus

- Respiratory compromise: lung disease, obesity, smoking

- Reflux risk, airway assessment, assess need for RSI

- Cardiac function

- Autonomic dysfunction e.g. diabetes

Premedication

- H₂ antagonist, anxiolytic

Intraoperative

Monitoring

- Routine: SpO₂, ECG, NIBP, gas analysis

- Arterial line if very obese

- Large IV

Induction

- Routine IV induction, balanced technique unless RSI indicated

Maintenance

- Volatile, O₂, air or N₂O.

- N₂O may worsen complications of gas embolus

- Narcotic analgesia, local anaesthetic in port sites

- High PIP may be required during pneumoperitoneum

- High degree of vigilance for signs of gas embolism

Complications

- Trocar insertion and insufflation

- Injury to bowel, bladder, large vessels

- Insufflation of CO₂ intravascularly

- Pneumoperitoneum

- CO₂ absorption

- Fall in cardiac output

- Difficulty in ventilation

- Usual surgical risks

- Haemorrhage, bile leak, damage to nearby structures

- Change to open procedure

Emergence

- Routine, extubation in lateral position

Postoperative

Analgesia

- Local, oral agents, IM narcotic

- Consider epidural if opened

- Ward level of care

Outline basic management of liver transplant surgery

Surgery

- High risk, semi-urgent procedure
- Requires tertiary hospital with special expertise

Issues

- Perioperative management of hepatic failure
- Coagulopathy and potential for haemorrhage
- Massive transfusion and fluid requirements
- Hypothermia, hyperkalaemia, acidosis
- Often paediatric patient
- Prolonged anaesthesia

Preoperative

Assessment

- Complications of liver failure
 - Electrolyte, acid base, glucose, fluid homeostasis disordered
 - Coagulopathy
 - Encephalopathy
- Other complications of primary cause of liver failure
 - Blood-borne virus, haemochromatosis (diabetes)
 - Crigler-Najjar syndrome (avoid barbiturates)
 - Budd-Chiari syndrome (may need anticoagulant prophylaxis)
 - Drug toxicity

Premedication

- Aspiration prophylaxis, no sedation with encephalopathy

Transport

- May be coming from ICU

Monitoring and access

- Emergency drugs drawn up
- Rapid infusor, cell saver, blood warmer, humidifier, patient warmer prepared
- Large bore IV access x 2, PA catheter, arterial line
- Thromboelastograph

Induction

- Increased risk of aspiration with ascites, risk of haematemesis, delayed gastric emptying may require RSI or FOB

Positioning

- Care for pressure areas, prolonged laparotomy

Maintenance

- Relaxant GA, balanced technique
- Air:oxygen:isoflurane does not compromise splanchnic blood flow
- N₂O avoided as it worsens bowel distension and gas emboli
- Increased dose requirement but prolonged action from NDB

Preanhepatic phase

- Major risks are haemorrhage and coagulopathy
- Oliguria treated with adequate filling, diuretic, dopamine

Anhepatic phase (hours)

- Portal vein, IVC, hepatic artery clamped, biliary drain
- Diaphragm retracted: impairs venous return, reduces lung compliance
- Renal venous congestion, oliguria
- Risk of hyperkalaemia, citrate toxicity from transfusion
- Calcium, magnesium, water infused to maintain usual hyponatraemia

Neohepatic phase

- Vascular anastomoses
- Immunosuppression with cyclosporin, azathioprine, prednisolone

Haemorrhage, coagulopathy still risks
Flushing cold hyperkalaemic fluid out of liver
Treat hypothermia, hyperkalaemia, acidosis

Emergence

ICU transfer, intubated
Risks of pneumonia, ARDS, anastomotic leaks, other infection

Anaesthesia with portal hypertension for shunt insertion.

Major abdominal surgery in a high-risk patient.

Preoperative

Assessment

Complications

Cardiac

↑ CO, ↓ SVR, ↑ \bar{SvO}_2 , BP and HR unchanged

Cardiomyopathy, arrhythmias

↓ responsiveness to α agonists

↓ renal blood flow

Respiratory

↑ 2,3 DPG causing right shift of Hb-O₂ dissociation curve

Vasodilators (VIP, glucagon, ferritin) cause pulmonary shunting,

↓ pulmonary vascular response to hypoxia

Ascites may splint diaphragm (closing volume > FRC)

↓ colloid oncotic pressure may predispose to pulmonary oedema

Haematological

↑ plasma volume, ↓ Hb (bleeding, B12 deficiency), ↓ albumen

Factor deficiencies: VII, V, X, fibrinogen

DIC may complicate surgery

Endocrine

Impaired glucose tolerance (↑ glucagon, ↑ GH, insulin resistance)

Feminization of male patients

Other

Encephalopathy

Renal failure (hepatorenal syndrome, ATN)

Altered pharmacodynamics

Varices, haemorrhage

Decide whether further optimization is possible

Treatment of complications

Vitamin K or FFP, platelets if required

Specific therapy

Vasopressin: preportal vasoconstriction

Also coronary, arteriolar vasoconstriction

Somatostatin: ↓ glucagon, gut activity, mesenteric blood flow

Propranolol: ↓ CO, splanchnic vasoconstriction, ↓ renin

Rebound bleeds with discontinuation

Investigation

FBE, U&E, LFT, clotting, XM, ABG

ECG, CXR if in failure

Premedication

Minimal if at risk of encephalopathy

↑ sensitivity to benzodiazepines

Antacid or H₂-blocker for ↑ reflux risk

Intraoperative

Monitoring and access

Large bore IV access (consider multiple)

Routine monitoring, plus

CVC, arterial line, IDC, temperature

Blood and fluid warmer available

ABG, Hb and glucose measurement available

Anaesthetic technique

High mortality in patient in hepatic failure

Surgery is the major determinant of hepatic damage, not anaesthesia

General anaesthesia

Rapid sequence induction if recent bleeding or full stomach suspected

Avoidance of hepatotoxic drugs (e.g. halothane)

Some evidence of \uparrow enzymes with ketamine, thiopentone and N_2O

\downarrow protein binding, so \downarrow dose of bound drugs such as thiopentone

Aim to maintain hepatic O_2 delivery: BP, Hb, PaO_2

Epidural analgesia

Contraindicated in coagulopathy or thrombocytopenia

Stress response reduces hepatic blood flow

Allows minimization of other anaesthetic drugs

Formation of shunt: flow from portal vein to IVC

\uparrow IVC flow

\downarrow hepatic blood flow causes release of glucagon, VIP (vasodilators)

\downarrow portal resistance, \downarrow SVR

reflex \uparrow SV, \uparrow CO

Postoperative

HDU or ICU care may be needed

Epidural analgesia or judicious opioids

Careful fluid management

General surgery

[Thyroid surgery](#)

[Physiological response to pneumoperitoneum](#)

Thyroid surgery

Preoperative

Assessment

Routine, plus

Thyrotoxicosis symptoms

Anxiety, tremor, heat intolerance, fatigue, weight loss

TFT, Ca²⁺, FBE, U&E, ECG, CXR, CT if indicated

Complications

Goitre, atrial fibrillation, SVC obstruction

Airway compromise, stridor, tracheomalacia

Eye complications of Graves' disease

Treatment

Antithyroid drugs, radioactive iodine

Complications of therapy: marrow suppression

Other therapy: β -blockers

Determine fitness for surgery

Euthyroid, little risk of thyroid storm

Airway and vascular compromise determined and manageable

Preparation, premedication, transport

Routine

Intraoperative

Monitoring, access

Routine

Induction

Routine relaxant technique

Tube placement commonly armoured tube with circuit over head

Care with positioning, secure connections, eye protection

Positioning

Supine with shoulder roll

Maintenance

Balanced technique, IPPV

Poor access to head and airway

Emergence

Request from surgeon to check vocal cord movement

Often will not change surgical management

Requires deep extubation when reversed and laryngoscopy

Postoperative

Airway distress

Upper airway obstruction due to soft tissues and reduced muscle tone

Laryngospasm, bilateral cord paralysis

Inadequate reversal

Wound haematoma

Laryngeal oedema

Tracheomalacia

Anaphylaxis

Hypocalcaemia due to hypoparathyroidism

May be early (1-3 hours), more commonly 1-3 days

Physiological response to pneumoperitoneum

Intraabdominal pressure 10-12 cmH₂O

CVS

Venous pooling in legs, IVC compression → ↑ RVR, ↓ venous return
↑ vascular resistance of intraabdominal organs → ↑ SVR

Respiratory

↓ compliance, ↑ intrathoracic pressure on IPPV

Neuroendocrine

↑ ADH, catecholamines, renin, angiotensin II

↑ sympathetic tone

Net effect

↓ CO, ↑ MAP

Minimized by filling, head-down position, α_2 -agonists

Regional effects

Venous stasis in legs → DVT

PCO₂ causes vasodilation if ventilation is not increased (↑ ICP)

Arrhythmia: bradycardia due to peritoneal manipulation

Miscellaneous surgery

[Outline management of a 20 year old man who is intoxicated for ORIF # mandible](#)

[Outline management of anaesthesia for cataract extraction](#)

[Ophthalmic anaesthesia](#)

[Penetrating eye injury](#)

Outline management of a 20 year old man who is intoxicated for ORIF # mandible.

Issues

- Semiurgent surgery in an intoxicated and non-fasted patient
- Trauma patient with possible associated injuries and airway compromise
- Shared airway surgery with likely bleeding
- Possibility of wiring the jaw closed with associated airway access compromised

Assessment

- Routine anaesthetic assessment, plus
- History of trauma, associated injuries
 - Jaw mobility, limited by pain or mechanical obstruction
- Intoxication
 - Drugs used, BAC measurement
 - Competence to consent
 - Complications of drugs
 - Full stomach, specific effects of other drugs: narcotics, amphetamines
 - Difficulty of detecting altered conscious state from head injury
 - Legal concerns if a driver: BAC sample handling dictated by law

Examination

- Mouth opening, careful airway assessment

Investigations

- Trauma x-rays
- Jaw x-rays or OPG
- Routine bloods, G&H

Decision on timing of surgery

- Often not necessary to proceed before patient is sober and fasted

Plan for anaesthesia

- Rapid sequence or awake nasal FOB if not fasted and surgery cannot be deferred
- Otherwise plan for GA with nasal intubation when fasted

Premedication

- Routine antacid and/or anxiolytic

Consent

- Discussion of plan with patient, especially if awake FOB planned

Intraoperative

Preparation

- Routine equipment check, suction
- Availability of difficult intubation equipment

Access and monitoring

- Routine: ECG, SpO₂, NIBP etc.
- IV access

Induction

- Good jaw mobility: conventional induction, nasal Rae
- Potentially difficult: awake nasal FOB
- Nasal lignocaine, phenylephrine
- Topical lignocaine to airway for awake FOB
- Throat pack insertion

Maintenance

- Conventional balanced technique
- Remember to remove throat pack if jaw is to be left wired
- Analgesia supplemented with local infiltration or nerve block
- Prophylactic antiemetic

Emergence

- Usually mandible plated and mobile

 - Remove throat pack, suction, inspect larynx for blood

 - Awake extubation in lateral position

 - Consider suctioning of ETT tube in nasopharynx and nose

- Jaw wired

 - Fully awake extubation required

 - Equipment on hand to cut wiring

 - Drugs and equipment for emergency reintubation

 - Pull tube through cords and leave as nasopharyngeal airway

Postoperative

- Analgesia

 - Usually PCA or intermittent narcotic plus oral adjuvant analgesics

- Level of care

 - PACU and normal surgical ward

Outline management of anaesthesia for cataract extraction.

Elective surgery with minimal physiological impact usually performed on elderly patients.

Issues

- Population with high incidence of concurrent disease
- Commonly a brief operation with high turnover

Preoperative

Assessment

- Routine, plus

Cataract

- Nature of surgery (intracapsular vs extracapsular)

- Previous cataract surgery

- Primary disease e.g. diabetes

Retrobulbar or peribulbar blockade

- Axial length

- Assessment of orbit and ease of access to retrobulbar space

Coexistent disease

- Particularly cardiac disease, respiratory disease

- Persistent cough, tremor, claustrophobia may make regional unfeasible

Premedication

- Minimal as sudden waking may be associated with movement

Intraoperative

Monitoring and access

- IV access

- Routine monitoring: HR and SpO₂ required during block

- ECG, NIBP, SpO₂, E_TCO₂ on Hudson mask

Block

- Deep intraconal ("retrobulbar") vs peribulbar vs topical plus infiltration

My practice

- Topical oxybuprocaine (benoxinate)

- Sterile solution 2% lignocaine, 0.4% bupivacaine, 15 U/ml Hyalase

Aseptic technique

- Medial canthus direct posteriorly 30g 12 mm 2.5 ml full depth

- Inferotemporal percutaneous 27g 32 mm 3.5 ml

- hub at level of limbus

- Slow injection with periodic aspiration

- Gentle massage, assessment of IOP and orbital pressure

- Honan's balloon if required by surgeon

- Supplementation for intact movement or sensation according to distribution and surgical requirements

- Facial nerve block usually not required

Issues intraoperatively

- Maintain communication

- Atropine available for bradycardia

- Surgeon may supplement with sub-Tenon's injection if required

Postoperative

- Usually good analgesia from block

Ophthalmic anaesthesia

Anatomy

Layers

Connective tissue globe: conjunctiva, sclera

Retina: nerve tissue

Choroid: vascular

Humour: aqueous and vitreous

Size: A-scan typically 20-24mm

High myopes may be > 25mm: increased risk with retrobulbar block

Muscles: 4 recti, 2 obliques, orbicularis oculi, levator palpebrae

Nerves

Motor: III MR, IO, IR, SR

IV: SO

VI: LR

Sensory: conjunctive nasociliary V₁

Parasympathetic: short ciliary br of III

Sympathetic: ciliary ganglion to V and carotid plexus

Physiology

IOP: 10-15 cmH₂O

Varies with volume of aqueous and blood in the globe and muscle tone causing extrinsic pressure

CVP transmitted readily to IOP

Rises with coughing, vomiting, head-down, IPPV

Suxamethonium causes a small rise

Induction agents: reduce IOP

Dizolamide, acetazolamide: reduce aqueous secretion

Atropine IV causes little mydriasis, little risk with closed-angle glaucoma

Complications of pressure changes

Rise: reduced perfusion pressure, exuding of contents if an open eye

Fall (removal of contents): potential for retinal detachment

Oculocardiac reflex: afferent V short ciliary n., ciliary ganglion, ophthalmic, reticular formation, efferent X

Bradycardia, standstill, nausea and vomiting

Can be elicited by other stimuli like NGT, faciomaxillary surgery

Classically eye traction or pressure (sometimes retrobulbar block, face mask pressure).

Does not require an intact eye: e.g. prosthesis fitting.

Management: tell surgeon to stop, deepen anaesthesia, prophylactic atropine or treatment.

Fatigues with repeated stimulation

Nausea and vomiting

Most common with squint surgery, vitreoretinal surgery

Usually post-recovery, continues up to 24 hours

Raises IOP, delays discharge

Cause: visual change after squint surgery causes "motion-sickness"

? oculogastric reflex: vagal effect

Prevention

General: hydration, low nausea anaesthetic (no opiates, N₂O...), antiemetics

premedication with benzodiazepine (esp. lorazepam)

midazolam blocks adenosine reuptake in area postrema (required for dopamine synthesis)

Other concerns: drug interactions, coexisting disease (esp. diabetes)

Vitreoretinal surgery

Often with poorly controlled diabetes or else ex-prem babies
Long cases, poor airway access
Immobility required
May have gas or oil: no N₂O while gas still present

Open eye injury

Need to know

Degree of injury: salvageable eye? Take care with IOP.

Urgency: clean vs dirty injury. Clean: wait until fasted

Dirty: RSI required

Children: LA cream for IV, sedative premedication

Minimize IOP rise with big induction agent dose, fentanyl, topical local to airway

EUA for glaucoma

Measurements require an anaesthetic which doesn't alter IOP much

Halothane: reduces IOP

Kids usually have multiple anaesthetics

NLD probe

Simple mask anaesthetic

Some babies have a mucocoele: aspiration of pus

Sub Tenon block

painless, fast onset, good motor block, no needle in retrobulbar space

catheter passed subconjunctivally

look up and out, nick conj fascia, probe around globe to post attachment of Tenon fascia

Outline management of anaesthesia for a penetrating eye injury

Issues

- Emergency surgery, usually a trauma patient with a full stomach
- Avoidance of rise in IOP with potential expulsion of globe contents

Assessment

- Routine, plus
- Trauma
 - Associated injuries, ABCDE, fasting status
- Eye
 - Nature of injury, acuity

Preoperative

- Premedication
 - Antacid, H₂ blocker, prokinetic

Intraoperative

- Monitoring and access
 - Routine: IV, ECG, SpO₂, NIBP, gas analysis, disconnect etc.
- Induction
 - Modified RSI
 - Preoxygenation
 - Predosing with lignocaine, remifentanyl, β -blocker IV
 - Induction with thiopentone or propofol
 - Relaxation options
 - Suxamethonium
 - Predose with NDB followed by suxamethonium
 - High dose NDB (e.g. rocuronium)
 - Trade-off between risk of coughing and \uparrow IOP with sux

Maintenance

- Lower IOP
 - Mild hyperventilation, β -blocker, acetazolamide, mannitol, hypotension
- Monitor muscle relaxation to prevent coughing
- Prophylaxis: antibiotics, tetanus

Emergence

- Prevention of coughing/vomiting and protection of airway are conflicting priorities
- Extubate awake in lateral position
- Give narcotic and antiemetic before emergence

[Cardiac disease in pregnancy](#)

[Management of post-partum haemorrhage for EUA](#)

[Management of 160kg female for Caesarean section](#)

[Justify an epidural test dose in obstetrics and contraindications to epidural for LUSCS](#)

[Outline management of a 32 week pregnant woman who fits at home](#)

[Outline differences between spinal and epidural for LUSCS](#)

[Management of a term female with moderate aortic stenosis for elective Caesarean section](#)

[Anaesthesia for LUSCS](#)

[Perinatal and Maternal Mortality 1997](#)

[Analgesia in Labour](#)

[Tocolysis](#)

[Antenatal class](#)

[Foetal monitoring](#)

[Trauma in pregnancy](#)

[Doses](#)

[Case scenarios](#)

Cardiac disease in pregnancy

Cardiac stresses

- pregnancy, labour, surgery (LUSCS), blood loss
- cardiac disease may worsen in pregnancy

Anaesthetic interventions

Major regional blockade

- Objective is to minimize physiological disturbance

 - Choice of drug: opioid vs local anaesthetic

 - Titration of drug to minimize high block

 - Volume loading to maintain preload

 - Posturing to maintain preload

 - Use of vasopressors

Degree of concern

- Normal patient

- Disease will improve with block e.g. AR

- Disease will worsen with block e.g. AS

Monitoring

- Routine

- HDU

- ICU

- Blockade for analgesia is safer than for anaesthesia

General anaesthesia

- Objective is to minimize physiological disturbance

- Modified RSI

 - e.g. more fentanyl, less thiopentone

- Cardiac induction

 - may compromise safe airway

General management of cardiac disease in pregnancy

Workup

- Nature of defect

- Severity e.g. NYHA grading

- Optimization e.g. valve replacement, medical therapy

- Assessment of likely outcome

- Counselling patient re termination

Objectives

- Survive to viability and early Caesarean (e.g. $\frac{32}{40}$)

- Aim for normal labour with monitoring

Anaesthetic plan

- Regional suitable for analgesia or anaesthesia?

- GA preferred?

- Technique, level of care pre- and post-op

Management of post-partum haemorrhage for EUA.

Post-partum haemorrhage

>600 ml blood loss from birth canal from third stage to 24 h post-delivery

Surgery

High risk, emergency surgery

Causes: uterine atony, retained products, vaginal or uterine laceration

Preop

Assessment

Determine reason for EUA

Define risk of procedure

Patient

Concurrent disease e.g. PE

Resuscitation status

Bloods, crossmatch, Hb

Anaesthesia

Epidural in situ?

IV access

Fluid management

Regional versus GA

Determined by urgency, haemodynamic stability, patient preference

Premedication

Effervescent ranitidine

O₂ by mask

Syntocinon infusion to continue

Induction

Rapid Sequence for GA

Equipment, suction, drugs

Preoxygenation

Cricoid, thiopentone, suxamethonium

ETT

Spinal or epidural or CSE

Maintenance

Reduced MAC requirement, volatiles cause uterine relaxation

Low volatile use unless uterine relaxation required

Physiological hypocapnia

Surgical issues

Haemorrhage, coagulopathy, warming of infusions

Oxytocic agents

Uterine relaxants: volatiles, GTN

Extubation

When awake and protecting airway

Postop

Ward/HDU/ICU as indicated

Management of 160kg female for Caesarean section.

Surgery

- Elective, urgent or emergency

- Determines opportunity for optimization

Risk factors

- Term pregnancy

 - Airway: oedema, vascularity, risk of difficult intubation, risk of aspiration

 - Ventilation: ↓ FRC, ↑ O₂ requirement

 - Circulatory: ↑ CO, ↑ blood volume, ACC

Surgery

- Haemorrhage

- Embolism: amniotic fluid, air

Obesity

- Airway difficulty

- ↑ gastric volume, ↓ pH

- ↑ O₂ requirement

- Difficulty ventilating

- Difficult access for IV, blocks

Preoperative

Assessment

- Pregnancy, complications

- Concurrent disease

- Medications, allergies...

Premedication

- Non-particulate antacid, sodium citrate: ↑ gastric pH

- H₂ antagonist, metoclopramide: ↑ pH, ↑ motility

Intraoperative

Positioning

- Supine with left lateral tilt 15°

- Avoid aorto-caval compression

Monitoring

- ECG, SpO₂, NIBP on frequent cycle and manual BP cuff

- Arterial pressure if likely to be unstable

- CTG or doppler prior to positioning for surgery

- Supplemental O₂ for all mothers

Regional

Advantages

- Avoids need to intubate potentially difficult airway

- Spinal may be as fast as GA in experienced hands

- Preemptive analgesia, reduced postoperative analgesic requirement

- Allows greater experience of birth, partner present

- Often preferred by patient

Disadvantages

- May delay surgery, especially epidural

- Spinal is of fixed duration, lacks flexibility

Complications

 - Failed block, hypotension, local anaesthetic toxicity, neuropraxia, PDPH

 - Minimized with careful technique: fluid loading, pressors...

