CARDIOVASCULAR PHYSIOLOGY

Structure and function of the heart ................................................................. 2
  1. General cardiac anatomy ....................................................................... 2
  2. Cardiac muscle ..................................................................................... 3
  3. Conductive and excitatory elements ..................................................... 5
Electrical Properties of the Heart ................................................................. 7
  1. Cardiac action potential ....................................................................... 7
  2. Cardiac excitation and arrhythmiae ..................................................... 11
  3. The electrocardiogram ........................................................................ 13
Determinants and Control of Cardiac Output ............................................ 16
  1. Preload, afterload and contractility ....................................................... 16
  2. The Frank-Starling mechanism ........................................................... 19
  3. Myocardial oxygen supply and demand .............................................. 20
  4. Cardiac output and venous return curves .......................................... 22
  5. Integrated factors determining cardiac output ..................................... 25
The Peripheral Circulation ............................................................................ 26
  1. General statements ............................................................................. 26
  2. Vascular smooth muscle ...................................................................... 27
  3. Control of local blood flow .................................................................. 29
Control of Blood Pressure ............................................................................ 32
  1. General statements ............................................................................. 32
  2. Medullary control ................................................................................. 32
  3. Rapid arterial pressure control ............................................................ 33
Applied Cardiovascular Physiology ............................................................. 36
  1. Exercise ............................................................................................... 36
  2. Pregnancy .............................................................................................. 36
  3. Normal aging ....................................................................................... 37
  4. Shock .................................................................................................... 37
  5. Cardiac failure ...................................................................................... 39
  6. Intermittent positive pressure ventilation ........................................... 40
Measurement of Cardiovascular Function ................................................ 41
  1. Blood Pressure .................................................................................... 41
  2. Cardiac Output .................................................................................... 43
Bibliography ............................................................................................... 45
Structure and function of the heart

1. General cardiac anatomy

The heart resides within the middle section of the mediastinum, which also contains the great vessels and pericardium which encloses the heart and great vessel roots. The pericardium is a double walled sack with both an external fibrous layer (fused with the tunica adventitia of the great vessels and tethered to the sternum anteriorly, central tendon of the diaphragm inferiorly and loose connective tissue posteriorly) and a serous parietal layer, which reflects onto the heart and great vessels as the visceral pericardium. The heart has:

four chambers

- Right atrium
- Right ventricle
- Left atrium
- Left ventricle

and four valves

- Tricuspid valve (three leaflets attached to anterior, posterior and septal papillary muscles via chordae tendineae)
- Pulmonary valve (trileaflet: anterior, left and right)
- Mitral valve (bileaflet with anterior and posterior papillary muscle attachments)
- Aortic valve (trileaflet: right, posterior and left)
- During expiration the pulmonary and aortic valves close simultaneously
- During inspiration the aortic closes prior to the pulmonary

three surfaces:

- Anterior (right ventricle)
- Diaphragmatic (left > right ventricle)
- Pulmonary (left ventricle)

and four borders:

- Right (right atrium extending between IVC and SVC)
- Inferior (right >> left ventricle)
- Left (left ventricle and auricle)
- Superior (right and left atria and auricles)

A fibrous skeleton of dense collagen forms four fibrous rings (surrounding valves), right and left fibrous trigones and interatrial and interventricular septa, and serves to:

- Maintain valvular patency and prevent valvular distension
- Attach valvular leaflets and cusps
- Attach myocardium
- Provide electrical insulation thus separating atrial and ventricular impulses, surrounding and providing passage for the AV bundle
Vascular supply of the heart:

- Dominance of the coronary supply refers to the artery giving rise to the posterior interventricular artery
- RCA arises from right aortic sinus, giving of a sinoatrial nodal branch (60% of people), right marginal branch (right border of the heart), AV nodal branch (80% of people)
- The posterior interventricular branch supplies both ventricles and the IV septum
- LCA arises from left aortic sinus, descends as the LAD and gives rise to the circumflex branch.
- The coronary sinus receives venous drainage from the great cardiac vein, middle and small cardiac veins, left posterior ventricular vein and left marginal veins

2. Cardiac muscle

Main divisions

- atrial and ventricular fibres
- excitatory fibres
- conductive fibres

Cardiac muscle:

- striated, containing actin and myosin filaments, and in this way is similar to skeletal muscle.
- A synctium of many cells connected in series via intercalated discs at the Z line
- Intercalated disks allow cell to cell adhesion, transfer of contraction and, via gap junctions, passage of electrical current
- gap junctions allow longitudinal diffusion of ions within the intracellular fluid through. Thus actions potentials travel near unhindered, with ~ 1/400 of the electrical resistance.
- Two synctia normally exist (atrial and ventricular) separated by insulating fibrous tissue (see above). Conduction occurs at ~ 0.3-0.5 ms\(^{-1}\) in atrial and ventricular muscle fibres. The refractory period for atrial muscle (0.15 s) is shorter than for ventricular muscle (0.25-0.35 s).
- Self excitation occurs in SA node (70-80), AV node (40-60) and ventricular Purkinje fibres (15-40)

Excitation-contraction coupling:

- AP → cardiac muscle membrane → spread to interior via T-tubules → depolarisation of sarcoplasmic reticulum → Ca\(^{2+}\) release (Concentration rises from a resting < 0.1 µM to ~ 100 µM
- Cardiac T-tubules are located at the Z line (cf A-I line in mammalian skeletal muscle)
- T-tubules in myocytes are 5 times the diameter and 25 times the volume cf skeletal muscle T-tubules. The mucopolysaccharide within the tubule system is electronegative and \(\therefore\) →↑Ca\(^{2+}\) binding
- Both the SR and ECF Ca\(^{2+}\) stores are important in cardiac contraction (cf skeletal muscle where SR >>> ECF)
- Extracellular Ca\textsuperscript{2+} influx via the voltage sensitive DHPR in the T-tubule system triggers sarcoplasmic Ca\textsuperscript{2+} release via the RyR.
- Troponin C combines with up to 4 Ca\textsuperscript{2+}.
- Troponin C "tugs" tropomyosin deeper into the actin filament "uncovering" actin active sites.
- The myosin head with its ATP-ase has attached ADP + P\textsubscript{i}, maintaining a perpendicular relationship to actin.
- Myosin, attracted to the uncovered actin binds, changes conformation (head tilting towards the arm) releasing ADP and P\textsubscript{i}.
- This "power stroke" causes actin and myosin filaments to slide past each other and thus contraction.
- Duration of contraction is dependent upon the duration of the AP (~0.2s for atrial and ~0.3s for ventricular muscle).
- As heart rate increases the proportion of time spent in contraction increases.
- The contractile strength (contractility) is very much dependent upon the amount of Ca\textsuperscript{2+} reaching to myofilaments.
- 80% calcium taken back into SR by Ca\textsuperscript{2+}-ATPase and 20% via sarcolemmal Na\textsuperscript{+}/Ca\textsuperscript{2+} (3 Na\textsuperscript{+} in for 1 Ca\textsuperscript{2+} out) exchangers or Ca\textsuperscript{2+}-ATPase which play a larger role in recovery of intracellular calcium following an action potential (cf skeletal muscle).
- Digitalis slows the 3Na/2K-ATPase which reduces the sodium gradient thus increasing the Ca\textsuperscript{2+}, contributing to its positive effect on contractile force.
- Cardiac muscle cells cannot be over activated to cause a fused (tetanic) state.
- Order of contraction: RA - LA - LV - RV.

Refractoriness:

- In fast response cells (atrial and ventricular muscle and His-Purkinje cells) Na\textsuperscript{+} channels remain inactivated following Phase 0 until part way through phase 3. Thus no AP is generated if a stimulus is applied. Here refractoriness is determined by the voltage-dependent recovery of Na\textsuperscript{+} channels from inactivation.
- An absolute refractory period (during which the muscle is refractory to further stimulation) occurs during phase 0-2 and part of 3 (until membrane potential reaches -50 mV): 0.25-0.3 seconds for ventricle.
- A relative refractory period (supranormal stimulus leading to stimulation) of ~0.05s then occurs prior to phase 4.
- In Ca\textsuperscript{2+} channel dependent slow response cells (SA & AV node, as well as cells with altered characteristics eg ischaemic damage) the determining factor in recovery from inactivation is time (and not membrane potential). This is known as decremental conduction.
- Slow conduction (as required for re-entrant arrhythmia generation) occurs also when Na\textsuperscript{+} currents are decreased by disease, membrane depolaristaion (eg ↑ K\textsuperscript{+} outside) which result in decreased Na\textsuperscript{+} channel availability (due to inactivation/intrinsic defects).

