CARDIOVASCULAR ANATOMY AND PHYSIOLOGY

Anatomy of the major arteries and veins

Anatomy of the heart, the pericardium and valves – FROM CICM

Anatomy of the heart

- heart located in thorax, enclosed within fibrous sac (pericardium)
- 3 tissue layers:
  - Epicardium: outer connective tissue layer
  - Myocardium: cardiac muscle
  - Endocardium: epithelial cells; line inner surface
- divided into R + L sides
  - each consisting of atrium + ventricle
  - separated by interatrial + interventricular septae
- 4 chambers: RA, RV, LA, LV
  - RA: receives deoxygenated blood from SVC + ICV; tricuspid valve
  - RV: crescent shape in transverse plane; triangular in longitudinal plane; pulmonary valve
  - LA: oxygenated blood returns from lungs through 4 pulmonary veins to the LA; mitral valve
  - LV: circular transverse section, conical longitudinal section; aortic valve
- Myocardium
  - "functional syncytium" – cardiac muscle = electrically, chemically, mechanically coupled together
  - Arranged in networks of striated cardiac muscle cells joined together by intercalated discs
  - Intercalated discs contain 3 different types of cell-cell interaction:
    - 1. Gap junctions: permit direct passage of intracellular ions + molecules from one cell to another → allows direct electrical spread of AP from cell to cell
    - 2. fascia adherens: anchor actin filaments within sarcomere to the cell membrane
    - 3. macular adherens (desmosomes): anchor cardiac cells to one another
- Fibrous skeleton
  - Dense collagen; forms 4 fibrous rings (surrounds valves); R and L fibrous trigones; and interatrial and interventricular septa
  - Maintains valvular patency and prevents distension
  - attach valvular leaflets and cusps
  - attach myocardium
  - provide electrical insulation, therefore separating atrial and ventricular impulses, surrounding and providing passage for the AV bundle

Pericardium

- Double walled sack:
  - external fibrous layer: fused with…
    - anteriorly: tunica adventitia of great vessels + sternum
    - inferiorly: central tendon of diaphragm
    - posteriorly: loose connective tissue
  - Serous parietal layer: reflects onto heart + great vessels as visceral pericardium

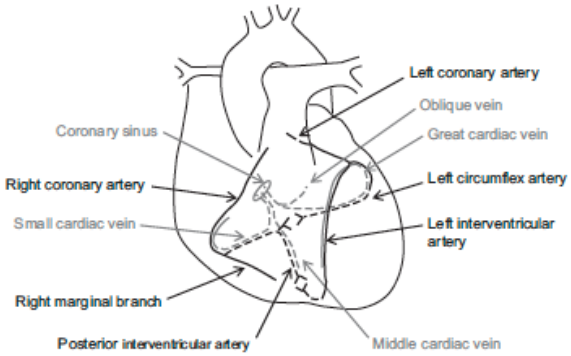
Cardiac valves

- consist of thin flaps of flexible, tough, endothelium-covered fibrous tissue that are firmly attached to the base of the fibrous valve rings
- movement of valve leaflets si essentially passive
- orientation of the valves is responsible for the unidirectional flow of blood through the heart
- 2 types of valves: atrioventricular + semilunar
  - Atrioventricular valves
    - Tricuspid: between RA and RV; 3 cusps
    - Mitral: between LA and LV: 2 cusps
    - Chordae tendinae arise from papillary muscles → attach to valves → prevent valves from everting during ventricular systole
  - Semilunar valves
    - Pulmonary: between RV and pulmonary artery
    - Aortic: between LV and aorta
    - Consist of 3 cusps
    - Reversal of blood flow at end of ventricular systole snaps cusps together → prevents regurgitation of blood
  - Sinuses of valsalva + eddy currentys develop → prevent obstruction of coronary ostia

Coronary artery anatomy

Coronary artery anatomy

- Heart receives 5% of CO = 250ml/min
- ventricular wall too thick for effective diffusion of O2:
  - Endocardium nourished directly
  - Bulk of cardiac muscle perfused by coronary circulation
- Coronary circulation
  - divided into L + R
  - Arise from aortic root at aortic sinuses ("sinuses of valsalva")
  - Eddy currents prevent valve cusps from occluding os of LM + RCA



LCA (L main stem)

- Origin: L posterior aortic sinus
- Course: along L AV groove → bifurcates into:
  - 1. LAD
    - *course*: along anterior interventricular groove to apex
    - *branches*: septal + diagonal perforators
    - *supplies*:
      - anterolateral myocardium
      - apex
      - ant 2/3 of interventricular septum
  - 2. L circumflex artery
    - *course*: L AV groove
    - *branches*: obtuse marginal branches

- anastomoses with terminal end of RCA
- *supplies*: posterolateral LV; SA in 40%

RCA

- Origin: anterior aortic sinus
- Course: along R AV groove
- Branches:
  - 1. SA branch: supplies SA node
  - 2. R marginal artery: along R margin of heart towards apex; supplies RV
  - 3. Posterior interventricular artery (posterior descending): supplies posterior septum + AV node
- continues in AV groove → anastomosis with L circumflex

Coronary dominance

- refers to the artery giving rise to the post interventricular artery
- Right dominant = PDA supplied by RCA; 60%
- Left dominant = PDA supplied by LCx; 20%

Venous anatomy

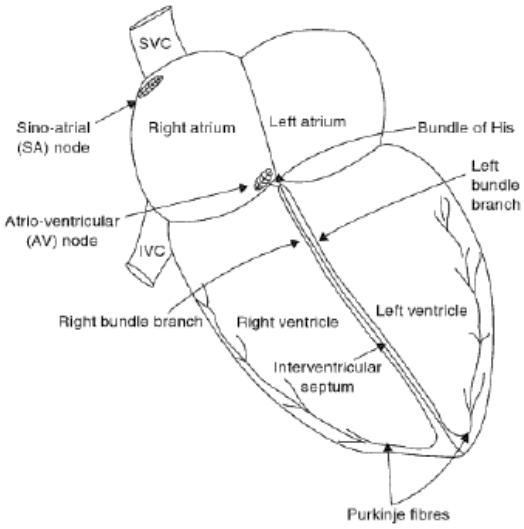
1. coronary sinus
   a. Venous blood from LV collected by cardiac veins → coalesce to form coronary sinus → opens into RA
   b. Cardiac veins: follow same path as arteries: include…
      i. great cardiac vein: runs with LAD
      ii. middle cardiac vein: follows PDA
      iii. small cardiac vein: runs with RCA
      iv. oblique vein: follows post part of LA
2. anterior cardiac veins: arise on ant surface of RV; drain into RA
3. thebesian veins: smallest; drain directly into 4 chambers of the heart

Anatomy of excitatory and conductive elements: MAKEUP

Excitatory and conductive elements

General conduction arrangement

- SA node → intermodal fibres → AV node → AV bundle L and R purkinje fibre branches
- Delay between SA depolarisation to AV node ~0.03s
- AV node → penetrating AV bundle delay ~0.09s
- AV penetrating to distal conduction a further ~0.04s delay
- Total time from SA node discharge to signal arrival at ventricles therefore ~0.16s



SA node

- normal cardiac pacemaker
- arises at junction of SVC + RA
- R vagus supplies SA (L vagus AV node) with SY innervation
- NA fibres are epicardial and Ach fibres are endocardial
- Ach acts presynaptically on SY nn → ↓NA release and NPY mayact to inhibit release of Ach
- An interatrial band conducts signals from R → L atrium

AV node

- located in post R atrial wall/ atrial septum, just above the opening of the coronary sinus
- receives connecting pathways from SA node
- signals arriving at the AV node travel to the penetrating and then distal portions of the AV bundle (bundle of His)
- unidirectional conduction normally

Purkinje fibres

- lead from the AV node through the AV bundle to the ventricular endocardium
- highly permeable gap junctions permits signal transmission at 1.5-4ms

Autonomic innervation

- arise from the VA (PSY) + cervical + upper thoracic SY ganglia
  - VA fibres = cardio-inhibitory → ↓rate of conduction of APs through AV node
  - SY fibres = cardio-acceleratory → ↑rate of conduction of APs through AV node

Electrical properties of the heart

Ionic basis of automaticity the normal and abnormal processes of cardiac excitation

Pacemaker action potential

Background:

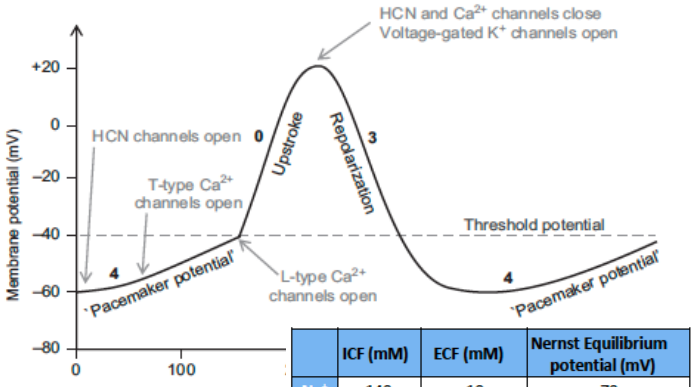
- **automaticity** = rhythmic depolarisation without external stimulation
  - several ionic currents contribute to slow diastolic depolarisation that occurs in automoatic cells in the heart
  - outward K current; hyperpolarization induced inward current; inward Ca2+ current
- **cardiac pacemaker cells** = specialised cardiac myocytes whose spontaneous activity results in generation of APs
  - Sites acting as pacemakers: SA + AV nodes
  - NB ventricular myocytes may also display automaticity under pathological conditions e.g. ischaemia

Ionic basis of automaticity

- pacemaker cells exhibit automaticity
  - have **no RMP** + undergo **spont depolarisation** → initiation of AP
  - cardiac myocytes: biphospholipid membrane – selective permeability to ions via ligand + voltage gated protein channels
  - difference in conc across cell membrane create EC gradient

***Phases of cardiac pacemaker AP*:**

- **Phase 4:**
  - hyperpolarization-activated cyclic nucleotide gated (HCN) c
  - membrane hyperpolarization opens HCN channels → Na +
  - slow depolarisation of CM from -60mV to -40mV
- **Phase 0: Depolarisation** via:
  - voltage-gated T-type + L-type **Ca2+ channels** → inward C
- **Phase 3: Repolarisation** via
  - Inactivation of funny, T-type + L type Ca2+ channels
  - activation of K channels → K efflux
- **Phase 4:**
  - Membrane potential returns to ~-60mV
  - Funny channels reactivated + cycle repeats



	ICF (mM)	ECF (mM)	Nernst Equilibrium potential (mV)
Na^+	140	10	70
K^+	135	5	-94
Ca^{2+}	<0.1	2	134

Factors affecting automaticity

- **ANS**
  - SA + AV node have ANS innervation
  - SY stimulation via cardioaccelerator T1-T4 nerves → B1 adrenoceptors → Gs GPCR → ↑cAMP → ↑influx through funny currents (steeper phase 4) + ↑Ca2+ influx (steeper phase 0) → ↑HR
  - PSY innervation (via VA): action at M2 acetylcholine Rs → Gi GPCR → ↓cAMP → ↓HR
- **Hypoxia**
  - ↓ATP → inactivation of Na/K ATPase → unable to repolarize cell → automaticity lost
- **temperature**
  - ↑temp → ↑actions of ion channels → ↑slope of phase 0 → ↑automaticity + HR
- **Age**
  - Pacemaker cells infiltrated by fibrotic tissue → ↓automaticity → ↓max attainable HR

How does the pacemaker AP differ from that in cardiac myocytes?

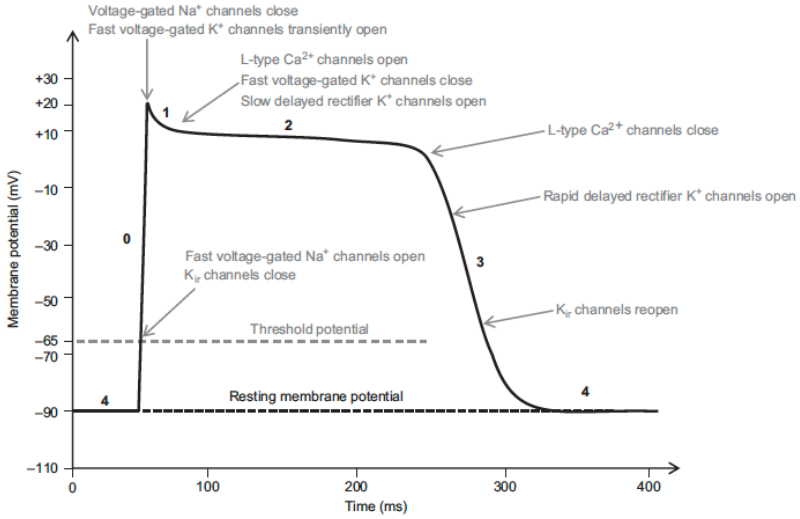
	Pacemaker AP	**Cardiac muscle AP**
Spontaneous depolarisation?	Yes	No
Membrane potential	-60mV	-90mV
Threshold potential	-40mV	-65mV
Slope of phase 0 (depol)	Less steep	Very steep
Depolarisation ion	L-type Ca2+ channels → Ca2+ into cell	Fast Na+ channels → Na+ into cell
Repolarisation	Single phase (phase 3)	Early rapid repolarization: phase 1 Final repolarization: phase 3
Plateau?	No	Yes

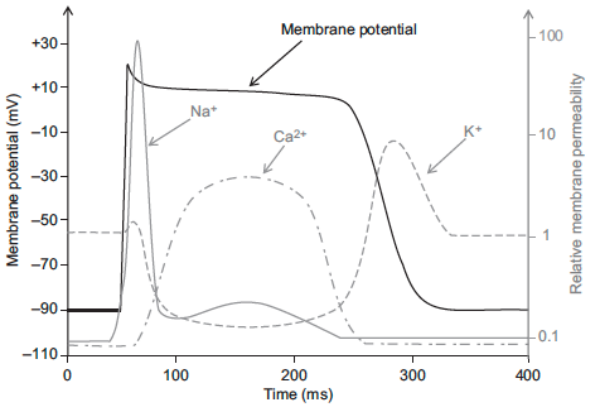
Cardiac muscle action potential

- cardiac muscle is activated by AP generated by cardiac pacemaker cells
- propagation of AP between myocytes is facilitated by intercalated discs (gap junctions)

Phases

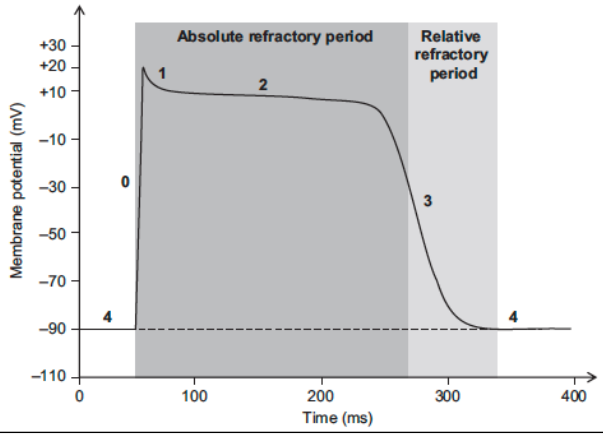
- **Phase 0 (rapid upstroke/ depolarisation)**
  - threshold potential (-65mV) reached
  - fast voltage gated (outward M gate) **Na+ channels** open → rapid Na influx to +30mV → depolarisation
- **Phase 1: repolarization (partial)**
  - Na+ channels close (inward H gate)
  - K+ channels open → transient outward (repolarizing) K current
  - No repolarization below 0mV
- **Phase 2: plateau phase**
  - Inward current: voltage gated L type Ca2+ channels open → Ca2+ down EC gradient → Ca2+ influx
  - Outward current: K efflux
  - Allows for sustained contraction of ventricular muscle fibres necessary for ejection of blood from ventricles
- **Phase 3: repolarization**
  - Voltage gated L type Ca2+ channels close
  - K efflux unopposed → repolarization
- **Phase 4: RMP**
  - RMP (-90mV) maintained due to:
    - Na/K/ATPase (3Na out; 2K in)
    - Na/Ca2+ exchanger
  - K conductance > Na + Ca2+ conductance → RMP





Excitability: ability of a cardiac muscle cell to reach hreshold in order to generate/ propagate an AP

- absolute refractory period (250ms):
  - cell is not excitable due to closure of fast Na+ channels (via m gate) + remain closed until -50mV
  - phase 0,1,2, early 3
- Relative refractory period (further 50msec)
  - Can excite cell to generate AP with supramaximal stimulus



Abnormal cardiac excitation

- **↑automaticity**: may occur in SA, AV, and His-Purkinje system
- **ectopic foci:** atrial, nodal, or ventricular extrasystoles
- **Blocks**
  - 1st degree
  - 2nd degree
  - RBBB / LBBB
  - Interruption to SA node: 3rd degree
  - Infranodal disease: ventricular PM 15-35BPM
- **atrial arrhythmia**
  - Atrial tachycardia: regular discharge of an atrial focus or re-entrant activity → rates up to 220/min
  - atrial flutter: 200-350/min; counter clockwise movement in RA; usually 2:1 block
  - AF 300-500/min; irregular + disorganised; ↓diastolic time + loss of atrial component in diastole
- **accelerated AV conduction**
  - WPW: bundle of Kent forms additional nodal or aberrant muscular connection between atria + ventricles
- **ventricular arrhythmia**
  - Ventricular premature beats: ↑QRS due to slow impulse spread
  - VF: irregular + ineffective discharge of multiple ventricular ectopic foci
- **After depolarisations + triggered automaticity**
  - Delayed after depolarisation (DAD): intracellular Ca2+ overload (myocardial ischaemia, adrenergic stress, digoxin toxicity, heart failure)
  - Early after depolarisation (EAD): prolonged AP interrupting phase III repolarisation.
    - inward Na or Ca2+ currents
    - More common with ↓HR, ↓K+, or drugs prolonging AP
    - Induced more readily in His-Purkinje system + mid myocardial
    - Torsades associated with EAD

Threshold: minimum level of memebrane potential depolarisation required for an AP to occur: cardiac threshold = -65mV; pacemaker -40mV

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Irritability: ↑RMP sually due to ↑K+
- More likely to reach AP threshold as there is less difference between RMP and threshold potential with aberrant discharges more likely (arrhythmias)

Physiological basis of the electrocardiograph in normal and common pathological states

Normal ECG

	Details	Normal duration	Pathology
P wave	Atrial depolarisation	<0.1s <2.5 small squares	AF: P wave absent L atrial hypertrophy: larger, bifid P waves
PR interval	Time between onset of atrial + ventricular depolarisation Represents AV nodal delay Beginning of P wave to beginning of Q wave	0.12-0.2s 3-5 small squares	Nodal block: ↑ PR interval WPW: delta wave → ↓PR interval
QRS	Ventricular depolarisation + propagation - septal depolarisation → small –ve depolarisation = Q wave - remaining ventricular muscle depolarisation → large +ve depolarisation = R wave - wave of depol flows towards base of ventricles away from electrode → electrical potential 0 - base of LV depolarizes → small –ve deflection = S wave	<0.12s 3 small squares	BBB: widened QRS Pathological Q waves
ST segment	Isoelectric segment that follows QRS Plateau phase of the cardiac AP		Ischamia: elevation/ depression
T wave	Ventricular repolarization		Ischaemia: inverted
QT interval	Time from onset of ventricular depolarisation to completion of ventricular repolarization Duration of the cardiac AP	QTc <0.44 (11 small squares)	↑QTc associated with ventricular dysrrhuthmias

- Potential difference between pairs of electrodes = lead
  - Each lead views electrical activity in heart from different angle
  - Limb leads: electrodes on R arm, L arm, L leg
  - Augmented limb leads (aVF, aVR, aVL):
  - 6 precordial leads (V1-V6)
  - +ve and –ve deflections indicate net electrical current flow towards + away from electrode
- Cardiac axis
  - Leads that view heart in coronal plane (6 limb leads + augmented limb leads) can be used to determine cardiac axis = net direction (or vector)
  - Axis -30 = L axis deviation → LVH
  - Axis +90o = R axis deviation → RVH

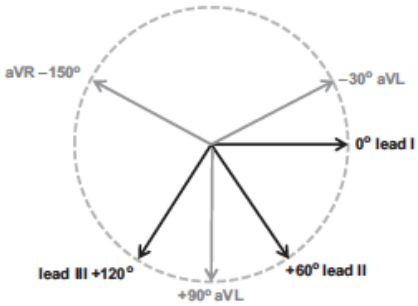
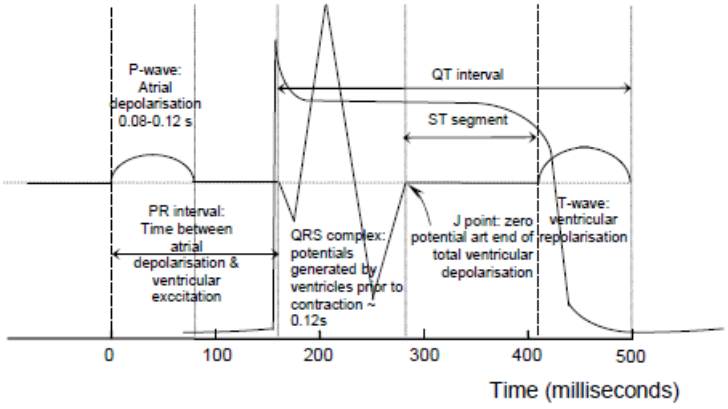


Figure 55.3 Vectors of the ECG leads.

Link the coronary circulation to leads of an ECG
- The leads of an ECG view different surfaces of the heart which are supplied by different arteries.
- Leads II, III, aVF = inferior surface of the heart → usually RCA or distal circumflex
- Leads VI to V4 = anterior surface → LAD
- Leads I, aVL, V6 = lateral surface → proximal circumflex artery
- VI and aVR = RA and cavity of LV

The normal ECG with a "fast fibre" AP superimposed



ECG + myocardial ischaemia
- Extent of myocardial ischaemia
  - subendocardial ischaemia/ infarction → ST depression
  - subpicardial or transmural infarction → ST elevation
- Location of ischaemia

Location of ischaemia	Leads affected	Supplied by	Effect of occlusion
Inferior wall	II, III, aVF	RCA	As RCA supplies SA node: occlusion → hypotension + bradycardia
Lateral wall	I, II, V5	Circumflex	LV dysfunction
Septal	V1, V2	Septal branch L interventricular a	As interventricular septum is site of bundle of His → BBB
Apical	V3, V4	Terminal portion of L interventricular a If R dominant: post	

		interventricular a	
Anterior wall	Can affect: I, aVL, V1-V6	L interventricular a	Complete occlusion: ischaemia of large portion of LV → severe LV dysfunction
Posterior wall	ST depression V1-V4	Circumflex + post interventricular a	L ventricular dysfunction

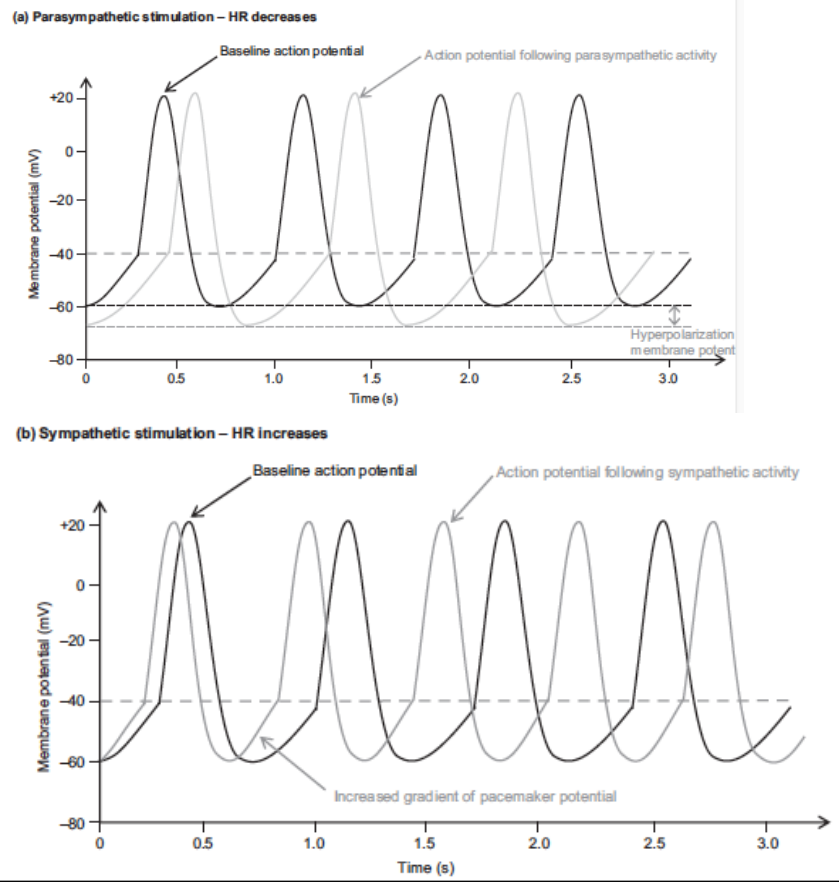
Factors that may influence cardiac electrical activity

- **ANS**
  - SY:
    - via NAd at B1 receptors: ↑HR by ↑rate of phase 4 depolarisation via ↑Na+ influx during phase 4
    - ↑Ca2+ influx which ↑ conduction through AV node → ↓PR interval (+ve dromotropic effect)
  - PSY:
    - ACh acting on muscarinic Rs → ↓HR by ↓Na+ influx + therefore extending phse 4 duration in the slow response myocytes + ↓Ca2+ influx which slows conduction through the AV node
- **Endocrine:** Adrenaline; Noradrenaline ; Thyroxine
- **Metabolic**
  - Na: ↓Na+ → ↓voltage ECG complexes
  - ↑K:
    - tall T waves – manifestation of paralysis of the atria + prolongation of the QRS complexes
    - ventricular arrhythmias
    - RMP ↓s as K↑s
    - Prominent U waves
  - Ca2+:
    - ↑Ca2+: ↑myocardial contractility; shortening of QT interval due to shorter ST segment
    - ↓Ca2+: ST prolongation → QT prolongation
  - Mg2+
    - ↓Mg: widening QRS; peaked T waves; prolongation of PR interval
- **Temperature:** ↑temp → ↑HR; ↓temp → ↓HR
- **Drugs**
  - Adenosine:
    - Adenosine Rs in atrial + nodal tissues
    - Activate K+ current which transiently hyperpolarises the cell → drives SA and AV nodal tissue further from threshold and → slows rate
    - Antagonises adenylyl cyclase → ↓intracellular Ca2+ → slows conduction
    - Transient AV node block
- **Pathology**

Describe the autonomic innervation of the heart and the direct effect of autonomic stimulation on cardiac function: PAST QUESTION

- ANS = portion of nervous system that regulates involuntary control of most organs (including heart)
- Heart has SY + PSY innervation
  - SY: mediated by NAd → stimulation results in ↑HR + ↑contractility
  - PSY: mediated by ACh → stimulation results in ↓HR; no effect on contractility (as ventricular muscle not supplied)

Property	**SY**	**PSY**
Efferent origin	Vasomotor centre in medulla	VA nn → dorsal motor nucleus/ nucleus ambiguous
Basal tone	↓activity at rest	↑activity at rest
Effect of baroreceptor reflex	Inhibitory	Stimulatory
Pathway	Paravertebral	Through neck → mediastinum
Pre-ganglionic fibres	T1-T4 Right = SA node; L = AV node + ventricle	VA (paired) R = SA node; L = AV node
Ganglia	Paravertebral chain Stellate (inferior) + middle cervical Nicotinic ACh receptor	Myocardium/ epicardium Nicotinic ACh R
Post galgnionic fibres	Epicardial plexus	SA/ AV nodal tissue
Neurotransmitters	Excitatory: glutamate, ADH, angiotensin, ACh, catecholamines Inhibitory: GABA, enkephalins	ACh
Receptors	B1 receptors (norad)	Muscarinic M2 receptors
Intracellular response to R activation	GPCR → ↑cAMP → ↑activity of protein kinases → open L type Ca2+ channels ↑release Ca2+ from SR ↑trop I + ↑phospholamban	GPCR → ↑K+ conductance directly without 2nd messenger → ↑K+ → cell hyperpolarization
End result of activation	↑inotropy ↑chronotropy ↑dromotropy ↑lusitropy ↑automaticity (↑upstrake of phase 4 pacemaker AP)	↓HR (↓automaticity) ↓tranmission through AV node ↑R-R
Duration of action	Slow onset but long lasting due to amplification via GPCR 2nd messenger system	Effect rapid but short lived due to AChE at cleft
Effect on LV curve	Rotate anti-clockwise	Rotate clockwise



Cardiac cycle: correlation of the mechanical events of the cardiac cycle with the electrical and ionic events

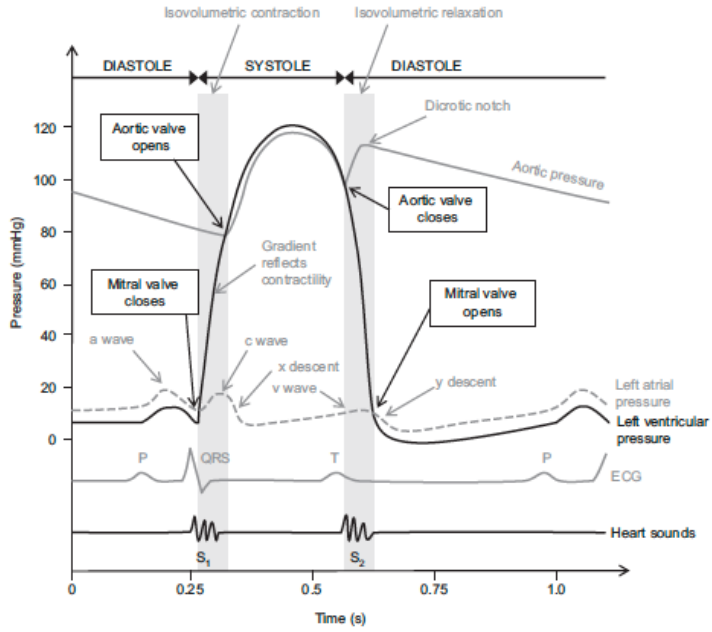
The cardiac cycle

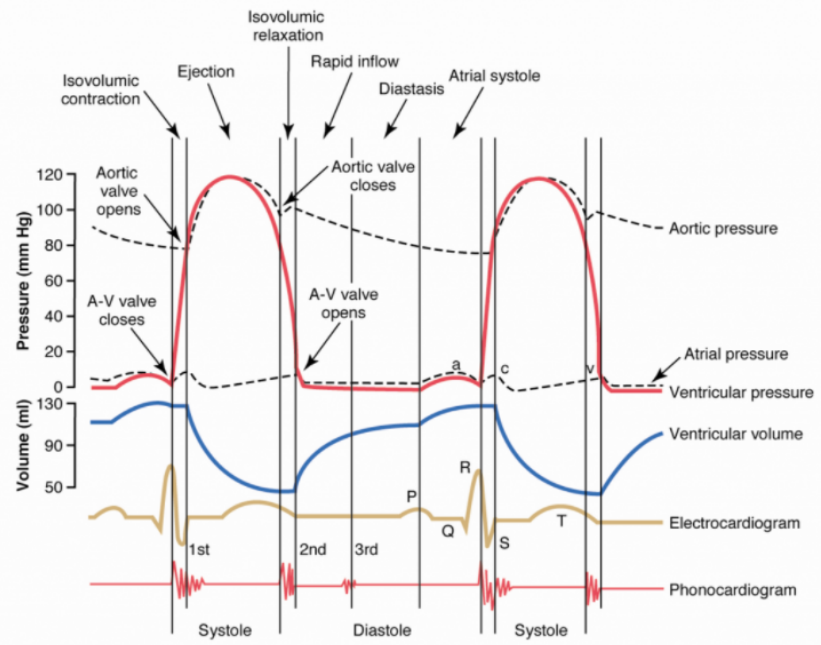
The cardiac cycle describes the events that occur during one heartbeat.