- Obese patient may require longer needle, ↑ technical difficulty, CSE is not possible with long epidural needle

Epidural

- Lumbar epidural catheter

- Suitable for urgent procedure if

 - Haemodynamically stable, block established

Bolus lignocaine 2% with adrenaline and bicarbonate, 5ml aliquots to T4
Additional epidural narcotic (fentanyl 100 μ g or pethidine 50 mg)
improves analgesia
May be combined with spinal (CSE)
May be supplemented intraoperatively

Spinal

L2-3 or L3-4
Fine pencil-point needle 26g minimizes PDPH
Hyperbaric bupivacaine 0.5% 2.2-2.5 ml
Fentanyl 10-20 μ g
Posture for block to T4
Test block with cold or painful stimulus

General

Advantages

Reliable and rapid onset of anaesthesia
Greater control of airway, ventilation and haemodynamics

Disadvantages

Potential for failed intubation, aspiration
Major causes of anaesthetic-related death in pregnancy
Greater post-operative narcotic requirement
Neonatal depression from volatiles, N₂O and induction drugs

Rapid sequence induction

Required in all pregnant women after early second trimester or with other indications
Suction and difficult airway equipment must be at hand
Preoxygenation: 100% O₂ by mask to denitrogenate FRC
Cricoid pressure
Thiopentone (4 mg/kg), suxamethonium (1.5 mg/kg) may be less in obese, correct towards LBM
Laryngoscopy, cuffed ETT

Maintenance

O₂/N₂O/isoflurane: FiO₂ \geq 50%, isoflurane \leq 1 MAC
Higher FiO₂ and PIP required with obese patient
 \uparrow sensitivity to non-depolarizing relaxants, esp. with Mg²⁺
Relaxants do not cross placenta significantly
Minimal narcotics prior to delivery, then morphine 0.2-0.5 mg/kg

Post-delivery

Oxytocics

Oxytocin 5-20 U plus infusion
Ergometrine 0.25-0.5 mg IV or IM if continued bleeding

Emergence

Extubation when awake and protecting airway

Postoperative

Analgesia, antiemetics
Appropriate review

Justify an epidural test dose in obstetrics and contraindications to epidural for LUSCS.

Test dose

Purpose

Determine incorrect placement of epidural catheter

Intravascular or subarachnoid or subdural

Aspiration is a useful test if positive: blood or CSF, but may be falsely negative

Procedure

After placement of the catheter, 3 ml of local anaesthetic solution (typically bupivacaine 0.25% or lignocaine 1%) containing adrenaline 5 μ g/ml is administered

The heart rate is observed for a rapid rise of 20-30 bpm in response to intravascular adrenaline

The degree of sensory and motor blockade is observed after 3-5 min for a dense spinal block as high as T10

Rationale

The potential morbidity from incorrect placement of an epidural bolus dose can be severe

Bupivacaine 25-75 mg or lignocaine 200-400 mg administered intravascularly can cause fitting due to neurotoxicity and cardiac arrest due to Type I antidysrhythmic effect

The same dose given subarachnoid may cause a total spinal requiring urgent intubation and ventilation

The cost or risk associated with a test dose is small: a 3-5 min delay in establishing a block

The test is not 100% sensitive or specific, especially in labouring women in whom the heart rate is typically high and variable, but it is the best readily available and rapid test

Contrast epidurography may be a better test, but involves fluoroscopy, requiring a radiation dose, and substantial delay and cost

Absolute contraindications

Refusal by a competent patient

Infection at the site of potential insertion

Hypovolaemic shock

Coagulopathy, severe thrombocytopenia

Intellectual disability or other reason for being unable to cooperate

Relative contraindications

Urgency of surgery, delay in establishing block may be 20 minutes

Unstable neurological disease

Cardiovascular disease requiring maintenance of SVR e.g. severe aortic stenosis

Treatment with anticoagulants, aspirin or other NSAIDs

Disease likely to cause technical difficulty or failure e.g. ankylosing spondylitis

Outline management of a 32 week pregnant woman who fits at home.

Immediate management

ABCDE

Lateral position, clear airway

Expired air resuscitation if not breathing, oxygen when available

External cardiac massage if no output

Requires supine position with left lateral uterine displacement

Summon assistance: ambulance

Aetiology

Eclampsia

Organic brain problem

Idiopathic epilepsy

Arteriovenous malformation

Tumour

Trauma

Metabolic disturbance

Drug withdrawal

Uraemia, hypoglycaemia, hyponatraemia etc.

General management

Once patient is well-oxygenated, fit is terminated and she is transported to a suitable hospital, the cause of the fit needs to be determined

Unless another cause is found, the aetiology is assumed to be eclampsia

Eclampsia

Immediate management

ABCDE as above

Mg²⁺ 2-4 g IV may terminate fit

Incidence

Preeclampsia 30 per 1000 births

Most common in young primigravidas

Eclampsia 0.4 per 1000 births

44% fit before delivery

37% during delivery

19% after delivery

Management

Definitive management is delivery of the foetus and placenta

Examine and test for complications

Hypertension, proteinuria, thrombocytopenia, hepatic dysfunction

Growth-retarded or distressed foetus

Monitoring

Fetal well-being: CTG

Mother: NIBP or IABP, urinary catheter, possibly CVC or PA catheter

Best managed in HDU or labour ward if adequately equipped

Magnesium

Anticonvulsant, vasodilator, tocolytic, bronchodilator, ↓ renin, ↓ ACE,
↓ platelet activity, ↓ prostacyclin release

Antihypertensives

Hydralazine, α-methyldopa, clonidine, prazosin, labetalol, nifedipine,
nitrates

Fetal management and delivery

Best done by experienced obstetrician

Epilepsy

Immediate management

- Fits usually self-limiting
- Administer oxygen
- Fit can be terminated with barbiturate or benzodiazepine if prolonged
- Incidence 50 per 100,000
- Pregnancy
 - May increase frequency of fits
 - Possibly due to increased clearance and altered distribution of drugs, electrolyte changes
 - Antiepileptic medication may be teratogenic
 - Phenytoin → cleft lip and palate, cardiac lesions, digital hypoplasia
 - Increased incidence of preeclampsia, complications and intervention
- Management
 - Careful monitoring of blood levels of anticonvulsant and adjustment of dose

Outline differences between spinal and epidural for LUSCS

Requirement

Both

- Surgical anaesthesia to T4
- Adequate duration for surgery

Anatomy, technique

Both

- Lumbar technique midline or paramedian
- Sitting or lateral position

Epidural

- Probably safer in lateral position (less risk of dural puncture)
- Tuohy needle 16g-19g used to approach epidural space
- Space identified with LOR to air or saline
- Catheter passed into space or single dose of anaesthetic given
- Test for incorrect placement with aspiration and test dose of adrenaline-containing solution

Spinal

- Commonly easier in sitting position
- Pencil point needle 25g-27g used to enter subarachnoid space
- Space identified with “pop” through dura and return of CSF
- Single dose of anaesthetic
- Clearer confirmation of correct placement of drug

Indications, contraindications

Safe techniques for elective and urgent LUSCS

- Spinal usually faster to get the case started
- Epidural can be fast if block already established
- Both thought to be safer than GA (no conclusive evidence)

Coagulopathy or thrombocytopenia: both contraindicated, but epidural more strongly

Haemodynamic compromise e.g. aortic or mitral stenosis

- Relative contraindication to regional
- Fall in SVR more rapid and uncontrolled with spinal
- May be safer to use graduated epidural

Drugs used

Epidural

- Local anaesthetic: lignocaine 2%, ropivacaine 0.5-1%, bupivacaine 0.5%
- Dose up to 20ml of 2% lignocaine
- Addition of fentanyl or pethidine or morphine

Spinal

- Local anaesthetic: bupivacaine 0.5%, cinchocaine (obsolete)
- Dose typically 2.2-2.5ml of hyperbaric bupivacaine 0.5%
- Addition of fentanyl 10-20 μ g or morphine 100-200 μ g

Reliability, duration

Spinal a more reliable technique

- Clearer end-point
- Denser block
- Fixed duration, typically 45-60 min of good surgical anaesthesia

Epidural

- May be patchy, unilateral
- Intraoperative supplementation allows longer duration

Complications, risks

Both

- Major risks of anaesthetic
- Failed block, inadequate block, headache, infection, neuropraxia, drug toxicity, hypotension

Major risks of surgery

Haemorrhage, embolism, nausea, vomiting, infection probably
unaffected by anaesthetic technique

Spinal

Less risk of failure, headache, local anaesthetic toxicity

Minor risk of respiratory depression with intrathecal morphine

Epidural

Larger dose of local anaesthetic, possible intravascular injection so greater
risk of toxicity

Management of a term female with moderate aortic stenosis for elective Caesarean section

Surgery

Elective, moderate risk

Preoperative

Assessment

Routine anaesthetic assessment

Obstetric issues

Size, obesity

Airway compromise

Obstetric complications, e.g. preeclampsia

Crossmatch

Aortic stenosis

Severity moderate

History

Symptoms of severity

Exercise limitation, dyspnoea, angina, drop attacks

Examination

BP, pulse character

Murmur, radiation

Signs of failure: creps, oedema

Investigations

CXR, ECG, echocardiographic findings required

Catheter study results if performed

Optimize condition

Consult with cardiologist, obstetrician

Symptoms often worsen with pregnancy, fall in SVR

Treat failure

Valvuloplasty if indicated

Premedication

Ranitidine or antacid

Benzodiazepine if anxiolytic required

Transport

Left lateral position

Supplemental O₂

Intraoperative

Monitoring and access

Large bore IV access

Routine monitoring, plus

Arterial line

If severe consider PA catheter or TOE

Induction

Position with 15° left lateral tilt and uterine displacement

Preload with fluid

Prepare resuscitation drugs

Vasoconstrictor agents: metaraminol, phenylephrine

Regional

Graduated epidural

L2-3 or 3-4 catheter

Incremental boluses of lignocaine plus fentanyl to block to T4

Maintain contractility, HR and BP with pressors and fluid

General

Preoxygenation, cricoid pressure

Narcotic plus midazolam titrated to unconsciousness

Relaxation with suxamethonium

Oral intubation

Pressors as needed to maintain BP

Maintenance

General

Remifentanyl infusion or

N₂O, O₂, low concentration volatile

Slow administration of required syntocinon to prevent hypotension

Expect neonate to require resuscitation: naloxone ± ventilation

Aggressive replacement of volume loss

Emergence

Awake extubation in lateral position

May be delayed by high narcotic dose

Postoperative

HDU or ICU care

Continue ECG, arterial BP monitoring

Analgesia with morphine PCA plus NSAID and paracetamol

Anaesthesia for LUSCS

Rate 62000/year Vic

Indications

Distress 20%

Malpresentation 15-20%

FTP 40%

Previous Caesar 30%

Maternal death rate 1/10000

Technique

Regional vs GA vs local

Urgency, patient choice, anaesthetic opinion, indication for LUSCS

Complications of pregnancy (PE, placenta praevia...)

Classify as needs of: mother, baby, obstetrician

GA

Advantages

Rapid, reliable, good conditions, safer in unstable conditions or coagulopathy, familiar to patients

Disadvantages

Requirement for airway control, awareness, fetal depression, increased analgesic requirement, ↓ breast feeding at 6 months, no participation in birth

Regional

Advantages

Participation, no airway problems, ↓ analgesic requirement, better

Apgar at 1 minute

Disadvantages

Limited duration, ? more hypotension, inadequate block, PDPH, neurological complications, total spinal, difficult conversion to GA, LA toxicity from IV injection

Assessing block

T4-T6 required for surgery

consider resiting epidural or CSE for poor block

Contraindications

Refusal, thrombocytopenia, coagulopathy, conditions markedly worsened by afterload reduction (e.g. AS), urgency of induction

Premedication

Possibility of conversion to GA, so non-particulate antacid immediately before, H₂ blocker or metoclopramide premedication

Complications

Hypotension

prevent with fluid load (0.5-1 l), left lateral tilt, suitable spinal dose or titrated epidural, early use of ephedrine, close monitoring of BP and symptoms of hypotension

High block, inadequate block

Supplemental oxygen

↑ maternal and foetal PO₂, given during block in case of hypotension

before uterine incision: load with O₂ before reduced placental perfusion

Doses

in [recipes](#)

GA

Complications

Aspiration, failed intubation management, aortocaval compression,

Priorities

Maintain oxygenation, adequate ventilation (PCO₂ 32-34), minimize incision to delivery time, avoid depressant drugs

Initial gas mixture: 50:50 + 0.5 MAC volatile (initial overpressure)
Reduced anaesthetic requirements (25-40% MAC reduction)
Reduced FRC → rapid hypoxia and rapid equilibration of anaesthetic gases
Awareness most likely: intubation and incision

Perinatal Mortality 1997

Declining birth rate (p. 8)

62000 in 1997, similar number of births since 1962, but rate has fallen from 21.1 per 1000 population to 13.4

Declining perinatal deaths (p. 5)

429 deaths, 6.9 per 1000 births

269 stillborn, 160 before 28 days post-delivery

Rates are lower using WHO criteria (4.3 per 1000 births)

count infants $\geq 1000\text{g}$ or 28 weeks rather than 500g or 22 weeks

Preventable causes of perinatal death (p. 13)

Mostly related to obstetric practice

Some anaesthetic relevance

Initiate management of maternal illness prior to transfer (e.g. controlling hypertension or treating preeclampsia)

Avoid surgery unless mandatory

Discourage smoking in pregnancy

Maternal Mortality 1997

Older population of mothers (p. 30)

Median age increased from 27 in 1984 to 30 in 1997

Perinatal mortality rate increases with maternal age (p. 29)

Method of delivery has changed (p. 34)

1984 16% forceps, 15% Caesarean

1997 10% forceps, 20% Caesarean

Duration of hospital stay has fallen (p. 38)

1985 84% stayed ≥ 5 days

1997 42% stayed ≥ 5 days

Maternal death (p. 72)

Rate continues to fall from 0.66 per 1000 births in 1953 to 0.08 in 1997

Only five deaths reported

36yo $G_4P_2^{29/40}$ massive PE with history of DVT

35yo $P_4^{41/40}$ vaginal haemorrhage, Caesar, *failed intubation*

32yo $P_1^{24/40}$ obese asthmatic hypertensive smoker, arrhythmia

32yo $P_2^{34/40}$ hypertensive, SAH in doctor's rooms

26yo P_0 recurrent glioma

Analgesia in Labour

Schema for examining analgesic techniques

Evidence

- Basic science

- Clinical

- Efficacy

- Costs

- Complications

 - Mother

 - Baby

- Monitoring requirement

- Technique, skill

- Effect on obstetric outcome

Analgesic options

- Psychological

 - Education, visualization...

- Pharmacological

 - Systemic: N₂O, pethidine

 - Regional: epidural, spinal, nerve blocks

Indications for early epidural

- Preeclampsia without severe thrombocytopenia

- Serious contraindication to GA

 - Failed intubation, morbid obesity

- Trial of scar

- Twins

- Poor cardiac reserve

- Likely Caesarean section

Indications for GA in labour ward

- Stuck second twin or shoulder dystocia without an epidural

Difficulties in pregnancy with epidural

- More likely to be fat, oedematous

- Increased lordosis, difficulty positioning

- Contractions increase risk of movement or bloody tap (?10%)

- Reduced volume of epidural space and increased sensitivity to LA

- Raised CO, low SVR before block

- Remote location

- ↑ O₂ consumption, ineffective CPR in pregnancy if complicated

Contraindications

- Risk/benefit consideration

 - Usual technique

 - Modified technique

- Fever

 - Generalized sepsis vs local vs febrile due to labour alone

 - Epidural abscess is rare even in septic patients

 - Modification of technique

 - More likely to use α agonist for hypotension

 - Close observation of neurological status post-procedure

- Thrombocytopenia

 - <80 usually contraindicated

 - >100 usually safe unless other contraindication

 - 80-100 consider other options: systemic analgesia, GA for Caesar, spinal with

 - 27g needle

- Hypovolaemia

- Valvular heart disease

 - Modified technique usually suitable

Gradual development of block
Closer monitoring

Tocolysis

Preterm labour

Preterm delivery (before 37 weeks) incidence 7%

Increased risk of respiratory distress, hypothermia, hypoglycaemia, jaundice

Risk factors

Young, low body weight, low socioeconomic class, unsupported, smokers

Previous preterm delivery, early bleeding, heart disease, cervical incompetence, multiple pregnancy, premature rupture of membranes

Causes

Medical induction

Infection

Streptococci, mycoplasma, fusiform bacilli

↑ IL-1β, IL-6, TNFα → PG production → labour

Risk might be reduced with antibiotics for *Gardnerella* vaginosis

Ruptured membranes

Multiple pregnancy

Rising incidence with IVF, GIFT etc.

1985-95: twins 10 to 14 per 1000 births, triplets 0.14 to 0.44

Polyhydramnios, intrauterine death, fetal abnormality, uterine abnormality, cervical incompetence

Diagnosis

Cervical dilatation too late for treatment

Fetal fibronectin in vaginal mucus unreliable

Diagnosis is clinical, 30-40% false positive

Management

Tocolytic drugs

Effective for less than 48 hours

Time for transfer or steroids

Greatest gains in 25-30 week gestations

β-agonists

Salbutamol 100 μg bolus

MgSO₄

Muscle weakness

Nitrates

GTN best acute agent (first report 1986)

200-600 μg dose IV

Onset 90 s, duration 3-5 min

Surprisingly little hypotension

Indomethacin

Causes DA closure after 34 weeks → pulmonary hypertension

Ca²⁺ channel blockers

Nifedipine → hypotension, uteroplacental flow dysfunction

In trials

Atosiban (oxytocin blocker), nimesulide (COX-II inhibitor)

Obsolete

Alcohol, isoxuprine, amyl nitrite

Contraindications

Chorioamnionitis

Antibiotics for ruptured membranes (unproven)

Steroids to prevent neonatal respiratory distress

Mode of delivery depends on presentation

Delivery should be in a centre with NICU

Other uterine relaxants

Volatile agents (and cyclopropane)

MAC equipotent

Indications

- Tocolysis (above)

- Manipulative delivery

 - Malpresentation, breech, second twin, abnormal uterine anatomy

- Manual removal of placenta

- Acute uterine inversion

 - Pain, bleeding, vaginal discharge, air embolism, venous congestion and difficulty reducing

- Acute hypertonus

 - Drug-induced, following axial blockade

- Intrauterine surgery

Antenatal class

Analgesia in labour

Historical perspective

e.g. Queen Victoria and chloroform

Potential benefit of analgesia in labour

Maternal distress

Possible tocolytic effect of endogenous catecholamines

Epidemiology

Caesarean section rate 20-25%

Epidural analgesia in primiparas ≈50%

Analgesic options

Psychological

Visualization, relaxation

Simple physical

Position, heat, massage

Pharmacological

Systemic

Oral analgesics

Narcotics, N₂O

Regional

Epidural

Spinal

CSE

For various techniques

Basic mechanism

Safety, efficacy

Advantages, disadvantages

Complications

Anaesthesia for Caesarean section

General

Indications

Advantages, disadvantages

Regional

Spinal vs epidural

Advantages, disadvantages

Post-operative analgesia

Foetal monitoring

Antenatal

Noninvasive

Simple

- Auscultation for foetal heart

- Palpation of uterus, fundal height (cm above *symphysis pubis* = gestational age - 20)

- Kick chart

Complex

Ultrasound

- Head and abdominal circumference

- Amniotic fluid index

- Anatomical anomalies

- Doppler flows in umbilical arteries

- Cardiotocography

- Biophysical profile

- Scoring system derived from movements (limb and breathing), tone, AFI and CTG

Invasive

- Amniocentesis

- Chorionic villous sampling

- Lecithin/sphingomyelin ratio
(oestriol)

Intrapartum

Noninvasive

- Foetal heart rate monitoring (auscultation or CTG)

- Examination of liquor for meconium

Invasive

- Foetal scalp electrode for CTG

- Foetal scalp pH (sensitive for stress)

- Vibroacoustic stimulation

Trauma in pregnancy (also in [Trauma](#))

Primary survey

A

Difficult airway, ↑ risk of aspiration

B

↑ VO_2 , ↓ PCO_2 , risk of hypoxia, fetal consideration

C

Resting tachycardia, expanded blood volume, altered resting BP, vasodilated
Potential for aortocaval compression
Blood loss related to pregnancy

Abruption

Abdominal assessment difficult e.g. retroperitoneal haemorrhage

Pelvic fracture causes greater bleeding with enlarged vessels

Coagulation altered, physiological anaemia, thrombocytopenia

Tests

Bloods: ↑ WCC, ↓ Hb, plt, ↓ PCO_2

ECG: LAD

Abdo: Altered US assessment, risk with DPL

Imaging: consider radiation dose

Additional assessment of fetus: CTG, consultation with obstetrician

Obstetric management

Resuscitation of mother is first priority

Suitable hospital for trauma

Management of fetus determined by mother's stability, fetal/placental well-being, uterine damage

Options

Expectant, delivery, Caesarean

Monitoring and frequent reassessment is important

Presentations

Arrest

ABC resuscitation, left lateral tilt, CPR may be ineffective

Caesarean if failed resuscitation at 4 min

Even if fetus is non-viable, improves CPR effectiveness

Major uterine injury

Rupture: pain, hypovolaemia, fetal distress or death, vaginal or IDC bleeding

Emergency laparotomy

Minor trauma, mother and baby apparently okay

↑ risk of premature labour, fetal distress

Monitoring with CTG, expectant management

If minor abruption

Risk of DIC: monitor fibrinogen, possible AFE

Fetomaternal haemorrhage: Kleihauer, anti-D if indicated

Doses

| | |
|-------------------|---|
| PGF _{2α} | 5 mg (1 amp) in 20 ml, 1-2 ml up to 20 ml in myometrium |
| Mg ²⁺ | 4 g bolus (30 min) 1-2 g/h 6 h'ly levels |
| Ergometrine | 250 µg IV, 250 µg IM |

Case scenarios

1. Inadequate perineal cover from epidural

LA bolus 5 ml 0.25% bupivacaine
± pethidine 25-50 mg
± clonidine 30-50 µg

still failed: lignocaine 2% or bupivacaine 0.5% to block motor and sensory

Caudal an option in theory (risk of toxicity and foetal injection)

2. Head at spines requests analgesia

CSE: 0.5 ml 0.5% bupivacaine, 25 µg fentanyl intrathecal
epidural infusion to start after ≈30 min

3. LUSCS with L3-4 epidural in situ top-up 15 ml 2% lignocaine, 50 µg fentanyl, block at T8

bolus 5ml lig.
still no block: resite epidural to ≈T12-L1

4. Inadequate perineal block with LUSCS open on table

Wait, bolus epidural, narcotic, N₂O, clonidine, ketamine
Lignocaine 0.5% applied by surgeon to bladder, pelvis

5. Late decelerations, emergency GA LUSCS. RSI, can't see cords

Ventilate?

