Prostaglandins are 20-carbon fatty acids derived from arachidonic acid (released from cell membrane phospholipids by phospholipases A$_2$, C). They are formed de novo in response to many chemical (noradrenaline) and physical (cell deformation) stimuli, and are not stored.

1. Named PGA to J depending on the ring structure
2. Number reflects the number of double bonds
3. PGA, B, C and J do not occur in vivo
4. PGI$_2$ and TXA$_2$ are short-lived (T$_{1/2}$ = 30s, 3min respectively)

Arachidonic acid $\rightarrow$ PGG$_2$ $\rightarrow$ PGH$_2$ $\rightarrow$ PGI$_2$, PGD$_2$, PGE$_2$, PGF$_{2\alpha}$, TXA$_2$

NSAIDs are non-specific inhibitors of cyclo-oxygenase, inhibiting synthesis of prostaglandins.

1. Aspirin (acetylsalicylic acid) irreversibly acetylates COX – hence more COX must be synthesised in order to overcome its effects. Useful for treatment of unstable angina
2. Reversible inhibitors act at a different site – indomethacin, naproxen, diclofenac
3. Effects of NSAIDs:
   a. Platelets – ADP, platelet TXA$_2$ $\rightarrow$ platelet plug formation (1° haemostasis)
      i. Aspirin increases bleeding time due to reduced TXA$_2$
      ii. PGI$_2$ (released from the vessel wall) inhibits platelet aggregation
      iii. Platelets have no nucleus (so can't synthesise more COX), while the vessel wall can still synthesise COX $\rightarrow$ net anticoagulant effect
   b. Inflammation – prostaglandins are an inflammatory mediator
      i. PGE$_2$ and PGF$_{2\alpha}$ are vasodilators (lead indirectly to oedema)
      ii. Prostaglandins $\rightarrow$ hyperalgesia (sensitisation of nerve endings)
   c. Rheumatoid arthritis – synovial membrane spreads across the articular surfaces, leading to cartilage and bone damage. NSAIDs help reduce pain, redness and swelling, but do not prevent damage (methotrexate)
      i. Aspirin has a short duration of action, so long-acting NSAIDs are more appropriate (as the tissue can still synthesise COX)
   d. Osteoarthritis – loss of articular cartilage and narrowing of the joint space, with less inflammation. Paracetamol is the first line treatment.
   e. Fever – IL-1 acts on the hypothalamus to increase body temperature, regulated by prostaglandins. Treatment is generally symptomatic (to make the patient feel better) except for cases of possible febrile convulsions.
   f. NSAIDs have been tried in pre-term labour, but this has not continued due to risk to the developing fetus (though they are effective for period pain)
      i. PGE$_2$ can be administered as a vaginal pessary to induce cervical ripening (and hence labour).

Adverse effects of NSAIDS

1. Renal (prostaglandins are compensatory in patients with impaired function)
   a. Decreased GFR – inhibition of PGE$_2$ and PGI$_2$ (renal vasodilators)
   b. Salt and water retention – inhibition of PGE$_2$ (inhibits Na$^+$ resorption in the tubules, and inhibits ADH action)
   c. NSAIDS can block the actions of ACE inhibitors, β-blockers and diuretics
2. Stomach and duodenum
   a. Increased ulceration – PGE$_2$ has cytoprotective effects, and increases mucus secretion, HCO$_3^-$ production and mucosal blood flow
   b. GI bleeding may also be due to decreased platelet aggregation
   c. Indigestion – misoprostol (PGE$_1$ analogue) $\rightarrow$ diarrhoea (replaced by PPIs)
3. CNS effects – dizziness, vertigo, drowsiness, confusion (especially in the elderly)
4. Liver – abnormal liver function tests, can lead to mild chemical hepatitis
5. Skin rashes
6. Aspirin-sensitive asthma (5-20% of patients)

Selective COX$_2$ inhibitors work on the principle that COX$_1$ is constitutive, while COX$_2$ is inducible (by IL-1, TNF-α etc). COX$_2$ is also produced at much higher levels than COX$_1$. 
1. Celecoxib (celebrex) and rofecoxib (Vioxx) are equally effective as NSAIDs, although rofecoxib has been associated with hypertension
2. Peptic ulceration and inhibition of platelet aggregation are substantially reduced, although renal impairment can still result
3. COX-2 inhibitors can be given safely in cases of aspirin-sensitive asthma

**Leukotrienes**

Asthma is a disease of inflammatory airway obstruction leading to transient breathlessness, coughing, and wheeze. Contraction of circular smooth muscle, airway wall oedema, and increased mucus secretion are mediated by leukotrienes (‘slow-reacting substance of anaphylaxis’).

1. Leukotrienes are synthesised from arachidonic acid, especially by eosinophils (stimulated by allergens) in asthma
2. LTD₄/CysLT₁ receptor antagonists e.g. montelukast (singulair) only work to a certain extent and in mild cases, as leukotrienes are not the only mediator in asthma
3. Inhaled low dose corticosteroids are more effective as they work on all mediators and are administered locally (rather than a tablet in the case of LTD₄ antagonists)

Arachidonic acid catalysed by 5-lipoxygenase
→ 5-HPETE (5-hydroperoxyeicosatetrocroic acid → 5HETE)
→ LTA₄
→ LTB₄ (5,12 diHETE)
Glutathione-S-transferase → LTC₄ → LTD₄ → LTE₄

**Histamine and Drugs used to treat Peptic Ulcers**

Peptic ulcers are focal lesions affecting both the mucosa and submucosa of the gastric and duodenal areas. They may be asymptomatic, or can present with pain, bleeding or rarely perforation. They affect ~10% of the population and have been treated with a variety of agents in the past including rest, a bland diet, anticholinergics and surgery (vagotomy).

**Histamine** is synthesised from histidine mainly in mast cells and basophils, but also in histaminergic neurones and entero-chromaffin-like cells in the gastric mucosa. It is preformed, and stored in intracellular granules.

Gastrin, vagus nerve, ACh → ECL cells → histamine release

**H₂ receptors** can be found on parietal cells in the stomach, and stimulate acid secretion by increasing activity of the H⁺/K⁺ ATPase (proton pump). Antihistamines that target the H₂ receptor (cimetidine, ranitidine, famotidine) are useful in treatment of GI ulcers by decreasing acid secretion over 4-6 weeks (duodenal) or 8-12 weeks (gastric).

1. **Notes:**
   a. Cimetidine has a short half-life (2-3hrs) so was initially given 4 times daily – however, as it has a wide therapeutic index it was possible to reduce frequency to once daily by taking a larger dose (800mg) at night.
   b. Ranitidine – 300mg at night (note that potency is a poor indication of maximum efficacy)
   c. Efficacy – 80-90% healing, long-term maintenance therapy (half dose) useful to prevent recurrence
2. **Adverse effects:**
   a. H₂ receptor antagonists can → confusion in the elderly (receptors in brain)
   b. Cimetidine binds to androgen receptors and acts as an antagonist (→ gynaeacomastia, decreased libido with high doses in rare cases)
   c. Cimetidine also inhibits some P₄₅₀ enzymes involved in the metabolism of warfarin (anticoagulant), theophylline (bronchodilator), and phenytoin (anticonvulsant). Note that these all have a narrow therapeutic index
   d. H₂ receptor antagonists are cleared renally (80-90%)
3. **Other drugs for the treatment of peptic ulcer disease:**
   a. Pirenzipine – M₁ receptor antagonist, blocks Ach to reduce acid secretion
   b. Colloidal bismuth subcitrate (denol) – <2mths due to bismuth encephalopathy
c. Proton pump inhibitors – omeprazole (losec) is an irreversible H⁺/K⁺ ATPase inhibitor (two molecules bind to the enzyme and inactivate it)
   i. Activated by acid (prodrug) and inhibits the final common pathway irreversibly – so is effective for 24hr inhibition (peak 95% inhibition of acid secretion) and allows faster healing of gastric ulcers
   ii. Adverse effects – inhibition of metabolism (2C19) of phenytoin, diazepam and R-warfarin; headache, abdominal pain, diarrhoea
   iii. Pantoprazole is half as potent but has fewer (if any) interactions
   iv. PPIs are more effective in the treatment of GORD (once daily rather than 2-3 times a day if H₂ antagonists are used)

d. Helicobacter pylori is found in 95% of duodenal and 70% of gastric ulcers
   i. H. pylori eradication (<15% relapse after 5 years) can reduce the risk of ulcer recurrence from 50% to 1% in the first year
   ii. Triple therapy – 1 proton pump inhibitor (prevents acid degradation of antibiotics, some indirect effect on H. pylori) and 2 antibiotics (omeprazole, amoxycillin, metronidazole/erythromycin)

e. NSAIDs bad. COX 2 inhibitors good.

H₁ receptors are involved with allergy/hypersensitivity reactions, leading to vasodilation, oedema, pain and airway smooth muscle contraction. H₁ antagonists are effective in the treatment of asthma, allergic rhinitis caused by grass or dust, urticaria, and prevent rhinorrhoea, sneezing and itching (but not blockage).

1. Mast cells in the respiratory mucosa react with IgE cross-linked by grass pollen by degranulating and releasing histamine and leukotrienes
2. Recent antihistamines do not cross the blood-brain barrier, and hence are non-sedating. These include fexofenadine (telfast), loratidine (claratine) and cetirizine (zyrtec)
   a. The enzyme that metabolises terfenadine is inhibited by erythromycin and ketokanazole – this leads in some cases to QT prolongation
   b. Fexofenadine is a metabolite of terfenadine which does not share this effect
3. Intranasal steroids are still the most effective treatment for hayfever

Drugs and the ANS

The peripheral nervous system can be divided into the somatic nervous system (conscious control of skeletal muscle) and the autonomic nervous system (unconscious control of viscera). The ANS has two major divisions, parasympathetic and sympathetic.

1. All preganglionics use acetylcholine as a neurotransmitter
2. Sympathetic nervous system (thoracolumbar outflow) – postganglionics use NA
   a. Ganglia located paravertebral close to the spinal cord
   b. External stress – increased heart rate, blood pressure and blood glucose, bronchodilatation, diversion of blood to skeletal muscle
3. Parasympathetic nervous system (cranosacral outflow) – postganglionics use ACh
   a. Ganglia lie close to the relevant organ (so short postganglionic fibres)
   b. Conservation of energy – decreased heart rate and blood pressure, increased GI function and bladder function
4. Adrenal medulla – similar to a SNS ganglion but uses adrenaline

Acetylcholine receptors:
1. Nicotinic – neurotransmission, skeletal neuromuscular junction, Na⁺/Ca⁺² channels
2. Muscarinic – parasympathetic postganglionic
   a. Receptor subtypes:
      1. M₁ – ganglia
      2. M₂ – myocardium
      3. M₃ – postsynaptic smooth muscle (bronchi, gut)
   b. M₁,₃,₅ are linked to G₃ which activates phospholipase C, while M₂,₄ is linked to Gᵢ which inactivates adenylate cyclase and leads to K⁺ channel activation
3. Drugs:
   a. Muscarinic agonists
      1. Only used in the treatment of glaucoma (pilocarpine increases outflow of aqueous humour via trabeculae)
530.305 – Regulation of Visceral Function

2. May mediate increased bladder emptying though not used clinically for this
3. Side effects – salivation, visual accommodation, abdominal cramps, sweating, hypotension, may aggravate asthma

b. Muscarinic antagonists
1. Atropine is a non-selective muscarinic antagonist used in the treatment of transient bradycardia (e.g. myocardial infarct)
2. Pirenzepine is a selective M1 antagonist used to treat peptic ulcers

4. Clinical aspects:
   a. Asthma
1. Ipratropium bromide (Atrovent) is an inhaled bronchodilator – it is a 4° ammonium compound so it is not absorbed (no systemic effects)
2. Salbutamol is a β agonist – fast onset, higher peak effect, shorter duration
b. Parkinson’s disease
1. Muscarinic antagonists dampen excessive cholinergic activity
2. Atropine is not useful as it has no CNS effects
3. Benztropine (Cogentin) helps to decrease rigidity, but has no effect on bradykinesia and is not as effective as L-dopa.
4. May also be co-prescribed in schizophrenia to decrease phenothiazine-related side effects

c. Travel sickness – hyoscine (scopolamine) taken orally as a transdermal patch (note drug reservoir, so removing the patch may not remove the drug)
d. Hyperactive bladder – oxybutynin (Ditropan) has antimuscarinic and antispasmodic activities
   e. Side effects include dry mouth, blurred vision, constipation, urinary retention and confusion/delirium. Many of the side effects associated with tricyclic antidepressants are related to their anticholinergic effects.

Adrenergic receptors – 2 α and 3 β receptors, and these are further divided into subgroups – adrenaline works better on α than β receptors, which are more sensitive to isoprenaline. IV or intramuscular adrenaline can be used in the treatment of anaphylaxis (excess → VF).

1. α → vasoconstriction
   a. α1, α2 – found postsynaptically near nerve endings (e.g. blood vessels)
   b. α2 – also occur presynaptically to provide negative neuromodulation
   c. Noradrenaline acts on α receptors to increase total peripheral resistance – this may be useful in cases of resistant shock to increase blood pressure

2. β receptors mediate a number of effects:
   a. Increased heart rate, increased myocyte contractility, increased BP
   b. Post-capillary venules – decreased permeability, decreased oedema
   c. Bronchodilator effects

3. Drugs:
   a. β agonists
      i. Bronchodilators, acting on β2 receptors on airway smooth muscle
         1. Adrenaline α > β1 = β2
         2. Isoprenaline β1 = β2
         3. Salbutamol (Ventolin) β2 >> β1
      ii. β2 agonists have a longer mode of action (4-6 hrs) as they are not broken down by COMT
      iii. Inhaled agents have faster onset, fewer systemic effects and can be used in lower doses
      iv. Side effects include tachycardia and tremor

   b. β blockers
      i. Used to treat angina by reducing myocardial contractility (i.e. O2 demand) and decreasing heart rate (β2-mediated effects)
      ii. Also used in the treatment of hypertension, mechanism unclear - possibly mediated by vasodilatation and renin secretion from JGA
      iii. Lipid solubility affects how the drugs are metabolised – these may be non-specific or β1-specific, and full or partial antagonists
         1. Propanolol is non-selective and lipid soluble
            a. Cleared by liver, and has high first-pass metabolism
            b. Metabolised by c450 system → high dose variability
530.305 – Regulation of Visceral Function

2. Atenolol is relatively $\beta_1$ selective and water soluble
   a. Cleared by the kidney
   b. Long half-life, so can be given once daily
3. Metoprolol
4. Celiprolol – $\beta_1$-selective, $\beta_2$ agonist at subtherapeutic doses
   a. May be useful with people with cold peripheries ($\beta_2$ blockade $\rightarrow$ decreased peripheral circulation)
   iv. Note that full beta blockade $\rightarrow$ pulse of around 60/min (helps determine whether further increase in dose will have effect)
   v. Contraindications:
      1. In diabetes, hypoglycaemia stimulates adrenaline, which acts on $\beta_2$ receptors on liver cells to $\rightarrow$ glucose ($\beta_1$ is fine)
      2. NEVER use beta blockers in patients with asthma
      3. Peripheral vascular disease might be aggravated in some patients – “suck on it and see”

* Drugs and Blood Vessels

**Calcium channel blockers**

1. **Categories**
   a. Phenylalkylamine group – verapamil
   b. Benzothiazepine group – diltiazem
   c. Dihydropyridine group – nifedipine, amiodipine, felodipine
2. **Mechanism of action**
   a. Block the inner part of voltage-dependent Ca$^{2+}$ channels (L-type) in vascular smooth muscle, decreasing Ca$^{2+}$ entry and interfering with muscle contraction
      i. Vascular – decreased arteriolar resistance $\rightarrow$ decreased BP
      ii. Cardiac – decreased SA nodal depolarisation $\rightarrow$ decreased HR, AV nodal conduction and force of contraction $\rightarrow$ decreased CO, BP
   b. No action on skeletal muscle, and effects on vascular smooth muscle occur at lower concentrations than for other smooth muscle
   c. Dihydropyridines are relatively selective for vascular smooth muscle $\rightarrow$ no nodal effect, minimal negative inotropic effect $\rightarrow$ hence can be used in heart failure (others are bad as they lead to decreased cardiac output)
3. **Indications**
   a. Hypertension – 3rd line therapy after thiazides and $\beta$-blockers/ACE inhibitors
   b. Angina – arteriolar vasodilator, although can lead to reflex tachycardia if short-acting (especially dihydropyridines)
   c. Atrial fibrillation/flutter – verapamil/diltiazem (adenosine is more common)
4. **Adverse effects**
   a. Flushing, dizziness, headache, ankle swelling – greater for dihydropyridines
   b. Worse with unsteady levels – better to use slow-release (amiodipine t$\frac{1}{2}$ long)
   c. Constipation – verapamil has effects on GI smooth muscle
   d. Cytochrome P$_{450}$ interactions – calcium channel blockers are metabolised by and inhibit 3A4 (note grapefruit juice, cyclosporin toxicity)
   e. Caution when using concurrent $\beta$-blockers due to slowed heart rate

**$\alpha$-adrenergic antagonists** (doxazosin)

1. **Mechanism** – dilatation of resistance vessels by interfering with postsynaptic $\alpha_1$ receptors (normally noradrenaline $\rightarrow$ vasoconstriction)
   a. Decreases blood pressure
   b. Relaxes prostate smooth muscle $\rightarrow$ decreased symptoms of prostatism
2. **Adverse effects**
   a. Early drugs blocked both $\alpha_1$ and $\alpha_2$ receptors – $\alpha_2$ are found presynaptically and inhibit release of NA. No feedback inhibition $\rightarrow$ vasoconstriction
   b. Postural hypotension
      i. Prazosin – short t$\frac{1}{2}$, postural hypotension
      ii. Doxazosin – longer t$\frac{1}{2}$, lower peak/trough ration (less hypotension)
      iii. First dose effect – postural hypotension greatest with first dose
3. **Indication** – last line (4th or 5th) treatment for hypertension
530.305 – Regulation of Visceral Function

a. Allhat study – greater incidence of heart failure in patients on doxazosin as opposed to other antihypertensives (suggests α-blockers are not protective)
b. Benign prostatic hyperplasia is the only case where α-blockers are first line

• Nitric Oxide

Early experiments showed that acetylcholine elicited the release of an unknown compound in blood vessels that led to relaxation. This was tentatively named endothelium-derived relaxing factor (EDRF), later identified as nitric oxide – note that NO has a short half-life, so only has a local effect.