- **2 phases → divided into 6 stages**
  1. **Diastolic phase –** ventricles fill with blood; 4 stages:
     i. Isovolumetric relaxation
     ii. Rapid ventricular filling
     iii. Slow ventricular filling (start of cycle)
     iv. Atrial contraction
  2. **Systolic phase** – ventricles contract and eject blood into aorta and pulmonary artery; 2 stages:
     v. Isovolumetric contraction
     vi. Ejection
- NB: a cycle begins in late diastole when the myocardium is relaxed and the ventricles are passively filling

Cycle:

Phase	Details	ECG	CVP
1. Slow ventricular filling (diastole)	Atrial pressure > ventricular pressure AV valves open → blood flows from atria to ventricles	P wave	
2. Atrial contraction (diastole)	Atrial "kick" → ~20% ventricular filling Vol of blood in ventricle at end of atrial contraction = EDV	PR interval	a wave: small pressure wave in great veins
3. Isovolumetric contraction (systole)	time between closure of AV valves → opening of aortic + pulmonary valves ventricular pressure ↑ without Δventricular vol	Start of QT interval	c wave: ↑RV pressure → TV bulges into RA
4. Ejection (systole)	Ventricular P > aorta/ pulmonary P → semilunar valves open 1. Rapid ejection 2. Reduced ejection eventually ventricular P < aortic/ pulmonary pressure → semilunar valves close Vol of blood within ventricle after valve closure = ESV	ST segment	x descent: shortening RV pulls RA down → ↓CVP
5. isovolumetric relaxation (diastole)	Initially AV valves remain closed as the pressure in ventricles > atrium		v wave: atrial pressure ↑s due to VR
6. Rapid ventricular filling (diastole)	Atrial pressure > ventricular pressure → AV valves open → blood from atria to ventricles		y descent: ↓atrial pressure





Describe the physiology of cardiac muscle and the mechanism of excitation contraction coupling

Cardiac muscle

- Special intrinsic properties:
  - Excitability
  - Automaticity
  - Rhythmicity
  - Conductivity
  - Contractility
- not all cardiac myocytes are contractile:
  - atrial + ventricular myocardial cells: capable of contraction + conduction of excitation
  - pacemaker + conducting cells: excitable but non-contractile
    - pacemaker cells: SA + AV node → generate spontaneous cardiac AP
    - conducting cells: Purkinje fibres → spread cardiac AP around ventricles
- Features of cardiac myocytes:
  - Striated appearance: thick + thin filaments within sarcoplasm
  - Sarcotubular system: T tubules + SR
  - Involuntary control: ANS + endocrine modulate function
  - Gap junctions: ↓resistance electrical connections → rapid conduction of APs throughout myocardium → functional syncytium

How are APs conducted through the heart?

- ensures synchronous contraction of ventricular myocytes
- APs generated in SA node are conducted via:
  - Internodal pathways:
    - relayed from SA to AV node
    - 3 pathways: anterior (Bachmann), middle (Wenkebach), posterior (thorel)

- AV node
  - Transmits AP between atria + ventricles
  - Elsewhere junction between A + V is insulated by annulus fibrosus
  - AV nodal delay → PR interval
- Bundle of His
  - R + L branches
  - L branch → L anterior + L posterior fascicles
- Purkinje fibres
  - Synchronise ventricular activation
- Cardiac myocytes
  - Mechanical + electrical connections
    - Connected end to end by intercalated discs → functional synsytium
    - Gap junctions: allow AP to pass between myocytes

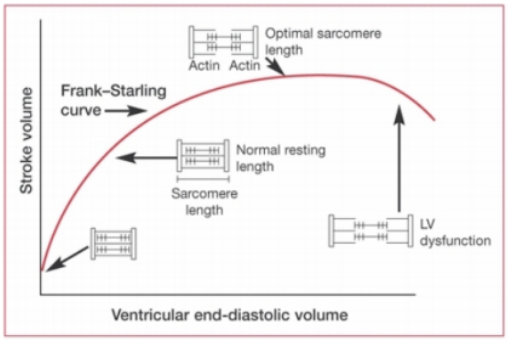
Excitation contraction coupling

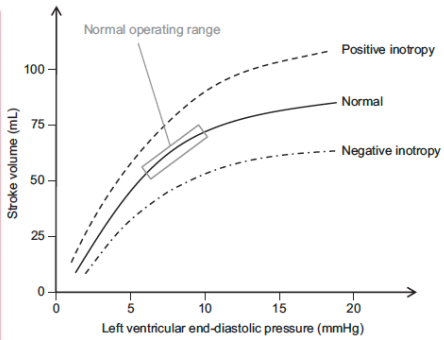
- Process by which the electrical stimulus (AP) of myocyte is converted to a mechanical response
  - **1. Ca2+ induced Ca2+ release**
    - AP at sarcolemma → membrane depolarisation → L-type Ca2+ channels open → Ca2+ from ECF to sarcoplasm
    - SR of cardiac muscle contains RyRs: Ca2+ influx opens RyR → SR releases Ca2+ → "Ca2+ induced Ca2+ release"
  - **2. Activation of cross bridging:**
    - Ca2+ binds to troponin C → conformational change in tropomyosin → uncovers myosin binding site on actin → myosin binds + forms cross bridge with actin
    - Cross bridge cycling occurs, powered by ATP hydrolysis → sarcomere shortening
    - Continues until cytoplasmic [Ca2+] ↓ during repolarization
  - **3. Termination of cardiac contraction**
    - as SR [Ca2+] ↓s, Ca2+ dissociates from troponin C → tropomyosin recovers actin binding site
    - actively removing Ca2+ from the cell
      - **Ca2+ ATPase pump**: primary active transport to remove Ca2+ from cell
      - **Na/Ca2+ exchanger**: 1 Ca2+ out: 3Na+ in. efflux of Ca2+ occurs down conc gradient and is driven by the low intracellular [Na+] due to Na/K ATPase pump (i.e. secondary active transport
      - **Sarcoplasmic/ ER Ca2+ ATPase pump (SERCA)**: sequesters Ca2+ in the SR

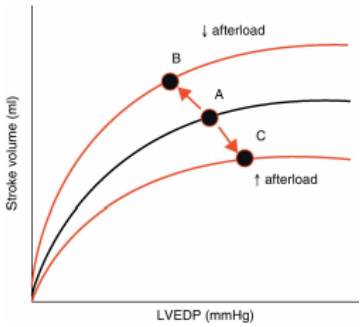
Determinants and control of cardiac output including implications for clinical practice

Frank Starling mechanism

- **Frank Starling mechanism = intrinsic ability of the heart to alter its force of contraction in response to ΔVR**
  - Relates myocardial sarcomere fibre length (or index thereof: LVEDV, LVEDP, CVP) to force generated (or index thereof: SV, LV pressure)
  - Simplest form: ↑VR → ↑LVEDV (preload) → ↑force of contraction; i.e. ↑LVEDV → ↑SV (to a point)
- attributed to length-tension relationship
  - Degree of overlap of actin + myosin myofilaments in diastole → determines extent of crossbridge formation on activation and therefore strength of contraction
  - Sarcomere length:
    - Peak effect at 2.2um → number of actin + myosin crossbridges is high → max force of contraction = LVEDP ~10-12mmHg
    - <2.2um; i.e. ↓EDV → ↓tension generated → contractile energy lost due to work against friction; sarcomere distorted
    - >2.2um: ↓actin-myosin crossbridges formed → ↓contraction (can occur in HF)
- The Frank starling mechanism is represented by the ventricular function curve → plots preload against SV (or CO)
  - Family of curves when afterload or inotropy are varied
    - R shift = -ve inotropy
    - L shift = +ve inotropy







Relationship to excitation contraction coupling

- Excitation- contraction coupling = process of converting electrical stimulus (AP) into mechanical response (contraction
  - Explained by sliding filament theory:
  - AP arrives at cardiac myocyte → depolarisation → Ca2+ influx → Ca2+ induced Ca2+ release from SR via ryanodine Rs → Ca2+ binds troponin C → removes inhibitory tropomyosin from actin → actin-myosin cross bridge cycline → actin and myosin filaments slide over each other = contraction
- Strength of contraction depends on initial sarcomere length
  - LV sarcomere resting length (healthy heart) = 1.8um
  - LV sarcomere length for optimal overlap = 2.2um
  - More optimal sarcomere length at end diastole →
    - optimization of actin/ myosin overlap + maximizes cross bridge formation
    - ↑sensitivity of myofilaments to Ca2+
    - ↑affinity for Ca2+ of troponin C
    - More force generated
  - NB excessive stretching → overstretching of LV sarcomeres → ↓force of contraction

Cardiac output

CO = vol of blood ejected by the L or R ventricle per minute

- **CO = SV x HR**
  - **HR**
    - set by SA node pacemaker activity → modulated by ANS
    - At rest: PSY tonically active → ACh continually released from PSY nerve terminals → resting HR 60-70bmp
    - Bradycardia → ↓CO
    - Tachycardia → ↑CO up to a point; >150bpm: diastolic time short (~0.15s) → ↓ventricular filling → ↓SV → ↓CO
  - **SV**
    - Vol of blood ejected from LV per heart beat
      - Vol of blood in LV prior to contraction = LVEDV
      - Vol of blood remaining in LV after contraction = LVESV
      - **SV = LVEDV – LVESV** → Typical values: LVEDV = 120ml; LVESV = 50ml → SV = 70ml
    - dependent on preload, afterload, cardiac contractility
- NB EF = proportion of blood ejected from LV per heart beat: EF = SV/ LVEDV

Measurement of CO

- **invasive**: PAC, CVC, or art line
  - **Fick principle:**
    - Based on law of conservation of mass
    - The amount of an indicator substance taken up per unit time = arterio-venous difference of substance x blood flow
    - Q = VO2 / CaO2 – CvO2
      - normal value: CO = 250ml/min / 0.2 (ml O2 per ml blood) – 0.15 = 5000ml/min
  - Methods based on Fick principle:
    - **Dye dilution method:**
      - Known amount of indicator dye (e.g. lithium) injected directly into pulmonary artery → concentration continuously sampled at peripheral arterial line → Δconcentration over time recorded as graph → CO calculated from AUC
      - CO = amount of indicator / AUC – time graph
    - **Thermodilution method:**
      - PAC with thermistor at tip → cold saline injected via proximal lumen into RA → Δpulmonary arterial blood temp measured by thermistor → termperature-time graph
      - CO calculated using modified Stewart-Hamilton Equation
  - **Pulse contour analysis** e.g. **PiCCO** (pulse contour cardiac output)
    - Morphology of arterial pressure waveform related to SV and SVR
    - Uses central line + thermistor tipped arterial line sited at femoral/ brachial/ axillary artery
    - CO estimated by analysis of arterial pressure waveform
    - Calibrated using transpulmonary thermodilution method – cold saline injected into CVC and Δblood temp detected at arterial line
- **minimally invasive:**
  - Based on proximity of heart and great vessels to oesophagus
  - **Oesophageal doppler:**
    - US transducer into oesophagus alongside descending aorta → beam reflects off RBC at different frequencies (Doppler principle)
    - Using doppler equation the velocity of blood flow within descending thoracic aorta can be calculared
    - CO calculated from aortic blood flow on the basis that 70% of SV passes through the descending thoracic aorta
  - **TOE**
    - CO calculated in 2 ways:
      - 1. Estimated volumes (EDV and ESV estimated);
      - 2. doppler: blood flow measured across LVOT using doppler principle + measured cross sectional area
- **Non invasive**: TTE, MRI

Preload

- myocardial sarcomere length just prior to contraction
- according to **Frank Starlings** law of the heart: the force of cardiac myocyte contraction depends on preceding diastolic length of the ventricular fibres
  - At cellular level: additional stretch → ↑number of myofilment crossbridges that interact and ↑myofilament Ca2+ sensitivity
  - Represented by ventricular function curve: plots preload against SV
- sarcomere length is not measureable → so clinically it is approximated by:
  - EDV (measured by ECHO)
  - EDP (measured using CVC or PAC); NB relationship between EDV and EDP depends on ventricular compliance
- ↑preload → ↑EDV → ↑ED fibre length of ventricular muscle → ↑velocity of muscle shortening for given afterload → ↑blood ejected
- Determinants of preload. Preload is a function of:
  - VR:
    - intrathoracic pressure: -ve pressure → ↓RAP and ↓PCWP → ↑RA filling
    - MSFP → ↑VR→ ↑EDV
  - Ventricular compliance: ↓compliance → ↓filling e.g. diastolic dysfunction, AMI
  - Pericardial compliance: ↑intrapericardial P → ↓ventricular filling
  - Valvular disease: AV disease will impair preload; semilunar valve disease will ↑preload
  - Atrial kick
  - Wall thickness: ↑ventricular wall thickness → ↓preload e.g. HOCM

Afterload

Describe the factors that oppose left ventricular ejection fraction (PAST QUESTION)

- Afterload = sum of forces that oppose LV output i.e. ventricular wall tension during contraction required to overcome impedance to ejection of blood into arterial circulation
- according to Law of LaPace:
  - wall tension = transmural pressure x radius / 2x wall thickness
  - transmural pressure = intracavity pressure – intrapleural pressure

Factors that determine afterload

- **L ventricular wall tension**

- LV transmural pressure
  - E.g. ↑ITP → ↓transmural pressure → ↓afterload e.g. IPPV
  - E.g. ↓ITP → ↑transmural pressure → ↑afterload
- LV radius
- LV wall thickness

- **SVR**
  - SVR = Resistance to blood flow by systemic vasculature
  - Heart = demand pump: blood flow autoregulated by tissues
  - Arterioles = main determinant of SVR
  - Hagen-Poisuelle: **R = 8nl/ πr4** where R is resistance; n = viscosity; l = length of tube; r = radius
    - Radius has most effect on SVR
    - Arteriolar caliber governed by:
      - Neural control: SY
      - Myogenic autoregulation: reflex arteriolar contraction in response to ↑stretch of wall to limit pressure to tissue
      - Metabolic autoregulation: release of vasoactive substances with ↑metbaolites, ↓pH, ↓pO2, ↑K+
      - Temperature: ↑temp → vasodilation
      - Age: ↑age → ↑SVR
- **L ventricular outflow tract resistance/ aortic root pressure**
  - Hagen-Poiseuille: ↓calibre → ↑resistance → ↑afterload e.g. aortic stenosis
- **Aortic root compliance/ aortic root pressure**
  - ↓compliance (e.g. atherosclerosis, ageing) → ↓SV stored as elastic recoil of arteries → ↑pulse pressure → ↑work required by heart to pump a given ejection fraction → ↑afterload

Effect of sudden ↑afterload

- time dependent process
- **immediate**
  - ↓SV, ↓CO
  - ↑ESV
  - ↑SBP and LVESP
- **5-15mins**
  - frank starling mechanism → ↑preload → ↑CO
  - Anrep effect: ↑sensitivity to Ca2+ → ↑CO
- **↑afterload →**
  - ↓rate and ↓extent of sarcomere shortening → ↓SV → ↑LVEDV → according to starlings law: ↑LVEDV → ↑SV. E.g.: sudden ↑afterload → ↓SV transiently before returning to normal
  - Anrep effect: ↑afterload → intrinsic ↑inotropy → smaller ↓SV than would be predicted from the frank starling mechanism alone
  - ↑myocardial O2 demand

Myocardial contractility

- intrinsic ability of cardiac myocytes to shorten, independent of preload and afterload
- Factors that ↑contractility = +ve inotropic effect (shift FS curve up + left); ↓contractility = -ve inotropic effect (shift FS curve down + right)
- Index of myocardial contractility is provided by the rate of Δpressure (i.e. gradient) during the isovolumetric contraction phase of cardiac cycle
- Primarily dependent on intracellular Ca2+

Determinants of contractility

- **1. SYNS:** NA from cardiac SY neurons → ↑contractility through action of B1 adrenoceptors
- **2. Tachycardia:** ↑HR → ↑contractility = Bowditch effect
  - Bowditch effect:
    - intrinsic autoregulatory phenomenon in which tachycardia → ↑myocardial contractility
    - Mechanism: ↑HR → ↑Ca2+ influx → Na+ efflux by Na/K/ATPase cannot keep pace with systolic influx of Na → ↑intracellular Ca2+ → +ve inotropic effect
- **3. Drugs with +ve inotropic effects:** doputamine, isoprenaline, glucagon, digoxin; -ve inotropic effects: CCB, BB, anaesthetics
- **4. Disease states:** sepsis, myocarditis, IHD, electrolyte and acid-base disturbance

Cardiac output and vascular function curves

Cardiac function curve:

- expression of Frank-Starling relationship
- CO depends on RAP (CVP)

Vascualr function curve

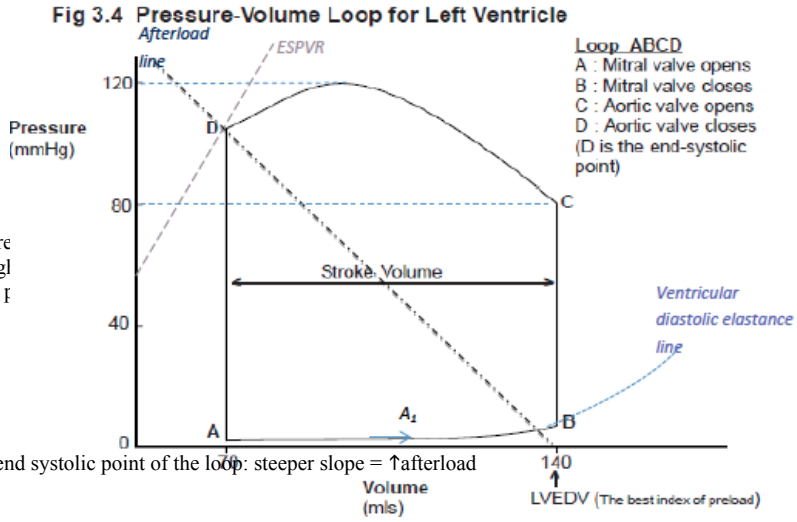
- analyse interactions between heart + vasculature
- shows how a ΔCO causes an inverse ΔCVP
  - when CO is suddenly ↓ → the rate at which blood flows from arteries to veins is temporarily > rate at which the heart pumps blood from the veins back to the arteries → net vol of blood transferred form arteries to veins → ↓Pa and ↑Pv
- **depends on:**
  - TPR: Pv varies inversely with TPR
    - Arteriolar tone: ↓tone → ↓resistance to VR → ↑VR
    - SNS → ↑tone → ↓VR
  - Arterial and venous compliance
  - Blood volume
  - MSFP
    - Blood volume:
      - Hypervolaemia shifts vascular function curve up + right → ↑MSFP reflecting overfilling of circulation. Cardiac function curve not affected. Net result = ↑RAP + VR
      - Hypovolaemia: ↓MSFP, ↓RAP, ↓VR
    - Venous tone
    - Muscle pump: muscular contraction compresses veins → promotes forwards flow → ↑MSFP
  - Posture
    - Blood pools in venous capacitance system

- Sudden change from supine to erect causes pooling of blood ↓VR → reflex ↑venoconstriction
- RAP
  - Thoracic pump during respiration → -ve ITP → ↑VR
- Independent of the characteristics of the heart

Pressure volume relationships in the heart

Ventricular pressure-vol curves have 4 segments:

- **Diastolic ventricular filling**
  - A: MV opens
  - A-B flat: rapid ventricular filling
  - A-B curbved: slow ventricular filling
  - Atrial systole
  - B: MV closes
- **Systole: Isovolumetric contraction**
  - B-C
- **Systole: Ventricular ejection**
  - C: AV opens when intraventricular P > aortic pre
  - C-D: upward slope: rapid ejection: ↓vol and sligl
  - C-D down slope: reduced ejection: ↓vol + ↓LV p
  - D: AV closes
- **Diastole: Isovolumetric relaxation**
  - D-A
  - AV + MV are closed

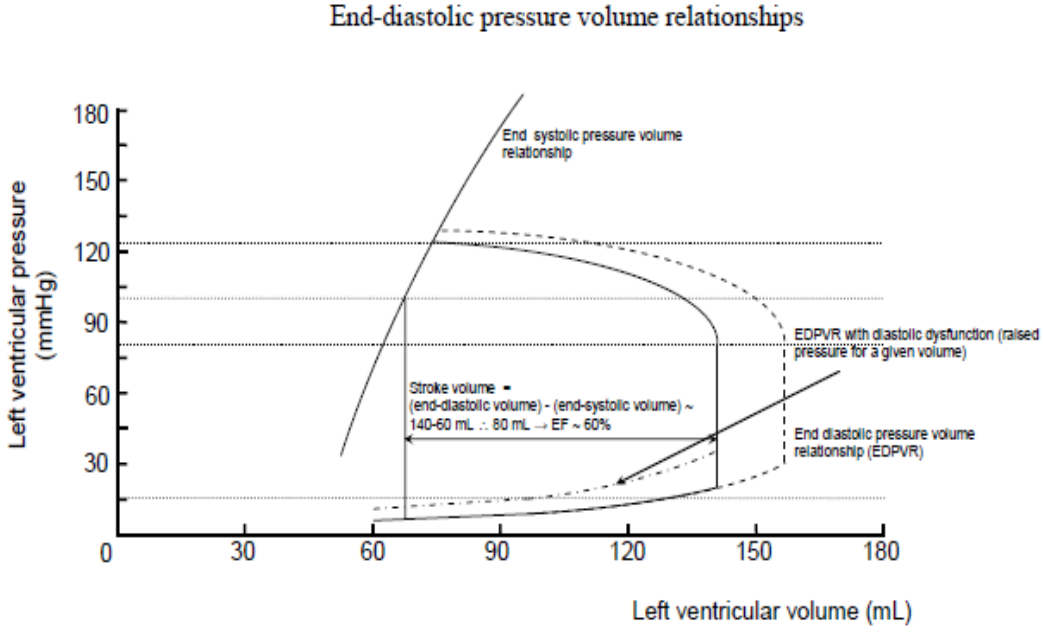


Information obtained from the loop

- **Afterload**: slope of straight line connecting LVEDV with end systolic point of the loop: steeper slope = ↑afterload
- **Preload**: LVEDV
- **Contractility** (end systolic pressure volume line)
  - Slope of end systolic pressure vol line
  - ↑ slope = ↑contractility
  - resulting pressure-vol curve has ↑SV + ↑work
- **SV**: width of the pressure-vol curve
- **Work**
  - Work = pressure x vol
  - Area inside the loop = external work performed by LV for that cycle
- **Ejection fraction**
  - EF = SV / EDV
- **Diastolic ventricular elastance**
  - ↓diastolic compliance: upward shift of pressure-vol curve
  - ↓diastolic relaxation due to:
    - ↓LV compliance
    - extrinsic restriction to LV filling
    - impaired relaxation due to ischaemia
    - slope of diastolic pressure – vol line = elastance i.e. change in pressure / change in volume

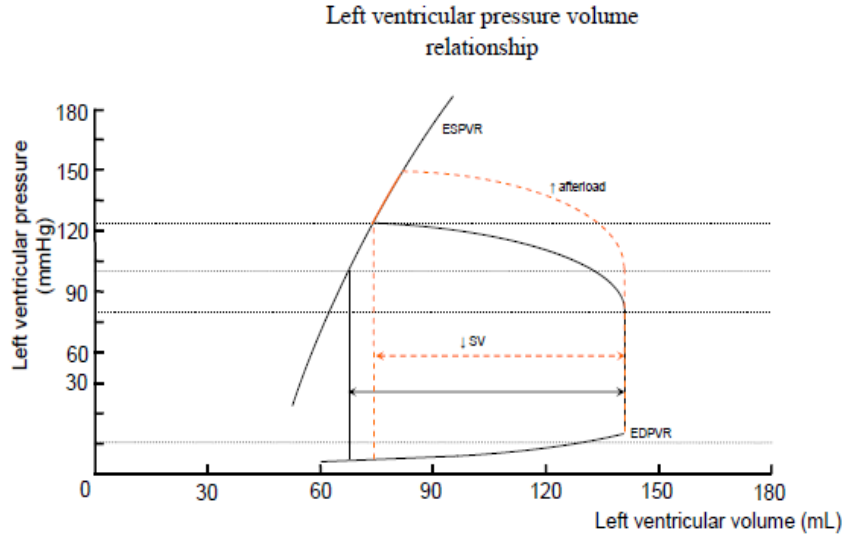
Preload and PV loop

- For a constant contractility and afterload, ↑preload → ↑SV → PV loop wider than normal.
- The LVESV is the same.



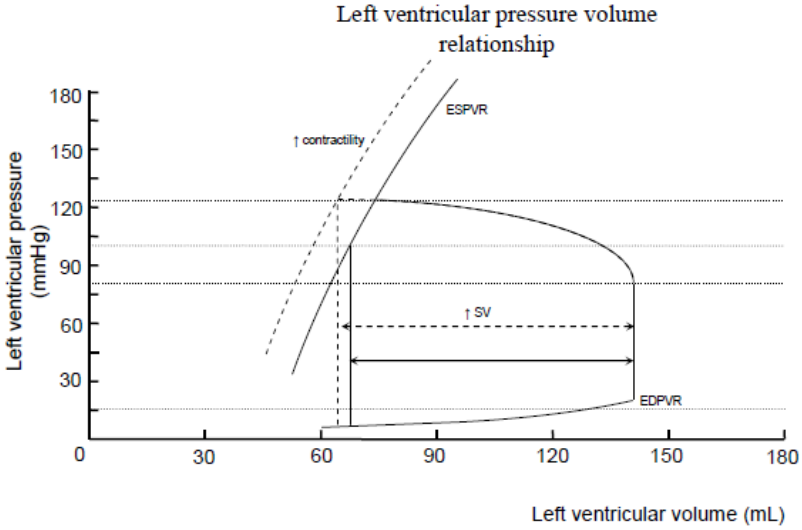
Afterload and PV loop

- PV loop taller and thinner
  - ↑afterload → ↑LVESV → ↓SV
  - LVEDV does not alter



Contractility and PV loop

- ↑myocardial contractility → ↑gradient of the slope of the ESPV + widening of PV loop
- Unlike the widening of the PV loop caused by ↑preload (which moves the end diastolic point to the R), ↑contractility widens PV loop by shifting end systolic point to the L



PV loop in ischaemic heart

- PV loop leans to **right**
  - due to early lengthening of ventricular fibres during isovolumetric contraction phase of systole that is not normally seen.
  - caused by bulging of the area of ischaemic muscle.
  - Hence, during isovolumetric contraction → pressure + vol ↑ → loop leans to the right
- during isovolumetric relaxation phase of diastole there is post systolic shortening of the ventricular muscle fibres caused by active shortening or elastic recoil of the ventricle with profound ischaemia → this ↓vol + ↓pressure within the ventricle.