Yes: introducer, bougie, Fastrach, FOB, wake-up → regional

No: help!, airway position, BURP position, different blade (straight, McCoy),
ventilation is a higher priority than intubation, two hands on mask, Guedel,
LMA, COPA, Combitube, cricothyroid puncture

Cricothyroid puncture

14G Jelco with syringe, aspirate air, attach 3 way tap, O₂ tubing, Sanders
injector (50 psi initially), airway to improve exhalation

Cricothyroidotomy

6. Post delivery, 14 hour labour, PPH 600 ml, BP 70 mmHg, HR 110 bpm, no IV access

Acute resuscitation: ABC

Supplemental O₂, large bore IV access, rapid fluid replacement

Blood specimen for crossmatch, FBE

Obstetric management of haemorrhage

Remove placenta, rub fundus, oxytocin, ergometrine, PGF_{2α}, aortic
compression, theatre

Anaesthesia in theatre

RSI with reduced doses, reduced volatile (uterine relaxant)

Rapid IV infusion: Level 1 or warmer with pump set

Scale up monitoring when time available: arterial line, CVC

Early access to blood products: packed cells, platelets, FFP likely to be needed

7. 39 weeks BP 155/95 mmHg, protein +, oedema, 95 kg, req. analgesia in labour at 4 cm

FBE, clotting, U&E, LFT, G&H, uric a., IDC (UO), CTG

Mg²⁺ bolus 4 g over 30 min, 1-2 g/h, 6 h'ly levels

Add hydralazine if still hypertensive after an hour 5 mg bolus, infusion

Aim 120-140/70-90 mmHg

If plt \geq 80 and clotting normal, epidural preferred with patient discussion of risks

Paediatrics

[Neonatal anaesthesia](#)

[Burns management](#)

[Outline airway problems in choanal atresia, Pierre-Robin syndrome, laryngomalacia](#)

[Outline your approach to paediatric bronchoscopy](#)

[Management of anaesthesia for teenage scoliosis surgery patient](#)

[Outline the management of anaesthesia for tracheoesophageal fistula surgery](#)

[Paediatric respiratory failure](#)

[Common sizes and doses](#)

Neonatal anaesthesia

Neonate

birth to 28d, more usefully up to 44w post conception

Anaesthesia

poorer outcomes with anaesthesia by non-experts

increasing numbers coming to theatre as they survive more commonly

Physiology

CVS

rate dependant CO

transitional circulation

caused by hypoxia, acidosis, hypercapnia, cold

treat with 100% O₂, hyperventilate

little sympathetic tone

HbF, p50 17 mmHg

higher haematocrit (depends on cord-clamping time)

blood volume 90ml/kg

inefficient myocardium due to poorly organized myofibrils

preferential blood supply of highest pO₂ to coronary, cerebral circulation

Respiratory

large head, short neck

small diameter airway

different laryngeal angle, anterior larynx

edentulous, but tooth buds can be damaged on intubation

short trachea

mouth breathing

increased MV

compliant chest wall, horizontal ribs

noncompliant lungs

prone to apnoea, sensitive to sedative drugs

Homeostasis

temperature maintenance

high SA to volume ratio

thin skin, rapid evaporative loss

little fat

no shivering, but non-shivering thermogenesis

poor vasoconstriction

thermoneutral zone

temperature requiring minimal O₂ consumption to maintain

temperature

neonate 28-32°C at term, higher for prems

maintaining temperature in anaesthesia extremely important

Fluids

increased body water

high evaporative losses

reduced renal function

low GFR, poor concentrating ability

requirements

day 1-2 40-60ml/kg/24h (more for prems up to 200ml/kg/d)

10% dextrose plus Na⁺ 2mmol/kg/d, K⁺ 2-3mmol/kg/d, Ca²⁺, Mg²⁺ as required

continue glucose intraop (or glucose component of TPN)

lowered renal threshold for glucose

risk related to Ca²⁺ administration: burns if extravasates

Diseases

HMD

lack of surfactant prior to 34w, later in IDM
increased work of breathing, ground glass x-ray
respiratory distress, cyanosis, tracheal tug, grunting
prevention

reduce risk of prematurity, steroids prior to delivery, tocolytics

treatment

oxygen, CPAP, intubation, ventilation: IPPV, HFJV, oscillation,
surfactant, PLV

complications

pneumothorax, IVH, ?NEC, chronic lung disease

Oxygen toxicity

retinopathy of prematurity

high pO_2 , vasoconstriction, neovascularization, haemorrhage, scarring,
retinal detachment

rare after 30w, $PaO_2 < 80$ mmHg, <4 h

Pulmonary O_2 toxicity

free radical generation by high FiO_2 , worse with IPPV, high FiO_2 , aim for
 $FiO_2 < 60\%$, endothelial damage

IVH

brain lesion associated with prematurity

neonates: fragile vessels around ventricles: haemorrhage with rise in BP, also
periventricular leukomalacia: ischaemia (watershed area in hypotension) with
venous haemorrhage

high risk at the time of intubation or volume expansion

graded by extent, detected by u/s through fontanelle

good prognosis unless very large

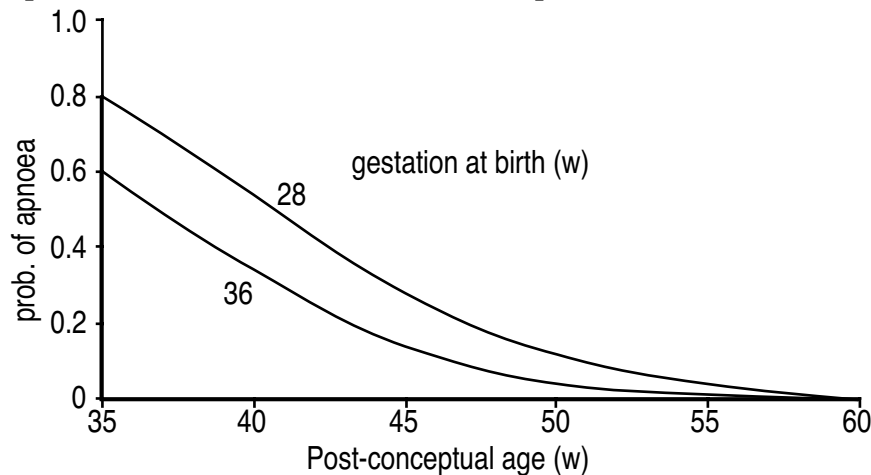
older babies: cortical lesions more common

Apnoea

More common with prematurity

central, obstructive or mixed

monitoring post anaesthetic up to 45w post conceptual in term babies here
up to 60w in some units or with ex-prems



NEC

abdominal distension, tram tracking, acidosis

Anaesthesia

Assessment

routine plus prematurity, associated abnormalities, recent course (ventilation,
glucose..)

Transfer

do case in neonates if sick, ?transfer to major hospital

Induction in theatre

temperature monitoring and maintenance

IV usually not too hard: little fat, some veins invariant
intubation different: view and tube manipulation
monitoring: standard plus ECG, T, SpO₂ x 2
laryngoscopy: straight or curved blade, pick up epiglottis or not
tube size, need for leak, PCV, taping technique, nasal vs oral

Maintenance

ventilation PCV 5-20 cmH₂O 20/min, 10 l/min flow
positioning: flexible, need for head support, lying on wires etc., access usually poor, improved with hand up, oximeter lead available, tubing for IV access
fluids: Albumex 4 (no evidence), continue dextrose
maintenance plus losses: e.g. open abdomen 10 ml/kg/h

Extubation

awake

Recovery location

depends on procedure and institution

Regional

no long-term studies, morph infusion OK, paracetamol effective, little use of NSAIDs

Fasting time

clear fluids 2h breast 3h formula 4h solids 5h

Burns Management

First aid

- Remove burning debris, extinguish flames, remove from area of smoke

- ABCDE management

- Transfer to hospital

Primary survey

- ABCDE

- Location and severity of burns

 - Rule of 9s for area burned, modified for children

 - Special areas

 - Face, mouth, airway

 - Eyes

- Associated injuries

 - Inhalational injury

 - More likely if facial burns

 - Cause of injury: smoke, toxic fumes, hot steam

 - Smoke inhalation

 - May have high COHb, give supplemental oxygen

 - Lung injury may produce respiratory distress syndrome

 - Airway burn

 - Develop oedema due to injury

 - Intubate early to secure airway

 - Other injuries

 - Electrical burns, chemical burns, blast injury etc.

 - Circumferential burns may require escharotomy

- Obtain IV access

 - Large bore in non-burned area

 - May need to be CVC or temporary intraosseous cannula

 - Take baseline bloods

 - Start hydration

 - Hartmann's solution

 - Maintenance (4/2/1 ml/kg formula), plus

 - Fasting time, plus

 - Burn losses 2-4 ml/kg/% burn over 24 hours

 - half in 8 hours

 - If young, may require glucose

 - Severe burns are often given some colloid

 - Monitor urine output to assess hydration

 - ≥ 0.75 -1 ml/kg/h desired

 - Give IV analgesia

 - Titrated doses of morphine IV

 - Reduced dose requirement due to fluid depletion and centralized circulation

- Maintain normothermia

 - Warm environment

 - Warmed fluids

- Involve surgical/burns unit for on-going management

Later issues

- Infection

 - Prophylactic antibiotics vary by institution

 - Silver sulfadiazine dressings

- Nutrition

 - Commonly require NGT or IV supplementation

 - Particularly Zn, ω_3 fatty acids

Anaesthesia

Surgery

- Commonly debridement and grafting
- Multiple procedures over weeks or months
- Commonly start about 5 days after injury

Preoperative

- Routine, plus
- Careful airway assessment
- Investigation
 - U+E to assess renal function
 - FBE, coagulation
 - Crossmatch for all debridements

Induction

- Good IV access required
- Commonly spontaneous ventilation with LMA
- Induction with
 - Thiopentone or propofol commonly
 - Ketamine: less fall in cardiac output than other IV agents
 - Halothane: vasodilator, myocardial depressant, ↓ platelet function but still commonly used
- Muscle relaxation
 - Often not required
 - Increased number of post-junctional receptors
 - Decreased sensitivity to non-depolarizing agents
 - Increased K⁺ rise with suxamethonium
 - Unsafe from around 1 week to 12 weeks (or healed)
 - Lower dose useable (in theory)

Analgesia

- IV narcotic
- Nerve blocks for donor sites
 - Posterior cutaneous nerve of thigh
 - $\frac{1}{4}$ of the way from ischial tuberosity to greater trochanter
 - In gluteal fold, LOR before reaching muscle or on withdrawal
 - Lateral cutaneous nerve of thigh
 - 2 cm inferior to ASIS between internal oblique and ilium
 - [Femoral nerve](#)
 - Lateral to femoral artery in the groin
 - 2 pops on insertion of 45° bevel needle
 - [Sciatic nerve](#)
 - Intersection of *biceps femoris* and sciatic nerve in leg
 - Nerve passes from midpoint of ischial tuberosity and greater trochanter to popliteal fossa
 - Muscle passes from ischial tuberosity to head of fibula

Outline airway problems in choanal atresia, Pierre Robin syndrome, laryngomalacia.

Choanal atresia

- Congenital atresia of the passage from nose into pharynx

- Unilateral or bilateral

- Membranous, cartilaginous or bony

- Presentation

 - Often detected at birth

 - Respiratory difficulty and hypoxia as neonates are obligate nose breathers

 - Tested for by occlusion of each nostril or passage of cannula

- Immediate management

 - Oral airway

 - Supplemental oxygen

 - Infants are typically pink and well-oxygenated when crying but hypoxic when feeding or asleep

Pierre Robin syndrome

- Congenital anomaly of the jaw, tongue and palate

- Cause uncertain

- Micro- or retro-gnathia, glossoptosis, cleft or arched palate (lip intact)

- Presentation

 - Obvious deformity at birth

 - Commonly respiratory obstruction when supine

 - May lead to cor pulmonale if untreated

- Anaesthetic problems

 - Usually difficult intubation

 - Difficulty usually reduced with age as mandible grows

 - May require gas induction and fiberoptic intubation

 - Assistant retracting tongue may be helpful

Laryngomalacia

- Infantile larynx

- Normal variant laryngeal anatomy

- Unusually soft cartilaginous structures

- Epiglottis and surrounding structures cause dynamic obstruction

- Presentation

 - Stridor developing soon after birth

 - Absent with quiet breathing

 - Increasingly noisy with distress

 - Resolves over first 6 months of life

- Anaesthetic problems

 - Increased risk of difficult intubation

 - Due to floppy laryngeal structures obscuring view

 - Difficulty with stridor after extubation

Outline your approach to paediatric bronchoscopy.

Rigid bronchoscopy

Surgery

- Elective for investigation of masses, respiratory symptoms
- Semi-urgent for removal of foreign bodies
- Emergency for massive haemoptysis, acute obstruction
- May be moderate or high risk
- Shared airway

Preoperative

- Anaesthetic assessment
 - Routine, plus
 - Careful assessment of mouth opening and potential for dental injury
 - Respiratory function testing if adult and compromised
- Assessment of indication for bronchoscopy
 - Respiratory compromise
 - Complications of disease e.g. cachexia from tumour
- Premedication
 - Anxiolytic, amnestic agent e.g. benzodiazepine
 - Anticholinergic to reduce secretions

Induction

- Preparation of the airway
 - Local anaesthetic
 - Topical spray or nebulized lignocaine
 - Transtacheal lignocaine
 - Nerve blocks: glossopharyngeal and superior laryngeal
 - Dental guard

Monitoring

- Routine: SpO₂, ECG, NIBP
- Plus arterial line if debilitated
- Secure IV access for TIVA

Induction

- Propofol plus short-acting relaxant (rocuronium or suxamethonium)
- Fentanyl to blunt haemodynamic response to bronchoscopy

Ventilation

- Jet insufflation through scope
 - Requires special equipment
 - No anaesthetic agent delivered so requires TIVA
 - Permissive hypercapnea limits duration of procedure
 - ↑ risk of arrhythmias
 - Risk of barotrauma if scope occluded
- IPPV through scope
 - T-piece circuit
 - Allows delivery of volatile agent
 - Intermittent ventilation as scope must be occluded
 - So high FiO₂ to allow for apnoea
 - Requires good communication with surgeon

HFJV

- Spontaneous ventilation without relaxant

Maintenance

- Intermittent boluses of IV anaesthetic agent and relaxant or infusion
- Extreme vigilance for ventilatory compromise

Emergence

- May require intubation and suctioning after procedure until awakening and muscle relaxant reversal

- Lateral position

- Risk of haemoptysis after resection or biopsy

Postoperative

- Usually little analgesia required

- Supplemental oxygen and saturation monitoring

Particular considerations in paediatric bronchoscopy

Patient population

- Commonly performed for foreign body aspiration

- Usually fiberoptic scope is not an option

- Often semi-urgent

- Higher metabolic rate, low FRC

- Rapid onset of hypoxia

- Particularly good communication with surgeon required

Airways

- Smaller calibre and softer tissue

- Increased risk of perforation or bleeding

- Increased risk of laryngospasm during emergence

Management of anaesthesia for a teenage scoliosis patient

Surgery

- Elective, high risk surgery
- Usually in teenage females
- Extensive thoracotomy, potential for massive blood loss, hypothermia
 - Posterior and anterior approaches
- May have coexisting neuromuscular disease
- Secondary respiratory or cardiovascular compromise
- Increased incidence of MH in this patient population

Preoperative

Assessment

- Routine history and examination, plus
- Scoliosis
 - Airway assessment vital
 - Degree, mobility
 - Complications
 - Respiratory function testing, restrictive deficit
 - Exercise tolerance

Investigations

- FBE, XM, RFT, ABG
- Autologous blood donation or directed donation

Consent

- Discussion of risks
- Possible need to wake intraoperatively to test neurological function

Premedication

- Oral benzodiazepine with regard to respiratory function

Transport

Routine

Intraoperative

Monitoring and access

- Usual emergency equipment, plus
 - Difficult airway equipment
 - Rapid infusion equipment available
 - Cell saver if indicated
- Routine monitoring, plus
 - Arterial line, temperature probe, IDC
 - SSEP or MEP monitor
 - Availability of ABG and Hb measurements

Induction

- Intubation required
 - Thoracotomy and commonly prone
- Prepare for difficult airway if likely
 - Consider spontaneously breathing induction or awake FOB if required
 - Otherwise routine IV induction
- Short-acting muscle relaxant if MEP required

Maintenance

Position

- Pressure care may be difficult if severe scoliosis
- Often prone, avoid abdominal pressure causing vertebral vein engorgement

Ventilation

- N₂O, O₂, low isoflurane dose
 - ± propofol for intraoperative awakening
- Controlled hyperventilation to cause vasoconstriction
- One lung often retracted for surgical access: OLV

Circulation

- May be large blood loss

- Maintain normotension for cord perfusion

- Fluid loading and pressors

Analgesia

- Consider spinal or caudal morphine either by surgeon or pre-incision

- Fentanyl bolus plus infusion

Emergence

- Awake extubation, lateral position

- May require ICU ventilation if severe respiratory compromise

- Aim for early assessment of neurological function

- Consider propofol “bookend”

- Supplemental O₂

- Postoperative CXR and FBE

- Prolonged immobilization in supine position

- Chest physiotherapy, ?DVT prophylaxis

Outline the management of anaesthesia for tracheo-oesophageal fistula surgery.

Tracheo-oesophageal fistula

1/3000 live births

Abnormal communication between oesophagus and trachea

Usually associated with oesophageal atresia

Classified by topology

85% distal TOF with proximal blind oesophagus

10% oesophageal atresia with no TOF

4% patent oesophagus with TOF (often diagnosed late)

Diagnosed shortly after birth

Associated with polyhydramnios

Failure to pass orogastric tube

Failure to feed or aspiration with feeding

Surgical management

IV hydration

Laparotomy, feeding gastrostomy, determination of "gap"

Thoracotomy, fistula closure, oesophageal repair

Surgery

Urgent, high risk

Preoperative

Assessment

History

Post-conceptual age, gestational problems

Family history

Diseases of prematurity

VATER abnormalities

Vascular (cardiac), vertebral, atresia in GI tract, TOF, renal, radial abnormalities

Examination

Cardiac, respiratory, general

15-25% incidence of cardiac defects

Aspiration common

Investigation

XM, FBE, U&E or gases

CXR

Contrast studies

Echocardiogram

Optimization

Hydration, antibiotics for pneumonia, treatment of lung disease

Premedication

Atropine, paracetamol, antibiotics

Intraoperative

Monitoring

Routine: ECG, NIBP, SpO₂, gas analysis, IDC

Consider arterial line if unstable or blood gases required

Temp probe **not** in oesophagus

Induction

Aim to avoid mask IPPV which causes gastric distension

Bradycardia and diaphragmatic splinting

Aspirate gastrostomy and leave open

Topical LA to airway

Inhalational induction, spontaneously breathing intubation, or

Rapid IV induction

ETT placement beyond level of TOF, may be at carina

Maintenance

Position

- Laparotomy at 45° head-up

- Thoracotomy in left lateral position unless right aortic arch (5%)

- Warming to maintain temperature

- High FiO₂ with potent volatile agent

- Hand ventilation often required

- ETT may migrate into fistula with positioning

- Low lung compliance

- Gas leak through fistula

- Retraction of right lung for access

- Retraction on mediastinum may cause tracheal occlusion

- Analgesia with LA in wound or intercostal blocks

- Close attention to blood loss and fluid management

Emergence

- Aim for extubation if stable

- Less stress on tracheal sutures than IPPV

- Avoid neck extension: stresses anastomosis

Postoperative

- NICU or neonatal unit level of care

- SpO₂ monitoring

- Morphine infusion for analgesia

Complications

- Pneumonia, anastomotic leak, tracheomalacia, fistula, reflux, stricture

Paediatric respiratory failure

Definition

$PO_2 < 60$ mmHg, $PCO_2 > 55$ mmHg, $RR > 35$
at BTPS, FiO_2 0.21, worse than normal function
Type 1 ventilation failure, acidic pH (raised PCO_2)
Type 2 oxygenation failure, normal pH

Diagnosis

Very broad range of clinical symptoms, essentially subjective
Apnoea
Increased work of breathing, other clinical features
Tachypnoea, but rate highly variable and not different between well and ill populations
Cyanosis
ABG criteria

Susceptibility of children

Less reserve, higher BMR for size
Small airways, less adherent mucosa, readily occluded by oedema
Narrow subcricoid level, airways cause 20% of resistance
Short horizontal ribs, little increase in AP chest diameter
Soft chest wall, poor inspiratory pressure generation
Type I muscle fibres, easily fatigued
Less alveoli, continued budding to age 1y
Few pores of Kohn, more variation in time constants
Increased susceptibility to infection, poor cellular immunity, no memory IgG response
Birth injuries: asphyxia, aspiration, RDS of newborn

Differences from adults

Adults recover slowly if at all (80% mortality)
Children require only brief ventilation (3-4 days), good outcomes (5-6% mortality)
Most deaths in neonates
Analysis
Cost per year independent life saved
Neonate \$1500, child \$170, adult \$1950
Cost per survivor
Neonate \$95500, child \$11500, adult \$27850
Cost per patient intubated
\$28650, \$8600, \$9750

Causes of respiratory failure in children

Epiglottitis
Marked decline due to haemophilus influenzae B vaccination
Croup
Nebulized adrenaline 0.5 ml/kg of 1:1000 or 0.05 ml/kg of racemic (1:88)
Steroids
Bronchiolitis
Asthma

Treatment

Ventilation
HFPPV
60-100 /min 3-4 ml/kg small dead space
pressure generator with "chopper"

HFJV

similar to Sanders jet ventilator

3-5 ml/kg intermittent

Trial evidence suggests benefit in neonates by intermediate indicators

HFOV

3-15 /sec alternates between positive and negative pressure

less than dead space ventilation

rescue ventilation

set rate, ΔP , mean airway pressure (FiO_2 usually .9-1.0)

CO_2 elimination better with high ΔP , low frequency

Mechanism of ventilation

Pendelluft: differing time constants

Assymetric velocity profiles: wave interference between in and out flow at joints

Taylor dispersion: wave diffusion at joints?

Molecular diffusion: simple diffusion

Trial (HIFI) showed no benefit, but done in centres inexperienced with HFOV. Increased IVH, PVL rate. Less risk of long term disease, fibrosis, ECMO etc.

Surfactant and NO can be delivered

Conventional ventilation is usually the first strategy as HFJV and HFOV are not available in obstetric hospitals

ECMO

Available if failed ventilation, correctable disease, 80% expected mortality

Physiological indices also determine entry

Anticoagulation problems

Femoro-femoral or femoro-atrial

Ventilation for lung recruitment

Common sizes and doses

Weight

Birth 3-4 kg
1 y 10 kg
age x 2 + 9 up to 9 y
age x 3 from 9 y

ETT size

Prem 2.5 mm
Term 3-3.5 mm 9 cm at lips
age ÷ 4 + 4 ≤ age + 10 cm at lips (or age ÷ 2 + 12)

Induction (single agent unpremedicated elective)

| | |
|---------------|---------------------|
| Thiopentone | 7 mg/kg |
| Propofol | 4 mg/kg |
| Ketamine | 2 mg/kg |
| Suxamethonium | 1.5-2 mg/kg |
| Atracurium | 0.5 mg/kg |
| Atropine | 10-20 µg/kg |
| Morphine | 0.1-0.2 mg/kg |
| Fentanyl | 1-3 µg/kg |
| β-lactams | 20 mg/kg |
| Metronidazole | 15 mg/kg |
| Gentamicin | 6 mg/kg (less <1 y) |

Reversal

| | |
|-------------|----------|
| Neostigmine | 50 µg/kg |
| Atropine | 24 µg/kg |

Resuscitation

| | |
|------------|---|
| Adrenaline | 10 µg/kg up to 100 µg/kg |
| Calcium | 0.1-0.15 mmol/kg (0.2 ml/kg CaCl ₂ , 0.5 ml/kg Ca gluconate) |
| DCR | 2-4 J/kg (1 J/kg for atrial arrhythmia) |

Hypotension

| | |
|---------------|---|
| Nitroprusside | 50 mg/500 ml 0-20 ml/h (=0-33 µg/min, 0-10 µg/kg/min) |
|---------------|---|

Thoracic anatomy

[Autonomic nervous system](#)

Autonomic nervous system

Division by direction

Visceral efferent

Preganglionic myelinated, postganglionic unmyelinated

Synapse in ganglia

Visceral afferent

Similar to somatic afferent

Cell body in CNS, peripheral processes travel with autonomic and somatic fibres

Division by outflow

Sympathetic

Thoracolumbar outflow: T1-L3

Synapse in sympathetic trunk ganglia or other ganglia near CNS

Preganglionic cholinergic, postganglionic predominantly noradrenergic (also adrenergic, cholinergic sudomotor and purinergic)

Parasympathetic

Craniosacral outflow: III, VII, IX, X, S2-4

Synapse adjacent to end-organs

Cranial nerve parasympathetic ganglia are traversed by other fibres but contain only parasympathetic synapses

Parasympathetic anatomy

III

Edinger-Westphal nuclei → oculomotor n. → n. to inferior oblique → **ciliary ganglion** → short ciliary nn. → ciliary muscle and *sphincter pupillae*

VII

Superior salivatory nucleus → *nervus intermedius* → facial n. → *chorda tympani* → lingual n. → **submandibular ganglion** → submandibular and

sublingual glands

Geniculate ganglion → greater petrosal n. → **pterygopalatine ganglion** → zygomatic and lacrimal nerves to lacrimal gland and nasal and palatine branches to nasal mucosa

XI

Inferior salivatory nucleus → glossopharyngeal nerve → tympanic plexus → lesser petrosal n. → **otic ganglion** → auriculotemporal n. → parotid gland and oral mucosa

X

Dorsal nucleus of vagus → vagus n. → minute ganglia in respiratory tract, heart, kidneys and gastrointestinal viscera from oesophagus to mid transverse colon. Most vagal fibres are **afferent**, there is a very large ratio of postganglionic to preganglionic efferent fibres.