A normal cardiac cell has a resting membrane potential (RMP) of -80 to -90 mV (negative to the exterior), influenced by:

- Selectively permeable lipid bilayer (ion channels, ion exchangers and ion pumps permitting passage through this membrane).
- RMP established principally by the Na/K-ATPase (3 Na out for 2 K in) and fixed intracellular anionic (ie negative) charges
- Na⁺, K⁺ and Ca²⁺ ions - the three main determinants of cardiac MP
- Ion channels (ligand or voltage gated) which can be in an open, closed or inactivated state
- Permeability of the cardiac membrane to ions that is governed by the state of the ion channel. High permeability refers to a large number of channels in an open state
- K⁺ equilibrium potential (4mM out and 145 mM in) ~ -90mV
- Na⁺ equilibrium potential (140mM out and 10mM in) ~ +70mV
- Ca²⁺ equilibrium potential ~ +100 mV
- Resting cardiac cells have low permeability to Na⁺ and Ca²⁺
- Though the resting membrane is permeable to K⁺ the RMP is close to the K⁺ equilibrium potential thus there is little K⁺ movement
- Alterations in membrane permeability to Na, K and Ca account for the various stages of the action potential (see below)

Pacemaker cells have a higher RMP (eg ~ -60mV in the SA node) and feature:
- Absent phase of rapid depolarisation (see later) due to absence of fast inward Na⁺ current
- Na leak producing a higher RMP
- Rhythmic decline in membrane potential (pacemaker potential or prepotential) to threshold → AP → return to RMP → pacemaker potential
- Action potential generated largely due to Ca²⁺ opening

3. Conductive and excitatory elements

General conduction arrangement:
- SA node → internodal fibres → AV node → AV bundle (penetrating then distal portions)→ left and right Purkinje fibres branches
- Delay between SA depolarisation to AV node ~ 0.03 s
- AV node → penetrating AV bundle delay ~ 0.09 s
- AV penetrating to distal conduction a further ~ 0.04s delay
- Total time from SA node discharge to signal arrival at ventricles thus ~ 0.16s
- Rate of discharge SA > AV > His-Purkinje

Sinoatrial node:
- The normal cardiac pacemaker
- Self excitation at a rate of 70-80 BPM
- Arises at the junction of the SVC and RA
- 3 x 15 x 1 mm in size
- Contains muscle fibres of 3-5 µm in diameter (cf 10-15 µm), nearly devoid of contractile filaments
- Develops from R side of the embryo
- Contains rounded "P" cells relatively deficient in organelles
- Right vagus supplies SA (left vagus the AV node) with sympathetic innervation arising ipsilaterally to parasympathetic
- Noradrenergic fibres are epicardial and ACh fibres are endocardial
- ACh acts presynaptically on sympathetic nn → ↓ Norad release and NPY may act to inhibit release of ACh
- Internodal fibres tracts (anterior, middle and posterior) conduct signals at 1.5 - 4 ms\(^{-1}\) to the AV node, compared to the 0.3 ms\(^{-1}\) through atrial muscle
- An interatrial band conducts signals from R → L atrium

Atrioventricular node:
- Located in posterior right atrial wall
- Receives connecting pathways from the SA node
- Signals arriving at the AV node travel to the penetrating and then distal portions of the AV bundle
- Unidirectional conduction normally
- AV node cannot conduct > ~ 230 impulses per minute

Purkinje fibres:
- Lead from the AV node through the AV bundle thence (via left and right bundle branches) to the ventricular endocardium
- Contain few myofibrils
- highly permeable gap junctions permits signal transmission at 1.5 - 4 ms\(^{-1}\)
Electrical Properties of the Heart

1. Cardiac action potential

Threshold:

- Electrical point at which the action potential is self propagating
- ~-65 to -70 mV in fast (e.g., ventricular) fibres
- ~ -40 mV in slow (e.g., SA node) fibres

Excitability:

- Refers to the slope of upstroke of Phase 0
- Related to conduction velocity
- ~ half way through Phase III at ~ -50 mV ~50% of $I_{Na}$ channels have recovered and will → an AP only in the presence of a greater than normal stimulus

Irritability:

- The difference between the RMP (-90 mV in fast fibres) and the threshold potential.
- As the difference decreases the cell membrane is more easily depolarised however gradient of Phase 0 (excitability) and conduction velocity are decreased

Phase 0:

- Phase of rapid depolarisation lasting ~1/10000th of a second
- Rapid Na\(^+\) channel opening (increased permeability of voltage gated channel) → influx of Na\(^+\) ions
- Suppression of inward rectifier current
- With rapid depolarisation from RMP to threshold Na\(^+\) channel activation gates open more quickly than the inactivation gates can close
- Does not occur in SA or AV nodal fibres as the slower rise to threshold from RMP allows Na channel activation and inactivation gates to open and close essentially simultaneously, thus permeability does not alter substantially

Phase I:
- Phase of rapid repolarisation
- Na\(^+\) channel deactivation due to +ve membrane potential
- Transient outwards (repolarising) K\(^+\) current (I_{To}, voltage gated K\(^+\) channel - rapidly inactivated) contributes
- Suppression of inward rectifier current

Phase II:
- Plateau phase
- Sustained reduction in K\(^+\) permeability (suppression of inward rectifier current)
- Slowly developed and sustained increase in Ca\(^{2+}\) permeability
- Open L-type Ca channels (voltage and ligand gated - decrease as Phase II progresses) → influx of Ca\(^{2+}\) ions
- Sympathetic stimulation and β-agonists enhance inward Ca\(^{2+}\) current
- Open K\(^+\) channels (delayed rectifier I_K which increase with time) → efflux of K\(^+\) ions
- Sympathetic activation → earlier activation of I_K and thus a shorter phase II
- Balance of the two → static membrane potential

Phase III:
- Repolarisation phase
- Closing of L-type Ca channels
- Ca\(^{2+}\) pumped into sarcoplasmic reticulum
- Delayed rectifier current - open K\(^+\) channels → efflux of K\(^+\) ions. Enhanced by increased intracellular Ca\(^{2+}\)

Phase IV:
- Inward rectifier: K\(^+\) channel (voltage gated) maintains high permeability
- RMP achieved
**Prepotential phase:**

- \( I_K \) (inward rectifier current) declines
- At the point of membrane hyperpolarisation a channel allowing both \( \text{Na}^+ \) and \( \text{K}^+ \) to pass inward is opened \( \rightarrow I_h \) also referred to as the "funny" current
- \( I_h \) forms the initial part of the prepotential
- \( \text{Ca}^{2+} \) channels open later in the phase: \( I_{\text{Ca}_T} \) (transient channel)
- Sarcoplasmic release of \( \text{Ca}^{2+} \) may contribute to the prepotential

**Action potential phase:**

- \( I_{\text{Ca}_L} \) (long acting) produces the impulse once threshold (~40 mV) is reached Due to the lack of contribution of \( \text{Na}^+ \) channel opening there is no sharp rise in the AP prior to the plateau

**Repolarisation phase:**

- At peak of impulse \( I_K \rightarrow \) repolarisation

**Cholinergic stimulation:**

- Leads to membrane hyperpolarisation and ↓ in the slope of the prepotential (thus slowed heart rate and slowed conduction - negative chronotropic and dromotropic effect)
- Mediated by \( \text{ACh} \rightarrow \uparrow \text{ed K}^+ \) conduction (permeability) via \( \text{M}_2 \rightarrow \text{BY G}_i \) protein mediated \( I_{K_{\text{ach}}} \) (ligand gated channel) opening \( \rightarrow \) slowed \( I_h \) depolarising effect
- ↓ diastolic permeability to \( \text{Na}^+ \)
- \( \text{M}_2 \oplus \rightarrow \downarrow \text{cAMP} \rightarrow \) slower \( \text{Ca}^{2+} \) channel opening and slower \( I_h \)
- The above effects are noted at both the SA and AV node
Noradrenergic sympathetic stimulation:

- ↑Ih :. ↑ rate of prepotential rise (increased HR)
- $\beta_1$ mediated $\uparrow$ cAMP $\rightarrow$ ICa (via increased channel opening) :. $\uparrow$ rate of depolarisation during AP
- Overall increased HR and rate of conduction (positive dromotropic effect)
  - Iontropic state increased 2° to $\uparrow$ $[\text{Ca}^{2+}]_i$
  - The rate of relaxation is enhanced via noradrenaline mediated phospholamban phosphorylation $\rightarrow$ $\uparrow$ rate of SR resequestration of $\text{Ca}^{2+}$

Hyponatraemia:

- Low voltage ECG complexes (relating to Phase 0)

Hyperkalaemia:

- As extracellular K increases the RMP decreases
- Fibres will eventually become unexcitable - diastolic arrest
- Causes a flaccid and dilated heart
- Bradycardia
- AV nodal blockade may occur
- Raised extracellular K$^+$ $\rightarrow$ less -ve RMP :. $\downarrow$ intensity of fast AP (due to higher number of Na$^+$ channels inactivated) $\rightarrow$ $\downarrow$ contractile strength
- K$^+$ $>$ 5.7 mM: Peaked T-waves; widened P waves
- K$^+$ $>$ 7 mM: P wave flattened or absent; AV block; QRS prolonged; prominent S wave
- K$^+$ $>$ 8 mM: S wave widened, deepened; QRS merges with T-wave
- VT/VF or idioventricular rhythm

Hypokalaemia:

- Prolonged PR interval
- Prominent U waves
- Occasional late T wave inversion
- ST depression
- QRS prolongation

Temperature:

- Increased temperature associated with an 18-20 BPM increase in HR per degree and a transient increase in contractile strength
- Lowered temperature and the associated decreased in ion permeability is associated with a decreased HR

Extracellular calcium:

- Hypercalcaemia $\rightarrow$ spastic contraction due to increased excitation of contraction. Systolic arrest may occur (calcium rigor)
- Hypercalcaemia $\rightarrow$ decreased HR due to a raised threshold potential
- Hypocalcaemia is associated with a cardiac muscle flaccidity, ST prolongation and thus QT interval prolongation

2. Cardiac excitation and arrhythmiae

Normal cardiac rhythm:

- Originates from SA node and is ~70 BPM at rest
- Bradycardia normal during sleep
- Tachycardia noted during emotion, fever and exercise etc
- In healthy individuals HR: ↑s during inspiration (via vagal transmission of stretch receptor impulses → cardio-inhibitory area in medulla oblongata → inhibition of tonic vagal discharge .: . HR ); ↓s during expiration
- Parasympathetic output fluctuations may cause a normal sinus arrhythmia

Enhanced automaticity:

- May occur in SA, AV and His-Purkinje system
- β adrenergic stimulation, hypokalaemia and mechanical stretch ↑ slope of prepotential
- Abnormal automaticity may occur in cells normally lacking spontaneous pacemaker activity (eg ventricular cells depolarised due to ischaemia)