Determinants of venous return + effect of GA: PAST QUESTION

- VR = vol of blood returning to the RA per minute + matches the CO
- Normal value = 5L/min
- Using derivation of Ohms Law (V = IR)
  - VR = (MSFP – RAP) / venous resistance
  - MSFP = mean systemic filling pressures → normal value 7mmHg
  - RAP = RA pressure → normal value 0mmHg
  - Venous resistance = resistance ot venous return

Determinants

- **MSFP**
  - Normal value = 7mmHg
  - When MSFP = RAP → flow ceases
  - ↑ blood vol; ↑venous tone, muscle pump → ↑MSFP
  - Affect of GA:
    - Venoudilation → ↓venous tone → ↓MSFP → ↓VR
    - Fasting → ↓vol → ↓VR
    - GA + stasis → ↓MSFP → ↓VR
- **RAP**
  - Thoracic pump during respiration → -ve ITP → ↑VR
  - GA: IPPV → +ve ITP → ↓VR
- **Venous resistance**
  - Arteriolar tone: ↓tone= ↓resistance to VR → ↑VR
  - SNS effect on arteriolar tone: ↑SYS → ↑tone → ↓VR

- **Other factors**
  - Patient positioning
    - Upright: ↓VR due to effect of gravity with loss of muscle pump
    - Trendelenburg: head down ↑VR due to favourable effect of gravity
    - Lithotomy: ↑intraabdominal pressure → ↓VR
  - Pneumoperitoneum
    - +ve intrabdominal pressure → ↑RVR → ↓VR

Relationship between CO and VR: PAST QUESTION

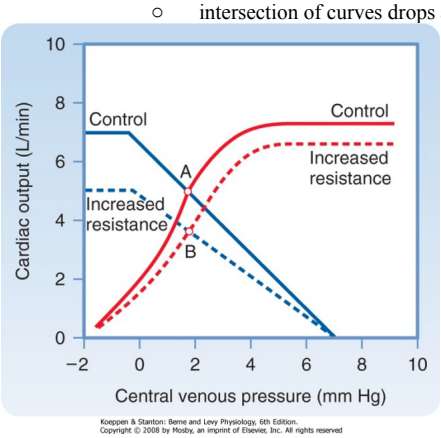
- R + L circuits pump in series; maintenance of stable circulation requires rapid equilibration between VR and CO
- Measurement of the same flow at different point in a series circuit
- Cannot differ for more than a few heartbeats before new equilibrium is reached
- Frank starling law: strength of cardiac contraction dependent upon initial fibre length of cardiac sarcomere → heart intrinsically adjust CO for ΔVR

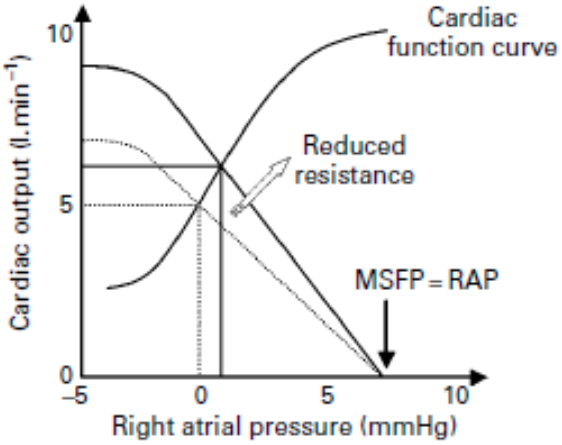
Factors affecting vascular function curve	Factors affecting cardiac function curve

VR = (MSFP – RAP) / RVR
1. MSFP
- Changes position but not shape
- When MSFP = RAP → flow ceases
- Affected by:
  ○ ↑with ↑blood vol
  ○ ↑ with ↑venous tone
  ○ muscle pump during exercise/ movement ↑VR
  ○ ↓momentarily with Δposture from sitting to standing until reflex venoconstriction
2. RAP
- Changes position but not shape
- Thoracic pump during respiration → -ve ITP → ↑VR
- Atrial contribution to ventricular filling → AF = 1/5th of ventricular filling → ↑RAP with ↓pressure gradient and ↓VR
3. 2Venous resistance
- Changes gradient
- Arteriolar tone → ↓tone = ↓resistance to VR → ↑VR
- SNS effect 16esponse16rict tone → ↑SNS → ↑tone → ↓VR
	1. CO
	- CO = HR x SV
	  ○ SV = preload; afterload; contractility
	- Cardiac function curve different to ventricular function curve (Starling)
	- Normal curve, steep upslope – small Δfibre length = large ΔCO
	- Plateau dependent on max cardiac pumping capacity; muscle stretches >2.2um → ↓force of contraction
	2. Hypereffective (higher curves): inotropy
	- ↑SNS, ↓PNS, ↑HR, contractility → ↑CO
	3. Hypoeffective (lower curves)
	- myocardial damage, ischaemia, toxicity
	- infection, neoplasm
	- external disturbance of cardiac rate/ rhythm

Interaction of both:

- relationship between curves is the coupling between the heart and the peripheral circulation
- point where the 2 curves cross = equilibrium point; this defines the CO and the RAP at which the CVS operates
- normal: CO 5L/min; RAP 0mmHg
- ↑Vol: cardiac function curve unchanges, venous curve shifted up and right
- ↑afterlaod
  - venous curve: ↑MSFP: ↑RAP essentially same (no change in position); ↑TPR so ↓gradient of curve
  - cardiac function curve: ↑afterload ↓SV for given preload and contractility → curve shifted down and to right
  - intersection of curves drops and shifts to right → ↓CO for given RAP





Coronary blood flow

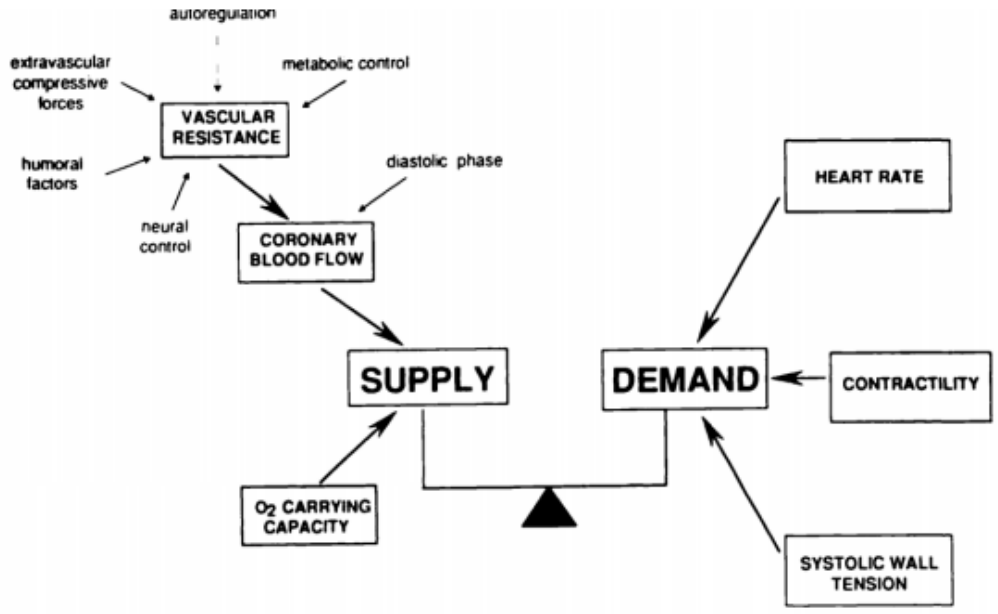
Myocardial oxygen supply and demand

Summary:

Myocardial O2 demand	**Myocardial O2 supply**	**Myocardial O2 extraction**
30ml O2/min Directly ∝: - HR - Contractility - Wall tension (afterload)	CBF = 250ml/min (5% CO) - O2 content of arterial blood: Hb, SaO2 - CorBF: ○ Coronary artery resistance ○ Aortic diastolic pressure ○ LVEDP ○ Perfusion timing (HR) ○ Blood viscosity	60% (very high) O2 supply can be ↑by ↑CBF and not by ↑myocardial O2 extraction

Myocardial O2 supply	**Myocardial O2 demand**
- Myocardium supplied by coronary circulation - NB high O2 ER (~70%) → therefore dependent on CorBF for O2 *myocardial O2 supply depends on:* **1. O2 carrying capacity** ○ O2 content of blood: Hb, SaO2 ○ O2 extraction ratio **2. Coronary blood flow** ○ Based on Ohms law: flow = pressure / resistance ○ CorBF = CorPP / CVR a. Coronary perfusion pressure ▪ Arterial pressure ▪ Intraventricular pressure b. Coronary vascular resistance ▪ Metabolic ▪ Myogenic control ▪ Humoral control ▪ Neural control ▪ Extrinsic compression/ intrinsic narrowing c. Variation throughout the cardiac cycle d. Variation between LV and RV	- amount of O2 consumed by myocardium is determined by amount + type of activity undertaken ○ resting O2 consumption ~8-10ml/min/100g ○ basal metabolism ~25% ATP consumed ○ muscle contraction ~75% ATP consumed ○ cardiac afterload ~50% energy used during isovolumetric contraction - Stroke work = SV x afterload - SV = preload, afterload, contractility - Therefore myocardial O2 demand determined by: ○ Myocardial wall tension (afterload) ○ Contractility ○ HR ○ Basal metabolism ○ External work *Myocardial o2 demand/ cardiac work depends on:* **1. HR** ○ ↑HR → ↑number of contractions/ min → ↑O2 consumption **2. Contractility** **3. Wall tension/ stress i.e. afterload** ○ LaPlace Law: ventricular wall tension = (LV pressure x LV radius) / LV wall thickness ○ NB energy utilization during isovolumetric contraction = directly related to wall tension

NB: ADP = aortic diastolic pressure

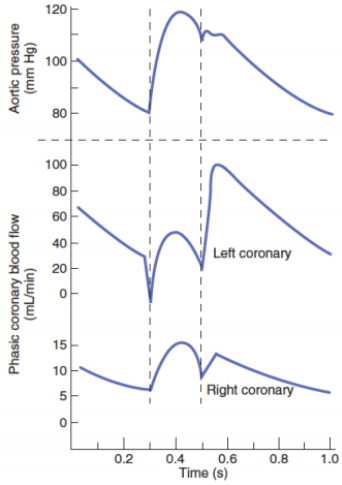


Coronary blood flow (MAKEUP)

- Heart supplied by coronary circulation
  - Aortic root → coronary sinus → L + R coronary arteries + branches → capillaries → veins → coronary sinus + anterior cardiac veins → RA
  - Thebesian veins drain capillaries → cardiac chambers
- Generally:
  - LCA supplies L side of heart + septum + part of posterior
  - RCA supplies R side of heart + part of septus + posterior
- CorBF
  - vol of blood flowing through the coronary circulation per unit time
    - Resting CorBF = 250ml/min or 5% CO
    - 80% CorBF + O2 supply occurs during diastole
  - Based on Ohm's law: flow = pressure / resistance. Therefore: **CorBF = CorPP/ CVR**
- Heart is highly metabolic; high O2 extraction ratio of ~70% at rest → therefore O2 delivery can only be significantly ↑ by ↑CorBF

Coronary blood flow is dependent on:

1. **CorPP**
   - Driving pressure for coronary circulation; Starling resistor
   - CorPP = ADP – LVDP (or RAP → whichever is greater) → LVDP and RAP <<< ADP → therefore CPP ~ = ADP
   - Dependent on:
     - Arterial pressure: Depends on CO, SVR; ↓arterial pressure → ↓CorPP
     - Intraventricular pressure: ↑intraventricular pressure → ↓CorPP
     - Coronary sinus / RAP
2. **Coronary vascular resistance**
   - Governed by Poiseuille equation: $R = 8\eta L/\pi r$
   - Governed by factors that alter coronary artery radius:
     - Metabolic autoregulation: vasodilator (NO, PGI2) release triggered by local metabolites (↓O2, ↑CO2, ↑H, ↑K, ↑adenosine)
     - Myogenic autoregulation: smooth muscle stretch → contraction
     - Autonomic + hormonal control: SNS, PSNS, adrenaline, ADH
     - Extrinsic compression
     - Intrinsic narrowing: CAD, vasospasm
   - Coronary artery = Starling resistor → caliber of vessels ↓ with ↑ intraventricular pressure which com
3. **Heart rate**
   - Tachycardia ↓diastolic time → ↓LV CorBF
4. **Variation throughout the cardiac cycle**
   - CorPP and CorVR varies with cardiac cycle
   - Systole: ↓CorPP; ↑CorVR → ↓CorBF
   - Diastole: ↑CorPP; ↓CorVR → ↑CorBF
5. **Variation between LV e.g. RV**
   - LV: large difference between CorPP in systole and diastole
     - Systole: LV pressure > coronary arterial pressure → intramuscular arterioles compressed -
     - Diastole: LV pressure < coronary arterial pressure → blood flow to myocardium
     - minimal CorBF during systole → LV perfusion mainly in diastole
   - RV: smaller difference btween CorPP in systeole and diastole → CorBF continuous + maintained in s



Regulation/ control of coronary blood flow:

1. **Autoregulated** (60-180mmHg)
   - Myogenic
     - ↑transmural P → ↑leakiness smooth muscle membranes → depolarisation
     - resistance ↑s proportionally to pressure → flow remains constant
   - Metabolic (1° mechanism)
     - CorBF tightly coupled to O2 demand
     - ↑cardiac work / anaerobic metabolism → ↓myocardial ATP + ↑AMP + **adenosine** released from myocardial cells → vasodilation of coronary arterioles → ↑CorBF
     - Other vasodilatory mediators: local metabolites = ↓O2, ↑CO2, ↑H, ↑K
2. **Autonomic / hormonal control**
   - Direct: PSY + SY innervation of coronary vessels: ACh, Nad, Ad
   - Indirect: autoregulation occurring with Δmyocardial work in response to PSY or SY stimuli

Summary:

Therefore: main factors that influence CorBF are:

- Coronary perfusion pressure
  - arterial pressure
  - intraventricular pressure
- coronary vascular resistance
  - Governed by Hagen-Poiseuille law
  - Regulation of coronary vessel radius depends on:
    - Metabolic control
    - Myogenic control
    - Humoral control
    - Neural control
- Heart rate
- cardiac cycle
- LV e.g. RV
- Myogenic autoregulation
- Metabolic autoregulation: O2 demand
- Autonomic/ hormonal control

NB:

- ADP: aortic diastolic pressure
- LVDP: LV diastolic pressure

- RAP: R atrial pressure

Methods to measure coronary blood flow – see "measurement of CO"

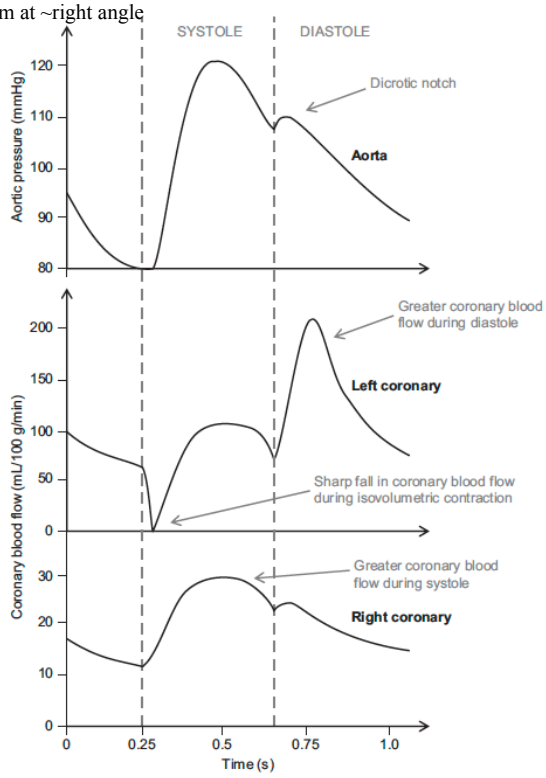
- Fick principle: flow = uptake of a substance / arterior-venous difference
- Thermodilution technique
- Thallium scanning or coronary angio: may indicate differences in regional flow

Methods of ↑coronary blood flow in pts with IHD

- GTN → coronary vasodilation
- B blockers → slow HR → allows ↑ time for diastole
- CABG and angioplasty may improve or bypass areas of inadequate flow

Coronary blood flow and variation throughout the cardiac cycle: MAKEUP

- Coronary arteries run along epicardial suface → arterioles penetrate into the myocardium at ~right angle
- CorPP and CorVR varies with cardiac cycle
- LV
  - Blood flow is intermittent
  - **Systole**: pressure within contracting muscle of LV > coronary arterial pressure → intramuscular arterioles compressed → prevent blood flow to myocardium
  - **Diastole**: heart relaxes → ↓pressure
- RV
  - Pressure generated within RV < LV
  - RV myocardium perfused throughout the cardiac cycle



Outline the factors that determine coronary vascular resistance: PAST QUESTION

Heart muscle supplied by coronary circulation

- Aortic root →
  - LCA supples L heart + septum
  - RCA supplies R heart + septum

Determinants of CVR

- Governed by Hagan-Poiseuille equation: **$R = 8\eta L/\pi r^4$**
  - n = viscocity
  - l = length
  - r = radius

1. **Radius has main effect: factors that alter coronary artery radius:**
   - i. Metabolic autoregulation:
     - Most important form of autoregulation
     - Release of vasoactive substances (NO, PGI2) in response to metabolite production (↓O2, ↑CO2, ↑H, ↑K, ↑adenosine) → vasodilation
   - ii. Myogenic autoregulation:
     - Operates to maintain CorPP
     - Changes between: 60-180mmHg counteracted by vasodilation/ constriction to maintain flow
     - smooth muscle stretch → contraction
   - iii. Autonomic + hormonal control:
     - SNS: chronotropy + inotropy → ↑metabolic demands of heart
       - Vasodilation via b-adrenoceptors → ↑CBF to meet requirements
       - a-adrenoceptors → vasoconstriction → ↓CBF
     - PSNS
       - Vasodilation + bradycardia
     - adrenaline, ADH
   - iv. Extrinsic compression
     - Starling resistor mechanism: caliber of vessels ↓ with ↑intraventricular pressure which compresses the vessels overlying it → interrupt flow
     - R = CorPP / CorBF
     - CorPP = aortic diastolic pressure – LVDP / CVR
     - ↑intraventricular pressure during systole: LV > RV

v. Intrinsic narrowing:
- CAD, vasospasm

2. Viscosity
- ↑viscosity → ↓CBF (e.g. ↑Hct)

3. CPP and CorBF
- R = CorPP / CorBF

Effect of severe aortic stenosis on myocardial O2 supply and demand: PAST QUESTION

Aortic stenosis = ↓ cross sectional area of the valve + immobile valve leaflets
- chronic narrow LV outflow tract → ↑mean pressure gradient across the valve to maintain flow + compensatory LV hypertrophy
- → relative ischaemia of LV myocardium, angina, arrhythmias, LV failure
- Severity grading:

Severity	Valve area	Mean gradient
Mild	>1.5cm²	<25mmHg
Moderate	1-1.5cm²	15-50mmHg
Severe	<1cm²	>50mmHg
Critical	<0.5cm²	>80mmHg

Myocardial O2 supply
- myocardium supplied by coronary circulation
- resting CorBF = 250ml/min (5% CO)
- high O2 ER ~70% → therefore dependent on CorBF for O2
- CorPP = driving pressure for coronary circulation
  - CorPP = ADP – (LVDP / RAP)
    - ADP: aortic diastolic pressure
    - LVDP: LV diastolic pressure
    - RAP: R atrial pressure
  - LVDP and RAP <<< ADP → therefore CPP ~ ADP
- ~80% CorBF + O2 supply occurs during diastole
- Severe AS – effect on myocardial O2 supply
  - **ventricular hypertrophy** → ↑muscle mass
    - ↓supply due to ↓calibre of coronary artery branches within myocardium → ↑resistance to flow + ↓blood flow
    - dynamic compression of coronary arteries → ↓lateral flow
  - **↑LV pressure during systole** (due to ↑afterload 2o narrow outlet)
  - **compensatory ↑HR**
    - Severe AS → ↓CO + ↓MAP → compensatory SY stimulation → ↑HR → ↓diastole:systole ratio → ↓CorBF
  - **↓aortic root pressure**
  - **↓lateral flow**
    - ↑flow velocity → large kinetic energy → ↓lateral pressure → ↓coronary blood flow + ↓O2 supply to myocardium

Myocardial O2 demand
- amount of O2 consumed by myocardium is determined by amount + type of activity undertaken
  - Dependent on: Ventricular wall tension (LaPlace); HR
- Severe AS – effect on myocardial O2 demand
  - **ventricular hypertrophy**: ↓wall stress → ↓O2 demand
  - **ventricular dilation**: decompensation → LV dilation + failure → ↑LV radius → ↑wall stress → ↑O2 demand
  - **ventricular pressure**: ↑afterload → ↑ventricular pressure to maintain CO → ↑wall stress → ↑O2 demand

Overall:
- ↓CorBF → ↓myocardial O2 supply + ↑myocardial O2 demans

Discuss the control of blood pressure and the distribution of blood volume and flow throughout the cardiovascular system including:

The factors determining systemic blood pressure and its regulation and control

MAP = CO x SVR
- maintained within narrow limits:
  - Fast, neurally mediated baroreceptor mechanism
  - Slower, hormonally regulated RAAS
- Achieved by:
  - Sensors: baroreceptors
  - Control centre: brainstem nuclei (vasomotor centre), medulla, hypothalamus
  - Effectors: SNS/ PNS efferents; RAAS

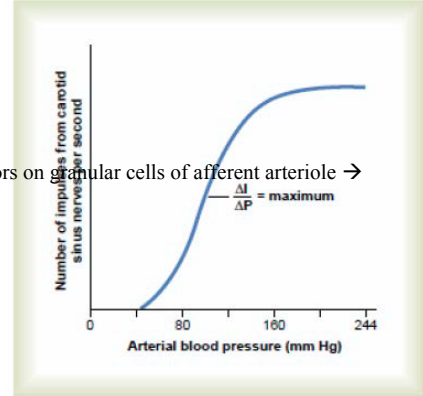
Short term regulation: Baroreceptor reflex
- afferent nerve cells (stretch Rs) in carotid arteries + aortic arch
- Fast, neural –ve feedback system; minutely regulation of arterial BP
- **Stimulus**: distension → ↑intraluminal pressure → ↑frequency of impulses discharged
- **Control centre**: send info to vasomotor centre (NTS) of medulla via CNX and CNIX
- **Effectors**: vasomotor centre: set point ~100mmHg → modify PSY (via CVLM) and SY (via RVLM)
  - Venous constriction → ↑VR + ↑preload → ↑CO
  - ↑HR, ↑contractility
  - vasoconstriction of arterioles → ↑TPR
- 2 types of baroreceptor:

	Location	Stimulus	MoA
High pressure	Aortic arch Carotid sinus	ΔBP by degree of stretch	↑MAP → ↑intraluminal P → ↑rate of firing CNX (aortic arch) CNIX (carotid) → inhib vasomotor centre → ↓SY activity → ↑excitation cardio inhibi centre → ↑VA tone → ↓HR,

			contractility, SV; ↓SVR (vaso + venodilation) progressive stimulation >MAP60: max effect 180mmHg
Low pressure (cardiopul)	RA + great veins	Δvol → stretch	↑vol (↑CVP) → CNX to medulla → ↑PNS, ↓SNS → inhibitory to heart → ↓HR/ contractility/ SV/ CO Also: ↓ADH, ↓thirst, ↑ANP

Intermediate term: RAAS

- slow hormonal system
- long term BP regulation via adjustment of blood vol
- **Stimulus**:
  - Baroreceptors: carotid/ aortic/ pulmonary + intrarenal
  - ↓renal perfusion sensed by juxtaglomerular cells (JGA)
- **Control centre:** vasomotor centre
- **Effectors**: renin
  - Secreted from granule cells into interstitium + afferent arteriole lumen.
  - acts on angiotensinogen to produce ATI → *ACE* → ATII
  - Regulators:
    - *Neural signals:*
      1. ↓BP → ↑renal SY nerve activity → activates B1 adrenergic receptors on granular cells of afferent arteriole → stimulates renin secretion via cAMP protein kinase A dependent process
    - *afferent arteriolar pressure*
      1. granular cells also act as intrarenal baroreceptors
      2. deform in response to Δafferent arteriolar pressure (reflection of arterial BP)
      3. ↓pressure → ↑renin production
    - *NaCl at mascula densa cells* of JGA + delivered to DCT
      1. ↑Na delivery → ↑uptake of NaCl by cells → osmotic swelling → release of NT *inhibit renin release*
      2. NB does not directly regulate BP, but contributes to regulation of renin secretion
  - Source of angiotensinogen = liver
  - ACE is expressed on luminal surgace of endothelial cells of vasculature – e.g. lungs; converts ATI to ATII
  - **ATII**
    - Most important in control of Na excretion + BP
    - Affects BP directly as vasoconstrictor → ↑PVR + indirectly via regulation of renal Na excretion
    - –ve feedback to inhibit renin production by acting directly on granular cells (interacting with AT1 receptors on granular cells to ↑intracellular Ca2+ concentration → inhibits renin production)



Long term control: aldosterone regulation of Na balance

Effectors

1. **Aldosterone**
   a. Vital in correction of prolonged ↓BP
   b. Primary effect: ↑Na reabsorption in CT and CD by principal cells (2% of total filtered Na^+)
   c. MOA:
      i. aldosterone enters principal cells → interacts with cytosolic aldosterone receptors →
      ii. aldosterone bound receptors interact with nuclear DNA to promote gene expression → translation of specific proteins →
      iii. ↑activity or # of luminal Na^+ channels + basolateral membrane Na-K-ATPase pumps → ↑reabsoption of Na+
   d. Control of aldosterone secretion
      i. Inputs to adrenal gland regulate secretion
         1. [ATII] → determined by plasma [renin] → determined by intrarenal baroreceptors, macula densa, renal SY nerves
         2. ↑plasma[K+]

Summary of system:

- ↓BP → rapid short term baroreceptor mediated vascular response → intermediate term renal mediated release of renin + production of ATII → reinforces the initial short term vascular response + stimulates adrenal cortex to produce altosterone

Mean arterial pressure

- MAP = Pd + (Ps – Pd / 3)
- MAP depends on 2 physical factors:
  - mean blood volume in arterial system. Depends on:
    - rate of inflow into arteries from heart (CO)
    - rate of outflow from the arteries through the resistance vessels (peripheral runoff)
  - arterial compliance
    - ratio of blood volume to mean blood pressure

Arterial pulse pressure

- pulse pressure = SBP – DBP
- principally a function of SV (determines the change in arterial blood vol during ventricular systole)

Total peripheral resistance and factors affecting it

Regional circulations

- Flow = pressure change/ resistance
- The % of each organ blood flow is dependent on the organ vascular resistance
- Majority of resistance in systemic system results from arterioles – state of contraction and relaxation of smooth muscle cells of arterioles which determines distribution of blood to organs
- **1. Extrinsic control**
  - Flow = pressure/ resistance. Important factors = TPR, CO, circulating vol
  - SYNS – controls vascular tone, HR, contractility
  - PSYNS – control sHR and vasodilation
  - Extrinsic hormonal control: RAAS, ANP, ADH
- **2. Intrinsic control**
  - Autoregulation
    - Ability of an organ to maintain relatively constant blood flow across variations in perfusion pressure
    - flow = pressure/ resistance → as the P changes, the R also changes to maintain flow
    - Outside limits of autoregulation: flow = dependent on driving pressure
    - Kidneys, brain, heart
  - Autoregulation is dependent on 2 mechanisms:
    - 1. Pressure autoregulation: myogenic stretch response to ↑ and ↓ in pressure → vasoconstriction, and vasodilation
    - 2. Metabolic or vasoactive autoregulation: direct action of locally derived metabolites and vasoactive substances e.g. platelets release thromboxane A2 → constriction in damage

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

- Peripheral resistance is largely maintained by SY tone, maintaining a basal level of vasoconstriction in vascular beds in skeletal muscle and skin
  - SY tone → vasoconstriction of arterioles via alpha receptors
- Skeletal muscle constitutes the largest single vascular bed and the major determinant of total peripheral resistance

Describe the relationship between vascular tone and tissue oxygenation
Describe the factors that influence the rate of blood flow through a capillary bed

- direct relationship between tissue oxygenation and vascular tone
  - ↓O2 = ↓vascular tone
  - blood flow is coupled to local tissue metabolic requirements
- Autoregulation = tissues ability to regulate its own blood supply so that it receives the flow it requires for its functions
  - Role of autoregulation in most tissues = to maintain delivery of O2 and nutrients to the tissues at a normal elvels + remove waste products despite Δarterial pressure
  - Metabolic autoregulation
    - ↑metbaolism or ↓O2 available to tissues → release of vasoactive substances that cause vasodilation
    - substances include: NO, adenosine, ↑CO2, ↑K, ↑Mg, ↑H
- E.g. reactive hyperaemia
- E.g. cerebral circulation

Describe the vasoactive substances released by the endothelium. Explain the role they play in regulating blood flow through the peripheral circulation: PAST QUESTION

Vasoactive substances

- primarily released to effect local arteriolar smooth muscle tone → match regional blood supply to metabolic demand

Vasodilators

- **NO (nitric oxide)**
  - Produce by NO synthetase activity on L-arginine
  - Release triggered by:
    - Shear stress
    - ↑NTs: Ach, bradykinin, 5-HT, substance P, histamine
    - metabolic activity of tissue: ↓PaO2, ↑pCO2, ↑[H+], ↑temp, ↑lactice acid, ↑pyruvate, ↓ATP, ↑ADP, ↑AMP, ↑adenosine
    - electrolytes: ↑[K+]
- **Prostacycline (PGI2)**
  - Derived from COX-1 activity on arachadonic acid
  - Triggered by: pulsatile flow ?shear stress
  - Effect site: ↓arteriolar smooth muscle tone via activation of adenylyl cyclase → ↑cAMP → ↓MLKC activity → vasodilation, inhibition of platelet aggregation (↓Ca2+ availability)

Vasoconstrictors

- **Endothelin**
  - Most potent of all vasoconstrictors
  - Acts locally + systemically
  - 3 types: ET1 (endothelium, brain, kidney); ET2 (GIT); ET3 (adrenals)
  - Trigger unknown
  - Effect site: ↑arteriolar smooth muscle tone via activation of G protiens → vasoconstriction

Others (non vasoactive)

- tissue factor
- heparin sulphate: ↑ATIII activity
- thrombomodulin: binds + inactivates throbin; activates protein C/S → ↑tPA + ↑fibrinogen

Regional circulations

The relationship between organ blood flow and demand and the role of autoregulation

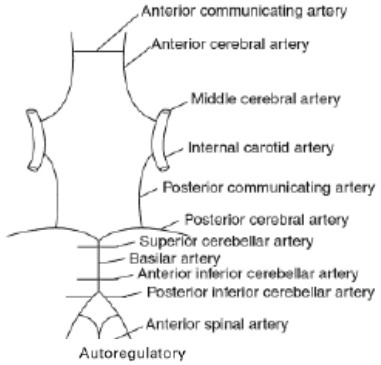
Distribution of blood volume	**Blood flow distribution at rest**			
- Pulmonary circulation 9% - Heart 7% - Arteries 13% - Arterioles 2%	**Tissue**	**%CO**	**ml/min**	**ml/min/100g**
	Brain	14	700	50
	Heart	4	200	70
	Bronchi	2	100	25

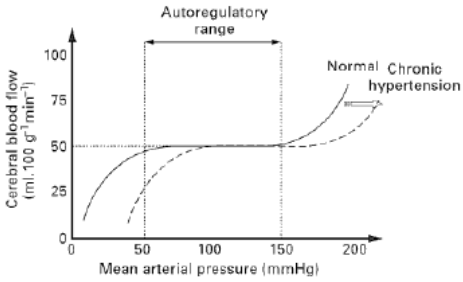
- Capillaries 5% - Veins 64%	Kidneys	22	1100	360
	Adrenal	0.5	25	300
	Liver	27	1350	95 (75% portal)
	Muscle	15	750	4
	Bone	5	250	3
	Skin	6	300	3

Clinically significant features of the coronary, cerebral, skin, muscle, renal, hepatic and splanchnic circulations

Cerebral and spinal cord circulation

- Blood supply to brain: internal carotid arteries (2/3) and vertebral arteries (1/3)
- At rest: 750ml/min of blood flow = 15% total CO
- Cerebral blood flow = 50ml/100g/min
  - White matter: 20ml/100g/min
  - Grey matter: 70ml/100g/min (metabolically more active)
- O2 consumption of brain: 3ml O2/100g/min = 50ml O2= 20% total consumption
  - Requires large amount of energy; limited capacity for anaerobic metabolism → absence of O2 · irreversible cell damage
- **CBF = CPP / CVR**
  - CPP = MAP – ICP
  - CVR: vasodilation (→ ↑blood vol → ↑ICP) → ↓CPP) e.g. vasoconstriction
  - Autoregulated between MAP 50-150mmHg (reset in chronic HTN)
- Control
  - **Autoregulation**
    - Myogenic stretch factors
    - Chemical factors:
      - [H+]
      - PCO2 → linear relationship with CBF from 20-80mmHg.
        - ↑PaCO2 → vasodilation → ↑blood vol → ↑ICP → ↓
        - ↓PaCO2 → vasoconstriction → ↓blood vol → ↓ICP
      - PaO2 <50mmHg → ↑CBF
    - ↑Cerebral metabolic rate → ↑CBF (e.g. pyrexia, seizures)
    - Local metabolic factors: adenosine, NO, H+
  - **Extrinsic nerve and hormonal** control have little influence on CBF
    - SY: vasoconstriction; shift autoregulation curve to right in HTN
    - PSY: vasodilation
  - Other
    - Blood viscosity: ↓viscosity → ↑flow (Hagen-Poiseuille's law)





Threshold values for cerebral ischaemia = CBF below which known neuronal physiological changes occur

- <50ml/100g/min → acidosis
- <40ml/100g/min → protein synthesis impaired
- <30ml/100g/min → oedema
- <20ml/100g/min → electrical function fails
- <10 ml/100g/min → cell death

Hepatic circulation

Blood supply to the liver

- Total hepatic blood flow: 1500ml/min = 60ml/100g/min = 30% CO
- Derived from:
  - *Hepatic artery*
    - 25% of flow; 40% O2 supply
    - 300-500ml/min; mean pressure 90-100mmHg
    - some autoregulation
  - *Portal vein*
    - 75% of flow; 60% O2 supply
    - 1000-1200ml/min; mean pressure 10mmHg
    - No autoregulation
    - Contains venous drainage from the bowel
- Hepatic triads: hepatic artery + portal vein + bile cannaliculus
- Sinusiuds:
  - Consist of: portal arteriole + venule
  - Forms low pressure microcirculation that optimizes exchange with hepatocytes
- Venous blood form the liver returns to the IVC through the R and L hepatic veins. A separate set of veins drain the caudate lobe of the liver

How is blood flow regulated?