S2-4

Anterior rami → sacral spinal nerves → pelvic viscera and pelvic plexus → bladder, erectile tissue, gonads, uterus and uterine tubes, hindgut from mid transverse colon to rectum

Sympathetic anatomy

Preganglionic efferent

Lateral column cell body → ventral root → white *ramus communicans* → sympathetic trunk → synapse in trunk or other ganglia or adrenal

Postganglionic

May ascend or descend in the trunk, rejoin **all** spinal nerves via grey *rami communicantes* or leave in direct branches to vessels or viscera

Distribution

Cranial

Internal carotid plexus arises from superior cervical ganglion and

- cerebral arteries and ophthalmic artery
- Cervical
 - Sympathetic chain condenses usually into three ganglia on each side: superior (C2-3), middle (C6) and cervicothoracic (stellate, T1) cervical ganglia
- Cardiac plexus
 - Derived from T1-4 (and X) via cervical and thoracic ganglia
 - Surrounds heart, great vessels and coronaries
- Pulmonary plexuses
- Coeliac plexus
 - Two ganglia opposite T12-L1 with large condensation of autonomic fibres
 - Gives rise to phrenic, splenic, hepatic, left gastric, intermesenteric, suprarenal, renal, gonadal, superior and inferior mesenteric plexuses which accompany arteries to their target organs
- Superior hypogastric plexus
- Inferior hypogastric plexus
 - Supplies hindgut, ureter, bladder, gonads, sex organs

Somatic levels of visceral afferents

| Organ | Sympathetic | Parasympathetic |
|--------------------|--------------------|------------------------|
| Heart | T1-5 | X |
| Lungs | T2-4 | X |
| Oesophagus | T5-6 | X |
| Stomach | T6-10 | X |
| Liver, gallbladder | T6-10 | X |
| Pancreas, spleen | T6-10 | X |
| Small bowel | T9-10 | X |
| Large bowel | T11-12 | X to mid transverse |
| Kidney, ureter | T10-L2 | X, S2-4 |
| Adrenal | T8-L1 | none |
| Gonads | T10-11 | S2-4 |
| Bladder | T11-L2 | S2-4 |
| Prostate | T11-L1 | S2-4 |
| Uterus | T10-L1 | S2-4 |

Anatomy

nose

bones

external: nasal processes of frontal bones, nasal bones, frontal processes of maxillae

internal: ethmoid, sphenoid, occipital, pterygoid, palatine, maxilla, conchae, vomer

arteries

facial: lateral nasal branch and others

superior labial: septal and alar branches

ophthalmic: dorsal nasal and anterior and posterior ethmoidal branches

maxillary: nasal branch of infraorbital branch, sphenopalatine branch

innervation

special sensory

smell (I) through cribriform plate

sensory

external

V¹ via anterior ethmoidal and external nasal branches of the nasociliary nerve to bridge and tip

V² via nasal branches of infraorbital nerve

internal

external nasal and infraorbital branches to vestibule

septum: V¹ anterior ethmoidal branch anterosuperiorly, V²

nasopalatine branch from pterygopalatine ganglion

posteroinferiorly

lateral wall: V¹ anterior ethmoidal, V² anterior superior alveolar branch, posterior and inferior nasal branches and greater

palatine nerves from pterygopalatine ganglion

motor: VII to muscles of facial expression

mouth

innervation

special sense

VII to palate via greater petrosal nerve

VII chorda tympani to lingual nerve supply anterior $\frac{2}{3}$ of tongue

IX to posterior $\frac{1}{3}$

sensory

V² and V³ via infraorbital, superior alveolar, nasopalatine, greater and lesser palatine, buccal, lingual, inferior alveolar and mental nerves

IX to posterior parts

motor

VII to muscles of facial expression

V³ to tensor veli palatini and muscles of mastication

IX, X and XI via pharyngeal plexus to palatoglossus

XII to tongue and floor of mouth

Larynx

Skeleton

Hyoid bone above, firmly attached by 3 thyrohyoid ligaments and thyrohyoid membrane

Three unpaired midline cartilages

Thyroid cartilage

Two laminae, fused in midline

Superior border attached to hyoid

Posterior borders attached to stylopharyngeus and palatopharyngeus

External surface attached to sternothyroid, thyrohyoid and inferior constrictor muscles

Inferior synovial joint with cricoid posteriorly and lateral and median cricothyroid ligaments

Internally attached to stem of epiglottis, vocal and vestibular ligaments and thyroarytenoid, thyroepiglottic and vocalis muscles

Cricoid cartilage

Complete ring of cartilage at level of C6

Attached to thyroid cartilage above

Inferior attachment to trachea

Posterior insertion of oesophageal muscle

Posterolateral origin of posterior cricoarytenoid muscle

Lateral and anterior origin of cricothyroid and inferior constrictor

Superior edge origin of lateral cricoarytenoid muscle and posteriorly articulation with arytenoid cartilages

Epiglottis

Leaf-shaped elastic cartilage

Inserts into thyroid cartilage

Anterior attachment to hyoepiglottic ligament

Median and lateral glossoepiglottic folds attach to tongue

Lateral aryepiglottic folds

Three paired cartilages

Arytenoids

Tetrahedral cartilages

Anterior vocal process attaches to vocal ligament

Lateral muscular process attaches to posterior and lateral cricoarytenoid muscles

Posterior surface attaches to transverse arytenoid muscle (to other arytenoid)

Anterolateral attachment to vocalis and thyroarytenoid muscle

Rotates to open or close vocal cords

Cuneiforms

Corniculates

Contained in aryepiglottic folds

Muscles

Extrinsic

Move the larynx

Intrinsic

Sphincter muscles

Transverse and oblique arytenoid, and aryepiglottic muscles bring the opening of the larynx closed

Muscles of vocal folds

Tensing of vocal cords by cricothyroid

Slackening of vocal folds by thyroarytenoid and vocalis muscles

Adduction of vocal folds by lateral cricoarytenoid and transverse arytenoid muscles

Abduction of vocal cords by posterior cricoarytenoid muscles
All supplied by recurrent laryngeal nerve except cricothyroid (external laryngeal nerve). Fibres from XI travelling in X.

Sensory innervation

X internal laryngeal nerve above vocal cords

X recurrent laryngeal nerve below vocal cords

Miscellaneous

[Somatic levels of visceral afferents](#)

Somatic levels of visceral afferents

| Organ | Sympathetics | Parasympathetics |
|--------------------|--------------|---------------------|
| Heart | T1-5 | X |
| Lungs | T2-4 | X |
| Oesophagus | T5-6 | X |
| Stomach | T6-10 | X |
| Liver, gallbladder | T6-10 | X |
| Pancreas, spleen | T6-10 | X |
| Small bowel | T9-10 | X |
| Large bowel | T11-12 | X to mid transverse |
| Kidney, ureter | T10-L2 | X, S2-4 |
| Adrenal | T8-L1 | none |
| Gonads | T10-11 | S2-4 |
| Bladder | T11-L2 | S2-4 |
| Prostate | T11-L1 | S2-4 |
| Uterus | T10-L1 | S2-4 |

Regional

Abdomen and pelvis

Lower limb

[Lumbar and lumbosacral plexus](#)

[Femoral block, three-in-one block](#)

[Sciatic block](#)

[Ankle block](#)

[Other lower limb blocks](#)

Spine and thorax

[Intercostal block](#)

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Upper limb

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Neck

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Lumbar and lumbosacral plexus

Lumbar plexus

Four roots: ventral rami of L1-4

L1 divides into superior and inferior branches

Superior: ilioinguinal and iliohypogastric nn.

Inferior: joins L2 to form genitofemoral n.

L2-3 give branches to form lateral femoral cutaneous n.

L2-4 give branches to form femoral and obturator nn.

Iliohypogastric nerve

Runs superior to iliac crest between internal oblique and *transversus abdominis*

Motor to abdominal wall

Sensory branches: lateral (hip) and anterior cutaneous (suprapubic)

Ilioinguinal nerve

Immediately inferior to iliohypogastric

Traverses inguinal canal

Cutaneous branches to upper inner thigh and root of penis or *labia majora*

Genitofemoral nerve

Genital branch traverses inguinal canal and supplies *cremaster* and lateral scrotal skin

Femoral branch arises medially and passes under inguinal ligament with external iliac a., passes through saphenous opening and supplies skin over femoral triangle

Lateral femoral cutaneous nerve

Passes under lateral part of inguinal ligament, deep to *fascia lata*

Supplies skin of lateral thigh from greater trochanter to above knee

Obturator nerve

Runs on the medial and posterior aspect of psoas, through the obturator canal

Supplies adductors, hip and knee joints and skin over medial thigh just above knee

Femoral nerve [below](#)

Lumbosacral plexus

Five roots: ventral rami of L4-S3

Collateral branches to gluteal region, pudendal plexus and hip joint

Anterior and posterior terminal branches

Form posterior cutaneous nerve of thigh

Anterior branches form tibial portion of sciatic nerve

Posterior branches form common peroneal portion of sciatic nerve

Psoas compartment block

Anatomy

Lumbar nerve roots run in compartment posterior to psoas muscle

Needle placement

Patient in lateral position, knees to chest, sedation required

15 cm needle inserted 5 cm lateral and 3 cm inferior to L4 spinous process

Strikes L5 transverse process

Redirected slightly superiorly and advanced until loss of resistance at 12±2 cm

Local anaesthetic

20 ml air to dilate space

30 ml of dilute solution

Indications

Analgesia or anaesthesia in region of femoral, obturator and lateral cutaneous n.

Femoral nerve block, three-in-one block

Anatomy

- Femoral nerve arises from L2-4 roots in lumbar plexus
 - Runs deep to psoas, comes lateral to psoas tendon at level of inguinal ligament
 - Lies lateral to femoral artery below inguinal ligament
 - Different fascial plane: deep to *fascia lata* and *fascia iliaca*
 - Divides into superficial and deep bundles
 - Superficial supplies anterior thigh and sartorius
 - Deep supplies quadriceps, knee joint, gives rise to saphenous nerve
- Obturator nerve arises from L2-4
- Lateral cutaneous nerve of thigh arises from L2-3

Needle placement

- Patient supine
- Short-bevel needle inserted 1-2 cm below inguinal ligament 1-1.5 cm lateral to femoral artery
- Two “pops” or paraesthesia elicited or nerve stimulator used to determine depth

Local anaesthetic

- Femoral nerve only
 - 10-20 ml of 0.5% bupivacaine
- Three-in-one
 - 30 ml of solution (may need to be more dilute than 0.5% to avoid toxic dose)
 - Distal pressure over nerve causes solution to flow proximally
 - Proximal spread to lumbar plexus anaesthetizes obturator and lateral cutaneous nerve of thigh

Indications

- Three-in-one may be combined with sciatic block for most leg surgery
- Ideal for muscle biopsy in MH testing
- Useful for knee examination and surgery
- Analgesia for femoral fractures

Complications

- Vascular
 - Femoral artery or vein injury, haematoma
- Neurological
 - Neuropraxia, sympathetic block to leg
- Common to all blocks
 - Local anaesthetic toxicity (esp. combined with sciatic block)
 - Poor effect
 - Infection

Sciatic block

Classic approach of Labat

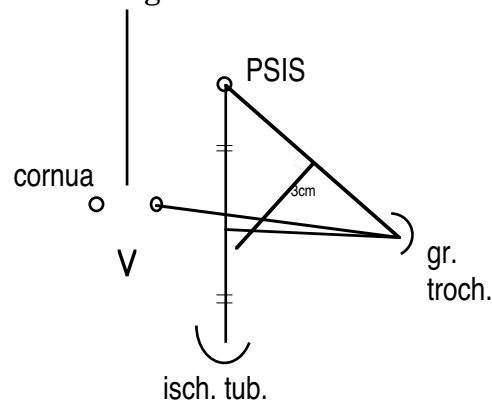
Lateral position, upper heel on lower knee

Line from greater trochanter to PSIS marks upper border of piriformis

Bisector of this line extended 3 cm inferiorly marks injection site

or intersection with line from greater trochanter to sacral cornu

or intersection with line from midpoint of line from PSIS to ischial tuberosity to greater trochanter



Advance 6-8 cm until bone is contacted

Geometric grid approach searching for paraesthesia or using nerve stimulator

Anterior approach of Labat

Supine anatomical position

Line of inguinal ligament identified

Medial trisector extended inferiorly

Intersection with a line parallel to inguinal ligament running through greater trochanter identified

Needle advanced slightly laterally strikes lesser trochanter

Walk medially off femur and identify LOR 4.5-6 cm beyond (or use nerve stimulator)

Lithotomy approach

Lithotomy position with full hip flexion

Line from ischial tuberosity to greater trochanter

Needle advanced through midpoint perpendicular to skin

LOR or nerve stimulator or paraesthesia determine depth

Lateral approach

Supine position

Needle inserted 3 cm distal to greater trochanter at posterior border of femur

Advanced immediately behind femur 8-12 cm total depth

Nerve stimulator or paraesthesia used to determine depth

Prone (Ian McKenzie's) approach

Prone position

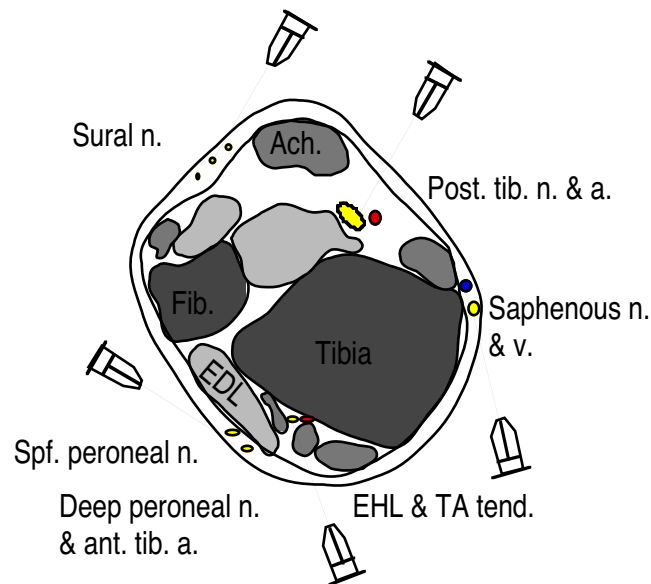
Line from ischial tuberosity to head of fibula marks biceps femoris

Line from midpoint between ischial tuberosity and greater trochanter to middle of popliteal fossa marks course of sciatic (tibial) nerve

Needle inserted at intersection of lines

LOR deep to biceps femoris

Ankle block



Saphenous n

Blocks postero-medial part of dorsum of foot
Superficial infiltration around long saphenous vein anterosuperior to medial malleolus

Tibial n

Needle entry medial to Achilles tendon or lateral to posterior tibial artery at upper border of medial malleolus
Determine depth with paraesthesia, nerve stimulator or 1 cm superficial to tibia
Alternatively infiltration either side of artery behind medial malleolus
Blocks sole, plantar surface of digits

Deep peroneal n

Needle entry between extensor hallucis longus and tibialis anterior tendons or lateral to anterior tibial artery
Blocks first web space and short toe extensors

Superficial peroneal n

Superficial infiltration from lateral border of tibia to upper part of lateral malleolus
Blocks dorsum of foot and toes except first web space

Sural n

Superficial infiltration from Achilles tendon to lateral malleolus
Blocks lateral side of foot and fifth digit

Other lower limb blocks

Lateral femoral cutaneous nerve

Anatomy

- L2-3 ventral roots
- Emerges at lateral border of psoas inferior to ilioinguinal nerve
- Runs between iliac fascia and *iliacus*
- Emerges inferomedial to ASIS from under inguinal ligament
- Crosses origin of *sartorius* and runs deep to *fascia lata*, dividing into anterior and posterior branches
- Supplies skin over lateral thigh

Needle placement

- Patient supine
- Short bevel needle inserted 2 cm inferior and 2 cm medial to ASIS
- Pop felt on passing through *fascia lata*

Local anaesthetic

- 10-15 ml placed deep and superficial to *fascia lata*
- Dilute solution required if multiple blocks are to be performed

Indications

- Combined with sciatic, femoral and obturator blocks for leg surgery

Obturator nerve

Anatomy

- L2-4 nerve roots
- Emerges medial to psoas at pelvic brim
- Runs around pelvis behind iliac vessels and ureter
- Enters obturator canal superior and anterior to obturator vessels
- Divides in canal into anterior and posterior branches
 - Anterior branch supplies anterior adductors, hip joint and medial thigh
 - Posterior branch supplies deep adductors and knee joint

Needle placement

- Patient supine, legs slightly abducted
- Point 1.5 cm lateral and 1.5 cm inferior to pubic tubercle identified
- Needle inserted AP, contacts superior pubic ramus at 1.5-4 cm depth
- Walked laterally into obturator canal and advanced 2-3 cm

Local anaesthetic

- 10-15 ml of dilute solution while advancing and withdrawing

Complications

- Intravascular injection in obturator vessels, haematoma

Tibial and common peroneal nerves in the popliteal fossa

Anatomy

- Sciatic nerve divides at apex of popliteal fossa
 - Tibial nerve continues lateral to vessels inferiorly between heads of *gastrocnemius*
 - Common peroneal nerve accompanies *biceps femoris* tendon laterally, passes around head of fibula and divides into superficial and deep branches

Needle placement

- Patient prone or lateral
- Margins of popliteal fossa identified: *semimembranosus*, *biceps femoris* and *gastrocnemius*
- Point identified 1 cm lateral to midline of fossa and 5 cm superior to skin crease
- Needle inserted angled 45°-60° anterosuperiorly, paraesthesia sought

Local anaesthetic

30-40 ml of dilute solution

Indication

Foot and ankle surgery

Saphenous nerve territory not covered (femoral origin)

Blood patch

Technique

Timing

Probably less effective in first 24 hours

Must wait until block is completely resolved

Volume

No clear evidence that large volumes are better

Commonly 10-20 ml

Bed rest

Two hours is better than 30 min or one hour

Indications

Moderate to severe PDPH

Prophylactic on catheter withdrawal after dural tap on insertion (controversial)

Contraindications

Needle placement

Coagulopathy, sepsis, local infection, anatomical abnormality

Autologous blood injection

Sepsis

No adverse sequelae in HIV infection

Raised ICP: increased further by injection

Complications of PDPH

Cranial nerve palsies unaltered

Hearing loss and tinnitus markedly improved

Seizures uncommon, no evidence of effect

Intracranial bleed and ↑ ICP: contraindication

Effectiveness

>90% initial relief

60-75% persistent relief after large needle puncture

Mechanism of action

Pressure effect from injection

Brief for crystalloids, minutes to hours for blood

“Plug” effect from sealing dural tear

Effect on subsequent epidural

Increased risk of dural puncture and poor block

Prophylactic use

Saline 40-60 ml reduces need for blood patch

Intercostal block

Anatomy

Intercostal nerve arises from T1-T11 nerve roots, T12 is similar (subcostal)

Branches

Grey *ramus communicans* from sympathetic chain

Posterior cutaneous branch arises beyond vertebral foramen and supplies paravertebral muscles and skin

Lateral cutaneous branch arises anterior to midaxillary line and supplies skin of lateral aspect of chest

Anterior cutaneous branch pierces *pectoralis major* or *rectus abdominis* and supplies breasts and anterior chest and abdominal wall

T1-3 give branches to axillary plexus and intercostobrachial nerve

T12 gives branches to iliohypogastric and ilioinguinal nerves

Nerve lies deep to internal and external intercostal muscles, superficial to *intercostalis intimis* and pleura

Neurovascular bundle lies immediately inferior to rib and consists of vein, artery and nerve from superior to inferior

Needle placement

Sitting, lateral or prone positions

Identify line of lateral margin of paravertebral muscles (6-8 cm lateral to midline)

Count ribs to identify correct level

Apply traction superiorly to skin, insert needle over rib

Allow skin to retract inferiorly and walk needle off inferior edge of rib

Inserted another 2-5 mm with aspiration

Local anaesthetic

Long-acting agent with adrenaline

2-5 ml of solution per nerve

Care with total dose as absorption is fairly rapid

Indications

Anaesthesia

Chest drain insertion, gastrostomy insertion

Other minor thoracic or abdominal procedures

Analgesia

Fractured ribs

Thoracotomy or laparotomy as adjuvant technique

Complications

Pneumothorax

Rare despite risks of entering pleura as the needle used is small

Managed conservatively

Local anaesthetic toxicity

Minimize with adrenaline-containing solution

Paravertebral block

Anatomy

Similar to intercostal block but placement 2 cm lateral to midline

Needle placement

Needle inserted postero-anteriorly onto transverse process

Walked off top or bottom of process and inserted 1 cm

“Hanging drop” can be used

Inject at every level or else rely on spread between levels

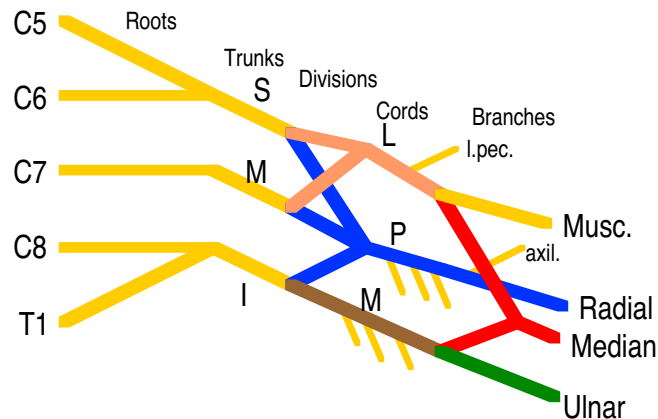
Local anaesthetic

Divide total dose between number of levels

Indications

Breast surgery, other surgery requiring unilateral block

Brachial plexus



Five nerve roots

- C5-8 branches to *longus colli* and *scaleni*

- C5-7 branch to long thoracic n.

- C5 contributes to phrenic n. and dorsal scapular n.

Three trunks

- Form between *scalenus medius* and *scalenus anterior*

- Superior, middle and inferior

- Superior gives off suprascapular n.

- Inferior gives off first intercostal n.