1. Releasers of EDRF include ACh, histamine, bradykinin and shear stress
2. Endothelium-independent factors include isoprenaline and prostacyclin

Glyceryl trinitrate is used to relieve angina

1. Physiology:
   a. Arterial dilatation → decreased preload → decreased wall tension → decreased O₂ and blood demand of the heart
   b. Venous dilatation → increased blood supply to the heart
   c. Side effects include dizziness and headache due to vasodilation
2. Absorption:
   a. Sublingual tablet/spray absorbed in buccal mucosa → works quickly, avoids 1st pass metabolism in the liver
   b. GTN patches used prophylactically – slow release over 24hrs
   c. Tolerance to patches after a few days – wear 16hrs/day, remove at night
3. Mechanism:
   a. Combines with cysteine in vascular smooth muscle → 5-nitrosocysteine → NO → increases levels of cGMP (via soluble guanylate cyclase in cytoplasm)
      i. cGMP → cGMP-dependent protein kinase, which phosphorylates protein
      ii. Lowering of Ca²⁺ levels → smooth muscle relaxation
   b. IV n-acetylcysteine can reverse tolerance with no withdrawal (increases number of cysteine groups available to GTN)

Isosorbide mononitrate can also be used to relieve angina, but can be given orally as it has a low first-pass metabolism. Comes as a slow-release preparation (16hrs) and is generally cheaper than the transdermal GTN patch.

Synthesis of NO

1. L-arginine → L-citrullin + NO (catalysed by NO synthetase)
2. Enzyme inhibitors (e.g. L-NMMA) bind to NO synthetase and inactivates it
   a. Infusing L-NMMA to forearm artery lowers blood flow → must be basal release of NO
   b. Note implications for regulation of blood pressure
3. Decreased cholesterol → decreased NO formation
4. 3 forms of NO synthetase – endothelial, neuronal, macrophage
   a. Neuronal NO synthetase
      i. CNS – e.g. glutamate → NO formation (long-term)
      ii. PNS → ANS → PNS, SNS, NANC (non-adrenergic, non-cholinergic)
      iii. Airways – ACh → smooth muscle contraction, NO → relaxation
      iv. Erection – NO involved via vasodilation
         1. Sildenafil is a selective inhibitor of cGMP-specific phosphodiesterase 5 (normally degrades NO), increasing NO levels → dizziness, faint
         2. ~4000x more selective for PDE5 than PDE3 (cardiac contractility)
         3. ~10x more selective for PDE5 than PDE6 in retina (may explain colour vision side-effects)
   b. Inducible (macrophage) NO synthetase
      i. Stimulated by TNF-α, IL-1; inhibited by corticosteroids
      ii. Makes larger quantities of NO for longer periods than other enzymes (mediates cytotoxic effects)
      iii. Inflammation, septic shock – contributes by acting as a vasodilator

• Corticosteroids
Corticosteroids activate or inhibit DNA transcription, acting on over 100 genes. They can be categorised into glucocorticoids (action on carbohydrate metabolism – cortisol) and mineralocorticoids (action on salt and water – aldosterone).

1. Mechanism
   a. Bind to receptors in the cytoplasm. These have DNA, glucocorticoid and transcription factor binding sites
   b. Glucocorticoid-receptor (G-R) complex dimerises, and this enters the nucleus to bind DNA at glucocorticoid response elements
   c. Inhibition may be by G-R binding transcription factor in the cytoplasm (e.g. NF_{κB}, involved in transcription of genes for inflammatory mediators)

2. Genes activated:
   a. β\textsubscript{2} receptors – helps β agonists to work for asthma therapy
   b. Lipocortin – inhibits action of phospholipase A\textsubscript{2} → decreased arachidonic acid → decreased prostaglandins/leukotrienes (anti-inflammatory effects)
   c. Surfactant – prevents respiratory distress syndrome in premature neonates
   d. Glucose-6-phosphatase

3. Genes inhibited
   a. TNF-α, COX-2, inducible nitric oxide synthetase (iNOS)
   b. IL-1 – ICAM (intracellular adhesion molecule), cell adhesion
   c. IL-3 – mast cell growth factor
   d. IL-4 – IgE production
   e. IL-5 – eosinophil growth factor

Synthetic glucocorticoids:

1. Types: inactive drugs → active drugs by metabolism in the liver
   a. Cortisone → cortisol (hydrocortisone)
   b. Prednisone → prednisolone (4x cortisol)
      i. Metabolised more slowly (double bond), so longer half-life
      ii. Less mineralocorticoid activity
   c. Dexamethasone (25x cortisol)
      i. Metabolised more slowly (fluorinated), so longer half-life
      ii. No mineralocorticoid activity

2. Adverse effects – most are only problems with long-term use
   a. Redistribution of body fat → moon face, buffalo hump, truncal obesity
   b. CHO metabolism → increased protein breakdown and gluconeogenesis
      i. Muscle wasting → weakness (proximal myopathy)
      ii. Skin thinning → easy bruising
      iii. Osteoporosis (increased reabsorption, decreased gut uptake) → #
      iv. Glucose intolerance → type 2 diabetes mellitus
   c. Hypertension – mineralocorticoid and glucocorticoid effects, possibly due to increased sensitivity of vascular smooth muscle to NO
   d. CNS – mood, rarely psychosis
   e. Cataracts, growth inhibition in children, immunosuppression (TB reactivation)
   f. Adrenal cortex atrophy – sudden withdrawal may → Addisonian crisis

3. Indications – mostly short-term, as this avoids side-effects
   a. Arthritis – intra-articular injection (tramcinolone)
   b. Renal transplantation – immunosuppression
   c. Eczema – can thin skin, so weak topicals used (e.g. 1% hydrocortisone)
   d. Allergic rhinitis, ocular disease (iritis)
   e. Asthma
      i. Inhaled route – 80% swallowed and can mediate topical side-effects
      ii. Newer drugs have a high first-pass metabolism in the liver and avoid systemic side effects. Note that low doses avoid systemic effects:
         1. Boclemasthones (Becotide) 100-800mcg/day – 80%
         2. Budesonide (Pulmicort) 100-800mcg/day – 90%
         3. Fluticasone (Flixotide) 50-400mcg/day – 99%
      iii. Topical side-effects include hoarseness (direct effect), candidiasis (due to local immunosuppression)
         1. Spacers can be used to get large particles out
530.305 – Regulation of Visceral Function

**Drugs and Blood Clotting**

**Anti-platelet agents** (e.g. heparin) – more useful for arterial/white clots
1. Heparin is an endogenous agent (glycosamine glycan – long polysaccharide chain) released from mast cells, prepared from porcine intestinal mucosa and bovine lung.
   a. Unfractionated – variable-length polysaccharide
   b. Low molecular weight heparin
2. Antithrombin is an inhibitor of coagulation by binding and irreversibly inactivating thrombin (factor IIa) and factor Xa. Heparin accelerates this by 1000 times.
3. **Administration**
   a. Too big to be absorbed orally, so must be given subcutaneously or via IV – has a rapid onset and is not absorbed across the placenta
   b. LMWH has a more predictable bioavailability and effect so can be given subcutaneously, while unfractionated heparin must be given intravenously
      i. LMWH binds Xa more than thrombin so doesn’t affect APTT as much
      ii. Enoxaprin – 1mg/kg subcutaneously twice a day
4. **Indications**
   a. Surgery – IV heparin lasts for 3 hours (LMWH orthopaedic, UH abdominal)
   b. DVT/PTE – LMWH can be given in the community subcutaneously, while UH must be given IV in hospital (heparin 5 days, then warfarin 3-6 months)
   c. Unstable angina – LMWH 2-3 days, aspirin (better than just aspirin)
5. **Adverse effects**
   a. Bleeding, stroke, GI bleeds
   b. Thrombocytopaenia (reversible) in 1-5% of those treated longer than a week
   c. Osteoporosis – long term full dose (weeks → months)

**Anticoagulants** (e.g. warfarin) – more effective in the venous system on red clots
1. Warfarin affects vitamin K dependent factors (II, VII, IX, X) that are synthesised in the liver – it blocks carboxylation of glutamate residues required for activation
2. Orally active (long-term treatment), slow onset of action (existing clotting factors not affected)
   a. Monitored using INR – therapeutic range 2.0-4.0, blood test weekly
3. **Drug interactions**
   a. Warfarin is metabolised by cytochrome P450 (2C9) → metabolism → decreased INR
      1. Phenytoin, carbamazepine, rifampicin, phenobarbitone
   b. Inhibitors decrease warfarin metabolism → increased INR
      1. R isomer inhibitors – cimetidine, omeprazole
      2. S isomer inhibitors – metronidazole, co-trimoxazole
      3. Both inhibitors – amiodarone
4. **Adverse effects**
   a. Bleeding – can give fresh frozen plasma or vitamin K to reverse
   b. Teratogenic – don’t give in pregnancy
   c. Antibiotics → change in flora → vitamin K effects → unpredictable effects
   d. Cephalosporins may alter carboxylation of factors → unpredictable effects

**Thrombolytics** (fibrinolytics) can be given IV to patient with myocardial infarcts to dissolve thrombus and reperfuse the infarcted area.
1. **Streptokinase**
   a. Can lead to antibody response, so not as effective second and third time
   b. Allergic response → fever, decreased blood pressure
2. **tPA (tissue plasminogen activator)**
   a. Only active when bound to fibrin, so in theory should be more specific, but it isn’t.

**Renin-Angiotensin-Aldosterone System – ACE Inhibitors**

There are two RAA systems in the body, circulating and tissue (including blood vessel walls – autocrine system).
1. **Circulating system**
   a. Renin granules in the JGA are released to the circulation on SNS activation, decreased arteriolar pressure and decreased Na⁺ at the macula densa
b. Renin converts angiotensinogen (liver) to angiotensin I, which is subsequently converted to angiotensin II by ACE in the lung
c. Angiotensin II is a potent vasoconstrictor, acting on AT1 and AT2 receptors
   i. AT1 on smooth muscle mediates vasoconstriction
      1. Afferent and efferent arterioles constrict (primarily efferent)
      2. Decreased RBF, increased FF → no change in filtered load
   ii. Stimulates aldosterone secretion → salt and water retention
      1. Potentiates SNS:
         a. Presynaptically – increased NA release
         b. Postsynaptically – potentiates NA effect
         c. Centrally – increases SNS outflow
   iii. Stimulates ADH release, thirst
d. Renal artery stenosis – angiotensin II maintains perfusion of glomerulus primarily by constricting the efferent arteriole

2. Tissue system - brain, kidney, adrenal, blood vessels, heart
   a. Locally formed angiotensin II
   b. Stretch of blood vessel walls → constriction of smooth muscle, hypertrophy and increased RAAS → positive feedback on hypertension

ACE inhibitors
1. General aspects
   a. Brazilian pit viper venom inhibits bradykinin breakdown by inhibiting kininase II, which was subsequently recognised as angiotensin converting enzyme
   b. The first ACE inhibitor was captopril (active drug), while enalapril is a prodrug (converted in the liver to enalaprilat)
   c. Differences in the drugs are related to pharmacokinetics
      i. Captopril – 2-3 times a day
      ii. Quinapril – 2 times a day
      iii. Enalapril – 1-2 times a day
      iv. Cilazapril – once daily
2. Indications
   a. Hypertension
      i. Works the same regardless of plasma renin levels (hence more likely related tissue RAAS rather than vessel RAAS)
      ii. Inhibits kininase II → increased bradykinin → increased NO, PGI2
      iii. Other treatments – thiazides, β-blockers, Ca2+ blockers, α-blockers
      iv. Thiazides are equally effective and cheap – a combination of thiazide and ACE inhibitor is even better
   b. Heart failure
      i. Decreased cardiac output → tiredness, activation of compensatory systems (SNS, RAAS) → fluid retention
      ii. RAAS → vasoconstriction → increased afterload → decreased CO
      iii. ACE inhibitors decrease angiotensin II and aldosterone, leading to increased CO and diuresis
      iv. Combination of loop diuretic (e.g. frusemide) and ACE inhibitors is effective at decreasing mortality
   c. Diabetic nephropathy – slows decline in renal function
3. Adverse effects
   a. Cough in 10% - due to increased bradykinin (stimulates cough receptors)
   b. Dizziness if dehydrated/volume depleted
   c. Angioedema in 0.1% - swelling of tongue, face, lips, throat due to bradykinin
   d. Decreased aldosterone → K+ retention, but diuresis → increased K+ loss
   e. Note renal artery stenosis:
      i. Bilateral may → renal failure
      ii. Loss of maintenance of constriction of afferent and efferent arterioles → decreased GF pressure
      iii. Hence check renal function via serum creatinine after a few days
AT1 antagonists (e.g. candesartan) work as well as ACE inhibitors, and have fewer adverse effects (no cough or angioedema) as there is no increase in bradykinin. However, these are generally expensive and currently there are restrictions on their use in NZ.

Overview – Drugs and Blood Pressure

A 55-year-old man visits his GP for a routine check-up. His blood pressure is noted to be 160/105. He is a smoker and fasting serum cholesterol is elevated at 6.5mmol/L (<5.5mol/L). His only medication is a salbutamol inhaler for asthma. Over the next three months his blood pressure is noted to be persistently elevated. A decision is made to start him on treatment for hypertension.

1. **What are the different classes of antihypertensive agents?**
   a. Thiazide diuretics, β/α blockers, ACE inhibitors, Ca\(^{2+}\) channel blockers
2. **Are any of these antihypertensive agents contraindicated in this patient?**
   a. β blockers, as none of these are specific enough (patient has asthma)
3. **Which one will you choose?**
   a. Adverse effects:
      i. Thiazide diuretics – hypokalaemia, hyperglycaemia, hyperuricaemia
      ii. β blockers – asthma, cough, angioedema, renal failure
      iii. Ca\(^{2+}\) channel blockers – headache, flushing, oedema
   b. Efficacy – thiazide diuretics, β blockers, ACE inhibitors and Ca\(^{2+}\) channel blockers (some issues with angina) are generally equally effective
   c. Factoring in cost, thiazide diuretics and ACE inhibitors are preferred

You start him on treatment with bendrofluazide 2.5mg/d. His blood pressure falls to 150/100. You decide his blood pressure is still not adequately controlled and that his medication needs to be changed.

1. **What do you do?**
   a. Make sure the patient is taking his medication – compliance is ~50%
   b. Could double dosage, but there are more adverse effects and few benefits
   c. Addition of an ACE inhibitor as it is effects, has effects on vascular endpoints and additive effects when thiazides and ACE inhibitors used in conjunction

You add in treatment with cilazapril in a dose of 2.5mg/day and his blood pressure drops to 130/84 (no point going any lower). He develops a persistent dry cough.

1. **What is the cause of this?**
   a. Two possibilities – ACE inhibitor, asthma
2. **What do you do about this problem?**
   a. Could stop the ACE inhibitor as the blood pressure is well controlled
   b. AT2 inhibitor

He remains on bendrofluazide 2.5mg/day but his cilazapril is changed to candesartan 4mg/day. His blood pressure remains well controlled but he develops central chest pain that comes on if he walks up stairs or if he runs.

1. **What is the cause of his chest pain?**
   a. Probably angina
2. **What additional treatment should you consider to relieve his pain?**
   a. Isosorbide mononitrate
   b. Aspirin
   c. Lipid-lowering drugs (statins/fibrates)
   d. Ca\(^{2+}\) channel blocker

He is started on aspirin (150mg/day), simvistatin (20mg/day) and diltiazem 180mg/day.

1. **What adverse effects may develop from using diltiazem?**
   a. Flushing, dizziness, headache, ankle swelling
   b. Constipation, cytochrome P\(_{450}\) interactions
   c. Bradycardia (caution when using concurrent β-blockers

One year later he develops prolonged chest pain. His ECG shows ST segment elevation.