- Arterial supply = regulated by intrinsic + extrinsic mechanisms
- portal venous flow = regulated by extrinsic factors only
- **Intrinsic**
  - Myogenic autoregulation
    - If hepatic arterial pressure ↓s → ↓hepatic arterial resistance → maintains flow
    - Portal vein has no autoregulation → therefore flow is proportional to the pressure gradient and resistance
  - Hepatic arterial buffer response
    - Compensatory Δhepatic artery:
      - ↓flow portal vein → compensatory ↓resistance in hepatic artery → arterial blood flow ↑s
      - Adenosine responsible: ↓portal flow → ↑[adenosine] around hepatic triads → arterial vasodilation
      - NB: ↓flow hepatic artery → no portal vein dilation with ↑adenosine → little compensatory Δportal flow
- **Extrinsic**
  - SYNS
    - Hepatic artery: contains a + b adrenoceptors
    - Portal vein: a receptors

- Constricts sinusoidal capacitance vessels → mobilises blood reservoirs → important in stress response
- ↓splanchnic blood flow → ↓portal venous flow / ↓hepatic artery flow

- Circulating factors:
  - Angiotensin
  - Endothelin
  - Vasopressin: constricts hepatic vasculature → ↓hepatic blood flow
  - Glucagon: vasodilation of hepatic artery + portal vein → ↑hepatic blood flow
  - Histamine
- Right heart function
  - RHF → ↑CVP → hepatic congestion as transhepatic gradient falls

Splanchnic circulation

Splanchnic

- 1250ml of CO = 25%
- Anatomically: blood derived from coeliac, SMA, IMA
- Partially in parallel (gastric, spleen, pancreas, small intestine, colonic) and partially in series – due to liver
- Important reservoir – pooling in capacitance vessels of mesentery, spleen, liver
- Control
  - Extrinsic: SYNS → ↑venous constriction → ↑circulating blood vol + ↑resistance of arterioles → diverts blood away from digestive system
  - Intrinsic: present in hepatic artery; metabolic control

Renal circulation

Renal

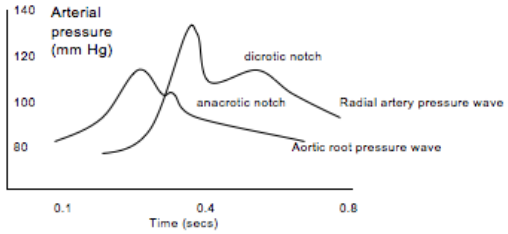
- Rest: 1250ml/min = 25% blood flow
- Autoregulation/ intrinsic control
  - 75-170mmHg
  - Myogenic stretchmechanisms
  - Tubuloglomerular feedback via afferent arteriole constriction: macula densa → releases adenosine if RPP↑s
- Extrinsic control
  - SY innervation
  - RAAS
  - ADH

Uteroplacental

Draw aortic root and radial artery pressure waveforms on the same axis. Explain the differences: PAST QUESTION

Aortic root waveform:

- ↑ pressure on opening of aortic valve during systole
- reaches peak pressure 120mmHg (normal adult)
- closure of aortic valve results in icisura on the 1st part of the pressure descent
- gradual ↓pressure due to Windkessel effect: elastic potential energy stretching the aorta during systole is converted back into kinetic energy to propel and blood during systeole



Radial artery waveform

- Measured distal to the aorta → delay in arrival of impulse (despite fact that pressure waveform travels faster than blood
- Higher peak pressure (taller) → due to resonance and reflection (summation of waveforms)
- ↑velocity of higher peak (narrowest peak)
- ↓compliance of arterial walls (loss of windkessel effect) → steeper upslope
- no incisura (notch) high pressure component damped out
- diastolic hump present → combination of reflection, resonance

Differences with age:

- ↓myocardial function: aortic = slower rise to peak pressure
- ↑stiffness of vessels:
  - Aortic: ↑peak pressure → lead to progressively less distortion of waveform distally
  - Radial: ↑peak pressure
- All changes ↓ in elderly due to ↓arterial compliance

Discuss the factors that influence the rate of blood flow through a capillary bed

- direct relationship between tissue oxygenation + vascular tone (↓O2 = ↓vascular tone)
- blood flow is coupled to local tissue metabolic requirements
- autoregulation = tissues ability to regulate its own blood supply to maintain DO2 + nutrients despite changes in arterial pressure
  - myogenic mechanism
  - metabolic mechanism
    - ↑rate of metabolism / ↓O2 available → release of vasoactive substances → vasodilation
    - e.g.: substance P/ NO/ adenosine/ ↑CO2/ ↑K /↑Mg2+/ ↑H+

The skin, kidneys, carotid bodies are examples of where specific organ blood flow is far in excess of that organs metabolic requirements. For each example, explain what the physiological role of the high organ blood flow is, why this high flow is an advantage to the person and a brief description of the mechanisms involved: PAST QUESTION

Physiological role of high organ blood flow

Organ	Basal flow	%CO	Physiological role	Mechanism involved

Skin	13ml/100g/min
	~450ml/min
		10%	Thermoregulation
			Other: blood reservoir
				- high flow via superficial arterioles + AV anastomoses
				  ○ arterioles: autoregulation via myogenic mechanism
				  ○ AV anastomoses: SYNS
				- Cold : SNS activation → vasoconstriction
				- Heat: loss via conduction/ convection/ radiation/ evaporation
				- Countercurrent mechanism
				- Sweating

Kidneys	400ml/100g/min ~1250ml/min	25%	Excretion of waste products Na/ H2O homeostasis	- 95% RBF to cortex; 5% to medulla - high flow via short large renal arteries, interlobular arteries +

			Acid base	parallel afferent arteriole branches - countercurrent exchange mechanism + ultrafiltration for waste products, Na/K/H2O homeostasis *Flow controlled by:* - myogenic mechanism in glomerular arteries - tubuloglomerular feedback
Carotid bodies	700ml/min	15%	Mediation of hypoxic ventilatory response via measurement of dissolved O2 content	- PaO2 determines stimulation level of peripheral chemoreceptors

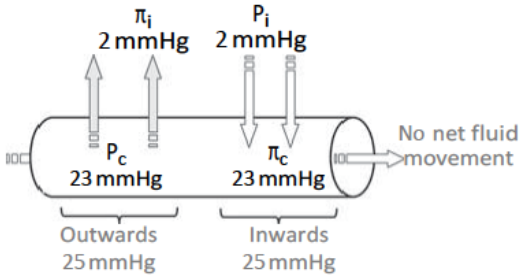
The essential features of the microcirculation including fluid exchange and its control

Physiological processes involved in the development of interstitial oedema: PAST QUESTION

- capillaries contain semipermeable membranes to allow the movement of fluid + solutes
- normally impermeable to large proteins
- plasma ultrafiltrate is filtered by bulk flow through the capillary wall by the action of opposing hydrostatic + oncotic pressures (Starling forces)

Starlings forces

- **capillary hydrostatic pressure (Pc)**
  - pressure exerted on the capillary by a column of whole blood within it
  - pressure pushing fluid out of a capillary
  - venous 15mmHg → arterial 25mmHg
- **Interstitial hydrostatic pressure (Pi)**
  - Pressure exerted on the capillary by the fluid in the interstitial space
  - Pressure pushing fluid into capillary
  - Usually 0mmHg
- **Capillary oncotic pressure (πc)**
  - Pressure that would be required to prevent the movement of water across a semipermeable membrane due to the osmotic effect of large plasma proteins
  - I.e. pressure pulling fluid into capillary
- **Interstitial osmotic pressure (πi)**
  - Pressure that would be required to prevent the movement of water across a semipermeable memebrane due to effect of interstitial fluid particles
  - I.e. pressure pulling fluid out of capillary



- Net filtration pressure (NFP) / fluid flux = outward forces – inward forces
  - NFP = Kf [(**Pc** – **Pi**) – σ(**πi** – **πc**)
    - Kf = filtration coefficient → reflects capillary permeability
    - σ = reflection coefficient → leakiness of membrane to protein

Parameters	Arterial (mmHg)	Venous (mmHg)
P_c	30	10
P_i	–6	–6
π_c	25	25
π_i	5	5
Net	**+16 (out)**	**–4 (in)**

Interstitial oedema

- Occurs when there is accumulation of interstitial fluid
- As oedema develops → changes in the interstitial Starling variables limit the formation of oedema
- Occurs with:
  - Imbalance of Starling Forces
    - ↑Pc → e.g. ↑arterial pressure, ↑precapillary sphincter, venous obstruction → fluid overload, CCF
    - ↓Pi → rare e.g. –ve pressure pulmonary oedema
    - ↑πi → e.g. low plasma protein → burns, plasma leak
    - ↓πc → ↓plasma protein e.g. liver failure, nephrotic syndrome, malnutrition
    - ↑NFP → greater driving force of fluid out of capillary → interstitial oedema
  - impaired lymphatic drainage e.g. LN removal
  - ↑Kf → infection/ inflammation → ↑leakiness of capillaries 2o cytokine production

Explain the local effects of a decrease in plasma colloid osmotic pressure in a skeletal muscle capillary bed: PAST QUESTION

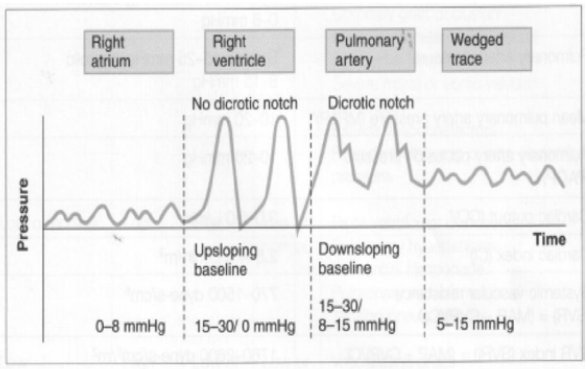
See above for explanaition of Starlings Forces

↓plasma colloid osmotic pressure

- Occurs with
  - ↓protein synthesis: end stage liver failure
  - ↑protein loss: protein losing nephropathy
- Effect: causes a ↓osmotic pressure exerted
  - All other forces remain equal → ↑bulk flow into interstitium: once this overwhelms the drainage capacity of lymphatics system → results in interstitial oedema
  - Incidentally, the movement of fluid into interstitium → results in ↓Pc which will favour absorption at the venous end
- Consequences:
  - ↑diffusion distance for: O2, nutrients into mitochrondria, waste products out of cells
  - ↓efficiency of excitation/ contraction coupling: ↓overlap of fibres
  - ↑Pi: ↓movement of solutes/ fluid → can lead to compression of capillary

Describe the waveforms and pressures that are seen in each anatomical location during insertion of a pulmonary artery catheter. What factors may increase these pressures? PAST QUESTION

Pulmonary artery catheter 110cm long catheter with 4 internal lumens used for:
- CVP monitoring
- Calculation of CO, mixed venous O2 saturations, PA pressures, wedge pressures



Conventionally the 'wedge' value or occlusion pressure is measured at the end of expiration.

Waveform features
- CVP and RA
  - Standard CVP waveform:
    - A wave: atrial contaction
    - C wave: bulging of tricuspid with ventricular contraction
    - X descent
    - V wave: passive filling of RA
    - Y descent
  - Normal CVP/ RAP: 0-8mmHg
- RV
  - Standard pressures: systolic 15-30mmHg; diastolic 0mmHg
  - EDP should be the same as RA
  - No dicrotic notch in RV pressure waveform + baseline upsloping due to pa
- Pulmonary artery
  - Standard systolic pressures are same as for RV (15-30mmHg); diastolic pressures 8-15mmHg
  - Descending systolic portion shows dicrotic notch related to pulmonary valve closure
  - Diastolic portion downsloping due to runoff into the LA
- Wedge pressure
  - Reflects LAP with shape characteristics similar to RA trace but with higher pressure values (5-15mmHg)
  - Trace less clear due to damped transmission through capillary vessels

Factors that ↑pressure
- CVP/ RAP: ↑preload/ filling; ↓CO; TR
- RVP: pulmonary stenosis; LVF
- PAP (i.e. pulmonary HTN): idiopathic, pulmonary thromboembolism, LVF, lung disease, CT disease
- PCWP: LVF

Cardiovascular responses to: changes in posture/ exercise/ valsalva/ PPV + PEEP/ pneumoperitoneum/ haemorrhage + hypovolaemia/ surgery + trauma

Cardiac reflexes:
- The cardiac reflexes are a series of reflex pathways which exist between cardiovascular and CNS and contribute to maintenance of homeostasis
- Receptors are located in atria, ventricles, pericardium, cardiac, and great vessels
- Afferent signals: VA nerve (other CN depending on reflex) → to nucleus of the solitary tract in cardiovasc centre of the medulla
- Efferent signals: VA

Important reflexes:

Reflex	Location of receptors	Stimulus	Travel via	Response/ effect
Baroreceptor reflex	Most important Second to second control of BP via circumferential and longitudinal stretch receptors located in carotid sinus + aortic arch	Stretch changes in MAP: 50-200mmHg (set point MAP 100mmHg)	Afferent signals: travel via C fibres in glossopharyngeal + VA nerve	alteration of autonomic activity (↓BP → inhibit PSY → ↑tonic SY activity)
Bainbridge reflex "atrial stretch reflex"	Stretch receptors in wall of RA and cavoatrial junction	Fire in response to ↑distending pressures	Vagus	↑SNS activity to SA node → tachycardia → aim to ↓blood vol back to normal
Bezold-Jarisch reflex	Chemo + mechanoreceptors in LV	Sense noxious stimuli	Vagus	hypotension + bradycardia + coronary artery vasodilation
Chemoreceptor reflex	Carotid + aortic bodies	Sense changes in PaO2 (<50mmHg) and pH	Carotid: glossopharyngeal Aortic bodies: vagus	Tachycardia/ HTN
Cushing reflex	↑ICP	↑ICP → ischaemia of vasomotor centre		Baroreceptors sense ↑arterial tension Reflex bradycardia
Occulo-cardiac reflex	Globe and surrounding structures	Pressure applied to globe or traction on surrounding structures	CNV + Gasserian ganglion to vasomotor centre → PSY response	Bradycardia + hypotension

Changes in posture

Describe the compensatory mechanisms in a fit person moving from the supine to the standing position

Effects on moving supine to standing
- ↑hydrostatic pressure 2° to gravity (circulation = column of fluid)
- ↑venous pooling → ↓VR → ↓SV → ↓CO → ↓MAP
- ↑vertical distance from hear to brain
  - ↓MAP at carotid sinus ~22mHg
  - CPP = MAP – CVR (ICP) therefore CPP ↓s ~20% initially

Compensatory mechanisms

Aim: maintain MAP + maintain CBF
- **Maintenance of MAP:** MAP = HR x SV x TPR

- Baroreceptor reflex (rapid response)
  - ↓VR → ↓MAP → detected as ↓stretch by high pressure baroreceptors (carotid sinus, aortic arch) → ↓firing receptors → removal of inhibition from vasoconstrictor centre
  - ↑SNS stimulation (↓PNS output):
    - ↑HR, ↑SV, ↑contractility → ↑CO
    - vasoconstriction → ↑TPR / ↑afterloada
    - venoconstriction → ↓venous capacitance + mobilisation of venous reservoir
  - ↑VR
    - venoconstriction
    - Muscle pump (contraction lower limb mm)
    - thoracic pump (with respiration)
    - Venous valves
- net effect = return MAP to normal in few seconds

- **Maintenance of CBF:** CBF = CPP / CVR → Where CPP = MAP – CVP (ICP)
  - Factors affecting CPP
    - MAP
    - ↓CVP: upright posture: drainage of outlet vessels to R heart
    - Monroe-Kelly doctrine : ↓CVP on standing → ↓ICP → ↑CPP and ↑CBF
  - Factors affecting CVR
    - Metabolic autoregulation
      - Local rapid redistribution of regional blood flow within brain based on metabolic demand
      - Via local release of vasoactive substances
    - Pressure autoregulation (myogenic mechanism)
      - ↓MAP → ↓CPP → ↓stretch on arterioles → reflex ↓resting tone of smooth mm → ↓CVR

Overall:
- on standing: MAP/ CBF ↓20% for few seconds → reflexes rapidly restore MAP/ CBF
- failure to correct CBF → faint → ↓vertical distance between heart and brain, remove hydrostatic effect of gravity on MAP → ↑CPP

Exercise

Cardiovascular response to exercise
- heart = demand pump: local tissue control of vascular beds determines amount of blood required to meet local metabolic demands
- Exercise can ↑CO by 5x
- Blood flow to skeletal muscle: 1L/min at rest (20% CO); ↑ to >20L/min during heavy exercise (80% CO)

Local control/ effects

Local factors are 1° determinant of skeletal muscle blood flow

1. Metabolic control (primary mechanism)
   - ↑metabolic demand of skeletal muscle: ↑O2, glucose, FFA, ketones (substrates for ATP production)
   - ↑metabolite production: ↓pH, ↓pO2, ↑pCO2, ↑K+, ↑adenosine
   - effect: reflex dilation of capillary beds → ↓TPR
2. Vasoactive substances
   - N2O produced by exercising muscle → dilation of capillary beds

Systemic effects

1. Catecholamine production
   - Ad/ Nad production from adrenals: stimulates heart B1 Rs + vascular a2 Rs
2. SNS activation → ↑CO:
   - ↑VR: arterial vasodilation (↓TPR); venoconstriction; blood shift/ muscle pump
   - ↑HR: ↓VA tone, ↑SY drie; ↑linearly with exercise
   - ↑SV: ↑with intensity of exercise by 10-35%; beyond this SV↓ as HR >200 due to ↓diastolic filling time
   - ↑BP + widened pulse pressure
   - ↓PVR: local metabolites in muscle
3. O2 carriage
   - Bohr effect
     - R shift OHDC in response to ↑pCO2, ↓pO2, ↑H+, ↑2,3DPG production → ↓affinity of Hb for O2
     - Improved loading fo O2 at the lung capillary + offloading at active tissues
4. Changes to regional blood flow
   - ↑flow to skin
     - dilation of cutaneous capillary beds: ↑heat loss through skin
     - ↑apocrine sweat gland activity → ↑heat loss through evaporation
   - redirection of splanchnic, liver, GIT blood flow via SNS activation to ↑availability for muscle + ↑catecholamine production from adrenals

Isometric I. isotonic exercise
- Isometric: sustained contraction of muscle → compression of capillary beds → ↑TPR due to ↑resistance in muscle beds
- Isotonic: contraction + relaxation of muscle → overall ↓TPR due to dilation of capillary beds

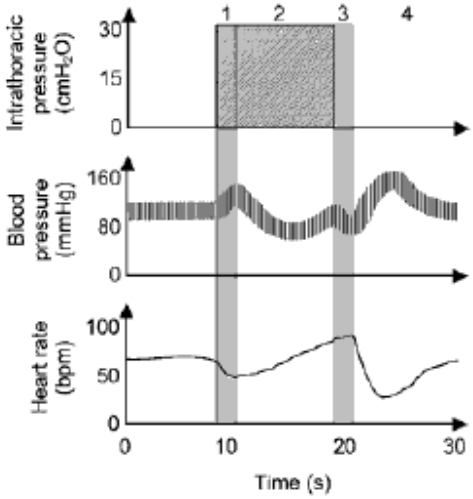
Valsalva manoeuvre

- action of forced expiration against a closed glottis after full inspiration
  - P_{AW}40mmHg should be achieved + held for 10 seconds
  - ↑intraabdo, intracranial, mouth, middle ear pressure

Uses:

- test of autonomic function
- Termination of SVT (due to ↑VA tone during 4th phase)
- Clear middle ear content
- Recruitment
- HOCM murmur

4 phases



1. **phase 1: Squeeze**
   - ↑BP, ↓HR
     - P_{AW} ↑to 40cmH2O → ↑Pintrathoracic
     - ↑SBP + DBP due to: compression of aorta + ↑LV preload due to eject
     - Reflexive ↓HR
2. **Phase II: ring out**
   - ↓BP, ↑HR
     - +ve Pintrathoracic maintained: ↓VR → ↓CO → ↓SBP + DBP
     - Carotid baroreceptors + SNS outflow: ↑HR + ↑SVR (peripheral vasoc
   - Pulse pressure narrow due to ↓CO (↓SBP) + vasoconstriction (↑DBP)
3. **Phase III: absorb (brief)**
   - ↓BP; no time for ΔHR
     - Valsalva ceases: P_{AW} returns to 0cmH2O
     - ↓PVR as alveolar vessels re-expand
     - SBP + DBP rapidly ↓ due to:
       - ↓PVR → ↓LV preload
       - Loss of high intrathoracic pressure compressing aorta
4. **Phase IV: overshoot**
   - ↑BP; ↑HR to normal
     - Baroreceptors respond to ↓BP by ↓afferent discharge/ inhibitory effect on pressor centre → vasoconstriction + ↑VR
     - BP recovers rapidly as CO restored; overshoots because blood is delivered into vasoconstricted periphery
   - Overshoot sensed by baroreceptors → reflex VA response → ↓HR + restores BP to normal

Abnormal responses

- Square waveform:
  - CCF, constrictive pericarditis, cardiac tamponade, valvular heart disease → when CVP markedly ↑; BP remains ↑ thoughout + returns to previous level at end
- Autonomic dysfunction:
  - BP ↓s + remains low until 28esponse28rict pressure released.
  - ΔHR + overshoot are absent
- IPPV or hypovolaemic patients:
  - exaggerated ↓in BP

Positive pressure ventilation and PEEP

Effects of IPPV on left ventricular output

- IPPV: ↑mouth / airway pressure to inflate lungs; in exp phase, pressure released to preset pressure (PEEP) or ambient pressure

LV output = vol of blood flowing out of the LV per unit time

- Dependent on:
  - LVEDV (preload):
    - related to degree of VR + stretch of LV mm fibres at end of diastole
    - dependent on HR + SV
  - Afterload: sum of forces that oppose LV output i.e. ventricular wall tension during contraction
    - according to **Law of LaPace:**
      - wall tension = transmural pressure x radius / 2x wall thickness
      - transmural pressure = intracavity pressure – intrapleural pressure
  - Contractility

IPPV: inspiration i.e.

- Inspiration = ↑ITP
  1. Initially ↑LV output
     - LVEDV: Initially pulmonary reservoir of blood mobilised 2° ↑ITP: transient ↑LA filling → ↑LV SV → ↑LV output → ↑CO
  2. Then ↓LV output
     - VR: As pressure ↑s: LV output ↓s as large systemic veins are compressed → ↑resistance to VR → ↓RV preload
     - RV outflow: ↑PVR → ↑RA afterload → septum bulges into LV → ↓LV compliance + filling
  3. Also a ↓afterload (LV outflow)
     - IPPV → ↑ITP → ↓transmural pressure → ↓afterload
- ***therefore***:
  - Initial transient ↑in LV output → followed by prolonged ↓LV output + ↓LV afterload
  - In pts with impaired myocardial contractility → IPPV may result in improved CO due to effect of ↑intrathoracic pressure on ↓afterload + ↓preload

IPPV: expiration

- Expiration = ↓ITP
  1. Initially:
     - ↓intrathoracic pressure → ↓PVR → ↑capacitance → ↑pulmonary blood vol
     - ↓LA return → ↓LVEDV → ↓SV → ↓CO
  2. Then:
     - ↑R heart VR (↑RV preload) → ↓RV afterload 2o ↓PVR → ↑LA preload + ↑CO

- NB: effect of ↓VR on CO is exacerbated by hypovolaemia, PEEP, hypoxia, hypercapnoea, autonomic neuropathy, ↓SYNS drive

Factors affecting above:

- **baroreceptor reflex:**
  - ↓MAP → ↓stretch high pressure baroreceptors (carotid sinus, aortic arch) → ↓firing cells sensed by vasomotor centre → ↑SNS activity/ ↓PNS activity → ↑HR
  - ↑contractility, vaso/ veno constriction to maintain MAP
- **PEEP/ hypovolaemia**
  - Both exacerbate effect of IPPV
  - Maintains ↓VR
  - PEEP → ↑PVR
  - Leads to exaggerated loss ↓MAP as compensatory mechanism impaired
- Overall effect on CVS:
  - depends on: Age, cardiac function, volume state
  - Young people with normal function: IPPV tends to cause ↓CO and ↓BP
  - Elderly with impaired LV function: IPPV tends to have nil effect or improve CO + BP

Pneumoperitoneum

Pneumoperitoneum involves insufflating the abdomen with gas

- Most commonly used gas = CO_2
  - Inexpensive
  - Inhibits combustion
  - Readily available
  - Rapidly absorbed + metabolised by the patient
- Used in laparoscopic surgery to aid exposure
- Intraabdominal pressure 10-12cm H_2O
- Effects can be mechanical or biological 2o insufflated gas

Mechanical

- CVS
  - Venous pooling in legs
  - IVC compression → ↑RVR, ↓VR → ↓CO
  - ↑vascular resistance of intra-abdo organs → ↑SVR
- Regional effects
  - Venous stasis in legs → DVT
  - PCO_2 → vasodilation if vent not ↑
  - Arrhythmias: bradycardia 2o peritoneal manipulation
- Resp
  - ↓compliance
  - ↑intrathoracic pressure on IPPV
- neuroendocrine
  - ↑ADH, catecholamines, renin, ATII
  - ↑SY tone
- Net result: ↓CO, ↑MAP → minimised by filling, head down position, $\alpha 2$ agonists

Biological effect of insufflated gas

- Hypercarbia
  - Once absorbed: $CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow HCO_3 + H^+$ → metabolic acidosis
  - Metabolic acidosis → myocardial depression, ↓CO, ↑PVR
  - Generally well tolerated; pts at ↑risk of complication: pulmonary HTN, CCF, sepsis, hypovolaemia, cardiomyopathy

Haemorrhage/ hypovolaemia

- Assessment of loss
  - <25% loss: ↑HR, BP normal, oulse pressure narrow; ↑CRT
  - 25-40% loss: ↑HR, ↓BP, ↑CRT, ↑RR, oliguria, altered mental state
  - >40% loss: shock; ↓HR, ↓BP, ↑RCT, ↑RR, anuria, coma → due to vagally mediated cardiac afferent C-fibre discharge caused by ventricular distortion + underfilling
- Loss of 1L of blood
  - Lose 40g albumin
  - 140mmol Na, 100mmol cl, 4mmol K

Summary of physiological effects of haemorrhage

- ↓blood vol → ↓VR, ↓CO
- ↓arterial BP → activation of baroreceptor reflex
- ↑SY → ↑HR, peripheral vasoconstriction, viscera, kidneys
- ↑vasopressin → vasoconstriction, Na+ H_2O retention, thirst

Effect in more detail:

- **Haemodynamic**: ↓filling pressure, ↓SV, ↓CO, ↓MAP
- **Baroreceptor** (response max at MAP 60): ↓stimulation at carotid sinus and aortic receptors; ↓VA tone, ↑SY tone → ↑HR, ↑contractility, peripheral vasoconstriction → ↑SVR, ↑filling pressure, centralised blood volume
- **Chemoreceptor**:
  - Some augmentation of SY response below MAP 60
  - Hypoxia, hypercapniea, acidosis → stimulate carotid and arotic bodies → ↑SY tone, ↑resp drive → minor ↑in VR
- **Cerebral ischaemic response**: further augmentation of SY tone <MAP 40mmHg; also ↑CA tone (maladaptive)
- **Autoregulatory vascular response**: arteriolar constriction due to myogenic mechanism
- **Reabsorption of tissue fluids:**
  - ↓capillary hydrostatic pressure
  - Reversed starling forces: transfer of fluid from interstitium into circulation; up to 1l/hr
  - Transfer from ICF to interstitial fluid also occurs in response to cortisol
- **Endogenous vasoconstrictors**

  - Adrenaline and noradrenaline: from adrenal medulla and SY nerves → responsible for acute SY 29esponse
  - ADH: rapid secretion from posterior pituitary in response to hypotension; vasoconstrictor, ↑water reabsorption from collecting ducts; ↑expression of vWF and VIII
  - Renin: catalyzes conversion of angiotensinogen to angiotensin I
  - Angiotensin II: vasoconstrictor; ↑ADH, aldosterone
- Renal conservation of fluid
  - ↓MAP → ↓RBF, GFR, and UO
  - ↑SY tone → afferent and efferent constriction → ↓RBF, GFR; ↑renin secretion (direct and via JGA)
  - ↑ATII → ↑Na reabsorption, arteriolar vasoconstriction
  - ↑aldosterone → ↑Na reabsorption from DCT + collecting ducts
  - ADH

NB: timecourse:

- seconds: baroreceptor, chemoreceptor, cerebral ischaemic response
- minutes: autoregulatory, angiotensin, ADH, capillary fluid shift
- hours: full effect of renal fluid retention

Response to haemorrhage occurs in 3 phases with sig overlap

- **hypovolaemia + cardiovascular compensation**
  - due to loss of circulating vol
  - no time for composition of intravascular fluid to change
  - osmoreceptors response: osmolality not yet changes → vaso released anyway by baroreceptors sensing loss of volue
  - baroreceptor response: ↓
    - VA tone → ↑SY tone → venous + arterial constriction → concentrating blood vol in central + cerebral circulation → ↑HR, ↑CO despite ↓preload
    - Can compensate for 10-15% loss and CO will no suffer very much
- **transcapillary flid redistribution and isovolaemic anaemia**
  - restoration of blod vol by transcap refill → net movement of fluid + protein from interstitial compartment into intravascarul compartment
  - SY: ↓diameter of arterioles → ↓pressure at capillaries
  - Oncotic pressure remains same; no longer balanced by high cap hydrostatic pressure → movement of free water out of the interstitial space and into the intravascular space → dilutes capillary fluid
  - Movement of interstitial albumin into intravascular compartment
- **renal fluid/ electrolyte conservation and haemopoiesis**
  - activation of RAAS →Na retention, Na+ distributed into extracellular fluid
  - BM attempts to replenish lost RBC

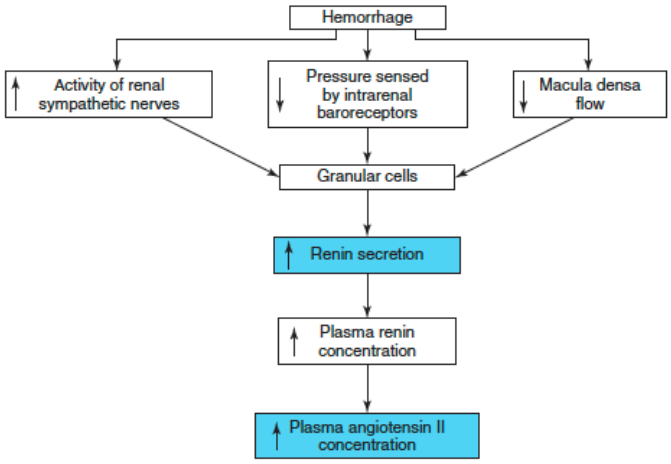


Figure 7–5. Schematic diagram showing the increase in renin secretion and the increased production of angiotensin II in response to a major hemorrhage. Three primary mechanisms activate renin secretion: (1) increased renal sympathetic nerve activity; (2) decreased pressure sensed by intrarenal baroreceptors; and (3) decreased sodium chloride delivery to the macula densa. The first two mechanisms directly stimulate renin release, whereas the third mechanism reduces inhibitory feedback, allowing more renin release. Renin promotes the formation of angiotensin II, which produces strong vasoconstriction and helps to correct the decrease in blood pressure that resulted from the hemorrhage.