- Divide into ventral and dorsal divisions at lateral edge of first rib

Six divisions

- Dorsal divisions supply extensors

- Ventral divisions supply flexors

- Form cords on entering the axilla

Three cords

- Lateral, posterior and medial

- Axillary artery lies between

- Posterior gives off five extensor branches

 - Two major: radial and axillary nn.

 - Three minor: thoracodorsal and two subscapular nn.

- Lateral gives off three branches

 - Two major: musculocutaneous n. and half of median n.

 - One minor: lateral pectoral n.

- Medial gives off five branches

 - Two major: ulnar and half of median n.

 - Three minor: medial pectoral and medial cutaneous nn. of arm and forearm

Interscalene block

Anatomy

Trunks of brachial plexus cross first rib behind *scalenus anterior* and subclavian artery at the level of C6

Needle placement

Patient supine with head turned away

Interscalene groove is palpable at the level of cricoid cartilage or Chassaignac's tubercle

Needle inserted with slight posteroinferior angulation

Walked posteriorly in C6 plane if required to elicit paraesthesia or twitches

Local anaesthetic

30-40 ml of lignocaine 2% or bupivacaine 0.5%

Indications

Most reliable from C4-C7

Shoulder surgery, reduction of dislocated shoulder

Supplementation required for hand of forearm surgery

More caudal needle placement to cover C8-T1/ulnar distribution

Complications

Phrenic nerve block common

Subarachnoid or epidural injection

Intravascular injection (subclavian or vertebral artery)

Pneumothorax

Supraclavicular block

Anatomy

- Plexus lies inferior to mid-clavicle
- Subclavian artery is anterior and medial to the plexus
- Both pass over the first rib together

Needle placement

Classical approach

- Relatively difficult to describe and teach
- Patient supine, arm at side, head turned away
- Interscapular roll and inferior displacement of the shoulder can make it easier
- Interscalene groove identified by palpation posterior to sternocleidomastoid
- Subclavian artery is often palpable behind clavicle
- Needle inserted 2 cm behind midpoint of the clavicle or immediately posterior to the artery
 - Lateral end of clavicle is medial to the acromion
- Directed inferiorly with slight posteromedial angulation
- Paraesthesia or nerve-stimulator indicates location at the plexus
- If no paraesthesia is elicited, the superior surface of the first rib is usually contacted
- Walking anteriorly along the rib surface should result in paraesthesia

“Plumb-bob” approach

- Patient supine, head turned away
- Lateral margin of insertion of sternocleidomastoid into clavicle identified
- Needle inserted directly anteroposterior
- Angled superiorly and then inferiorly until paraesthesia elicited

Sternocleidomastoid approach

- 10 cm needle inserted at junction of clavicular and sternal heads of sternocleidomastoid
- Directed posterolaterally aiming at posterior of midpoint of clavicle
- Nerve stimulator indicates plexus

Local anaesthetic

- 15-25 ml of lignocaine, bupivacaine or ropivacaine
- Periodic aspiration

Indications

- Most reliable from C5-T1
- Most upper limb surgery
 - Proximal block: compact plexus, above most branches, small volume required
- Shoulder surgery may require supplemental cervical plexus block for overlying skin

Complications

Pneumothorax

- 0.5-6.0% in different series
- Usually small and managed conservatively

Phrenic nerve block

- 40-60%, usually asymptomatic

Stellate ganglion block

- Increased incidence with volume of anaesthetic
- Up to 90% with 50 ml of solution
- Horner's syndrome

Vascular injury

Local anaesthetic toxicity

Axillary

Anatomy

- Brachial plexus has formed terminal branches in the axilla
- Musculocutaneous lies in coracobrachialis
- Median, ulnar and radial nerves lie in close relation to the axillary artery from superficial to deep
- Fascial septa divide the branches of the plexus at this level

Needle placement

- Patient supine with arm abducted to 90°, externally rotated and flexed 90° at the elbow
- Course of the axillary artery determined by palpation
- Skin wheal and needle insertion adjacent to artery
- Paraesthesia or twitching elicited in appropriate nerves
- Alternatively LA deposited in all quadrants around artery
- Infiltration in mass of coracobrachialis to block musculocutaneous n.

Local anaesthetic

- 20-30 ml of lignocaine or bupivacaine with adrenaline
- Hyaluronidase, bicarbonate for more rapid spread (but less duration)

Indications

- Most reliable from C7-T1
- Best for distal limb surgery (hand or forearm)
- Suitable for indwelling catheter placement

Complications

- Intravascular injection (axillary artery or vein)
- Haematoma and plexus compression

Elbow

Median

Anatomy

Lies medial to brachial a. where it emerges medial to biceps tendon

Needle placement

Arm supinated and extended at the elbow

Plane of epicondyles of humerus identified

Brachial artery palpated

Needle insertion immediately medial to artery

Local anaesthetic

3-5 ml of lignocaine 1% or bupivacaine 0.25%

Radial

Anatomy

Pierces lateral intermuscular septum above the elbow

Lies between brachialis and brachioradialis

Needle placement

Position and level as for median nerve

Point 2 cm lateral to biceps tendon

Local anaesthetic

Fan-like injection of 4-6 ml

Ulnar

Anatomy

Nerve runs behind medial epicondyle

In groove between epicondyle and olecranon

Needle placement

Elbow in full flexion

Epicondyle identified

Needle inserted 1 cm proximal to epicondyle (**not** in groove)

Local anaesthetic

3-5 ml lignocaine 1% or bupivacaine 0.25%

Medial cutaneous nerve of forearm

Anatomy

Continuation of musculocutaneous nerve

Ramifies superficially over medial forearm

Needle placement

Infiltration in a band across medial forearm one third of the way from elbow to wrist

Indications

Supplementation of brachial plexus block with inadequate cover

Not commonly used alone

Wrist

Median

Anatomy

- Lies deep to and between FCR and palmaris longus tendons
- Inside carpal tunnel

Needle placement

- Line from ulnar styloid to distal tip of radius identified
- Needle inserted on this line between FCR and palmaris longus
- Flexor retinaculum penetrated

Local anaesthetic

- 3-5 ml, plain solution probably advisable

Radial

Anatomy

- Already divided into terminal branches at the wrist
- Spread over radial and dorsal aspect of the wrist

Needle placement

- Infiltration over anatomical snuff-box and further medially
- Superficial to EPL

Local anaesthetic

- 5-6 ml

Ulnar

Anatomy

- Lies lateral to FCU and medial to ulnar a.
- Has already given off palmar cutaneous and dorsal braches
- Divides into deep motor and superficial sensory braches at the level of pisiform

Needle placement

- Approach from anterior or medial aspect just proximal to pisiform
- Medial approach allows infiltration to all branches from one puncture

Local anaesthetic

- 3-5 ml plus infiltration

Indications

- Supplementation of brachial plexus block with inadequate cover
- Not commonly used alone

Complications of retrobulbar and peribulbar eye blocks

Complications of any block

Needle

- Local pain

Drug

- Systemic local anaesthetic toxicity

- Allergy, anaphylaxis

Technique

- Failure of aseptic technique: cellulitis, ophthalmitis, meningitis

- Failure of block: pain intraoperatively or postoperatively

Complications of eye blocks

Vessels

- Retrobulbar haemorrhage, retinal vascular occlusion, optic nerve trauma, late optic atrophy

 - Variable presentation: arterial vs venous haemorrhage

 - More common with large needle insertion in vascular areas e.g. superonasal

 - Microvascular disease increases risk of ischaemia e.g. diabetes

 - Manage with local pressure, IOP measurement, IOP reduction measures, surgical decompression if necessary

 - Haemorrhage within the optic nerve sheath results in rapid ocular venous congestion

Intravascular injection

 - Retrograde flow with rapid injection

 - Injection of antibiotics or steroids by the surgeon can also be intravascular, causing embolism

Nerve

- Optic nerve injection

- Injury to III, IV or VI uncommon

- Other cranial nerve block related to facial nerve block at stylomastoid foramen

 - Vagus, glossopharyngeal block

 - Swallowing difficulty, respiratory obstruction

Brainstem anaesthesia

 - Associated with long, sharp needles

 - Onset over 2 to 20 minutes, lasts up to three hours

 - Symptoms highly variable: unconsciousness to isolated nerves or nuclei blocked

 - Contralateral eye signs one of the earliest markers

Atonic pupil

 - One case related to ciliary ganglion needle damage

 - More commonly direct trauma

 - Test with pilocarpine

Muscle

- Extraocular muscle dysfunction

 - Block duration up to 48 h with bupivacaine or ropivacaine

 - Longer duration suggests nerve or muscle damage

 - Most commonly intramuscular injection which resolves over weeks

Persistent ptosis

 - Common in cataract patients regardless of surgery

 - May be intramuscular injection or bridle suture damage

 - Extraocular muscle injection may cause muscle rupture and diplopia

Globe

Ocular penetration and perforation

More common in long eyes

High myopes for retinal surgery or radial keratotomy

Prevention

Known axial length, open eye during needle placement, avoiding displacement of the globe into the path of the needle

Commonly accompanied by pain, retinal detachment, haemorrhage

Corneal injury

Careful attention to padding and taping the anaesthetic eye

Ischaemia related to Honan's balloon or other compression device

Suprachoroidal haemorrhage

Related to hypertension

May be secondary to coughing or full bladder

Sympathetic ophthalmia

Reflex

Oculocardiac reflex

Bradycardia after injection

May persist longer than during surgery

Most common in children and young adults

Treat with atropine or glycopyrrolate

Ear

Anatomy

Cervical plexus branches greater auricular and lesser occipital supply posterior surface of auricle and lower third of anterior surface

Greater auricular also supplies posterior part of external canal

Auriculotemporal branch of mandibular division of trigeminal nerve supplies superior two thirds of anterior surface

Auriculotemporal also supplies superior part of external canal

Auricular branch of vagus supplies inferior part of external canal

Tympanic branch of glossopharyngeal and facial nerve supplies drum

Needle placement

Superficial cervical plexus block or infiltrate over mastoid for cervical plexus branches

Infiltrate at posterior aspect of zygoma for auriculotemporal block

Canal supply from exterior blocked by infiltration at junction of bony and cartilaginous parts

Drum anaesthetized with topical lignocaine spray 4-10%

Nose

Anatomy

Trigeminal nerve, ophthalmic division (V_1), nasociliary nerve, anterior ethmoidal and external nasal branches to bridge and tip and superior and anterior parts of septum and lateral wall

Trigeminal nerve, maxillary division (V_2), infraorbital nerve, nasal branches to remainder of external nose

V_2 pterygopalatine ganglion, nasopalatine branch to posterior and inferior septum

V_2 anterior superior alveolar branch to anterior and inferior lateral wall

V_2 pterygopalatine ganglion, posterior and inferior nasal branches to posterior and superior lateral wall

V_2 pterygopalatine ganglion, greater palatine nerve to posterior and inferior lateral wall

Needle placement

External nose: supraorbital notch & medially, infraorbital foramen, junction of nasal bone and cartilage all infiltrated

Cavity

Topical or soaked cotton bud applied to anterior ethmoidal by inserting along the line of the external nose until it reaches a superior limit

Same applied to sphenopalatine ganglion by insertion at 20° - 30° to horizontal

Floor anaesthetized with topical local

Trigeminal nerve

Ganglion

Anatomy

Ganglion is intracranial in Meckel's cave, a reflection of dura
Closely related to superior orbital fissure, *foramen rotundum*, and *foramen ovale* through which branches leave the skull
Foramen ovale is in the horizontal plane of zygoma, vertical plane of mandibular notch, dorsolateral to pterygoid process

Needle placement

Skin wheal at anterior border of masseter, 3 cm lateral to corner of mouth, opposite second upper molar
10 cm needle advanced in plane of the pupil, superiorly, medially and posteriorly
Contact with inferior surface of greater wing of sphenoid at 4.5-6 cm
Walked posteriorly along sphenoid until enters *foramen ovale*, 1-1.5 cm beyond first bony contact

Local anaesthetic

1-3 ml of any solution injected in small aliquots with aspiration

Indications

Facial neuralgias
Major facial surgery in patient unable to receive GA

Complications

Technically difficult
Subarachnoid injection of LA
Unconsciousness reported with 0.25 ml of 1% lignocaine
Local pain, haematoma formation

Maxillary nerve

Anatomy

Leaves the cranium through the *foramen rotundum*, deep to the pterygoid plate
Passes through the pterygopalatine fossa
Enters the floor of the orbit through the inferior orbital fissure
Emerges through the infraorbital foramen

Needle placement

Skin wheal over mandibular notch
8 cm needle inserted superomedially through mandibular notch
Strikes lateral pterygoid plate at 5 cm depth
Walked off anterior margin of lateral pterygoid plate into pterygopalatine fossa
Inserted 1 cm into pterygopalatine fossa

Local anaesthetic

5 ml of any solution

Indications

Facial neuralgia

Complications

Vascular region of insertion → haematoma formation
Close proximity to infraorbital fissure
Disturbance of eye movement or vision
"Black eye" from haematoma formation

Mandibular nerve

Anatomy

Leaves the cranium through the *foramen ovale*, posterior to lateral pterygoid plate
Divides into anterior and posterior divisions

Anterior division is motor supply to muscles of mastication, sensory to buccal branch

Posterior division is motor to *** sensory: auriculotemporal, lingual and inferior alveolar nerves

Needle placement

Skin wheal over mandibular notch

8 cm needle inserted superomedially through mandibular notch

Strikes lateral pterygoid plate at 5 cm depth

Walked posteriorly off lateral pterygoid plate

Advanced **only** 0.5 cm to avoid superior constrictor, pharynx

Local anaesthetic

5 ml of any solution

Indications

Facial neuralgia

Dental work (usually transmucosal approach)

Complications

Haematoma

Injury to the superior constrictor, entering the pharynx

Other head and neck

Greater occipital nerve

Anatomy

- Greater occipital n. is the dorsal ramus of C2
- Emerges over atlas, deep to cervical musculature
- Becomes subcutaneous near superior nuchal line
- Immediately medial to occipital a.
- Supplies sensation to posterior scalp to vertex

Needle placement

- Patient sitting with neck flexed
- Superior nuchal line from occipital protuberance to mastoid
- Nerve lies approximately at medial $\frac{1}{3}$ point, near artery
- Infiltration of 3-5 ml around artery

Indications

- Occipital tension headache, diagnostic aid

Complications

- Low risk block

Cervical plexus

Anatomy

Formed by ventral rami of C1-4

Direct motor branches to prevertebral muscles

Cutaneous branches form “superficial” plexus

Lesser occipital, greater auricular, transverse cervical and supraclavicular nerves

Emerge from behind the midpoint of sternocleidomastoid

Ansa cervicalis innervates infrahyoid and geniohyoid muscles

Phrenic nerve (C3-5) is central sensory and sole motor supply to diaphragm

Emerges lateral to *scalenus anterior* and enters the thorax medial to it

Contribution to CN XI motor supply to sternocleidomastoid and trapezius

Needle placement

Deep

Patient in supine position with head turned away

Line drawn 1 cm posterior to line from mastoid to Chassaignac’s tubercle (transverse process of C6)

C2 transverse process palpable 1.5 cm inferior to mastoid

C3 and C4 transverse processes identified relative to C2 and C6

Needles placed on transverse processes of C2-4

Withdrawn 1-2 mm off bone

Caudal angulation to reduce chance of entering foramina

Aspiration to check for vertebral artery puncture

Superficial

Short bevelled needle inserted posterior to midpoint of sternocleidomastoid

Injection immediately deep to superficial cervical fascia

Infiltration along posterior border of sternocleidomastoid superiorly and inferiorly

Local anaesthetic

Deep

15-20 ml of lignocaine 1.5% or ropivacaine 0.75%

Superficial

15 ml of lignocaine 1.5% or ropivacaine 0.75%

Indications

Carotid endarterectomy, lymph node biopsy, plastic surgery to neck

Complications

Deep

Phrenic nerve block, hypoventilation

Vertebral artery injection, convulsions

Dural sheath injection, total spinal

Superficial

External or internal jugular vein injection

Stellate ganglion

Anatomy

Cervical sympathetic trunk is a continuation of the thoracic sympathetics

Lies anterior to cervical transverse processes

Composed of three ganglia

Superior cervical ganglion opposite C1

Middle cervical ganglion opposite C6

Stellate ganglion opposite C7-T1

Commonly closely related to subclavian and vertebral arteries

Needle placement

Patient supine with neck extended

Chassaignac's tubercle identified (at level of cricoid cartilage)

Firm palpation medial to carotid artery either side of C6 transverse process

Short needle inserted onto transverse process of C6 directly A-P

Withdrawal 1-2 mm before injection

Local anaesthetic

5-10 ml of 0.25% bupivacaine with adrenaline

Frequent aspiration

Indications

Complex regional pain syndrome of upper limb

Poor perfusion of upper limb

Complications

Vertebral artery injection, convulsions

Blockade of recurrent laryngeal or phrenic nerves

Airway

Principles

Trigeminal

Nasopharynx down to soft palate

Maxillary division

Glossopharyngeal

Soft palate to epiglottis

Pharyngeal nerves to pharyngeal mucosa

Tonsillar nerves to tonsils and soft palate

Posterior third of tongue

Vagus

Below epiglottis

Superior laryngeal nerve arises from inferior ganglion of vagus

Crosses cornu of hyoid and divides into internal and external laryngeal branches

Internal branch penetrates thyrohyoid membrane and innervates mucosa from epiglottis to cords

External branch supplies cricothyroid m.

Vagus gives off recurrent laryngeal nerve below aorta (L) or subclavian a. (R)

Penetrates cricothyroid membrane laterally and innervates the mucosa below the cords and muscles of the larynx

Glossopharyngeal nerve

Anatomy

Exits the skull through the jugular foramen lateral to X, ICA and IJV, anterior to XII and XI

Descends in the carotid sheath, passes between ICA and ECA before branching

Branches lie submucosally posterior to tonsil, deep to posterior tonsillar pillar

Needle placement

Intraoral route

Mouth opened with laryngoscope, topical anaesthesia to tongue and tonsil

9 cm curved needle inserted submucosally in caudal part of posterior tonsillar pillar

Careful aspiration for blood (ICA is adjacent)

Peristyloid route

Patient supine, head in neutral position

Line from mastoid to angle of jaw identified

Skin wheal at midpoint of line, styloid may be palpable

Short needle inserted medially to contact styloid

Walked off posterior aspect of styloid

Careful aspiration of blood (IJV and ICA)

Local anaesthetic

5-7 ml of lignocaine 0.5%

Indications

Awake intubation

Complications

Intravascular injection, convulsions

Superior laryngeal nerve (internal br.)

Anatomy

Leaves the vagal trunk above the hyoid

Crosses the cornu of the hyoid

Penetrates the thyrohyoid membrane inferior to the hyoid

Accompanied by superior laryngeal artery and vein

Needle placement

Patient supine with neck extended

Hyoid displaced toward side of block

Skin wheal over greater cornu

Needle inserted medially to make contact with greater cornu

Walked inferiorly off cornu and advanced 2-3 mm

Should lie between thyrohyoid membrane and laryngeal mucosa

Local anaesthetic

3-4 ml of lignocaine 0.5%

Indications

Awake intubation

Complications

Entering the larynx, coughing with injection

Intravascular injection is uncommon

Translaryngeal block

Needle placement

Needle or IV cannula inserted in midline through cricothyroid membrane until air is aspirated

Local anaesthetic

3-4 ml of lignocaine 4% topical solution rapidly injected and needle withdrawn before coughing

Recipes for regional anaesthesia

Eye block (Royal Victorian Eye and Ear Hospital)

lignocaine 10% 2 ml
bupivacaine 0.5% or ropivacaine 1.0% 7 ml
hyalase 150 U in 1 ml bupivacaine 0.5% or ropivacaine 1.0%
oxybuprocaine topical to conjunctiva
30g 12 mm medial canthus 2-3 ml
27g 32 mm inferotemporal 3-4 ml

Bier's

prilocaine 0.6% 40 ml
prilocaine 0.5% 0.5 ml/kg (2.5-3.0 mg/kg)
lignocaine 2-3 mg/kg

Interscalene

15-20 ml

Supraclavicular to Axillary

30-40 ml

Cervical

lignocaine 1.5% with adrenaline
± ropivacaine
superficial 15 ml
deep 5-7 ml x 3

Caudal (Royal Children's Hospital)

bupivacaine 0.25% 0.5-1 ml/kg
bupivacaine 0.5% 0.5 ml/kg up to 20ml
add clonidine 2 µg/kg

Spinal

LUSCS (Mercy Hospital for Women)

bupivacaine 0.5% heavy 2.2 ml (2-2.5)
fentanyl 15 µg or morphine 100 µg

Manual removal (MHW)

bupivacaine 0.5% plain 1.2 ml (1.2-2)
fentanyl 15 µg

Neonatal for hernia repair(RCH)

bupivacaine 0.5% plain 0.2 ml/kg, min 0.4ml

THJR

bupivacaine 0.5% plain 3-4 ml
D Williams: bupivacaine 0.5% plain 2 ml, midazolam 2 mg, morphine 250 µg

Knee scope, ESWL, other short procedures

procaine 2% 5 ml

CSE

Labour (MHW)

bupivacaine 0.5% plain 0.5 ml
fentanyl 25 µg

Epidural

Labour (MHW)

bupivacaine 0.25% 6-10 ml
fentanyl 100 µg
plus infusion 0.1% bupivacaine, 2 µg/ml fentanyl 10 ml/h

Labour PCEA (MHW)

bupivacaine 0.125%, fentanyl 5 µg/ml 15 ml + 5 ml if inadequate at 15 min
bupivacaine 0.625%, fentanyl 2 µg/ml 5 ml bolus, 10 min lockout

LUSCS (MHW)

lignocaine 2% up to 20ml
fentanyl 100 µg or pethidine 50 mg or morphine 3-4 mg

Paediatric (RCH)

bupivacaine 0.125% \approx 0.25 ml/kg/h
 \pm fentanyl or clonidine 2 μ g/ml

EMST

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[Transfer to Definitive Care](#)

Initial Assessment and Management

Preparation

Pre-hospital

Minimize scene time

Priorities

Airway maintenance

Control external bleeding and shock

Immobilization

Immediate transport to the closest appropriate facility

Obtain information for hand over

Criteria for transfer to trauma centre

GCS <14, RR <10 or >29, systolic <90 mmHg, RTS <11, PTS <9

Flail chest, >2 proximal long bone fractures, amputation proximal to wrist or ankle, penetrating trauma proximal to elbow or knee, limb paralysis, pelvic fracture, trauma with burns

Consider trauma centre for

Ejection from car, death in same compartment, pedestrian thrown or run over, high speed crash, extrication time >20 min, fall >6 m, roll over, pedestrian struck at >8 km/h, motorcycle crash at >32 km/h or with separation of bike and rider

Age <5 or >55, pregnancy, immunosuppression, cardiac or respiratory disease, diabetes, cirrhosis, morbid obesity, coagulopathy

In hospital

Resuscitation area

Airway equipment, warm IV solutions, monitoring

Means to summon medical help, means to summon diagnostic services

Transfer agreement with trauma centre

Universal precautions to be observed

Triage

Revised Trauma Score

Respiratory rate

| | |
|-------|---|
| >29 | 4 |
| 10-29 | 3 |
| 6-9 | 2 |
| 1-5 | 1 |
| 0 | 0 |

Systolic BP

| | |
|-------|---|
| >89 | 4 |
| 76-89 | 3 |
| 50-75 | 2 |
| 1-49 | 1 |
| 0 | 0 |

GCS

| | |
|-------|---|
| 13-15 | 4 |
| 9-12 | 3 |
| 6-8 | 2 |
| 4-5 | 1 |
| <4 | 0 |

Paediatric Trauma Score

| | |
|----------------|----|
| Weight | |
| <20 kg | 2 |
| 10-20 kg | 1 |
| <10 kg | -1 |
| Airway | |
| Normal | 2 |
| O ₂ | 1 |
| Intubated | -1 |
| Systolic BP | |
| >90 | 2 |
| 50-90 | 1 |
| <50 | -1 |
| Consciousness | |
| Awake | 2 |
| Any LOC | 1 |
| Coma | -1 |
| Fracture | |
| None | 2 |
| Single closed | 1 |
| More / open | -1 |
| Skin | |
| Intact | 2 |
| Lac. <7 cm | 1 |
| More | -1 |

Score >8 should have zero mortality.