Abnormal pacemakers and conduction:

- Ectopic foci may discharge once or continuously causing atrial, nodal or ventricular extrasystoles
- Third degree block occurs as a result of complete interruption of SA to ventricular conduction
- This block may arise as a result of AV nodal disease (AV block) or infranodal block
- With AV nodal block the non-diseased nodal tissue institutes a rate of ~ 45 BPM
- With infranodal disease (bundle of His) the ventricular pacemaker ranges from 15-35 BPM
- Stokes-Adams syndrome (bradycardia/asystole resulting in cerebral ischaemia → pre-syncope/syncope
- First degree (prolonged PR but atrial impulses reach the AV node)
- Second degree - variable conduction (2:1 or 3:1); Wenckebach phenomenon
- Right or left bundle branch blocks: normal ventricular rate with QRS prolongation
- Left bundle branch blocks may be subdivided further into anterior (left axis) or posterior (right axis) blocks

Atrial arrhythmiae:

- Atrial tachycardiae: regular discharge of an atrial focus or re-entrant activity → rates up to 220 per minute
- Atrial flutter (200-350/min) most commonly associated with counterclockwise circus movement in the right atrium. Almost always associated with 2:1 block (AV node cannot conduct > ~ 230 impulses per minute)
- Atrial fibrillation (300-500/min): irregular and disorganised fashion. Ventricular rhythm usually 80-160 BPM. May originate as far as 4 cm from heart within pulmonary veins
- Associated with decreased diastolic time, loss of atrial component in diastole (~20% of filling) → diminished CO +/- heart failure
- Vagal stimulation (carotid sinus/oculocardic reflex) → decreased conduction rate in atrial and AV node

Accelerated AV conduction:
- In Wolff-Parkinson-White syndrome the bundle of Kent for an additional nodal or aberrant muscular connection between the atria and ventricles, which conducts faster than the slower AV nodal connection
- A shortened PR interval is noted, with a normal interval between the start of the P wave and end of the QRS
- A premature beat will either be carried down the AV node → ventricles → bundle of Kent → atria (more common) or via bundle or Kent → ventricles → retrograde via AV node → atria → circus movement.

Ventricular arrhythmiae:
- Ventricular premature beats (VPB) are associated with a prolonged QRS due to slow impulse spread
- VPBs may obscure underlying P waves but are not usually conducted in a retrograde manner to the atria
- Not strong enough to produce a pulse (ie palpated/transduced in the radial artery) if early in diastole. May not open aortic/pulmonary valves → no second heart sound
- VPBs are common and in the absence of IHD benign
- VF: irregular and ineffective discharge of multiple ventricular ectopic foci. May be produced by a shock/extrasystole during the "vulnerable period" ie R on T
- Application of DC shock may be effective in depolarising all myocardium (thus abolishing at least temporarily heterogeneous pathways)

After-depolarisations and triggered automaticity:
- Delayed after-depolarisation (DAD) may occur with intracellular Ca\(^{2+}\) overload (myocardial ischaemia, adrenergic stress, digitalis intoxication, heart failure)
- If DAD reaches threshold then a triggered beat(s) may occur
- DAD triggered beats are more common if the underlying cardiac rate is rapid
- Early after-depolarisation (EAD) may occur with a prolonged AP interrupting Phase III repolarisation. EADs may reflect inward Na\(^+\) or Ca\(^{2+}\) currents
- EAD is more common with slow HR, hypokalaemia or in the presence of drugs prolonging the AP
- EADs are induced more readily in the His-Purkinje system and mid-myocardial (as opposed to epi or endocardial cells)
- Torsades (Polymorphic VT with prolonged Qt) is associated with EAD
- Prolonged QT syndrome is associated with mutations in the Na\(^+\), Ca\(^{2+}\) or repolarising (ie \(I_K\) rectifier) associated channels

Anatomically defined re-entry:
- Occurs when pathways with heterogeneous electrophysiological pathways conduct impulses between two points in the heart eg WPW
- In WPW as AV nodal conduction slows, the likelihood of the bundle of Kent being no longer refractory increases thus retrograde conduction may occur
- AV re-entrant tachycardia determined by (1) Presence of anatomically defined circuit (2) Heterogeneity of refractoriness (3) Slow conduction down one part of the circuit
- AV nodal re-entrant tachycardia where re-entry occurs in the region of the AV node
- Atrial flutter is a form of atrial re-entry tachycardia
- AV nodal re-entry and AV re-entry are both forms of PSVT

Functionally defined re-entry:

- Occurs in the absence of anatomically defined pathways
- Altered cell-cell coupling following AMI: scarring, rapid longitudinal and slow transverse conduction → re-entrant VT
- Ischaemic or other electrophysiological changes → region of slow conduction → impulses leaving this region → excitation of non-refractory myocardium
- AF and VF are a form of the above wherein cells are re-excited just following the absolute refractory period → unorganised activation patterns and uncoordinated contractile activity

3. The electrocardiogram

The normal ECG with a "fast fibre" AP superimposed

The ECG provides information regarding cardiac:

- rhythm
- rate
- conduction

Conventions:

cardiovascular physiology.doc - Timothy Southwood
- In depolarisation the normal distribution of charge adjacent to the sarcolemma (+ve outside and -ve inside) reverses (-ve outside and +ve inside)
- A small charge separation (dipole) exists within the extracellular fluid of polarised (ie at RMP - +ve outside) and depolarised (-ve outside)
- A net dipole existing at any moment reflects the general direction of the wavefront of depolarisation
- Dipole magnitude is determined by (1) Number of cells simultaneously depolarising (2) Consistency of orientation of the dipoles
- Dipole formed during ventricular depolarisation has same polarity as that formed during repolarisation (as last ventricular cells to depolarise are first to repolarise)
- Voltages (ie potential differences) are measured as positive electrode relative to negative
- An upward deflection occurs when the positive (active electrode) become positive
- A downward deflection occurs when the active electrode becomes negative
- 1 cm vertical deflection ~ 1 mV
- Large interval 0.2 second; small intervals 0.04 second

The bipolar limbs leads (Einthoven's triangle):
- Lead I: Negative terminal on R arm; positive terminal on L arm
- Lead II: Negative terminal on R arm; positive terminal on L leg
- Lead III: Negative terminal on L arm; positive terminal on L leg

Augmented (unipolar) limb leads:
- Two limbs connected through resistances to the negative terminal and the third to the positive
- aVR: Positive terminal on R arm
- aVL: Positive terminal on L arm
- aVF: Positive terminal on L leg

Unipolar chest leads:
- V1-6
- Single lead to positive electrode
- Negative electrode (indifferent electrode) connected through equal electrical resistances to the R and L arm and L leg leads.

Myocardial infarction is associated with three major abnormalities, all changes → ST elevation
- Initial abnormal rapid repolarisation after discharge of infarcted muscle → K⁺ efflux lasting minutes. The ECF in this area is thus more positive relative to the normal region. Extracellular current therefore flows from the positive to negative regions (conventional current as cationic flow). Electrodes over the injured area register this positivity, manifest at ST segment elevation
- Subsequent decline in RMP (ie closer to zero) due to K⁺ efflux. Current therefore flows extracellularly into this infarcted region ("current of injury") during ventricular diastole (T-Q interval) resulting in depression of the TQ segment (recorded as ST elevation)
- Slowed depolarisation (~30 minutes following infarction) in infarcted fibres relative to the normal surrounding fibres. Thus the infarcted fibre is relatively positive during early repolarisation → ST elevation
Determinants and Control of Cardiac Output

The above diagram relates left ventricular pressure to left ventricular volume and provides the following information:

- Left ventricular EDPVR (a measure of elastance)
- Left ventricular end-diastolic volume (an approximation of preload)
- Stroke volume and ventricular ejection fraction
- Stroke work
- Opening pressure (an approximation of afterload)
- Left ventricular end-systolic pressure-volume relationship (an approximation of contractility)

1. Preload, afterload and contractility

Preload:
- The tension within the myocardial wall developed by the end of diastole
- The end diastolic pressure when the ventricle is filled
- The length of muscle fibres at the completion of diastole
- An increase in preload → ↑ shortening during the subsequent contraction
- While ↑ preload → ↑ *initial* muscle fibre length it does not change the *final* muscle length after shortening
- As muscle fibre length cannot be determined in an intact heart end-diastolic pressure or volume within the cardiac chamber is used as an estimate
- The end diastolic length of muscle fibres (preload) is proportional to end diastolic volume (EDV). Inference of volume from pressure estimates rely upon left ventricular...
compliance (which may be effected by right ventricular volume or pressure, pericardial pressure, coronary artery perfusion and alterations to the series elastic component)

- A curvilinear relationship exists between cardiac preload and EDV
- The preload/EDV relationship is flat and linear over the normal operating range of the heart
- A change in filling pressure will normally $\rightarrow \uparrow$ in EDV by $\sim 25$ mL
- At EDV $> 170$ mL compliance alters (due to relatively indistensible cardiac fibrous tissue and pericardium)
- Outflow valve (aortic/pulmonary) opening pressures are 80 and 10 mmHg respectively

Factors effecting end-diastolic volume:

- $\uparrow$ intrapericardial pressure $\rightarrow \downarrow$ extent of ventricular filling (eg tumour/fluid)
- $\downarrow$ ventricular compliance $\rightarrow \downarrow$ extent of ventricular filling (AMI, infiltrative diseases)
- contribution of atrial contraction ($\sim 20\%$)
- Factors affecting venous return: blood volume ($\uparrow$ EDV); RAP ($\uparrow \rightarrow \downarrow$ VR); mean systemic filling pressure ($\uparrow \rightarrow \uparrow$ VR); resistance to blood flow ($\uparrow \rightarrow \downarrow$ VR)