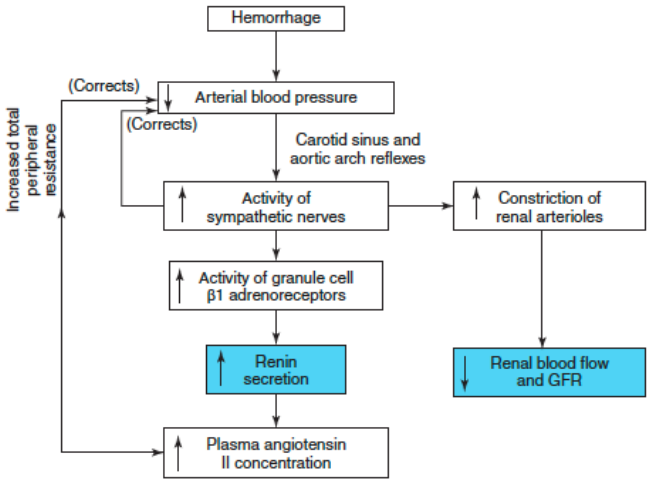


Figure 7–6. Schematic diagram showing the vascular response to a major hemorrhage. The baroreceptor reflex increases sympathetic activity. Besides the effect of sympathetic neurotransmitters on β_1-adrenergic receptors to stimulate renin release, they also stimulate α_1-adrenoreceptors (like those present on other vascular smooth muscle cells) to cause afferent arteriolar contraction and a reduction in renal blood flow. In the kidney, most of this reduction in blood flow is blunted by tubuloglomerular feedback (see Figure 7–14). GFR, glomerular filtration rate.

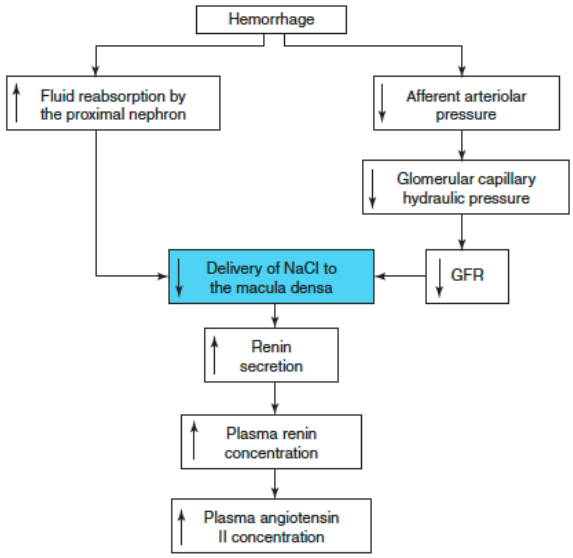


Figure 7–7. The macula densa NaCl load sensor. Macula densa cells in the thick ascending limb sense sodium chloride delivery by changing the uptake of salt with subsequent osmotic swelling (see Figure 7–3). Changes in cell volume lead to the release of chemical transmitters that alter renin secretion from the granular cells: When sodium chloride delivery increases, renin production decreases. GFR, glomerular filtration rate.

Surgery/ trauma

Central neuraxial blockade: PAST QUESTION

Overview:
- central neuraxial blockade achieved by: subarachnoid (spinal) or epidural
- LA (bupivacaine, ropivavaine) +/- opioid (fentanyl, morphine)
- Effects are more pronounced in:
  - Elderly (↓physiological reserve)
  - Fixed cardiac output states
  - ↓blood volume

CVS response
- ↓ MAP due to:
  - blockade of alpha + beta SY chain fibres that innervate venous smooth muscle + control vasomotor tone
    - Run in thoracolumbar region (T5-T11) → level of block will affect degree of ↓MAP
    - MoA
      - Removes tonic SNS activity on vascular smooth muscle
      - Blocks a1 adrenoceptors (GPCR) → ↑PKC → ↑IP3/DAG → ↑Ca2+ → constriction
      - Blocks b2 receptors (GPCR) → ↑cAMP → ↓Ca2+ → dilation
    - Result
      - Vasodilation (arteriolar) → ↓afterload
      - Venodilation (venous) ↑capacitance → ↓VR → ↓CO
      - Veno effect >> arterial effect → 75% blood vol pools in venous circulation
- Level of block of SNS + effect of CVS response
  - Sacral block: nil SY chain blockade (only PSY fibres) → minimal effect on peripheral vascular tone
  - mid thoracic/ renal level → ↓GFR → activation fo RAAS by ↓afferent arteriolar stretch
  - "high block": T1-T4 cardio-acceleratory centre → blockade → unable to ↑HR/contractility with SNS stimulation
  - brainstem block: inhibition of vasomotor centre → unable to activate SNS response → profound ↓MAP

Detector/ compensatory systems
- high pressure baroreceptors (carotid sinus + aortic arch)
  - sense: ↓stretch → ↓inhibitory input to SNS → stimulation of vasomotor centre
  - Result:
    - ↑SNS: ↑HR, ↑contractility; vasoconstriction; venoconstriction
    - activation of RAAS: ↑renin; ATII: direct vasoconstriction; ↑ADH; ↑H2O reabsorption from DVT
- Low pressure baroreceptors (RA, great vessels)
  - Sense: ↓stretch → ↓ANP secretion
  - Result:
    - ↓inhibition RAA/ ADH system; ↓Na/H2O releas

Cardio – other

Cardiovascular changes that occur with ageing

Ageing = physiological time-dependent process which results in ↓cellular function + ↓reserve

Heart
- Muscle
  - ↓number of myocytes; LVH + ↑cardiac mass
  - ↑collagen + fibrous tissue deposition → impair compliance + early LV diastolic filling

- LV relaxation less efficient in diastole → ↓compliance
- Atrial contraction more important to ventricular filling contributing ~40% LVEDV (AF can lead to significant ↓CO)

- Innervation
  - Downregulation of B adrenoceptors
    - ↓affinity + alteration in signal transduction
    - attenuated Breceptor responses → ↓max HR + ↓peak EF → ↑susceptibility to cardiac failure
    - ↑SNS activity → ↑plasma catecholamine concentration
- Electrical
  - Calcific + fibrotic degeneration of conducting pathways + fatty infiltration of pacemaker cells
    - AF common; SSS
    - ↓intrinsic sinus rate but overall HR preserved by ↑SY tone
    - ↓max HR

Vessels

- calcification + intimal thickening + breakdown of elastin
  - ↓compliance
  - widened pulse pressure
  - loss of elastin in prox thoracic aorta + prox branches of greater vessels → progressive central aortic dilation
- Degeneration of coronary vessels
  - Atherosclerotic change -- ↓calibre of coronary vessels → ↑CVR + ↓CorBF
- Baroreceptors
  - ↓sensitivity: ↓reflex adaptations to hypotension → more labile BP
- Calcification of aorta
  - ↓compliance → ↑afterload → LVH → ↓compliance
  - ↑SBP ↑DBP
  - ↑aortic stiffness resulting in ↑pulse wave velocity
  - ↓time between systole + diastolic peak pressures

Cardiovascular changes that occur with morbid obesity

Obesity

- excessive fat accumulation in adipose tissue
- WHO classification based on BMI (weight in kg/ height in m2)

Changes in CVS

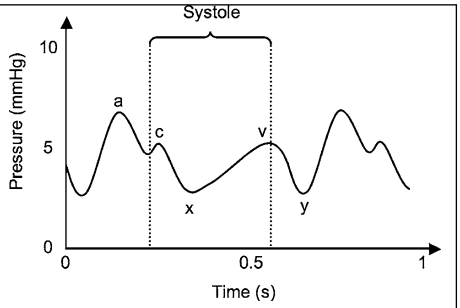
- depend on extent + duration of obesity
- extra adipose tissue needs ↑CO
  - ↑SNS
    - ↑HR + ↑SV
    - ↑RAAS → Na+ retention → ↑blood vol → ↑MAP
    - ↑MAP → LVH → LV dilation → LV failure
- OSA
  - Pulmonary HTN → cor pulmonale
  - Polycythaemia → ↑viscosity
- Compression of abdominal + leg vessels
  - ↓VR → supine hypotension + ↑risk DVTs
- insulin resistance + hyperlipidaemia → inflammatory mediator upregulation → disrupt endothelial function → IHD + cerebrovascular disease + PVD
- direct deposition of fat in myocardium → conduction disease + cardiomyopathy

CVS diseases associated with obesity:

- associated with HTN, HF, IHD, cardiomyopathy, sudden cardiac death, arrhythmias, PVD, DVT, CVD

List the physiological factors that affect left atrial pressure (LAP) and explain their effects. Draw LA pulse trace I. time: PAST QUESTION

- LA: receives all of CO returning from pulmonary circulation
- Pulmonary circulation = low pressure (0-25mmHg)
- Normal LAP = 0-8mmHg



LAP trace

- **a wave:** atrial contraction
- **c wave:** ventricular contraction → bulging of mitral valve into LA
- **x descent:** pressure ↓ 2° shortening of ventricles → atria pulled → ↑atrial capacity with ↓pressure
- **v wave:** atrial filling against closed MV
- **y descent**: passive ventricular filling after opening of mitral valve

Factors affecting LAP

- **LA filling**
  - Blood vol passes through pulmonary circulation + drains into LA via pulmonary vein
  - Influenced by:
    - Blood vol: ↑filling → ↑LAP
    - Posture: upright → ↓VR → ↓LAP; supine → ↑VR → ↑LAP
    - Pulmonary venous tone: ↑tone → vasoconstriction → ↑VR → ↑LAP
    - ITP:
      - ↑pressure (expiration/ IPPV/ PEEP) → ↓VR → ↓LAP
      - ↓pressure (inspiration) → ↑VR → ↑LAP
- **LA emptying/ ventricular filling**
  - Passive + active (atrial kick)
  - AV ring size: ↓outlet through AV ring → ↑resistance → ↑LAP
  - Mitral valve incompetence: regurgitation of blood → ↑LA volume → ↑LAP
  - Atrial contraction: absence of contraction: ↑LAP
- **Ventricular emptying**
  - Aortic valve incompetence: inadequate closure at end-systole → regurg of blood → ↑ES LV vol → ↑diastolic filling pressure → ↑LAP

(e.g. aortic stenosis/ sclerosis)
  - LV contractility: ↓LV function → ↑LVESV → ↑diastolic filling pressure → ↑LAP (e.g. lateral MI, LVF)
  - Aortic valve outlet size: ↓LV outlet size → ↑LV pressure → ↑LAP (e.g. aortic stenosis/ sclerosis)
  - IPPV: ↓wall tension → ↓afterload

Describe the pathways whereby myocardial ischaema may be experienced as pain in the throat or arm regions: PAST QUESTION

- pain: unpleasant sensory + emotional experience associated with actual or potential tissue damage or described in terms of such damage
- referred pain: pain perceived as coming from an area or situation remote from its actual origin

Supply vs. demand
- inadequate supply of blood to supply the O2 required for the metabolic demands of the heart
- heart = dependent on aerobic metabolism
- metabolic demands (vol of O2 consumed) by heart = determined by amount + type of activity of the myocardium (stroke work)
  - stroke work = SV x afterload
    - Afterload: pressure against which the blood is ejected by LV
    - SV determined by: preload, afterload, contractility
  - Myocardial O2 ER ~70% = nearly maximal under basal conditions → O2 supply is dependent on CBF (flow limited)
  - ↑HR, ↑afterload, ↑contractility → ↑O2 requirement → ischaemia if CorBF does not ↑ to meet demands

Myocardial ischaemia
- ischaemia → ↓ATP formation → accumulation of metabolic products that stimulate pain endings in the myocardium → ↓pH, ↑lactate, serotonin, bradykinin, histamine, O2 species, adenosine
- adenosine = primary mediator of angina: stimulates A1 adenosine R GPCR → Gi → adenylyl cyclase inhibition → ↓intracellular cAMP
- c fibres travel along SY afferent pathways from heart → enter SC through superior thoracic ganglia of SY trunk

Myocardial ischaemia as referred pain
- type of referred pain: i.e. irritation of visceral organ → produces pain in somatic structure that may be distance away
- pain of myocardial ischaemia or infarction commonly radiates from substernal region + L pectoral region to shoulder/ L arm/ throat
- convergence-projection theory
  - convergence of somatic + viscareal pain fibres on same 2nd order neuron in dorsal horn that project to thalamus → somatosensory cortex
  - axons of 1o sensory neurons enter spinal cord segments C7-T4
  - end point: cardiac pain follows dermatomal rule: heart developed at same embryonic segmental origin as the arm → therefore is referred to the L side fo the chest + medial aspect of the arm

Explain how O2 supply of organs is maintained during isovolaemic haemodilution: PAST QUESTION

Isovolaemic haemodilution

- replacement of a portion of blood vol with fluid which doesn't possess O2 carrying capacity e.g. NS/CSL → therefore nil effect on circulating vol
- Effect:
  - ↓concentration of blood components + ↓[Hb]
  - O2 content in blood determined by:
    - CaO2 = O2 bound in blood + dissolved O2
    - CaO2 mg/L = ([Hb] x SaO2 x 1.34) + (PaO2 x 0.003)
    - 99% O2 bound to Hb; 1% dissolved in solution → therefore ↓[Hb] → ↓O2 carrying capacity of blood
  - O2 flux equation describes delivery of O2 to organs
    - DO2 = CaO2 x CO
    - Therefore during isovolaemic haemodilution, O2 supply can be maintained by changes to CO

Maintenance of O2 supply

- **changes to CO**
  - CO directly proportional to [Hb]
  - O2 supply usually maintained by ↑CO (CO = HR x SV)
  - Viscosity
    - Isovolaemic haemodilution → ↓viscosity due to loss of blood components
    - According to Hagan -Poiseulle: flow = πrp4 / 8ηL → ↓viscosity → ↑flow
    - ↓viscosity → ↑CO
      - Via FrankStarling reflex: ↓viscosity → ↑VR → ↑SV → ↑CO
      - ↓viscosity → ↓SVR and ↓afterload → ↑CO
  - SNS stimulation
    - Metabolic organ blood flow autoregulation: ↓PO2 → ↑lactate/ H+ and ↓pH → ↓TPR
    - ↓TPR → ↓MAP → high pressure baroreceptors → ↑SNS stimulation → ↑preload 2o venoconstriciton → ↑VR, ↑HR, ↑SV/ contractility
- **improved O2 ER**
  - Fick: VO2 = Q(CaO2 – CvO2)
    - Where: CaO2 = arterial O2 content; CvO2 = venous O2 content; Q = CO
    - Therefore ↑O2ER can occur with ↓CvO2
  - Bohr effect
- **Redistribution of blood to vital organs**
- **↑EPO production**

CARDIOVASCULAR PHARMACOLOGY

Describe the autonomic nervous system and its physiological roles including: • Autonomic receptors and cellular effects of receptor activation • Autonomic transmitters, their synthesis, release and fate

- Subdivided into central ANS + peripheral ANS
- regulates visceral functions + involuntary control → haemodynamics (CO, SVR), respiration, GI, urination + defecation, thermoregulation, sexual function

1. Central ANS

- Hypothalamus, brainstem, spinal cord
- Neural + endocrine role
- tonic output to: smooth muscle, heart, exocrine/ endocrine organs, GIT, GU
- 4 regions:
  - 1. Anterior hypothalamus: supraoptic + paraventricular nuclei → controls PSY, heat loss, ADH + oxytocin
  - 2. Medial hypothalamus: ventro + dorsomedial n. → energy + sexual behaviour
  - 3. Lateral hypothalamus: emotions, thirst, food
  - 4. Posterior hypothalamus: SY outflow; vasomotor centres

2. Peripheral ANS

- Divided into: SY + PSY. Differ in: length of neurons, location of ganglia (synapses), and NT

Feature	**Division of ANS**	
	SY	**PSY**
Location of preganglionic neuron cell bodies	Lateral horn of spinal segments T1-L3	Brainstem, lateral grey areas of spinal segments S2-4 Cranial outflow: CN III, VII, IX, X Sacral outflow: S2-4
Length of preganglionic neuron	Short	Long

Location of postganglionic cell bodies	SY chain + prevertebral ganglion
	- SY chain = paravertebral ganglia
	  ○ *Cervical*: head + neck
	  ○ *Thoracic*: upper thoracic (T1-5 → heart, lungs, aorta); lower thoracic (T6-12 → foregut + midgut viscera)
	  ○ *Lumbar*: hindgut viscera
	  ○ *Sacral*: pelvic viscera
	- Prevertebral ganglia: coeliac; sup mesenteric; inf mesenteric
		Ganglia close to target organ

Preganglionic NT **Post-ganglionic receptor**	**ACh** Nicotinic receptor	**ACh** Nicotinic receptor
Length of post-ganglionic neuron	Long	Short
Post-ganglionic NT **Target organ receptor**	**Norad** Adrenergic receptor	**ACh** **Muscarinic receptor**
Modulators	enkaphalin, neuropeptide Y, dopamine, adrenaline, prostaglandin, GABA, neurotensin	
Exceptions	1. Adrenal medulla: directly innervated by pre-ganglionic neurons, with ACh as NT. No post ganglionic fibres 2. Sweat glands: post ganglionic fibres release ACh + act via mAChR 3. Metarterioles in skeletal muscle beds: innervated by SY cholinergic fibres.	
Effect	- direct neural innervation, or adrenaline release ***Effect*** - Eyes via cervical → pupillary dilation - Lungs via thoracic → bronchodilation - Heart via thoracic: ↑HR, ↑inotropy, ↑conduction velocity - Vasculature via sacral → constriction - MSK via sacral → sweating - Endocrine via lower thoracic → release NAd + Ad - GIT via thoracic + lumbar → ↓motility, ↓salivation - GY: ↑tone, sphincter contraction, detrusor relaxation	Supply: - cranial:upper ½ of body to splenic flexure - sacral: viscera lower ½ body ***Effect*** - CNIII: edinger westphal → pupil constriction + lacrimation - Lungs via CNX → bronchoconstriction - Heart via CNX → ↓HR, ↓inotropy, ↓conduction velocity - GIT via VII (salivary glands); CNX (stomach to transverse colon) → salivation, ↑motility - GU via hypogastric plexus: detrusor contraction
Drugs	***Agonists*** - Direct: α1 phenylephrine; α2 clonidine; β adrenaline, dobutamine, isoprenaline - Indirect: ephedrine - Reuptake inhibitors: cocaine ***Antagonists*** - Direct: α1 prazocin, α2 yohimbine, β propranolol - Indirect: reserpine	***Agonists*** - Direct: acetylcholine - Indirect: neostigmine, organophosphates ***Antagonists*** - Direct: muscarinic (atropine, glycopyrolate, ipratropium), nicotinic (trimetaphan) - Indirect:AchE reactivators e.g. pralidoxime

Enteric plexus

- autonomic nerves in GIT free of CNS control
- sensory + integrative neurons + excitatory + inhibitory motor neurons
- excitatory interneurons + motor neurons release ACh as NT
- other interneurons release serotonin, vasoactive intestinal peptide, NO

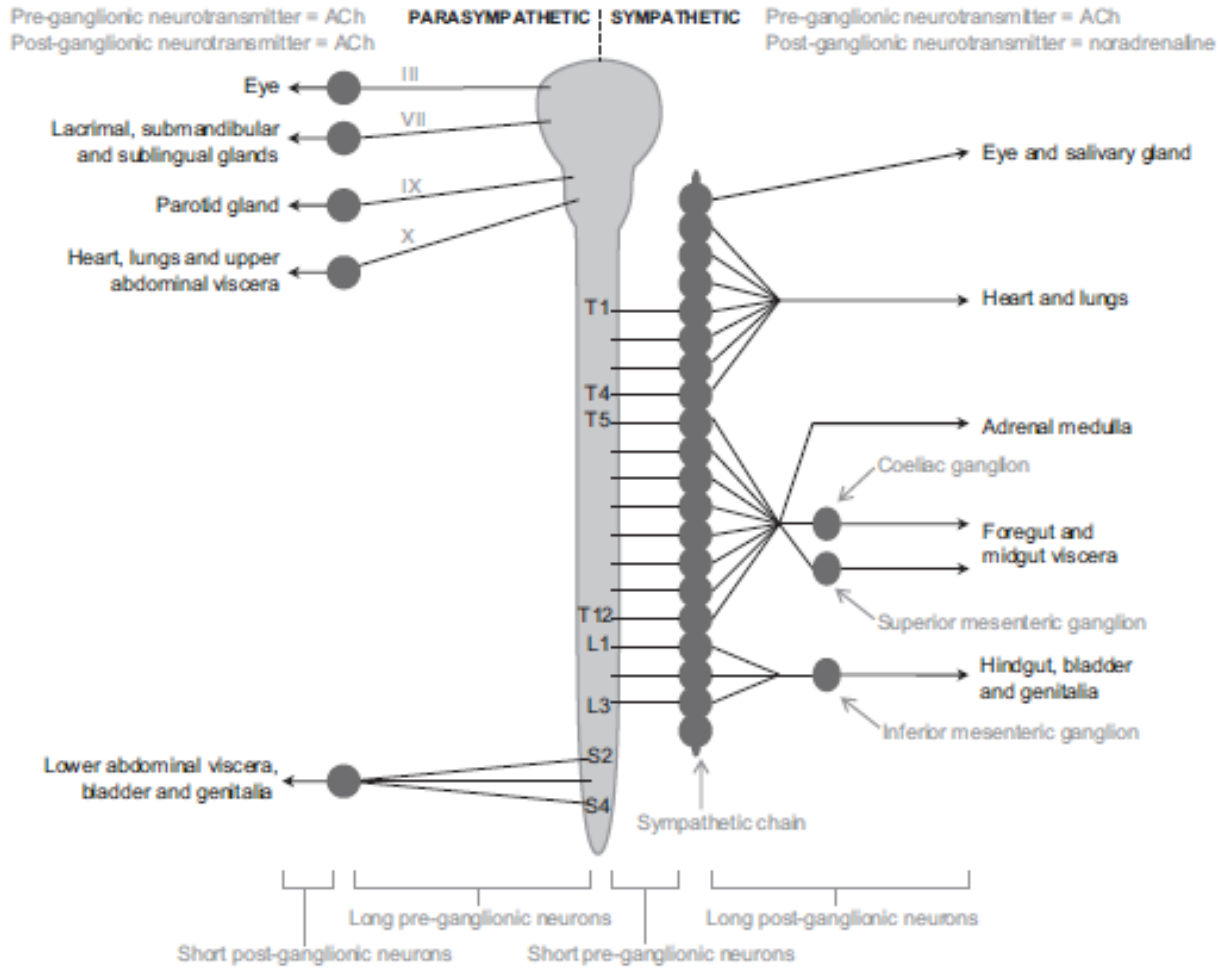
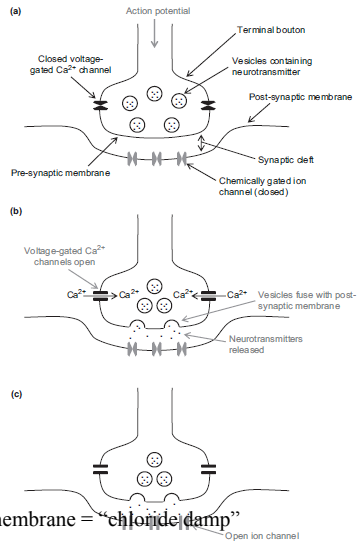


Figure 56.1 Layout of the ANS.