Priorities

Multiple casualties are treated in order of severity.

Mass casualties (exceeding capacity of available facilities) are treated in order of probability of survival with least expenditure of resources.

Primary Survey

Examination and management take place simultaneously

Airway maintenance with cervical spine protection

Assess patency of the airway: fractures, foreign bodies

Establish a patent airway

Definitive airway is usually required if GCS \leq 8

Cervical spine must be immobilized in any multi-system trauma

Deterioration of conscious state may demand reassessment of airway

Breathing and ventilation

Requires function of lungs, chest wall and diaphragm

Examine the chest for acute causes of impaired ventilation

Tension pneumothorax, open pneumothorax, flail chest with pulmonary contusion, massive haemothorax

Intubation may worsen pneumothorax

Chest x-ray is required as soon after intubation as practical

Circulation and haemorrhage control

Haemorrhage is the commonest cause of post-injury death treatable in hospital

Volume status is assessed by conscious state, skin colour and pulse rate and strength

Hypotension is caused by hypovolaemia until proved otherwise

Bleeding is controlled by local pressure

Occult haemorrhage occurs into the chest or abdomen, retroperitoneum following pelvic fracture or soft tissues following long bone fracture

Blood pressure is not a good indicator of volume status

Disability (neurologic evaluation)

Rapid assessment of GCS or AVPU status

Impaired consciousness after correction of hypoxia and hypovolaemia is usually due to CNS trauma

Drugs may confuse examination findings

Frequent reassessment is required

Exposure and environmental control

Complete exposure is required for examination

Prevention of hypothermia is required, using warming blankets, warmed

IV fluids and early control of haemorrhage

Resuscitation

Airway

Definitive airway if there is doubt about the patient's ability to maintain an airway

Application of a hard collar for cervical spine immobilization

Breathing and ventilation

All patients should receive supplemental oxygen

Circulation

Two large IVs should be inserted

Blood taken for crossmatch, baseline bloods and pregnancy test

IV fluid administration, initially warmed Hartmann's 2-3 l

Hypovolaemic shock is treated with operative intervention to stop bleeding and continued fluid resuscitation, not pressors, steroids or bicarbonate

Adjuncts to primary survey and resuscitation

ECG monitoring

Signs of cardiac injury, pulseless electrical activity, hypoxia or hypoperfusion

Urinary and gastric catheters

Urine output provides an indication of volume status

Catheter should not be inserted if the urethra might be injured

Blood at meatus, perineal ecchymoses, blood in scrotum, high riding prostate, pelvic fracture

Gastric catheter reduces the risk of regurgitation and aspiration, but does not eliminate it

Nasogastric insertion is contraindicated if the cribriform plate might be disrupted

Other monitoring

Ventilatory rate and ABGs

CO₂ confirmation of ETT placement

Pulse oximetry

Blood pressure

Diagnostic studies

CXR and pelvis x-ray can guide resuscitation but must not cause delay

Lateral cervical spine x-ray is useful if it shows an injury

Further tests during secondary survey

Consider need for transfer

However life saving interventions should start at the time the problem is identified

Secondary survey

Begins when resuscitation is underway and vital signs are normalizing

History

Allergies, medications, past illnesses or pregnancy, last meal, events related to the injury (mnemonic: AMPLE)

Physical examination

Head

Complete examination for soft tissue or bony injury

Eye examination for acuity, pupils, hyphaema, penetrating injury, contact lenses, lens dislocation, muscle entrapment

Facial bones for fractures

Cervical spine and neck

Head or face injury implies cervical spine injury until it is excluded

Penetrating injuries should be explored in theatre

Cervical spine injury should be excluded as soon as convenient and hard collar removed

Chest

Inspection and palpation of the entire thorax

Auscultation for heart sounds and breath sounds

Bony or soft tissue injury makes visceral injury likely

Children have a more compliant chest wall which may hide deeper injuries

Abdomen

Specific diagnosis is not as important as recognizing that an injury exists

Repeat examination for changing signs may be necessary

If injury is suspected

Ultrasound or lavage

CT if stable

Perineum

Inspection, PR, PV, urinary catheter

Musculoskeletal

Limbs must be inspected and palpated

Pelvis integrity should be assessed

The back must be examined

Soft tissue injury may be difficult to detect in an unconscious patient

Neurological

Assess conscious state (and reassess)

Examine for peripheral signs of nerve or cord injury

Prevent abrupt rises in ICP in head-injured patients

Specialized diagnostic tests (as indicated)

X-rays

CXR, pelvis, cervical spine, thoracolumbar spine, sites of injury

CT

Head (\pm MRI), chest, abdomen, spine

Contrast studies

Urography, angiography

Ultrasound

Abdomen, gynaecological, transoesophageal

Endoscopy

Bronchoscopy, gastroscopy

Tests requiring transport demand a stable patient

Reevaluation

Continuous monitoring of vital signs

ECG, BP, SpO₂, conscious state, urinary output, ABG, E_TCO₂

Analgesia

Definitive care

Surgical intervention

Transfer to an appropriate facility

Documentation

Essential for continuity of medical care and evidence in case of medicolegal problems

A dedicated record-taker is needed in the resuscitation setting

Consent should be obtained before procedures if possible

If criminal involvement is likely, evidence must be preserved

Airway and Ventilatory Management

Airway

Problems

Maxillofacial trauma, neck trauma, laryngeal trauma

Signs

Talking patient: airway is patent and not compromised

Agitation, obtundation, cyanosis, rib retraction, accessory muscle use

Noisy breathing, stridor, hoarseness, confusion (hypoxia)

Palpable larynx and trachea

Ventilation

Problems

Airway patency, chest and lung integrity, innervation, CNS function

Signs

Chest movement

Breath sounds

Oximetry

Management

All require protection of cervical spine if injury is suspected

Airway maintenance

Chin lift, jaw thrust, Guedel airway, nasopharyngeal airway

Definitive airway

“A tube present in the trachea with the cuff inflated, the tube connected to some form of oxygen-enriched assisted ventilation, and the airway secured in place with tape.”

Orotracheal, nasotracheal, surgical options

Indications

Apnoea, inability to maintain a patent airway, protection from aspiration, impending or potential airway compromise, closed head injury (GCS ≤ 8), inadequate oxygenation with face mask ventilation

Intubation

Method depends on practitioner's experience, usually oro-tracheal

Cervical immobilization, preoxygenation, cricoid pressure, drugs (if

required), laryngoscopy, ETT placement, auscultation, CO₂ analysis, CXR

Nasotracheal intubation is only used in spontaneously breathing patient

Induction agents typically suxamethonium and benzo.

Surgical Airway

Needle cricothyroidotomy

12g or 14g cannula inserted through cricothyroid membrane

Intermittent jet O₂ insufflation (1 s on 4 s off)

Contraindicated in glottic obstruction (\rightarrow barotrauma)

Provides 30-45 minutes oxygenation (limited by PCO₂)

Surgical cricothyroidotomy

Palpate thyroid notch and sternal notch, find cricothyroid

Local anaesthetic if required, prepare skin

Stabilize trachea with one hand, transverse incision through skin and cricothyroid membrane

Insert scalpel handle or artery and dilate opening

Insert cuffed tube (5-6 mm), inflate cuff and check ventilation

Secure tube

Oxygenation

All patients require supplemental oxygen

Oximetry should be used where available

unreliable with poor peripheral perfusion, anaemia, abnormal Hb

Ventilation

Bag-valve-mask is best performed with two operators

Ventilation is required during prolonged attempts at intubation

Pressure-limited ventilation is required post-intubation

Shock

Assessment

Signs

Peripheral vasoconstriction, tachycardia, narrowed pulse pressure
Hypotension is a late sign (>30% volume loss)
Haemoglobin is not a measure of volume status

Causes

Haemorrhagic

Present in most patients with multiple injuries, responds to filling

Non-haemorrhagic

Cardiogenic, tension pneumothorax, neurogenic, septic

Haemorrhagic shock

Haemorrhage is the acute loss of circulating blood volume

Normal blood volume is 70 ml/kg in adults (80-90 ml/kg in children)

Classification

Class I

Loss up to 15% of blood volume

Usually fully compensated

Recovers by transcapillary refill within 24 hours

Class II

15%-30% blood volume lost

Tachycardia, tachypnoea, reduced pulse pressure, anxiety

Urine output 20-30 ml/h

Responsive to crystalloid filling

Class III

30%-40% blood volume lost

Marked tachycardia, tachypnoea, hypotension, mental changes

Urine output low 5-15 ml/h

Will require transfusion

Class IV

More than 40% blood volume lost

Immediately life-threatening

Minimal urine output

Requires immediate transfusion and usually surgery

Soft-tissue haematoma may consume litres of blood.

Management

Examination

ABCDE

Gastric decompression

Urinary catheter insertion

Vascular access

Large peripheral IVs initially (16g or 14g short)

Cut-down if required depending on level of experience

Intraosseous infusion if under 6 years and no other access

CVC insertion is not the best choice for rapid infusion

Blood taken for crossmatch, investigations including β hCG, ABG

Initial fluid therapy

20 ml/kg Hartmann's as a bolus

Further therapy guided by response to initial bolus and on-going losses

Response

Urine output, conscious state, peripheral perfusion, CVP

Evaluation of resuscitation

- Normalization or improvement of HR, BP and pulse pressure

- Urine output >0.5 ml/kg/h (1 ml/kg/h in children, 2 ml/kg/h in infants)

- CVP or PAOP or CO (if PA catheter inserted)

- ABG

 - Initial respiratory alkalosis followed by metabolic acidosis

 - Persistent metabolic acidosis if peripheral perfusion is inadequate

Response to initial therapy

- Rapid response

 - Haemodynamic normalization with bolus fluid

- Transient response

 - Deterioration following initial response to bolus fluid indicates inadequate resuscitation or ongoing losses

 - Likely requirement for transfusion and surgery

- Minimal or no response

 - Likely exsanguinating haemorrhage requiring surgery, or

 - Non-haemorrhagic cause for shock

 - Differentiate using CVP or echocardiography

Choice of fluid

- Blood

 - Usually packed cells

 - Used to replace oxygen carrying capacity

 - Not the first choice for volume replacement

 - Type-specific or O negative can be used in extreme urgency

 - Component therapy for coagulopathy as indicated by pathology tests

- Crystalloids

 - Hartmann's or normal saline

 - Heated to 39°C

Special considerations

- Use of vasopressors is contraindicated in haemorrhagic shock

 - ↑ SVR, ↓ CO → "death spiral"

- Elderly have reduced physiological reserve

- Tachycardia may be a poor sign if on β-blockers or pacemaker or in athletes

- Hypothermia may prevent a response to fluid

- Always suspect ongoing haemorrhage if response is poor

- Under-resuscitation is far more common than fluid overload

- CVP can guide fluid therapy

Thoracic Trauma

Primary Survey

Airway

Assess air movement at nose and mouth, inspect oropharynx, observe for intercostal retraction

Laryngeal injury or posterior dislocation of sternoclavicular joint can obstruct the airway

Breathing

Expose chest, observe, palpate and auscultate

Tension pneumothorax

Decompress with large Jelco in second intercostal space in midclavicular line followed by chest tube in the fifth intercostal space between the midaxillary and anterior axillary lines

Open pneumothorax

Flap-valve dressing, surgical closure and chest tube

Flail chest

Underlying pulmonary contusion is usually the major concern

Administer oxygen, limit IV fluids unless shock is present, analgesia

May require intubation and ventilation

Circulation

Assess pulse, blood pressure, JVP

Monitor ECG and SpO₂

Massive haemothorax

Rapid accumulation of more than 1500 ml in the chest cavity, usually manifest as shock with absent breath sounds and dullness on one side of the chest

Rapid IV fluid administration, decompression with a chest tube, thoracotomy likely if >1500 ml or >200 ml/h evacuated or persistent transfusion requirement or penetrating injury medial to nipple or scapula

Cardiac tamponade

15-20 ml in pericardial space is enough to cause haemodynamic compromise

Difficult to diagnose acutely, echocardiography may help

IV fluid may produce transient improvement

Pericardiocentesis may be performed without definitive diagnosis

Open pericardiotomy may be required to evacuate clot and inspect the heart

Resuscitative thoracotomy

May be helpful in penetrating chest injury with pulseless electrical activity

Only performed by an appropriate surgeon

Secondary survey

Further examination

Upright CXR, ABG, SpO₂, ECG

Simple pneumothorax

Decreased breath sounds, resonant percussion

Chest tube inserted in fifth intercostal space, underwater seal drain, CXR to confirm lung re-expansion all required before IPPV or air transport

Haemothorax

Usually due to laceration of intercostal or internal thoracic arteries, bleeding is usually self-limiting
Chest tube allows drainage of blood and monitoring ongoing loss
Thoracotomy for severe bleeding

Pulmonary contusion

Most common potentially lethal chest injury, gradual respiratory failure
 $P_aO_2 > 65$ mmHg or $SpO_2 < 90\%$ demands intubation and ventilation
Repeated assessment of ABG, ECG and SpO_2

Tracheobronchial tree injuries

Most injuries are within 2.5 cm of the carina and cause death at the scene
Haemoptysis, subcutaneous emphysema or tension pneumothorax
Large air leak after chest tube insertion, two chest tubes may be required
Diagnosis confirmed at bronchoscopy, may require double lumen tube, may require urgent surgical repair

Blunt cardiac injury

Pain, hypotension with \uparrow CVP, wall motion abnormality, conduction abnormalities (PVCs, ST, AF, RBBB, ST Δ)
Treatment of arrhythmia as indicated, ECG monitoring

Traumatic aortic disruption

Common cause of death after severe deceleration injury
Survivors to hospital have contained haematoma
Signs on CXR: widened mediastinum, obliterated aortic knob, tracheal deviation to right, no space between aorta and PA, depressed left main bronchus, deviation of oesophagus to right, widened paratracheal stripe, widened paraspinal interfaces, apical cap, left haemothorax, fractures of first or second rib or scapula
Diagnosed at angiography or TOE

Traumatic diaphragmatic injury

Commonly missed, may be diagnosed on CXR with NGT or contrast, or by drainage from chest tube of DPL fluid, or at thoracoscopy or laparotomy
Treated by direct repair

Mediastinal traversing wounds

Penetrating injury crossing from one hemithorax to the other or with metallic fragment lodged in the mediastinum
50% unstable, 20% mortality
Early surgical consultation
Injury to great vessels, tracheobronchial tree, oesophagus, heart, spinal cord and lung must be considered
Chest tubes may be required bilaterally, early operation if unstable
Stable patients require angiography, contrast swallow, gastroscopy, bronchoscopy, CT or echocardiography

Associated problems

Subcutaneous emphysema

Crush injury

Rib, sternum and scapula fractures

Ribs 1-3 protected by upper limb; fracture suggests great vessel injury

Ribs 4-9 most commonly injured, require greater force in the young

Ribs 10-12 fracture suggest hepatic or splenic injury

Analgesia is required for good ventilation

Blunt oesophageal rupture

Due to forced expulsion of gastric contents with oesophageal tearing or instrumentation

May present as left pneumothorax without rib fracture, particulate matter in chest tube

Required operative repair to prevent mediastinitis and sepsis

CXR examination

Confirm ID of film

Trachea and bronchi

Interstitial or pleural air, pneumomediastinum, pneumothorax, subcutaneous or interstitial emphysema, pneumoperitoneum

Pleural space and lung parenchyma

Lung infiltrate, consolidation or haemothorax

Mediastinum

Altered cardiac silhouette, signs of aortic rupture (above)

Diaphragm

Elevation, disruption, obscured, mass above or air below

Bony thorax

Clavicle, scapula, ribs, sternum fractures or dislocation

Soft tissues

Tubes and lines

Abdominal Trauma

Assessment

History

Mechanism of injury: e.g. vehicle crash, speed, direction, position in car etc. or weapon and range in penetrating trauma

Location of pain and referral of pain

Examination

Inspection

Including posterior abdomen and chest and perineum

Auscultation, percussion

Palpation

Guarding, pregnancy

Evaluation and local exploration of penetrating wounds

Dependent on surgical experience

25%-33% of anterior stab wounds do not penetrate peritoneum

Assess pelvic stability

Perineal, penile/vaginal and rectal examination

Signs of pelvic fracture or urethral injury

Gluteal examination

Intubation

Insertion of NGT, urethral catheter (if no indication of injury)

Blood and urine sampling

Imaging

Screening x-rays: cervical spine, CXR, pelvis

Supine and erect AXR (lateral decubitus if can't be sat up)

Contrast studies

Urethrography, cystography if injury suspected

IVP only if contrast CT unavailable

GI contrast studies if injury suspected and patient stable

Special investigation

Diagnostic peritoneal lavage

98% sensitive for intraperitoneal bleeding

Indications

Haemodynamically abnormal, multiple blunt injuries

Altered conscious state

Spinal cord injury

Equivocal abdominal examination

Prolonged "loss of contact" with abdomen expected (e.g. CT)

CT or US not available

Relative contraindications

Previous surgery, morbid obesity, cirrhosis, coagulopathy

Lavage catheter inserted and aspirated

If no aspirate, 1000 ml Hartmann's used for lavage

Positive if $\geq 100,000$ RBC/mm³, ≥ 500 WBC/mm³ or gram stain +ve

Ultrasound

As good as DPL or CT in experienced hands

Gives views of pericardium, hepatorenal fossa, splenorenal fossa, pelvis

Repeat scan at 30 minutes to detect slow bleeding

Computed tomography

Time-consuming, only for stable patients

Most specific test for injury

Will miss some diaphragmatic, bowel and pancreas injuries

Special investigation in penetrating trauma

Lower chest wounds

Serial examination and imaging, laparoscopy, thoracoscopy

Anterior abdominal stab wounds

Serial examination or DPL help to detect asymptomatic penetration of peritoneum

Back or flank stab wounds

Serial examination or contrast CT or DPL plus follow up beyond 24 hours if asymptomatic

Indications for laparotomy

Blunt trauma with

Positive DPL or ultrasound

Hypotension despite resuscitation

Peritonitis

Penetrating trauma with

Hypotension

Bleeding from GI or urogenital tract

Gunshot wounds

Evisceration

AXR with free air, diaphragmatic defect or retroperitoneal air

CT with ruptured viscus, injury to bladder, renal pedicle or other viscus

Pelvic fractures

Classification

Anteroposterior compression injury

Commonly sacral fracture or dislocation

Haemorrhage from posterior venous or internal iliac vessels

Lateral compression injury

Pubis commonly injures bladder or urethra

Haemorrhage less common

High energy shear force injury

Disrupts sacrospinous and sacrotuberous ligaments

Major instability

Assessment

Inspection for bruising, lacerations, urethral injury, PR

Manual test of mechanical stability

X-ray

Management

Exsanguination

ABCDE, PASG, operate if open or DPL positive, post-op fixation

Angiography if unstable and DPL negative

Stable following resuscitation and unstable fracture

ABCDE, PASG, operate if DPL positive, post-op fixation, angiography if still unstable

Normal BP

ABCDE, PASG if hypotension develops, treat other injuries, fix

DPL technique

Urinary catheter, NGT

Prep, local below umbilicus

Vertical incision to fascia, peritoneal incision (alternatively Seldinger tech.)

Insert catheter, advance into pelvis

Aspirate, irrigate, agitate, drain after 5-10 min

Send sample for RBC, WBC counts and gram stain

Head Trauma

Classification

Mechanism: blunt or penetrating (dura)

Severity: by GCS: severe 3-8, moderate 9-13, mild 14-15

Morphology

Usually determined at CT scan

Skull fractures

Vault: linear or stellate, open or closed, depressed or not

Basilar: with or without CSF leak, VII nerve palsy

Intracranial lesions

Focal

Extradural haematoma

9% of comatose head injuries

Lenticular lesion, usually arterial

Subdural haematoma

30% of severe head injuries

Cover entire hemisphere, usually venous

Intracerebral haematoma or contusions

Usually frontal and temporal and associated with subdural

Diffuse "concussion"

Mild, classical and diffuse axonal injury

Management

Mild

80% of head-injury presentations

All require CT scan if any LOC, amnesia or headache

Skull x-rays only for penetrating injury

Usual cervical spine x-rays, blood tests etc.

Avoid narcotics

12 hours of observation (can be at home) even if normal CT

Discharged only if asymptomatic, uninjured, living nearby and in the company of a responsible adult

Moderate

10% of head-injury presentations

10 - 20% will deteriorate

History

Examination

Investigations

CT head (40% abnormal), baseline bloods

Surgery if indicated (8% on CT scan)

Admission for observation

Repeated examination and CT if any deterioration

Severe

10% of head-injury presentations

ABCDE

Hypotension and hypoxia are associated with 75% mortality

Require rapid resuscitation

Early intubation, moderate hyperventilation (PCO₂ 25-35 mmHg)

Maintenance of cerebral perfusion pressure

Management of other injuries as indicated

Priority of CT versus DPL/US depends on response to fluid resuscitation: poor response → DPL/US first

High incidence of other injuries

Long bone or pelvic fracture 32%

Mandible or maxillary fracture 22%

Major chest injury 23%

Thus detailed secondary survey

Neurologic examination

GCS and pupils at least prior to relaxation

Serial examinations over time, recording best responses on each side

Diagnostic procedures

Emergency CT scan unless precluded by instability

Looking for lesions and midline shift

Medical management of head injury

36% mortality for severe head injury

IV fluids: maintain euvolaemia with saline or Hartmann's (**not** glucose)

Maintain perfusion pressure ≥70 mmHg

Moderate hyperventilation: PCO₂ 25-35 mmHg

Mannitol for oedema if normotensive

Furosemide and anticonvulsants with surgical consultation

Steroids and barbiturates probably not beneficial

Surgical management

Scalp laceration without underlying fracture

Closed after shaving and irrigation

Depressed fracture

Elevated surgically if depressed more than the skull thickness

Mass lesions

Transfer to neurosurgical unit

Emergency burr holes by a non-specialist are rarely justified

Spine and Spinal Cord Trauma

Epidemiology

450 spinal injuries per year in Australia, 2% mortality

Level of injury

| | |
|--------|-----|
| C4-7 | 48% |
| T3-6 | 13% |
| T10-12 | 18% |
| other | 21% |

Classification of injury

Level

The most caudal segment with normal sensory and motor function

Dermatomes

Myotomes

| | |
|----|-----------------------|
| C5 | deltoid |
| C6 | wrist extension |
| C7 | elbow extension |
| C8 | middle finger flexion |
| T1 | finger abduction |
| L2 | Hip flexion |
| L3 | Knee extension |
| L4 | Ankle dorsiflexion |
| L5 | Toe extension |
| S1 | Ankle plantar flexion |

Differs from bony level of injury

Severity

Complete, incomplete

Cord syndromes

Central cord

Anterior spinal artery compromise

Usually cervical extension injury

Upper limb weakness > lower limb

Anterior cord

Anterior spinal artery infarction

Pain and temperature sensation loss, paraplegia

Intact vibration, proprioception

Brown-Sequard

Cord hemisection

Ipsilateral motor and vibration/proprioception loss

Contralateral pain and temperature loss two segments lower

Morphology

Fracture, fracture dislocation, SCIWORA, penetrating injury

Stable or unstable (all assumed to be unstable)

X-ray evaluation

Cervical spine

Must see BOS to T1

May require lateral and swimmer's views: 85% sensitivity for fractures

Addition of AP and open-mouth views: 92% sensitivity

Addition of oblique views: slight ↑ in sensitivity

CT scan if unable to see low vertebrae or injury suspected

10% of cervical spine fractures have a second vertebral fracture

To detect spinal cord compression: MRI or CT myelography

Thoracic and lumbar spine

AP views routine

Lateral or CT if injury suspected

Management

Rules for cervical spine

Paraplegia or quadriplegia suggests cervical instability.