1. **What should you do?**
   a. ST segment elevation and the history suggest transmural acute ischaemia
b. Start him on a β-blocker (e.g. propanolol) – if symptoms continue, consider surgery

**Drugs Influencing Cardiac Rate and Rhythm**

**Arrhythmias:**
1. Rate – bradycardia, tachycardia
2. Rhythm – ectopic beats, fibrillation
3. Site – nodal tachycardia, ventricular fibrillation

Action potential and channel blockers – there are three types of ion channels involved in the propagation of a cardiac cell action potential (Na⁺, Ca²⁺ and K⁺)

1. There are two types of calcium channels in the heart:
   a. Voltage-gated Ca²⁺ channels – SA node, AV node pacemaker cells
      i. K⁺ pacemaker current slowly depolarises
      ii. Activation of voltage-dependent Ca²⁺ channels
      iii. Triggering of Ca²⁺ influx
      iv. K⁺ repolarisation current
   b. Receptor-gated Ca²⁺ channels
      i. NAÆβ₁ receptors in the heart
      ii. Opening of receptor-operated Ca²⁺ channels
      iii. Triggering of Ca²⁺ influx
      iv. Increased heart rate and force
2. Calcium channel blockers (verapamil, diltiazem, propanolol)
   a. Target voltage-gated (verapamil – direct) or receptor-gated (propanolol – indirect)
      i. Slows pacemaker, decreases force
      ii. Slows atrial and AV nodal conduction
   b. Indications – atrial tachycardia, nodal tachycardia, atrial fibrillation
3. Sodium channel blockers (lignocaine, quinidine, disopyramide, flecainide)
   a. Can target the active channels (quinidine) or all channels (lignocaine)
      i. Decreases the rate of depolarisation
      ii. Slowed Purkinje and ventricular conduction
   b. Indications – ventricular ectopic beats, ventricular tachycardia, ventricular fibrillation
4. Potassium channel blockers (amiodarone – also Na⁺, sotalol)
   a. Actions:
      i. Decreases rate of repolarisation
      ii. Slowed Purkinje and ventricular repolarisation
   b. Indications – atrial tachycardia, atrial fibrillation, ventricular ectopic beats, ventricular tachycardia, ventricular fibrillation

Other important aspects:
1. Life-saving anti-arrhythmics – β-blockers after MI can greatly increase survival (1 death postponed per 150 patients treated)
2. Pro-arrhythmic effects:
   a. K⁺ (possibly Na⁺) channel blockers → long QT interval
   b. Torsade de Pointes
   c. Cardiac Arrhythmia Suppression Trial – mortality increased after ventricular ectopic beats were suppressed following MI
3. Digoxin-quinidine interaction
   a. Quinidine syncope – fainting and sudden death
   b. Increased digoxin concentrations (x2) – decreased renal and non-renal digoxin clearance by quinidine (50%)
   c. Long QT interval

**Drugs that Modify Cardiac Contractility**

**Positive inotropes:**
1. Cardiac glycosides (e.g. Digoxin, from Digitalis purpurea)
   a. Mechanical action – note hydrophilic sugar, lipophilic steroid subunits
      i. Inhibits Na⁺/K⁺ ATPase
         1. Decreased Na⁺ out of cell → increased intracellular Na⁺
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2. Low Na\(^+\)/Ca\(^{2+}\) exchange → increased intracellular Ca\(^{2+}\)
3. Increased contractility

b. Electrical action
   i. Slows AP duration
      1. Increased intracellular Ca\(^{2+}\)
      2. Increased K\(^+\) conductance
      3. Increased fibrillation rate → more AV block
   ii. Depolarisation
      1. Increased intracellular Na\(^+\)
      2. Decreased intracellular K\(^+\)
      3. Slower conduction → more AV block

c. Parasympathetic action
   i. Increased vagal activity
      1. Slowed heart rate
      2. Decreased AV node conduction
   ii. Note – atropine blocks muscarinic receptors in the heart

d. Indications:
   i. Heart failure, 3rd line treatment (ACE inhibitors, diuretics)
   ii. Anti-arrhythmic – atrial fibrillation, control of ventricular rate

e. Adverse effects:
   i. Gastrointestinal – anorexia, nausea
   ii. Cardiac – arrhythmias
   iii. CNS – yellow/green colour disturbance

2. Catecholamines
   a. Noradrenaline acts within minutes
   b. Adrenaline acts within seconds
   c. Dobutamine – β\(_1\) agonist given IV for acute heart failure only

3. Bipyridines
   a. Phosphodiesterase inhibition → decreased clearance of cAMP
   b. Amrinone, milrinone (increased mortality)

Negative inotropes:
1. β blockers
   a. Propanolol – non-specific liver metabolism
   b. Atenolol – 60% renal elimination (so lower doses used in the elderly)
   c. Used to treat heart failure (may be hyperactive) and may prevent arrhythmia

2. Calcium channel blockers – verapamil > diltiazem >> nifedipine
3. Combination therapy – useful in angina, poor for heart failure

• Drugs and the Kidney

Loop diuretics (e.g. frusemide, bumetanide):
1. Actions
   a. Inhibit salt reabsorption in ascending loop of Henle (Na-K-2Cl co-transporter)
   b. Potent – high capacity for Na\(^+\) reabsorption in the loop of Henle, high diuretic concentration in tubules, increases % not reabsorbed to 25% (normally 1%)
   c. Increased distal tubule Na\(^+\) → increased K\(^+\), H\(^+\) exchange → hypokalaemia
   d. Increased Ca\(^{2+}\) and Mg\(^{2+}\) excretion
   e. Venodilating effects (useful in heart failure)

2. Properties
   a. Given orally (poor) or via IV (full bioavailability – potent and rapid diuresis)
      i. Effective at higher doses in patients with impaired renal function
   b. Secreted to the proximal convoluted tubule (protein-bound)
   c. Onset in 30min (IV), 1hr (oral) and lasts for 4hrs – can be given as a continuous infusion for patients with resistant heart failure

3. Indications
   a. Pulmonary oedema
   b. Peripheral oedema (e.g. cirrhosis, nephrotic syndrome)
   c. Hypercalcaemia (weak effects)
4. Side-effects
   a. Dehydration (and renal hypoperfusion), hypokalaemia (use K supplements), hypotension, deafness at high doses (may be irreversible)
   b. Nausea, allergy, metabolic alkalosis
   c. Hyperglycaemia (in theory), hyperuricaemia

Thiazide diuretics (e.g. bendrofluazide, indapamide, cyclopenthiazide)
1. Actions
   a. Inhibit salt reabsorption from the distal tubule (Na-Cl co-transporter)
   b. Increased Na⁺ in distal tubule → increased K⁺, H⁺ exchange → hypokalaemia
2. Properties
   a. Given orally, weak diuretic
      i. Not effective in patients with impaired renal function
      ii. Flat dose-response curve (increased dose doesn’t increase effects after plateau – use low doses without titrating to avoid side-effects)
   b. Secreted into proximal tubule (competes with uric acid)
   c. Takes 4 hours to work and lasts 10 hours
3. Indications
   a. Hypertension (→ mild diuresis and vasodilation)
   b. Congestive heart failure (used with frusemide)
4. Side-effects
   a. Weakness, impotence, skin rash, hypokalaemia, hyponatraemia
   b. Hyperuricaemia (→ gout), hyperglycaemia, hyperlipidaemia
   c. Allergy (rarely), metabolic alkalosis, hypomagnesaemia
5. Adverse drug reactions
   a. Thiazide-induced hypokalaemia → digoxin toxicity → arrhythmias

Potassium-sparing diuretics (e.g. spironolactone, amiloride, triamterine)
1. Actions
   a. Spironolactone – blocks binding of aldosterone in distal tubule
   b. Amiloride, triamterine – block Na⁺ channels in the distal tubule
2. Properties – given orally, weak diuretic
   a. Spironolactone – well absorbed orally, lasts 16 hours
   b. Triamterine – well absorbed orally, onset 2 hours, lasts 12 hours
   c. Amiloride – poorly absorbed orally, onset 4 hours, lasts 24 hours
3. Indications
   a. Spironolactone – ascites in liver disease, CHF, Conn’s syndrome
   b. Amiloride/triamterine – hypertension (used with thiazides)
4. Side-effects
   a. Spironolactone – hyperkalaemia (beware ACE inhibitors), gynaecomastia, GI upset, rashes, lethargy, impotence
   b. Amiloride/triamterine – hyperkalaemia, GI upset, rashes, lethargy, impotence
5. Adverse drug reactions
   a. With ACE inhibitors may induce hyperkalaemia
   b. Spironolactone can lead to digoxin toxicity
Body Fluids: Volumes and Composition

For a male cadaver weighing 65kg:

<table>
<thead>
<tr>
<th>Mass (kg)</th>
<th>% body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>11</td>
</tr>
<tr>
<td>Fat</td>
<td>9</td>
</tr>
<tr>
<td>CHO</td>
<td>1</td>
</tr>
<tr>
<td>Minerals</td>
<td>4</td>
</tr>
<tr>
<td>Water</td>
<td>40</td>
</tr>
</tbody>
</table>

Measurement in the living – water is the most abundant component at 45-75% (by weight)

1. Compartments:
   a. Intracellular fluid – 55% of total body water (TBW)
   b. Extracellular fluid – 45% of TBW
      i. Plasma 7.5%
      ii. Interstitial fluid 20%
      iii. Bone and dense connective tissue 15%
      iv. Other 2.5% (GI, UG, biliary, intraocular, CSF, serosal spaces)

2. Clinical approximation (note that these depend on a number of factors)
   a. ECF = 1/3 TBW (20% by weight)
   b. ICF = 2/3 TBW (40% by weight)
   c. TBW = 60% by weight

3. Principles of indicator dilution:
   a. Volume = (Mass administered - mass eliminated) / Concentration in compartment
   b. This formula can be used to estimate TBW, ECF and plasma volume
      i. Infusion/equilibrium – steady infusion, equilibrium plasma concentration
         1. Volume of distribution = amount excreted / equilibrium constant
      ii. Kinetic – known volume injected, zero-time equilibrium extrapolated back
         1. Volume of distribution = amount injected / zero-time equilibrium
   c. Properties of an ideal indicator:
      i. Non-toxic without effects on solute and fluid distribution
      ii. Uniform distribution, confinement to measured compartment
      iii. Losses and metabolism amenable to estimation
      iv. Plasma concentration representative and easily measured

4. Units for measuring solute concentrations:
   a. SI units – molL\(^{-1}\) (mmolL\(^{-1}\))
   b. Electrical equivalents – eqL\(^{-1}\) (meqL\(^{-1}\))
      i. Add up the valences (1 mmol Na\(^+\) = 1meq, 1 mmol CaCl\(_2\) = 4meq)
   c. Osmoles – osmolL\(^{-1}\) or osmol/kg H\(_2\)O
      i. Add 1° particles (1mmol Na\(^+\) = 1mosmol, 1mmol CaCl\(_2\) = 3mosmol)
      ii. Osmolarity is preferable to osmolality as it is independent of temperature and volume of other solutes in solution

<table>
<thead>
<tr>
<th></th>
<th>Male % Body wt</th>
<th>Male Volume (L)</th>
<th>Female % Body wt</th>
<th>Female Volume (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>4.5</td>
<td>3</td>
<td>3.75</td>
<td>2.25</td>
</tr>
<tr>
<td>Interstitial/lymph</td>
<td>12</td>
<td>8.5</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Dense c.t./cartilage</td>
<td>4.5</td>
<td>3</td>
<td>3.75</td>
<td>2.25</td>
</tr>
<tr>
<td>Inaccessible bone</td>
<td>4.5</td>
<td>3</td>
<td>3.75</td>
<td>2.25</td>
</tr>
<tr>
<td>Transcellular</td>
<td>1.5</td>
<td>1</td>
<td>1.25</td>
<td>0.75</td>
</tr>
<tr>
<td>TOTAL ECF</td>
<td>27</td>
<td>19</td>
<td>22.5</td>
<td>13.5</td>
</tr>
<tr>
<td>TOTAL ICF</td>
<td>33</td>
<td>23</td>
<td>27.5</td>
<td>16.5</td>
</tr>
<tr>
<td>TBW</td>
<td>60</td>
<td>42</td>
<td>50</td>
<td>30</td>
</tr>
</tbody>
</table>
Total body water can be measured using indicators that distribute throughout all body fluids (e.g. $^{2}$H$_{2}$O, $^{3}$H$_{2}$O, antipyrine). A plasma sample can then be used to estimate TBW.

1. The water component of tissues depends mainly on the amount of adipose tissue
2. Generally body water decreases with age (increasing amounts of adipose tissue)
3. Females tend to have a lower amount of TBW (~10% less)
4. Younger children have a greater daily water turnover, hence have a greater TBW (62-80%)
   a. At birth the ICF compartment is smaller than the ECF compartment, but by 12 months the situation reverses and proportions are similar to that in the adult

Extracellular fluid includes plasma, interstitial fluid/lymph, connective tissue and bone

1. Measurement of ECF in general (plasma sample used to estimate)
   a. Indicator must cross the capillary endothelium but be excluded from cells
   b. Radioisotopes of ions can be used, though these enter cells
   c. Non-metabolisable saccharides (inulin, mannitol, raffinose) do not penetrate bone and dense connective tissue
2. Plasma and interstitial fluid (‘functional ECF volume’)
   a. Na$^{+}$ is the predominant cation, Cl$^{-}$ and HCO$_{3}^{-}$ are the predominant anions
   b. Higher protein (act as anions by buffering H$^{+}$) levels in plasma is due to limited permeability of the endothelium to larger solutes
   c. When correction is made for plasma filled by protein and lipid, concentrations of small non-electrolytes are identical in plasma and interstitial fluid
   d. Measurement of plasma:
      i. Radio-iodinated albumin or Evan’s blue dye used – note that there is a small amount of protein leakage (even more in burn patients)
      ii. Labelled erythrocytes allow the blood volume to be determined
      iii. Plasma volume = blood volume x (1 – haematocrit)
3. Electrolytes differ due to the Gibbs-Donnan effect (non-mobile anionic protein in plasma)
   a. The equilibrium between plasma and interstitial fluid is characterised by:
      i. Small diffusible ions do not have equal concentration (more cations in plasma, more anions in the interstitial fluid)
      ii. Total concentration of equivalents of charge is greater in plasma
      iii. Electrical neutrality is maintained
   b. Electrolyte concentrations in plasma reflect that in interstitial fluid
   c. Hyperproteinaemia – [Na$^{+}$] in meq/L of plasma volume decreases, while [Na$^{+}$] in meq/L of plasma H$_{2}$O is normal
4. Other extracellular compartments include bone and dense connective tissue fluid (similar to interstitial fluid) and transcellular fluid (unique composition)

Intracellular fluid is not a continuous fluid phase and hence differs in different tissues

1. Measurement of intracellular fluid:
   a. Dilution methods can’t be used so it is estimated from other measurements
   b. ICF = TBW – ECF
2. Low concentrations of Na$^{+}$, Cl$^{-}$, HCO$_{3}^{-}$ – K$^{+}$ is the predominant cation, while the predominant anions are organic phosphates (ATP) and proteins
3. Na$^{+}$/K$^{+}$ ATPase is the main factor driving ion balance
4. Cell membrane has selective permeability via pumps and channels
5. Gibbs-Donnan effect:
   a. Small diffusible cations are greater in the intracellular fluid
   b. Small diffusible anions are greater in the interstitial fluid
   c. Total concentrations of equivalents of charge is greater in intracellular fluid
   d. Electrical neutrality is maintained (small differences in membrane potential)
   e. Subcellular organelles differ in composition

Measurement of total electrolyte content depends on electrical neutrality within a compartment and membrane effects (selective permeability, ion/metabolic pumps, protein distribution/binding).

1. Similar to body fluid volume dilution techniques
2. Radioisotope of the ion is used as a marker – this determines the ‘exchangeable pool’
3. For Na$^{+}$ and K$^{+}$, the exchangeable pool is a large proportion of total body content
4. For Ca$^{2+}$ and Mg$^{2+}$ the exchangeable pool is a small proportion
Mechanisms of solute exchange:
1. Membrane permeability – depends on size, charge, fat solubility, channel density
2. Passive transport – simple diffusion, facilitated diffusion, coupled transport
3. Active transport – primary and secondary (co-transport, counter-transport)

Mechanisms of water exchange depend on osmotic and hydrostatic forces.
1. Osmolality of body fluids
   a. Plasma, ISF and ICF are iso-osmotic despite differences in composition as endothelium and cell membranes are freely permeable to water
      i. The primary determinant of distribution of water between ECF and ICF compartments is the number of osmotically active solute particles
   b. Plasma, ISF and ICF have different total concentrations of equivalents of charge. Some fluids are exceptions (e.g. kidney peritubular fluid and urine)
   c. Osmolality of plasma exceeds that of ISF by 1-2mosmol/kg H2O
      i. This difference is due to:
         1. Osmotic contribution of plasma proteins (2/3)
         2. Larger concentration of diffusible ions in plasma due to the Gibbs-Donnan effects (1/3)
      ii. → oncotic pressure (colloid osmotic pressure, π) ~25mmHg
      iii. Small amount of protein in the ISF → oncotic pressure of 3mmHg
   d. There is no osmolality difference between ISF and ICF despite intracellular protein and the Gibbs-Donnan effect
      i. The Na⁺/K⁺ ATPase actively transports 3Na⁺ out and 2K⁺ in, preventing an osmolality difference from accumulating
2. Contributions to plasma osmolality
   a. Plasma osmolality can be estimated as (electrolytes + glucose + urea)
   b. Na⁺ and its attendant ions are the major electrolytes – we can assume that the osmolality of electrolytes = osmolality of Na⁺ and attendant ions
      i. Assuming each Na⁺ is paired with a univalent ion, the osmolality of electrolytes (mosmol/kg H2O) = 2PNa (mmol/L)
      ii. Urea and glucose contribution can be estimated at 10mosmol/kg H2O so a reasonable estimate is Posm = 2PNa + 10
   c. Note that PNa is not a good index of total osmotically active solute or TBW, and it cannot be used to approximate Posm in the following situations:
      i. High plasma glucose or urea
      ii. Hyperlipidaemia or hyperproteinaemia, as PNa is measured per L of plasma volume rather than per L of water
3. Starling’s equilibrium:
   a. Net filtration (Jv) = Kf [(Pc – Pif) – δ (πp – πif)]
      i. Kf – filtration coefficient (net permeability of the capillary wall)
      ii. Pc – mean capillary hydrostatic pressure
      iii. Pif – mean interstitial fluid hydrostatic pressure
      iv. δ – reflection coefficient for plasma proteins
      v. πp – plasma colloid osmotic (oncotic) pressure
      vi. πif – interstitial fluid osmotic pressure

Transcapillary exchange – the capillary endothelium is impermeable to proteins and large molecules, but is permeable to lipid-soluble substances (non-lipid soluble substances must pass through membrane pores). Delivery and uptake of diffusion-limited substances depends on capillary transport time, while hydrostatic and osmotic pressures govern fluid movement.
1. Diffusion is by far the major transport process for nutrient and metabolic exchange
   a. Small lipid soluble molecules (O2, CO2) diffuse freely across cell membranes and through pores
   b. Lipid insoluble diffusion-limited substances show diffusion rate a size
   c. Water and water-soluble substances move through interendothelial pores
      i. Small water-soluble substances (NaCl, glucose) are flow-limited
530.305 – Regulation of Visceral Function

d. Diffusion is driven by the concentration gradient for the solute and affected by intercapillary distance, blood flow, capillary permeability and capillary surface area.
ed. Fick’s Law describes the relationship of concentration gradient, permeability and surface area (concentration gradient decreases along the capillary).