Neurotransmitters and receptors in general

Neurotransmitters

- Substance released by a neuron at a synapse → affects post-synaptic cell
- NT release
  - NT stored in vesicles on pre-synaptic membrane
  - AP into terminal bouton: N-type voltage gated Ca^{2+} channels open → ↑presynaptic [Ca2+]
  - Exocytosis: Ca^{2+} binds to vesicular memebrane protein (synaptotagmin) + SNAREs → trigger vesi synaptic cleft
  - Diffusion across synaptic cleft down conc gradient
  - Binding to post-synaptic Rs → excitation / inhibition
- **Classified as:**
  1. **Amino acids: Glutamate; GABA; Glycine**
  2. **Monoamines: ACh; Serotonin; Histmaine**
  3. **Catecholamines: Dopamine; Noradrenaline; Adrenaline**
- Termination of neurotransmission
  - NT removed from synaptic cleft via diffusion or degradation
  - Neuronal reuptake: active transport back into presynaptic membrane eg NA, dopamine



Receptors

1. **Inotropic**
   - Ligand gated post-synaptic ion channels e.g. GABA, NMDA
   - EPSP or IPSP
     - EPSP: NT binding at post-synaptic membrane opens non-specific cation channels → N intracellular movement of +vely charged ions → depolarisation
     - IPSP: ligand gated K+ or Cl channels on post synaptic membrane
       - K mediated: K down EC gradient out of cell → efflux +vely charged ions -
       - Cl mediated: intracellular movement of Cl → ↑difficulty depolarising cell membrane = "chloride clamp"
2. **Metabotropic**
   - effects via chemical 2nd messengers e.g. muscarinic ACh
   - NT binds → conformational change → **GPCR** (no ion channel opening)

Neurotransmitters in the ANS

Neurotransmitters in the ANS

2 main NT:

1. **ACh**
   - Role
     - Preganglionic NT in SY + PSY
     - Postganglinoinc NT in PSY
     - Adrenal medulla pre-ganglionic neurons → ACh
     - Sweat glands: post ganglionic fibres release ACh
   - ***Receptors:***
     - ***Nicotinic***
       - ligand gated; at NMJ
       - large protein; 5 subunits (α1, α2, β, y, delta)
       - ACh binds to α chains → conformational change → opens ion channel → inward Na + outward K
       - Agonist = nicotine / Antagonist = curare
     - ***Muscarinic***
       - GPCR (metabotropic); in heart → activates PLC, inhibits AC, or opens K ion channels
       - **5 subtypes**
         - **M1:** CNS, autonomic ganglia, gastric parietal cells → ↑intracellular IP3 + DAG → ↓K conductance + ↓depol
         - **M2:** atrial + conducting tissue of heart → ↓intracllular cAMP → ↑K conductance → inhibitory
         - **M3:** glandular secretion + visceral SM contraction 2° ↑IP3
         - **M4 + M5**: CNS
2. **Noradrenaline**
   - Released at postganglionic nerve endings of SYNS → excitatory (vasoconstriction) + inhibitory effects
   - Located in: locus ceruleus, medullary + pontine nuclei
   - Synthesis: dopamine → converted to NA by dopamine-hydroxylase in neuons + adrenal medulla
   - Fate: metabolised to inactive compounds by MAO (oxidation) and COMT (methylation)
   - Adrenergic receptors (adrenoceptors) = GPCR; 4 main subtypes

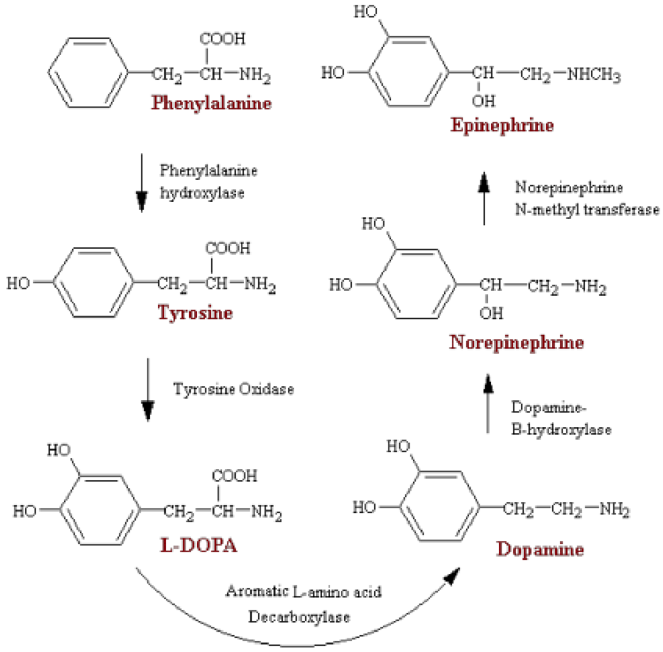
	Type	Location	Action	Agonist	Antagonist
α1	GqPCR	Smooth muscle	Activates PLC → IP3 + DAG → - Vaso/ venoconstriction - GIT sphincter contraction - Glycogenolysis - gluconeogenesis	NAd Metaraminol phenylephrine	Prazosin
α2	GiPCR	Pancreas Arterioles CNS	Inhibits AC → - vasodilation - inhibition of insulin release - analgesia, sedation - platelet aggregation	Clonidine (partial agonist)	Yohimbine
β1	GsPCR	Heart Juxtaglomerular cells Platelets	+ve inotrope; +ve chronotrope Renin secretion Platelet aggregation	Ad NAd	Bisoprolol
β2	GsPCR	Bronchi Heart Uterus Vascular smooth muscle	Bronchodilation Smooth muscle relaxation Glycogenolysis Gluconeogenesis tremor	Ad	

Neuromodulators:

3. Peptides:
   - E.g.: encephalin, neuropeptide Y, vasoactive intestinal peptide, neurotensin
   - Modulate synaptic excitability: ↑ or ↓ efficacy of synaptic transmission without acting directly as NTs = "neuromodulation"
4. Other chemical mediators
   - Prostaglandins
   - Adenosine
   - Dopamine
   - Serotonin
   - GABA

Outline the main biochemical events involved in noradrenergic transmission. Outline how these may be altered by the use of monoamine oxidase inhibitors: PAST QUESTION

- post synaptic SY nerve fibres (except SY innervation of sweat glands + sl
- CNS pathways governing mood / pain



NAd synthesis
- Occurs in axoplasm of terminal nerve endings
- **phenylalanine** → *phenylanaline hydroxylase* in liver → **tyrosine** → *tyro* cytoplasm → **dopamine** → *dopamine β-hydroxylase* in cytoplasm → **No**

NAd storage + release
- stored in vesicles in nerve terminal of post-ganglionic fibres
- AP arrives: open voltage gated Ca2+ channels → Ca2+ influx → Ca2+ d

Interaction of NAd + receptor
- NAd acts of presynaptic adrenergic Rs
  - α2 adrenergic R: Gi → ↓AC → ↓[cAMP] → ↓PKA → ↓[Ca2
  - modulate own release from presynaptic terminal
- NAd acts on post-synaptic adrenergic Rs
  - α1 adrenergic R: Gq → IP3/ DAG → downstream effects
  - β1 R: Gs → ↑AC → ↑[cAMP] → ↑PKA → downstream effe
  - β2 R: Gs → ↑AC → ↑[cAMP] → ↑PKA → downstream effe

Metabolism + reuptake
- NAd in synaptic cleft →
  - Uptake 1 (major pathway): reuptake into pre-synaptic terminal → oxidative deamination by MAO0A → metabolites resynthesised into NAd or elimination from synapse + excreted in urine
  - Uptake 2 (minor pathway): diffusion away from synaptic cleft → methylation by COMT (not found in SY nerve terminals)
- Terminal metabolites: VMA + MHPG → excreted in urine

MAOI
- 2 types of MAO located on outer mitochondrial membrane
  - MAO-A deaminates NAd, Ad, 5HT
  - MAO-B deaminates tyramine + 2-phenylethylamine
- Therefore inhibition of MAO-A → ↓metbaolism of NAd, Ad, 5HT → ↑availability and action → ↑SNS activity, CNS excitation
- MAOI may interact with other meds: e.g.
  - Sympathomimetics: prolong action → ↑SNS
  - SSRI: precipitate serotonin syndrome
  - Tyramine rich foods e.g. cheese → catecholamine release → HTN crisis
- MAO inhibitors
  - Non selective MAOI: phenezine
  - Selective MAO-A inhibitor: moclobemide
  - Selective MAO-B inhibitor: selegeline

Describe the mechanism of action and effects of sympathomimetic and anticholinergic drugs used clinically

Sympathomimetic drugs	Anticholinergics

- stimulant comounds which mimic the effects of endogenous agonists of the SYNS
- Can be classified based on MoA, structure, or naturally occurring vs. synthetic
MoA
- Direct vs. indirect
  ○ Direct: attach directly to R eg adrenaline, NAd, phenylephrine, isoprenaline, dobutamine
  ○ Indirect: cause release of NAd e.g. metaraminol (direct + indirect)
- Adrenergic R
  ○ Mixed α/ βagonists: Ad, ephedrine, dopamine
  ○ αagonists: phenylephrine, metaraminol, NAd
  ○ βagonists: dobutamine
Structure
- Basic structure = benzene ring + amine side chain at C1
- If hydroxyl group also present at C3 and C4 = catecholamine
- E.g. catecholamine = Ad, NAd, dopamine, isoprenaline, dobutamine vs. non-catecholamine = ephedrine, etaraminol, phenylephrine
Naturally occurring vs. synthetic
- Naturally occurring: Ad, NAd, dopamine
- Synthetic: isoprenaline, dobutamine, ephedrine, metaraminol
	Naturally occurring:
	- Atropine
	- hyoscine
	Synthetic (quaternary amines)
	- glycopyrolate

Structure activity relationship of sympathomimetics: MAKEUP

- Catecholamine
  - Cetechol + ethylamine
    - Catechol: benzene ring; -OH groups on C3 and C4
    - Ethylamine: α and β carbons + terminal –NH2
- Metabolism
  - Catecholamines: 3,4-di-hydroxy-benzene structures → metabolised by MAO + COMT (COMT requires both –OH groups on C3 and C4
  - Synthetic non-catecholamines: lack of –OH group on C4; emtabolised only by MAO → slower
- Direct vs. indirect activity
  - Direct activity: OH group on C3; OH group on βC
  - Indirect activity: ephedrine
- Receptor selectivity

- Adrenaline
  - Ultimate catecholamine
  - Any change in chemical structure → change in α +/- β activity
- Norad:
  - Lack of –CH3 group on terminal amine → catecholamine (OH group on C3 and C4); direct activity (OH group on C3 and βC); mainly α1 activity; some β activity
- Phenylephrine
  - Lack of OH group on C4 → non catecholamine; direct activity; ↑α1 activity; no β activity
- Isoprenaline
  - Isopropyl group on terminal amine → catecholamine; direct activity; βactivity; no α activity

Describe the pharmacology and clinical application of adrenergic agonists

Adrenergic / sympathomimetic drugs:	Non-adrenergic drugs
- adrenaline - noradrenaline - dopamine - dobutamine - isoprenanline - metaraminol - ephedrine - phenylephrine	- vasopressin - Phosphodiesterase III inhibitors (milrinone) - Calcium sensitisers (levosimendin)

Sympathomimetics / adrenergic agonist

	Adrenaline	**Noradrenaline**	**Dopamine**	**Dobutamine**
Chem	Natural catecholamine	Natural catecholamine	Natural catecholamine	Synthetic isoprenaline derivative
Uses	Anaphylaxis / airway oedema / asthma Asystole/ PEA arrest Low CO states Glaucoma Addition to LA	Refractory hypotension To ↑SVR	Low CO states Septicaemic shock Impending renal failure to promote diuresis	Low CO: MI, cardiac surgery, cardiomyopathy, septic shock Cardiac stress testing
Pres	CCS 1/1000 (1mg/ml) or 1/10 000 (100microg/ml) adrenaline hydrochloride Aerosol spray MDI 280microg Epipen 0.3mg	CCS containing 2mg/ml of noradrenaline acid tartrate for dilution prior to infusion	CCS 40/160mg/ml dopamine hydrochloride	Solution for inection 12.5/50mg/ml dobutamine hydrochloride for dilution prior to injection
Action	Direct acting α+ β adrenoceptor agonist Dose dependent: ↓dose β; ↑dose α - **0.01-0.02**microg/kg/min: **β2** - **0.02-0.2**microg/kg/min: **β1** - **0.2-0.3**microg/kg/min: **α**	Direct acting sympathomimetic α1 >> β agonist	Direct acting sympathomimetic Dose dependent - <3microg/kg/min: D1 + D2 Rs - 3-10microg/kg/min: β1 (inotrope) - >10microg/kg/min: α1 (vasoconstrictor)	+ve inotrope Acts directly on catecholamine receptors (**β1,** β2) to activate adenylate cyclase (catalyses the conversion of ATP to cAMP) → ↑CM permeability to Ca2+
CNS	↑CPP; ↑MAC; ↑pain threshold	↓CBF + ↓cerebral O2 consumption	cannot cross BBB; ↑IOP	Stimulation in high dose ranges
CVS	**β1**: ↑HR; ↑CO; ↑contractility; ↑pulse pressure, ↑myocardial O2 consumption **β2**: ↑coronary vessel flow; dilate muscle vasculature **α**: ↑VR; ↑MAP; ↑SVR/PVR; constricts skin +ve inotrope; +ve chronotrope	Arterial vasoconstriction → ↑SVR Venous vasoconstriction → ↑VR Reflex bradycardia 2o VA stimulation ↑PVR → ↑SBP + ↑DBP CO unchanged or ↓ Coronary vasodilation → ↑CorBF	**β effects**: inotrope, chronotrope, ↑CorBF, NAd effects **α effects:** ↑SVR, ↑VR, ↑BP Splanchnic vasodilation ↓renal vascular resistance; ↑RBF	**β1:** ↑ contractility, ↑automaticity → ↑HR ↑AV nodal conduction velocity **β2:** ↑myocardial perfusion**;** ↓LVEDP, ↓SVR → ↑CI in pts with severe CCF
Resp	Bronchodilation	Bronchodilation; ↑MV	↓ventilatory response to hypoxia	
Other	↑glucose (glycogenolysis), lipolysis, ketogenesis, ↑glucagon ↓insulin, ↓peripheral glucose uptake ↑FFA, glycerol – lipolysis, ↑chol ↑lactate ↑BMR 20-30% ↓RBF	↓hepatic and ↓splanchnic blood flow ↓RBF*;* GFR maintained ↓insulin secretion → ↑BSL	↓GI motility diuresis via D1 Rs on PCT natriuresis by inhibition of Na/K/ATPase ↓aldosterone + PRL production	↑UO (2o ↑CO) ↓BSL; ↑FFA concentration
Toxicity/ SE	↑HR; dysrhythmias; myocardial ischaemia	Anxiety, sweating, headache, chest pain Extravasation → tissue necrosis	N+V (direct action on CTZ) Tachycardia, dysrhythmias, angina, HTN Extravasation: tissue necrosis	Dysrhythmias, ↑↑HR, HTN, fatiue, chest pain
Route/ dose	IV bolus 0.1-1mg for asystole/ PEA Infusion: Subcut: 0.1-0.5mg; Inhalation 2mg nebs Additive to LA 1:200 000	0.05-0.5microg/kg/min via central vein	must be via central vein 0-10microg/kg/min	IV: 0.5-40microg/kg/min
Onset	Rapid <5 min	Rapid	<5min	1-2mins
Duration	<5min	1-2min	10min	
A	-	Sig 1st pass metab + inactive when administered PO	Ineffective when administered PO	
D	-	Vd: 0.2L/kg		Vd 0.2L/kg
M	**Neural**: MAO on outer surface mitochrondria **Extraneural**: liver via COMT to metadrenaline + normetadrenaline **Inactive metab**: 3-methoxy 4-hydroxylphenylethylene + methoxy 4-hydroxymandelic acid	**Oxidative deamination** → aldehyde via mitochrondria MAO in liver, brain, kidneys **Methylation** by cytoplasmic catechol-O-methyl transferase to normetanephrine metab in urine = VMA	Liver/ kidney: COMT → 3 methoxytyramine MAO (plasma) → 34dihydroxy phenylacetic acid 25% converted to NAd within adrenergic nerve terminals	Liver Methylation via COMT to 3-methyldobutamine → conjugation to glucuronide
E	Urine	5% unchanged clearance = 27.9-100ml/min/kg	Urine as homovanillic acid + derivatives Small fraction unchanged	Urine 20% faeces
T1/2β	2min	2min	3min	2min
Special			Inactivated by alkaline solutions e.g. NaHCO3	Do not use in cardiac outflow obstruction e.g. AS

	Isoprenanline	**Metaraminol**	**Ephedrine**	**Phenylephrine**
Chem	Synthetic catecholamine	Synthetic sympathomimetic amine Non catecholamine	Natural sympathomimetic amine Non catecholamine	Synthetic sympathomimetic amine Non catecholamine
Uses	Complete heart block while awaiting pacing Asthma Torsades de pointes / Inotrope	Hypotension	Hypotension Nocturnal enuresis / Narcolepsy / hiccups Diabetic autonomic neuropathy / Nasal decongestant/	Hypotension Nasal decongestant Mydriatic agent
Pres	CCS 1mg/ml isoprenanline hydrochloride to be diluted in water or 5% glucose Aerosol 80/400microg isoprenaline sulfate	CCS 10mg/ml metaraminol tartrate	CCS 30mg/ml; 4 isomers; L-isomer active Tablets 15/30/60mg	CCS 10mg/1ml
Action	**β-adrenergic agonist** actions mediated by membrane bound adenylate cyclase + subsequent formation of cAMP	Direct + indirect sympathomimeic + vasoconstrictor **Direct: α1-agonist (minimal β activity)** **Indirect**: NAd + adrenaline release	**Direct**: α+ β agonist **Indirect**: NAd release from SY nerve terminals	Peripheral vasoconstriction Direct acting sympathomimetic α1 agonist; no βeffect
CNS	CNS stimulant	↓CBF	CBF; ↑MAC	Nil
CVS	B1: ↑HR, ↑CO, ↑automaticity, ↑inotropy, ↑AV nodal conduction B2: ↓SVR → ↓DBP ↑CorBF → offset ↑myocardial O2 consumption	↑SVR → ↑SBP + DBP ↑PVR reflex bradycardia +ve inotrope ↑CorBF; ↓RBF	+ve inotrope +chronotrope → ↑CO, myocardial work, ↑myocardial O2 consumption ↑BP; ↑CorBF ↑myocardial irritability	↑SVR → ↑BP reflex bradycardia → ↓CO
Resp	Potent bronchodilator ↑anatomical dead space + V/Q mismatching → hypoxia	↑PVR, slight ↓RR/TV	Resp stimulant; bronchodilation	Nil
AS	↓GI tone + motility ↑mesenteric blood supply↓	↑BSL	Splanchnic vasoconstriction	
Other	↓renal blood flow ↑plasma FFA, ↑BSL	↑glycogenolysis; inhibits insulin → ↑BSL lipolysis → ↑FFA	**Tachyphylaxis** ↓RBF; ↓GFR ↓uterine tone ↑glycogenolysis; ↑BMR	↓uterine artery blood flow
Toxicity/ SE	↑↑HR, palpitations, angina, dysrhythmias, hypotension, sweating	Headaches, dizziness, tremor, N+V Extravasation → tissue necrosis + abscess	Insomnia, anxiety, tremor, dysrhythmias, N+V Hypertensive crisis if: MAOI, BB, oxytocin	Headaches, sweating, tremor, urinary retention Extravasation → necrosis
Route/ dose	IVI: 0.5-8microg/min titrated to response	IV: bolus 0.5-1mg IVI: 0.5-10mg	IV: 3-6mg q3min to max 30mg PO: 30mg	Subcut/ IM: 2-5mg IV: 50-100microg
Onset		<1-2mins	IV: rapid PO: 1hr	IV: <30s
Duration		<20mins	IV: 1hr PO: 3-5hrs	IV: 5-10mins IM: <1hr
A	Extensive 1st pass metabolism	Nil data	PO: rapid + completely absorbed	?
D	65% protein bound	45% protein bound does not cross BBB	Accumulation in liver, lungs, kidneys, spleen, brain Crosses placenta Vd 100-300L	?
M	Liver COMT to sulfated conjugates	Liver No COMT	Liver No MAO/COMT Small: N-demethylation to norephedrine (active)	Liver MAO No COMT
E	Urine 15-75% unchanged; remainder as sulfated conjugates ½ life 1-7mins	Nil data	Urine (>50% unchanged) elimination ½ life 6hrs clearance 13-44L/hr urinary excretion pH dependent	½ life 2hrs
Special points	Hypoxia, hypercapnia ↑arrhythmias Tachyphylaxis can occur	Excessive HTN when administered to pts with hyperthyroidism or MAOI	Tachyphylaxis	Excessive HTN in hyperthyroidism, MAOIs Risk of dysrhythmias if TCA, quinidine

Non-adrenergic agonists

	Vasopressin	**Phosphodiesterase inhibitors (milrinone)**	**Calcium sensitisers (levosimendin)**
Chem	Synthetic nonapeptide analogue of endogenous ADH	Bipyridine molecule	Propanedinitrile derivative
Uses	Diabetes insipidus Haemorrhage + oesophageal varices Catecholamine refractory septic shock	Severe treatment resistance CCF Low CO states	Acute heart failure
Pres	Terlipressin: CCS Desmopressin: oral lyophilizate	CCS 10/20ml ampoules 1mg/ml pKa 9.7	Clear / yellow/ orange solution for injection 2.5mg/ml in 5 and 10ml ampoules for dilution prior to administration
Action	Antidiuresis + vasoconstriction **V1 Rs**: vascular smooth muscle/ platelets: Gq proteins → ↑IP3/DAG → ↑Ca2+ → vasoconstriction + platelet aggregation **V2 Rs**: CD; Gs proteins → ↑cAMP → ↑Ca2+ → insertion of aquaporins **V3 Rs:** ant pit → ↑ACTH release Some oxytocin effects	+ve inotrope + vasodilation → "inodilator" **selective phosphodiesterase III inhibitor** within myocardium + vascular smooth muscles → ↑intracellular iCa2+ + ↑contraction cAMP dependent protein phosphorylation → vascular muscle relaxation No β activity	+ve inotrope + vasodilation ↑Ca2+ by binding to myocardial troponin C → stabilization + ↑duration of Ca2+ binding → ↑myocardial contractility without impairment of myocardial relaxation or ↑O2 demand also stimulates ATP-sensitive K+ channels → vasodilation
CNS			
CVS	↑MAP 2o vasoconstriction (V1) → ↑SVR coronary artery vasoconstriction → angina, MI, VT/VF	Improves LV diastolic relaxation +ve inotrope → ↑CO; ↑CI 30% ↓SVR ↓MAP; may ↑AV nodal conductance Minimal effect on HR and BP	↑myocardial contractility via ↑Ca2+ sensitivity No ↑myocardial O2 demand Coronary + peripheral vasodilation
AS	N+V		
Other	↑vWF; ↑uterine contraction	↑UO ↑GFR 2o ↑CO + renal perfusion	
Toxicity	↓cutaneous + splanchnic perfusion	Ventricular ectopics, arrhythmias, hypotension	
Route/ dose	IV: 0.04 units/min DDAVP: 4-8microg PO/ SL/ nasal	IV: loading 50microg/kg over 10mins → then IVI 0.4-0.75microg/kg/min	IVI: 6-12microg/kg loading dose over 10mins → IVI 0.1-0.2microg/kg/min
Onset	Minutes		
Duration	Up to 6 hours		
A	Poor PO bioavailability	-	
D	Not PB Vd 0.14L/kg	70% PB Vd 0.4L/kg	98% PB to albumin Vd 0.2L/kg
M	Vasopressinases (peptidases to amino acids) ½ life 10-20mins	10% hepatic metabolism → O-glucuronide metabolite	95% hepatic conjugation to cyclic or N-acetylated cysteinylglycine and cysteine conjugates 5% intestinal reduction to aminophenylpyridazinone
E	Recycled into aa pool	80% urine ½ life 2hrs; clearance 0.1L/kg/hr	54% urine; <1% unchanged; 44% faeces elimination ½ life 3hrs clearance 3ml/kg/hr

Anticholinergics

	Atropine	**Glycopyrolate**	**Hyoscine**
Chem	Alkaloid from Atropa belladonna **Tertiary amine** – eser of tropic acid and tropine Racemic mix: only L-isomer active	**Quaternary** ammonium compound Anticholinergic No isomerism	Naturally occurring **tertiary amine** Racemic mix: only L-isomer active
Uses	Bradycardia	Rx bradycardia; hyperhidrosis	Premedication / antispasmodic / motion sickness / palliative care
Pres	CCS: 0.5-0.6mg/ml Tablets: 0.6mg	CS; 200microg/ml of glycopyrronium bromide	CCS 400microg/ml hydrobromide 20mg tablets: butylbromide racemic: L-hyoscine active
Action	Muscarinic ACh receptor antagonists: - competitive - reversible - central activity: only tertiary amines cross BBB - peripheral activity: both tertiary + quaternary amines		
CNS	**Crosses BBB →** - central anticholinergic syndrome - ↑IOP - ↑ confusion, sedation, mydriasis - amnesia, antiemetic	**Cannot cross BBB → no CNS effects**	**Crosses BBB** ↑↑↑Anticholinergic syndrome ↑↑↑Confusion, sedation, mydriasis
CVS	Can cause initial brady 2o partial agonist at cardiac mAchR ↑CO, **↑↑↑HR**, ↓AV conduction time	minimal BP; **↑↑HR**; vagolytic	↑HR
Resp	Bronchodilation (↑dead space) ↓bronchial secretions	bronchodilator ↑physiological dead space	↓↓↓bronchial secretions
AS	↓salivation, mild antispasmotic ↓LOS tone ↓gastric acid secretion; ↓GI motility	↓↓salivation, mild antispasmotic ↓LOS tone ↓gastric acid secretion; ↓GI motility	↓↓↓salivation, mild antispasmotic ↓LOS tone ↓gastric acid secretion; ↓GI motility
Other	↓sweating		
Toxicity/ SE	Arrhythmias central anticholinergic syndrome: somnolence, confusion, amnesia, agitation, hallucinations, dyarthria, ataxia, delirium	Anticholinergic syndrome Confusion, sedation, mydriasis	
Route/ dose	IV / IM: 15-20microg/kg PO: 0.2-0.6mg Total vagal block 2-3mg	IV/ IM 200-400microg;	IM: 8-15microg/kg PO 20mg q6hr IV / IM / PO / TOP / subcut
Onset	1min	3 mins	
Duration	30-60mis	30-60min	<60min
A	Bioavailability 10-25%	bioavailability 5%	Bioavailability 10%
D	Vd 2-4L/kg	rapid redistribution; 90% disappears from plasma in 5 mins; crosses placenta; VD 0.2-0.6L/kg	Vd 2L/kg
PB	50%		10%
M	**Liver + tissues** Hydrolysis to topine + tropic acid	hydroxylation and oxidation in liver	**Liver**: scopine + scopic acid
E	94% urine clearance 70L/hr	urine (85% unchanged), bile (15%) Clearance 0.9L/min	Renal + bile Clearance 45L/hr
T1/2β	2.5hr	1hr	2.5hr

Describe the mechanism of action of inotropes and provide examples: PAST QUESTION

Inotropes = drugs that ↑cardiac contractility (i.e. ↑SV for given preload + afterload)
Cardiac contractility

- main determinant = intracellular [Ca2+]
- ↑cAMP → ↑intracellular [ca2+] → ↑inotropy

Myocardial excitation contraction coupling:

- AP reaches cardiac myocyte
- Ca2+ moves own conc gradient → influx mainly via L-type Ca2+ channels
- Ca2+ induced Ca2+ release form SR via RYR
- ↑↑intracellular [Ca2+] from 0.1uM to 10uM
- Ca2+ binds troponin C → actin myosin interaction → contraction

β1 adrenoceptors = GPCR → coupled to Gs → activation stimulates AC → ↑cAMP → ↑PKA →

- phosphorylates + activates L type Ca2+ channels → ↑Ca2+ entry
- phosphorylates + activates sites on SR → ↑RyR release of Ca2+ → ↑CICR

Inotropes

Class	Examples	Mechanisms
Direct β1 agonist	Dobutamine / Dopexamine Adrenaline / NAd Dopamine	β1 agonist → ↑cAMP → ↑intracellular [Ca+]
Indirect β1 agonist	Ephedrine	↑presynaptic NAd release + ↓uptake of NAd → indirect β1 adrenoceptor activation
Cardiac glycoside	Digoxin	Inhibits Na/K ATPase → ↑intracellular [Na+] → ↓activity of Na/Ca2_ exchanger → ↓Ca2+ efflux → ↑intracellular [Ca2+]
Phosphodiesterase inhibitor	Milrinone PDE3 Theophylline (non specific)	PDE3 inhibition → ↓breakdown of cAMP → ↑[cAMP] → ↑intracellular [Ca2+]
Adenylate cyclase stimulation	Glucagon Histamine	↑AC activity → ↑[cAMP] → ↑intracellular [Ca2+] NB independent of β1 → useful in BB OD NB not very potent + extremely limited by SE
Ca2+ sensitiser	Levosimendan	↑sensitivity of troponin C for Ca2+ → ↑excitation contraction coupling → ↑inotropy (at cost of ↓lusitropy)
Ca2+	Ca2+	↑extracellular [Ca2+] → ↑intracellular [Ca2+]

Describe the pharmacology of commonly used alpha and beta receptor blocking agents, their clinical use, adverse effects and use in the perioperative period

Alpha blockers: phentolamine; phenoxybenzamine; Prazosin
Beta blockers: **cardioselective**: metoprolol; atenolol; esmolol / **non-cardioselective**: propranolol; sotolol; labetolol; carvedilol

Alpha blockers

	Phentolamine	**Phenoxybenzamine**	**Prazosin**
Chem	Imidazoline	Tertiary amine: haloakylamine	
Uses	Dx + periop mx phaeochromocytoma HTN crisis (from sympathomimetics) Acute rx HTN post anaesthesia Rx LVF complication MI	HTN crisis Raynauds Preop phaeo	Essential HTN CHF Raynauds BPH
Pres	Clear straw solution 10mg/ml phentolamine mesilate	10mg tablets CCS 50mg/ml phenoxybenzamine hydrochloride	PO: 0.5mg + 2mg tablets
Action	hypotension, +ve inotrope, chronotrope **Competetive α-adrenergic antagonist (α1 > α2)** Mild β-adrenergic agonist + anti-5HT activity	vasodilation (arterial) **Irreversible competitive α- antagonist** ↑rate of turnover of NAd + amount of NAd released by blockade of presynaptic α2-receptors inhibit response to 5HT, histaminergic, and cholinergic stimulation	**Competetive α1 antagonist** → inhibits post-synaptic α-adrenergic Rs → arterial + venous dilation → ↓BP
CNS	-	↓CBF	
CVS	Marked ↓SVR → ↓BP + reflex ↑HR +ve inotrope (indirect effect a2 blockade → NAd release) ↑CorBF class I antiarrhythmic HF: ↑HR ↑CO ↓PAP, ↓SVR, ↓LVEDP	↓PVR → ↓DBP + orthostatic hypotension reflex ↑HR + ↑CO inhibits catecholamine induced cardiac dysrhythmias Fluid shift from interstitial to vascular compartment due to vasodilation of pre and post capillary resistance vessels	Vaso/venodilation (inc coronary a) → ↓SVR + ↓PVR, ↓VR Little reflex ↑HR ↓VR benefit in CHF → improved CO
Resp	↑VC, ↑FEV1 prevent histamine induced bronchospasm ↑resp secretions pulmonary artery vasodilator	-	
AS	↑salivation, gastric acid, GI motility	-	
Toxicity	Orthostatic hypotension, dizziness, abdo discomfort	Dizziness, sedation, dry mouth	
Route/ dose	IM: 5-10mg IVI 0.1-0.2mg/min	PO: 10-60mg/day IVI: 10-40mg over 1 hour	
Onset	1-2mins	IV: 60mins	PO: <2hr
Duration	5-10min	3-4 days	10-24hr
A	Bioavailability 20%	Bioavailability 20%	Bioavailability 80%
D	50% protein bound	Highly lipophilic	97% protein bound
M	Extensively metabolised	Liver By deacetylation	Liver (extensive)
E	10% unchanged in urine ½ life 10-15mins	Urine + bile ½ life 24hrs	Urine 10% Bile → faeces