Alert, normal and pain-free patients can be cleared if full-range voluntary movement is pain-free.

Alert, normal patients in pain need lateral, AP and open-mouth films. If a flexion lateral film is also of good quality and clear there is no need for CT.

Unconscious or confused or uncommunicative patients require AP, lateral and, if possible, open-mouth films before assessment by a surgeon before being cleared.

If there is doubt, the collar should be left on.

Neurosurgical or orthopaedic referral is required for all suspected injuries.

Paralyzed patients should be removed from a backboard as soon as practicable.

Never force the neck.

If operation is required prior to clearing the neck, the collar should be left on.

Assess the cervical spine x-rays for

- Bony deformity

- Fracture of the vertebral body or processes

- Loss of alignment

- Increased distance between spinous processes

- Narrowing of the canal

- Increased prevertebral soft-tissue shadow

Immobilization

A semirigid collar does not ensure immobilization.

A collar, backboard, tape and straps should be applied before definitive transfer.

Sedation, paralysis and intubation may be required to maintain immobilization.

Two-handed technique for cricoid may reduce cervical spine movement

Steroids

Not used in Australia for spinal cord injury

Musculoskeletal Trauma

Primary survey

- Occur in 85% of trauma patients

- Major importance in primary survey is haemorrhage

 - Control with local pressure

- Fracture immobilization

 - Aim to reduce fracture, minimize pain and bleeding

 - Not more important than ABCDE

- X-rays

 - Obtained when convenient

 - AP pelvis is indicated early in multi-trauma

Secondary survey

- History

 - Detail of mechanism of injury: time, force...

 - Environment: temperature, poison, fragments, contamination

 - Preinjury status: AMPLE...

 - Prehospital observations

- Physical examination

 - Complete exposure

 - Detection of life-threatening, limb-threatening and other injuries

 - Systematic examination: skin, neuromuscular, circulation, skeletal and ligamentous

 - Look, feel, pulses/circulation, x-ray

Potentially life-threatening extremity injuries

- Major pelvic disruption with haemorrhage

 - Falls, motorcycle or pedestrian accidents are associated with ring-opening injuries: sacroiliac disruption and major haemorrhage

 - Motorcar accidents are associated with lateral force injuries with genitourinary injury and less incidence of haemorrhage

 - Signs

 - Progressive swelling or bruising

 - Failure to respond to fluid resuscitation

 - Signs of urethral injury

 - Mechanical instability

 - X-ray findings

 - Management

 - Haemorrhage control with immobilization \pm PASG

 - Rapid fluid resuscitation

 - Early surgical consultation

- Major arterial haemorrhage

 - Penetrating or blunt injury with fracture or dislocation

 - Signs of ischaemia or haematoma

 - Management

 - Direct pressure

 - Fluid resuscitation

 - Surgical consultation

- Crush syndrome

 - Prolonged crush injury to muscle causes rhabdomyolysis

 - Signs: dark urine, hypovolaemia, acidosis, hyperkalaemia, hypocalcaemia, DIC

 - Management fluid loading, osmotic diuresis, urinary alkalinization

Limb-threatening injuries

Open fractures and joint injuries

Communication between external environment and bone

Management sterile dressing, examination of soft-tissue, circulatory and neurological involvement, surgical consultation

Tetanus prophylaxis

Vascular injuries, traumatic amputation

Suggested by circulatory insufficiency associated with limb trauma

May result from circumferential dressings or casts

Urgent surgical revascularization

Replantation is indicated only in isolated limb injuries, not in patients requiring intensive resuscitation

Amputated part is washed in Hartmann's, wrapped in penicillin-soaked gauze and transported on crushed ice

Compartment syndrome

Caused by injury within a closed fascial space or external compression

Compartment pressure exceeds perfusion pressure

High risk: tibial and forearm fractures, tight dressings or casts, severe crush injuries, interstitial oedema due to reperfusion, increased capillary permeability or exercise

Signs

Unexpectedly severe pain, worse with stretching

Dysfunction of nerves in the compartment

Tense swelling

Weakness and loss of pulses are late signs

Compartment pressure >35-45 mmHg

Management

Removal of dressings or casts

Fasciotomy if no improvement over 30-60 min.

Neurologic injury secondary to fracture dislocation

Assessment of nerve function requires a cooperative patient

Documentation of progression of disability and repeat examination is important, especially after reduction manoeuvres (table below)

Other extremity injuries

Contusions and lacerations

Examine for associated injury

Superficial injury from crushing or degloving may be minor

Tetanus risk increased: >6 h old, abraded, >1 cm deep, due to burn, cold or missile, contaminated

Joint injuries

May not be associated with fractures

Hyperextension or hyperflexion soft tissue injury

Examine for associated nerve or vessel damage

Immobilize

Fractures

Usually associated with soft tissue injury

Clinical examination to make diagnosis, accompanied by x-rays in two planes

Joint above the injury must also be x-rayed

Examine for associated nerve or vessel injury

Immobilize

| Nerve | Motor | Sensation | Injury |
|--------------------------------|-------------------------------|-----------------------------|--|
| Ulnar | Index finger abduction | Little finger | Elbow injury |
| Median (distal) | Thenar opposition | Index finger | Wrist dislocation |
| Median (anterior interosseous) | Index tip flexion | | Supracondylar fracture of humerus |
| Musculocutaneous | Elbow flexion | Lateral forearm | Anterior shoulder dislocation |
| Radial | Thumb, finger MCP extension | 1st dorsal web space | Distal humeral shaft, anterior shoulder dislocation |
| Axillary | Deltoid | Lateral shoulder | Anterior shoulder dislocation, proximal humerus fracture |
| Femoral | Knee extension | Anterior knee | Pubic rami fractures |
| Obturator | Hip adduction | Medial thigh | Obturator ring fractures |
| Posterior tibial | Toe flexion | Sole of foot | Knee dislocation |
| Superficial peroneal | Ankle eversion | Lateral dorsum of foot | Fibular neck fracture, knee dislocation |
| Deep peroneal | Ankle/toe dorsiflexion | Dorsal 1st to 2nd web space | Fibular neck fracture, compartment syndrome |
| Sciatic | Plantar flexion | Foot | Posterior hip dislocation |
| Superior gluteal | Hip adduction | | Acetabular fracture |
| Inferior gluteal | Gluteus maximus hip extension | | Acetabular fracture |

Physical Examination

Look

Age, sex
 Wounds, deformity, position
 Colour of extremities
 Spontaneous activity: evidence of pain or paraplegia
 Urine colour

Feel

Palpate pelvis for instability
 Peripheral pulses and capillary refill
 Muscle compartment palpation
 Joint stability
 Neurological examination: sensory and motor

Injures Due To Burns And Cold

Immediate management

ABCDE

Airway

Immediate intubation if inhalational injury likely

Facial burns, eyebrows or nasal hair singed, acute inflammation or carbon deposits in mouth, carbonaceous sputum, history of confinement in burning environment, explosion with burns to head or torso, COHb > 10%

Stop the burning process

Remove all clothing, chemical residue

Rinse with water

Intravenous access

Required if burns > 20% of BSA

Large bore, upper limb preferable, unburned area preferable

Assessment

History

AMPLE history, tetanus status

Examination

Area burned

“Rule of nines” for adults, modified for children

Adult: head, arm, half of leg, quarter of torso = 9%

Infant: head = 18%, half of leg = 7%

Palm excluding fingers = 1%

Depth of burn

First degree

Erythema, pain, no blisters e.g. sunburn

Second degree, partial thickness

Red or mottled, blisters, weeping, hypersensitive

Third degree, full thickness

Dark and leathery, painless, dry

“Major” burns

>10% full thickness or >25% partial or inhalational injury

Stabilization

Airway

Early intubation if any suggestion of inhalational injury

Breathing

Injury mechanisms

Thermal injury

Upper airway oedema, obstruction

Inhalation of smoke and toxins

Tracheobronchitis, oedema, pneumonia

CO poisoning

< 20% COHb asymptomatic

20-30% headache and nausea

30-40% confusion

40-60% coma

> 60% death

Treat with high FiO₂ (hyperbaric if pregnant)

Circulation

IV access and IDC required for management

Aim for urine output 1 ml/kg/h in children, 30-50 ml/h in adults

Initial fluids

Hartmann's 2-4 ml/kg/%burn over 24 h

Half given in 8 hours, half in next 16
Plus acute losses and fasting requirements
Adjust according to urine output, vital signs

Examination

Document extent and depth of burns
Assess for associated injuries
Weigh patient

Investigations

FBE, XM, ABG (COHb), glucose, U&E, β hCG if indicated

Adjuncts to initial management

Assessment of limbs with circumferential injury for circulatory compromise, escharotomy if necessary
NGT insertion for gastric stasis and nausea initially
Later may be required for hyperalimentation
Analgesia with IV narcotic or ketamine
Small graduated doses, as circulation is centralized in shock
May worsen hypotension, hypoxia if not adequately resuscitated
Dress burns with clean linen
Prevent hypothermia

Special burns

Chemical injury

Alkali, acid or petrochemical burns
Alkali burns are generally the most serious
Remove all traces of chemical and irrigate
Burns to the eye may require continuous irrigation

Electrical burns

Frequently small entry and exit burns with extensive deep tissue injury underlying
Rhabdomyolysis common
Manage the same except
High index of suspicion of rhabdomyolysis, cardiac injury
ECG monitor, urine colour observation
Osmotic diuresis \pm alkalinization of urine

Trauma in Women

Alterations in pregnancy

Uterus

- Intrapelvic until week 12, thick-walled, embryo well cushioned
- At umbilicus by week 20
- At costal margin at week 34-36, thin-walled, vulnerable to injury
- Protects bowel from blunt trauma
- High risk of placental abruption with trauma

CVS

- ↑ blood volume, ↓ Hb, ↑ WCC ($15-25,000 \text{ mm}^{-3}$), ↓ albumin (22-28 g/l)
- ↑ CO (by 1-1.5 l/min), ↑ HR (10-15/min), ↓ BP (5-15 mmHg), ECG LAD

Resp

- ↑ MV, ↓ PCO_2 , ↓ RV, FRC

Other

- ↑ gastric emptying time
- ↑ RBF, GFR, uterine compression of ureters
- ↑ pituitary size
- ligamentous laxity

Assessment and management

Primary survey and resuscitation

Mother

- Usual ABCDE
- Except left lateral tilt with uterine displacement unless spinal injury suspected
- Vigorous fluid resuscitation to prevent uterine vasoconstriction and fetal hypoxia
- Indicated x-rays must be performed, risk to fetus is low

Fetus

- Good maternal resuscitation is good fetal management
- Assessment by abdominal examination
 - Signs of uterine rupture
 - Signs of abruption
- Fetal heart sounds, ultrasound, CTG

Secondary survey

- Usual, including DPL or ultrasound
- Except DPL must be above the umbilicus
- Additional attention to uterine contraction, obstetric pelvic examination
- Admission and fetal monitoring is required for even minor injuries

Specific conditions

Uterine rupture

- Massive haemorrhage and shock if severe
- Abnormal fetal position, extended limbs, free intraperitoneal air
- Laparotomy required if rupture suspected

Abruption

- Leading cause of fetal death after trauma
- Vaginal bleeding, pain, uterine rigidity, shock
- 30% show no external bleeding

Amniotic fluid embolism

- Hypotension, hypoxia, DIC

Fetomaternal haemorrhage

- Fetal anaemia and death
- Maternal isoimmunisation (use anti-D even if Kleihauer negative)

Perimortem Caesarean section

Transfer to Definitive Care

Remote anaesthesia

[Anaesthesia in a hyperbaric chamber](#)

[Anaesthesia in a dental surgery](#)

[Problems in transporting patients](#)

Anaesthesia in a hyperbaric chamber

Hyperbaric chamber

- Increased atmospheric pressure, usually up to 3 atm
 - Commonly chamber contains air, but oxygen headboxes or masks are used to deliver high FiO_2

Indications

- CO poisoning, gas embolism, decompression illness
- Acute infections, sports injuries
- Maintenance of oxygen transport in anaemia
- Increased arterial oxygenation in anaesthesia

Physiological effects

- Increased barometric pressure
 - Pressure reversal of anaesthesia requires much higher pressures
- Increased partial pressure of oxygen, risk of toxicity

Practical use

- Limited duration
 - Oxygen toxicity
 - Decompression obligation
 - Monitoring difficulty
 - Patient discomfort

Equilibration

- Middle ear and lung

Equipment

- Increased fire hazard so minimal use of electrical devices
- Monitors usually placed outside chamber with long cables
 - Pressure devices need adjustment
 - Catheter balloons need deflation prior to compression or decompression (e.g. Swan)
 - Blood gas assessment is complicated by decompression of sample
- Defibrillation is hazardous
- IV giving set air-fluid level changes with pressure change
- Anaesthetic machine
 - Flow meters under read
 - Vaporizers deliver same partial pressure but reduced vol%
 - Special ventilators required

Anaesthesia

Trials in

- Carotid, caesarean, lung lavage

Would you anaesthetize in a dental surgery?

College Policy T5 (1995)

Principles of anaesthetic care

- Suitable medical practitioner
- Medical preanaesthetic consultation
- Compliant monitoring
- Anaesthetist has discretion to cancel cases

Staffing

- Assistant to the anaesthetist
- Assistance for positioning
- Technical assistance for equipment service

Equipment

- Anaesthetic machine for each anaesthetizing location
 - Calibrated vaporizers
 - Suitable breathing systems
 - Paediatric breathing systems if children are being anaesthetized
 - Safety devices
 - Indexed gas connection, oxygen reserve supply, oxygen failure warning device, oxygen analyzer, anti-hypoxic interlock, pressure relief valve, non-slip common gas outlet connection, scavenging
- Separate ventilating device with independent oxygen supply
- Compliant suction equipment
- Other equipment
 - Gloves, masks, eye protection etc.
 - Stethoscope, sphygmomanometer, compliant monitoring
 - Range of face masks, airways, ETTs and connectors
 - Two laryngoscopes and a range of blades
 - Introducers, syringe, clamps, Magill's forceps, tapes, scissors, lube, throat pack
 - Tourniquets, IV equipment, sharps container
 - Regional equipment
 - Defibrillator

Environment

- Good lighting
- Emergency lighting
- Telephone or intercom
- Refrigerator
- Environmental temperature control
- Chair which allows rapid head-down or horizontal positioning

Drugs

- Anaesthetic agents
- Emergency drugs for initial management of
 - Anaphylaxis, arrhythmias, cardiac arrest, pulmonary oedema, hypotension, hypertension, bronchospasm, respiratory depression, hypoglycaemia, hyperglycaemia, adrenal dysfunction, malignant hyperpyrexia (dantrolene at nearby hospital), coagulopathy
- Mechanism for checking use-by dates

Maintenance

- Routines for checking equipment
- Twice yearly service of anaesthetic machine with documentation
- Protocol for checking the anaesthetic machine

Recovery

- Compliant recovery room
- Contingency plan for emergency transfer to hospital care

Problems in transporting patients.

Assistance

- Two staff minimum for patient transport
- One to resuscitate, one to get help
- At least one must be familiar with the route and destination

Airway and breathing

- If intubated, the ETT must be well-secured
- Ventilation
 - Apnoeic for short periods (e.g. induction room to OR)
 - Self-inflating bag
 - Gas-powered ventilator (e.g. Dräger Oxylog)
 - Battery-powered ventilator (e.g. some Siemens models, Dräger Julian)
- Portable oxygen source adequate for expected duration of transport
- Portable suction
- N₂O and anaesthetic vapours usually not available
- Vaporizers do not operate correctly when shaken

Circulation

- External pacing device must have adequate battery power and leads secure
- Intravenous infusions must have adequate length and be well-secured
 - Best attached to bed
- Warming devices will not operate without AC power
- Circulatory support devices must have adequate tubing length and battery power and triggering not subject to interference (e.g. IABP, LVAD)

Monitoring

- SpO₂, ECG, NIBP or invasive pressure usually available
 - Adequate lead length and battery power required
- Gas analysis, complex monitors usually not available
- Vibration in transport may interfere with all monitors
 - Greater dependence on clinical signs: pulse, colour, chest movement
 - Conflicts with need to keep patient covered and warm

Drugs and equipment

- Awake patient
 - Emergency induction drugs and airway equipment
- Maintenance of anaesthetized patient
 - Sedative or hypnotic agents
 - e.g. midazolam, morphine, thiopentone, propofol
 - Relaxants
 - longer-acting agents preferred
- Emergency drugs
 - Resuscitation drugs, pressors
 - Specific agents depending on patient's condition
 - e.g. anticonvulsants, vasodilators

Other

- Surgical drains
 - Chest drains clamped or placed so as to ensure no "backflow"

College Policy: Minimum Standards for Transport of the Critically Ill (P23)

Administrative guidelines

- Central coordination to minimize delays
- Clear determination of responsibility
- Appropriate documentation
- Quality assurance mechanism

Categories of transport

- Prehospital, interhospital (emergency and semi-elective), intrahospital

Staffing

Prehospital: appropriate ambulance service personnel

Interhospital: experienced medical, nursing, technical and ambulance staff

Specifically trained personnel for neonatal and infant transport

Intrahospital: appropriate medical and nursing personnel

Transport

Vehicle determined by availability, urgency, distance, conditions

Requirements for safety, space, gases and energy, access, lighting, temperature control, restraints, noise and vibration, speed, communication, pressurization, headsets for auditory alarms

Special issues with aircraft: pressure, space, motion, noise

Fundamental requirement for stable vital signs, secure airway, secure IV, secure catheters and appropriate monitoring before departure

Equipment

Regard to size, weight, durability, battery life, restraint

Respiratory

Oxygen, airways, masks, nebulizer, self-inflating bag with PEEP, suction, ventilator with pressure and disconnect alarms, intubation set, cricothyroidotomy set, pleural drainage set

Circulatory

Monitor, defibrillator, pacer, oximeter, anaeroid sphygmomanometer, cannulae, fluids, pump set, infusion pumps, arterial pressure transducer, syringes, needles, MAST

Other

NGT, IDC, Cophenylcaine, instruments, sutures, dressings, prep, gloves, insulation, thermometer, splints

Drugs

Resuscitation drugs for all likely emergencies

Arrest, hypotension, hypertension, arrhythmia, APO, anaphylaxis, bronchospasm, hypoglycaemia, hyperglycaemia, raised ICP, uterine atony, adrenal dysfunction, narcotic depression, convulsions, agitation, pain, vomiting, electrolyte disturbance

Monitoring

Appropriate to the situation

Clinical monitoring is fundamental

Circulation: pulse and BP

Respiration: frequent assessment

Oxygenation: observation and pulse oximetry

Minimum standards

O₂ supply failure alarm, pulse oximeter, disconnect or ventilator failure alarm, high airway pressure alarm, ECG

Policies

| | | | |
|----------------------|--|-----------------------|---|
| E1 | Registrar Posts | PS17 | Bronchoscopy |
| TE3 | Supervision of Trainees | P18 | Monitoring |
| TE4 | Regional Education Officers | P19 | Monitored Anaesthetic Care |
| TE5 | Supervisors of Training | P20 | Postoperative Responsibilities |
| E6 | Duties of an Anaesthetist | P21 | Sedation for Dental Procedures |
| TE7 | Secretarial Services | P22 | Patients' Rights and Responsibilities |
| TE9 | Quality Assurance | P23 | Transport of Critically Ill |
| TE11 | Formal Project | P24 | Sedation for Endoscopy |
| E13 | Provisional Fellowship Year | (P25) | Pain Management Centres Offering the CPM) |
| E14 | In-Training Assessment | PS26 | Providing Information about Anaesthesia |
| TE15 | Certificate in Pain Management | P27 | Standards for Extracorporeal Perfusion |
| TE16 | Pain Management Centres Offering Training | P28 | Infection Control |
| TE17 | Advisors of Candidates | PS29 | Children in Non-Paediatric Centres |
| EX1 | Examination Illness | PS31 | Checking the Anaesthetic Machine |
| T1 | Minimum Facilities in Operating Suites | PS33 | Minimum Facilities in ECT |
| T3 | Minimum Facilities in Radiology | PS36 | Sedation for Eye Surgery under Regional |
| (T4) | Minimum Facilities in ECT) | PS37 | Regional and Allied Health Practitioners |
| T5 | Minimum Facilities in Dental Surgeries | PS38 | End of Life Decisions |
| T6 | Minimum Facilities in Delivery Suites | PS39 | Intrahospital Transport of Critically Ill |
| P1 | Training for GP Anaesthetists | PS40 | Relationships with the Healthcare Industry |
| P2 | Privileges | IC1 | Standards for ICU |
| PS3 | Major Regional Anaesthesia | IC2 | Duties of an ICU Specialist in a Training Hospital |
| P4 | Recovery | IC3 | Training Posts in ICU |
| (P5) | Care of Patients made Unconscious) | IC4 | Supervision of ICU Trainees |
| P6 | Anaesthesia Record | IC5 | Education Officer in ICU |
| PS7 | Preanaesthetic Consultation | IC6 | Supervisor of Training in ICU |
| PS8 | Assistant for the Anaesthetist | IC7 | Secretarial Services to ICU |
| P9 | Sedation | IC8 | Quality Care |
| PS10 | Handover of an Anaesthetic | IC9 | Ethics and Patients' Rights and Responsibilities |
| P11 | Bypass | IC11 | In-Training Assessment in ICU |
| PS12 | Smoking | | |
| P13 | Autologous Blood | | |
| PS14 | Epidural Anaesthesia in Obstetrics | | |
| P15 | Day Surgery | | |
| P16 | Standards of Practice | | |

E1 Registrar Posts

3-15 months ICU
No more than 4 years in one hospital
At least one consultant per trainee
Access to library, journals, texts, computers

TE3 Supervision of Trainees

Four levels of supervision

- 1 One consultant to one trainee
- 2 One to two
- 3 Consultant available within the hospital
- 4 Consultant exclusively rostered and available from home

General requirements

- Level 1 and 2 for $\geq 25\%$ of work in first four years
- Level 4 for $\leq 30\%$ of work in first four years
- Out of hours work 25-50% of work in first four years
- Supervisor must attend if asked to
- Level 1 supervision in an unfamiliar area

First year

- Level 1 supervision for at least 3 months
- Level 1 or 2 for most in-hours cases
- Supervisor notified of all out-of-hours cases, 25% to be level 1 or 2

Second year

- Level 1 or 2 for about half of in-hours cases
- Level 1 or 2 for at least 20% of out-of-hours cases

Third year

- Level 3 for many in-hours cases
- Level 1 for cardiac, obstetric, major paediatric work

Fourth year

- Level 3 for previously encountered work

PFY

- Consultation and supervision available at all times

E6 The Duties of an Anaesthetist

Clinical

- Providing anaesthesia and other consultative services
- Preoperative assessment and postoperative care
- Supervising trainees and other staff
- Supervising recovery
- Supervising day surgery anaesthesia areas
- Maintaining an acute pain service
- Associating with a pain management service
- Acute resuscitation for emergencies
- Management of ICU patients
- Consultative service in preoperative assessment and management
- Supervising cardiopulmonary bypass

Other

- Administrative duties in the Department and Hospital
- Educational activities for doctors, trainees, nurses, students, the public
- Peer review and quality improvement activities
- Continuing medical education
- Professional associations
- Research and reviews

Contributing to hospital or health committees
Activities to safeguard the wellbeing of colleagues

TE9 Quality Assurance

“An organized process that assesses and evaluates health services to improve practice or quality of care.”