2. Filtration (bulk fluid movement) results from a hydrostatic, osmotic or oncotic (colloid osmotic) pressure across a membrane. It occurs at the arterial end, with absorption at the venous end.
a. Filtration coefficient – depends on the tissue, may vary with physiological conditions (inflammatory mediators can increase the coefficient).
b. Capillary hydrostatic pressure – may be modified by changes to the precapillary and postcapillary resistance vessels (vasomotion).
c. Interstitial fluid hydrostatic pressure – may be above zero in pathology.
d. Plasma oncotic pressure – high due to proteins (albumin, globulin).
e. ISF osmotic pressure – low.

3. Large molecule movement can occur by vesicular transport (micropinocytosis) or by convection through capillary fenestration (e.g. protein leak).

The lymphatic system functions to return excess ISF and proteins to the intravascular compartment. Endothelium is similar to blood vessels with little or no basement membrane, pinocytosis and wide fenestrations between cells. Arteriolar vasomotion, pulsation and muscle contraction influence lymph flow – valves prevent retrograde flow.

1. Flow of substances between blood and lymph
a. Rapid, continuous exchange between intravascular and extravascular compartments occurs by diffusion.
b. Transcapillary filtration occurs without perturbation of circulating volume.
c. Proteins do leak to the ISF, but are quickly removed by lymphatics.

2. Composition and flow of lymph – increased movement of fluid from capillaries leads to increased lymphatic flow if there is no obstruction.
a. Protein – concentration is lower than plasma.
b. Coagulation factors and antibodies.
c. Electrolytes – essentially the same as plasma.
d. Lipids – vary with nutritional state.
e. Cells – lymphocytes, monocytes, granulocytes (infection), plasma cells.

3. Functions of the lymphatic system
a. Return of protein, water, electrolytes from tissue spaces to the blood.
b. Important in the absorption of fats from the GI tract.
c. Removes RBCs and bacteria from the ISF (haemorrhage, infection).

4. Conditions that increase lymph flow:
a. Increased capillary pressure.
b. Increased capillary surface area (increased pressure, temperature, perfusion).
c. Increased capillary permeability (increased temperature, poisons; low O2).
d. Hypertonic solution infusion.
e. Increased activity (metabolites → increased osmolality, vasodilation).
f. Massage, tissue movement.

Oedema is the excessive accumulation of fluid in the tissue spaces due to a disturbance in the mechanisms of fluid balance.

1. Causes – decreased protein content of plasma, increased blood pressure, increased capillary permeability, increased filtering surface (dilation), obstruction of lymph flow.
2. Pathology – cardiac oedema, mechanical venous obstruction, renal disease, inflammation, oedema of malnutrition (or toxins), chronic lymphatic obstruction.

Magnitude of daily fluxes:

1. Internal – major sites
a. Across the capillary wall
   i. Diffusion – 80,000 L.
   ii. Starling’s filtration – 20L/day (18 reabsorbed, 2 lymph flow).
b. Renal glomerular filtration and tubular reabsorption
   i. 180L filtered, 1.5L excreted.
c. GI secretion and reabsorption.
530.305 – Regulation of Visceral Function

i. 1L oral, 1.5L saliva, 2.5L gastric juice, 0.5L bile, 1.5 pancreatic juice, 1L intestine
ii. 1.5-2L reaches the colon, while 100mL is excreted

2. External – steady state exchanges
   a. Water – 2-4L/day
   b. Sodium – 100-400mmol/day
   c. Potassium – 50-100mmol/day

<table>
<thead>
<tr>
<th>Total content</th>
<th>Compartment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium 48-60mmol/kg</td>
<td>50% ECF, 10% ICF, 40% bone of which 20-35% exchangeable</td>
<td>Exchangeable is 60-70% of total content</td>
</tr>
<tr>
<td>Potassium 50-54mmol/kg</td>
<td>95% ICF (muscle), 5% ECF</td>
<td>85% exchangeable</td>
</tr>
<tr>
<td>Calcium 450mmol/kg (1-2% weight)</td>
<td>99% in skeleton</td>
<td>99% non-exchangeable</td>
</tr>
<tr>
<td>Magnesium 20mmol/kg</td>
<td>65% bone, 22% muscle, 4% ECF</td>
<td></td>
</tr>
<tr>
<td>Chloride 33-36mmol/kg</td>
<td>ECF (main ion)</td>
<td>Most exchangeable ECF anion</td>
</tr>
<tr>
<td>Bicarbonate 13mmol/kg</td>
<td>50% ECF, all exchangeable</td>
<td>Regulated in acid-base balance</td>
</tr>
</tbody>
</table>

- Regulatory Mechanisms of Osmotic and Volume Homeostasis

Note that regulation of volume and osmolality of ECF is dependent almost exclusively on Na⁺ and H₂O, and these determine volume and osmolality of ICF (as membranes are permeable to water).

**Water:**
1. **Input:**
   a. Water content of food – 1L/day
   b. Water from oxidation of food – 0.5L/day
   c. Water consumed as liquid – 1-2L/day (main means for variation)
2. **Output:** Insensible, sweat and faecal losses are obligatory, as well as part of the urine volume (500-600mL) in order to excrete the minimum 650mosmol/day
   a. Insensible loss – 1L/day (expired in air, transpiration)
   b. Sweat – <0.2L/day to 8-10L/day (in response to thermal stress)
   c. Faeces – 0.1-0.2L/day
   d. Urine – 1-2L/day (main means for variation – note ADH control)
3. **Regulation:** Primarily by ingested liquid, and urine output (note SON, PVN)
   a. Osmoreceptors – if water is removed from cells, the decreased TBW or increased solutes from ICF will stimulate thirst and ADH secretion
      i. Sensitive to small changes, so are the main control
   b. Baroreceptors – located in low (atria) and high (carotid sinus, aortic arch) pressure regions and respond to decreased pressure
      i. Result in a stronger response and are activated in extreme situations
      ii. Volume over-rides tonicity
   c. Thirst and ADH secretion can also be stimulated/inhibited by other conditions (osmotic, volume and hypotensive stimuli) and pharmacological agents
      i. Hypertonicity – hypothalamic sensors
      ii. Hypovolaemia – baroreceptors and angiotensin II
   d. Renal response:
      i. Renal concentration – antidiuresis and plasma dilution
      ii. Renal dilution – diuresis and plasma concentration

**Sodium:**
1. **Input:** depends on Na⁺ content of food and liquid consumed, but generally ~100-400mmol/day
2. **Output:** changes to meet input
   a. Sweat – negligible under normal circumstances (depends on volume)
   b. Faeces – negligible
   c. Urine – 100-400mmol/day (main means for variation)
3. **Sensory mechanisms:** stretch receptors in atria, carotid sinus, aortic arch, afferent arteriole
530.305 – Regulation of Visceral Function

a. Low pressure – sense central venous filling → neural/humoral response (ANP)
b. Arterial receptors – sense volume and stretch → neural/hormonal response (RAAS)

4. Regulation: (note that it takes 4-5 days to correct an acute change in input)

a. Changes in glomerular filtration rate
i. Regulated by renal plasma flow and net filtration pressure:
   1. Increased Na⁺ → increased plasma osmolality → thirst, ADH
   2. Increased plasma volume → increased atrial natriuretic peptide →
      dilatation of afferent arterioles
   3. Baroreceptors → decreased renal sympathetic nerve activity →
      dilatation of afferent arterioles

ii. Dilatation of afferent and arterioles increased RBF and net filtration pressure,
    leading to increased GFR and Na⁺ excretion

iii. Note that these have probably only a minor role in regulation of Na⁺, due to
     autoregulation, tubuloglomerular feedback and load-dependent reabsorption

b. Aldosterone (produced in the adrenal cortex) – increases Na⁺ reabsorption in the
   collecting duct via the Na⁺ channel. Also stimulates K⁺ and H⁺ secretion.
   i. Stimulated by high angiotensin II, Pk and plasma ACTH; or low ANP and PNa
      1. Decreases in PNa have weak effects on aldosterone, and changes in
         Na⁺ intake do not change PNa much
      2. Primary mediators of secretion are angiotensin II and ANP
   ii. Renin is secreted by the juxtaglomerular apparatus in response to:
      1. Decreased renal perfusion (stretch receptors in afferent arteriole)
      2. Changes in the composition of tubular fluid (macula densa)
      3. Stimulation of renal sympathetic nerves
      4. A number of other factors
   iii. Inhibition by increased Na⁺:
      1. Increased Na⁺ → increased plasma volume via thirst, ADH
      2. → decreased renal SNA → decreased renin, increased renal
         perfusion pressure → decreased aldosterone
      3. → increased ANP → decreased aldosterone

b. Third factor effect (not well understood) – increased Na⁺ output in response to
   increased Na⁺ input, independent of GFR and aldosterone
i. Increased Na⁺ intake → increased plasma volume
   1. → decreased SNA, Na⁺ resorption in the proximal tubule and renin
      secretion (also increased GFR, decreased aldosterone)
   2. → decreased angiotensin II → increased proximal tubule Na⁺
      reabsorption, Na⁺ excretion (and decreased aldosterone)
   3. → increased ANP → decreased Na⁺ resorption in collecting duct →
      increased Na⁺ secretion (also increased GFR, lower aldosterone)

ii. Increased peritubular capillary hydrostatic pressure (or decreased oncotic
    pressure) will inhibit the ability to resorb fluid, which affects all solvents
    and solutes being absorbed

d. Overall response is influenced by the increased plasma volume from a Na⁺ load
i. Restoration of Na⁺ balance after an acute change in intake occurs over the
   period of several days

• Potassium Homeostasis

Potassium plays an important role in the excitability of nerve and muscle cells, metabolism and other
physiological processes. Small changes in Pk can have serious consequences as its concentration is
so low – this is affected by input/output as well as distribution between ECF and ICF compartments.

Distribution of potassium – plasma [K⁺] = 3.2-5.0mmol/L
1. High concentrations in the ICF are generated by the Na⁺/K⁺ ATPase
2. Cells are relatively permeable to K⁺ and are in a steady state normally
3. Changes in Pk can result from a change in the active uptake or passive diffusion of K⁺
   a. Changes in active K⁺ uptake:
      i. Accelerated by insulin (probably stimulates Na⁺/K⁺ ATPase)
      ii. β₂ adrenergic agonists also stimulate K⁺ uptake in some cells
      iii. Digitalis can inactivate the Na⁺/K⁺ ATPase (→ hyperkalaemia)
530.305 – Regulation of Visceral Function

b. Changes in passive K⁺ diffusion:
   i. Exit of K⁺ may be accelerated by cell injury or death (e.g., haemolysis)
   ii. Decreased arterial pH (even mild acidosis) → K⁺ diffusion out of cells
   iii. Reciprocal relationship between K⁺ and H⁺ in maintaining electrical neutrality
        of cells – in acidosis H⁺ enters cells and K⁺ is released

4. Input depends on K⁺ content of food and water – around 50-100mmol/day
   a. Membrane Na⁺/K⁺ ATPase is the main factor – modified by insulin, ANS/adrenergic
      receptors, acid/base status, chronic disease states

5. Output:
   a. Sweat – negligible as the concentration in sweat is similar to that in plasma
   b. Faeces – 5-10mmol/day
   c. Urine – 45-90mmol/day (main means for regulating K⁺)

Regulation:
1. Factors relating to initial increased P[K⁺]
   a. Secretion – proximal tubule, thick ascending limb, distal nephron
      i. Secretion in the proximal tubule and thin descending limb is such that the
         quantity of K⁺ reaching the hairpin can exceed filtered load (720mmol/day)
      ii. Distal secretion is regulated for external balance
         1. High tubular [K⁺] – active uptake
         2. Passive diffusion is determined by cell-lumen K⁺ gradient,
            transepithelial potential, lumen K⁺ permeability
   b. Absorption – proximal tubule (independent of K⁺ input and output), thick ascending
      limb, distal nephron, thick descending limb
      i. Absorption in the thick ascending limb is such that <10% of filtered load
         reaches the distal nephron independent of intake
      ii. Regulation must occur in the distal nephron (receives 72mmol/day)
   c. Factors that influence initial changes in P[K⁺] include:
      i. Changes in K⁺ uptake by tubular cells (Na⁺/K⁺ ATPase)
      ii. Permeability of the luminal membrane to K⁺
      iii. Intracellular K⁺ concentration (concentration gradient for diffusion)
      iv. Transepithelial potential difference (electrical gradient for diffusion)
   d. Increased K⁺ input → small increase in P[K⁺] → increased secretion (increased uptake
      by tubular cells) and increased aldosterone
      i. → increased activity of Na⁺/K⁺ ATPase
      ii. → increased reabsorption in the distal nephron → increased transepithelial
          potential difference
      iii. → increased permeability of the luminal membrane to K⁺

2. Na⁺ reabsorption in the distal nephron
   a. Determines transepithelial potential difference
   b. Increased Na⁺ reabsorption → increased H⁺ and K⁺ excretion
   c. Diuretics – often cause hypokalaemia due to increased K⁺ secretion

3. Impermeant anions in tubular fluid – sulphate ad nitrate cannot be reabsorbed as readily as
   Cl⁻, so more K⁺ is secreted when these are high in tubular fluid

4. Rate of tubular fluid flow – increased tubular fluid flow → more favourable concentration
   gradient due to washing-out of K⁺ (occurs with some diuretics)

5. Acid-base status:
   a. Acute alkalojisis → increased K⁺ secretion (K⁺ is exchanged for H⁺ in cells)
   b. Increased transepithelial potential difference, increased permeability of the luminal
      membrane
   c. Increased HCO₃⁻ (acts as an Impermeant anion) → increased K⁺ secretion
   d. Increased pH of tubular fluid → increased permeability of luminal membrane

Additional information
1. The relationship between total body potassium and plasma [K⁺] is not straightforward:
   a. Acid-base balance has an important influence
   b. Increases in total body K⁺ are minimal/rare, but depletion may be severe
   c. Serum [K⁺] is an unreliable guide to total body K⁺ except in the case of K⁺ depletion,
      then [K⁺] is roughly equivalent to the degree of negative balance

2. Abnormalities in serum [K⁺]:
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a. Hypokalaemia – serum [K⁺] <3.2mmol/L
   i. Associated with increased loss (vomiting, diarrhoea, laxatives, diuretics)
   ii. Deficits of 20-30% total body K⁺ are possible

b. Hyperkalaemia – serum [K⁺] >5.0mmol/L (note >10 is often fatal)
   i. Impaired renal excretion – acute oliguric renal failure
   ii. Transcellular shifts – tissue catabolism, insulin deficiency, metabolic acidosis, severe exercise (transient)

- Acid-Base Balance and Regulation of H⁺ Excretion

Major threats to the pH of body fluids are metabolically formed acids:

1. Volatile acids – CO₂
   a. Major end-product of the oxidation of carbohydrates, fats and amino acids
   b. Gaseous and can be eliminated by the lungs (hence volatile)
   c. Huge amounts are produced (10,000mmol/day) – exercise, hypermetabolism

2. Fixed acids – sulphuric acid, phosphoric acid
   a. Sulphuric acid is an end product of the oxidation of methionine and cysteine
   b. Phosphoric acid is the product of phospholipid, nucleic acid, phosphoprotein and phosphoglyceride metabolism
   c. Production varies with diet – usually 50-100mmol/day of H⁺

3. Organic acids – lactate, acetoacetate, β-OH butyrate
   a. Formed during the metabolism of carbohydrates and fat
   b. Normally further metabolised to H₂O and CO₂ – pathology → acidosis (hypervolaemic and other shock, diabetic ketoacidosis)

Acid-base buffer systems act to maintain pH of body fluids – the inherent buffer capacities of body fluids also provide immediate defence against pH changes. The ideal buffer has a pKₐ of 7.4 and high concentration (see law of mass action, Henderson-Hasselbalch equation)

1. Proteins (haemoglobin)
   a. Proteins have several ionisable groups that can act as weak acids
   b. Imidazole groups of histidine and N-terminal amino acids have a pKₐ close to 7.4, and are high in concentration in plasma and in cells
   c. Haemoglobin is the main blood buffer – high concentration, lots of histidine residues

2. Phosphate – H₂PO₄⁻ H⁺ + HPO₄⁻
   a. pKₐ is 6.8, but not all body fluids have sufficient concentrations to be effective
   b. Much more effective in ICF as concentration is higher and pH is lower
   c. Also effective in the renal tubule as phosphate is concentrated and pH lower

3. Bicarbonate – H₂CO₃ H⁺ + HCO₃⁻
   a. pKₐ is 3.7, though the equilibrium of HCO₃⁻ and CO₂ increases this to 6.1
   b. An important buffer as the concentrations of its constituents can be independently regulated – CO₂ by the lungs, HCO₃⁻ by the kidneys
   c. Changes in the ratio of HCO₃⁻ to CO₂ sets the pH, and also affects the ratio of other buffers (isohydric principle)

Respiratory regulation of pH:

1. Lungs regulate PA CO₂ as CO₂ is blown off by ventilation (these are inversely proportional)
2. H⁺ is added to blood when CO₂ enters capillaries for transport from the periphery, but this is countered by the haemoglobin buffer
3. Chemoreceptors in the medulla, aortic and carotid bodies respond to increased PA CO₂ by stimulating increased ventilation
4. Chemoreceptors in the carotid bodies respond to decreased arterial pH (occurring independently of PA CO₂) by increasing ventilation

Renal regulation of pH:

1. Kidneys regulate HCO₃⁻ by controlling the amount reabsorbed from the glomerular filtrate, replacing that used as a buffer, and secreting some in chronic alkalosis
2. Reabsorption/generation achieved by secretion of H₂CO₃-derived H⁺ from tubular epithelium
   a. CO₂ + H₂O CO₂⁻ (carbonic anhydrase in proximal tubules, distal nephron)
   b. H⁺ enters the lumen, HCO₃⁻ is transported through the basolateral membrane by a carrier-mediated system
530.305 – Regulation of Visceral Function

c. H⁺/Na⁺ antiport is responsible for acid secretion in the proximal tubule
d. H⁺ is actively secreted in the distal nephron (HCO₃⁻ is exchanged for Cl⁻)

Bicarbonate and renal regulation:
1. Recovery of filtered bicarbonate:
   a. H⁺ reacts with HCO₃⁻ in the lumen \( \rightarrow \) H₂O and CO₂, with a HCO₃⁻ released to blood
   b. Normally 90% of the HCO₃⁻ is reabsorbed in the proximal tubule, and most of the remaining 10% is reabsorbed in the distal nephron (99.9% recovery)

2. Generation of new bicarbonate:
   a. 50-100mmol of HCO₃⁻ is made to replace that used to buffer strong acids produced by the body. Note secreted H⁺ reacts with buffers in tubular fluid (minimum pH is 4.5)
   b. Ammonia – NH₄⁺ \( \Leftrightarrow \) H⁺ + NH₃
      i. pKₐ of 9.3, so is protonated in almost all body fluids
      ii. Synthesised in the cells of the proximal tubule and distal nephron
      iii. NH₃ (lipid soluble) diffuses through the membrane and is immediately converted to NH₄⁺, dragging more out (diffusion trapping)
   c. Phosphate – HPO₄²⁻ + H⁺ \( \Leftrightarrow \) H₂PO₄⁻
      i. pKₐ of 6.8 – most of the buffer can react with H⁺ in glomerular filtrate
      ii. Proximal tubule concentration is insufficient to be an effective buffer
      iii. In the distal nephron, allows the excretion of only 12-40mmol of acid per day

3. Secretion of bicarbonate
   a. In chronic alkalosis a subpopulation of cells in the cortical collecting duct can secrete HCO₃⁻ - the mechanism is similar to H₂CO₃-derived H⁺ secretion
   b. H₂CO₃ (epithelial cells) \( \Leftrightarrow \) HCO₃⁻ + H⁺
   c. HCO₃⁻ is secreted in exchange for Cl⁻, and H⁺ is actively transported across the basolateral membrane
   d. This is also a mechanism for transcellular Cl⁻ absorption

Acid and renal regulation
1. Quantitation of acid secretion
   a. Secretion of H⁺ in the urine is as NH₄⁺ or a titratable acid (= UNH₄V + UTAV)
   b. Some HCO₃⁻ is excreted, so net HCO₃⁻ generated = UNH₄V + UTAV – UHCO₃V
   c. This is the net acid secretion (~50-100mmol/day – as HCO₃⁻ excretion is negligible)

2. Control of bicarbonate-derived H⁺ secretion:
   a. An important determinant in both proximal tubule and distal tubule is the intracellular pH (determined by arterial pH and plasma K⁺ concentration)
   b. Arterial pH:
      i. H₂CO₃-derived H⁺ secretion is increased in acidosis, decreased in alkalosis
      ii. Adaptation to changes in arterial pH takes 4-5 days to develop fully
      iii. Intracellular pH is immediately sensitive to changes in arterial P₇CO₂, as CO₂ crosses the cell membranes readily
   c. Plasma K⁺ concentration:
      i. Intracellular pH is directly proportional to plasma K⁺ concentration (increased in hypokalaemia, decreased in hyperkalaemia)
      ii. Cells have a large number of anions, so must have a large number of cations to maintain electrical neutrality (main one is K⁺)
      iii. The roles of K⁺ and H⁺ are reciprocally related – in hypokalaemia K⁺ leaves the cell along its concentration gradient, and H⁺ enters
         1. \( \rightarrow \) decreased intracellular pH, increased H⁺ secretion
         2. Plasma becomes mildly alkalotic as H⁺ enters
      iv. Functional renal tissue and carbonic anhydrase inhibitors also important

3. Control in the proximal tubule
   a. Coupled to the movement of Na⁺ from the tubular lumen to epithelium, so H⁺ secretion is affected by proximal tubular Na⁺ reabsorption
   b. H₂CO₃-derived H⁺ secretion is decreased in plasma volume expansion and increased in plasma volume contraction

4. Control in the distal nephron
   a. Not directly coupled to Na⁺ reabsorption, though H⁺ secretion is stimulated by increased Na⁺ reabsorption
   b. H⁺ secretion is increased by aldosterone and increased Na⁺ delivery
Mannitol inhibits Na⁺ reabsorption in the proximal tubule, while frusemide and bumetanide inhibit it in the thick ascending limb.

Thiazide diuretics increase Na⁺ delivery to the collecting duct.

Diuretics that impair reabsorption in the collecting duct (amiloride, spironolactone, triamterene) decrease the transepithelial potential difference and lead to decreased H⁺ secretion.

Introduction to Acid-Base Disturbances

The lungs and kidneys help restore acid-base homeostasis when the pH becomes abnormal – note that they can be responsible for imbalances in themselves.

1. Acidosis can be produced by increased $P_{aCO_2}$ or decreased $[HCO_3^-]_p$ and vice versa.
2. Respiratory disturbances affect $P_{aCO_2}$, metabolic disturbances affect $[HCO_3^-]_p$.
3. Acid-base disturbances are characterised by an acute uncompensated phase and a chronic compensated phase – note that compensation does not restore pH to normal.

Respiratory acidosis

1. Primary abnormality is increased $P_{aCO_2}$.
2. Major cause is hypoventilation (barbiturates and other drugs, lung disease).
3. Moves to the left on the blood-buffer line.
4. If the cause persists, the kidneys compensate (moves along isobar).
   a. Decreased intracellular pH $\Rightarrow$ increased H⁺ excretion and HCO₃⁻ generation.
5. Mild acidosis remains after compensation.

Respiratory acidosis

1. Primary abnormality is decreased $P_{aCO_2}$.
2. Major cause is hyperventilation (altitude, CNS disorders, psychological disorders).
3. Moves to the right along the blood-buffer line.
4. If the cause persists, the kidneys compensate (falls along the isobar).
   a. Increased intracellular pH $\Rightarrow$ decreased H⁺ secretion and HCO₃⁻ generation.
5. Mild alkalosis remains after compensation.

Metabolic acidosis

1. Primary abnormality is decreased $[HCO_3^-]_p$.
   a. Severe renal failure – H⁺ can't be excreted, HCO₃⁻ can’t be produced.
   b. Seldom develops acutely (would be along the $P_{aCO_2}$ isobar).
2. Compensation occurs in the lungs.
   a. Decreased $[HCO_3^-]_p$ stimulates osmoreceptors $\Rightarrow$ reflex stimulation of alveolar ventilation $\Rightarrow$ decreased $P_{aCO_2}$.
   b. Ratio increases towards normal along new blood-buffer line.
   c. Decreased $P_{aCO_2}$ sensed by chemoreceptors in the medulla, carotid and aortic bodies – this attenuates the ventilatory response.
3. When the cause is non-renal, kidneys can compensate (decreased filtered load of HCO₃⁻).
4. In chronic states it moves along a new blood-buffer line.
5. There is considerable renal compensation (due to limited respiratory response): 
   a. $H_2CO_3$-derived H⁺ excretion may be normal or slightly elevated.
   b. Increased filtered load means that H⁺ secretion is insufficient to recover all HCO₃⁻ so its concentration falls.
   c. Most cases involve plasma volume contraction $\Rightarrow$ Na⁺ reabsorption in proximal tubule and distal nephron $\Rightarrow$ increased $H_2CO_3$-derived H⁺ secretion.
   d. H⁺ secretion may perpetuate the alkalosis if there is volume contraction.
The Cellular Basis of Cardiac Rate and Rhythm

Cardiac muscle is structurally similar to skeletal muscle with T-tubules invaginating the sarcolemma at the Z-line, although the sarcoplasmic reticulum is less extensive. Each cell is about 10-20 x 50-100μm (much smaller than skeletal myocytes), and branch and anastomose.

1. Electrical continuity is mediated by gap junctions, especially at the intercalated disk
2. Ion homeostasis in the cardiac myocyte:
   a. Calcium homeostasis:
      i. Intracellular Ca^{2+} is maintained at low levels by Ca^{2+} pumps in the SR
      ii. A Ca^{2+}/Na^{+} exchanger in the membrane allows Ca^{2+} to leave the cell
      iii. The sarcolemma contains an active Ca^{2+} pump
   b. Na^{+}/K^{+} ATPase is electrogenic → negative intracellular charge
   c. Ca^{2+}/Na^{+} antiport is passive, relying on the sodium gradient generated by the Na^{+}/K^{+} ATPase (secondary active transport – also electrogenic)

<table>
<thead>
<tr>
<th>Ion</th>
<th>Extracellular concentration (mM)</th>
<th>Intracellular concentration (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na^+</td>
<td>145</td>
<td>10</td>
</tr>
<tr>
<td>K^+</td>
<td>4</td>
<td>135</td>
</tr>
<tr>
<td>Ca^{2+}</td>
<td>2</td>
<td>10^-4</td>
</tr>
</tbody>
</table>

The duration of the cardiac action potential is similar to the time course of contraction, and during most of this period the myocyte is absolutely refractory (cannot be re-excited).

1. Refractory periods:
   a. ARP – restimulation will not elicit an AP
   b. RRP – slowly propagating AP can be generated
2. Cardiac action potential varies at different sites in the heart:
   a. SA and AV nodes have unstable membrane potential during diastole (pacemaker)
   b. Purkinje fibres have fast phase 0 upstroke (rapid transmission of electrical activation)
   c. Summations of action potentials → characteristic ECG
3. Vulnerable period – late in the T wave (ventricular repolarisation) corresponding to ventricular RRP. Excitation → slowly propagated APs → rapid ventricular ectopic beats → fibrillation

Ionic basis of the cardiac AP – K^+ currents outward, Na^+ and Ca^{2+} currents inward

1. Diastole – inward rectifying K^+ channels (I_{K1}) are open, other channels closed
   a. Large transmembrane concentration gradient drives K^+ diffusion out of the cell → electrical gradient → drives K^+ ions into the cell
   b. At equilibrium the inward and outward fluxes are equal:

   \[ E_K = 61.5 \log \frac{[K^+]_o}{[K^+]_i} \]

   c. Normally the K^+ equilibrium potential is around –90mV, though this is not reached due to influences of other ions (e.g. Na^+)

2. Characteristics of fast sodium channels:
   a. Mediate rapid depolarisation in phase 0
   b. Voltage-dependent gating with activation and inactivation gates
      i. Inactivation gates remain closed while cell is depolarised (phase 2, early phase 3) – prevents Na^+ entry → ARP
      ii. Time- and voltage-dependent resetting → recovery of I gates
   b. RRP – Na^+ channels reset at slightly different voltages, so if restimulation occurs when only a few channels have reset the density of available channels is reduced

3. Characteristics of calcium channels:
   a. Ca^{2+} current is smaller than the fast Na^+ current
   b. Two components (different channels) - I_{Ca(L)} and I_{Ca(T)}
   c. I_{Ca(L)} is voltage-dependent, reaches a peak quickly and inactivates slowly – it doesn’t normally reactivate within the duration of a single AP

4. Characteristics of potassium channels:
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a. $I_{K_1}$ is the main contributor to resting membrane potential – note anomalous inward rectification (open at rest, reduced permeability on depolarisation)
b. $I_{to}$ (carried by $K^+$ ions) is responsible for the notch in phase 1 repolarisation
c. $I_K$ (delayed rectifier) → initiates final repolarisation
   i. Fast ($I_{K_f}$) and slow ($I_{K_s}$) components – differences in AP duration across the ventricle wall are due to different channel densities
   ii. Catecholamines, hyperkalaemia → lower $I_K$ delay → increased AP duration
d. $I_{KATP}$ is activated when ATP is reduced in acute ischaemia

5. Basis of automaticity – note that SA and AV node cells are characterised by a slow rise in potential during phase 0, and relatively unstable potential during diastole
   a. Depolarisation of SA and AV nodes is due to slow inward Ca$^{2+}$ current
   b. SA pacemaker is dependent on the interaction between the inward Ca$^+$ current and the outward current carried by $I_K$ (delayed rectifier)
      i. $I_K$ is greatest during repolarisation, but decays during phase 4
      ii. $I_f$ (time-dependent Na$^+$) gives early polarisation during phase 4
c. Catecholamines increase the magnitude of SA node currents and accelerates changes in the $I_K$ channel → increased rate of diastolic depolarisation
d. ACh increases membrane $K^+$ permeability → hyperpolarisation and slower rate of diastolic depolarisation → increased time to threshold

<table>
<thead>
<tr>
<th>Major ion fluxes</th>
<th>Ion</th>
<th>Movement</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{Na}$</td>
<td>Na$^+$</td>
<td>In</td>
<td>0 (depolarisation)</td>
</tr>
<tr>
<td>$I_{K_1}$</td>
<td>K$^+$</td>
<td>Out</td>
<td>1 (early repolarization)</td>
</tr>
<tr>
<td>$I_{Ca}$</td>
<td>Ca$^{2+}$</td>
<td>In</td>
<td>2 (plateau)</td>
</tr>
<tr>
<td>$I_{K_1}$</td>
<td>K$^+$</td>
<td>Out</td>
<td>4 (resting membrane potential)</td>
</tr>
<tr>
<td>$I_K$</td>
<td>K$^+$</td>
<td>Out</td>
<td>3 (repolarisation)</td>
</tr>
<tr>
<td>$I_f$</td>
<td>Na$^+$</td>
<td>In</td>
<td>4 (pacemaker)</td>
</tr>
</tbody>
</table>

Determinants of the rate of propagation of cardiac excitation:
1. Cardiac cell membrane separates and stores charge (capacitor), and conducts current via pores (resistor), while the electrical resistance of intracellular and extracellular spaces determines the axial currents which flow in these compartments
   a. The electrical properties of the myocyte are determined by $C_m$, $R_m$, $R_i$, and $R_o$
   b. When current is injected into a resistor and capacitor in parallel, the potential across the capacitor increases exponentially to a steady level
   c. Along a row of myocytes, membrane potential changes quasi-exponentially and varies along the length of the row. Time course depends on $C_m$ and $R_m$
2. Time taken to reach threshold sets the rate at which the AP spreads – it is affected by the electrical properties of the myocyte and the magnitude of the injected current
   a. Inward current injected during activation is determined by density and status of membrane Na$^+$ channels (determined by membrane potential)
   b. In SA and AV nodes the cells are small, have few gap junctions (high $R_i$) and have few Na$^+$ channels (rely on slower Ca$^+$ currents)
      i. Excitation spreads slowly in regions near the SA and AV nodes
   c. Purkinje fibres are large and have many gap junctions (low $R_i$) and Na$^+$ channels

Mechanisms of arrhythmia:
1. Normal coordination of impulse propagation and cardiac excitation
   a. Entrainment and suppression of lower pacemakers
   b. Specialised conduction system
   c. Prolonged myocardial refractory system
2. Arrhythmia due to failure of normal coordination:
   a. Early discharge of a lower pacemaker (automaticity)
   b. Conduction abnormalities
   c. Inhomogeneity of repolarisation
   d. Triggered activity – unstable membrane activity in working myocytes → early afterdepolarisation (systole) or delayed afterdepolarisation (diastole)
3. Re-entrant circuit model
   a. Re-entrant arrhythmia occurs when excitation enters a region of the heart where conduction is blocked one direction and slow in the other (e.g. myocardial ischaemia)
530.305 – Regulation of Visceral Function

b. If delay is sufficient, proximal tissues recover excitability → tachyarrhythmia due to circular re-entrant activation

4. Decremental conduction and unidirectional block
   a. Progressive slowing of conduction when an impulse enters a region where the density of Na⁺ channels that can be opened, is progressively reduced
   b. Amplitude and rate of rise of the AP decreases, and eventually will not be enough to excite the tissues ahead
   c. Can → unidirectional blockage and slowed conduction in the other direction

5. Cardiac rhythm during acute ischaemia
   a. Marked increase in risk of arrhythmia – increased \([\text{K}^+]_o\), decreased \([\text{Na}^+]_i\) and \([\text{ATP}]_i\)
   b. \([\text{K}^+]_o\) → lowered RMP → Na⁺ channel inactivation → slow conduction
   c. Activation of \(I_{\text{KATP}}\) and increased \([\text{K}^+]_o\) → decreased AP duration producing inhomogeneous repolarisation
   d. Lower [ATP] → lower Ca²⁺ ATPase activity and [Ca²⁺], rises. Spontaneous release of Ca²⁺ from SR → activation of Na⁺/Ca²⁺ antiport → large inward current → DAD

6. Channelopathies and early afterdepolarisation
   a. EAD occurs when a second AP is generated late in plateau or during repolarisation
   b. Typically the AP is prolonged, allowing time for \(I_{\text{Ca(L)}}\) to recover and reactivate
   c. Hereditary channelopathies lead to long QT syndrome and increased risk of EAD:
      i. LQT1 – reduced \(I_{\text{Ks}}\)
      ii. LQT2 – reduced \(I_{\text{Kr}}\)
      iii. LQT3 – linked with a late component of \(I_{\text{Na}}\) (delays repolarisation)

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The circulation functions to distribute sufficient blood to the periphery to meet their metabolic requirements and to return this blood to the heart.