Afterload:

- The tension developed in the myocardium by the end of the isometric portion of systole
- The tension at which isotonic contraction begins
- The tension in the left ventricular wall that resists ventricular ejection or the arterial input impedance (ratio of instantaneous pressure change to instantaneous change in flow)
- Series elastic component (vessels, connective tissue, neural structures) within myocardium is "stretched" until the myocardial wall tension is sufficient to overcome the load placed upon it
- Analogous to mean systemic arterial pressure

\[
\text{Stroke volume} = (\text{end-diastolic volume}) - (\text{end-systolic volume}) = 140-60 \text{ mL} - 80 \text{ mL} \rightarrow \text{EF} - 60\%
\]
May also be regarded as the "resistance" against which blood is expelled during ventricular systole

- ↑ afterload is associated both with increased myocardial oxygen demand/utilisation as well as ↓ cardiac muscle shortening (thus decreased stroke volume) as the muscle cannot shortened beyond the point at which the peak iso-metric tension generating potential = total load
- ↑ afterload is associated with: ↓ velocity of left ventricular shortening
- Tension = [(Transmural pressure ie intracavity - intrapleural) x radius] / 2 x wall thickness

Contractility:

- The peak isometric tension a muscle may generate for a given preload and afterload
- Any intervention → ↑ peak isometric tension a muscle can develop at a fixed length (preload) → ↑ cardiac muscle contractility (ie a positive inotrope)
- May be regarded as the "resistance" against which blood is expelled during ventricular systole
- ↑ contractility also → ↑ rate of muscle fibre shortening and development of myocyte tension development.
- Increased inotropic state shifts the Frank-Starling curve upward and to the left. Decreased inotropic state shifts the Frank-Starling curve downward and to the right
- Factors which influence cardiac contractility include: Sympathetic tone/circulating catecholamines (↑→↑), parasympathetic tone (↑→↓), myocardial "quantity", hypoxia/hypercapnoea/acidity (↓), force-frequency relationship, pharmacologic agents (barbituates, quinidine, procainamide)
- ↑ HR has a mild effect on contractility due to: ↑ Ca$^{2+}$ influx/minute and ↑ Ca$^{2+}$ release from the sarcoplasmic reticulum ("staircase phenomenon"). This is a form of homeometric regulation
- $\beta_1$ receptor $\oplus$ via $G_s$ receptor $\rightarrow \oplus$ of adenylyl cyclase $\rightarrow \uparrow$ cAMP $\rightarrow \oplus$ of protein kinase A (PKA) $\rightarrow$ phosphorylation of Ca$^{2+}$ channels $\rightarrow \uparrow$ Ca$^{2+}$ current during phase II of AP and therefore (i) $\uparrow$ intracellular [Ca$^{2+}$] per cycle and (ii) raised calcium stores and release from the SR (via phosphorylation and phosphalamban - "positive lusitropic effect")
- Calcium sensitivity is directly related to sarcomere length

![Left ventricular pressure volume relationship](image)

2. The Frank-Starling mechanism

The Frank Starling law states that the energy of contraction of is proportional to the initial length of the cardiac muscle fibre. The Frank Starling principle states:

- Within normal physiologic limits a greater degree of cardiac muscle stretch will lead to a greater degree of force of contraction and a greater volume of blood pumped
- An increase in end diastolic volume (EDV) will $\rightarrow \uparrow$ cardiac ejection (stroke volume) and $\uparrow$ peak left ventricular pressure in isovolumic beats
- Within normal limits the heart pumps all the blood coming to it without excessive damming of blood within the venous system
- Stroke volume increases as cardiac filling increases
- The relationship between end-diastolic volume of SV is expressed graphically as the Frank-Starling curve
- Regulation of cardiac output due to alterations in fibre length is referred to as heterometric regulation
- This heterometric regulation matches right and left ventricular outputs and accommodates changes in posture and breathing
- Ventricles as well as atria (in exercise/resistance to early diastolic ventricular filling) exhibit this property
The Frank-Starling mechanism has at its molecular foundation the more near-optimal interdigitation of cardiac actin and myosin filaments (peak effect at sarcomere length of 2.2 µm) associated with a greater degree of muscle fibre length and thus cardiac chamber volume and pressure. Above and below this length performance decreases.

3. Myocardial oxygen supply and demand

General statements:

- The heart receive ~ 225 mL/min of blood, accounting for 4-5% of CO
- This equates to 70 mL/min/100g (normal range 60-90)
- This flow may increase 4 to 5 fold during exercise and conditions of stress
- Basal O₂ consumption is ~ 2 mL/min/100g with 9mL/min/100g in the beating heart
- The stroke work (area under the ventricular PV loop) is ~ 7 x greater in the left cf the right ventricle (aortic pressure ~ 7 x greater than pulmonary arterial)
- The coronary A-V difference in content is 114 mL−1
- This compares to the brain (50 mL/min/100g; AV Δ 62), renal (360 mL/min/100g; AV Δ 14) and hepatic (95 mL/min/100g; AV Δ 34)
- 70% of O₂ within the coronary arterial blood is removed in a normal resting heart
- Myocardial oxygen extraction cannot increase to a large degree above this resting value
- Subendocardial blood flow <<<< when compared to mid and outer myocardial supply. The subendocardium in part compensates for this with a richer arterial network.
- In adults 60-90% of cardiac ATP is generated from fatty acid oxidation
- In the foetus and neonate (first four weeks) glucose and lactate are the predominant energy substrate
- Cardiac muscle will, however, metabolise FFAs, TGs, ketones, glucose and lactate
- Cardiac muscle has a heavy reliance upon aerobic ATP production: (i) +++ mitochondriae and (ii) high []s of myoglobin
- High turnover of ATP (every 10 seconds) with low reserve pool
Determinants of oxygen consumption:

- Basal metabolism ~ 25% of ATP consumed
- Muscle contraction ~ 75% of energy used mainly in ATP splitting during cross-bridge cycling. Some used during Ca\(^{2+}\) sequestration
- Cardiac afterload accounts for ~50% of energy used during isovolumetric contraction. Raised afterload $\rightarrow$ $\uparrow$ $\therefore$ $\uparrow$ \(O_2\) consumption
- Preload: $\downarrow$ $\rightarrow$ $\downarrow$ wall tension and $\therefore$ $\downarrow$ \(O_2\) consumption
- Heart rate for two reasons: (i) Increased number of contractions/min $\rightarrow$ $\uparrow$ \(O_2\) consumption and (ii) associated $\downarrow$ diastolic time and $\therefore$ diminished delivery
- Energy utilisation during isovolumetric contraction is directly related to wall tension
- Myocardial contractility: $\uparrow$ $\rightarrow$ $\uparrow$ energy expended with Ca\(^{2+}\) transport with more energy expended in a more rapid development of a given tension and end systolic fibre length
- More efficient energy expenditure with a low HR and high SV

Coronary blood flow is influenced by metabolic, mechanical, autonomic and endothelial factors:

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

- Autoregulation (metabolic and myogenic) occurs between systemic arterial pressures of 60-140 mmHg
- Local metabolic demand, responding rapidly to changes in myocardial oxygen consumption causes local control via vasodilatation regulated by: adenosine (thought to predominant contributor), AMP, K\(^+\), H\(^+\), CO\(_2\), bradykinin, prostaglandins all of which are produced in states of relative \(O_2\) lack
- Mechanical regulation: phase of the cardiac cycle, left or right ventricle location and depth within the myocardium. Subendocardial compression is greatest in systole, mid-endocardial flow is $\sim$ equal during both phases and subepicardial flow is slightly higher in systole when compared to diastole.
- \(Ner\) flow to the subendocardium is augmented by virtue of a high vascular density $\rightarrow$ $\sim$ 1.1:1 sub-endo to sub-epicardial flow overall.
- Coronary blood flow is impaired during left ventricular systole due to the compressive effect of the intramural tension. Diastolic flow therefore accounts for the majority of left ventricular flow and thus aortic diastolic pressure
- Blood flow to the right ventricle is phasic but the overall difference is far less due to lower intramural pressure
- The rich sympathetic innervation ($\rightarrow$ constriction) of coronary arterioles is outweighed by the production of vasodilator substances in conditions of raised sympathetic tone due to the concomitant rise in myocardial \(O_2\) consumption which accompanies the $\uparrow$ HR and contractility
- Larger epicardial arteries have both $\alpha$ and $\beta$-adrenergic receptors mediating constriction and dilatation respectively
- Parasympathetic muscarinic stimulation $\rightarrow$ dilatation although the significance clinically is unknown of this effect
- $\beta_2$-adrenergic receptor $\oplus$ on smaller cardiac arteries $\rightarrow$ vasodilation
- During exercise $\alpha$-adrenergic mediated constriction of large and medium coronary arteries coupled with $\beta$-mediated arteriolar vasodilatation assist in maintenance of subendocardial blood flow
Nitric oxide (the principle EDRF) is a potent vasodilator produced by the vascular endothelium in response to stress (hypoxia/ADP accumulation), vascular distending forces (eg during exercise). NO mediates reactive hyperaemia, myogenic vasodilatation and effects of acetylcholine and bradykinin.