Process

Planning, implementation, review cycle
Setting standards

Activities

Assess Department structure and performance relative to other Departments or ANZCA policies

With regard to staff, physical facilities, management and education

Criteria-based audit

Clinical indicators, periop mortality or morbidity, ICU stats, utilization

Formulation of guidelines or protocols

Critical incident review

Risk management

Peer reviews

Patient surveys

T1 Minimum Facilities for Safe Anaesthetic Practice in Operating Suites

T2, T5, PS33 (Radiology, Dental, ECT) similar

T6 (Delivery Suite) similar with addition of paediatrician, specifications for delivery room

Principles

Anaesthesia should be administered by appropriately trained doctors

Every patient should have a preanaesthetic consultation with a doctor trained in anaesthesia

Appropriate monitoring must occur during anaesthesia

Staffing

In addition to surgical staff

An assistant to the anaesthetist

Assistance for positioning

Technical assistance

Anaesthetic equipment

Anaesthetic machine: O₂, N₂O, volatiles, breathing circuits (adult, paediatric), air if necessary

Safety devices: indexed gas supply, O₂ reserve, O₂ failure warning, pressure relief valve, O₂ analyzer, antihypoxic device, non-slip CGO

Separate ventilating device

Suction, scavenging

Monitoring, IV, airway, regional equipment

Difficult intubation equipment, rapid infusion device, warming, chest drain, defib.

Other equipment

Appropriate lighting, emergency lighting, telephone or intercom, refrigerator, airconditioning, trolleys

Drugs

Usual anaesthetic drugs

Drugs required to manage complications

Cleaning and servicing procedures

Recovery area

PS3 Major Regional Anaesthesia

Principles

- Administered only by appropriately trained doctors
- The anaesthetist must not also be the operator
- Informed consent required
- Monitoring requirements as for any anaesthetic
- Anaesthetist must be present until the block is stable or procedure complete

Epidural catheters

- IV access required
- Catheter clearly labelled "Epidural"
- Management as prescribed by anaesthetist
- Protocols for management of complications
- Protocol for monitoring for complications
 - Observations must be charted
- Catheter removal and condition must be documented
- Management may be delegated to a nurse or APS
 - With specific training and experience

P4 Recovery

Principles

- Specific area, close to theatre, trained staff able to contact anaesthetist

Design

- Part of the operating suite, accessible in street clothes
- 9 m² per bed with access to patient's head
- 1.5 spaces per theatre
- Each bay
 - O₂, suction, SpO₂, sphygmomanometer, stethoscope, thermometer, power, lighting, emergency lighting, space for monitors
- Nurses station, drugs, linen, utility room, scrub area, x-ray box
- Clock with second hand
- Telephone and emergency alarm, emergency power

Equipment

Present

- Ventilating device per two spaces, intubation drugs and equipment, resuscitation drugs, IV equipment, analgesics, syringes and needles, ECG per three spaces

Available

- 12-lead ECG, invasive pressure monitor, gas analyzer, defibrillator, nerve stimulator, bronchoscope
- Warming cupboard, refrigerator, procedure light, surgical tray, blood gases, x-ray

Trolleys

- Firm base and mattress, tilt 15° up and down, manoeuvrable, brakes, able to sit patient up, removable side rails, IV pole, mountings for monitors and transport equipment

Staff

- Trained recovery staff present at all times
- Flexible ratio: up to 1 to 3, but 1 to 1 for unconscious patients

Management

- Written protocols for management
- Routine for checking equipment and drugs
- Appropriate recording of consciousness, SpO₂, RR, HR, BP, temp.
- Established criteria for discharge
- Anaesthetist responsibilities
 - Accompany patient until handed over, provide written and verbal

orders, specify O₂ therapy, remain nearby until patient is safe to be left, supervise recovery and authorize discharge or delegate the discharge decision

P6 Minimum Requirements for the Anaesthesia Record

Basic information

- Name, hospital, UR, age, gender, weight
- Date of preop consult and operation
- Anaesthetist's name (also supervisor's name and level of supervision)
- Surgeon's name and procedure planned and performed

Prior to anaesthesia

- Preop assessment and ASA status
- General medical history, drug therapy, allergies
- Previous anaesthesia and surgery
- Airway, dental and reflux assessment
- Investigations
- Premed
- Documentation of anaesthetic plan discussed

Anaesthesia

- Drugs used, including by the surgeon
- Anaesthetic technique and any problems
- Time of events, observations and interventions
- Airway instrumentation and problems
- Details of vascular access and fluids given
- Blood loss
- Position
- Monitoring
- Other interventions

Post anaesthesia

- Observations and events as required in recovery standards
- Plan for pain management, fluid therapy, O₂ therapy
- Clinical indicators and QA markers
- Post-anaesthetic visit

PS7 The Pre-Anaesthesia Consultation

Principles

- Performed by the anaesthetist administering the anaesthetic even if already performed by someone else or questionnaire
- Appropriate time before surgery and in privacy
- Not to be modified except for the welfare of the patient (emergencies)

Including

- Identification and introduction
- Concise medical history and examination, investigations indicated
- Consultation if required
- General discussion of anaesthetic management significant to the patient
- Informed consent
- Ordering premedication
- Written summary

PS8 Assistant for the Anaesthetist

Principles

- A trained assistant is essential
- Present for preparation and induction until no longer required

- Available at short notice during maintenance
- Present for conclusion of anaesthesia
- Required for anaesthesia or sedation
- Equipment as required by other policies
- Deployment
 - Number and status of assistants determined by nature and workload of anaesthesia
 - Assistant is exclusively responsible to the anaesthetist while assisting
 - The assistant is essential: staffing and rostering must allow for one
- Education
 - Must have attended a suitable training course
 - EN or RN in clinical work or VCE required
 - Content
 - Lecture course of at least 150 hours with significant anaesthetic input
 - Practical instruction by anaesthetists with a log book kept
 - Completion of assignments, internal assessment and examinations
 - Duration
 - Three years full-time if no previous hospital experience
 - Two years full-time for EN or equivalent
 - One year full-time for RN
 - May be part-time
 - Regular continuing education

P9 Sedation for Minor Procedures

- Equipment and care must conform to requirements for anaesthesia in other policies
- Consultation, record, monitoring, recovery
- Principles
 - Preanaesthetic assessment required
 - Serious medical condition or possible airway compromise mandates constant presence of the anaesthetist
 - Practitioner administering sedation must understand drugs, potential complications and effect of patient illness on drug action
 - Single operator sedation is permissible only if rational verbal communication is maintained with the patient, otherwise an anaesthetist must be present
- Facilities
 - Tiltable table, space and drugs for resuscitation, suction, lighting, oxygen, ventilation equipment, pulse oximeter, defibrillator

PS10 Handover of responsibility

- Transfer
 - Satisfied of competence of relieving anaesthetist
 - Reliever willing to take over responsibility
 - Patient details: past history, present condition
 - Anaesthetic details: drugs, lines, airway, fluids, events, likely problems
 - Plan for further management if permanent handover
 - Compliant anaesthetic record
 - Check anaesthetic machine, lines and monitoring
 - Notification to surgeon (and supervising anaesthetist if a trainee)
- Relief
 - Patient stable and likely to remain so
 - Facts relevant to safe management explained to reliever
 - Reliever not to substantially change management unless an emergency
 - Anaesthetist available to return at short notice

P11 Cardiopulmonary bypass

Principles

A medical practitioner must take responsibility for CPB

Must be trained in CPB techniques

Should be assisted by a clinical perfusionist or technician

Should assess the patient pre-op and follow post-op

Must communicate with practitioners with overlapping responsibility

PS12 Smoking

Smoking is addictive and can damage the health of smokers and those around them

Benefits of ceasing

↓ COHb $t_{1/2}$ 4 h, so 12 h cessation significantly improves O₂ carriage

Polycythaemia and ↑ viscosity reverse in days

Nicotine ↑ HR, BP, peripheral vasoconstriction, improved within 12-24 h

↑ mucus, ↓ ciliary clearance improve over 6 weeks

Small airway function improves over 1-6 months

Chest infection rate reduced at 2 months, normal at 6 months

Immune response normalizes over 6 months

Increased analgesic requirements normalize over 6-8 weeks

Complication rate higher in plastic and reconstructive surgery

Impaired microcirculation

P13 Autologous blood

Standard label with unique identifier on unit

Signature and name of person collecting blood

Label with patient name, UR, date and time of collection attached

If stored for more than 6 hours, must be stored as for homologous blood

Checking prior to infusion as for homologous blood

PS14 Regional in obstetrics

Epidural or spinal to be performed by practitioner experienced in the techniques

Mother must be under care of an obstetrician

Anaesthetist

Ensures the mother is informed of risks

Is available to supervise management of the blockade

Is competent to deal with complications of block

Provides full instructions for management

Techniques must be recorded in mother's notes

A trained assistant is required for performing a block

Further epidural doses may be given by nurses or other doctors

When prescribed by the anaesthetist with appropriate written instructions

When competent to give the bolus and to monitor the mother and fetus

When skilled staff are available to manage complications

Care during infusion

Monitoring for mother and fetus, assessment of block and adverse effects, management of the labour

Handover as for any anaesthetic

IV cannula must be present throughout

PCEA must be explained to mother and nursing staff

Removal of catheter must be documented

P15 Periop care of day cases

Suitability for day surgery

Surgery

- Minimal risk of postop haemorrhage, airway compromise
- Pain controllable with outpatient techniques
- No special nursing requirements
- Rapid return to normal oral intake

Patients

- Willingness and understanding to follow postop instructions
- ASA I or II, or stable III and IV with anaesthetic consultation
- Term infants over 3 months or ex-prems over 60 weeks PCA

Support

- Responsible person to take the patient home and be present overnight

Decision ultimately rests with the anaesthetist

Preparation

Preanaesthetic consultation may be assisted by questionnaire or nurse

Prior referral in case of doubt as to suitability

Written patient information on process as day case and fasting requirements

Recovery

Compliant recovery room

Reclining seating area for after recovery

Nursing supervision, oxygen, suction, resuscitation equipment

Discharge

Wheelchair, car and ambulance access

Criteria

Obs stable for 1 h, orientated, adequate analgesia, able to dress and walk, no nausea or vomiting or dizziness, tolerating oral fluids, minimal bleeding, has voided

Responsible adult for transport, discharge authorized by surgeon and anaesthetist, written instructions and emergency contact information, 24 hours of analgesic drugs

Telephone follow up next day

PS17 Endoscopy of the airways

Principles

Procedure supervised by an experienced practitioner

Preoperative assessment may indicate the need for a second practitioner

Informed consent should be obtained

Equipment must be checked

Local, sedation or GA may be required

Sedation or GA require a second practitioner

Pulse oximetry and other compliant monitoring

Reliable venous access

Supplemental O₂ before, during and after bronchoscopy

Compliant recovery

Record of administration of sedation

Facilities

Tiltable table

Space and drugs for resuscitation

Suction, lighting, oxygen, ventilation equipment, pulse oximeter, sphygmomanometer, ECG and defibrillator

Reversal agents for benzos and opiates

Discharge as for day surgery

P18 Monitoring during anaesthesia

Personnel

- Appropriately trained doctor present from induction to recovery room
- Responsibility only for anaesthesia

Patient monitoring

- Pulse and BP at frequent and clinically appropriate intervals
- Ventilation monitored continuously, directly and indirectly
- Oximetry interpreted with clinical observation
- Adequate lighting to assess colour

Equipment

- Must be in use
 - O₂ failure, O₂ analyzer, pulse oximeter
 - Disconnect alarm if mechanically ventilated
- Must be available
 - ECG, temperature, capnograph, nerve stimulator, agent analysis

P19 Monitored Care

For procedures under local anaesthesia or sedation or in situations such as IV contrast in possibly sensitive patients.

Preanaesthetic consultation, monitoring, sedation, recovery, anaesthetic record, facilities as specified in other policies.

P20 Postoperative responsibilities

Shared responsibility with surgeon for

- Monitoring, analgesia, fluids, respiratory therapy

Responsibilities in recovery

- Handover when stable
- Availability for management of problems, or covered by another anaesthetist
- Safe criteria for discharge to ward
- On-going adequate care after recovery

Suitability for day surgery if discharged home

Quality assurance

- Recognition, management and documentation of adverse events
- On-going audit of anaesthesia care
- Inform patient of any matters relevant to future anaesthetics

P21 Sedation for Dental Procedures

As in [P9](#) plus

Dental practitioners administering sedation must be appropriately trained

- Dosage and administration of drugs
- Management of complications: resuscitation, CPR

Equipment

- Chair able to be laid flat, space for resuscitation, lighting
- Monitoring: BP, SpO₂ for IV sedation
- Resuscitation: suction, oxygen, means of ventilation, drugs

N₂O, O₂ sedation

- Minimum flow of 2.5 l/min O₂, minimum 30% O₂
- Maximum flow 7-10 l/min N₂O
- Flow meters, O₂ failure device, non-return valve, at least 2 cm diameter tubing, nose-piece incorporating air dilution valve, O₂ flush, scavenging to maintain N₂O below 25-50 ppm
- Installation and regular servicing by qualified personnel

IV sedation

SpO₂ required, IV access which will remain patent throughout, reversal drugs
Recovery
Adequately equipped and staffed, plan for transfer to medical care if needed

P22 Patients' Rights and Responsibilities

Rights

- To be treated with skill, consideration and dignity regardless of age, gender, race, religion, disabilities, health and legal status
- To know the identity and status of attending staff and refuse the presence of others during treatment
- To be informed of proposed care and alternatives, side-effects and risks
- To refuse proposed treatment without prejudice to alternative strategies provided the implications are understood by all involved
- To be provided anaesthesia by an anaesthetist after written consent
- To request a second opinion without prejudice
- To know of any involvement in teaching or research and to understand that non-involvement will not prejudice treatment
- To know that all aspects of care will remain confidential
- To know the broad financial implications of therapy
- To the presence and support of next of kin, partner or friend when practicable
- To expect decisions to be made on their behalf after discussion with next of kin should they be unable to communicate
- To be informed of any matters which may affect anaesthesia in the future

Responsibilities

- To inform staff of all relevant medical history including the possibility of infectious disease
- To comply with agreed treatment or inform staff of their intention not to comply
- To consider participation in teaching and research which may improve the care of others in the future
- To consider their ability to meet their financial obligations in relation to care

P23 Transport of the Critically Ill

Administration

- 24-hour coordinated transport by road and aircraft
- Delay minimized by central coordination and communication
- Transfer should not be delayed by waiting to identify a receiving unit
- Reliable communication between sending and receiving hospitals and transfer team
- Clear determination of responsibility and hand-over
- Documentation of condition before and during transport, therapy and history
- On-going quality assurance activities

Classification

- Prehospital, interhospital, intrahospital

Staffing

- Team of staff familiar with transport
 - Ambulance officers
 - Nursing and medical staff
 - Special expertise for neonatal and paediatric transport

Vehicle

- Choice determined by urgency, location, availability, nature of illness
- Requirements
 - Safety, space, power and gas supply, access, lighting, air-conditioning, restraints, noise and vibration, speed, communication system,

- pressurization
- Equipment
 - Determined by patient condition and expected duration
 - Attention to battery life and restraint in vehicle
 - Respiratory equipment
 - Airways, masks, nebulizer, self-inflating bag, suction, ventilator with alarms, sets for intubation, cricothyroidotomy and chest drain
 - Circulatory equipment
 - Monitor-defibrillator, oximeter, sphygmomanometer, IV equipment, arterial transducer, pacemaker, MAST
 - Other
 - NGT, IDC, dressings, sutures, instruments, splints, blankets, temperature monitor
 - Drugs
 - As required to manage resuscitation and likely emergencies as well as sedatives and relaxants
 - Ensure all lines and ETT are well-secured prior to transport
- Monitoring
 - Similar to intraoperative requirements

PS26 Providing Information about Anaesthesia

- Principles
 - Information is to be provided in such a way that the patient and relatives are able to understand
 - Where options exist, they should be outlined together with advantages and disadvantages
 - The patient should be made aware of the financial implications of the service
- Presentation
 - Basic information should be provided, even if the patient requests no information. If information is refused it should not be forced on the patient, but the refusal recorded in the notes.
 - Questions should be encouraged and answered
 - An interpreter should be used when necessary
 - Where blood products may be required, their advantages, risks and alternatives should be discussed
- Risks
 - Known risks should be disclosed for common, mild adverse effects and rare but serious ones.
 - Uncertainty in risk and difficulty in applying population risks to an individual should be explained
- Emergencies
 - No discussion of risks may be possible. Attempts should be made to provide information to the family as soon as possible.
- Incompetent patients
 - An explanation appropriate to the patient's understanding should be given.
 - Appropriate consent should be sought from a guardian or next-of-kin.

P28 Infection Control

- Cleaning and disinfection as per AS 4187-1994
- Handwashing
 - Before handling a new patient or equipment for a new patient
 - After leaving a patient
 - Whenever contaminated
 - Gloves to be worn whenever hands may contact blood, saliva or any bodily

- fluid
- Invasive procedures
 - IV
 - Wash hands, wear gloves, disinfect skin, ensure tip and cannula remain sterile
 - CVC
 - Full aseptic technique (mask, gown and gloves), skin preparation, sterile drapes
 - Regional anaesthesia
 - Peripheral blocks: as for IV
 - Axial block or catheter insertion: as for CVC
- Anaesthetic apparatus
 - Disposable items should not be reused
 - ETTs and airways to remain sterile until inserted
 - Face masks and upper airway instruments (laryngoscopes) to be disinfected
 - Circuit to be disinfected or protected with a filter
 - Sampling lines can be reused but returned gas must pass through a viral filter
 - CO₂ absorber and valves to be disinfected regularly and protected with a filter
 - Ventilator to be disinfected regularly
 - Fibreoptics to be cleaned as per AS
- Drugs for injection
 - Multi-dose ampoules only used where all doses drawn up before first is given
 - Single-dose ampoules should be used for only one patient
- For immune-suppressed patients, more stringent practices may be required

PS29 Paediatric Anaesthesia in the Non-specialist Hospital

Non-paediatric centres treating children should have a policy on management of children

Factors

Age (and prematurity), medical and nursing staff experience and familiarity

Equipment

Airway, IV, monitoring, temperature maintenance equipment suitable for children

A separate ward area

Policy

Criteria for transfer to a specialist centre

e.g. neonates, PCA <52 weeks, history of apnoea, ASA 3 or worse

PS37 Regional and Allied Health Practitioners

Practitioners such as dentists, podiatrists and nurses may administer local anaesthetic

Requirements

Training in the use of LA, pharmacology, complications and their management

Certified competence in CPR

Patients should not be denied a GA when indicated

Arrangements for transfer of care if required

PS38 End of Life Decisions

ANZCA's mission statement is *"To serve the community by fostering safety and quality patient care in anaesthesia, intensive care and pain medicine"*.

ANZCA supports

- Provision of adequate pain relief in terminal illness, even though it may shorten the patient's life, where the intention is relief of pain and not the death of the patient
- Relief of pain in non-terminal illness to restore quality of life and minimize the risk of suicide
- The right of competent patients to refuse treatment, even though it may be life-saving
- The right of Fellows and patients to their individual beliefs
- ANZCA does not support
 - The application of therapies which offer no benefit to the patient
 - The application of therapies in which the primary intent is the death of the patient

PS39 Intrahospital Transport of Critically Ill

Principles

- Hospital must have a protocol for transport
- Benefits of interventions requiring transport must outweigh risks of transport

Equipment

- Dedicated durable trolley capable of fitting in lifts and through doorways
- Suitable for the intervention area (e.g. MRI), gas, suction and electricity available at destination
- No equipment placed on the patient
- Basic monitoring: ECG, HR, BP, SpO₂
- Desirable monitoring: ETCO₂, MV,
- Basic equipment: defibrillator, suction, self-inflating bag if on ventilator, spare batteries, airway equipment
- Basic drugs: analgesics, sedatives, relaxants, resuscitation drugs

Policy

- Checking of transport equipment
- QA process for evaluation of transport

Staff

- Designated nurse, orderly and doctor familiar with equipment and emergency management

Departure check

- Notify destination
- Check monitors and alarm limits, ventilator and alarms, self-inflating bag, suction, gas cylinders and spare cylinder, batteries and spare battery, emergency equipment and drugs, patient films and notes
- Check patient: paralyze and sedate if indicated, replace near-empty infusions, check airway, ventilation, alarms, drains, lines, monitors, security on trolley, haemodynamic stability

In transit

- Best route planned, lifts held in advance, communication facilities in transit
- Vigilance in monitoring, documentation of interventions

Arrival

- Check fixed gas, suction, electrical and monitoring equipment
- Transfer to fixed equipment and recheck patient
- Formal handover of care if required

IC1 Minimum Standards for Intensive Care Units

Level 1

- Provides immediate resuscitation, short-term cardiorespiratory support, and monitor and prevent complications in "at risk" patients
- Suitable for uncomplicated myocardial ischaemia, post-surgical, unstable

medical and short-term ventilated patients

Should have

Access to emergency, theatre, imaging, laboratory and physiotherapy services

Policies for admission, discharge and referral

Supervision by a suitably qualified doctor, consultant support always available and 24-hour resident cover

1:1 nurse:patient ratio for critically ill patients

Programs for education, orientation and audit

Technical and clerical support with adequate office space

Level 2

In addition

Ventilatory support, invasive monitoring and dialysis support

Designated medical director who is an intensivist

Medical staff present at all times

Nursing staff to have ICU certification

Access to a nurse educator

Isolation

Formal audit

Level 3

In addition

The widest level of care: all aspects of intensive care medicine

Greater than 1:1 nurse:patient ratio for complex patients

Formal nursing education program and nurse educator

Medical education programs

Research program

Physical facilities

20 m² per bed

One washbasin per two beds

One single room per seven beds with own washbasin

Adequate service outlets

Level 3: 3 O₂, 2 air, 3 suction, 16 power per bed, compliant with standards

Lighting, air-conditioning, windows, privacy