1. Vascular anatomy
   a. High proportion of vascular smooth muscle in small artery and arteriole walls
   b. Postcapillary vessels have less smooth muscle than precapillary vessels
   c. Microcirculation is in close contact with tissues (small diffusion distances)
   d. Sympathetic adrenergic nerves supply all vascular beds in the body – post-ganglionic processes with regular varicosities (adrenergic nerve terminals)
      i. Arteries and arterioles densely innervated
      ii. No direct innervation of precapillary sphincters or capillaries
      iii. Veins sparsely innervated (innervation increases as they get larger)
   e. Parasympathetic cholinergic innervation of precapillary vessels in the cerebral, coronary, GI, pulmonary and genital circulations

2. Functional classification:
   a. Large arteries – minimal pressure drop (conduit vessels)
   b. Small arteries and arterioles – most variable resistance to blood flow (precapillary resistance vessels)
   c. Veins – store most of the blood in the systemic circulation, also provide some resistance (capacitance and postcapillary resistance vessels)

3. Vascular smooth muscle
   a. Blood distribution, vascular capacitance and venous return depend on the contractile status of vascular smooth muscle
      i. Smooth muscles are electrically coupled to their neighbours
      ii. Separated from blood by the intima
      iii. Outer smooth muscle is most directly affected by neural control
   b. Maintains a level of spontaneous contractile activity (basal tone) and a relatively steady level of contractility
   c. Spread of local pacemaker activity is facilitated by electrical coupling
   d. Regulation of contractile function:
      i. Contractile state reflects myoplasmic Ca²⁺ concentration
         1. Depolarisation opens voltage-dependent Ca²⁺ channels, leading to a graded increase in intracellular Ca²⁺ concentration
         2. Depolarisation leads to an increase in spontaneous AP generation
      ii. Neurotransmitters and hormones may activate smooth muscle by opening membrane channels or stimulating Ca²⁺ release from SR
iii. Neurotransmitters and hormones that increase intracellular concentrations of cAMP and cGMP induce relaxation:
   1. cAMP-dependent kinases increase activity of Ca^{2+} pumps in the SR and sarcolemma
   2. cAMP acts directly as a calmodulin antagonist (deactivation of myosin light chain kinase)
   3. cGMP acts directly to inhibit interaction between contractile proteins

Local control of vascular function:

1. Experimental evidence for local control
   a. Autoregulation – intrinsic tendency of an isolated organ to maintain constant blood flow despite changes in perfusion pressure
      i. Changes in perfusion pressure → blood flow compensation within seconds
      ii. Level at which blood flow is regulated depends on tissue metabolic needs
      iii. Effectiveness of autoregulation varies between vascular beds:
         1. Cutaneous circulation is barely autoregulated, while the cerebral circulation is tightly autoregulated
         2. There are limits to the range of perfusion pressures over which blood flow is regulated (50-180mmHg in cerebral)
   b. Reactive hyperaemia – when occlusion of a blood vessel is released, blood flow rises above pre-occlusion levels for a period proportional to the period of occlusion

2. Myogenic control
   a. Elevated transmural pressure in blood vessels increases vascular contraction
   b. Most potent in medium arterioles and small and medium veins
   c. Increased pressure → distension of vessel wall → depolarisation, contraction
   d. Probably mediated by stretch sensitivity of membrane ion channels

3. Metabolic control
   a. Local vascular contraction is related to the perivascular concentration of vasoactive substances, determined by rate of production and removal
   b. Decreased pH may → smooth muscle hyperpolarisation, vascular relaxation
   c. Hypoxia may → vascular relaxation by opening ATP-sensitive K^+ channels
   d. Linkage between blood flow and metabolism is most potent in terminal precapillary vessels – the effects of vasodilator metabolites on postcapillary vessels is limited

4. Endothelial control - vasoactive substances are produced and released
   a. ACh is a vasodilator in normal vessels, but constricts vessels with a damaged endothelium (hence endothelium make another substance)
      i. EDRF has been identified as NO, which increases cGMP levels
   b. Endothelin is a Ca^{2+} channel agonist and potent vasoconstrictor
   c. Other factors may modulate adrenergic neurotransmission
   d. Noradrenaline, serotonin, vasopressin and angiotensin II act to release EDRF, which limits the extent of their constrictor activity

5. Flow-induced vasodilation – increased blood flow causes vascular relaxation, endothelium is exposed to greater shear forces (mechanism probably involves EDRF and/or prostaglandins)

6. Integrated model of local control
   a. All of these mechanisms probably contribute to vascular changes in exercise
   b. Metabolically mediated dilatation of terminal arterioles → proximal vessels dilation:
      i. Reduces vascular pressures in more proximal precapillary vessels
      ii. Increases blood flow
   c. In the venous compartment vasodilators and increased blood flow have little effect – increased vascular pressure elicits a myogenic response → increased venous return

Neuro-humoral control of vascular function – neurotransmitters or hormones alter blood vessel tone by binding to receptors on smooth muscle or endothelium.

1. Sympathetic adrenergic nerves
   a. Electrical activation of sympathetic adrenergic nerves → migration of NA vesicles to the cell membrane where it is released
      i. NA binds α receptors on smooth muscle, opening ligand-gated Ca^{2+} channels and activating G-protein coupled 2nd messengers IP_3 and DAG → contraction
         1. α_1 receptors are ubiquitous in vascular smooth muscle
         2. Post-junctional α_2 receptors are more sparsely distributed
b. Modification of sympathetic adrenergic neurotransmission:
   i. ACh inhibits sympathetic adrenergic neurotransmission
   ii. Adenosine and other metabolites inhibit SAN
   iii. Noradrenaline binds to presynaptic receptors to inhibit SAN

c. Co-transmitters
   i. Other transmitters (neuropeptide Y, ATP) are released with NA
   ii. Neuropeptide Y has a similar action to NA, but is only released at high levels of stimulation and is long-acting

2. Cholinergic nerves – mainly parasympathetic, though there are some sympathetic vasodilator nerves to precapillary resistance vessels in skeletal muscle
   a. NA inhibits cholinergic neurotransmission
   b. ACh binds to presynaptic muscarinic receptors (inhibit cholinergic neurotransmission)
   c. ATP is synthesised and released as a co-transmitter from adrenergic neurons

3. Nitroxidergic nerves – NO transmits information from non-adrenergic, non-cholinergic nerves that mediate vasodilation in cerebral arteries

4. Purinergic system
   a. ATP is released from both types of nerve (SNS and PNS)
   b. Acts as a potent vasodilator, binding to endothelial P2Y receptors \( \rightarrow \) EDRF
   c. May act at P2X receptors on the vascular cell membrane \( \rightarrow \) IP3, DAG
   d. ATP is degraded to adenosine, which is a potent vasodilator

5. Effects of circulating catecholamines
   a. Exogenous NA \( \rightarrow \) widespread vasoconstriction (except coronary, cerebral)
   b. Exogenous adrenaline \( \rightarrow \) NA effects (skeletal and splanchnic circulations vasodilate)
   c. \( \alpha \) and \( \beta \) receptors have different affinities for NA and adrenaline – the \( \beta_2 \) receptor in vascular smooth muscle is coupled via G proteins to the cAMP system \( \rightarrow \) relaxation
      i. NA is a stronger \( \alpha_1 \) agonist, but adrenaline is stronger for \( \alpha_2 \)
      ii. Adrenaline is a substantially more potent \( \beta_2 \) agonist \( \rightarrow \) vasodilation

6. Other hormones:
   a. Angiotensin II is a potent vasoconstrictor, acting directly on smooth muscle and also facilitates adrenergic neurotransmission
   b. ADH acts directly as a vasoconstrictor and has a number of other indirect effects

Integration of vascular function in different circulations:

1. Skeletal muscle circulation – dense sympathetic adrenergic innervation, which can effectively shut down muscle blood flow in the resting state
   a. Linkage between metabolism and blood flow in the skeletal circulation is evident, and it exhibits precise autoregulation
   b. Exercise decreases vascular resistance in the skeletal muscle circulation
      i. At moderate to high levels of exertion SNS influence is useless
      ii. Increased perivascular vasodilator concentrations in exercise
         1. Relax vascular smooth muscle directly (or via endothelium)
         2. Inhibit sympathetic adrenergic neurotransmission
      iii. Resistance vessels are innervated by cholinergic fibres that may be activated in the anticipatory phase of exercise
      iv. Mixed population of adrenoceptors in skeletal muscle resistance vessels – high levels of circulating adrenaline sustain vasodilation\( \backslash \)
      v. Histamine is released in exercise, dilating precapillary vessels and inhibiting sympathetic neurotransmission
   c. Metabolic accumulation has little effect on vascular tone in post-capillary vessels during exercise – myogenic responses, sympathetic activation, catecholamines and histamine act to cause venuconstriction (facilitating venous return)
   d. Speed/magnitude of muscle hyperaemia is not fully explained by these mechanisms

2. Skin circulation – low capillary densities and many A-V shunt vessels
   a. Slight link between metabolism and blood flow, as blood flow considerably exceeds metabolic demand – autoregulation is poorly developed
   b. Blood flow is under the control of the sympathetic adrenergic system – resistance vessels receive dense innervation
      i. Adrenoceptors are limited to \( \alpha \) receptors
      ii. Cutaneous blood flow is affected by local factors – the affinity of \( \alpha \) receptors for NA decreases as the temperature rises and vice versa
c. Sympathetic cholinergic innervation of sweat glands → kallikrein → kinins
   i. Bradykinin, lysylbradykinin dilate precapillary vessels and constrict postcapillary vessels
   ii. These local factors increase cutaneous blood flow and heat loss

3. Cerebral circulation
   a. Tight link between metabolism and blood flow, with precise autoregulation occurring between 60 and 180mmHg.
   i. Autoregulation fails when perfusion pressure falls below 50mmHg
   ii. Oxidative metabolism may be impaired for perfusion <40mmHg
   b. Cerebral blood flow remains constant, but distribution of flow to different parts of the brain varies – this is mainly regulated by local control mechanisms
      i. Perivascular concentrations of pH, pCO₂, pO₂ and [K⁺]
      ii. Severe hypercapnia – blood flow can reach twice resting values
      iii. Severe hypocapnia – blood flow can drop to ¼ resting values
      iv. Severe hypoxia – blood flow can reach twice resting values
   c. Circulating catecholamines have little effect on cerebral circulation as they do not cross the tight endothelial junctions of the cerebral capillaries
   d. Vessels are sparsely innervated – sympathetic stimulation can produce substantial transient responses

Myocardial Oxygen Supply and Demand

Myocardial oxygen consumption depends on:
1. Basal metabolism (small fraction of total consumption) – including the metabolic cost of maintaining cell organelle systems and the activation of the contractile process
2. Mural force development
   a. Magnitude is directly proportional to pressure generated, but also dependent on ventricular geometry – e.g. LV dilatation increases required mural force
   b. O₂ demand is related to the magnitude and the duration it is maintained
3. Inotropic state
   a. Alters the number and rate of interactions between contractile proteins, changing the magnitude and duration of mural force development
   b. Shift in myocardial O₂ utilisation also occurs independently of mural force
4. Heart rate
   a. Changes in the frequency of force development
   b. Changes in heart rate are usually associated with changes in inotropic state

Coronary circulation:
1. Structure and function – coronary arteries arise from the root of the aorta, forming an arterial system in the epicardial surface of the heart. Venous return is through the coronary sinus and anterior cardiac veins to the right atrium.
   a. Vasculature is dense and in close contact with myocytes (one capillary per myocyte).
   b. Large proportion of O₂ entering the coronary circulation is extracted
   c. Coronary blood vessels are affected by mural forces during systole
2. Myocardial oxygen supply
   a. \( Q_C \times (C_{a(O_2)} - C_{v(O_2)}) \)
   b. Requirements can be met by increased arterial content, increased coronary extraction or increased coronary blood flow – normally O₂ supply is matched to demand via changes in blood flow as the other two factors are fixed.

Determinants of coronary blood flow:
1. Mechanical factors – perfusion pressure and instantaneous resistance to blood flow
   a. In the left ventricle there is a sudden and almost complete cessation of blood flow during isovolumetric contraction (compression of vessels)
      i. Some recovery during systole, but blood flow is still low
      ii. Blood flow rebounds during isovolumetric relaxation then follows the pattern of aortic pressure
   b. Diastolic pressure-time index reflects the effects of mechanical determinants to the subendocardial region of the left ventricle
      i. Assumes compressive forces on vessels are similar to forces in the ventricle
ii. Subendocardial flow is determined by the difference between left ventricular pressure and aortic pressure

iii. Diastolic interval sets relative duration of blood flow to the subendocardium

2. Coronary blood flow and metabolism – coronary vascular resistance is controlled mainly by local microvascular factors, linked to balance of O₂ supply and demand

3. Neural and hormonal influences
   a. SNS acts directly on the coronary circulation to cause vasoconstriction
      i. Tends to be overridden during stress by a concurrent increase in O₂ demand (metabolites → vasodilation)
   b. PNS activation can cause a transient vasodilation
   c. α (vasoconstriction) and β₂ (vasodilation) receptors are in coronary vessels
      i. β₂ receptors may be more specific to NA than other vascular beds

Coronary reserve is the amount by which it is possible to increase coronary blood flow – resting blood flow is 100mL/min/100g, and this can be increased to 450mL/min/100g (limited by the extent of maximal vasodilation). The heart normally works within its reserve capacity, but if perfusion pressure is decreased or O₂ requirements are very high, coronary reserve can be exhausted. Increased heart rate will hinder coronary blood flow and decrease reserve.

- The Cardiovascular Control System

Regulation of arterial pressure and distribution of cardiac output depends on autonomic nerves, hormones and local factors. Note that the brainstem plays an important role, and receives feedback from receptors located throughout the cardiovascular system.

Activation of cardiovascular afferents (most importantly mechanoreceptors) depends on transmural pressure and the distensibility of the wall in which they are located. Stretch-sensitive ion channels may be involved, and may be modulated by local ion concentrations.

1. Systemic arterial baroreceptors – carotid sinus (CNIX), aortic arch (CNX) and others (CNIX) along the common carotid and subclavian arteries. They receive efferent innervation, and give rise to myelinated and unmyelinated afferents.
   a. Threshold – <30-50mmHg, decreased pressure does not affect firing rate
   b. Saturation – >150-180mmHg, increased pressure does not affect firing rate
   c. Rate-sensitivity – rate of firing is greater for pulsatile pressure than steady
   d. Slowly adapting – occurs over days if a steady pressure is applied
   e. Sensitivity is affected by smooth muscle contractility and endothelial factors (EDRF and PGI₂ → increased sensitivity, endothelin → decreased sensitivity)

2. Cardiac receptors with myelinated afferents – endocardium at veno-atrial junctions
   a. Type A – burst of firing during the a wave of JVP (atrial contraction)
   b. Type B – burst of firing during v wave of JVP (ventricular contraction – atrial filling)

3. Cardiac receptors with unmyelinated afferents
   a. C fibre afferents form a diffuse network (many more than myelinated afferents)
   b. Sparse and irregular discharge, but aggregate output increases markedly with increased cardiac filling

Integration of cardiovascular control by the CNS

1. Inputs and outputs
   a. Nucleus tractus solitarius – receives sensory afferents from all systemic arterial baroreceptors and cardiopulmonary receptors
   b. Intermediolateral column (thoracic spinal cord) – preganglionic sympathetic neurones in this area are the ultimate pathway for sympathetic neural drive
      i. Regulate postganglionic sympathetic nerves that innervate heart and blood vessels via cervical and thoracic ganglia
   c. Cardioinhibitory centre – cardiac vagal motor neurones in the medulla regulate activity in preganglionic vagal efferent fibres that innervate the heart
      i. Two nuclei in mammals – nucleus ambiguus, dorsal vagal nucleus

2. Role of the ventrolateral medulla – discrete groups of neurones play a pivotal role in the tonic and reflex control of sympathetic nerves innervating heart and blood vessels
   a. Rostral ventrolateral medulla – provides a major tonic excitatory contribution to sympathetic outflow to heart and vessels (critical part of central pathways)
b. Caudal ventrolateral medulla – inhibitory control over the RVLM, tonically active

3. Role of higher centres – CVS control is not entirely reliant on medullary reflexes
   a. Hypothalamus – role in the response to arousal and thermal stress
   b. Cortex – influences response to exercise

4. Pathways:
   a. From NTS to CVLM (excitatory)
   b. From NTS to cardiac vagal motor neurons (excitatory)
   c. From RVLM to preganglionic sympathetic neurons of IML (excitatory)
   d. From CVLM to RVLM (inhibitory)
   e. From hypothalamus to RVLM

5. Neurotransmitters – classical neurotransmitters are unlikely to mediate transmission in these central pathways as they have slow and prolonged action. Amino acids are the most likely candidate (glutamate/aspartate excitatory, GABA inhibitory)

Role of the neuroendocrine system in cardiovascular control
1. Adrenal medulla – synthesises adrenaline (80%) and noradrenaline (20%)
   a. Receives preganglionic sympathetic innervation – activation releases adrenaline (and noradrenaline to a lesser extent) into the bloodstream

2. Renin-angiotensin-aldosterone system
   a. Juxtaglomerular apparatus releases renin in response to:
      i. Sympathetic stimulation (β₁ receptors)
      ii. Decreased pressure in afferent arterioles
      iii. Decreased Na⁺ load at macula densa
   b. Renin converts angiotensinogen into angiotensin I, which is converted into angiotensin II by ACE in the brush border of lung capillaries.
   c. Angiotensin II has a number of effects on the CVS:
      i. Penetrates the BBB at the area postrema – activates pathways that modulate sympathetic outflow and facilitate ADH synthesis.
      ii. Potentiates ganglionic transmission at paravertebral ganglia (SNS)
      iii. Increases synthesis and release of NA, and inhibits reuptake
      iv. Acts directly on vascular smooth muscle → vasoconstriction
      v. Promotes formation and release of aldosterone from adrenal cortex

3. ADH alters renal water handling, and also acts directly as a vasoconstrictor

4. ANP (BNP in ventricles) – released in response to distension of atrial chambers
   a. Acts as a vasodilator
   b. Increased GFR and filtration fraction
   c. Antagonises effects of ADH and angiotensin II
   d. Decreases secretion of renin, angiotensin II and ADH