Other factors influencing coronary vascular resistance and hence blood flow include:

- Disease states eg atherosclerosis causing raised vascular resistance
- Blood viscosity (↓→↓)

4. Cardiac output and venous return curves

Hypereffective heart associated with:

- Cardiac muscular hypertrophy eg marathon runners with 50-75% ↑ in myocardial mass
- Nervous excitation: SNS ⊕ → ↑ HR and contractility

Hypoeffective heart associated with:

- Inhibition of nervous excitation
- Abnormal heart rhythm/rate
- Valvular disease
- Raised arterial pressure (afterload)
- Myocardial damage (infarction/infiltration/inflammation)
- Congenital cardiac disease

Three main determinants of venous return (VR):
- **Msfp**: Mean *systemic* filling pressure ~ 7 mmHg: the simultaneous pressure in the systemic circulation when blood flow ceases. This is the systemic equilibrium pressure reached by a failing heart with compensatory mechanisms inhibited at the point where venous stasis has been reached due to the rise in right atrial pressure and thus cardiac output also reaches zero. It is measured following the cessation of circulation and requires clamping of the great vessels such that the systemic circulatory pressure is isolated from the pulmonary vessels. This distinct from mean *circulatory* filling pressure (Mcfp) which is determined when the heart ceases pumping (eg shock → VF) and the equilibrated pressure is then measured for the entire circulation (systemic and pulmonary). In effect Msfp and Mcfp are essentially equal given the low capacitance (~1/8) and volume (~1/10) of the pulmonary circulation when compared to the systemic.

- **RAP**: Right atrial pressure which exerts a "backwards" force to the venous system from the right atrium. Normally ~ 0 mmHg. Thus, while RAP exerts a positive influence on CO (via the Frank-Starling mechanism) it also exerts a negative effect on VR.

- **RVR**: The resistance to venous return. Normally 1.4 mmHgL$^{-1}$. Arise mostly within the venous system (2/3) (with some also from the small arteries/arterioles ~ 1/3). As venous resistance increases, "damming" of venous blood occurs. The resultant pressure change upstream from the point of resistance is unable to overcome the rise in resistance and therefore blood flow and therefore venous return decreases. When blood accumulates within the arterial circulation (which possess a capacitance ~ 1/30 of veins) the resultant pressure rise overcomes the resistance to a far greater extent.

Features of the venous return curve:

- Plateau caused by the subatmospheric RAP (generally at < -2 mmHg) leading to collapse of the veins entering the chest.
- Transitional zone
- Downslope to Msfp

Two factors effecting mean filling pressures: blood volume and vascular tone

- The venous pool has a compliance of ~ 100mLmmHg$^{-1}$ over normal range of 5-10 mmHg
- Raised venous volume or tone (via sympathetic stimulation) will raised peripheral venous filling pressures and thus mean filling pressure causing an ↑ VR
- This will shift the VR curve upward to the right. The reverse also holds

As shown on the curve below a raised VR will correspond to an increased cardiac output (intersection points of both curve) by the following mechanism:

- ↑ Msfp → ↑ pressure gradient and thus VR will increase for a given RAP - thus the curve shifts upwards
- As VR will cease at only at a higher RAP (given ↑ Msfp) - the curve shifts right
- Raised VR and RAP will result in increased ventricular stroke volume (via Starling’s mechanism)
- Initial ↑ed RV SV → temporary R/L output imbalance → ↑ LAP and pulmonary pressures. ↑ LAP then → ↑ LV SV and thus biventricular stroke volume will be matched with concomitant right and left atrial pressure increases.
- Overall, cardiac output increases
- The reverse is also true with ↓ Msfp

Alterations to RVR will alter the gradient of the venous return curve but not the Msfp. Sympathetic activation causes alterations to the CO (upwards shift) and VR (Msfp increases) curves. Increased blood volume (transfusion) in association with sympathetic stimulation (eg during resuscitation in hypovolaemic shock) causes alteration to the CO (upwards shift) and VR curves (Msfp increases; RVR decreases due to blood vessel distension)
5. Integrated factors determining cardiac output
The Peripheral Circulation

1. General statements

Blood flow to tissues achieves:

- Delivery of O\textsubscript{2}
- Delivery of carbohydrates, FAs and protein
- Removal of CO\textsubscript{2}
- Removal of H\textsuperscript{+}
- Maintenance of ionic concentration
- Transport of hormones/other substances

Three principles of circulatory function:

- Blood flow to each tissue is precisely controlled relative to the tissue needs
- Cardiac output is controlled in the main by the sum of all local tissue flows
- Arterial pressure is controlled independently of either local blood flow or cardiac output control

Distribution of the blood volume:

- 50% in systemic veins
- 18% in pulmonary circulation
- 12% in cardiac chambers
- 8% in arteries
- 5% in capillaries
- 2% in aorta
- 1% in arterioles

Distribution of blood flow:

<table>
<thead>
<tr>
<th>Region</th>
<th>%</th>
<th>mL min\textsuperscript{-1}</th>
<th>mL 100g\textsuperscript{-1} min\textsuperscript{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>15</td>
<td>750</td>
<td>50</td>
</tr>
<tr>
<td>Heart</td>
<td>4.5</td>
<td>225</td>
<td>70</td>
</tr>
<tr>
<td>Liver</td>
<td>20</td>
<td>1200</td>
<td>95</td>
</tr>
<tr>
<td>Kidneys</td>
<td>20</td>
<td>1200</td>
<td>360</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>15</td>
<td>750</td>
<td>3-4</td>
</tr>
<tr>
<td>Skin</td>
<td>6</td>
<td>300</td>
<td>3</td>
</tr>
<tr>
<td>Bone</td>
<td>5</td>
<td>250</td>
<td>3</td>
</tr>
<tr>
<td>Adrenals</td>
<td>0.5</td>
<td>175</td>
<td>300</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
<td>50</td>
<td>160</td>
</tr>
</tbody>
</table>

Pressures within the circulation:

- mean pressure increases by 0.77 mmHg per centimetre below heart level
- in general, pressure decreases from large to small arteries due to increased resistance to flow
- capillary pressures: arteriolar end ~32 mmHg and venule end ~ 15 mmHg. Functional pressure of ~ 17 mmHg
- Central venous pressure: the pressure in the great veins at the entrance to the right atrium. Normally ~ 4.6 mmHg
- Arterial pressures: systolic ~ 120 mmHg and diastolic ~ 80 mmHg
- Mean atrial pressure = \( \frac{2}{3} \times \text{diastolic pressure} + \frac{1}{3} \times \text{systolic pressure} \)
- Pulmonary arterial pressures: systolic ~ 25 mmHg and diastolic ~ 8 mmHg

Resistance to blood flow:
- The resistance in the entire circulation (total peripheral resistance) is 1 mmHg·mL\(^{-1}\)·s\(^{-1}\)
- CGS units (dyne·sec·cm\(^{-5}\)):
  \[ \text{Resistance} = 1333 \times \text{mmHg} \times \text{mL}^{-1} \times \text{s}^{-1} \]
- Total pulmonary vascular resistance ~ 1/7 that of the TPR

The thoracic pump:
- Inspiratory diaphragmatic excursion → ↓ intrathoracic pressure favouring venous return
- Raised intra-abdominal pressure will in general favour venous return (nb excessive pressure as with insufflation during laparoscopic surgery may diminish venous return)

The muscle pump:
- In the absence of rhythmic skeletal muscle mediated venous compression peripheral venous pressure can rise to 85-90 mmHg
- With rhythmic contraction this may decrease to ~ 30 mmHg
- Pulmonary arterial pressures: systolic

Statement of the Starling forces within the capillary bed:

\[
\text{Filtration rate} = Kf \times \left( [P_c - P_i] - \sigma(\pi_c - \pi_i) \right)
\]

- \( Kf \) is the filtration coefficient (product of the permeability and surface area of the capillaries): ~6.67 mL·min\(^{-1}\)·mmHg\(^{-1}\)
- \( P_c \) and \( \pi_c \) are the capillary hydrostatic and plasma colloid oncotic pressure respectively
- \( P_i \) and \( \pi_i \) are the interstitial hydrostatic and plasma colloid oncotic pressure respectively
- \( \sigma \) is the reflectance coefficient
- Normal \( \pi_c \) is ~ 28 mmHg (19 mmHg from dissolved protein and 9 mmHg from cations held within the plasma by proteins - the Donnan effect)
- At the arterial end of the capillary \( P_c \) is 30 mmHg, \( P_i \) -3 mmHg and \( \pi_c \) 28 mmHg and \( \pi_i \) 8 mmHg → net outward (ie from capillary to interstitium) force of 13 mmHg. Around 0.5% of plasma flowing flows outward under this force
- At the venous end of the capillary \( P_c \) is 10 mmHg, \( P_i \) -3 mmHg and \( \pi_c \) 28 mmHg and \( \pi_i \) 8 mmHg → net inward force of 7 mmHg. Given the number and permeability of the venous capillaries ~ 9/10 of filtered fluid is reabsorbed, the remainder transported via the lymphatic system
- Net balance of forces (28.3 mmHg outward and 28 mmHg inward) causes a net filtration of ~ 2 mL·min\(^{-1}\)

2. Vascular smooth muscle

General features:
Small fibres lacking cross striations 1 - 5 µm in diameter and 20 - 500 µm in length
- Actin filaments attached to dense bodies with myosin filaments interspersed in between with 5-10 x more actin that myosin present
- Fibres arranged in circumferential or slightly helical manner around vessels
- Strength of contraction controlled primarily by changes in [Ca\(^{2+}\)] intracellularly
- Calcium sensitivity of the contractile machinery also influences activity
- Slower contraction/relaxation cf skeletal muscle: 30 x length of skeletal muscle (0.2 - 30 seconds)
- Cross-bridge cycling occurs 1/10 to 1/300 the frequency of skeletal muscle
- Tension may be developed over a greater range of muscle lengths cf skeletal muscle
- "latch mechanism": myosin heads remain attached to actin following a ↓ in [Ca\(^{2+}\)] and enzyme activity thereby maintaining tension without ATP use
- Can be activated by stretch
- "stress relaxation": despite initial ↑/↓ in tension accompanying an ↑/↓ in volume, over 15-60 seconds of this sustained volume the pressure will return to the original level prior to change
- Contractile activity may result from action potentials, changes in membrane potential (electromechanical) as well as changes in intracellular [Ca\(^{2+}\)] without alteration to the membrane potential (pharmacomechanical coupling)
- Calcium may enter from the ECF via voltage or ligand gated channels or from the sarcolemma via action potential medicated activation of the RyR or IP\(_3\)R Ca\(^{2+}\) channels