Beta blockers

- 3 different types of β adrenoceptors

Type	Location	Function	Mechanism
β1	Heart Kidney	↑chronotropy ↑inotropy ↑dromotropy ↑renin secretion by JGA	GPCR (Gs)
β2	Bronchial smooth muscle Adipose tissue Skeletal muscle Uterus Endocrine Liver	Bronchodilation Lipolysis Vasodilation, anabolism Uterine relaxation Insulin secretion Glycogenolysis, gluconeogenesis	GPCR (Gs)
β3	Adipose tissue	Lipolysis	GPCR (Gs)

- B blockers competitively antagonist βadrenoceptor activation by endogenous Ad + NAd
- Divided into:
  - β1 selective: e.g. esmolol, bisoprolol, atenolol, metoprolol
  - non selective β blockade e.g. propranolol
  - non selective α + β blockade e.g. labetalol, carbefilol
  - others: e.g. sotalol (also acts on K channels as class III antiarrhythmic)
- Therapeutic uses

Clinical use	**Mechanism**
Antihypertensive	↓HR, ↓inotropy → ↓CO some β blockers also have αblocking or NO releasing (carvidilol) properties → ↓SVR
Antianginal	↓chronotropy, ↓inotropy → ↓myocardial O2 demand
AF rate control	↓chronotropy, ↓dromotropy → ↓ventricular response
Antiarrhythmic	Sotalol inhibits K channels → class II + III antiarrhythmic effects ↓dromotropy → terminate SVT
Cardiac failure	Multiple mechanisms - attenuate catecholamine toxicity: ↓renin → ↓RAAS - antiarrhytmic: ↓chronotropy → ↑diastolic filling time - antiangina: ↓HR + ↓inotropy → ↓myocardial O2 demand - ↓ventricular remodelling
Hyperthyroidism	↓HR + ↓tremors → symptomatic mx
Phaeochromocytoma	Blocks SNS stimulation by Adr
Migraine prophylaxis	Unknown ?inhibit arterial vasodilation
Essential tremors	Unknown ?via muscle fibre + muscle spindle β2 blockade

- side effects

Side effect	**Mechanism**
Hypotension	↓chronotropy, ↓inotropy → ↓CO → ↓MAP ↓MAP → inadequate organ perfusion → ↑risk intraop ↓BP + periop stroke/ MI
↓HR +/- heart block	↓inotropy ↓chronotropy, ↓dromotropy → heart block ↓SA node automaticity, ↓AV conduction
Cardiac failure	↓inotropy + ↓chronotropy → ↓CO → may precipitate APO
Bronchospasm	β2 inhibition → bronchial smooth muscle constriction
CNS effects	Disruption of central adrenergic transmission → confusion, lethargy, nightmares, vivid dreams, insomnia
Hypoglycaemia	Antaginse symptoms of SNS stimulation associated with ↓BSL → silent hypos
Peripheral vasoconstriction	More likely with older agents (NB newer agents have vasodilating properties) Block peripheral vasoilatin β2 effect → vasoconstriction → may worsen PVD / raynauds
Erectile dysfunction	β2 blockade → vasoconstriction within erectile tissue
Foetal bradycardia	Lipophilic β blockers cross placenta

	Metoprolol	**Atenolol**	**Esmolol**
Chem	Cardioselective	phenoxypropranolamine **Cardioselective**	aryloxypropanolamine Cardioselective
Uses	HTN Angina Tachydyshythmias CCF; thyrotoxicosis; glaucoma	HTN Angina Tachydysrhythmias Acute phase of MI infarction+ prevention of reinfarction	Acute SVT (AF/ flutter) Periop HTN Hypotensive anaesthesia
Pres	Tablets: 50-200mg IV CCS 5mg metoprolol	25/50/100mg tablets 0.5% syrup CCS 0.5mg/ml atenolol	CCS 10mg/ml as 10-250ml esmolol hydrochloride
Action	-ve inotrope + -ve chronotrope MoA: reversible competitive B1 blockade (Gs coupled)	-ve inotrope + -ve chronotrope → ↓myocardial O2 consuption antihypertensive + antiarrhythmic MoA: reversible competitive blockade of cardiac B1 Rs + some B2 action	-ve inotrope + -ve chronotrope MoA: cardioselective competitive β1 blockade → ↓GsPCR → ↓AC → ↓cAMP → ↓intracellular [Ca2+] Little or no intrinsic sympathomimetic activity
CNS	BBB: nightmare, lethargy, depression, fatigue	Poor CNS penetration → little effect Vivid dreams/ sleep disturbance	
CVS	-ve inotrope: ↓HR, ↓AVN conduction, ↓BP ↓arrhythmia ↓O2 demand ↑diastole + O2 supply	↓SA node automaticity; ↓AV nodal conduction ↑refractory periods of atrial + AV nodes nil effect on His Purkinje system -ve inotrope + -ve chronotrope → ↓myocardial O2 consumption	↓BP dose dependent ↓HR ↓CO (20%) ↓AV conduction ↓conttractility obtund CVS response to intubation
Resp	Bronchospasm	Min	Min due to β1 selective
AS			
Other	↑K, ↓renin, ↑TG, ↓HDL, ↓BSL	↑TGs, ↓HDL	
Toxicity/ SE	↓↓HR and BP	Exacerbation PVD; bronchospasm;	↓BP ↓HR bronchospasm, N+V
Route/ dose	PO: 12.5-200mg IV: 1-5mg titrated	PO: 50-100mg daily IV: 2.5-10mg	IVI: 10mg increments or IVI 50-150microg/kg/min
Onset	IV: 20 min PO: 1-2hr	PO: <3hr Peak plasma time: 2-4hr	IV: 2-10mins
Duration	IV:5-8hr PO: 3-6hr	PO: 12-24hr	<20mins
A	Highly lipid soluble High first pass metabolism 50% bioavailability	Bioavailability 50%	IV only
Lipid sol	↑	↓	↑
D	VD 3L/kg	Vd 0.7L/kg	Vd 3.5L/kg
PB	20%	10%	60%
M	Liver by CYP2D6	<10% liver	Hydrolysis by red cell esterases to methanolol + primary acid metabolite
metab	Inactive	Inactive	Weak → inactive
E	95% urine: <10% unchanged Clearance 15ml/kg/min	**Unchanged in urine***** Clearance 70ml/kg/min	70% urine; 1% unchanged clearance 300ml/kg/min
T1/2β	3-7hr	6-7hr	10min
Special points		Can lead to regression of LVH in HTN pts ↓dose in renal failure Dialysable	

	Propranolol	**Sotalol**	**Labetolol**	**Carvedilol**
Chem	Aromatic amine Non-cardioselective Racemic mix S and R isomers	Non-cardioselective Racemic mix D and L isomer	Non-cardioselective	Non-cardioselective
Uses	HTN; angina; tachydysrhythmias Essential tremor; anxiety; thyrotoxicosis HOCM; phaeo MI; migraine; oesophageal varices	Vent tachycardias Not for MI/ angina/ thyroid	HTN Hypotensive anaesthesia Blunting SY response	Same + CCF
Pres	Tablets: 10/40/80/160mg CCS 1mg/ml propranolol hydrochloride		Tablet: 100-800mg BD IV:	Tablets
Action	-ve inotrope + -ve chronotrope **MoA**: non selective β blockade competitive antagonist of B1 + B2 adrenoceptors No intrinsic sympathomimetic activity Membrane stabilizing effect when used in ↑↑doses 2o inhibition of Na+ currents	Antiarrhythmic: cass II (beta blockade) + class III (prolongs AP and repolarization) B1 + B2	Intrinsic sympathomimetic activity Some alpha blocker A1 + B1 + B2	a + b
CNS	Crosses BBB ↓physiological tremor; ↓IOP	Less BBB	Crosses BBB	Crosses BBB
CVS	-ve inotrope; -ve chronotrope ↓myocardial O2 consumption ↑PVR (B2 blockade)	↑QT	**α1 block** → ↓SVR/ SBP/ MAP ↑Blood flow	
Resp	↓FEV1; ↑airways resistance bronchospasm	Bronchospasm	Bronchospasm	
AS	↓uterine tone			
Other	↓renin activity; suppresses aldosterone release ↓plasma FFA; ↓BSL; ↑total body Na+			
Toxicity/ SE	Can precipitate heart failure/ heart block; exacerbate PVD; bronchospasm; sleep disturbance Crosses BBB so OD → seizure, ↓GCS			
Route/ dose	PO:30-320mg/day IV: 1-10mg titrated	PO 80-160mg BD IV: 50-100microg/20mins	PO: 100-800mg BD IV: 5-20mg titrated	PO: 3.125-50mg BD
Onset	PO: 1-2hr IV: 2-10min	IV: 1-2hr	PO: 20-120min IV: 2.5min	PO: 1hr
Duration	Immediate release: 6-12hr Extended release: 24hr		3hr	24hr
A	Bioavailability 30% due to extensive 1st pass metabolism	Bioavailability 90%	Bioavailability 25%	Bioavailability 30%
Lipid sol	↑	↓	↑	
D	Vd 3.5L/kg	Vd 1.2L/kg	Vd 3.5L/kg	Vd: 2L/kg
PB	90% (α1 acid glycoprotein)	**0%**	50%	98%
M	**Liver** (extensive) oxidative deamination + dealkylation → glucuronidation → 4hydroxy metabolite is active	None	Liver: conjugation to glucuronide metabolites	Liver 4-hydroxyphenyl
metab	**Active**	Inactive	Inactive	Active (13x ↑potent)
E	Urine; <1% unchanged clearance 15ml/kg/min	Urine (unchanged)	urine (60%); faeces via bile	faeces 60%; urine 15%
T1/2β	4-5hr	12hr	6-8hr	7-10hr

Outline clinically important drug interactions with the autonomic nervous system

Physiological and pharmacological basis of antiarrhythmic therapy including classification based on electro-physiological activity and mechanism of action

Physiological

- heart composed of pacemaker, conducting, contractile tissue
- SA node:
  - in RA; fastest rate of spont depolarisation → sets HR
  - slow spont depol due to ↑Ca2+ conductance
  - at -40mV, slow voltage gated Ca2+ channels (L channels) open → membrane depolarisation
  - repolarisation due to ↑K+ conductance + closing Ca2+ channels
- Cardiac muscle
  - Stable RMP -80mV
  - Phase 0: rapid repolarisation 2o ↑Na+ conductance through voltage gated Na+ channels
  - Phase 1: closure of Na+ channels
  - Plateau phase: Ca2+ influx via voltage sensitive L type Ca2+ channels; absolute refractory period (prevents myocardial tetany)
  - Phase 3: Ca2+ channels inactivated; ↑K+ conductance; relative refractory period
  - Phase 4: Na/K/ATPase maintains ionic concentration gradient
- Tachyarrhythmias
  - ↑automaticity where RMP of contractile tissue loses stability → reaches threshold for depolarisation prior to SA node (e.g. ischaemia + hypokalaemia)
- Bradyarrthymias
  - Due to failure of conduction from SA node to surrounding tissue

Pharmacological

- **Classification based on electro-physiological activity - Vaughan-Williams classification**

Class	Mechanism	Site of action	Drugs
Ia	Na channel blockade - ↓slope of phase 0 - ↑duration refractory period - ↑duration AP	Atria Ventricles Accessory pathways	Quinidine / Procainamide
Ib	Na+ channel blockade - small ↓ slope of phase 0 - ↓duration of refractory period - ↓duration AP	Ventricles	Lignocaine / Phenytoin
Ic	Na channel blockade - pronounced ↓ in slope of phase 0 - no effect refractory period - no effect duration of AP	Atria Ventricles Accessory pathways	Flecainide
II	β-adrenoceptor blockade - no change in phase 0 - ↑duration refractory period - ↑duration AP	SAN AVN	Propranolol / atenolol / esmolol
III	K channel blockade - no change in phase 0 - prolonged repolarisation phase 3 - ↑↑duration of refractory period - ↑duration AP	Atria Ventricles Accessory pathways	Amiodarone / sotalol
IV	Ca2+ channel blockade - no change in phase 0 - ↓duration of plateau phase 2 - ↓duration of AP	AVN	Verapamil / diltiazem

  - NB: VW classification does not include all drugs + individual agents fall into multiple categories
- **Classification based on clinical use:**
  - SVT: digoxin / adenosine / verapamil / βblockers / quinidine
  - VT: lignocaine
  - SVT + VT: amiodarone / flecainide / procainamide / sotalol

Describe the pharmacology of antiarrhythmic agents and their clinical applications including the following agents: lignocaine, flecainide, beta blockers, amiodarone, sotalol, ibutilide, calcium antagonists, digoxin, adenosine and magnesium

Antiarrhythmics (from CICM)

- Sodium channel blockers
  - Procainamide (B)
  - Lignocaine (A)
  - Flecainide (B)
- Beta blockers (A) – *See section on B blockers*
  - Sotalol (A) – *See section on B blockers*
- Potassium channel blockers
  - Amiodarone
  - Sotalol
- Calcium channel blockers (A)

    - non-dihydropyridines:
        - phenyl alkamines: verapamil
        - benzothiazepines: diltiazem
    - dihydropyridines: nimodipine, nifedipine, amlodipine
- Other
    - Amiodarone,
    - Digoxin (A)
    - Adenosine (A)
    - Magnesium (A)

NB on CCB:

- cauton when using with BB
- ↑serum concentration of dig
- NB volatiles ↓Ca2+ release from SR and ↓Ca2+ flux inot cardiac cells: -ve inotropic effects are additive
- ↓MAC
- ↑efficacy of NMB

Sodium channel blockers

	Procainamide	**Lignocaine**	**Flecainide**
Chem		Tertiary amine	Amide LA
Class	**1A**	**1B**	**1C**
Uses	LA Arrhythmias	LA VT esp. ischaemic	VT; WPW; AF/ SVT
Pres	Solution for injection	CCS 0.5-2% lignocaine hydrochloride 1:200 000 LA + adrenaline	Tablets: 50-100mg 10mg/ml solution flecainide acetate
Action	Membrane stabilizing: Direct membrane depressant; ↓conduction velocity, ↑refractoriness, ↓automaticity, ↓repolarisation abnormalities	diffuse as uncharged base through neural sheaths + axonal membrane to internal surface of Na channels → combine with H+ ions to form cationic species → **blockade of Na channel** → ↓Na+ conductance + prevents depolarisation	Na+ channel blocker ↓max rate of depolarisation → ↓conduction (esp. HP system) profound effect on accessory pathway conduction; suppresses ventricupar ectopic
CNS		Reversible neural blockade: biphasic	Visual disturbance
CVS	↓conduction velocity, ↑refractoriness, ↓automaticity, ↓repolarisation abnormalities	↓rate phase O (block Na+ channels) ↓RP ↑threshold potential ↑dose: AV block; hypotension	BP + HR stable ↓rate phase 0 ↑threshold no effect on AP or RP -ve inotropy
Resp		bronchodilation	
Toxicity/ SE	↑ANA hypotension	LA toxicity; ↓myocardial contractility; resp depression Doses >600mg: methaemoglobinaemia	Reversible liver damage, dizziness, paraesthesia, headaches, nausea
Route/ dose	IV for arrhythmias: 100-200mg or 15mg/kg over 30mins Maintenance: 1-4mg/min	IV for arrhythmias: 1mg/kg over 2 mins → infusion	PO: 100-200mg BD IV bolus 2mg/kg over 10mins → IVI 1.5mg/kg/hr 1hr →0.25mg/kg/hr
Onset	IV: Peak plasma time 15-60min		PO: Peak plasma time 2-3hr
Duration			
pKa		7.7 25% unionized at pH 7.4	
A	Bioavailability 80%	70% protein bound (alpha1 acid glycoprotein)	Rapid + complete Bioavailability 90%
D	15% protein bound Vd 2L/kg	70% protein bound Vd 1L/kg	50% protein bound Vd 5-10L/kg
M	Liver Acetylated to form N-acetylprocainamide (NAPA) (Active)	**Liver** N-dealkylation with hydrolysis to monoethylglycine and xylidide	Liver 2 major metabolits: meta O-dealkylated flecainide + lactam (active)
E	Urine ½ life 3hrs (parent drug); 6hrs (NAPA) clearance 300ml/min	<10% unchanged in urine clearance: 7-11ml/min/kg elimination ½ life: 90-110mins	Urine 10-50% unchanged Clearance 10mg/kg/min Elimination ½ life 7-15hrs
Special points		clearance ↓ in cardiac + hepatic failure	↑plasma dig levels when administered concurrently ↓K+ reduces effectiveness of drug ↓dose in renal/ hepatc failure

Calcium channel blockers

	Verapamil	Diltiazem	Nifedipine	Amlodipine	Nimodipine
Chem	Phenyl alkamines	Benzothiapine	Dihydropyridine	Dihydropyridine	Dihydropyridine Structural analogue nifedipine
Class	IV antiarrhythmic				
Uses	HTN / Angina / SVT/ AF/ Aflutter	HTN / angina / SVT Raynauds, migraine, achalasia	HTN / angina / Raynauds / coronary artery spasm	HTN/ CAD / angina	Cerebral vasospasm (2o SAH) Migraine Aacute CVA Drug resistant epilepsy
Pres	Tablets: 40-240mg CS racemic mix verapamil hydrochloride 2.5mg/ml	Tablets 60-300mg diltiazem hydrochloride	Tablets: 5/10mg Slow release preparation	Tablets: 10mg	IVI 200microg/ml nimodipine + ethanol Tablets 30mg
Action	Antihypertensive + antianginal **MoA**: ALL competitive **block of α1 subunit of L type Ca2+ channels** → ↓influx Ca2+ into vascular smooth muscle + myocardial cells → electromechanical decoupling + inhibition of contraction + relaxation of cardiac and smooth muscle fibres → coronary + systemic arterial vasodilation L channel is responsible for slow, sustained Ca2+ entry into vascular smooth muscle cells Differ in tissue selectivity, binding site on a1 subunit, and mechanism of Ca2+ blockade 1. **Phenylalkylamines**: bind to intracellular portion of a1 subunit of L type Ca2+ channel when in open state + occlude channel a. AV node e.g. verapamil 2. **1,4 Dihydropyridines**: prevent Ca2+ entry by extracellular allosteric modulation of L type Ca2+ channel a. Peripheral arteriolar beds e.g. nifedipine, amlodipine b. Cerebral vessels e.g. nimodipine 3. **Benzothiazepines**: MoA unknown a. E.g. diltiazem				Cerebral vasodilation → ↑cerebral perfusion **MoA**: specific action on cerebral arterioles; slow Ca2+ channel blocker → vasodilation
CNS	Cerebral vasodilation		Slight ↑CBF		↑CBF
CVS	peripheral + coronary artery vasodilator + -ve dromotrope –ve inotrope - Arterial vasodilation → ↓SVR, ↓BP, ↑corBF, ↑cerebral blood flow; ↓HPV; ↑CO 2o ↓afterload - Minimal venous vasodilation - Reflex tachycardia - ↓myocardial contractility → may precipitate cardiac failure - ↓automaticity: ↓SA node activity → ↓HR - ↓conduction velocity, ↑refractory period				↓SVR ↑CO
Resp			Bronchodilator Inhibit HPV		
AS		↓LES in achalasia	↓GUT contractility ↓LES pressure		
Other	↓renovascular resistance	Renal artery dilation → ↑RPF → diuresis	No effect on RBF ↑renin activity ↑catecholamines impaired platelet aggregation		
Toxicity/ SE	Dizziness/ flushing/ nausea 1st – 2nd degree heart block may precipitate HF in LV dysfunction VT/ VF in WPW	2-10%: flushing, headaches, peripheral oedema, ↓HR	20%: flushing, dizziness, headache (vasodilation) oedema, gum hyperplasia		Flushing, headache, nausea, ↓BP
Route/ dose	PO: 240-480mg/ day IV: 5-10mg	PO: 30-120mg 6-8hrly IV	PO: 10-20mg 8hrly 100-200microg via coronary artery catheter over 2min	PO: 5-10mg / day	IVI via central vein PO 60mg q4hr <4days SAH
Onset	IV 3-5min	IV: 3min	PO: 20min	24-96hr (peak plasma time 6-12hr)	
Duration	IV: 10-20min	IV: 1-3hr	PO: 8hr (24hr SR)	24hr	
A	Completely absorbed Bioavailability 10-20% due to sig 1st pass	90% absorbed bioavailabilty 40%	Completely absorbed Bioavailability 50-60%	Bioavailability 70-90%	Bioavailability 3-20%
D	90% protein bound Vd 3-5L/kg	80% protein bound Vd 5L/kg	95% protein bound Vd 1L/kg	90% protein bound	98% protein bound Vd 0.1-2L/kg
M	Liver	Liver	95% liver to 3 inactive metabolites	Liver	Liver

	Demethylation + dealkylation Some active metabolites	Demethylation + deacetylation → conjugation to glucuronide + sulfates (active)		Inactive metabolites	Demethylated + dehydrogenated to inactive pyridine analogue
E	70% urine 16% faeces clearance 7-17ml/kg/min elimination ½ life 3-7hr	1-4% urine unchanged clearance 11-21ml/kg/min elimination ½ life 2-7hr	90% urine 10% faeces clearance 30-60L/hour elimination ½ life 1-10hr	Urine 70% ½ life 30-50hr	50% in urine 30% faeces clearance 450L/hr elimination ½ life 1-7hrs
Drug interactions	Anaesthetics: - vasodilating + myocardial depressant effects of CCB + GA = similar - use CCB cautiously in pts with impaired LV function/ hypovolaemia NBMD - potentiate depolarizing + NDNMB - antagonism of NMB may be impaired due to ↓presynaptic ACh release LA - verapamil has LA activity; may ↑risk of toxicity in regional anaesthesia K+ containing solutions - CCB delay inward movement of K+ Dantrolene - Dantrolene + verapamil or diltiazem (inhibits K homeostasis) can cause ↑K + cardiovascular collapse Digoxin - May ↑plasma dig concentration by ↓ clearance				

TABLE 18-2. *Comparative pharmacologic effects of calcium channel blockers*

	Verapamil	Nifedipine	Nicardipine	Diltiazem
Systemic blood pressure	Decrease	Decrease	Decrease	Decrease
Heart rate	Decrease	Increase to no change	Increase to no change	Decrease
Myocardial depression	Moderate	Moderate	Slight	Moderate
Sinoatrial node depression	Moderate	None	None	Slight
Atrioventricular node conduction	Marked depression	None	None	Moderate
Coronary artery dilation	Moderate	Marked	Greatest	Moderate
Peripheral artery dilation	Moderate	Marked	Marked	Moderate

Other antiarrhythmics

	Amiodarone	**Digoxin**	**Adenosine**	**Magnesium**
Chem	Iodinated benzofuran derivative (resembles thyroxine)	Glycoside (foxglove)	Purine nucleoside composed of adenine + d-ribose	Divalent cation / inorganic sulfate
Class	III (block K+)			
Uses	Tachyarrhythmias – SVT, AF, flutter, WPW, ventricular tachycardia, cardiac arrest (shockable rhythm)	SVT/ AF/ flutter/ CCF	SVT 2o reentry circuits involving AVN CI: asthma, 2nd + 3rd degree AV block; SSS	Pre-eclampsia/ eclampsia / tocolytic HypoMg / asthma / barium poisoning AMI / Torsades / cardioplegic solutions Cerebral oedema/ autonomic hyperreflexia
Pres	Tablets 100/200mg Ampoules 30/50mg/ml amiodari=one hydrochloride	Tablets: 62.5/125/250microg CCS 250microg/ml digoxin	CCS 3mg/ml adenosine in saline	CCS 2.03mmol/ml ionic magnesium 50%
Action	**Class III antiarrhythmic** (also exhibits **Ia, II, IV**) MoA: 1. **Class Ia:** Na channel blockade → ↑threshold + ↑refractory period **2. Class II:** Non-competitive partial α+ β block → ↓inotropy, ↓chronotropy, ↓dromotropy 3. Class III: **K block**: ↓delayed slow outward K+ current → slows repolarization → ↑AP duration 4. Class IV: CCB → ↑dromotropy 5. Non competitive α1 blockade → vasodilation → ↓SVR, ↓MAP	+ve inotrope + slow ventricular response **Direct**: - **inhibit Na/K/ATPase** → ↑intracellular [Na+] + ↓intracellular [K+] - ↑intracellular [Na+] → ↓extrusion of Ca2+ via Na/Ca2+ exchange pump → +ve inotropic effect - ↓intracellular [K+] → slowing of AV conuction **Indirect**: release ACh at cardiac mACh Rs → ↓SAN automaticity + ↓AVN conductivity → -ve chronotrope	↓SA + AV nodal activity → slow conduction Antagonizes cAMP mediated catechol stimulation of ventricular muscle → -ve inotropy + -ve chronotrope **MoA**: direct agonist at adenosine A1 Rs → GiPCR → ↓cAMP → opening of K+ channels → ↑K efflux → hyperpolarization → -ve chronotropic effect	cofactor in >300 enzyme systems Involved in oxidative phosphorylation Membrane stabilizing effect Physiological antagonist of Ca2+ ↓SAN automaticity and ↓AVN conductivity **MoA**: dose dependent presynaptic inhibition of ACh release at NMJ
CNS			↑CBF neuropathic pain, hyperalgaesia, ischaemic pain	CNS depressant anticonvulsant
CVS	**↑refractory period** ↓speed of depolarisation + ↑duration of AP → ↓AV nodal automaticity; ↓AV nodal conduction no effect on His or ventricular myocardium ↓SVR; ↑coronary sinus flow ; may ↓LV contractility	+ve inotrope ↑automaticity ↓HR (VA) → ↑filling ↑AV node refractory period ECG: ↑PR, ST depression, T wave flatten, short QT	Depression of SA + AV nodal acivity → termination of paroxysmal SVT ↓chronotropy / ↓dromotropy Coronary artery vasodilation (A2 Rs)	Vasodilation Antiarrhythmic ↓BP ↓SA node; ↑SA conduction time, ↑PR interval, ↑AV nodal effective refractory period
Resp			SOB/ bronchospasm ↑depth + RR ↓PVR	Bronchodilator ↓HPV
AS	LFT abnormalities 50% Thyroid abnormalities due to inhibition of T3			Osmotic laxative
Other			Inhibits lipolysis + stimulates glycolysis	Renal vasodilator + diuretic ↓uterine tone + ↓contractility ↑placental perfusion crosses placenta → neonatal depression ↑clotting time, ↓TXA2
Toxicity/ SE	**Opthal**: corneal microdeposits **CNS**: 1/3 CNS toxicity, peripheral neuropathy **CVS**: ↓↓BP, CC, dysrhythmias esp. if ↓K+; ↑QTc **Resp**: pneumonitis/ interstitial lung disease **GIT**: hepatitis; LFT derangement 50%, cirrhosis, GI upset; metallic taste **Thyroid**: hyper / hypo **Derm**: photosensitivity; slate grey appearance **Drug interactions**: potentiates effect of ↑PB drugs → displaces from plasma proteins (dig, BB, warfarin) → ↑effects, inhibit P450	Low therapeutic index: **toxicity** >2.5microg/ml Rapid admin → vasoconstriction → HTN, ↓CorBF **CNS**: headache, drowsiness, confusion, visual disturbance, muscular weakness, coma **CVS**: arrhythmia (esp. junctional bradycardia, ventricular bigemini, 2nd/ 3rd degree HB) **GI**: anorexia, N+V, abdo pain Dig tox: phenytoin/ atropine/ pacing Risk factors: ↓K, ↑Ca2+, acid/base disorders, renal failure	May induce Aflutter Transient facial flushing, SOB, chest discomfort Lightheadedness / impending doom/ blurred vision / paraesthesia Induced bradycardia predisposes to ventricular excitability → VF Heart block / asystole/ VF CI heart block	Warmth, flushing, nausea, headache, dizziness Somnolence, areflexia Toxic effects reversed by Ca2+
Route/ dose	IV: load 5mg/kg over 30mins – 1hr IVI: 15mg/kg/day PO: 200mg 8hrly → ↓100-200mg daily after 1 week Therapeutic level 0.1microg/ml	PO/IV: load 10-20microg/kg 6hrly IV maintenance: 10-20microg/kg/day	Rapid IV bolus: 6mg → 6mg → 12mg	IV/ IM 10-20mmol over 20mins PO
Onset	Peak serum time 3-7hr PO	PO: 0.5-2hr	<10s	IV: immediate

		IV: 5-30min		PO: 1hr
Duration	**Up to 50d**	3-4d	10-20s	IV: 30min PO: 6hr
A	Incompletely absorbed Bioavailability ~50% (wide variation 20-80%)	Highly variable Bioavailability 60-90%	Inactive when PO	PO 25-60% absorbed
D	95% protein bound Vd 2-70L/kg depending on dose – one of the largest Vd 2° ↑affinity for fat, muscle, heart, thyroid	20-30% protein bound Vd: 5-10L/kg	**Rapid deamination in plasma + RBC** → inosine + hypoxanthine	30% protein bound
M	Liver Major metabolite: **desethyl-amiodarone** (antiarrhythmic) CYP450 inhibitor	Liver 10% by stepwise cleavage of sugar moietie	Adenosine deamoinase in vessel wall + RBC	>50% urine
E	**Bile + faeces** Skin/ sweat/ tears/ Urine 1-5% Clearance 0.14-0.6L/min	**50-70% urine unchanged** clearance dependent on renal fnction		
T1/2β	**15-140 (average 50 days)**	1.5days	<10sec	
Special points	No dose modification in renal impairment Actions of dig, CCB, anticoagulants, Bblockers can be potentiated by amiodarone due to displacement from plasma proteins	↑risk arrhythmias in pts with B agonists, sux, panc ↑risk dig toxicity: ↓K, ↑Na, ↑Ca2+, renal failure not removed by dialysis	No dose adjustment in renal/ liver	↑effect of CNS depressants + NMB agents

Describe the pharmacology of anti-hypertensive agents and their clinical application, including the following agents: clonidine, alpha-methyl dopa, alpha and beta blockers, nitric oxide, sodium nitroprusside and glyceryl trinitrate, calcium antagonists, ACE inhibitors and angiotensin receptor antagonists, hydralazine and the potassium channel activators