Cardiovascular reflexes
1. Systemic arterial baroreceptors – fall in arterial pressure → fall in firing rate → decrease in NTS excitation → decreased activity of depressor neurons to CVLM and CVM neurons → augmented sympathetic outflow, reduced cardiac vagal activity:
   a. Increased heart rate, inotropic state
   b. Graded constriction of precapillary resistance vessels in skeletal muscle, splanchnic, cutaneous and renal beds (not coronary or cerebral)
   c. Venoconstriction of capacitance vessels (splanchnic and cutaneous)
   d. Increased catecholamine secretion by adrenal medulla

2. Cardiac receptors
   a. Myelinated afferents – activation of atrial receptors leads to:
      i. Increased heart rate – may mediate the Bainbridge reflex (transient elevation of heart rate caused by rapid volume loading of the heart)
      ii. Decreased renal SNS stimulation
      iii. Decreased secretion of ADH from the posterior pituitary
   b. Unmyelinated afferents – qualitatively similar to arterial baroreceptors, but quantitatively different (greater effect on renal than muscle circulation)

3. Other receptors – chemoreceptors, nociceptors and pulmonary receptors can lead to substantial responses, but do not have a major role in cardiovascular homeostasis.
Blood volume is the sum of plasma volume and red cell volume, while plasma volume is a subset of extracellular fluid volume – these subdivisions identify short, medium and long-term mechanisms involved in regulation of blood volume. Reflex adjustments in the face of acute blood loss include:

1. **Intrinsic mechanisms**
   a. Decreased peripheral venous pressure → decreased venous return → decreased preload → decreased SV → decreased CO → decreased MAP
   b. Decreased renal perfusion → decreased diuresis, RAAS activation

2. **Receptor-mediated mechanisms**
   a. Cardiac receptors – decreased cardiac filling → decreased aggregate firing
   b. Systemic arterial baroreceptors – decreased MAP → decreased firing rate

Fluid exchange between plasma and interstitial space
1. A fall in capillary hydrostatic pressure will change the Starling forces across the capillary in favour of fluid absorption – this is amplified by ANS reflex responses
2. Precapillary vasoconstriction → greater pressure drop through resistance vessels, leading to significant translocation of interstitial fluid into the vascular compartment
3. Skeletal muscle (with large interstitial fluid volume) is an important reservoir
4. Initiated rapidly, and limited by the dilution of plasma proteins (800mL maximum)

Neurohumoral control of ECF volume
1. Decreased firing of cardiac receptors → increased renal SNS activity (RAAS activation), increased ADH release, increased thirst
2. Thirst is stimulated directly by the altered afferent profile of cardiovascular receptors, and augmented by increasing circulating levels of angiotensin II
3. ADH and aldosterone affect renal handling of salt and water:
   a. ADH reduces water loss from the collecting ducts (minutes)
   b. Aldosterone favours sodium retention and hence prevents water loss (hours)
4. Restoration of ECFV usually occurs within 12-72 hours

Regulation of RBC volume and other blood constituents
1. Mechanisms involved in restoration of red cell volume and synthesis of other blood constituents operate over a period of days to weeks
2. Small amounts of preformed albumin enter the circulation immediately after blood loss, while hepatic synthesis restores the rest over 3-4 days
3. EPO generated in response to decreased O₂ tension stimulates red cell synthesis, and normal levels are maintained by 4-8 weeks

Acute loss of blood volume
1. **Nonhypotensive haemorrhage** – <10% blood volume, controlled by cardiac receptors
   a. MAP unchanged (unchanged systemic arterial baroreceptors), pulse pressure drops
   b. Neurally mediated reflexes maintain CVS homeostasis in these conditions:
      i. Decreased firing of cardiac receptors → increased aldosterone, ADH
      ii. Generalised activation of SNS → increased heart rate, inotropic state

2. **Hypotensive haemorrhage** – >10% of blood volume
   a. Graded decrease in systemic arterial pressure reflecting the volume deficit (varies)
   b. Increased aldosterone, ADH
   c. Increased heart rate and inotropic state, and vessel contraction becomes more intense (shuts down some vascular beds)

3. **Haemorrhagic shock** – occurs when substantial blood loss remains uncompensated for long periods. Replacing lost blood volume may not restore CVS homeostasis.

4. **Effects of posture** – similar to non-hypotensive haemorrhage
   a. Getting up → blood pools in the leg veins due to gravity (500mL)
   b. Neurally mediated reflexes increase HR and inotropic state, minimising the fall in CO
   c. Constriction of resistance vessels (particularly in skeletal muscle) increase TPR
   d. Arterial baroreceptors may also play a role (mediate transient changes in arterial blood pressure but are not essential to maintenance of homeostasis)

• Regulation of Arterial Pressure
530.305 – Regulation of Visceral Function

While systemic arterial baroreceptors have an important role in the short-term regulation of arterial pressure, the interaction of a number of factors is more important in the long term.

**Arterial baroreceptors:**
1. Response of systemic arterial baroreceptors in the short-term is well described, but the extent to which they monitor and maintain long-term pressure is controversial
   a. Resetting of arterial baroreceptors in persistent hypertension is consistent with the observation that these receptors are slowly-adapting
2. Arterial baroreceptors detect changes in MAP on a beat-to-beat basis, but are not a good source of information on the absolute level of arterial pressure
   a. Function is also modified (actively set) by the CNS via efferent nerves
3. Mediate buffering of short-term MAP changes around a set point maintained by other factors

**Cardiopulmonary receptors** – afferents give rise to powerful aggregate activity despite the fact they are unmyelinated and conduct slowly
1. Receptors in the atria, ventricles and lungs exert a tonic inhibitory influence on the CVS
2. Cardiopulmonary afferents affect renal resistance vessels more than skeletal muscle
3. Atrial afferent activity directly inhibits release of ADH from the posterior pituitary
4. Cardiopulmonary receptors may help set MAP – activity is affected by structural changes (hypertrophy) and are reset by sustained volume loading

**Other inputs:**
1. Chemoreceptor reflexes – stimulate bradycardia and constriction of resistance vessels in response to poor O2 associated with low arterial pressure (<70-80mmHg)
2. CNS ischaemic response – cerebral perfusion is impaired at low arterial pressure (<60-70mmHg) activating vasomotor neurones in the ventrolateral medulla (hypoxia, hypercapnia) and exciting cardiac vagal nuclei (hypoxia)
   a. Increased SNS outflow Æ vasoconstriction, catecholamine release
   b. Increased cardiac vagal activity Æ decreased heart rate

**The renal barostat** – medium to long-term regulation of arterial pressure is closely linked with regulation of plasma and ECF volume (increased PV Æ increased CO Æ increased MAP)
1. Renal fluid regulation (modulated by cardiac receptors) may provide a platform around which arterial baroreceptors buffer arterial pressure
2. JGA is affected by arterial pressures at the terminal end of the afferent arteriole
3. As pressure drops below 90mHg, renin production stimulates the RAAS
4. Angiotensin II stimulates release of ADH and aldosterone, and also acts directly on the CVS:
   a. Penetrates the BBB at the area postrema to activate descending pathways that modulate sympathetic outflow to the CVS and adrenal medulla
   b. Facilitates ganglionic transmission and neurotransmission at paravertebral ganglia
   c. Increases synthesis/release of NA from sympathetic nerve terminals and inhibits reuptake – facilitates sympathetic neurotransmission in heart/vessels
   d. Acts directly on vascular smooth muscle to mediate constriction

**Mild hypertension** is defined as a blood pressure around 135/90mmHg – 80-85% are idiopathic (essential/primary hypertension). There is a strong genetic predisposition and clear environmental linkage (advanced cultures, stress, diet).
1. Cardiac output is normal, and there is no apparent problem in renal handling of ECF (renin, angiotensin II and aldosterone levels are approximately normal)
2. Baroreceptor firing rates are normal as they have adapted to a higher set point
3. Structural changes – smooth muscle proliferation Æ increase peripheral resistance
4. There is also evidence for CNS involvement
5. Hence there is an interaction between a number of factors to increase CO/TPR/both
   a. Transient excessive CO or exposure to increased pressure
   b. Structural changes in the peripheral circulation
   c. Vascular wall thickening, narrowing of lumen
   d. Resetting of arterial baroreceptors and the renal barostat
   e. Cardiac hypertrophy resets cardiac receptors
   f. CO, ECF volume are normal, but hypertension is set by increased TPR
Energy balance (EB) = Energy intake (EI) – Energy expenditure (EE)
Total energy expenditure (TEE) = Basal metabolic rate (BMR) x Physical activity level (PAL)

A positive energy balance results in accumulation of body stores (fat) and weight gain. To maintain body weight, energy balance must be regulated via energy intake, exercise or both.

Components of daily energy expenditure:
1. Basal Metabolic Rate
   a. Calculated indirectly from sex, age, weight and height:
      i. Male 18-30: BMR = 0.063wt – 0.042ht + 2.953
      ii. Female 18-30: BMR = 0.057wt – 1.184ht + 0.411
   b. Can be directly calculated from measurements of O2 consumption and CO2 production using a mask, hood or whole body chamber
   c. Total body energy expenditure can be estimated from BMR:
      i. Very sedentary = 1.2 x BMR
      ii. Sedentary = 1.4 x BMR
      iii. Active = 1.6 x BMR
      iv. Very active = 1.8 x BMR
2. Thermogenesis (dietary-induced, thermoregulatory)
3. Activity

Average daily energy expenditure:
1. Active man (23yrs, 80kg, 1.80m)
   a. BMR = 7.92MJ/d
   b. DEE = 1.27MJ/d = 3035kCal/d
2. Active woman (23yrs, 60kg, 1.70m)
   a. BMR = 5.84MJ/d
   b. DEE = 9.4MJ/d = 2246kCal/d

Obesity
1. Accumulation of fat stores can be estimated by the BMI (kg/m²)
   a. Normal = 20-25, overweight = 25-30, obese = 30+
   b. High and low BMI is associated with increased mortality
   c. Obesity considerably increases the risk of mortality from type 2 diabetes mellitus, coronary vascular disease and some cancers (incl breast and colon)
2. Prevalence (increasing)
   a. 50% of men are overweight, 10% are obese
   b. 30% of women are overweight, 10% are obese
3. Potential causes
   a. Low metabolic rate – dependent on body size and composition (fat to lean ratio), but this is rarely the primary cause of obesity
   b. Brown fat hypothesis – obese people don’t have enough
      i. Brown fat is metabolically active (futile cycles) due to high mitochondrial content and thermogenic capacity
      ii. Found in the dorsal thorax beneath the scapula, and important in babies, animals <2kg body weight and hibernating animals
      iii. Comprises <2% total body fat and is physiologically unimportant
   c. Obesity genes – Ob gene (monogenic effect)
      i. Leptin is the gene product – absence in rats leads to obesity
      ii. Mice are homozygous recessive (ob/ob)
      iii. Human homologue exists, but are heterozygous (ob)
      iv. Obese humans have an excess of leptin (may be a receptor defect)
      v. Probably polygenetic
   d. Appetite regulation (macronutrient composition)
   e. Exercise levels
Control of Energy Intake

One of the main factors controlling energy intake is the macronutrient (fat, CHO, protein and alcohol) content of the diet. These have different effects on hunger, satiety, oxidation and storage, and hence feedback on EI differs. Current recommendations to reduce EI are to consume a diet where no more than 30-35% of total EI comes from fat.

Appetite regulation:
1. **High fat diets lead to increased energy intake**
   a. When fat content is covertly increased and subjects allowed to eat to appetite, energy intake greatly increases (high fat hyperphagia)

2. **Fat tends to be less satiating than CHO**
   a. Individuals feel more hungry following a high fat meal than following an isoenergetic meal of high carbohydrates
   b. Lunch time intake increases if individuals have a high-fat breakfast

3. **Adipose storage of fat**
   a. Fat and CHO oxidation rates can be calculated from O₂ consumption and CO₂ production (determines rate at which macronutrients are stored/utilised)
      i. Respiratory quotient (RQ) = CO₂ produced / O₂ consumed
      ii. RQ = 0.7 (fat) to 1.0 (CHO)
   b. CHO is quickly oxidised, while fat is not readily oxidised and is preferentially stored in adipose tissue

4. **There is very poor regulation of fat balance in humans**
   a. Fat balance = fat in – fat oxidised
   b. Covert feeding of a high fat diet leads to a positive fat balance – there are no mechanisms to detect this and reduce appetite
   c. Covert feeding of a low fat diet leads to a negative fat balance – there is loss of body fat despite eating to appetite

5. **There is little de novo lipogenesis in humans**
   a. Fat stored in adipose tissue comes mostly from ingested fat
   b. Very little carbohydrate is converted to fat
530.305 – Regulation of Visceral Function

**Respiratory Function**

- **Pathophysiology of Respiratory Failure**

  **Respiratory failure** occurs when the lung fails to oxygenate arterial blood adequately and/or fails to prevent undue CO₂ retention (and to prevent acidosis)
  1. There are various types of respiratory failure associated with different derangements
  2. No absolute definition, but in practical terms:
     a. \( P_aO_2 < 60 \text{mmHg} \) – hypoxic, type 1
     b. \( P_aCO_2 > 50 \text{mmHg} \) – hypercapnic, type 2

  **Hypercapnia:**
  1. In health \( P_aCO_2 \) is normally maintained within a narrow range:
     a. \( P_aCO_2 = \frac{V_{CO_2} \times k}{V_A} \) (i.e. \( P_aCO_2 \propto 1/V_A \))
     b. \( V_E = \frac{k \times V_{CO_2}}{P_aCO_2 (1 - V_D / V_T)} \)
  2. Hypoventilation in association with metabolic alkalosis may cause hypercapnia
     a. Decreased drive – drugs, polio, intracranial lesions
     b. Lower neuromuscular transmission – myasthenia gravis, curare, muscular dystrophy
     c. Muscle weakness/fatigue – fatigue, electrolytes, malnutrition, abnormal length/tension relationship (bell curve)
     d. Abnormal load – increased resistive load, increased lung elastic load, chest wall elastic load, minute ventilation load
  3. **V/Q mismatch**

  **Hypoxia** – note that \( P_aO_2 \) is only one factor in the delivery of \( O_2 \) to the tissues:
  1. Reduced \( FIO_2 \)
  2. Hypoventilation
  3. **Diffusion** – e.g. diffuse interstitial lung disease
     a. Alveolar gas equation – \( P_AO_2 = (P_b - P_{H,O}) \times FIO_2 \times \frac{P_aCO_2}{R} + k \)
        i. Allows distinction between pure hypoventilation (or hyperventilation) and intrinsic lung disease (i.e. A-a gradient)
        ii. Normal A-a gradient 1-2kPa
     b. Alveolar-capillary block, V/Q mismatch, more likely to be operational during exercise, use of CO (diffusion limited, zero back pressure)
     c. Restricted lung volumes, hypocapnic/respiratory alkalosis, pattern of respiration/work of breathing
  4. **V/Q mismatch**
     a. 3-compartment model (dead space, alveolar – V/Q of 1, alveolar – V/Q of 0)
        i. Worsening disease \( \rightarrow \) unable to compensate hyperventilation \( \rightarrow P_aCO_2 \) increases (but pH is normalised)
        ii. Loss of CO₂ drive and respiration dependent on hypoxic drive
        iii. Danger of administered high inspired \( O_2 \)
            1. Hypoxic drive abolished, depression of ventilation increase in \( PaCO_2 \) and development of acidosis with depressant effects
            2. Even if \( O_2 \) discontinued, may get profoundly hypoxic and take time to unload CO₂ due to large body stores
        iv. Danger of monitoring only \( O_2 \) saturation
     b. Results of elevated \( P_aCO_2 \)
        i. Depends on rate of increase
        ii. CO₂ narcosis/encephalopathy is multi-factorial – intracellular acidosis, hypoxia, reduced CO, sleep deprivation etc.
        iii. Effects of respiratory acidosis – reduced muscle contractility, reduced endurance time, arterial vasodilation, increased cerebral blood flow
     c. Consequences – increased \( P_aCO_2 \), reduced pH
530.305 – Regulation of Visceral Function

d. Hypercapnia may be adaptive to reduce work of breathing/distress of dyspnoea – note that V̇e can reduce if PaCO₂ rises or if V̇d/V̇t decreases

5. R-L shunt – distinguish from V/Q mismatch via administration of 100% O₂
   a. If V/Q mismatch is severe, it may take some time to wash out N₂ and some N₂ continues to be washed out of the peripheral tissues
      i. N₂ splinting occurs in areas with very low V/Q (absorption atelectasis)
      ii. Effects of relaxation of hypoxic vasoconstriction (PₐO₂ rise is less)
   b. With severe V/Q mismatch (even with relatively high FIO₂) PₐO₂ response is initially modest
   c. With a shunt, the shunted blood does not see the added O₂ and depresses the arterial PO₂ (due to the shape of the dissociation curve)
   d. Useful gains in PₐO₂ do follow administration of O₂ in patients with a shunt due to dissolved O₂ – the PₐO₂ does increase with administered O₂, but less than would be expected in the absence of the shunt (widened A-a gradient)

If we have someone with a 20% R-L shunt and given them oxygen – saturation goes 80%→90%, does this exclude a R-L shunt? No – understand why this is the case for the exam.

**Sleep and Breathing**

Sleep is a period of sustained quiescence in a species-specific state accompanied by reduced responsiveness to external stimuli. It is quickly reversible to the wakeful condition, and there are characteristic EEG changes and endogenous periodicity.