Molecular basis of contraction:
- Ca\(^{2+}\) forms the calcium-calmodulin complex (up to 4 Ca\(^{2+}\) bind)
- Ca\(^{2+}\)-calmodulin complex activates myosin light-chain kinase
- MLCK phosphorylates myosin at serine 19 →↑ ATPase activity
- Myosin phosphorylation then allows cross-bridge formation and cycling
- Myosin phosphatase then dephosphorylates the myosin head

Membrane potential:
- RMP ranges from -40 to -60 mV
- RMP largely determined by K\(^+\) permeability
- Inward rectifying K\(^+\) channel (predominant channel), ATP-dependent K\(^+\) channel (thought important in matching blood flow to demand as open when ATP levels are low)
- Infrequent action potentials, initiated primarily by inward Ca\(^{2+}\) current (voltage operated calcium channels)
- Repolarisation achieved by K\(^+\) efflux via delayed K\(^+\) channel and calcium activated K\(^+\) channels
- Stretch sensitive cation channels may regulated to smooth muscle response to stretch

Electromechanical coupling:
- Depolarisation →↑ open state of Ca\(^{2+}\) channels thus contraction
- Hyperpolaristaion → relaxation and vessel dilatation

Pharmacomechanical coupling:
- Vasoconstrictors (eg noradrenaline) may bind to membrane receptors (eg $\alpha_1$-adrenergic receptor) $\rightarrow$ (i) G protein mediated channel opening thus $\uparrow$[Ca$^{2+}$] or (ii) activation of a secondary messenger pathway - IP$_3$ formed $\rightarrow$ sarcolemmal channel opening

Relaxation:

- Hyperpolarisation $\rightarrow$ vessel dilatation
- G protein ligand binding via cyclic AMP pathway ($\beta_2$-receptor binding, histamine and VIP) $\rightarrow$ $\Theta$of adenylate cyclase $\rightarrow$ $\uparrow$ cAMP $\rightarrow$ $\Theta$ of protein kinase A $\rightarrow$ Ca$^{2+}$ efflux
- cyclic GMP (NO mediated): NO $\rightarrow$ $\Theta$ guanylyl cyclase $\rightarrow$ $\uparrow$ cGMP

3. Control of local blood flow

Is achieved by:

- Acute control: eg constriction/dilatation of arterioles, metarterioles and pre-capillary sphincters
- Long-term adaptation: change in size and number of blood vessels supply a tissue bed

Autoregulation:

- Autoregulation describes the capacity of tissues to regulate there own blood flow.
- An intrinsic capacity to compensate for moderate changes in perfusion pressure by changes in vascular resistance

Myogenic theory of autoregulation:

- $\uparrow$ perfusion pressure $\rightarrow$ $\uparrow$blood vessel distension $\rightarrow$ vascular smooth muscle contraction $\rightarrow$ $\downarrow$ perfusion pressure
- Relates to the intrinsic contractile response of smooth muscle cells to stretch

Metabolic theory of autoregulation:

- The greater the rate of metabolism within a tissue bed or the less available O$_2$ is to a tissue bed the greater the rate at which vasodilator substances (adenosine, CO$_2$, AMP, $K^+$, H$^+$, histamine) are formed
- $\downarrow$ blood flow $\rightarrow$ accumulation of vasodilator substances $\rightarrow$ vasodilatation and $\uparrow$ blood flow $\rightarrow$ clearance of vasodilator substances
- O$_2$ lack also decreases the ability of ATP driven smooth muscle contraction (basal tone and active contraction) to be maintained $\rightarrow$ vasodilatation
- A lack of other nutrients essential in ATP production (glucose, thiamine) also $\rightarrow$ vasodilatation via impaired contraction

Reactive hyperaemia:

- Occurs following the cessation of blockade of the vascular supply to a region (seconds to hours) and is characterised by an increase blood flow to this region afterwards, “repaying” the accumulated oxygen debt
Metabolic and myogenic autoregulation may contribute

Active hyperaemia:

- Increased local metabolism (muscle, brain, GIT during secretion) causes increased production of vasodilator substances and thus increased tissue flow

Endothelial factors:

- Nitric oxide: produced from arginine by nitric oxide synthase (NOS) and inactivated by haemoglobin. There are three isoforms of NOS: NOS1 in CNS, NOS2 macrophages/immune cells, NOS3 in endothelial cells. NOS1 and NOS3 are activated by increased intracellular Ca\(^{2+}\) which may caused by Ach, bradykinin, VIP, substance P or (via stretch sensitive calcium channels) sheer stress on vascular walls. Endothelial derived NO → vascular smooth muscle → \(\oplus\) of guanylyl cyclase → \(\uparrow\) cGMP and smooth muscle relaxation

Humoral agents:

- Prostaglandins: inhibit platelet aggregation and promote vasodilatation
- TXA\(_2\): elaborated by platelets, promotes platelet aggregation and causes vasoconstriction
- Endothelins: potent vasoconstrictors. Endothelin-1 acts via binding to a G protein coupled receptor → PLC \(\oplus\) → IP\(_3\) formation
- Carbon monoxide derived from haeme may act as a vasodilator

Long-term regulation:

- Principally related to altered tissue vascularity
- Strong influence of oxygen on vascularity: \(\downarrow\)→\(\uparrow\) and vice-versa
- Growth factors involved include: vascular endothelial derived GR; fibroblast growth factor; angiogenin. All cause “sprouting” of new vessels from pre-existing ones.
- Eventual increase in vascularity determined by maximal rather than average tissue need.
Control of Blood Pressure

1. General statements

Rapid acting response to hypotension (seconds):

- Baroreceptors → RVLM
- Chemoreceptors → RVLM
- Central ischaemic response all leading to…
  - ↑ HR
  - ↑ force of cardiac contraction
  - ↑ cardiac output
  - Vasoconstriction → ↑ TPR
  - Venoconstriction → ↑ venous return and CO via Frank-Starling mechanism

Minutes to hours:

- Activation of the renin-angiotensin system
- Stress relaxation of vasculature
- Tissue capillary fluid shifts altering blood volume

Long term:

- Renal regulation of Na⁺/H₂O content
- Pressure diuresis/natriuresis
- RAA system

2. Medullary control

The vasomotor centre resides on the pial surface of the rostral ventrolateral medulla (RVLM). Higher centres (limbic system via hypothalamus) provide input to RVLM (mediating changes seen this arousal/anger). RVLM neurons descend in the intermediate gray region of the spinal cord, with glutamate acting as an excitatory transmitter.

The vasomotor centre contains:

- Vasoconstrictor area (bilaterally in the anterolateral superior medulla) which interact with all spinal levels → excitation of SNS vasoconstrictor neurons
- Vasodilator area (bilateral in the anterolateral inferior medulla) which projects upwards to the vasoconstrictor area → inhibition of the vasoconstrictor activity and ∴ vasodilatation
- Sensory area (bilaterally in the tractus solitarius) which receives signals from the vagus and glossopharyneal nn

The vasomotor also responds:
Directly to ↓PO₂ ↑PCO₂
- Excitatory centre stimulation: pain pathways, brainstem reticular formation
- Lung inflation via vagal afferents → inhibition of vasomotor discharge

The autonomic nervous system plays a central role in blood pressure/heart rate control:

- Without the tonic vasoconstrictor centre activity vasomotor tone falls with BP decreasing (eg spinal anaesthesia) to ~ 50 mmHg
- In the absence of autonomic nervous input (PNS and SNS) HR ~ 100
- In the absence of the PNS HR ~ 150-180
- In the absence of the SNS HR ~ 35-40
- Vasodilator area (bilateral in the anterolateral inferior medulla) which projects upwards to the vasoconstrictor area → inhibition of the vasoconstrictor activity and ∴ vasodilatation
- Skeletal muscle also contains sympathetic cholinergic vasodilatory nervous input

3. Rapid arterial pressure control

Baroreceptors:

- Spray-type nerve endings located in vessel walls and the cardiac chamber
- Rapidly respond to *changing* blood pressure and are stimulated by stretch
- Baroreceptors adapt over hours to days → ↓ rate of firing following and increase in BP
- Carotid sinus (located above the carotid bifurcation) and aortic arch receptors monitor the arterial circulation
- Signals from the carotid sinus travel via Hering’s nerve, the glossopharyngeal nerve arriving in the nucleus tractus solitarius
- Aortic arch receptors travel via the vagus to the vasomotor centre.
- Firing rate ↑ with ↑ blood pressure and ↓ with ↓ blood pressure. Firing from the baroreceptors is essentially ceased between 0 – 50 mmHg. Linear response between 70-110 mmHg with little increase beyond 150 mmHg
- Receptor activation by an ↑ blood pressure → excitatory glutamate release in the caudal VLM → GABA secretion in the rostral VLM and thus inhibition of the vasoconstrictor centre and PNS excitation → (i) Decreased tonic SNS discharge and (ii) increased vagal input to the myocardium.
- Receptor activation thus overall causes (i) ↓ HR (ii) vasodilatation and venodilatation (iii) ↓ BP (iv) ↓ CO
- Decreased baroreceptor firing rate → (i) arteriolar constriction ∴ ↑ TPR and thus ↑ BP (ii) venoconstriction → displacement of blood within the venous system towards to heart ∴ ↑ VR → ↑ CO (via Frank-Starling mechanism) and thus ↑ BP (iii) direct cardiac stimulation → ↑ HR, ↑ rate of conduction and ↑ inotropic state ∴ ↑ CO and thus ↑ BP. These changes occur within 5-10 seconds

Peripheral chemoreceptors:

- Located in the carotid (at bifurcation) and aortic bodies
- Chemoreceptor cells are sensitive to (i) O₂ lack (ii) CO₂ excess (iii) H⁺ excess
- Are not stimulated strongly until arterial pressure is < 80 mmHg
- Are supplied by a nutrient artery
- ↓ BP → ↓ flow → ↓ PO₂, ↑PCO₂ and ↑ H⁺ → ↑ rate of signal transmission via Hering’s nerve and the vagus nerve → ↑ stimulation of the vasoconstriction centre.
- Mayer’s waves occur in hypotension with slow fluctuations in BP every 20-40 seconds. These are thought to occur as transient ↑s in BP due chemoreceptor stimulation → ↓ rate of firing from chemoreceptors → ↓ BP : lowered perfusion of chemoreceptors → ↑ rate of firing → ↑ BP and so on.