Centrally acting drugs	**Adrenoceptor angatonists**	**Direct vasodilators**	**ACEI/ ARBs**
a. Clonidine b. Methyldopa	a. Alpha blockers: - Prazosin b. Beta blockers: c. Mixed α+ βblockers - labetalol - carvedilol *See B blockers*	a. calcium channel blockers *(see CCB above)* - non-dihydropyridines: ○ phenyl alkamines: verapamil ○ benzothiazepines: diltiazem - dihydropyridines: nimodipine, nifedipine, amlodipine b. Nitric oxide *(see resp pharmacology)* c. GTN d. Sodium nitroprusside e. Hydralazine f. K channel activators - nicorandil - minoxidil	ACEI - sulfylhydryl-containing agents e.g. captopril - dicarboxylate containing agents e.g. analapril, ramipril, perindopril - phosphate containing agents e.g. fosinopril ARB

Centrally acting antihypertensives

	Clonidine	**Methyldopa**
Chem	Aniline derivative	Phenylalanine derivative
Uses	Premedicaion/ anxiolysis Intraoperative haemodynamic stability: ↓SNS outflow; blunt response to stimuli Post op analgesia / shivering Prevention of periop myocardial schaemia Anaesthetic sparing HTN/ HTN crisis Migraine/ menopausal flushing/ chronic pain/ opiate or etoh withdrawal	HTN Pre-eclampsia
Pres	Tablets: 100-300microg CCS 150microg/ml clonidine hydrochloride	Tablets: 125/250/500mg IV: 50mg/ml methyldopa hydrochloride
Action	Antihypertensive + analgesia + sedative + anxiolytic **MoA**: Partial agonist at α-adrenoceptor; α2:α1 selectivity 200:1 α2 adrenoceptors: - Present on target tissues: presynaptic on SY nerve fibres (peripheral); post synaptic within CNS/ SC (central); platelets - GPCR Gi coupled adenylyl cyclase inhibition → ↓cAMP α2 presynaptic adrenoceptor agonist → ↓NAd release from SY nerve terminals → ↓SY tone + ↑VA tone Analgesic: ↓NAd transmission at dorsal horn + ↑inhibitory descending pathway	Antihypertensive MoA: methyldopa metabolised to alpha-methyl NAd → stored in adrenergic nerveterminals within CNS Alpha methyl NAd = potent alpha2 agonist + ↓entral SY discharge → ↓BP
CNS	Sedation + analgesia: via central α2 agonism → inactivation o locus ceruleus + activation of descending inhibitory pain pathways Spinal analgesia: via spinal α2 Rs in dorsal horn → depress wide dynamic range neurons involved in peripheral nociceptive input ↓adrenergic transmission in CNS ↓CBF ↓IOP SY depressant ↓post op shivering 2o αa stimulation in spinal cord	
CVS	α2 agonist → ↓SNS outflow from BS vasomotor centre → ↓SVR ↓HR ↓MAP initial ↑MAP due to peripheral vasoconstriction 2° α1 R stimulation sustained ↓MAP with 2o central α2 activation (↓NAd release) NB prolonged use: upregulate α-adrenoceptors → rebound HTN NB no direct effect on heart, but ↓circulating catecholamines	↓SVR little change in HR or CO
AS	↓gastric + small bowel motility Antiemetic: ↓sensitivity of CTZ	
Other	↓renovasc resistance ↓plasma catecholamine activity ↑BSL (alpha)	↓plasma renin ↓NAd concentration
Toxicity/ SE	Drowsiness + dry mouth 50% CNS disturbance, fluid retention, constipation Rapid withdrawal → rebound HTN + ↑HR	CNS: sedation, depression, weakness, paraesthesia, dizziness CVS: Orthostatic hypotension, bradycardia, peripheral oedema GIT/ derm/ haem: ↓platelets, haemolytic anaemia, hepatic damage
Route/ dose	PO: 50-600microg 8hrly IV: 150-300microg	PO: 0.5-3g/day divided doses
Onset	IV: 10mins	
Duration	IV: 3-7hrs	
A	Bioavailability 100%	Variable absorption / Bioavailability 8-62%
D	Very lipid soluble: penetrates BBB / 20% protein bound Vd 2L/kg	50% protein bound Vd 0.2-0.3L/kg
M	50% liver to inactive metabolites	Conjugated to sulfate as crosses intestinal mucosa + liver
E	65% unchanged in urine 20% faeces elimination ½ life 6-23hrs	20-40% urine (2/3 unchanged) clearance 2-4ml/kg/min elimination ½ life 2.5hrs
Special points	↓MAC coadministered volatiles prolongs duration of LA when coadministered for neural blockade	Nasal congestion

Direct vasodilator antihypertensives

	Nitric oxide	**GTN**	**Sodium nitroprusside**	**Hydralazine**
Chem	NO Inorganic gas Produced by L-arginine	Organic nitrate – ester of nitric acid Prodrug metabolized to NO	Inorganic complex; functions as prodrug	Phthalazine derivative
Uses	Selective pulmonary **vasodilator** in pulmonary HTN / RHF ARDS	Anigina/ LVF/ HTN/ AMI	HTN crises Aortic dissection prior to surgery LVF	HTN/ acute severe HTN/ pre-eclampsia/ CCF
Pres	Aluminium cylinders containing NO + nitrogen (pure NO is toxic + corrosive)	SL: 300-600microg Buccal: 1-5mg PO spray: 400microg per dose Transdermal patch: 5-10mg/24hour CS for IV (must be protected from light): 0.5/1/5mg/ml	IV: 10mg/ml sodium nitroprusside for dilution Protect from light	Tablets: 25/50mg Ampoules 20mg hydralazine hydrochloride White lyophilized powder reconstituted in water
Action	NO produced in vivo by NO synthase 00< diffuses into vascular smooth muscle layer → stimulates ↑expression of guanylate cyclase → ↑ production of cGMP → ↑smooth muscle relaxation ↓platelet aggregation + ↓angiogenesis	**Vasodilation of veins > arteries** **MoA**: GTN → prodrug metabolised to nitric oxide (NO) → stimulates guanylate cyclase → ↑cGMP → ↓Ca2+ influx into vascular smooth muscle → relaxation + vasodilation	**Vasodilation arteries + veins → hypotension** **MoA**: SNP → RBC → reacts with oxyhb to form MetHB, 5 cyanide molecules, and NO NO → activates guanylyl cyclase → ↑cGMP → ↓Ca2+ entry into smooth muscle + ↑uptake into SR → vasodilation	Peripheral vasodilation **MoA**: direct on vascular smooth muscle: interfers withCa2+ entry into cell or release of Ca2+ from intracellular stores → electromechanical decoupling + inhibition of contraction
CNS	No ↑ CBF Physiological role as a NT within ANS + CNS	Cerebral vasodilation → ↑ICP	Cerebral vasodilation → ↑ICP Shift autoregulatory curve to L	↑CBF
CVS	Inhibits platelet aggregation + adhesion	↓doses <2microg/kg/min): venodilation - ↓VR ↓preload → ↓LVEDP + ↓wall tension → ↓O2 demand +↑CorBF ↑doses: venous + arterial vasodilation - arteriolar dilation → ↓SVR + ↓BP - Reflex: ↑HR ↑contractility ↓CorBF CO unaltered or ↓slighlty ↑subendocardial blood flow + redistribution into ischaemic areas ↑myocardial O2 supply + ↓CMRO2 ↓coronary vasospasm + dilates arterioles → ↓afterload ↓angina: ↓myocardial O2 demand (2° ↓LVEDP + ↓ wall tension)	Arterial vasodilation: ↓SVR, ↓BP Venous vasodilation: ↓VR, ↓preload, ↓myocardial O2 consumption Reflex ↑HR LVF: ↑CO 2° ↓VR and ↓SVR	Arteriolar vasodilation → ↓SVR Compensatory ↑HR → ↑CO
Resp	preferentially dilates vessels of well perfused alveoli → ↑V/Q matching inhibits HPV	Bronchodilation May ↑intrapulmonary shunting	Reversible ↓PaO2 due to ↓HPV	
AS			↓LES tone	
Other	Insulin release modulated by NO	↓uterine tone 2o NO ↑uterine blood flow → ↑risk haemorrhage	↑[catecholamine] ↑renin metabolic acidosis	↑RBF 2o ↑CO Na+ retention; ↑renin activity
Toxicity/ SE	Exposure to 500-2000ppm → methaemoglobinaemia + pulmonary oedema Discontinuation can lead to rebound arterial hypoxaemia + pulmonary HTN Inhaled NO + high FiO2 → oxidized to NO2 (pulmonary toxin) Severe hypotension if dose reaches systemic circulation	↓BP, ↑HR N+V; headaches Rarely precipitates **methaemoglobin** ↓platelet aggregation **Tachyphylaxis/ tolerance** 2o depletion sulfhydryl groups	Toxicity related to products of metabolism: ***Cyanide toxicity:*** - Uncouple oxidative phosphorylation → impaired aerobic metabolism -_> tissues unable to utilize O2 - ↑by hypothermia, malnutrition, ↓vitB12 - signs: ↑HR, dysrhythmias, hyperventilation, sweating, metabolic acidosis ***thiocyanate (SCN)*** - liver metabolite formed by metabolism of cyanide + thiosylfate - neurotox (N+V, tinnitus, fatigue) - rx: dialysis ***MetHb:*** cyanometHb doesn't bind O2 ***NO***	Headache, flushing, sweating, N+V May precipitate angina in pts with myocardial ischaemia

			Photoreduction of SNP	
Route/ dose	Inhalation; 5-20ppm	SL: 300microg Spray: 400-800microg IV: 10-400microg/min	IV: 0.5-6microg/kg/min titrated to response	PO: 50-200mg/day divided IV: 5-20mg slowly
Onset		SL/ buccal: 1-3mins; IV: 90sec	immediate	IV: 10mins; PO: 20-30min
Duration		SL: up to 30mins; IV: 3-5mins	1-10min	IV: 1-4 hr; PO: 3-8hr
A	↑lipid soluble	PO: bioavailability 3% (extensive 1st pass metab) Rapid absorption from SL mucosa and GIT	Not absorbed PO	Bioavailability 15-35%
D		60% protein bound Vd large 0.04-3L/kg	Confined to plasma Vd small - same as extracellular space (15L)	90% protein bound Vd 4L/kg
M	Combins with oxy-Hb → methaemoglobin + nitrate	**Rapid hepatic + RBC** hydrolysis to dinitrates, mononitrates, nitrites (↓active)	***↓conc:*** rxn with sulfhydryl groups of aa ***↑conc:*** rapid hydrolysis within RBC → reacts with oxyhb to form **MetHB, 5 cyanide molecules, and NO** - 1 CN + metHb → cyanometHb - 4 CN molecules enter plasma → 80% react with thiosulfate → thiocyanate; 20% react with hydroxycobalamin to form cyanocobalamin (vitB12)	**Liver** Acetylation + oxidation → conjugation NB fast + slow acetylators / metabolisers
E	70% excreted as nitrate in urine <48hrs ½ life <5s	80% urine; trace amounts exhaled as CO2 clearance 0.3-1L/kg/min	Thiocyanate + cyanocobalamin excreted unchanged in urine → caution in renal failure	50-90% urine (1-2% unchanged)/ 10% faeces clearance 1.4L/kg/hr
T1/2β	<5s	1-3min	SNP: 2min; thiocyanate 2days	3hr
Special points	↑FiO2 not recommended → combines with NO to form toxic NO2 Abrupt cessation can cause profound ↓PaO2 + ↑PAP ?downregulationof endogenous NO or guanylate cyclase activity monitor [nitrogen dioxide] CI in neonates know to have circulation dependent on R to L shunt	40-80% dose of IV GTN is absorbed onto plastic giving sets	Removed by IHD **Renal failure + SNP → ↑↑↑toxic metabolites**	

K channel activators
Nicorandil
Minoxidil

ACEI/ ARBs

	ACEI – ramipril / perindopril / captopril	**ARB – Irbesartan / telmisartan**
Chem	Derived from peptides originally isolated from venom of pit viper Bothrops jararaca	Tetrazoles group
Uses	HTN / CCF / diabetic nephropathy	HTN / CCF / diabetic nephropathy/ pts intolerant of ACEI
Pres	Tablet / capsule	Tablet/ capsule / liquid / oral suspension
Action	Antihypertensive MoA: competititve ACE inhibition → block conversion of ATI to ATII: - ↓aldosterone release from adrenal cortex - ↓ADH release - ↓Na+ and H2O reabsorption - ↓catecholamines - i.e. prevents ATII mediated vasoconstriction + stimulation of SNS - Modulate kallikrein-kinin-prostaglandin system 3 groups: - active drug metabolised to actie metabolites – captopril - prodrugs activated by hepatic metabolism – enalopril, ramipril - active drug extreted unchanged in urine - lisinopril	Selectively block GPC ATII R AT1 → prevent effects of ATII via RASS (i.e. prevent vasoconstriction) - ↓aldosterone release from adrenal cortex - ↓ADH release - ↓Na+ and H2O reabsorption - ↓catecholamines - i.e. prevents ATII mediated vasoconstriction + stimulation of SNS - Nil effect on bradykinin induced vasodilation
CNS		
CVS	Arterial vasodilation → ↓SVR → ↓↓afterload > ↓preload → ↓MAP ↓aldosterone → natriuresis + diuresis regression of LV remodeling post infarct ↑CO by up to 25% esp. in HF baroreceptor reflexes + HR unaffected	Similar to ACEI
Resp	Dry cough (bradykinin) Bronchospasm	Nil sig
AS		
Other	Renal: disrupt renal autoregulation esp. during hypovolaemia → ↓GFR ↓proteinuria hyperkalaemic metabolic acidosis	Similar to ACEI
Toxicity/ SE	Hypotension, dizziness, fatigue, dry cough (bradykinin), GI upset, rash ↓renal function/ AKI drug interactions: - combination with K sparing diuretics → ↑K - NSAIDs + diuretics → ↓GFR +/- ↓RBF → AKI	Dizziness 2o hypotension Angioedema (rare) drug interactions: - combination with K sparing diuretics → ↑K - NSAIDs + diuretics → ↓GFR +/- ↓RBF → AKI
Route/ dose	PO only	
Onset	Ramipril: 1hr Perindopril: 1-2hr Captopril: 15-30min Enalapril: 1hr	Irbesartan: 1-2hr Valsartan: 2hr Candesartan: 2-3hr Losartan: 6hr
Duration	Ramipril: / Perindopril: 24hr / Captopril: 8-12hr / Enalapril: 12-24hr	Irbesartan: 24hr / Valsartan: 24hr / Candesartan: >24hr / Losartan: 24hr
A	Bioavailability: captopril 75% > perindopril 75% > ramipril 50-60% > Enalapril 40% > Lisinopril 25%	Bioavailability: irbesartan 60-80% > losartan 33% > valsartan 23% > candesartan
D	Protein bound: Perindopril 75% > ramipril 73% > Enalapril 50% > captopril 30% Vd: captopril 0.7L/kg	Protein bound: candesartan 99% > losartan 99% > valsartan 95% > irbesartan 90%
M	Minimal; **liver** Captopril: 50% hepatic; metabolism to disulfide dimer + cysteine disulfide Enalapril + perindopril = prodrugs → metabolised to active forms	Irbesartan: hepatic glucuronide conjugation + oxidation to inactive metabolites Candesartan = prodrug → rapid ester hydrolysis in intestinal wall to active drug Losartan: extensive hepatic metabolism Valsartan: minimal hepatic metabolism
E	½ life: perindopril 30-120hr > ramipril 50hr > Enalapril 35hr > lisinopril 12hr > captopril 2hr clearance: perindopril + Enalapril 300ml/min urine + faeces	Irbesartan: ½ life 10-15hr Candesartan: 75% unchanged in urine + faeces Losartan: 35% urine, 60% faeces; ½ life 2hr parent + 6-9hr active metabolite Valsartan: 80% unchanged (83% faeces, 13% urine); ½ life 5-9hr

Management of hypertensive crisis: PAST QUESTION

Hypertensive crisis = severe HTN + acute end organ impairment
- may be associated with: APO, MI, arterial dissection, eclampsia, SY crisis, cocaine OD, renal failure

Classification of antihypertensives based on site of action
- **Vasodilators**
  - **Direct arteriolar dilators**
    - Hydralazine: activates guanylate cyclase → ↓Ca2+ release + entry into cells, electromechanical decoupling → smooth muscle relaxation; arterial > venous; onset 10mins; duration 3-6hrs
    - Minoxidil: ↑K into vascular smooth muscle → hyperpolarization → ↓smooth muscle contraction + vasodilation
    - Diazoxide: K channel activator → ↓Ca2+ into cell → smooth muscle relaxation
  - **NO stimulators**
    - Sodium nitroprusside: direct acting, non selective vasodilator. Interacts with oxyhb → dissocates → metHb + released CN + NO → NO activates guanylate cyclase → ↑cGMP → ↓Ca2+ entry → vasodilation
    - GTN: generates NO → ↑cGMP activation → dilation
  - **CCB**
    - Nicardipine: dihydropyridine CCB; prevents Ca2+ entry into vascular smooth muscle by allosteric modulation of L type VG Ca2+ channels. Onset: 10mins; duration 4-6hrs
- **Sympatholytics**
  - **BBlockers**
    - Esmolol: cardioselective β1 antagonist; antagonizes effects of ADr + NAd at β1 ; ultra short acting
  - **a+B adrenergic blockers**
    - labetalol: α1, β1, β2 antagonist; ↓SVR; onset 2-5mins; peak 10mins; lasts 3hr
  - **a-blockers**
    - prazosine: selective post synaptic α1 antagonist → ven + art vasodilation
    - phentolamine: α1:α2 5:1 → ↓SVR
  - **centrally acting blockers**
    - methyldopa: metbaolised to a-methyl NOad → a2 agonist at presynaptic terminals → ↓SNS discharge
    - clonidine: centrally acting a2 agonist → ↓SNS output
- **inhibition of RAAS**
  - (less likely to be used in crisis due to difficulty titrating)
  - ACEI: blocks conversion of ATI → ATII → ↓vasoconstriction, ↓aldosterone, ↓SNS activation, ↓Na + H2O retention
  - ATII: blocks vasoconstrictive effects of ATII
- **anaesthetic agents** with hypotensive SE
  - volatile anaesthetics
  - opioids e.g. morphine: histmiane release + ↓SY tone
  - Propofol: vascular smooth muscle relaxation; inhibition of SY vasoconstrictor nerve activity; -ve inotrope
  - LA: neuraxial blockade → dilation of vessels

Describe the mechanism and treatment of the toxicity of sodium nitroprusside: PAST QUESTION

SNP = mixed vasodilator + venodilator

Structure + metabolism of SNP
- MoA:
  - Structure: $Na_2[Fe^{III}(CN)_5(NO)]$
  - Prodrug; exerts action via release of NO
  - SNP oxidises Hb in RBC to MetHB → dissociates into Fe3+ + 5CN + NO
  - NO acticates soluble GC → ↑cGMP → protein kinase G → ↓intracellular [Ca2+] → inhibit MLCK activity → smooth muscle relaxation → vaso + veno dilation)
- Metabolism
  - Results in: CN, NO, Fe3+, MetHb
  - CN further metabolised in 3 ways:
    - 1. MetHb + CN → cyanomethaemoglobin (non-toxic)
    - 2. VitB12 + CN → cyanocobalamin (renal excretion)
    - 3. thiosulfate + CN → catalysed by hepatic rhodanese → thiocyanate (renal excretion)

Toxicity
- warning signs: ↑venous PO2, metabolic acidosis, tachyphylaxis

Product	Toxicity	Treatment
CN (cyanide)	***Mechanism***: CN inhibits mitochondrial complex IV → disrupts ETC → histotoxic hypoxia ***Clinically***: diaphoresis, ↑HR, ↑MV, met acidosis Risk when SNP infusion rate **>2microg/kg/min** → exhaust ability to sequester CN (i.e. thiol groups, metHb, vitB12)	Cease SNP infusion O2 Correct acidosis with NaHCO3 1. Na thiosulfate: acts as thiol donor → converts CN to SCN (less toxic) 2. Hydroxycobalamin: binds CN to form cyanocobalamin (non toxic) 3. sodium nitrite: oxidises Hb to MetHb which can sequester CN
SCN (thiocyanate)	Less toxic than CN Toxicity onset slower but more common than CN tox Usually in renal impairment or when SNP given rapidly or for prolonged periods ***Clinically:*** tinnitus, hyperreflexia, psychosis, coma	Cease SNP infusion Dialysis
NO (nitric oxide)	Excessive hypotension Pulmonary vasodilation → impairs HPV → worsens V/Q mismatch Cerebral vasodilation → ↑ICP + headache Impairs platelet aggregation via cGMP pathways	Titrate SNP infusion rate to BP O2
MetHb	↑MetHb → ↓O2 carrying capacity of blood → hypoxia ***clinically:*** met acidosis, blue skin colour	Cease infusion Emthylene blue reduces MetHb back to Hb NB: ↓MetHb → less capacity to sequester CN → ↑risk CN toxicity

Describe the pharmacology of drugs used to manage myocardial ischaemia/infarction, including: nitrates, beta blockers, calcium antagonists, anti-platelet agents, anticoagulants and fibrinolytic agents

Myocardial ischaemia results from inadequate circulation of blood to the myocardium

- rx aims to improve ration between O2 supply + demand
- Myocardial O2 demand determined by:
  - HR: ↑chronotropy → ↑demand
  - Contractility: ↑inotropy → ↑demand
  - Myocardial wall tension: ↑wall tension → ↑demand
- Myocardial O2 supply determined by:
  - CorBF
  - MAP
  - HR: ↑HR → ↓diastolic filling time → ↓supply (esp. LV)

	Metoprolol	**GTN**	**Diltiazem**
Action	Selective β1 adrenoceptor agonist (β2 at high doses) No intrinsic SYmimetic activity	Organic nitrate ester of nitric acid Venodilation at low doses + venous + arterial vasodilationa t high doses	Class III benzothiapine CCB
MoA	β1 adrenergic R (Gs) antagonism → ↓AC → ↓cAMP → ↓PKA → ↓intracellular [Ca2+] → ↓inotropy + ↓chronotropy	NO production via glutathione-S-transferase → activates GC → ↑cGMP → ↓intracellular [Ca2+] in smooth muscle → venodilation > vasodilation	1. Blocks L type voltage gated Ca2+ channels → ↓Ca2+ entry during phase 2 → ↓HR 2. Blocks Ca2+ channels in vascular smooth muscle → smooth muscle releaxation → venodilation + vasodilation
CVS			
HR	↓SA node automaticity + ↓AV conduction → ↓HR ↓myocardial O2 demand ↑diastolic filing time → ↑supply	May ↑ via baroreceptor reflex → ↓diastolic filling time → ↓supply → exacerbate ischaemia	↓HR
Contractility	↓	-	↑
CO	↓	↓preload / ↓VR/ ↓wall tension	↓
MAP	↓	↓	↓
CorPP	↑	↑ ↑CorBF to subendocardial areas	↑
Renal			
Renin	↓renin → ↓ATII → ↓vasoconstriction → ↓SVR → ↓MAP → ↓LV wall stress	-	-
RBF	↑RBF → mild diuresis → ↓presload → ↓LV wall stress	-	-
Adverse effects			
CNS	Hallucinations/ nightmares/ depression	↓CVR → ↑CBF → ↑ICP → headache	Headache
CVS	Hypotension / heart failure / APO / heart block / bradyarrhythmias	Hypotension tachyphylaxis (due to depletion of stores of sulphydryl groups within vascular smooth muscle)	Hypotension / heart block / bradyarrhythmias / peripheral oedema / flushing
Resp	Bronchoconstriction		Bronchodilation
Endo	Masks ↓BSL ↓insulin secretion / ↑lipids and TGs		
Haem		Methaemoglobinaemia	

Primary effects = ↓HR + ↓contractility → ↑diastolic filling time + ↓O2 demand → ↑supply
NB the clinical effects + potential for adverse effects are synergistic with each of these + other agents

Describe the pharmacology of drugs used to manage acute or chronic cardiac failure, including: sympathomimetics, phosphodiesterase inhibitors, digoxin, diuretics, ACE inhibitors, nitrates and beta blockers

Classes of drugs used clinically to treat chronic LVF (past question)

- LV unable to provde sufficient pump action to distribute blood flow to meet metabolic demand of systemic circulation; or can only do so from elevated filling pressures (i.e. ↑CVP)
- Classification
  1. LV **systolic failure**: impaired LV **contractility**
  2. LV **diastolic failure**: impaired LV **filling**
  3. Mixed LV **systolic** + **diastolic failure**
- Compensatory mechanisms:
  4. ↑preload (via ↑RAAS, ↑ADH → fluid retention)
  5. ↑SY tone → ↑contractility
  6. over time, compensatory mechanisms fail → worsen LV failure
- Clinical features:
  7. Pulmonary congestion (SOB, orthopnoea, PND, ↓ET, fatigue)
  8. Fulctional classification based on NYHA
     - Class I: no limitation
     - Cass II: mild limitation of activity; comfortable at rest/ minimal exertion
     - Class III: marked limitation of activity; only comfortable at rest
     - Class IV: symptoms at rest

Drugs used in HF

- **Systolic + diastolic HF**
  1. ACEI
     - **↓afterload** / ↓preload

- Blocks conversion of ATI to ATII
- ↓vasoconstriciton + aldosterone release + ↓SVR + ↓Na + H2O retention + ↓LV remodeling

2. ATII R blockers
   - Competitive inhibition of ATII at AT1 R
   - Effects as for ACEI
3. B blockers
   - B1 selective (metoprolol, bisoprolol, carvedilol) → competitive antagonist of Adr and NAd at B1 R
   - *Cardiac*:
     - ↓activation of adenylate cyclase → ↓cAMP → ↓Ca2+ release → -ve inotrope/ -ve chronotrope/ -ve dromotrope
     - ↓myocardial O2 demand
     - ↑diastolic perfusion time
     - ↑O2 supply
   - *Renal*
     - ↓renin release from JGA → ↓ATII → ↓preload/ afterload
   - Mortality:
     - **Antiarrhythmic**: ↓chronotropy → ↑diastolic filling time
     - **Anti-ischaemic:** ↓chronotropy + ↓inotropy → ↓myocardial O2 demand
     - **Attenuate catecholamine tox** → ↓renin → ↓RASS
     - ↓LV remodeling
4. Diuretics
   - ↓intravascular vol → ↓preload → maintains failing LV at top part of Frank Starling curve → maximizes LV ejection
   - No survival benefit/ have symptomatic benefit
   - Loop diuretics: frusemide: inhibit Na/K/2Cl reabsorption in TAL LoH → Na+ H2O excretion, vasodilation → ↓SVR
   - Aldosterone/ K sparing (spironolactone): competitive antagonism of aldosterone Rs → ↓basolat Na/K pumps in DT + CD → ↓Na, H2O retention while preserving K+ → ↓preload
   - Thiazides : ↓Na/H2O reabsorption in DCT

- **Systolic only**
  1. Digoxin:
     - **↑contractility**: inhibits Na/K ATPase → ↑Na+ + ↑Ca2+ → ↑contractility
     - direct ↑VA cardiac activity → ↓conduction at AV node → ↓HR → ↑diastolic filling time → rate control in AF
     - nil improvement in mortality; improvement in morbidity
  2. Nitrates:
     - **↓preload / ↓afterload**:
     - NO activates guanylate cyclase → ↑cGMP → ↓cytoplasmic Ca2+ → venodilation, ↓preload
  3. Hydralazine:
     - **↓afterload / ↓preload**
     - ↑cGMP → ↓cytopasmic Ca2+ → venodilation → ↓afterload/ ↓preload
  4. PDIII inhibitors: (e.g. milrinone)
     - **↑contractility**
     - ↓breakdown cAMP → ↑contractility, ↓SVR
- **Diastolic only**
  1. CCB: competitive blockade of L-type Ca2+ channel → ↓Ca2+ in SA + AV node + contractile tissue → ↓chronotropy, ↓O2 demand, ↑coronary artery dilation

Diuretics

- drugs that act on the kidney to ↑UO
- clinically used in rx of:
  - HTN
  - Fluid overload in cardiac, renal, hepatic failure
  - APO
  - ↑ICP

	MoA	SE	Clinical use
Thiazides	Block Na/Cl symporter in early **DCT** → ↓Na, Cl, H2O reabsorption Late DCT → ↑Na exchange with K/H → ↑K secretion	↓: K+, Na, Cl, Mg ↑: Ca2+, urcaemia, BSL hypochloraemic metabolic alkalosis	Moderate HTN LVF
Loop (frusi)	Inhibit Na/K/2Cl symporter in medullary ascending LOH → ↓Na and Cl reabsorption → impairs counter-current multiplier system, ↓tonicity of medulla → ↓H2O reabsorption in CD	↓: Na, K, Cl, Ca2+ ↑uricaemia, BSL, cholesterol metabolic alkalosis NB induces PG synthesis, ↑renal vasodilation, ↑RBF, ↑diuresis	CCF to ↓oedema Renal failure to promote diuresis
K sparing (Amiloride)	Block Na/K exchange in late DCT independent of aldosterone → ↑Na excretion, ↓K excretion → ↓H2O reabsorption	↑K	Diuretic Prevents hypoK
Aldosterone antag (spironolactone)	Cortical CD Intracellular aldosterone R antagonists → ↓Na + H2O reabsorption → ↑diuresis; ↓K secretion	↑K antiandrogens effects	
CAH inhibitors	Competitive antagonism of carbonic anhydrase in PCT → ↓conversion of CO2 + H2O to H2CO3 then HCO3 + H → ↓HCO3 reabsorption and ↓H secretion ↓Na/H exchange → ↑Na/HCO3 excretion + diuresis	Weak diuretic only Hyperchloraemic metabolic acidosis	Altitude sickness Glaucoma Resp alkalosis in ICU
Osmotic (mannitol)	Freely filtered at glomerulus; not reabsorbed or metabolised ↑osmolarity of plasma + tubular fluid (filtrate) → ↓reabsorption H2O, Na, Cl via washing out medullar concentration gradient → ↑urine vol, ↑ECF vol → ↑RBF		Rapid ↓ICP in space occupying lesions
Dopamine agonists (dopamine)	D1 Rs ↑cAMP in renal vessels → vasodilation and ↑blood flow + GFR + ↓Na + H2O tubular reabsorption		

hypochloraemic metabolic alkalosis in thiazides:

- ↑Na+ reaches CD → ↑exchange of Na for K by Na/K pump in principal cells → ↑K in CD → ↑exchange of K for H by K/H pump in type A intercalated cells → loss of H
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