1. Reasons for sleep
   a. Restorative – energy conservation, chemical influences
      i. Factor S (muramyl peptides) is strongly sleep-inducing
      ii. Cytokines (e.g. in infection) also mediate sleepiness
   b. Alertness/wakefulness promotion – reticular activating system
   c. Sleep promotion – solitary tract nucleus, raphe nucleus, medial forebrain

2. Stages of sleep – note that REM and non-REM alternate every 90-120 minutes
   a. Non-REM sleep
      i. Stage I – beta activity
      ii. Stage II – characterised by K complexes and spindles
      iii. Stage III – delta activity, slow wave sleep
      iv. Stage IV – delta activity, slow wave sleep
   b. REM sleep
      i. Increased cerebral metabolic activity
      ii. Increased CNS excitation (dreaming)
      iii. Inhibition of motor activity – including pharyngeal muscles
      iv. Cardiorespiratory instability

3. Sleep and age
   a. Newborns and infants:
      i. Enter sleep through REM, non-REM and REM cycle every 50-60min
      ii. EEG patterns on non-REM emerge between 2-6 months and consolidate into the sleep cycle
      iii. SWS becomes prominent when brain structure/function develop
   b. Young adults:
      i. Enter sleep through non-REM, cycle every 90-120min
      ii. SWS dominates the first 1/3 of the night (linked to sleep initiation)
      iii. REM dominates the last 1/3 (linked to circadian temperature rhythms)
      iv. About 20% of sleep is SWS, 20-25% is REM in 4-6 episodes. Note there are short periods of wakefulness (<5%) throughout the night.
   c. Effects of age:
      i. SWS fades with age (halves in adolescence)
      ii. By 60 years, there is almost a complete loss of SWS in some men which may correlate with loss of cortical synaptic density
      iii. REM % of sleep is maintained in healthy old age, correlates with retention of normal intellectual functioning
      iv. Arousals increase with age with reduced overall needs for sleep

4. Sleep structure
530.305 – Regulation of Visceral Function

a. Amount of sleep needed/favoured by an individual is variable, but in general performance decreases with <5hrs
b. Sleep patterns are habitual, and people can adapt to bizarre sleep patterns and appear to function effectively – lack of consistency is the problem
   i. Shift workers have increased physical and psychological morbidity
c. Sleep deprivation leads to a “sleep debt” of SWS and REM:
   i. Lack of SWS → decrease psychomotor performance
   ii. Lack of REM → irritability, mood swings, etc.
d. Proportions of each stage vary with age – significance is unclear

Sleep and breathing

1. Non-REM sleep
   a. Decreased respiratory drive (fluctuations in stages I and II)
      i. Decreased stem effect of wakefulness
      ii. Decreased chemosensitivity
   b. Non-chemical inputs are minimised – however, breathing still regulated by metabolic respiratory controls (in deeper stages, stable)
   c. Decreased V_E and slight increase in PaCO_2

2. REM sleep
   a. Irregular respiratory drive
   b. Transient reduction of ventilatory response to chemical/mechanical stimuli
   c. Short periods of central apnoea
   d. Generalised inhibition of skeletal muscle tone (including pharyngeal muscles)
   e. Decreased thoraco-abdominal movement coupling

3. Physiological impact of sleep on breathing:
   a. Very little in normal individuals
   b. Very important consequences in those with disturbances of respiratory structure and function – e.g.
      i. Decreased metabolic drive
      ii. Decreased diaphragmatic strength
      iii. Decreased intercostal and accessory muscle function activity in those with structurally small oro-pharynx

4. Pharyngeal muscles
   a. Principally pharyngeal dilators
      i. Genioglossus is predominantly an inspiratory phasic muscle
      ii. Tensor palatini is a tonic postural muscle
   b. Act as ’respiratory’ muscles (output from CNS):
      i. Respond to standard respiratory stimuli (CO_2, O_2)
      ii. Respond to negative pressure via superior laryngeal nerve

5. Upper airway function
   a. Upper airway function involves a balance of forces promoting:
      i. Patency – pharyngeal dilator muscles
      ii. Compliance – pharyngeal compliance
      iii. Collapse – high upstream resistance, small starting size
   b. Snoring is due to partial collapse of pharynx/hypopharynx, leading to increased upper airway resistance → turbulent airflow → vibration
   c. Effects of airway narrowing in sleep involves increased respiratory effort →
      i. Sleep disruption
         1. Sleepiness
         2. Road traffic crashes (over 20% in the US)
      ii. Arousal
      iii. Raised blood pressure (adrenergic stimulation) →
         1. Cerebrovascular accidents
         2. Cardiovascular disease
Humans are homeothermic – they maintain their core body temperature within narrow limits in order to maintain organ function. Enzyme reaction rates are temperature-dependent, and metabolic activity changes ~25% for each 1°C change in temperature. Note that temperature can be lowered for a time, but can’t be increased greatly or for very long without problems.

1. **Core temperature** – everything deeper than 25mm, accounts for ~50% of mass
   a. Measured in various ways – oesophageal is best, but tympanic is easier
   b. Difficult to specify normal core temperature (independent variability)
      i. Females hotter than males
      ii. Exhibits a diurnal rhythm, and varies with menstruation in women

2. **Shell/skin temperature**
   a. Variation amongst different parts of the body and with ambient temperature
   b. At comfortable room temperature of 24-25°C, mean skin temperature is 33°C (ranges from 28.6°C hands to 34.6°C head)
   c. Can fluctuate by 10°C around its mean with no permanent damage
      i. <18°C can lead to anoxia, pain, tissue damage
      ii. >45°C can lead to burns, oedema, pain

3. **Mean body temperature**
   a. No single temperature represents the body as a whole
   b. 2/3 of body mass is considered to represent core and 1/3 to represent shell
   c. Relative proportions of core and shell are affected by ambient temperature

**Heat transfer:**

1. **Within the body**
   a. Major organs produce heat – transfer down the temperature gradient must be controlled in order to maintain constant core temperature
   b. In cold conditions, involuntary rhythmic muscle contraction \(\rightarrow\) heat/shivering
   c. Conductive heat transfer is slow – convective via blood is more important
   d. Contraction/expansion of core \(\rightarrow\) alteration of insulation of the body
      i. Achieved by controlling the amount of blood flow to the surface

2. **With the environment**
   a. Conduction, radiation, convection, evaporation
   b. \(M - W = E + R + C_n + C_v + S\)
      i. \(M\) – rate of metabolic energy production
      ii. \(W\) – rate of external working
      iii. \(E\) – evaporation (always negative)
      iv. \(R\) – radiation
      v. \(C_n\) – conduction
      vi. \(C_v\) – convection
      vii. \(S\) – heat storage (\(\Delta\) mean body temperature \(\times\) specific heat of tissue mass)

**Thermoregulatory control system**

1. **Model of the control system**
   a. Negative feedback control system – most complex in the body
   b. Input – temperature sensors in skin and deep structures
   c. Effector mechanisms – vasomotor, metabolism, shivering, sweating
   d. Comparator mechanism in the preoptic hypothalamus

2. **Neural substrate for control of body temperature**
   a. Thermoregulatory control system has 2 receptor types – cold and warm
      i. Both exhibit combined static (steady state) and dynamic (rate of change) response to temperature
      ii. Cold supplied by A\(_\delta\) fibres, warm by C fibres
   b. Afferents are carried in the ventrolateral spinothalamic tract
      i. Give branches to noradrenergic and serotonergic brainstem nuclei
      ii. Project to the VPL of the thalamus \(\rightarrow\) hypothalamus, sensory cortex
   c. Temperature-sensitive neurones are found throughout the body
      i. Preoptic anterior hypothalamus is exquisitely temperature sensitive
530.305 – Regulation of Visceral Function

1. High Q_10 neurons – large increase in firing with temperature
   ii. Efferents are ANS, voluntary motor system and neuroendocrine
2. Low Q_10 neurons – smaller increase with temperature
3. Neural realisation of body temperature control – the hypothalamus is extremely sensitive, but is probably not the critical sensor (would rely on changes in the thing we are trying to control)
   a. System contains a feed-forward element from receptors in the shell

**Fever, Hyperthermia, Hypothermia**

There is a set of systemic reactions (collectively known as the acute phase reaction) that mitigate deleterious effects of invading pathogens and ultimately restore health – most obviously, fever.

1. **Body temperature control during fever**
   a. Controlled state – core temperature is raised/maintained about an elevated set-point
   b. Onset \(\rightarrow\) shivering vasoconstriction \(\rightarrow\) fever \(\rightarrow\) breaks \(\rightarrow\) sweating vasodilatation
2. **Mediators of the febrile response**
   a. Cascade of endogenous pyrogens (cytokines) mediate fever and the acute phase reaction. Produced by mononuclear phagocytes activated by exogenous pyrogens
      i. IL-1\(\alpha\), -1\(\beta\), -6, -8, -11, IFN-\(\alpha\), -\(\gamma\), TNF-\(\alpha\), -\(\beta\)
      ii. Act on the preoptic anterior hypothalamus to increase set point
   b. Cytokines are hydrophilic (won’t cross the blood-brain barrier)
      i. Transport hypothesis – across BBB
      ii. Organum vasculosum laminae terminalis hypothesis – leaky BBB
      iii. Neural hypothesis – active peripheral vagal afferents (Kupffer cells)
   c. POAH and OVLT regions lack cytokine receptors, and there is a delay in the onset of fever after injection of bacterial LPS
3. **Neural mediation of the rapid febrile response**
   a. LPS in blood activates complement (C3a, C5a) which bind to Kupffer cells
   b. Kupffer cells release mediators (cytokines, PGE\(_2\)) which stimulate vagal afferents (subdiaphragmatic) that project to the nucleus tractus solitarius
   c. Afferent input to the NTS is transmitted to noradrenergic groups A1 and A2, which project via the ventral noradrenergic bundle to the POAH and OVLT
   d. Noradrenaline produced stimulates local release of PGE\(_2\) \(\rightarrow\) fever
4. **Benefits of fever** – associated with a significantly increased survival rate in animals
   a. Associated with elevated plasma iron levels (inhibit bacterial growth)
   b. Inhibitors of prostaglandin synthesis (aspirin, indomethacin) reduce fever – this may not be desirable in the long run

**Hyperthermia** is an equilibrium condition rather than a controlled state (set point not raised)

1. Work is associated with increased core temperature
2. When work is done at high ambient temperatures, regulation fails \(\rightarrow\) fulminating hyperthermia
3. Outside the prescriptive zone, it is incorrect to call hyperthermia an equilibrium state
4. The physiological demands of body temperature regulation and exercise are conflicting
5. Death from heatstroke is multifactorial but probably due to DIC

**Hypothermia** – condition where core temperature falls below 35°C

1. Environmental hypothermia is a killer – immersion at 2°C \(\rightarrow\) hypothermia in 1hr
2. Heat production cannot match heat loss, despite maximal vasoconstriction

35°C – onset of hypothermia
34°C – hyperreflexia, confusion
32°C – shivering ceases (body temperature regulation impaired)
31°C – consciousness clouded
30°C – pupils dilate, hyperreflexic, incipient death
28°C – heat production halved
27°C – coma (Body temperature regulation lost)
26°C – loss of deep reflexes
24°C – survival doubtful
20°C – EEG flat
17°C – lowest limit of reported survival
PHYSIOLOGY OF EXERCISE

Physiology of Exercise

Physical activity initiates an integrated response via neural/humoral mechanisms depending on type, intensity and duration of the activity. Repetition → adaptations increasing skill, capacity & efficiency

1. Muscles derive energy from ATP hydrolysis (from PCr, CHO, lipid, not much protein)
2. Maximum power is brief as the energy supply from 2° organs is limited at high rates
   a. Products of anaerobic metabolism (H+, ADP, PO4−) inhibit power production
   b. Power output for more than a few minutes depends on ATP replenishment
3. Oxygen transport capacity (VO2) can be measured and VO2max can be defined
4. From oxygen consumption, total body energy expenditure can be calculated

Sources of energy for muscle action:
1. The fuel substrate varies with intensity and duration
   a. Rest – 50-60% fat, remainder is CHO
   b. Exercise (increased intensity) – shift from lipid to CHO utilisation (glycogen)
   c. Submaximal sustained exercise – gradual shift to lipid and circulating fuels
2. Fuel homeostasis modulated by insulin, catecholamines, glucagon, cortisol, GH
3. Increased hepatic GNG/glycogenolysis, FFA mobilisation and muscle glycogenolysis
4. Magnitude of neurohumoral response depends on intensity, diminishes with training

Effects of endurance training
1. Prolonged exercise at 50-80% several times a week → skeletal muscle adaptations improving functional capacity (O2 delivery, uptake, use). Remission follows inactivity.
   a. Selective hypertrophy of slow-twitch muscle fibres with higher number of capillaries
   b. Increased size/number of mitochondria and capacity to generate ATP
   c. Increased capacity to oxidize lipid and CHO (with reliance on lipid as fuel)
   d. Higher glycogen and triglyceride content
2. Changes also occur in the metabolic response to a bout of acute exercise – in general, the hormonal response is significantly attenuated and there is increased endurance capacity
   a. Lower respiratory exchange ratio and respiratory quotient (lipid > CHO)
   b. Smaller rise in plasma FFA
   c. Lower utilisation of blood glucose by muscle, lower accumulation of lactate
   d. Increased oxidation of lipid (relative to CHO), use of intramuscular triglyceride
3. Examples of health applications of training adaptations
   a. Type 2 diabetes mellitus – increased habitual physical exercise → decreased insulin resistance and improved glucose homeostasis
      i. Insulin-independent effects and increased insulin sensitivity involved
      ii. Decreased hepatic glucose output → better glucose level control
      iii. Effects are short-lived, so exercise must be at least 3x a week
      iv. Prevents onset of type 2 diabetes mellitus in at-risk individuals
   b. Regular endurance exercise → lower cholesterol, TAG, LDL; higher HDL

In steady state aerobic exercise, rate of O2 supply is equal to the rate of utilisation:
1. VO2 = QT x (CaO2 – CvO2), QT = HR x SV
2. O2 intake and CO both increase linearly with work rate
3. O2 extraction is curvilinear

Arterial O2 content
1. Determined by ventilation and gas transfer in the lungs
   a. CaO2 = (SaO2 x [Hb] x 1.34) + (PaO2 x solubility)
   b. In healthy individuals there is reserve – CaO2 preserved until intense exercise
2. Determinants of oxyhaemoglobin saturation:
   a. Alveolar ventilation increases linearly with work until lactic acidosis → hyperventilation
   b. Vp/Qr ratio – increases with moderate exercise, but deteriorates at near maximum exercise (major cause of A-a P02 difference)
   c. Venoarterial shunt (Qs/Qt)
   d. P50 of Hb (temperature, Pao2, pH, DPG) – increases with exercise, facilitates unloading of O2 at the tissues without impairing lung function
530.305 – Regulation of Visceral Function

i. Contributes to differences in $CaO_2$ and $V_{O_2}$ between males/females
ii. Haemoconcentration is due to intensity-related hypovolaemia

3. Blood gases are relatively unchanged until reaching maximum exercise (start to decrease)
4. Regulation of exercise ventilation is by both neural and chemical components
   a. Adaptation to habitual exercise doesn’t involve the respiratory system
   b. Respiratory limitations may limit exercise

Venous oxygen content and mixed venous oxygen content
1. Determined by peripheral circulation and muscle metabolism (tissue $O_2$ uptake)
2. Local muscle blood flow increases with exercise intensity and local metabolism (CO)
3. Control mechanisms – precapillary vessels, feed vessels, ascending vasodilation, mechanical effects, neural redistribution of CO
4. Diffusion from capillaries to mitochondria depends on Fick’s Law (area, thickness, diffusion coefficient, pressure gradient) – habitual physical activity and training $\rightarrow$ increased capillary density and vasodilator capacity $\rightarrow$ increased area, decreased thickness

Cardiac output – note that $EDV = SV + ESV$
1. Linear increase in CO with increased workload is achieved by both SV and HR
   a. HR (PNS/vagal withdrawal $\rightarrow$ SNS drive, age, drugs) is linear until near max effort
   b. SV reaches maximum by 40% maximum $O_2$ uptake – continues to increase in elite athletes via faster left ventricular emptying and particularly faster left ventricular filling
2. End-diastolic volume – overall, increases with intensity. Determined by:
   a. Venous return – thoracic (respiratory) and muscle pumps
   b. Blood volume – increases with training
   c. Pericardial limitation, ventricular compliance
   d. Atrial contraction – increases with exercise (filling time lower with faster HR)
3. End-systolic volume – overall, decreases with intensity. Determined by:
   a. Myocardial contractility – determined in part by Starling preload
   b. Neural (sympathetic) and hormonal (catecholamines) control mechanisms
   c. Afterload – factors that resist ejection (TPR, arterial pressure)
4. Arterial pressure increases with exercise intensity, but there are differences between dynamic and static exercise that reflect different CO and TPR (increased in static, reduced in dynamic)
5. CVS adaptations adjust blood flow to match supply and metabolic demand:
   a. SV at a given intensity increases, so baseline HR can decrease
   b. Maximum HR is the same, but at this rate a greater SV and CO are obtained
   c. Increased CO is matched by increased vasodilator capacity of muscle
   d. $O_2$ extraction is increased – overall there is an increase in $V_{O_2max}$

Thermoregulation:
1. Substrate catabolism $\rightarrow$ heat (60% of utilised energy) that must be dissipated
2. Some substrate is stored $\rightarrow$ increased body temperature with exercise
3. Mechanisms of heat loss activated – significant sweat loss may $\rightarrow$ circulatory stress
4. Distribution of CO is modified to increase blood flow to the skin
5. Increases in temperature reach a plateau if the athlete is properly hydrated

Fluid homeostasis and renal function
1. Internal fluid – high ICF/ISF osmolality, high mean capillary hydrostatic pressure
   a. Starling changes $\rightarrow$ shift from plasma to ISF/ICF $\rightarrow$ lower plasma volume
2. External fluid loss impairs performance and can be life-threatening – sweat rate and ability to lose heat diminishes $\rightarrow$ core temperature rises
3. RBF and GFR decline in exercise (filtration fraction increases) – urine output lower even with normal hydration (SNS activation, ADH increases with intensity, ANP – mechanism unclear)
4. Training effects – total blood volume increases and plateaus
   a. Increased plasma volume (peak then to above baseline level); RBC mass increases
      1. Sports anaemia – plasma volume increase without RBC mass increase
   b. Decreased plasma volume in exercise is less of a stress to CVS system

Gut absorption
1. GI motility and absorptive capacity are maintained in all but extreme exercise
2. Fluid and energy replacement during exercise are effective to replenish losses