Atrial stretch receptors:
- React to wall distension: Type A during systole and Type B at end diastole
- Type B discharge is ↑ ed with ↑ venous return and ↓ ed with IPPV
- Activation of atrial stretch receptors → ↑ HR, ↓ BP and venodilatation
- Atrial stretch also associated with ANP release

Cardiopulmonary receptors:
- Low pressure receptors
- Minimise arterial pressure changes that might otherwise occur with changes in blood volume
- Activation causes bradycardia, hypotension
- Bezold-Jarisch reflex: hypotension, bradycardia, apnoea then rapid shallow breathing due to activation of chemosensitive C fibres in the cardiopulmonary region

Valsalva manoeuvre:
- Forced expiration against a closed glottis
- Airway pressure is increased to ~50 cmH₂O for 30 seconds
- Initially blood pressure increases due to a raised intrathoracic pressure adding to aortic pressure
- This high intrathoracic pressure then decreases venous return → ↓ CO and BP and bradycardia due to increase baroreceptor discharge
- The decreased BP decreases baroreceptor discharge thus increasing peripheral resistance and heart rate as well as peripheral venous tone (mean filling pressures)
- These changes tend to mitigate the decline in BP
- When the glottis is reopened and intrathoracic pressure returns to normal, venous return and therefore cardiac output increases. However the peripheral resistance remains elevated thus BP rises and "overshoots"
- This increased blood pressure increases the baroreceptor discharge → (i) bradycardia and (ii) normalised blood pressure
- In autonomic insufficiency the heart rate changes are absent
- With sympathectomy (eg spinal anaesthesia) the heart rate changes remain but systemic vasoconstriction does not compensate for the decline in BP accompanying raised intrathoracic pressure. Therefore BP continues to decline during this period.
- With primary hyperaldosteronism the heart rate does not change and the blood pressure rises with normalisation of intrathoracic pressure
With raised end-diastolic pressure or left ventricular failure there is no decline in BP following the onset of raised intrathoracic pressure as cardiac output is not limited by end-diastolic pressure in a failing heart. Moreover, given the unchanged cardiac output no compensatory increase in peripheral vascular resistance or heart rate occurs. Therefore, when the raised intrathoracic pressure is relieved by glottic opening no "overshoot" occurs. A square pattern is thus obtained when plotting blood pressure against time.

CNS ischaemic response:

- Neurons in the vasomotor centre respond directly to CNS ischaemia → \( \Theta \) of vasoconstrictor centre → near total occlusion of peripheral vessels
- Not significant until BP < 60 mmHg and maximal between 15-20 mmHg

Cushing reflex:

- Arises due to compromised blood supply to the RVLM with raised ICP → local ischaemia, hypoxia and hypercapnoea → direct stimulation of the vasoconstrictor centre → \( \uparrow \) BP.
- Peripheral baroreceptors sense the raised BP and thus mediate the associated bradycardia seen with the Cushing reflex

Dive reflex:

- Bradycardia and vasoconstriction in all organs except the heart and brain seen in aquatic animals in response to diving
Applied Cardiovascular Physiology

1. Exercise

Three major adjustments occur:

- Mass sympathetic discharge
- ↑ arterial pressure
- ↑ cardiac output

Sympathetic discharge:

- Central muscle control centre sends signals via the corticohypothalamic pathway to the vasomotor centre → ↑ SNS and ↓ PNS (especially to the heart)
- Cardiac sequelae: ↑ HR, ↑ inotropic state and ↓ PNS inhibition of cardiac function
- Arterioles (save those in active muscle which have cholinergic sympathetic input and locally mediated vasodilatation) constrict → ↑ peripheral resistance. The cerebral and coronary circulations are relatively spared due to their relative deficiency in vasoconstrictive innervation. Skeletal muscle blood flow increases by ~ 2Lmin⁻¹.
- Veins and capacitance vessels contract → ↑ Msfp
- ∴ overall increase in venous return and cardiac output (cardiac function curve shifted ward)

Arterial pressure increases by 20 – 80 mmHg:

- ↑ CO and ↑ TPR → ↑ BP
- Extent of rise in BP is inversely proportional to degree of skeletal muscle vasodilatation

Venous return curve:

- Shift right due to ↑ Msfp
- Shifted upwards due to ↓ RVR as a result of skeletal muscle vessel dilatation
- Overall increased venous return

Skeletal muscle:

- Venous return augmented by the muscle pump
- Chemo and mechanoreceptor afferent signals to the car

2. Pregnancy

The following changes occur:

- Upward and leftward cardiac displacement
- Aortocaval compression after 20/40 with associated maternal hypotension and decreased uteroplacental flow (hence left lateral positioning)
- Placental blood flow of 625 mL min⁻¹
- 30-50% increase in circulating volume (mediated by aldosterone, oestrogen and progesterone)
- ~12% ↑ in HR
- 25% ↑ in stroke volume
- 30-40% ↑ in cardiac output
- 20-40% decrease in TPR due to the placental circulation (low resistance running in parallel with other systemic organs)
- 5-10 mmHg ↓ in diastolic pressure at 12-20/40
- ↑ renal plasma flow and GFR (75% and 50% respectively)
- During labor: 300-500 mL autotransfusion with uterine contractions and ~ 25% ↑ in cardiac output

3. Normal aging

Myocardial changes include:

- Decrease in the resting and maximum cardiac index
- Decrease in the maximum heart rate
- Decreased diastolic compliance
- Decrease in the number of functioning myocytes
- Accumulation of pigment within the myocytes
- Increase in contraction and relaxation time (cardiac cycle) of the heart
- Decreased sensitivity to catecholamines

Peripheral vascular changes include:

- Increase in total peripheral resistance
- Decrease in arterial and venous compliance
- Decrease in capillary density in some tissue beds

A blunted baroreceptor response mechanism due to:

- Decreased afferent activity due to reduced arterial compliance
- Decreased efferent activity due to decreased noradrenaline within cardiac sympathetic nerves (and the aforementioned decreased sensitivity to catecholamines)

Haemodynamic consequences of the above include:

- Increased pulse pressure and mean arterial pressure
- Increased afterload due to raised blood pressure

4. Shock
In the broadest sense shock may considered as tissue hypoxia resulting from compromised blood supply. The categories of shock are:

Cardiogenic:
- Cardiac pump failure due to myocardial infarction or coronary occlusion, valvular malfunction or arrhythmiae
- SVR is increased and CO reduced due to impaired contractility, rate, altered chamber compliance

Obstructive shock:
- Due to pulmonary embolus, tension pneumothorax or cardiac tamponade
- Impaired left ventricular filling

Hypovolaemic:
- Reduction in circulating volume due to haemorrhage (≥ 20%), burns, GI disturbance
- Primary disturbance is a decrease in mean filling pressure causing decreased venous return, thus preload and therefore cardiac output

Septic:
- Arising from peripheral vasodilatation (venous and arteriolar tone decreased) due to infection (bacterial, fungal, viral etc) and raised capillary permeability
- Myocardial depression may accompany septic shock
- Mean filling pressure, cardiac contractility and SVR are decreased
- Endotoxin (a lipopolysaccharide) released by bacteria induces nitric oxide synthase

Anaphylactic:
- Type I hypersensitivity reaction mediated by IgE cross linking and mast cell degranulation in response to an antigen (insect bites, foods)
- Decreased peripheral resistance (venous and arteriolar) and increased capillary permeability
- Decreased mean filling pressure, decreased venous return and decreased total peripheral resistance

Neurogenic:
- Loss of vascular tone due to inhibition of the tonic vasoconstrictor sympathetic nerves
- Cardiac contractility, arteriolar tone and mean filling pressures all diminished

The associated decrease in arterial pressure with any of the above forms of shock decreases the baroreceptor firing rate and \( \rightarrow \uparrow \) vasoconstrictor and sympathetic tone and \( \downarrow \) PNS tone resulting in:
- Increased HR and cardiac contractility
- Raised arteriolar tone ($\uparrow$ TPR) and decreased capillary pressures ($\rightarrow$ net interstitial fluid reabsorption)
- Increased mean filling pressure, venous return and thus preload
- Overall increased MAP and decreased organ blood flow

Other compensatory mechanisms include:

- Rapid shallow breathing augmented the thoracic pump $\rightarrow\uparrow$ venous return
- Activation of the renin-angiotensin-aldosterone system
- Vasopressin released from the posterior pituitary in response to decreased firing form the atrial and cardiopulmonary receptors
- Raised levels of circulating catecholamines
- Glycogenolysis within the liver mediated by adrenaline and noradrenaline $\rightarrow$ 20 mOsm increase in the extracellular tissue which in conjunction with decreased capillary pressure $\rightarrow$ intra to extracellular hence intravascular movement of fluid
- Renal sodium and water retention
- Stimulation of thirst

5. Cardiac failure

The failing heart - progress from acute (A$\rightarrow$B) to chronic (C$\rightarrow$E)systolic dysfunction
6. Intermittent positive pressure ventilation

Raised intrathoracic pressures during positive pressure ventilation cause the following changes in a healthy heart:

- Decreased venous return due to abolition of the thoracic pump, and decreased RA and Msfp difference
- Impaired RV filling due to ↓ VR
- Impaired RV filling and emptying with raised RV afterload due to ↑ pulmonary vascular resistance at high ventilatory pressures
- Impaired LV filling due to reduced RV output
- Impaired LV filling (diastolic compliance) due to left shift of interventricular septum in the presence of raised RV volumes (with ↑ PVR)
- Unaltered LV contractility
- Decreased LV afterload due to decreased LV transmural pressure (thus increasing LV stroke volume and decreasing O₂ consumption)
- Possible inhibition of cardiovascular regulatory centres due to PEEP causing impaired constriction of resistance and capacitance vessels
- Overall and decrease in cardiac output and peripheral resistance and thus a fall in blood pressure

In a failing heart:

- Decreased venous return may benefit an overloaded RV, returning it to a more favourable section of the Frank-Starling curve improving RV output and thus LV filling
- Decreased LV afterload will improve stroke volume
- Decreased extent of left septal shift will also improve LV filling
- Thus application of positive airway pressures may be beneficial to the failing heart
Measurement of Cardiovascular Function

1. Blood Pressure

Indirect (non-invasive) measurements based upon determination of blood flow rather than an intraarterial pressure. External pressure applied by a cuff (bladder width 40% and length 60% of the circumference of the extremity measured) to an extremity with flow then determined by palpation, auscultation, transmitted pulsation or pressure or with Doppler analysis.

Indirect methods may be divided into manual and automated methods

Riva-Roca (manual):

- Inflation of syphgmomanometer cuff around extremity and auscultation over an artery distal to the occlusion
- Sounds from artery under pressure (Korotkoff sounds) indicate systolic (level when sound is first audible) and diastolic (disappearance/abrupt diminution of sounds) pressure
- Advantages: low-cost, simple and reliable
- Disadvantages: operator variability, environmental noise disturbance, absence of Korotkoff sounds at low pressures.

Manual oscillation method:

- The first discontinuity in the needle movement of an aneroid manometer is taken an systolic blood pressure
- Disadvantages: does not measure diastolic pressure, poor correlation with direct pressure measurement

Palpation, Doppler and pulse-oximetric measurement (manual):

- Systolic pressure can be determined by any method that detects flow as cuff pressure is deflated
- Thus, artery palpation, the reappearance of a pulse oximetric trace or flow signal on Doppler can be used to determine systolic blood pressure, but not diastolic
- Direct palpation has been used in low pressure settings to estimate systolic blood pressure: radial (80 mmHg), femoral (60 mmHg) and carotid (50 mmHg)

Oscillometry (automated):

- Cuff senses pressure fluctuations caused by vessel wall oscillations in the presence of pulsatile blood flow
- Maximum oscillation is seen at mean arterial pressure
- Electronic processing of the signals with digital display of derived systolic and diastolic pressures
- Disadvantages: ulnar nerve palsy; impaired limb venous return with frequent (minutely) measurement; motion artifact may result in erroneous/missed reading; irregular rhythms may increase time to generate reading/diminish accuracy of the reading
Direct invasive blood pressure measurement requires:

- Placement of an arterial catheter (radial, brachial, axillary, femoral or dorsalis pedis)
- Transmission of the arterial pressure wave along a non-compliant fluid column within a tubing system
- Constant flush device
- Transduction via a low compliance diaphragm of the transmitted pressure wave which creates a volume change in response to the applied pressure
- The volume change alters the resistance of a Wheatstone bridge which is then converted into an electrical signal
- Display of both the number and pressure wave form
- Such a system is referred to as an underdamped second-order dynamic system.
- The dynamic response of this system is determined by the resonant (or natural) frequency and damping coefficient $\zeta$ (zeta)

Sources of error with direct pressure monitoring:

- Improper zeroing (ie not a level of the heart)
- Catheter blockage (thus a continuous flush may be employed)
- Catheter migration
- Natural frequency of the oscillator system - frequency at which the system oscillates independent of changes in the measured variable. Signals with wavelengths below but near the natural frequency are amplified and thus overshoot occurs. Signals above are attenuated thus a lower pressure is recorded. Accurate recording systems require a natural frequency $\geq 5$ times (at least 20 Hz) the fundamental frequency (3 - 5 Hz for physiologic arterial waveforms)
- Hydraulic component signal amplification: as the hydraulic component has a resonant frequency of 10-20 Hz, amplification may occur and damping may be required
- Damping coefficient: how quickly an oscillating system comes to rest - high coefficient implies good absorption of mechanical energy and thus signal loss; low coefficient implies underdamping and thus overshoot
- At resonant frequencies of 7.5 Hz systems will distort the waveform regardless of the damping coefficient. At 24 Hz a damping coefficient of 0.15 to 1.1 is acceptable and not associated with pressure waveform distortion.
- Optimal fast flush test: undershoot, followed by a small overshoot then a return to a normal waveform
- Overdamped traces are usually produced by: air-bubbles, clot formation, overly compliant tubing, loose connections, deflated pressure bags or anatomical factors
- Underdamped traces occur with excessive tubing length, increased inotropic or chronotropic state

Advantages:

- Constant arterial pressure monitoring without intermittent vessel occlusion
- Relatively low risk of complication (infection, thrombosis, insertion complication)
- Ease of access for arterial gas analysis and phlebotomy
- Analysis of pulse and systolic pressure variance with respiration (predictor of responsiveness to fluid challenge: $> 13\%$ variance in PPV associated with $\geq 15\%$ increase in CO following a fluid challenge)
2. Cardiac Output

Measuring techniques include:

- Thermodilution with PAC
- Transpulmonary thermodilution (CVP injection, peripheral arterial measurement) eg PICCO
- Continuous cardiac output measurement: heating filament warms blood in a computed (pseudorandom binary) sequence with thermistor at a PAC tip measuring blood temperature change (eg Vigileo). CO calculated by computation.
- Dye-indicator dilution technique eg lithium/cardio-green
- Pulse contour analysis (used to determine stroke volume) eg PICCO
- Oesophageal Doppler: when a transmitted sound wave is impeded by a structure, the reflected wave will vary in a frequency dependent manner with the characteristics of that structure. With a fluid filled tube (eg the aorta) the magnitude of the Doppler shift will vary in proportion to the flow in the tube. The reflected sound wave can therefore be used to calculate the velocity of the flow which when multiplied by the aortic cross-sectional area (measured by ultrasound also on the oesophageal probe) and ejection time produces and estimate of stroke volume. Correlates well with thermodilution. Corrected flow time also correlates directly with cardiac preload.
- Indirect Fick method via partial CO₂ rebreathing (intubated patients but NB altered minute ventilation and severe lung injury with CO₂ shunting).
- Thoracic electrical bioimpedance (useful for trend monitoring rather than for diagnostic purposes)

The Fick Principle:

\[
\dot{Q} = \frac{X_{\text{consumed}}}{C_{\text{arterial}}} - C_{\text{venous}}
\]

Where \( \dot{Q} \) is the blood flow through a region per unit time, \( X_{\text{consumed}} \) is the uptake into that region of a substance \( X \) per unit time and \( C_{\text{arterial}} - C_{\text{venous}} \) is arterio-venous content different of substance \( X \). Thus cardiac output (or other organ blood flow) may be calculated if the uptake of a substance (eg O₂, CO₂, N₂O) is known and the arterial and venous content across the organ are also known. For oxygen:

\[
\dot{Q} = \frac{\left(250mL\cdot min^{-1}\right)}{\left(190mL\cdot L^{-1} - 140mL\cdot L^{-1}\right)} = 5L\ min^{-1}
\]

Thermodilution technique:

- A known quantity of a cold solution (10 mL cold saline via the RA port of a PAC) is introduced into the circulation and adequately mixed (through two valves and a ventricle) and the resultant cooling curve recorded downstream (via a thermistor on the PA tip within the pulmonary artery)
- Cardiac output is inversely proportional to the area under the time-temperature curve
- The Stewart-Hamilton formula relates total blood flow ($Q_t$) to volume injected ($V$), blood and injectate temperature ($T_B$ and $T_I$), the integral of the $T_B$-time curve ($K_1$ and $K_2$ being computational constants):

$$Q_t = \frac{V(T_B - T_I) \times K_1 \times K_2}{\int T_B(t) dT}$$

- The thermodilution technique limitations: requires PAC (with concomitant complications: failure of insertion, arterial puncture, pneumothorax, arrhythmiae, atrial/ventricular puncture, knotting, infection), possibly inaccurate with tricuspid regurgitation, and left to right cardiac shunting.
Bibliography

Guyton and Hall 10th Edition
Ganong's Review of Medical Physiology 23rd Edition
Cardiovascular Physiology 7th Edition
Hurst's the Heart 12th Edition
Clinical Anaesthesia Procedures of the Massachusetts General Hospital 7th Edition
Nunn's Applied Respiratory Physiology Sixth Edition
Moore's Clinically Oriented Anatomy Fourth Edition
Procedures, Techniques and Minimally Invasive Monitoring in Intensive Care Medicine Fourth Edition